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INTERNATIONAL SOCIETY OF PHARMACOVIGILANCE

ABSTRACTS

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INTERNATIONAL SOCIETY OF PHARMACOVIGILANCE

The International Society of Pharmacovigilance (ISoP) is devoted to developing its activities on a worldwide basis towards supporting safer use of medicines in clinical practice.

ISoP aims to promote the use of all types of information and methodologies in providing optimal drug treatment for patients. The Society is not only for clinical pharmacologists, pharmaceutical industry representatives, epidemiologists and regulators, but also for practising clinicians, other healthcare professionals and anyone else who is interested in learning about better ways for patients to receive and use medicines safely.

Countries where there are ISoP members:

From Argentina to USA, from Europe to Asia and Australia, we have members in all five continents.

"By becoming a member of ISoP, you will have the opportunity to share your knowledge and ideas and to contribute to improving pharmacovigilance activities worldwide."
Hervé Le Louet, President of the International Society of Pharmacovigilance

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International Society of Pharmacovigilance

ISoP Secretariat Ltd
140 Emmanuel Road, London SW12 0HS, UK
Tel and Fax: +44 (0) 20 3256 0027
administration@isoponline.org

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Abstract Code: ISP3404-39

PROSPER (Patient-Reported Outcomes Safety Event Reporting) Consortium Guidelines for Validating PRO AEs

A. Banerjee[1], S. Ingate[1], S. Mayall[1], S. Okun[2], P. Wicks[2], J. Heywood[2]

(1) Drug Safety, regulatory & risk management, Pope Woodhead & Associates, St Ives, Cambs, UK, PE27 5BZ, (2) Patients Like Me, Boston, MA, USA

PROSPER comprises industry, regulatory authority, academic, private sector and patient representatives interested in the area of patient-reported outcomes of adverse events (PRO-AE) was convened to improve safety reporting by better incorporating the perspective of the patient.. It has developed guidance on PRO-AE data, including the benefits of wider use and approaches for data capture and analysis.

PROs encompass the full range of self-reporting, rather than only patient reports collected by clinicians using validated instruments and have become increasingly important across healthcare. Patient-centred models of care are integrating shared decision making and PROs at the point of care; comparative effectiveness research seeks to include patients as participatory stakeholders; and industry is expanding its involvement with patients and patient groups as part of the drug development process. Additionally, recent pharmacovigilance legislation from regulatory authorities in the EU and the US calls for the inclusion of patient-reported information in benefit-risk assessment of pharmaceutical products. For patients, technological advancements have made it easier to be an active participant in one's healthcare. Simplified internet search capabilities, electronic and personal health records, digital mobile devices, and PRO-enabled patient online communities are examples of tools that allow patients to gain increased knowledge about conditions, symptoms, treatment options and side effects of drugs.

Despite this increased attention and the perceived value of PROs, their full potential has yet to be realised in pharmacovigilance. Current safety reporting and risk assessment processes remain heavily dependent on healthcare professionals, even in the face of known limitations such as underreporting and discordance between patient and clinician reports.
PROSPER offers an innovative framework to differentiate patient populations. The framework considers populations that are prespecified e.g. clinical trials, observational studies and some registries; and non-prespecified populations e.g. claims databases, PRO-enabled patient support sites, and social websites in general. While the main focus of this guidance is on post-approval PRO-AEs from both prespecified and non-prespecified population groups, PROSPER also considers pre-approval, prespecified populations.

The guidance covers a minimum core dataset for industry and regulators to structure PRO-AEs and how collected data might be evaluated to better inform on the safe and effective use of medicinal products. Structured collection of such patient data can be considered both a means to an end (improving patient safety) as well as an end in itself (giving patient 'voice').

PROSPER directs this guidance to industry, regulators, prescribers and patients to better define the benefit-risk profile of new and existing medicines.

Abstract Code: ISP3408-43

The Implications of 'Off-Label' Use in Primary Care in England: An Example From a Post-Marketing Cohort Study

V. Osborne[1], D. Layton[1], S.A. Shakir[1]

(1) Drug Safety Research Unit, Southampton, UK; School of Pharmacy and Biomedical Science, University of Portsmouth, Portsmouth, UK

Background: Off label use is where a medicinal product is used for a medical purpose not in accordance with the authorised product information. As a result, real-life populations using a product 'off-label' could differ from RCT populations in terms of risk profile. Modified Prescription-Event Monitoring (M-PEM) is a post-marketing methodology able to systematically gather data on such 'off-label' use and quantify it. In this example we examined post-marketing use of Intrinsa®, which is a transdermal testosterone patch indicated for use in hypoactive sexual desire disorder (HSDD) in bilaterally oophorectomised and hysterectomised women receiving concomitant oestrogen therapy.
Objective: To describe drug utilisation of Intrinsa® and assess, where possible, if the product is being used according to the authorised product information.
Methods: A M-PEM study was conducted. Patients were identified from dispensed prescriptions that had been issued by general practitioners (GPs) for Intrinsa® between March 2007 and August 2010. 'Green Form' questionnaires were sent to GPs 6 months following the date of the first prescription for Intrinsa® for each individual patient, requesting drug utilisation information. Summary descriptive statistics were calculated.
Results: The final cohort consisted of 3073 patients. The majority of patients were reported to be female (3017, 98.2 %) with a median (IQR) age of 50 years (44–55 years). The most commonly reported indication was the licensed indication of HSDD in 2324 female patients (77.0 %). Under half of female patients (n = 1313, 43.5 %) were reported to have been hysterectomised and bilaterally oophorectomised (surgically induced menopause) prior to starting Intrinsa®; 584 (19.4 %) were naturally menopausal and 184 were pre menopausal. For 1029 (34.1 %) patients the GP specified that the patient was not using concomitant oestrogen therapy. Overall, only 643 patients (20.9 %) in the cohort were being prescribed Intrinsa® according to the authorised product information.
Conclusions: This study has shown that in real-life clinicians are prescribing some medicinal products outside the recommended terms of the licence, with only 20.9 % of patients receiving Intrinsa® according to prescribing guidelines. This highlights that the real-life patient population using Intrinsa® may have a different risk profile to the patients that were examined in RCTs. Evidence obtained solely from RCTs might not be relevant as a result, so evidence from post-marketing observational studies is important to ensure a product's safety and effectiveness in real-life use and will inform the risk management process.

Abstract Code: ISP3409-44

Characteristics of Patients with Aberrant Behaviours Using Fentanyl Citrate Buccal Tablets: Results From a Post-Marketing Cohort Study

V. Osborne[1], D. Layton[1], S.A. Shakir[1]

(1) Drug Safety Research Unit, Southampton, UK; School of Pharmacy and Biomedical Science, University of Portsmouth, Portsmouth, UK

Background: Fentanyl citrate buccal tablets (Effentora™; Cephalon) are indicated for Breakthrough Pain (BTP) in cancer, in adults receiving maintenance opioid therapy for chronic cancer pain. This study was conducted as part of the risk management plan and requested information on aberrant behaviours (ABs) such as escalating drug use and unclear aetiology of pain
Objective: To describe characteristics of patients with reported ABs and patients without ABs, quantifying off-label use
Methods: An observational cohort post-marketing study. Exposure data collected from dispensed prescriptions issued by general practitioners March 2009–April 2011. Outcome data (utilisation and events) from questionnaires sent to GPs ≥6 months after the drug was 1st prescribed for a patient. Descriptive statistics calculated and univariate analysis performed
Results: Final cohort = 551 patients. 46 patients (8.4 %) had ≥1 ABs reported. Median age of patients with ABs reported was lower than patients without ABs reported (48 years [IQR: 35, 63] vs 63 years [IQR: 52, 73]). Age was found to be significantly associated with ABs (Chi-square df(9) = 35.1; $p < 0.001$). Patients with ABs had 3.5 times the odds of having an indication other than BTP in cancer, compared to patients with no ABs reported (95 % CI: 1.1, 10.8). For dose, there was significantly different distributions between patients with and without ABs. Median duration of treatment was 87 days (IQR: 14, 276) for patients with ABs reported and 21 days (IQR: 1, 64) for patients with no ABs reported. Duration of treatment was found to be significantly differently distributed between patients with and without ABs (rank-sum $p < 0.001$). The odds of alcohol misuse, substance misuse and psychiatric disorders were significantly increased in patients with ABs. Where specified (n = 20), 11 patients with ABs had these prior to starting Effentora™. Median time to onset of ABs for the remaining 9 patients was 265 days (IQR: 140, 329)
Conclusion In conclusion, patients with ABs reported whilst using Effentora™ had several different characteristics to patients without ABs. Use outside the terms of the license tended to occur more frequently in these patients, however the prevalence was low.

Abstract Code: ISP3411-37

What Do Veterinarians Dedicated to Small Animal Practice Know About Pharmacovigilance in Uruguay?

A.R. Dib Brusales[1], E. Fernandez Costa[1], A. Aldrovandi Landini[1]

(1) Universidad de la Republica, Montevideo, Uruguay

Introduction: Many small animal practice veterinarians update their academic knowledge concerning to the commonly prescribed drugs rational use, and to adverse drug reactions (ADRs). However, the concept of Pharmacovigilance itself is rather new in Uruguay among the veterinarian community. No studies about veterinarians' general knowledge on this matter have been undertaken in our country.

Aim: To evaluate the small animal practice veterinarians' knowledge on the rational use of commonly prescribed drugs, the meaning of Pharmacovigilance, and the willing to ADRs voluntary notifications in Montevideo, Uruguay.
Methods: A personal interview based on the pharmacological properties, and the rational use of six drugs was performed. Anonymous and voluntary veterinarians were randomly organized in 3 groups according to the period of time after their college graduation, Group 1: from 0 to 3 years, (n = 24); Group 2: from 3 to 10, (n = 3), and Group 3: more than 10 years after college graduation, (n = 45).

Thirty forced binary (true/false) questions about drugs acting upon the central nervous system, antiparasitic drugs, and antimicrobial drugs, were asked. The authors established three levels of difficulty for each question according to an academic criteria: high$^{(HD)}$: (mechanism of action and pharmacological classification), medium$^{(MD)}$: (ADRs), and low$^{(LD)}$: (posology).

Two forced (yes/no) binary questions (meaning of Pharmacovigilance, and the willing to ADRs voluntary notifications), were also asked in each interview. Data analysis was performed using the Calc Free Office 4.0., Chi-squared test (χ^2), (CI = 95 %, $p < 0.05$ significant).
Results:

Table 1 (a) Responses (true option), according to questions' difficulty level (b) Responses (yes option), according to the concept of Pharmacovigilance and ADRs voluntary notification

(a)	HD (%)	MD (%)	LD (%)
G 1	62,85	74,31	85.76
G 2	62.37	84.34	88.64
G 3	53.33	74.81	85.74

(b)	Pharmacovigilance concept (%)	ADRs Voluntary Notification (%)
G 1	66.66	95.10
G 2	30.10	93.54
G 3	20.45	90.47

G group, *HD* high difficulty, *MD* medium difficulty, *LD* low difficulty, *ADRs* adverse drug reactions

Conclusions: This study has identified a very poor knowledge on the concept of Pharmacovigilance in veterinarians with more than 3 years after college graduation, when compared with recent graduates. This can be explained because drug safety and Pharmacovigilance as a dynamic clinical and scientific *discipline,* has been recently introduced in our Veterinary College. The need to educate the veterinary community about the importance of Pharmacovigilance, has the highest priority in our country.

Abstract Code: ISP3412-38

Biologic Drugs and Psoriatic Disease: The Influence of Adverse Drugs Reactions (ADRs) on Patients Compliance and Therapeutic Failure

A. D'alessio[1], R. Fraschetti[1], L. Celleno[2], C. De Simone[3], N.V. Pecora[4], E.M. Proli[1], L. Fabrizio[1]

(1) Hospital Pharmacy, University Hospital A. Gemelli, UCSC Rome, (2) Dermatology Unit, Columbus Integrated Complex, Rome, Italy (3) Dermatology Unit, University Hospital A. Gemelli, UCSC Rome, Italy (4) Hospital Pharmacy, Columbus Integrated Complex, Rome, Italy

Background: Biologic drugs are a therapeutic option in treatment of psoriasis. Their efficacy and safety profile have been widely documented. However patient compliance needs more attention, because it's possible cause of therapeutic failure. The ADRs are one of the factors than can influence the patients compliances

Objective/Aim: Objective is to evaluate the influence of ADRs on patients compliance and therapeutic failure.

Methods: Patients under treatment with biologic drugs (TNF-α blockers Etanercept and Adalimumab and anti-IL12/23 Ustekinumab) during 2011 were included in a prospective observational study conducted by Gemelli Hospital and Columbus Integrated Complex pharmacies. Pts data collected included: age, sex, disease and drug. The sample was characterized by compliance and therapy duration using mean and standard deviation (for continuous variables), frequency and percentage (categorical variables). Time to drug discontinuation was evaluated as the difference between starting date of treatment and date of drug termination or end of study. Differences in drug discontinuation time were analysed using Kaplan–Meier curves and assessed by the log-rank test. The identification of the reasons for therapy discontinuation was performed using a multivariate Cox regression model. Results were expressed as hazard ratios (HRs) and confidence intervals at 95 % (95 % CI).

Results: 180 pts with a mean age of 49 years (±13.2) and mean treatment duration of 18.6 months (±15.3) were analyzed. Overall global retention rate was 75 % (Eta 72.9 %, Ada 74.2 %, Ust 86.4 %). Adverse reactions occurred in 30 pts (16.7 %) including: skin (10 %), neurological (6.6 %), kidney (6.6 %), liver (6.6 %), oncological (3.3 %), immunological (3.3 %), heart (3.3 %) diseases and infections (3.3 %) inefficacy (56.6 %).

Conclusions: The results obtained demonstrate influence of ADRs in the treatment of psoriasis diseases in terms of non compliance and therapy discontinuation. Adherence was influenced by the occurrence of ADRs included inefficacy.

Discussion: Data highlight the ADRs may determine therapeutic failure of biological drugs, but these findings need further confirmation in larger population, with a longer follow-up.

Abstract Code: ISP3418-44

Drug Induced Gastrointestinal ADRs in Hospitalized Patients

M. Ponte[1], M. Ragusa[2], G. Keller[3], G. Di Girolamo[3], A. Wachs[2]

(1) Hospital Argerich. Buenos Aires, Argentina, (2) Hospital Argerich. Buenos Aires, Argentina, (3) Universidad de Buenos Aires, Argentina

Introduction and Aim: Most gastrointestinal Adverse Drug Reactions (ADRs) are mild and rarely serious. Some of them can be life threatening and are a great problem to medical institutions because they cause hospital admissions or prolong a lot inhospital stay. The aim of this study was to determine the incidence, types and drugs most frequently involved in gastrointestinal ADRs.

Material and Method: The study was performed in a tertiary care hospital in Buenos Aires City. Argentina. The hospital is¨Cosme Argerich¨, a public hospital with 350 beds approximately. The information was taken from the pharmacovigilance committee and the period of time included was June 2008 to march 2013. Naranjo Score Was performed to assess the causability. All ADRs were timely reported to our regulatory agency (ANMAT).

Results: In this period, 2780 ADRs were detected by the Pharmacovigilance Committee. 183 were gastrointestinal ADRs. The average age of patients suffering this ADRs was 59.53 years (IC 95 %: 58.03 – 61.03); 55.73 % (CI 95 %: 48.54–62.93) appeared in females and 44.26 % (37.06–51.45) in males. The most frequently observed ADRs were: upper gastrointestinal bleeding 55 events (30.05 %, CI 95 %: 23.41–36.69); pseudomembranous colitis 39 events (21.31 %; CI 95 %: 15.37–27.24); severe diarrhoea 28 events (15.30 %; CI 95%: 10.08–20.51); lower gastrointestinal bleeding 11 events; infections (Candida or cytomegalovirus) 5 events and 4 pancreatitis. We found also 3 bisphosphonates induced esophagitis, one with a stricture as complication; and two neutropenic enterocolitis. 132 events (72.13 %; IC 95 %: 65.63–78.62) were serious and there were 80 ADRs related admissions due to gastrointestinal ADRs.

Conclusions: Less than ten per cent of all ADRs were gastrointestinal but near two third of them were serious, mainly because they caused hospital admissions. The most important thing to remark is that most of gastrointestinal ADRs were preventable (gastrointestinal bleedings, bisphosphonates induced esophagitis, etc). What we found is similar to what is reported in international bibliography.

Abstract Code: ISP3419-45

Drug Induced Central Nervous System ADRs in Hospitalized Patients

M. Ponte[1], M. Ragusa[1], G. Keller[2], G. Di Girolamo[2], A. Wachs[1]

(1) Hospital Argerich, Buenos Aires, Argentina, (2) Universidad de Buenos Aires, Buenos Aires, Argentina

Introduction and Aims: Central Nervous System (CNS) Adverse Drug Reactions (ADRs) are very relevant in hospitalization because some of them can lead in hospitalization or in a prolonged hospital stay like confusional syndrome, seizures, neuromuscular blockade or haemorrhagic stroke. The aim of this study was to determine the incidence of these ADRs and the drugs most frequently involved in a tertiary care hospital.

Material and Method: The study was performed in a tertiary care hospital in Buenos Aires City. Argentina. The hospital is¨Cosme Argerich¨, a public hospital with 350 beds approximately. The information was taken from the pharmacovigilance committee and the period of time included was June 2008 to march 2013. Naranjo Score Was performed to assess the causability. All ADRs were timely reported to our regulatory agency (ANMAT).

Results: In this period, 2780 ADRs were detected by the Pharmacovigilance Committee and 151 affected Central Nervous System. The average age of people who suffered this type of ADRs was 56.60 years (CI 95 %: 54.97–58.22); 52.31 appeared in females (CI 95 %: 44.35–60.28) and 47.68 % in males (CI 95 %: 39.71–55.64 %). The ADRs most frequently detected were depression of consciousness 22.51 % (CI 95 %: 15.85–29.17); confusional state 18.54 % (CI 95 %: 12.34–24.74 %); extrapiramidalismo 10.59 % (CI 95 %: 5.68–15.50); ataxia and dizziness 8.60 % (CI 95% 4.13–13.08) and neuromuscular blockade 2.64 % (CI 95 %: 0.87–5.21). Drugs most frequently involved were neuropsychiatric drugs 50.33 % (CI 95 %: 42.35–58.30); antibiotics 15.23 % (CI 95 %: 9.50–20.96) and gastrointestinal drugs 8.60% (CI 95 %: 4.13–13.08). 39.07 % (CI 95 %: 31.29–46.85) were serious.

Conclusion: Neuropsychiatric ADRs are not so frequent in hospitalized patients but the can cause great morbimortality. Nearly half of all these ADRs can be preventable. Most of serious ADRs were because they prolonged hospitalization mainly in elderly patients.

Abstract Code: ISP3420-37

Drug Induced Liver Injury in Hospitalized Patients

M. Ponte[1], M. Ragusa[1], F. Cseh[2], A. Wachs[1]

(1) Hospital Argerich, Buenos Aires, Argentina, (2) USAL, Buenos Aires, Argentina

Introduction and Aims: Drug Induced Liver Injury (DILI) is a common ADR but infrequently is serious. Is also the first cause of drug withdrawal with several examples in the past few years. Specifically, for hospitalized patients, the proportion of serious cases of DILI are higher because they prolong hospitalization frequently. The aim of this study was to describe the incidence, drugs involved and seriousness of DILI in a tertiary care hospital.
Material and Method: The study was performed in a tertiary care hospital in Buenos Aires City. Argentina. The hospital is "Cosme Argerich", a public hospital with 350 beds approximately. The information was taken from the pharmacovigilance committee and the period of time included was June 2008 to march 2013. Naranjo Score Was performed to assess the causability. All ADRs were timely reported to our regulatory agency (ANMAT).
Results: In this period, 2780 ADRs were detected by the Pharmacovigilance Committee and 428 were DILI. The average age of patients suffering DILI was 52.21 years (CI 95 %: 51.28–53.15). 39.71 % (CI 95 %: 35.08–44.35) occurred in females and 60.29 % (CI 95 %: 55.44–64.68) in males. 4.38 % (CI 95 %: 2.24–6.32) were serious, mainly because they prolonged hospitalization and there were two DILI—related deaths. Drugs most frequently involved were antibiotics 58.41 % (CI 95 %: 53.74–63.08); neuropsychiatric drugs 13.78 % (CI 95 %: 10.51–17.05); NSAIDs 9.81 % (CI 95 %: 6.99–12.63) and cardiovascular drugs 8.64 % (CI 95 %: 5.98–11.30 %).
Conclusions: DILI is common in hospitalized patients and less than 5 % were serious. This is similar than reported in international bibliography. Clinical and laboratory systematic controls can decreased severity of DILI in hospitalized patients.

Abstract Code: ISP3421-38

ADRs Caused by Anticoagulants and Antiplatelet Drugs in Hospitalized Patients

M. Ponte[1], M. Ragusa[1], A. Wachs[1]

(1) Hospital Argerich, Buenos Aires, Argentina

Introduction and Aims: Haemorrhagic Stroke or gastrointestinal bleeding are devastating ADRs that sharply increase morbimortality in patients. They are also some of the most common causes of ADRs—related admissions in hospitals. The aim of this study was to determine the types of ADRs caused by anticoagulants and antiplatelet drugs.
Material and Method: The study was performed in a tertiary care hospital in Buenos Aires City. Argentina. The hospital is¨Cosme Argerich¨, a public hospital with 350 beds approximately. The information was taken from the pharmacovigilance committee and the period of time included was June 2008 to march 2013. Naranjo Score Was performed to assess the causability. All ADRs were timely reported to our regulatory agency (ANMAT).
Results: In this period, 2780 ADRs were detected by the Pharmacovigilance Committee and 87 were caused by anticoagulants or antiplatelets drugs. The drugs most commonly involved were acenocumarol 40 events; heparins 23 events; aspirin 17 events; warfarin 4 events and combinations 3 events. The events most frequently detected were: gastrointestinal bleeding 39.08 % (CI 95 %: 28.82–49.33); heparin induced thrombocytopenia 20.68 % (CI 95 %: 12.17–29.20 %) and SNC bleeding 14.94 % (CI 95 %: 7.45–22.43). 64.70 % of gastrointestinal bleeding were upper GI bleeding and 23.52 % were lower GI bleeding. 82.81 % (CI 95 %: 73.56–92.05 %) of all events were serious, mainly because they caused hospitalization.
Conclusion: Gastrointestinal bleeding was, as reported in international bibliography, the most common type of ADRs of anticoagulant and antiplatelet drugs. Most of this ADRs were preventable.

Abstract Code: ISP3425-42

Stability Problems of Dosage Forms Available in Iraq

M. Younus[1], I. Ibrahim[2]

(1) Iraqi Pharmacovigilance Center, Baghdad, Iraq (2) ALRasheed College of Pharmacy, Madinah, Iraq

Background: medication stability is the ability of medicine to remain fit to its established chemical and physical properties. To insure the proper effect and safety of medicines, stability of its designed form should be evaluated.
Objectives: The main aim of this study was to determine the stability of medicines available in Iraq in terms of identity, physical property, quality, and purity.
Method: A retrospective study was conducted through reviewing stability reports available at pharmacy department of Ministry of Health in Iraq from 2007 to 2009. The required information was gathered by the use of a special form designed by the researcher to assess the physical stability of medicines. Then, data was analyzed by SPSS version eighteen.
Results: The majority of reports (95.7 %), of all 141, revealed a physical stability, while the rest were about clinical adverse events. The source of medicines in these reports were private local companies (16.3 %), states manufactures (6.4 %), imported from Middle East regions (12.8), and imported from international companies (64.5 %). Most reported stability problems were impurities (4.3 %), changes in the color of a medicine (24.1 %), precipitations (63.9 %), spots (2.8 %), bad smell (2.8 %), leaking (1.4 %), split of the needle for injectable use (0.7 %). Further, the dosage forms of the reported problems were vials (11.6 %), ampoules (15.9 %), intravenous infusions (14.5 %), tablets (26.2 %), suspensions (5.9 %), syrups (15.9 %), eye drops (1.4 %), gels (5.8 %), infusion-sets (1.4 %), and cannulas (1.4 %)
Conclusions: although all medicines in Iraq passes through the quality assurance laboratories before reaching the consumer, still many problems arises before and during their use due to various causes including heat, moisture, oxidative conditions, and chemical reactions resulting in significant loss of potency over medications' shelf- life. Medicines recalls is still the major way to overcome this problems. Gap analysis and understanding stability of medicines in their different dosage forms will aid the regulatory decision in assessing and controlling such problems.

Abstract Code: ISP3427-44

Predictors of Serious Adverse Drug Reactions in Association with Complementary and Alternative Medicine in Malaysia

Z. Aziz[1], S. Shaikh Abdul Rahman[2], R. Isahak[2]

(1) Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia (2) National Pharmaceutical Control Bureau, Ministry of Health Malaysia, Petaling Jaya, Malaysia

Introduction: In Malaysia, Complementary and Alternative Medicines (CAM) products are easily available and increasingly used. Our spontaneous reporting system has received many reports of serious adverse events associated with the use of CAM products. Yet, little is known about factors influencing the development of serious adverse drug reactions (ADRs) due to CAM products.
Aim: To identify risks factor associated with serious ADRs due to CAM products.
Methods: All adverse reactions associated with CAM products (including CAM health supplements) submitted to the National Pharmaceutical Control Bureau (NPCB) between 2000 and 2012 were reviewed and analysed. ADRs were considered serious if the reactions led to death, hospitalisation or prolongation of hospitalisation, that were life threatening, or that caused significant disability. A multiple binary logistic regression was used to identify factors associated with serious ADRs in the reports.
Results: From a total of 43,444 reports received by NPCB, 732 (1.7 %) involved CAM products. Of 732 patients, 220 (30.1 %) developed serious ADRs, of which 27 died. Twelve deaths were attributed to unregistered products. Patients mainly use CAM products for health maintenance (31.8 %), for the treatment or prevention of minor ailments (17.9 %), for chronic illnesses (32.4 %), weight loss (5.2 %) and also for serious illnesses such as cancer (1.1 %). Multiple binary logistic regression analysis revealed three variables (patients having concomitant diseases, ethnic group and indications of CAM use) to be predictive of the ADRs seriousness. The odds of someone with concomitant diseases experiencing serious ADR were about two-fold compared to someone without concomitant diseases [odds ratio (OR) 1.91, confidence interval (CI) 1.12–3.25]. Being Chinese was associated with increased odds of experiencing serious ADRs compared to being Malays [OR 2.35, CI 1.61–3.44]. The odds of someone experiencing serious ADRs also increased if the CAM products were used for chronic illnesses compared to if the products were used for health maintenance [OR 1.66, CI 1.12–2.47]. The variables age, sex, and concomitant drugs were not significant predictors of serious ADRs.
Conclusions: The proportion of serious ADRs associated with CAM products was high, with several deaths. Chinese patients and those who used CAM products for chronic illness and patients with concomitant diseases were at an increased risk for developing serious ADR. The findings could be useful for planning strategies to prevent serious ADRs due to CAM products.

Abstract Code: ISP3430-38

Real-Time, Behavioural Evaluation of Effectiveness of Risk Minimisation Tools

S. Ingate[1], J. Mann[1], S. Wells[1], S. Wooder[1], S. Mayall[1], A. Banerjee[1]

(1) Pope Woodhead & Associates, St. Ives, Cambridge, UK

Background: Evaluation of the effectiveness of drug product risk programmes is a regulatory requirement that closes the audit loop, ensures the maintenance of the risk management plan (RMP), facilitates optimum understanding and communication of drug risks to stakeholders, and, ultimately, drives a positive benefit: harm ratio for drugs. Several approaches are being deployed to measure the effectiveness of risk minimisation tools and programmes. Our previously described 5 level evaluation model shows tool distribution metrics at the most basic level, increasing through tool utilisation, risk knowledge, behavioural change and, finally, to improving safety outcomes at the highest level.
Objectives/Aims: To report our experience with behavioural evaluation of effectiveness of risk minimisation tools, including behavioural surveys and web-based tools collecting real-time HCP/patient behavioural metrics, which can be combined with data on tool utilization, knowledge, and outcomes
Methods: A review of surveys and real time web based checklists collecting evaluation effectiveness data, including correlation with safety outcomes.
Results: A current limitation of evaluation approaches is the lack of guidance to aid marketing authorisation holders (MAH) understand the objectives and structure needed to appropriately assess the effectiveness of its implemented risk minimisation and satisfy regulatory goals. Behavioural surveys must have an adequate sampling frame, with a margin of error of less than 20 %. Tool uptake is improved through web channels. Today c.50 % of EU hospitals are paper-free (or near paper-free) and this trend is increasing—although channels need to be adapted for individual member states.
Conclusions: Usage of voluntary risk minimisation tools can be improved by providing value added but non-promotional functionality to HCPs and patient tools, e.g. lab-test reminders. The results of evaluation; including levels of penetration, utilization and appropriate behaviours, can be aligned with corresponding corrective actions, e.g. improved communication or deployment redesign of tool content or programme design as appropriate.

Abstract Code: ISP3434-42

Design and Evaluation of the Pharmacovigilance Course in Pharmacy School (Kulliyyah) in Malaysia

R. Elkalmi[1], O. Al-Lela[1], S. Jamshed[1], A. Awadh[1], A. Alshami[1]

(1) Department Of Pharmacy Practice, Kulliyyah of Pharmacy, International Islamic University Malaysia, Kuantan, Pahang, Malaysia

Background: Deficiencies in pharmacovigilance education may contribute to low involvement and ADR underreporting among pharmacists. There is a need for Malaysian pharmacy students to be adequately trained and exposed to the challenges and the current problems in pharmacovigilance.
Objectives: To describe the development and evaluate of new pharmacovigilance course for undergraduate pharmacy program in Malaysia and students' evaluation of the course.
Design: 3 hours face-to-face lectures and 2 hours tutorial base have been integrated in required 3-credited-hours course (research in pharmacy and pharmacoepidemiology). The course designed to provide an overview of Introduction to the concept of pharmacovigilance, clinical classification of adverse drug reactions, the role of the pharmacist in the reporting of adverse drug reporting, discuss the Malaysian guideline for adverse drug

reactions reporting, vaccination and pharmacovigilance and training on completing adverse drug reactions form. The training provides hands-on training on adverse drug reactions reporting and undertaking causality assessment. To ensure the goals and learning objectives are presented and featured in class. An assessment approach using *pre-* and *post-course evaluations*, in-class quizzes and case study -take home message has been made. Descriptive and inferential statistics using SPSS 20.0 were undertaken.

Results: 104 self-completion questionnaires were administered at the end of the semester. 91 completed questionnaires were returned, the rest were either unanswered or partially answered (response rate: 87.6 %). about two-thirds of the respondents were female (n = 67, 73.6 %), the mean age of students was 21.9 SD ±0.43.

The overall perception of the students regarding the course was positive. All of the respondents believed that the knowledge gained from the course would be required in their future practice of pharmacy (n = 91, 100 %). The vast majority of the students (n = 83, 91.2 %) felt they had benefited from the pharmacovigilance course and were glad that such a course was offered to them. Over 90 % of the students found that the hands-out given in the course were meaningful and useful for a pharmacist (n = 88, 96.7 %). The majority (n = 81, 89.0 %) of the students indicated that they understood the role of pharmacist in pharmacovigilance on safety of vaccines activities after attending the course.

Conclusion: A pharmacovigilance course was successfully designed and implemented in the BPharm curriculum. With regard to the students' opinions about the course: additional and procedural amendments to the course content should be done. Involvement of the pharmacovigilance relevant regulatory bodies in delivering of the course will contribute significantly to efficient implementation of the course.

Abstract Code: ISP3435-43

New Tools for an Old Concept: Protecting Patient Safety

G. Furlan[1], M. Bertazzoli[2], B. Burnstead[3]

(1) Corporate Drug Safety, Helsinn Birex Pharmaceuticals Ltd, Dublin, Ireland (2) Corporate Drug Safety, Helsinn SA and ISOP Swiss-Austrian Chapter Treasurer, Lugano, Switzerland (3) Independent consultant, Swindon, UK

The intention of the new European pharmacovigilance legislation was to create a robust system that could permit the early detection of new drug risks and to assess them in the light of the overall medicinal product benefit-risk balance.

These new concepts represent a significant improvement towards a better understanding of the drug safety profile and its therapeutic value. Unluckily, good intentions are not always seamlessly implemented.

The new requirements have increased the workload for Pharmaceutical Companies: the frequency for Periodic Safety Update Reports (PSURs) has decreased according to a risk based approach but the complexity of these documents has increased. PSURs are not anymore needed for drug renewal, but the newly required benefit-risk evaluation[1] is, in practice, a PSUR. Developmental Safety Update Reports (DSURs) have replaced Annual Safety Reports increasing the complexity of aggregate reporting with investigational medicinal products and the same applies to Risk Management Plans (RMPs) that are now required for every new Marketing Authorization Application. Signal detection reports represent an additional burden since they need to be prepared on a monthly basis.

The need for all of these documents has been questioned, because there is a significant overlap between them and in a resource constraint environment redundancies cause inefficiencies and reduce effectiveness: the resources are diverted from science (which leads to patients' protection) to bureaucracy making the system frailer. The aggregate report modular approach that is being pursued represents only a partial answer to the need of reducing redundancy since it is applied only to a limited number of aggregate report chapters and because the periodicity of the aggregate reports may not match. Furthermore, simultaneously preparing a DSUR, PSUR and RMP for the same product represents a significant workload which consumes resources that would otherwise be engaged in scientific and clinical assessment.

Merging the PSUR, DSUR, RMP Safety Specification and signal detection assessment report into one single Drug Safety Master File[2] that could also be used for answering the questions of regulators within the context of a referral and serve as a basis for identifying the risks to be included in a formal benefit/risk assessment report could represent a solution for avoiding redundancy.

Furthermore unifying the serious adverse event data acquisition procedures and ultimately the Clinical and Drug Safety databases[3] could free resources for scientific driven pharmacovigilance. This is achieved by avoiding duplicate entry of adverse event information in two databases, eliminating reconciliation and making clinical trial safety date more accessible to drug safety personnel.

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Abstract Code: ISP3436-44

Ceftriaxone Induced Anaphylactic Shock in 7 Year Old Male Patient

V. Radovic[1]

(1) STADA Hemofarm A.D., Belgrade, Serbia

Background: This report was received from a physician via Medicines and Medical Devices Agency of Serbia (Authority case No. 515-00-01420-2013-2) on 2013-Apr-24.

Methods: Case report.

Results: A 7-year-old male patient was administered Azaran (INN: ceftriaxone) 1000 mg powder for solution for injection/infusion, 1500 mg once daily, on 2013-Mar-31 at 00.15 h for respiratory infection. At the beginning of the drug administration (the drug was diluted in 20 ml of solution for injection, and less than 1 ml was administered) the patient developed scratching in throat and cough. Administration was ceased immediately. The patient then developed heavy breathing and was transferred to intensive care unit in 1 min time, where he arrived without heartbeats. The patient was intubated and put on mechanical ventilation,

and Adrenalin (INN: epinephrine), Synopen (INN: chloropyramine), and Urbason (INN: methylprednisolone) were administered. Normal heartbeat was restored. The patient was hypotensive and received Dopamine (INN: dopamine) and i.v. rehydration. After few hours, the patient was extubated without any consequences. Diagnosis of the manifested reactions: anaphylactic shock. According to the reporter the events were life-threatening. The patient's medical history included kidney transplantation. Concomitant medications were Pronison (INN: prednisolone), cyclosporine, Cellcept (INN: mycophenolic acid), and Hemomycin (INN: azithromycin).

Conclusion: This case was classified as serious. The causal relationship between the suspected drug and the suspected adverse reaction was assessed as possibly related based on the temporal association and the known safety profile of ceftriaxone, which includes anaphylactic reactions. The suspected adverse reaction is listed according to the current Reference Safety Information (RSI). This case does not change the overall benefit-risk balance of the medicinal product.

Abstract Code: ISP3440-39

Drug-Induced Liver Injury in the 21st Century

S. Ormarsdottir[1]

(1) Hepatotoxicity Safety Knowledge Group, AstraZeneca, Molndal, Sweden

Idiosyncratic drug-induced liver injury (DILI) remains a major cause of safety-related drug marketing withdrawals. Due to its rarity and human specificity, DILI is typically not detected during drug development. According to the FDA guideline on the evaluation of DILI pre-marketing, even a single case of a well defined severe DILI (Hy's Law case) during drug development is regarded as a strong signal of a new drugs potential to cause severe DILI post-marketing and is likely to result in non-approval. Consequently causality assessment of liver cases in clinical trials has become a major challenge to industry. Differential diagnoses that have received attention recently include hepatitis E and reactivation of hepatitis B due to immunosuppressive drugs. Drug development in patients with liver diseases, such as hepatitis C, is challenging from a DILI perspective. In addition, inclusion of patients with liver diseases in development programs in non-liver diseases is a matter of debate. While it is desirable to include in late stage trials a broad population reflecting the users of the drug once marketed, the general rule is to exclude high risk patients from clinical trial participation. It is currently unclear if patients with underlying liver disease are at a greater risk of experiencing DILI and accordingly whether it is safe to include them. Patients with hepatic impairment, however, should be excluded from confirmatory studies for a non-liver indication.

Ongoing research activities in the field of DILI bring hopes that some of the current problems of predicting, characterizing and managing DILI pre-and post-marketing may be solved. Genetic studies have found strong HLA associations with a number of drugs that cause liver injury including flucloxacillin, lumiracoxib and ximelagatran. The IMI SAFE-T consortium is a collaboration project involving academia, industry and regulators, with the aim of identifying protein biomarkers that can predict the clinical outcome of DILI. Biomarkers for differentiating between tolerators, adaptors and susceptibles to liver injury, e.g. during anti-tbc treatment, are also being studied.

Abstract Code: ISP3441-40

Validity of a Patient-Reported Adverse Drug Event Instrument

S.T. De Vries[1], F.M. Haaijer-Ruskamp[1], D. De Zeeuw[1], P. Denig[1]

(1) Department of Clinical Pharmacology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

Background: Increasing attention is paid to incorporating patient-reported outcomes in the assessment of ADEs. Previously, we developed a patient-reported ADE questionnaire [1], but its construct and concurrent validity were not yet assessed.

Objective: To assess the

1. construct validity by testing whether patients who report an ADE have a lower quality of life (QoL) than patients who do not report an ADE;
2. concurrent validity by testing whether a) ADEs that patients relate to specific drugs are reported in the Summary of Product Characteristics (SmPC) of those drugs; b) patients who report to have experienced an ADE with the use of metformin on a treatment-specific questionnaire, also report that drug as a cause of their ADE on the ADE questionnaire.

Methods: Patients using oral glucose-lowering drugs completed the ADE questionnaire and the World Health Organization Quality of Life-BREF [2] and Treatment Satisfaction Questionnaire Measurement (TSQM) [3]. The TSQM was applied for the use of metformin.

The construct validity was assessed using t-tests and χ^2-tests. For the concurrent validity, a percentage of agreement of 70 % with the SmPC, and proportion positive agreement (PPA) of $\geq$0.5 between the ADE questionnaire and the general ADE item of the TSQM were considered satisfactory.

Results: 135 patients were included; 125 of whom were using metformin. Patients who reported an ADE reported a significantly lower general and physical health ($P < 0.05$), but not general QoL ($P = 0.052$). ADEs that patients related to specific drugs were in 65 % of the cases in agreement with the information in the SmPC. There was moderate agreement of reporting an ADE with the use of metformin between the ADE questionnaire and the TSQM-item (PPA = 0.51).

Conclusion: The construct validity of the ADE questionnaire is adequate but the concurrent validity is unsatisfactory.

Discussion: Although the SmPC and the TSQM as gold standard may have limitations, the concurrent validity with these measures is low and adjustments are needed to solve the methodological problems of the patient-reported ADE questionnaire.

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Abstract Code: ISP3442-41

Advocacy for Dedicated Pharmacovigilance Systems in Oncology to Promote the Reporting of Adverse Drug Reactions

P. Quillet[1], D. Heath[2], D. Bourneau-Martin[1], C. Devys[3], P. Lainé[1]

(1) Pharmacovigilance, University College Hospital of Angers, France, (2) The School of Pharmacy, Ferris State University, United States, (3) Pharmacy, Centre Paul Papin, Angers, France

Introduction: The main obstacle in the Pharmacovigilance (PV) system is the underreporting of adverse drug reactions (ADR). Reasons for this include pre-existing workload and lack of time of healthcare professionals [1]. To facilitate access to PV system in the oncological setting, bi-monthly visits were established at a 250-bed cancer center by an expert from PV center. One year after conducting visits, we were interested in assessing the impact this new collection system had on ADR reporting.
Objectives: Compare the number and nature of ADR reports in a one year period before and after establishing PV visits in the oncology setting.
Methods: We performed a signal detection analysis on ADR reporting by the cancer center from Dec. 2011 to Nov. 2012. Data collected from Dec. 2010 to Nov. 2011 were used as control. The χ^2 test was utilized to determine significance.
Results: Before the dedicated PV system, 0.88 % of all reports received by the PV center were from the cancer center. After establishing visits, the reporting rate increased to 3.84 % ($p = 0.01$, Table 1) with 41 ADR reports in 1 year. They involved 46 ADR and about 29 separate drugs, 20 of which were causally linked to the reaction. There were 28 ADR classified as serious, but not fatal reactions. Most reported ADR were anaphylactic reactions (26.1 %) or dermatological effects (19.6 %) involving anticancer drugs. We saw an increase in unexpected ADR reports, but not statistically significant. Among the five unexpected ADR reported in 2012, the reaction was considered serious for four, and the role of drugs appeared likely for two.
Conclusion: Implementation of a new ADR collection system utilizing bi-monthly visits increased the number of ADR reports from the cancer center and promoted the reporting of unexpected ADR.
Discussion: The primary focus of a spontaneous reporting system is to detect serious and unrecognized ADR. Routine visits by one focal person from a PV center created a closer relationship with healthcare professionals and thereby improved the reporting process in the oncology setting. This can be used to improve unexpected ADR collection, which is needed to generate early warnings and to promote drug safety.

Table 1 Main study results

	Before dedicated PV system	After dedicated PV system
Total reports	678 = 100.0 %	1069 = 100.0 %
Reports from cancer center	6 = 0.88 %	41 = 3.84 %
Expected ADR	8 = 100.0 %	41 = 89.1 %
Unexpected ADR	0 = 0.0 %	5 = 10.87 %

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Abstract Code: ISP3444-43

Methodological Considerations in Evaluating Safety of Novel Anticoagulants in Secondary Care Setting in the UK: Defining the Contextual Comparator Cohort

D. Layton[1], M. Davies[1], A. Evans[2], S.A.W. Shakir[1]

(1) Drug Safety Research Unit, Southampton, UK; University of Portsmouth, Portsmouth, UK, (2) Drug Safety Research Unit, Southampton, UK

Background: Increasingly the choice of medicines for patients in healthcare is guided by published national/regional guidelines. A post-marketing Specialist Cohort Event Monitoring (SCEM) safety study has been initiated by the DSRU as part of a broader Post-Authorisation Commitment requested by CHMP to further investigate the safety of rivaroxaban (XARELTO®) in clinical practice. It aims to monitor short-term (first 3 months) safety and drug utilisation of rivaroxaban prescribed for medical conditions requiring anticoagulation by specialists in the secondary care setting in England and Wales.
Objectives: To discuss methodological considerations in identifying a comparator cohort within a large pharmacoepidemiological study.
Methods: The SCEM study aims to collect data on 1700 evaluable patients treated for the prevention of stroke and systemic embolism in adults with non-valvular atrial fibrillation (AF) (with $\geq$1 stroke risk factors) [n = 561], and for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) and prevention of recurrent DVT and PE in adults [n = 1005]. They will be identified via a network of specialists, and data obtained post consent on prognostic/risk factors, exposure and specific outcomes. Since the counterfactual ideal comparator cohort cannot be identified, a contextual comparator cohort of evaluable new user patients treated via best practice standard care is proposed to characterise the adoption of rivaroxaban into clinical practice. Analysis will explore the importance of measured explanatory factors on variability of treatment decisions and selected safety risks across institutions.
Results: The study has been adopted by the Stroke Research Network and identification of site specific investigators, recruitment and data collection is in progress.
Conclusions: By capturing data on a contextual cohort we hope to gain better understanding of the variability of, and influence on, treatment decisions and prescribing of novel treatments which appear to have some advantages but for which there are significant differences within the health care community about recommended use.

Abstract Code: ISP3445-44

Side Effects of Cade Oil in Morocco: An Analysis of Reports in the Moroccan Herbal Products Database

S. Skalli[1], A. Chebat[1], N. Badrane[1], R. Soulaymani Bencheikh[1]

(1) Centre Anti Poison et de Pharmacovigilance du Maroc, Rabat, Morocco

Introduction: Cade oil is a dark, faintly aromatic oil which is distilled from the branches and wood of *Juniperus oxycedrus*. Although this oil is

known to have toxic effects, cade oil continues to be used in folk medicine.

Objective: To discuss the Moroccan pharmacovigilance center experience in terms of Cade oil adverse effects, and aids in the determination of the safety of this oil, along with data from the scientific literature.

Methods: The Moroccan pharmacovigilance of herbal products database was analyzed in as retrospective manner from January 1, 2004 to December 31, 2012. WHO-UMC causality assessment was used. Descriptive statistics were used for data analyses.

Results: From a total of 1251 reports of side events in the Moroccan database, associated with herbal medicines, thirty cases (2.4 %) of adverse effects to Cade oil were reported. The age range of patients was 1 week to 74 years (mean 11.9 ± 19.4 years). The oil was used for a number of folk medicine indications. Reported cases were mainly from topical application in 60 % of cases and oral ingestion in 36.7 %. Adverse effects reported in patients have concerned all system organ classes. 76.7 % patients improved and were discharged. Three deaths 10 % were registered in relation with this use.

Discussion: There are often debates regarding Herbal medicines safety, efficacy and quality [1]. This is particularly the case with Cade oil and its local knowledge of use in Morocco and in many other countries [2]. Phenol is the most toxic component and responsible for the majority of systemic symptoms [3, 4]. Observed in Cade oil side effects. Its absorption is rapid and its metabolism is mainly hepatic.

Conclusions: The data on the adverse effects of Cade oil suggests that it could have life-threatening effects. Its side effects should be considered in patients with multi-organ symptoms. Pharmacovigilance herbal products database is a potentially effective data source for signal detection of adverse effects associated with these products.

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Abstract Code: ISP3446-45

Antiretroviral Induced Adverse Drug Reactions in HIV Infected Patients in Mali: A Resource-Limited Setting

A.A. Oumar[1], O. Dogoni[2], R. Abdi-Bogoreh[1], M. Cisse[2], J.P. Dembélé[3], I.A. Maiga[4], O. Koita[5], P. Tulkens[6], S. Dao[3]

(1) Faculté de Médecine, et d'odontostomatologie, Bamako, Mali, (2) Centre d'Ecoute, de sSoins et d'aAcCompagnements des personnes vivant avec le PVVIH (CESAC) Bamako, Mali, (3) Service de Maladies infectieuses, Centre Hospitalier Universitaire du Point «G» CHU point G, Bamako, Mali, (4) ESTHER, Ensemble pour une Solidarité Thérapeutique Hospitalière En Réseau Mali, Bamako, Mali, (5) HIV/TB Research and Training Center Bamako, (SEREFO), Bamako, Mali, (6) Cellular and Molecular Pharmacology and Centre of Clinical Pharmacy, Catholic University of Louvain, Brussels, Belgium

Purpose: To our knowledge, there is a rare report regarding antiretroviral induced adverse drug reactions (ADRs) in Malian patients who were infected with the human immunodeficiency virus (HIV). We have evaluated the frequency of antiretroviral therapy (ART) induced ADRs in this population and have assessed some risk factors of these reactions.

Methods: This is a prospective cohort study that was performed in the Human Immunodeficiency Virus/Acquired Immune Deficiency Syndrome Research Center (The CESAC) of Mali during years 2010–2011. Adults patients, who were infected with HIV and newly started on ART, were included in this study and by laboratory and clinical follow-up was performed for at least 6 months to detect the occurrence of any ADR. Naranjo's scale of classification has been used to characterize the side effects.

Results: During this study 94.6 % of patients showed at least one ADR and 5.3 % at least two ADRs. Prevalence of ADRs based on affected organ was 3.1 % gastrointestinal (GI), 15.4 % hematological, 45.9 % neurological, 10.6 % cutaneous, 1.4 % hepatic, and 20.4 % metabolic adverse effects. Adverse events were highly probable according to the Naranjo score (83.7 %).The use of Zidovudine and Stavudine was observed as risk factors for anaemia, and peripheral neuropathy, and lipodystrophy, respectively, while nevirapine and female gender were identified as risk factors for skin reactions, lipohypertrophy by bivariate logistic regression.

Conclusions: Side effects were frequently encountered in our study. The nature of these adverse events was mostly peripheral neuropathy, lipoatrophy, lipodystrophy, and anemia. The link between the use of antiretroviral drugs and adverse events was highly probable according to the Naranjo probability scale. We recommend an active clinical and laboratory monitoring of antiretroviral therapy to strengthen pharmacovigilance in Mali.

Abstract Code: ISP3447-46

Adverse Drug Reactions of Antiretroviral Therapy in a Cohort of Malian Patients in a Decentralized Environment: Proactive Pharmacovigilance Study

A.A. Oumar[1], A.A. Traore[2], L. Samake[3], M. Diarra[4], J.P. Dembele[5], Y. Sidibe[6], I.A. Maiga[7], O. Koita[8], S. Dao[9]

(1) Université des Sciences, des Techniques et des Technologies de Bamako/Faculté de Médecine, et d'odontostomatologie de Bamako, Bamako, Mali, (2) Centre de Santé de référence de Sikasso, Sikasso, Mali, (3) Hopital de Sikasso, Pharmacie hospitalière, Sikasso, Mali, (4) Université des Sciences, des Techniques et des Technologies de Bamako, Faculté de Médecine, et d'odontostomatologie de Bamako, Bamako, Mali, (5) Centre Hospitalo Universitaire du Point G/Service de Maladies Infectieuses, Bamako, Mali, (6) Kenedougou solidarité Organisation, Sikasso, Mali, (7) Esther Mali, Bamako, Mali, (8) Université des Sciences, des Techniques et des Technologies de Bamako/Faculté de Pharmacie de Bamako/Centre de Recherche et de Formation sur le VIH/TB, Bamako, Mali, (9) Centre Hospitalo Universitaire du Point G/Service de Maladies Infectieuses, Bamako, Mali

Objective: To our knowledge, there is no report regarding antiretroviral-induced adverse drug reactions (ADRs) in Malian patient infected with human immunodeficiency virus (HIV). We have evaluated the frequency of antiretroviral therapy (ART) induced ADRs in this population. The aim of this study was to assess the adverse effects of ARVs in adult patients infected with HIV in decentralized Sikasso.

Methods: This study is a proactive from 1 January 2011 to 30 June 2011 in Sikasso hospital (medical service). Adult patients with HIV infection and just started on ART for more than 3 months were included in this study and follow-up laboratory and clinical research for active adverse Medicated (EIM) for at least 6 months. WHO scale side's effects classification was used to search and characterize the side effects.

Results: Women were more concerned with a rate of 58 %. The age group most represented was 26–47 years (73.6 %). Among the 178 patients, 61.2 % had manifested an ADR. The ADR was the most represented 21.3 % followed by nausea peripheral neuropathy 15.2 %, followed by pruritus and rash 6.7 and 4.5 %. Stavudine was the molecule most implicated in 24.8 %. The degree of toxicity according to WHO type 4 was represented in 3.4 %. Score according to WHO causality "certain" was 29.8 %.

Conclusion: The adverse effects of ARVs are multiple and can be life-threatening in the short and long term. It is essential to ensure regular monitoring of patients receiving these triple therapy, and treatment-related complications. We recommend active surveillance of antiretroviral therapy to strengthen the Pharmacovigilance Mali.

Abstract Code: ISP3448-47

Quality Versus Quantity in Pharmacovigilance Safety Signals

G. Ladds[1]

(1) PharSafer, Ripley, UK

This article looks at Pharmacovigilance in terms of two aspects that can be conflicting and contradictory—the need to report adverse reactions to Regulatory Agencies on time whilst at the same time ensuring the Quality of that data in terms of accuracy and completeness.

Both of these elements are discussed in this article together with the conflict faced within Pharmacovigilance—the need for quality information to understand what is happening when a patient says they have experienced an adverse reaction and the number of times the adverse reaction has been reported to the Company.

Allied to this are the legislative requirement from the Regulatory Agencies on the need to supply adverse reaction reports from various sources within certain timeframes and to provide follow up information on those cases to improve the quality of the information received in order to understand why the event is occurring.

This article looks at the various elements–Quantity; Quality; and Accuracy in relation to safety signal determination and what stage we are at in terms of being able to offer better protection to patients.

Abstract Code: ISP3450-40

Analysis of Adverse Drug Reactions During 3 Years in a Single Tertiary Hospital in Busan

Y. Nam[1], H. Nam[2], W. Kim[3], D. Jeon[4], H. Lee[4], N. Yoon[4], S. Um[4], C. Son[4], S. Lee[1]

(1) Department of Internal Medicine, College of Medicine, Dong-A University; Dong-A University Hospital Regional Pharmacovigilance Center, Busan, Korea, (2) Department of Pharmacy, Dong-A University Hospital; Dong-A University Hospital Regional Pharmacovigilance Center, Busan, Korea, (3) Dong-A University Hospital Regional Pharmacovigilance Center, Busan, Korea, (4) Department of Internal Medicine, College of Medicine, Dong-A University, Busan, Korea

Introduction: Adverse drug reactions (ADRs) are an important cause of morbidity and mortality, accounting for up to 6.5 % of all hospital admissions [1, 2]. Spontaneous reporting of ADRs is the most common method to report ADRs and fundamental to pharmacovigilance, however, under reporting is estimated higher than 90–95 % [3, 4].

Aim: To assess and compare ADRs during 3 years in a single tertiary hospital.

Methods: ADR data were collected from January 2010 to December 2012. A computerized ADR reporting system was first developed in Dong-A University Hospital in December 2009, and which was improved to report and access more easily since February 2011.

Results: A total of 1027 reports were collected during 3 years. ADRs included 'certain', 'probable/likely' and 'possible' by World Health Organization-Uppsala Monitoring Center criteria were 779 cases, which were analyzed in this study. The number of reported ADRs increased from 2010 to 2012. The mean ages of the patients was 54.65± 17.33 years, 55.3 % (n = 431) occurred in women. The majority of the ADR reporters were doctors (83.3 %), others were nurses (8.7 %), pharmacists (4.9 %) and radiology technicians (3.1 %). Antibiotics (44.7 %) were the most common causative drugs, followed by miscellaneous drugs (18.7 %), nonsteroidal anti-inflammatory drugs (14.5 %), and, radiocontrast media (11.3 %). The ADRs were mainly cutaneous, systemic including fever and fatigue, and gastrointestinal manifestations.

Conclusion: The ADR reports was significantly increased from 139 to 421 cases during 3 years. Antibiotics were the most common causative drugs and most frequently occurred in cutaneous system, and the majority of the ADR reporters were doctors.

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Abstract Code: ISP3451-41

Serious Adverse Drug Reaction Reports Associated with Use of Antidiabetic Medicines in Thailand

W. Rungapiromnan[1]

(1) Health Product Vigilance Center, Thai Food and Drug Administration, Nonthaburi, Thailand

Background: A number of diabetes patients have increased around the world including Thailand. Thailand has provided Universal Health Coverage for Thai people including supply of antidiabetic medicines. Health Product Vigilance Center (HPVC) has responsibility for collecting adverse drug reaction (ADR) reports in Thailand since 1984. In the fiscal year 2010–2011, National Health Security Office (NHSO) supported a part of health budget for governmental hospitals according to number and quality of ADR reports submitted to the HPVC but considered the ADR reports submitted during the calendar year 2009–2011 [1].

Aim: To describe the frequency and characteristics of serious ADR reports associated with use of antidiabetic medicines in Thai pharmacovigilance database.

Method: I performed a retrospective study of serious ADRs relating to the use of antidiabetic medicines in Thai pharmacovigilance database between the fiscal year 2003–2012.
Results: A total of 2,675 ADR reports associated with the use of antidiabetic medicines submitted to the HPVC came from 600 sources across Thailand during the study period, of which 16.9 % (452 reports) were serious ADR reports with 3,941 events. The number of serious ADR reports dramatically increased since the fiscal year 2009. The most category of seriousness ADR reported was admission to the hospital/prolongation of hospitalization (14.1 % [378/452]). However, most diabetes patients exposing serious ADRs recovered without sequelae (67.92 % [3.7/452]). Metformin, glibenclamide and insulin were the top three medicines reported to the HPVC with 205, 155 and 113 events respectively. The top three serious ADRs reported were hypoglycemia (153 events), lactic acidosis (33 events) and maculopapular rash (21 events).
Conclusions: The HPVC increasingly received serious ADR reports relating to the use of antidiabetic medicines across Thailand since the fiscal year 2009. It might be a result of budget support of the NHSO as 2009 was the year that the NHSO started considering ADR reports in Thai pharmacovigilance database. Thus, the NHSO should continually support this budget for ADR reporting to maintain this increase and encourage healthcare professionals to report ADRs of newly marketed medicines required intensive ADR monitoring due to their limited safety information. For this study, metformin was the most common medicines associated with serious ADRs and the most common serious ADR reported was hypoglycemia.

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Abstract Code: ISP3453-43

Drug Induced ADRs in Elderly Patients

M. Ponte[1], F. Fernandez[2], M. Ragusa[1], A. Wachs[3]

(1) Hospital Argerich, Buenos Aires, Argentina, (2) Pharmacology Chair, Salvador University, Buenos Aires, Argentina (3) Hospital Argerich, Buenos Aires, Argentina.

Introduction and Aim: Adverse drug reactions (ADRs) are a major cause of morbidity and hospitalization among elderly patients. The elderly are more susceptible to adverse drugs effects due to a variety of factors, such as excessive and concomitant use of several drugs, administration errors, physiological changes in the body that alter the pharmacodynamics and pharmacokinetics. The aim of this study was to determine the incidence, types and drugs most frequently associated to ADRs in elderly patients.
Material and Method: The study was performed in a tertiary care hospital in Buenos Aires City. Argentina. The hospital is¨Cosme Argerich¨, a public hospital with 350 beds approximately. The information was taken from the pharmacovigilance committee and the period of time included was June 2008 to March 2013. Naranjo Score Was performed to assess the causality. All ADRs were timely reported to the national regulatory agency (ANMAT).
Results: In this period, 987 ADRs in elderly patients were detected by the Pharmacovigilance Committee. The average age of patients was 76.38 (CI 95 %: ±0.48 years) years; 49.24 % (CI 95 %: 46.12–52.39) appeared in female while 50.76 % (CI 95 %: 47.64–53.88) occurred in men. The drugs that were most frequently related to ADRs were: 37.69 % (CI 95 %: 34.66–40.71) to cardiovascular drugs; 22.49 % (CI 95 %: 19.89–25.10) to antibiotics; 9.8 % (CI 95 %: 7.97–11.68) to neuropsychiatric drugs; 7.6 % (CI 95 %: 5.94–9.25) to corticosteroids and 7.09 % (CI 95 %: 8.69–5.49) to NSAIDs. About organ or systems involved in ADRs, 80.59 % (CI 95 %: 78.11–83.07) were not serious while 19.4 % (CI 95 %: 16.93–21.88) were serious, including the need of hospitalization (10.43 %; CI 95 %: 8.53–12.34). The average of drugs taken by patients was 3.31 (CI 95 %: ±0,12) drugs; 23.50 % (CI 95 %: 20.86–26.15) consumed 1–3 drugs; 40.42 % (CI 95 %: 37.36–43.49) 4–6; 8.1 % (CI 95 %: 6.40–9.81) 7–9 and 1.31 % (CI 95 %: 0.60–2.03) used more than 10 drugs.
Conclusions: One of the main issues that appear when working with an elderly patient is the fact that they usually are already taking 4–6 drugs. Although the cardiovascular, corticosteroids and NSAIDs were observed causing most of the adverse effects, these are drugs that most people need when they get old. Fortunately, most of the ADRs are not serious being death and life threatening effects very uncommon.

Abstract Code: ISP3454-44

Indirect Economic Burden of ADRs in Hospitalized Patients

M. Ponte[1], M. Ragusa[1], A. Wachs[1]

(1) Hospital Argerich, Buenos Aires, Argentina

Background and Aims: ADRs represent a great and increasing cost in health. The number of hospitalization and the hospital prolongation due to drugs represent a significative percentage of total hospitallary days. There are some studies about the direct costs of ADRs but very few about the indirect costs. The indirect costs are the ones generated because of absence to work, absence to school of the patients and the caregivers.
Material and Method: We performed the work with the pharmacovigilance committee of a tertiary care hospital, Hospital Argerich, Buenos Aires, Argentina. The time included was from June 2008 to march 2013. We considered all the hospitallary days generated by ADRs related—hospitalization and the prolongation of hospitallary stay because of ADRs. The cost of every day was calculated according to the average salary of every.
Results: In the period included in this work, ADRs represented 4542.68 bed/days, and a total economic burden of 191,455.93 dollars for patients and 95,727.96 dollars for caredrivers. Of all this economic burden, 152,190.37 dollars were preventable. The greatest costs were detected in Internal Medicine, kidney transplant and Intensive Care Unit rooms. There were 156 events of hospital prolongation because of ADRs.
Discussion: ADRs generate a great indirect economic burden and near a half of it is preventable. These results lead to the aim of strengthening the pharmacovigilance activities to diminish the preventable ADRs.

Abstract Code: ISP3455-45

Cancer in Patients Exposed to anti-TNF: Analysis of the French Spontaneous Reporting Database for a Controversial Adverse Drug Reaction

L. Saliba[1], M. Aboutaam[2], V. Rousseau[1], L. Chebane[1], N. Petitpain[3], B. Baldin[4], P. Gillet[4], J.L. Montastruc[1], H. Bagheri[1]

(1) Département de Pharmacologie Clinique, Centre Régional de Pharmacovigilance, de Pharmacoepidémiologie et d'Information sur le médicament, INSERM UMR 1027, Equipe de Pharmacoépidémiologie, Toulouse, France (2) Département de Pharmacologie Clinique, Centre Régional de Pharmacovigilance, Reims, France (3) Département de Pharmacologie Clinique et de Toxicologie, Centre Régional de Pharmacovigilance, Hôpital Central, Nancy, France (4) Département de Pharmacologie, Centre Régional de Pharmacovigilance, Hôpital de Cimiez, Nice, France

Background: According to the literature, cancer risk in patients exposed to Tumor Necrosis Factor (TNF) inhibitors remains controversed. The aim of the study was to investigate the association between anti-TNF exposure and reporting of "cancer" using the French Pharmacovigilance database (FPVDB).

Methods: All serious cases registered in FPVDB were analysed retrospectively from January 2000 to October 2010. The case/non-case method was used to measure the association between cancer and exposure to anti-TNF versus classic immunosuppressant agents. Cases were defined as reports corresponding to the Adverse Drug Reaction (ADRs) of interest (i.e. cancer) and non-cases were all reports of ADRs other than that being studied. Exposure was considered as the presence of the drug of interest (e.g. TNF inhibitor). Patients exposed to classic immunosuppressant agents were considered as "unexposed". We applied the case/non-case method, comparing cases of cancer to other "serious" cases of ADRs regarding the exposure to anti-TNF in comparison to other immunosuppressant agents, allowing to calculate Reporting Odds Ratio (ROR) of cancer and its confidence interval (CI). A survival analysis using Kaplan Meier method test was performed.

Results: Between a total of 3315 cases of serious ADRs (2035 cases in the exposed group and 1280 in the other one) identified in FPVDB with 371 (11 %) cases related to cancer, of which 310 (84 %) was in the exposed group. Sex ratio was 0.55 and mean age was 52 years old. The main indication was rheumatoid arthritis (52 %). Exposure to TNF inhibitor was associated to a higher rate of cancer reporting (ROR 3.6 CI 2.7–4.8; $p < 0.0001$). In the anti-TNF group, solid cancers were more reported than hematological tumors (ROR 2.2 CI 1.3–3.9; $p < 0.0001$). The delay of occurrence of cancer reporting was significantly higher in the unexposed group ($p < 0.0001$). After a period of 20 years, cancer was reported for about 60 % of exposed group versus 40 % for unexposed group.

Discussion: According to FPVDB, exposure to TNF inhibitor was associated to a higher rate of cancer reporting. Hematological and skin cancers were the most frequently reported. The delay of occurrence was shorter in patients exposed to anti-TNF. Considering the limits of on spontaneous reporting, we will perform a Cox regression to take into account the confounding factors such as gender, age, indication, duration of drug exposure or antecedents of cancer.

Abstract Code: ISP3456-46

Pregnancy Outcome in Women Exposed to Aripiprazole During the Embryonic Period: A Prospective Multicentric Cohort

F. Bellet[1], M.N. Beyens[1], N. Bernard[2], D. Beghin[3], E. Elefant[3], T. Vial[2]

(1) Pharmacovigilance Center, University Hospital, Saint-Etienne, France, (2) Pharmacovigilance Center, Hospices Civils de Lyon, Lyon, France, (3) Centre de Référence sur les Agents Tératogènes, Armand Trousseau Hospital, Paris, France

Objectives: Aripiprazole, an atypical antipsychotic, is not recommended during pregnancy because of teratogenicity suggested in animal studies and the paucity of clinical data. The main objective of our study was to evaluate whether aripiprazole exposure during the embryonic period was associated with an increased risk of major malformations. Secondary objectives were to evaluate the risks of miscarriage, prematurity, fetal growth retardation and maternal complications and to describe possible neonatal adverse effects.

Methods: We conducted a multicenter cohort study using data prospectively collected by the French Regional Pharmacovigilance Centres participating to the Terappel program and the Centre de Référence sur les Agents Tératogènes (CRAT) between 2004 and 2011. "Exposed patients" were pregnant women exposed to aripiprazole during embryogenesis, i.e. 4 to 10 weeks after the last menstrual period (exclusion of patients co-exposed to known teratogenic agent). "Unexposed patients" were pregnant women without exposure or exposed to non-teratogenic agent during embryonic period. Each "exposed patient" was matched with two "unexposed patients" for age (±2 years) and gestational age at call (±2 weeks).

Results: Eighty-six patients were included in the exposed group and 172 in the unexposed group. Compared to unexposed patients, exposure to aripiprazole was not associated with a significant increased risk of major malformations (OR=2.30; 95 % CI = 0.32–16.69) or miscarriage (OR=1.66; 95 % CI = 0.63–4.38) or gestational diabetes (OR = 1.15; 95 % CI = 0.33–4.04); but was associated with a significant increased risk of prematurity (OR = 2.57; 95 % CI = 1.06–6.27) and fetal growth retardation (OR = 2.97; 95 % CI=1.23–7.16). Among the 19 newborns exposed to aripiprazole near delivery, there were one case of withdrawal syndrome with pulmonary hypertension and respiratory distress and one case of amniotic fluid aspiration pneumonia.

Conclusion: Our study suggests that aripiprazole is not associated with a major teratogenic risk. These preliminary results support the reassuring limited published data, but must be confirmed by more powerful studies.

Abstract Code: ISP3459-49

Emergency Admission for Adverse Drug Reactions in Emilia-Romagna in 2012

A. Bin[1], A. Marra[1], R. Carletti[1], G. Vighi[2], G. Mereafaps[3]

(1) Dipartimento Farmaceutico Interaziendale, Azienda Ospedaliero-Universitaria di Ferrara, Ferrara, Italy, (2) S.C. Qualità Privacy e Rischio Clinico Azienda Ospedaliera "Ospedale Niguarda Ca' Granda", Milano, Italy (3) Regione Emilia Romagna, Italy

Introduction: Adverse drug reactions (ADRs) are a frequent cause of mortality and morbidity, and their costs are very high for the healthcare system. In western countries, ADRs cause 3–5 % of all hospital admission and are responsible for about 5–10 % of hospital expenditure.
Aim: To monitor outpatients' ADRs causing emergency room admission. This study explores the ADRs incidence, classification, severity, preventability, and impact of medication-related emergency department (ED) admissions in 8 hospitals of Emilia-Romagna Region (RER) in 2012, using data from MEREAFaPS project.
Methods: We used MEREAFaPS database to extract ADR data; this database has been implemented with ADR reports collected by physicians during ED visits. ED physicians inform clinical pharmacist of any ADRs by "flagging", an alert in the ED database. Pharmacist writes up ADRs form and implements MEREAFaPS database. We analysed characteristics of the affected population, ADR seriousness and avoidability (according to standardized criteria), number and therapeutic class of drugs involved in each ADR, symptoms and signs classified by preferred terms and System Organ Classification (SOC). The estimated annual population rate of ADR was calculated.
Results: Over the one year study period, 479 ADRs were reported and adults (16–65 years) were the most exposed group to ADRs (63.0 %). The women were prevalent (65.3 %). ADRs classified as serious were 64.3, 42.6 % of these led to hospitalization and 2.5 % caused death. Furthermore, 20 % of ADRs were assessed as potentially avoidable. The average number of prescribed drugs per patient was 3.0. Nervous system agents were the most involved class (31.7 % of reports), followed by antimicrobial drugs (20.2 % of reports) and musculoskeletal system drugs (14.4 % of reports). The most common ADRs involved the skin and subcutaneous tissue. The estimate incidence of admission due to ADR was 0.8 per 1,000 patients treated in ED. In 2012, the first year of RER hospitals involved in MEREAFaPS project, the total ADR reports in RER increased by 71 % compared to the previous year.
Conclusions: Our data suggest that MEREAFaPS project had highlighted the importance of ED as monitoring unit for ADRs affecting outpatients in RER. The collaboration of clinical pharmacist with ED physicians has been essential in ADRs reporting and in promoting pharmacovigilance culture. Moreover, this study suggests that practitioners need an educational intervention in order to improve the recording of ADRs and to assess the real morbidity and mortality caused by ADRs.

Abstract Code: ISP3460-41

Anti-Psoriasis Induced Teratogenicity

M. Al-Amiry[1], A. Mankhi[1], A. Mahmood[1]

(1) Iraqi Pharmacovigilance Center, Baghdad, Iraq

A 3 years old male baby had congenital abnormalities; her mother said that she was on topical anti-psoriasis agent during pregnancy (used as a mixture of more than one agent). The mother suffered from psoriasis and after consult the dermatologist she continued using the topical anti-psoriasis agent without knowing that she was pregnant.

The congenital abnormality of the baby included a big head; shortening of upper limbs with small hands and decrease the number of fingers (three fingers in each hand and fusion the other two fingers). The left lower limb is normal but the other right limb shows no thigh, knee with shortness in its length, normal foot and normal toes.

Abstract Code: ISP3461-42

Reduction of Toxicity of Traditional Chinese Medicine Aconite in the Domestic Setting

K.Y. Lau[1], W.P. Lai[1], S. Dufay[1], A. Worsley[1]

(1) Department of Pharmacology and Pharmacy, The University of Hong Kong, Hong Kong SAR

Introduction: *Aconitum* plants had been employed in Traditional Chinese Medicine for its analgesic, anti-inflammatory, cardio-stimulative properties. Their roots contain highly toxic diester diterpene alkaloids (DDAs) namely aconitine, mesaconitine and hypaconitine which can persistently activate the sodium channels in muscles and nerves to cause arrhythmia and muscle weakness [1]. DDAs can undergo sequential hydrolysis to produce much less toxic monoester diterpene alkaloids (MDAs), (benzoylaconine, benzoylmesaconine and benzoylhypaconine) and non-toxic aconines (aconine, mesaconine and hypaconine) [2, 3]. Because of the high toxicity, the *Aconitum* plants are industrially processed to hydrolyze most toxic DDAs to MDAs but the amount of DDA is still sufficient to cause acute toxicity [4]. Therefore, it is recommended that they should be decocted for one to two hours at home to hydrolyze the remaining toxic alkaloids (2). Nevertheless, there were confirmed acute poisoning cases every year in Hong Kong because of inadequate decoction of the *Aconitum* products [5].
Aims:

1. Investigate the amount of the common *Aconitum* alkaloids and their hydrolytic products remaining in the decoctions after different length of decoction.
2. Define an optimum decoction time for different *Aconitum* products based on the known toxicological data of the alkaloids

Materials and Methods: Three raw materials of *Aconitum* sp., Heishunpian (黑顺片), Shengfuzi (生附子) and Baifupian (白附片) were decocted for 30, 45, 60, 90, 180 and 240 min to about 250 mL. Chloroform extracts were evaporated and injected into the HPLC to determine amount of each *Aconitum* alkaloid. The quantification was carried out with Agilent Prep-C18 column with a mobile phase aqueous 0.5 % (v/v) acetic acid and 0.2 % (v/v) triethylamine and acetonitrile (1.0 mL/min).
Discussion: The amount of DDA was highest in Shengfuzi followed by Baifupian and Heishunpian. The rate of hydrolysis of DDAs is in the order, Mesaconitine > Aconitine > Hypaconitine. Similar trend was shown for MDAs content. The defined safe level containing 0.15 mg DDA in the decoction was obtained in 2–3 h for Heishunpian and Baifupian and 7 h for Shengfuzi which are much longer than the recommended decoction time.
Conclusions: This study has showed that the total DDA content decreases as the length of decoction increases. It is discovered that the commonly recommended decoction length of aconite product may not be sufficient to detoxify the decoction especially with higher dose of aconite product. A review on the suggested decoction time is necessary.

Abstract Code: ISP3462-43

Monitoring the Effectiveness of Risk Minimisation in Patients Treated with Pioglitazone-Containing Products in Europe

I. Leal[1], V. Ehrenstein[2], S. Ulrichsen[2], L. Li[3], J. Rungby[2], P. Rijnbeek[1], D. Weibel[1], M. Sturkenboom[1], H.T. Sorensen[2], S. Jick[3]

(1) Department of Medical Informatics, Erasmus University Medical Center, Rotterdam, The Netherlands, (2) Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark, (3) Boston Collaborative Drug Surveillance Program, Boston University School of Public Health, Lexington, MA, USA

Introduction: Observational studies suggested a slightly increased risk of bladder cancer (BC) with Pioglitazone [1, 2]. In July 2011, the European Medicines Agency recommended restricting use of the drug to patients with unknown risk factors for BC [3]. The marketing authorization holder issued a "Dear Health Professional Communication" (DHPC) in July-August 2011.
Objectives: To study the drug utilisation patterns of pioglitazone-containing products, and adverse events in patients discontinuing, continuing or starting pioglitazone after the DHPC in Europe.
Methods: We used automated prescription records in the United Kingdom (CPRD); the Netherlands (IPCI); and in Denmark (Aarhus University Research Database [AU]). We assessed the number of prescriptions, new users, prevalent users, and terminators by year and by month from July 2010 until February 2012 in AU and IPCI, June 2012 for CPRD; described baseline characteristics of new users before and after DHPC, initiation and termination of pioglitazone in persons with potential contraindications and risk factors for BC, and changes in glycated haemoglobin (HbA1c) and fasting plasma glucose (FPG) around the DHPC.
Results: Before the DHPC there were 32017 new pioglitazone users in CPRD, 667 in IPCI and 897 in AU. Thereafter 1291, 47 and 35 subjects, respectively. The number of new users peaked in late 2010 and prevalent users and prescriptions decreased in 2011. Based on CPRD data, 0.4 % of new users before DHPC had a history of BC, and 0.2 % after it. Patients with a history of BC, haematuria and some patients older than 80 years were taken off pioglitazone in the months following DHPC. After termination, there was a net mean increase in concentration of HbA1c and FPG in the UK (exceeded 0.5 %).
Conclusions: There was a change in pioglitazone prescribing around the time the DHPC was issued. Fewer subjects with contraindications in the DsHPC received pioglitazone. It seems that there was a slight increase in glucose levels post DHCP.

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Abstract Code: ISP3463-44

Incidence of ADRs According to Sexes

M. Ponte[1], F. Cseh[2], D. Corzo[2], M. Ragusa[1], A. Wachs[1]

(1) Hospital Argerich. Buenos Aires. Argentina, (2) Salvador University. Buenos Aires, Argentina

Introduction and Aims: The aim of this study was to determine if there is a difference in the incidence of Adverse Drug Reactions between sexes in a tertiary care hospital in Buenos Aires.
Material and Method: The study was performed in a tertiary care hospital in Buenos Aires City. Argentina. The hospital is "Cosme Argerich", a public hospital with 350 beds approximately. The information was taken from the pharmacovigilance committee and the period of time included was June 2008 to march 2013. Chi square was performed to determine the significance of difference between sexes.
Results: In this period, 2780 ADRs were detected by the Pharmacovigilance Committee. 1291 (46.62 %; CI 95 %: 44.76–48.48) cases were detected in females and 1478 (53.37 %; CI 95 %: 51.51–55.23 %) in males. There were 466 endocrine-metabolic ADRs in the female group and 512 in the male group (chi square: 0.42). 121 immunosuppressants—associated infections were detected in females and 97 in the male group (chi square: 0.006). 105 cases of nephrotoxicity were detected in females and 205 cases in males (chi square: 0.00001). Considering drug induced liver injury, 170 cases were noticed in females and 258 in males (chi square: 0.001). 78 cases of gastrointestinal ADRs were present in the female group and 58 for male group (chi square: 0.01). 83 hematologic ADRs were for the female group and 89 for the male group (chi square: 0.65). For neuropsychiatric ADRs, 82 events were seen in females and 73 in males (chi square: 0.10). 56 cardiovascular ADRs in females and 49 in males (chi square: 0.15). 95 drugs-induced hypersensitivity reactions were observed in females and 90 in males (chi square: 0.18).
Conclusions: There was a slightly higher absolute incidence of ADRs in males. We detected significant differences between sexes in DILI, nephrotoxicity, infectious complications and gastrointestinal ADRs. In other ADRs as endocrine—metabolic, neuropsychiatric or hypersensitivity ADRs there was not differences between sexes.

Abstract Code: ISP3464-45

Additional Documents Attached to the Reporting Form and its Contribution to the Documentation of ADRs

P. Van Der Horst[1], L. Harmark[1]

(1) Netherlands Pharmacovigilance Centre Lareb, 's-Hertogenbosch, The Netherlands

Introduction: In August 2012 The Netherlands Pharmacovigilance Centre Lareb introduced a new digital form for reporting ADRs. The aim of the new reporting form is to make reporting as easy as possible but still collect information which is vital for the assessment of the report. With the new reporting form healthcare professionals and patients are able to attach easily additional documents such as photo's, medication lists, hospital discharge letters, lab results etc. to further document their report. The use of this new upload function has not been previously examined.

Aim: To examine the contribution of additional documents attached to the reporting form.
Methods: The use of the upload function was investigated in three groups medical doctors (specialist doctors/general practitioners/physicians with own pharmacy), pharmacists and patients. A random selection of 50 spontaneous reports per group received by the Netherlands Pharmacovigilance Centre Lareb between 1 January 2013 and 1 April 2013 was made. It was established how often an additional document was attached to the reporting form by each group and the nature of the additional document.
Results: 19 out of the 150 reports contained an additional document. Pharmacists attached a document most often (26 %), followed by medical doctors (10 %) and patients (2 %). The type of document most attached was the medication list (16 times). Medical doctors used the upload function only for attaching medication lists. One pharmacist attached photos of the ADR and another pharmacist attached hospital correspondence to the reporting form. Hospital correspondence was also attached by a reporting patient.
Conclusions: The patient's medication list is the most frequently attached additional document by healthcare professionals. Attaching a document, such as medication lists, hospital discharge letters, lab results and other documents saves the reporter time. It also provides the Netherlands Pharmacovigilance Centre with an accurate overview of suspect and concomitant drugs that were administrated at time the ADR occurred and medical treatment. Photographs, for example of skin reactions, contribute to the imaging of the adverse drug reaction. The possibility of attaching a document to the reporting form makes reporting easy and provides information that is relevant for the assessment of the ADR.

Abstract Code: ISP3466-47

Increasing the Number of Reports of OTC Drugs to a National Spontaneous Reporting System by Co-operation with Drugstores

S. Van De Koppel[1], L. Harmark[1]

(1) Netherlands Pharmacovigilance Centre Lareb, 's-Hertogenbosch, The Netherlands

Introduction: Over the past decade, evidence has shown that patient self-reporting of symptomatic adverse drug reactions is both feasible and informative and contribute to the detection of signals, one of the primary aims of spontaneous reporting systems. Studies in the Netherlands show that patients reports are of high quality and patients are motivated to report to a spontaneous reporting system. Drugstores could play an important role in promoting patient reporting of ADR's especially concerning OTC drugs. Over 90 % of the Dutch drugstores are collaborating in the umbrella organization Central Bureau Drugstore Business (CBD). Lareb and the CBD, have decided to cooperate with the intention to increasing the number of reports of OTC drugs and promote the safe use of OTC medicines in the Netherlands. The aim of this abstract is to describe the process of implementing spontaneous reporting in Dutch drugstores.
The Method: Since there is no experience about reporting from drugstores three different methods will be tested and evaluated.

- When purchasing the drug in the drugstore, the consumers will receive a card with information how to report an ADR via the Lareb website.
- Consumers reports their ADR in the drugstore, the personnel note the email address and passes it to Lareb, who sends the consumer a link to the online reporting form.
- CBD develops an abbreviated report form which is filled in by the drugstore personnel. The reports are than electronically transmitted to Lareb.

Steps: In order to implement reporting of ADRs from drugstores, the following steps need to be undertaken:

1. Training: Prior to the implementation of the project an internal training of the drugstore personnel in how to detect and report ADRs will be provided by Lareb.

2. Promotion: The CBD provides a large-scale promotion campaign in order to inform their consumers about the importance of ADRs reporting.

3. Pilot: In pilot drugstores, the personnel will be asked to actively promote the reporting of ADRs using one of the three possible routes described above.

4. Implementation in All Drugstores: After evaluation and adaptations the best method of reporting of ADRs will be introduced in all drugstores.

5. Information Dissemination: When the drugstore reporting system is up and running, Lareb will inform CBD about current and relevant ADRs of OTC drugs and will help CBD in updating their information material about ADRs of OTC drugs.

Abstract Code: ISP3467-48

Pharmacovigilance in Moroccan Tuberculosis Control Programme

D. Soussi Tanani[1], A. Tebaa[1], R. Benkirane[1], R. Soulaymani Bencheikh[1]

(1) Centre Anti Poison et de Pharmacovigilance du Maroc, Rabat, Morocco

Introduction: Public Health Programs are well structured but often represent a favorable model for the development of adverse events (AEs) by irrational use of drugs.

The objective of this work is to demonstrate the interest of integrating pharmacovigilance in National Tuberculosis Control Programme (NTP).
Design and Data Collection:

- Integration of pharmacovigilance in NTP was conducted in October 2012 with the Global Fund support.
- Using Targeted Spontaneous Reporting (TSR).
- Comparison of spontaneous reports before and after the integration of pharmacovigilance in MTCP (January 2010–October 2012/October 2012–April 2013).
- Detection of Moroccan signals using the Information Component of VigiMine.
- Using SPSS Version 10.0 for data analysis.

Results: As reports indicators: the average number of spontaneous reports increased from 3.6 to 37.4 cases/month (10.3 times, $p < 10^{-3}$).

As AEs indicators: the average age was 40.7 ± 17.5 years, the sex ratio was 0.8. Hepatic reactions (32.7 %) predominated during the first period while skin reactions (22.7 %) were in second period ($p = 10^{-4}$), 40.9 % of cases in the first period were serious against 23.5 % in second period ($p = 0.003$), 4.7 % of cases in the first period have been fatal against 0.7 % in second period ($p < 10^{-4}$). Two signals were generated during the first period (arthralgia, skin rashes) and 7 in second period (hepatic cytolysis, hepatic cholestasis, jaundice, acne, pruritus, peripheral edema, anorexia).
Conclusion: The integration of pharmacovigilance in National Tuberculosis Control Programme allowed rapid identification of events that are

likely to affect adherence to treatment and determination new signals of antituberculosis drugs.

Abstract Code: ISP3468-49

Severe Cutaneous Reactions to Black Henna (Lawsonia inermis): A Case Series Reports

H. Sefiani[1], R. Benkirane[1], R. Soulaymani[1]

(1) Centre Anti Poison et de Pharmacovigilance du Maroc, Rabat, Morocco

Introduction: Moroccan women use a lot of traditional cosmetics to embellish themselves. Henna is one in palette of various natural products which refers in cosmetic, to the dye prepared from the plant *lawsonia inermis*. It is used to dye skin, hair and nails. Traditional henna, which colors range between orange, red or brown, rarely causes side effects [1]. However, to obtain black color, many ingredients are mixed with this plant such as paraphenylenediamine and solvents [2].
Objective: To describe and discuss severe cutaneous side effects caused by black henna collected by the Centre Anti Poison et de Pharmacovigilance du Maroc.
Methods: We analyzed our adverse cosmetic events database regarding to adverse reactions associated with the use of black henna received during 2012. The case severity and cutaneous localization of adverse reactions were the inclusion criteria. We analyzed the demographic characteristics of patients, adverse reactions and type of exposure.
Results: Nine serious cutaneous cases were observed, which represented 26.4 % of the cases related to black henna use and 6.42 % of all the adverse cosmetic events. All patients were female and two children were concerned. Hospitalization and sequelae were the reason of seriousness in 3 and 6 cases respectively. Clinical signs were bullous rash maculopapular in 6 cases, two cases of generalized oedema and one case of erysipelas. The outcome was favourable in all cases, 6 cases suffered sequelae such as keloid scars, hypo and hyper pigmentation.
Conclusion: the severity of those cases showed the importance of cosmetics pharmacovigilance and the urgent need of establishing regulatory of cosmetics in Morocco.

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Abstract Code: ISP3469-50

Medicines Mishaps: A Ten-Year Profile of Product Defect Safety Alerts in the UK

S. Lendon[1], D. Brown[1]

(1) School of Pharmacy and Biomedical Sciences, University of Portsmouth, Portsmouth, UK

Introduction: Medicines are authorised for sale having achieved acceptable standards against quality, efficacy and safety benchmarks. From time to time, these standards may be compromised due to process failures in manufacturing, storage or supply.
Aim: to undertake a quantitative and qualitative analysis of product safety alerts to look for trends and signals in a time-series of safety alerts.
Methods: Alerts directed at pharmacists and published in the UK Pharmaceutical Journal from January 1st, 2000 to December 31st 2009 were subject to a systematic content analysis [1]. Reports were corroborated by reference to the MHRA website [2]. Key extracted data included formulation details, reasons for the safety alert and advised action to be taken. Assessment of potential patient risk was assessed using NPSA criteria [3]. Data were analysed using SNAP software (Mercator).
Results: 213 cases were included. The most common dosage forms were tablets and capsules (82; 38.5 %), parenterals (73; 34.4 %) and inhalers (13; 6.1 %). The most common therapeutic categories were cardiovascular (39; 18.3 % %), anti-infectives (30; 14.1%) and CNS (27; 12.7 %). The defects cited were faults with the inner product packaging (66; 31.0 %), substandard product quality (36; 16.9 %), labelling errors (26; 12.2 %), potential contamination (23; 10.8 %), presence of particulate matter (15; 7.0 %), doubts of sterility (11; 5.2 %); potential counterfeit (8; 3.8 %), poor product appearance (4; 1.9 %) and unexplained adverse reactions to the product (4; 1.9 %). The majority of notices were product recalls (193; 90.6 %); helpline advice was made available in 203 (95.3 %) of cases. The potential severity of using the product was judged to be life threatening in 13 cases (6.1 %), serious in 12 (5.6 %), moderate in 68 (31.9 %), minor in 73 (34.3 %) and of no harm in 47 (22.1 %). The median annual number of notices was 22 (IQ range: 16.5–24.5).There was no obvious trend in annual notice rate over the study period (Pearson's $r = 0.051$) and a runs test indicated the absence of data clustering and oscillation.
Conclusions: Only a small minority were associated with actual patient harm and almost half had the potential to cause only minor or no harm (99; 46.5 %); however, defect reporting and safety notices remain an essential part of attempts to optimise patient safety. A spectrum of product defects was demonstrated, illustrating the need for constant vigilance on the part of those who manufacture, handle and supply medicinal products.

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Abstract Code: ISP3470-42

Results of the Experience With the Use of Varenicline in Daily Practice Using Intensive Monitoring

I. Oosterhuis[1], L. Harmark[1], E. Van Puijenbroek[1]

(1) Netherlands Pharmacovigilance Centre Lareb, MH 's-Hertogenbosch, The Netherlands

Background: Although a concise overview of Adverse Drug Reactions (ADRs) of varenicline is known, little is known about the time related information about ADRs of varenicline such as for example latencies.
Objectives: To gain insight in the experience and safety of varenicline in daily practice as reported by patients through web-based questionnaires using an intensive monitoring system.

Methods: A prospective, observational, non-interventional cohort study was conducted. First-time users of varenicline were defined as patients who have not filled in a prescription of varenicline in the previous 12 months using the first prescription signal in that particular pharmacy. All first-time users of varenicline in participating pharmacies between 1 December 2008 and 31 March 2012 were invited for the study. Patients could sign up for the study on a dedicated website. Electronic questionnaires were sent after 1, 2 and 6 weeks, 3 months and 4 months after they started to use varenicline. In these questionnaires questions about drug use and ADRs were asked for. The main outcome was information about the ADR, seriousness, and action taken when experiencing an ADR. Descriptive analysis was done using Microsoft Access.

Results: 1418 patients signed up for the study. Response rates for the various questionnaires vary from 31.3 to 62.5 %. 58.8 % of the patients reported at least one ADR. The most frequently reported ADRs were nausea (30.8 %), abdominal pain (11.2 %) and abnormal dreaming (10.3 %) which are listed in the Summary of Product Characteristics of varenicline (SmPC). Median latency times were 3–7 days, with exception for depressed mood (10 days). The number of ADRs did not abate over time. No signals were detected.

During treatment 43.9 % of the patients stopped using varenicline. The main reasons for stopping were the occurrence of ADRs (42.2 %) and other (40.0 %) unspecified reasons.

Conclusions: This study indicates that varenicline is a relatively safe drug. The reported ADRs correspond with the ADRs mentioned in the SmPC of varenicline with a median latency of 3–7 days. The number of ADRs do not abate over time.

Abstract Code: ISP3472-44

Five Cases of Severe and Chronic Diarrhoea in Patients Treated by Olmesartan

H. Théophile[1], X. David[2], G. Miremont-Salamé[1], F. Haramburu[1]

(1) Centre Régional de Pharmacovigilance, Département de Pharmacologie, CHU de Bordeaux, Université de Bordeaux, INSERM U657, Bordeaux, France (2) Gastro-entérologie, Polyclinique Côte Basque Sud, Saint Jean de Luz, France

Olmesartan is one of the several angiotensin II receptor blockers used for treatment of hypertension. We describe five cases of severe chronic diarrhoea during olmesartan treatment.

Case 1: a 79-year old man was hospitalized for severe asthenia, dehydration, renal insufficiency, diarrhoea and weight loss. The colonoscopy was normal and the stool culture for *Clostridium difficile* was negative. After discontinuation of all medicines, diarrhoea disappeared. Two weeks later, the patient, who had restarted treatment by olmesartan, was re-hospitalized for profuse diarrhoea. The gastro-colonoscopy showed a bulbar ulcer, villous atrophy (Marche score IIIb) and two polyps. The diarrhoea disappeared after polyp ablation, discontinuation of olmesartan and a gluten-free diet. Two months later, the control gastroscopy was normal. During the following months, the patient resumed olmesartan and was once more re-hospitalized for diarrhoea, hypokalemia and renal insufficiency. After permanent discontinuation of olmesartan and continuation of gluten-free diet, diarrhoea did not recur.

Case 2: an 82-year old woman was hospitalized for persistent diarrhoea, weight loss and failure of antidiarrheal treatments. All investigations were normal except for a steatorrhea. The diarrhoea disappeared rapidly after discontinuation of olmesartan and nebivolol and did not recur thereafter.

Case 3: an 87-year old woman was hospitalized for profuse diarrhoea, asthenia, dehydration, metabolic acidosis, hypokalaemia. The gastro-colonoscopy showed villous atrophy (IIIb). After all drug discontinuation, she recovered within 24 hours. Most of her drug treatment, but not olmesartan, was reintroduced thereafter, without recurrence.

Case 4: an 83-year old man was hospitalized for diarrhoea, weight loss, dehydration, renal insufficiency. The gastroscopy showed a partial villous atrophy (IIIb). The outcome was favourable after discontinuation of all medicines. Later, the patient took again olmesartan and the same day was hospitalized for profuse diarrhoea. Olmesartan was definitively stopped and a gluten-free diet started. There was no villous atrophy few months later. When gluten was reintroduced, diarrhoea did not recur.

Case 5: A 78-year old man was hospitalized for diarrhoea, weight loss. The gastro-colonoscopy showed a partial atrophy (IIIa). Outcome was favourable after discontinuation of olmesartan.

The Mayo clinic has published similar enteropathy in patients treated by olmesartan, leading the FDA to add olmesartan to the list of drugs under safety surveillance. Here, the diarrhoea recurrence in 2 patients after drug reintroduction was strongly in favour of olmesartan responsibility. The possible occurrence of a severe sprue-like enteropathy, inducing serious clinical consequences, significant investigations, hospitalization costs should be kept in mind in patients treated by olmesartan.

Abstract Code: ISP3473-45

QTc Interval Prolongation Induced by Opiates. Correlation Between Plasma Concentration and Action Potential Changes in Perfused Myocardium

G.A. Keller[1], M.L. Ponte[2], C. Bagnes[3], R.A. Diez[4], G. Di Girolamo[1]

(1) Pharmacovigilance Unit, Second Chair of Pharmacology, School of Medicine, Universidad de Buenos Aires, Argentina, (2) Internal Medicine Department Hospital General de Agudos Cosme Argerich, Ciudad Autónoma de Buenos Aires, Argentina, (3) Oncology Unit, Hospital General de Agudos Dr. Enrique Tornú, Ciudad Autónoma de Buenos Aires, Argentina, (4) Second Chair of Pharmacology, School of Medicine, Universidad de Buenos Aires, Argentina

Long QT syndrome is an important adverse effect. In 2010, FDA issued the withdrawn of propoxyphene products, based on cardiac toxicity risk (at higher doses than those currently approved in Argentina). To cope with such differences, the Pharmacovigilance Department of ANMAT (Argentina's drug national regulatory agency) changes the surveillance of propoxyphene products, with proactive actions to increase the data concerning cardiovascular effects at the dose authorized in Argentina.

Between 2010 and 2012, we had evaluated 1270 patients for QT-Interval Prolongation in a Multicenter Study to Detect Drugs More Frequently Associated in the Clinical Practice. A significant number of patients received such treatment dextropropoxyphene (228 combined with dipyrone and 214 with ibuprofeno), without exceeding the authorized intravenous daily dose of 200 mg/day during 72 h [1, 2]. The analysis showed no risk for the development of QTc interval prolongation defined as anyone of the following four criteria's of QTc interval prolongation [3]: QTc >450 ms in men or 470 ms in women, delta QTc delta (difference between the baseline and the intra-treatment QT) >30 ms, QTc >500 ms or delta QTc >60 ms. From these results we are conducting a research project to evaluate QTc interval changes induced by therapeutic doses of

dextropropoxyphene, tramadol and meperidine. Changes in QTc will be correlated with drugs' plasma concentrations, including dextropropoxyphene and its main metabolite, in samples taken at the time of intra-treatment ECG registration. Besides, changes in duration of action potential (DPA), in particular, DPA90 and DPA30-90, will be determined in a separate set of experiments in perfused murine whole heart. The concentration plasma level ranges were used, aiming to estimate safety index for each drug. This information should provide a more correct estimation of the risk/benefit balance for the different opiates, at the doses approved in Argentina.

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Abstract Code: ISP3474-46

Do Older Patients Take More Drugs and are They at Higher Risk of ADRs? What Do Spontaneous Reports Tell Us?

T. Stammschulte[1], H. Pachl[1], U. Gundert-Remy[1]

(1) Drug Commission of the German Medical Association (DCGMA), Berlin, Germany

Background: According to the 2011 German Report on Drug Prescriptions (Arzneiverordnungsreport), drug usage in statutory health insurance increases with age: from 66 defined daily doses (DDD) per insured person between the ages of 20 to 24, to up to 1,521 DDDs for the age group 85–89 years [1]. The risk of adverse drug reactions (ADR) presumably depends, among other things, on the characteristics of the drugs administered, the number of drugs administered to one patient, the age of the patient, and concomitant diseases. Thus, the ADR risk should be reflected in the number of spontaneous reports detected for different patient age groups.
Objective and Methods: We analyzed the association of drug usage with the number of spontaneous reports in different age groups of patients (≥20 years of age) by means of the German Report on Drug Prescriptions from 2006 to 2010 and the German spontaneous reporting database.
Results: 60,525 of 84,905 spontaneous ADR reports from 2006 to 2010 were included in the analysis. Reports without information about the age of the patient (n = 24,380) were excluded. The rate of spontaneous ADR reports was 586 reports per 1 million insured persons between the ages of 20–24 years, and increased up to 1,630 reports per 1 million in the 75–79 age group. In the ≥85 age group, the reporting rate decreased to 1,184 reports for patients older than 90 years. Taking into account the drug usage in the different age groups, the reporting rate was 0.19 reports per million DDD prescribed for patients aged 85–89 years, and 1.96 reports for 20–24 year olds.
Discussion: The rate of spontaneous reports increased up to an age of 79, but declines in older age groups (≥85 years). If the age-related differences in drug usage are considered, the reporting rate of suspected adverse drug reactions is about ten times lower in elderly patients with high drug usage compared to younger age groups. Since many studies have revealed a higher risk of adverse drug reactions in older patients, the reason for this observation requires further investigation.

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Abstract Code: ISP3476-48

Observational Assessment of Safety in Seroquel (OASIS)—Design, Recruitment and Baseline Patient Characteristics

S. Clarke[1], D. Layton[2], S. Shakir[2], J. Reilly[3], A. Hale[4]

(1) Drug Safety Research Unit, Southampton, UK (2) Drug Safety Research Unit, Southampton, University of Portsmouth, Portsmouth, UK (3) Durham University, Durham, UK (4) University of Kent, Canterbury, UK

Background: Prolonged-release quetiapine fumarate (Seroquel XL), a once-daily atypical antipsychotic, was launched in the UK in September 2008. The XL formulation was developed to improve tolerability and the administration of once daily dosing. OASIS was incorporated into the EU risk management plan to extend the post-authorisation safety knowledge in this area, with particular emphasis on safety during titration and at higher doses.
Objectives: The study was designed to examine the short-term safety and use (up to 12-weeks) of quetiapine XL, with quetiapine IR as a comparator, when prescribed by psychiatrists under normal conditions of use.
Methods: OASIS aimed to recruit 1500 patients with a clinical diagnosis of schizophrenia or bipolar mania, newly initiated on quetiapine XL or IR (750 each). Adult patients were recruited from over 50 NHS trusts throughout England over 3 years from December 2009 to December 2012. Questionnaires completed by study investigators collected baseline data on patients' demographics, medical history and planned dosage, and follow up information 12-weeks post index date to determine rate of events.
Results: A team of study facilitators established a cohort of psychiatrists in collaboration with the Mental Health Research Network. Patient recruitment increased over the 3 year period, with 26 % of the total cohort recruited in the final 6 months. In March 2012, the Seroquel XL patent expired in the UK. 900 patients were recruited, less than the planned 1500. One explanation includes prescribing guidelines that encourage generic product use. Patients' baseline mean age was 40.2 years, with 56.1 % female. Baseline evaluation indicates that fewer patients were recruited in the IR cohort than the XL, and fewer patients were prescribed higher doses than expected.
Conclusions: Important information on quetiapine XL utilisation and safety will still be obtained from OASIS, despite lower than planned recruitment. The influence of external factors such as prescribing guidelines and expert committee recommendations on cohort accrual are being explored.

Abstract Code: ISP3478-50

Use of Non-Prescribed and Prescribed Medications Other Than Highly Active Antiretroviral Therapy (HAART) in HIV Positive Patients in Coventry

S. Allan[1], B. Kumari[2], Y. Beh[3], P.D.R. Singer[4]

(1) Warwick Medical school, University of Warwick, Coventry, UK, (2) Coventry and Warwickshire Partnership Trust, Coventry, UK, (3) Coventry and Warwickshire Partnership Trust, Coventry, UK, (4) University Hospital of Coventry and Warwickshire, Coventry, UK

Introduction: It is estimated that two thirds of severe adverse drug reactions (ADRs) may be preventable [1]. There are serious concerns about risk of adverse reactions from use of other prescribed and non-prescribed medications by HIV positive patients especially those who are taking HAART.

Aim: To assess the use of prescribed and non-prescribed medications by HIV positive patients who are taking HAART.

Methods: We audited medication use by 79 patients currently taking HAART and attending one consultant's clinic (SA) in Coventry between 1st February 2013 and 31st March 2013. After routine clinical consultation, medication history was recorded using a standard, validated questionnaire.

Results: 36 males and 43 females participated, 60 were of Black African-Caribbean origin. 53 were currently using alcohol, with lager and red wine being the most popular. 47 participants reported drinking <20 units of alcohol/week and 2 reported a high intake of >30 units/week. Thirty participants had other medical conditions in addition to HIV(13 hypertension, 6 diabetes, 3 raised cholesterol, 2 cancers; 8 had multiple conditions), 26 (33 % 95 % CI 24–44 %) taking additional prescribed medications (8 antihypertensives, 5 metformin, 4 statins, 7 unspecified or unknown). 37 participants (47 % 95 % CI 36–58 %) reported use of over-the-counter medications (OTCs), paracetamol the most common drug (22 patients), other analgesics 8, multivitamins 13, herbal teas and supplements 4, anti-tussives 2. 11 (14 % 95 % CI 8–23 %) reported using recreational drugs (cannabis 10), 6 within the previous month.

Conclusions: Many HIV patients took other prescribed (26) and non-prescribed medications (37). Four were on statins that could potentially interact with HAART, causing myositis or rhabdomyolysis. Four were taking supplements for which we did not know the composition or potential interactions with HAART. Two patients admitted to drinking alcohol excessively and 11 to taking recreational drugs. Heavy alcohol intake and illicit drug use have been associated with non-adherence to HAART, which may compromise treatment. Prescribed, non-prescribed and illicit drug use needs to be recorded and updated at each consultation to avoid potential drug interactions and identify recreational drug use as an index of possible non-adherence to HIV medication.

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Abstract Code: ISP3479-51

Serious Cutaneous Adverse Reactions to Drugs: A Retrospective Analysis of the Moroccan Pharmacovigilance Center

R. Ouled Errkhis[1], S. Belamaalem[2], A. Tebaa[1], R. Benkirane[1], R. Soulaymani Bencheikh[1]

(1) Centre Antipoison et de Pharmacovigilance, Rabat, Morocco, (2) Laboratory of Genetics and Biometry, Faculty of Sciences, University IbnTofail, Kenitra, Morocco

Introduction: Cutaneous drug eruptions are one of the most common types of adverse reaction to drug therapy. Although most drug-related skin eruptions are not serious, some are severe and potentially life-threatening. The incidence of serious cutaneous adverse drug reactions (SCARs) ranges from 0.4 to 7.4 cases per million persons per year [1]. The pathogenesis of SCARs can be classified into immunological and non-immunological reactions. SCARs include angio-oedema, erythroderma, Stevens–Johnson syndrome and toxic epidermal necrolysis, Dress Syndrome.

Aims: to describe the SCARs reported to the Moroccan Pharmacovigilance Centre in order to identify the therapeutic classes most involved and the risk factors.

Methods: Retrospective analysis of the Moroccan Pharmacovigilance centre database for the period from January 2010 to March 2013.

Results: During this period, 246 SCARs were recorded, which represented 17.5 % of all cutaneous adverse drug reactions collected during this period. Spontaneous reports represented 76.4 %. The most common morphological reaction-types observed were Dress Syndrome (10 %), Stevens–Johnson syndrome (SSJ) (9.2 %), Rash maculopapular (7.8 %), Erythema multiforme (7.8 %), Toxic epidermal necrolysis (TEN) (7.5 %). The median time to onset (15.6 ± 16.2 days). Two new cases have been reported: Sweet's syndrome in ciprofloxacin, cisplatin, and vitiligo at the site of interferon injection. The reactions were classified serious because they led to the hospitalization of patients (76 %), resulted in sequelae (1.6 %), engaged the life prognosis (3.9 %) or resulted in death (4.5 %). In the 14.3 %, the type of severity was not specified. The fatal reactions include TEN (6 reports), rash purpuric (2 reports), angioedema (1 report) and, SSJ (1 report). The most common offending drugs were: Paracetamol (21 reports), recombined Isoniazid/Ethambutol/Pyrazinamide/Rifampicin (21 reports), Allopurinol (18 reports). Polymedication was noticed in 28.5 % of the cases.

Discussion: The analysis highlighted that polymedication represented a potential risk factor. Among prescription drugs, Antibacterials for systemic use (19 %), Antimycobacterials (15 %), Analgesics (8 %), Antiepileptics (7 %), Vaccines (7 %) and, Antigout preparations (5 %) ATC groups caused the most side effects; this can be explained by their frequent use. TEN has the highest mortality (26 versus 3.8 % SSJ).

Conclusion: Drug should be always considered as a possible cause of SCARs. Pharmacovigilance centres plays an important role in the diagnosis, the appropriate management and prevention of these reactions.

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Abstract Code: ISP3480-43

Sequence Symmetry Analysis: A Valid Tool with Potential to Enable Global Pharmacosurveillance

E. Roughead[1], I. Wahab[1], L. Kalisch[1], N. Pratt[1]

(1) Centre of Research Excellence in post-market surveillance of medicines and medical devices, School of Pharmacy and Medical Sciences, University of South Australia, Australia

Introduction: Sequence Symmetry Analysis (SSA) has been used on a case by case basis to explore safety issues associated with medicine initiation. The method has the potential to become a tool for global Pharmacosurveillance of medicines because it employs a simple algorithm, is computationally fast and requires a minimum data set of only 3 variables, drug name, date of supply and a patient identifier. We have previously shown the method is valid [1] and can be employed in a distributed model to undertake multi-country analyses [2].
Aim: To compare the performance of SSA and traditional methods of signal detection in detecting a set of positive and negative controls for adverse drug reactions. To compare the performance of SSA in detecting a positive and negative control in three different countries.
Methods: Using 43 positive and 114 negative adverse drug reaction pairs, we determined the sensitivity and specificity of Proportional Reporting Ratio (PRR), Reporting Odds Ratio (ROR), Bayesian Confidence Propagation Neural Network (BCPNN) and SSA, as well as the proportion of events detected by combinations of the methods. Using a distributed model, we also determined the ability of SSA to detect the positive control of amiodarone induced hypothyroidism and the negative control of thyroxine induced allopurinol prescription, using datasets from Taiwan, Korea and Australia.
Results: SSA, PRR, ROR and BCPNN had a sensitivity of 65, 49, 49 and 51 % respectively. Specificities were similar across methods ranging from 89 to 97 %. Using all four methods, 86 % of true positives were identified; 30 % were detected by all methods, SSA detected an additional 35 %, while PRR, ROR and BCPNN detected an additional 21 % of true positives. Despite differing trends in utilisation of medicines, amiodarone induced hypothyroidism was identified in all three countries (Taiwan ASR 2.7 (95 % CI 1.8–3.8); Korea ASR 1.5 (95 % CI 1.29–1.8), Australia 3.4 (95 % CI 2.9–4.), with the negative control having no positive association.
Conclusions: These results suggest PSSA has a place as a complementary tool to existing methods as a safety signal detection tool and is feasible to use in multi-country studies.

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Abstract Code: ISP3483-46

A Survey of the Adverse Reactions to Narcotic Analgesics

E.J. Jo[1], H.K. Park[1]

(1) Department of Internal Medicine, Pusan National University School of Medicine, Busan, Korea

Background: The use of narcotic analgesics for cancer or non-cancer pain control is increasing worldwide [1]. For safe and effective pain control, the appropriate administration of analgesics to the individual patient is important, and it is necessary to ensure proper monitoring of hazardous reactions to narcotic analgesics [2].
Aim: To investigate the computational reports of adverse drug reactions (ADRs) to narcotic analgesics.
Methods: In January 2011, Pusan National University Hospital (PNUH) Information System (PHIS) and new electronic medical recording (EMR) system was started in PNUH, then, the assessment and reporting systems of ADRs using EMR system were established. We analyzed the ADRs reports registered in EMR system from January to December 2012.
Results: The ADRs to the narcotic analgesics was 29.7 % of total analgesics. The narcotic analgesics in PNUH were 15 kinds and 44 items, the overall reports of ADRs to the narcotic analgesics were 437. The most frequently used analgesic was morphine sulfate (60.4 %), followed by remifentanyl (21.3 %) and fentanyl citrate (17.6 %). The most common adverse reactions were gastrointestinal symptoms such as nausea, vomiting or dyspepsia. The other adverse reactions were neurologic symptoms (tremor, headache or deterioration of consciousness) and dermal symptoms (rash or pruritus).
Conclusion: The gastrointestinal, neurology, and dermal symptoms after narcotic analgesics were administered to the patients have to be monitored and adjusted, and it is necessary to establish the alarm systems for how to respond in the event of ADRs to the narcotic analgesics.

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Abstract Code: ISP3484-47

Possible Interaction Between Fluindione and Turmeric (Curcuma)?

A. Daveluy[1], G. Miremont-Salamé[1], L. Thibaud[2], H. Géniaux[1], M. Mallaret[3], F. Haramburu[1]

(1) Centre régional de pharmacovigilance, département de pharmacologie, CHU, Univ. de Bordeaux, U657, Bordeaux, France, (2) Médecine générale, Basse-Terre, France (3) Centre Régional de pharmacovigilance, CHU, Grenoble, France

Background: Fluindione is an oral anticoagulant (OA), vitamin K antagonist (VKA) exclusively marketed in France and Luxembourg, representing more than 80 % of VKAs used in France. Less studied than warfarin, few data are available about this medicine. However, interactions observed with fluindione are very similar to those observed with warfarin. Potential interactions between herbal products/nutrients and warfarin have been described (St. John's wort, garlic, menthol, cranberry, etc.).
Aim: To report a possible interaction between fluindione and turmeric, not yet reported in the literature with OAs.
Case: A 56-year-old woman was treated since 1993 by fluindione for mitral valvulopathy. The international normalized ratio (INR) has always been stable in the target value (range 2–3). Even though, there had been no recent change in fluindione dosage, concomitant treatment or diet, the patient's INR rose suddenly from the therapeutic value to 6.5. The patient reported that she had been taking an infusion of turmeric (one coffee spoon) each evening for 5 days. Fifteen days after withdrawal of turmeric, the INR was again within the target value.
Discussion: Traditionally used in herbal medicine to help relieve flatulent dyspepsia, turmeric is associated with theoretical risk of bleeding, as turmeric has been reported to exhibit antiplatelet activity and to have anticoagulant effect that had been demonstrated in vivo or in vitro. Moreover, turmeric is an inhibitor of the 2C9 and CYP3A4 isoenzymes of cytochrome P450, of which warfarin and fluindione are the substrate. To our knowledge, this is the first case report of an interaction between an oral VKA and turmeric. Fortunately, the patient did not show any clinical sign.
Conclusion: The possible interaction between oral vitamin K antagonist and turmeric is not known in France, whereas a warning has been made in Canada. Patients treated with oral VKA must be warned about the risk of interaction with herbal products, turmeric in particular, more and more used as alternative medicine for its antioxidant effects.

Abstract Code: ISP3485-48

French Prescribers and Secure Prescription Forms

A. Daveluy[1], M. Courné[2], C. Collin[2], M. Lapeyre-Mestre[3], M. Heil[1], F. Haramburu[1]

(1) Centre d'Addictovigilance, département de pharmacologie, CHU, Univ. de Bordeaux, U657, Bordeaux, France, (2) ANSM, France (3) Centre d'addictovigilance, UMR Inserm 1027, Service de pharmacologie, Hôpitaux de Toulouse, Unité de pharmacoépidémiologie, Université de Toulouse, France

Background: In France, since 1999, prescription of narcotics must be written on a secure prescription form with watermarked paper, identification of the prescriber printed in blue, a batch number and a printed square, in which the number of medicines prescribed must be noted. Dosage and daily dose of medicines shall be written out entirely in letters. These prescription forms are also mandatory for buprenorphine, clorazepate, clonazepam and tianeptine, owing to traffic, abuse or diversion. The Ministry of Health intends to generalize secure prescription forms for all medicines.
Objective: To assess the use of standard and secure prescription forms and the acceptability of the generalization of the latter to all medicines.
Methods: An opinion survey was performed within 3 randomized samples of 1,500 prescribers (1,400 physicians, 50 dentists and 50 midwives). A postal questionnaire was sent with a prepaid return envelope. Questions concerned the frequency of use of secure prescription forms, their ease of use, the history of theft or falsification and the opinion of prescribers about a possible generalization of secure prescription forms. A reminder phone call was made until a response rate of 25 % in each sample.
Results: Of the 403 participating prescribers, 373 were physicians (92.5 %), 14 dentists (3.5 %) and 16 midwives (4 %). Physicians used a weekly median of 50 standard prescription forms (specialists) to 160 (general practitioners) and a weekly median of 1–10 secure prescription forms. Dentists and midwives seldom used secure prescription forms. Secure prescription forms were used by 215 prescribers (76.2 %), but only by 5.1 % ($n = 11$) in a computerized version, whereas, for standard prescription forms, 61 % ($n = 172$) used computer assisted prescription software. The main reason was the inability of the prescription software to print these forms or to respect the mandatory prescription rules for narcotics. Theft and falsification of prescriptions had ever occurred (working life) respectively for 5.5 and 10.7 % of prescribers for standard prescription and for 4 and 2.7 % for secure prescription forms. Most prescribers (62.5 %) were against the generalization of secured prescriptions (too complicated or expensive, satisfied of the current regulation, software inadequacy, etc.). Those in favour were for a generalization to all medicines (65 %) and not only to psychotropic agents.
Conclusion: Generalization of secure prescription forms is not a consensual solution to prevent medicines' diversion. Some prescribers alluded to the possibility of dematerialisation and electronic transmission of prescription forms, which could avoid theft, forgery or falsification.

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Drug Products Withdrawn from the EU Market Between 2002 and 2011 for Safety Reasons and Contributing Evidence

R. Mcnaughton[1], G. Huet[2], S. Shakir[1]

(1) Drug Safety Research Unit, Southampton, UK; University of Portsmouth, Portsmouth, UK, (2) Drug Safety Research Unit, Southampton, UK

Introduction: Studies have shown that evidence used to support a decision to remove a drug product from the market for safety reasons was primarily based on spontaneous case reports, with case-control, cohort studies and randomised controlled trials only used in one-third of determinations [1–3].
Aim: To determine the nature of evidence used to support the withdrawal of marketing authorisations of drug products for safety reasons throughout the European Union (EU) between 2002 and 2011.
Methods: Products withdrawn, during the period 2002–2011, were identified by conducting detailed searches of the World Health Organization (WHO), the EMA (European Medicines Agency) and national medicines agency websites. The scientific evidence used to support the decision was identified from a search within PubMed, the EMA and national medicines agencies websites. Information about spontaneous case reports entered into EudraVigilance that are not freely available on the EMA website was received by email from the EMA.
Results: Nineteen drugs were withdrawn from the EU market for safety reasons in the period 2002 to 2011. Case reports were cited in 95 % of withdrawals (18/19) and case-control studies, cohort studies, randomized controlled trials (RCTs) or meta-analysis were cited in 63 % of withdrawals (12/19). Cardiovascular events or disorders were the main reason for withdrawal (9/19), followed by hepatic disorders (4/19) and neurological or psychiatric disorders (4/19).

Conclusions: This study has shown that the level of evidence used to support drug withdrawal has improved, with an increased use of case-control studies, cohort studies, RCTs and meta-analyses. This research has identified that such studies have contributed to decision-making in almost two-thirds of cases which is in line with the research conducted by Paludetto et al. in 2012 [4].

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Abstract Code: ISP3487-50

Analysis of Spontaneous Reports of Thromboembolic Adverse Drug Reactions Associated with Cyproterone/Ethinylestradiol

F. Van Hunsel[1], E. Van Puijenbroek[1]

(1) Netherlands Pharmacovigilance Centre Lareb, 's-Hertogenbosch, The Netherlands

Introduction: After media attention on thromboembolic adverse drug reactions (ADRs) and the use of cyproterone/ethinylestradiol [1], the Netherlands Pharmacovigilance Centre Lareb received a high number of reports about this association, which called for a more detailed analyses.

Aim: To provide an overview of the characteristics of all reports of thromboembolic ADRs associated with the use of cyproterone/ethinylestradiol submitted to Lareb until April 3rd 2013 focusing on character, circumstances, off-label use and degree of recognition of the ADRs.

Methods: Reports were selected from the Lareb database based on ATC-code G03HB01 using an MS Access® query. Lareb analysed the reporter type, seriousness of the reaction according to the CIOMS criteria, patient's age at the occurrence of the ADR, patient's BMI (kg/m^2), indication, ADRs classified as arterial thrombosis (including MedDRA® Preferred Terms like myocardial infarction, transient ischemic attack), venous thrombosis, pulmonary embolism or unspecified thrombosis, latency period, outcome of the reaction, treatment of the ADR, delay between the first symptoms and diagnosis of the ADR, presence of risk factors including smoking and Factor-V-Leiden deficiency.

Results: On April 3, 2013 Lareb had received a total of 621 reports about cyproterone/ethinylestradiol, including 309 reports of thromboembolic ADRs which were further analysed. Reported ADRs consisted of arterial thrombosis (N = 52), venous thrombosis (N = 40), pulmonary embolism (N = 155) and thrombosis with an unspecified location (N = 128). A total of 299 reports of thromboembolic ADRs were classified as serious, including 18 cases with a fatal outcome. Patient's mean age was 30.5 years and mean BMI was 24.3 kg/m^2. The primary indications for use were acne (N = 147), oral contraceptive (N = 122), hirsutism (N = 10), other (N = 15) or the indication was unknown (N = 15). Of the 309 patients with a thromboembolic ADR, 261 were known to have been treated with anticoagulant drugs. In 31 cases the thromboembolic ADR was initially not recognized as such by either the patient or their healthcare professional. The median time to onset was 2–3 years, however many patients reported a longer latency period. There was no distinction between the time of onset in respect to the reported ADR. No differences in risk factors seem to exist between labeled and off-label indications. In 291 out of 309 reports, the reporter was a consumer.

Conclusions: The reported thromboembolic ADRs are a known risk related to the use of cyproterone/ethinylestradiol, but may be misdiagnosed initially. From the reports that Lareb received it is evident that t off-label use is frequent.

Abstract Code: ISP3488-51

Does Substitution of Brand Name Medications by Generics Differ Between Pharmacotherapeutic Classes? A Population-Based Cohort Study in France

A. Molinier[1], V. Rousseau[1], R. Bourrel[2], L. Valton[3], A. Sommet[1], J.L. Montastruc[1], H. Bagheri[1]

(1) Laboratoire de Pharmacologie Médicale et Clinique, INSERM U1027, Faculté de Médecine, Toulouse, France, (2) Direction Régionale du Service Médical Midi-Pyrénées (CNAMTS), Toulouse, France, (3) Service de Neurologie, CHU, Toulouse, France

Introduction: Substitution of brand name medications by cheaper generic alternatives allows to reduce healthcare costs. For antiepileptic drugs (AEDs), substitution by bioequivalent generics has been linked to reports of loss of seizure control. According to a meta-analysis [1], increase in seizures was only found in observational studies but not in clinical studies. This increase could be probably explained by anxiety of patients (what is called "anticipatory anxiety").

Aim: To measure the proportion of patients switching from generics to branded drugs among users of antiepileptics compared to 2 other pharmacotherapeutic classes (neuroleptics, beta-blockers).

Methods: We performed a prospective observational study of the switchback (i.e. from generic drug back to its branded drug) rates. We conducted a cohort study involving subjects included in the French health insurance system database from January 2009 to November 2012. The maximum follow-up duration was 44 months. Selected patients took the branded drug therapy for 60 days or more during the 90 days preceding the generic substitution. Association with gender, age, treatment characteristics, number of switches between generics, type of prescriber when switching were estimated using Relative Risk. Descriptive statistics and the Cox proportional hazard regressions used SAS 9.3.

Results: 6,964 patients were included in the cohort, 2,176 with antiepileptics, 2,612 with neuroleptics and 2,176 with beta-blockers. Rate of switchback was estimated to 69 % (n = 4,805). Compared with beta-blocker users, adjusted relative risks (RRa) were 1.78 [95 % CI 1.63–1.95] for antiepileptics and 1.03 [0.94–1.13] for neuroleptics. Swichback risk was less important for prescription from general practitioners than from specialists (RRa = 0.91 [0.84–0.98]). Relationships between switchback, patient demographic data and drug characteristics will be discussed.

Conclusions: A higher switchback risk to branded drugs was found among AEDs users compared to beta-blocker (+78 %) or neuroleptic (+72 %) users. These results could reflect a poor acceptance of switching AEDs to generic compounds in France.

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Abstract Code: ISP3489-52

The Impact of Therapeutic Drug Monitoring in Optimizing the Treatment of Tuberculosis

L. Ait Moussa[1], R. Benkirane[1], A. Soulaymani[2], R. Soulaymani Bencheikh[1]

(1) Centre Anti poison et de Pharmacovigilance du Maroc, Rabat, Morocco (2) Faculté des sciences de Kénitra, Morocco

Introduction: Adverse drug reactions (ADRs) to Antituberculosis (AT) drugs are common. It was estimated that between 4 to 5 % patients developed ADRs respectively to isoniazid and Rifampicin [1]. They are variables and are usually mild but sometimes can be severe. Therapeutic drug monitoring (TDM) may be useful to prevent and minimize some ADRs to AT.

Aim: To evaluate the usefulness of therapeutic drug monitoring to prevent and minimize ADRs to AT

Method: We conducted a retrospective analysis of the TDM performed by the laboratory of the Moroccan Poison control and Pharmacovigilance centre (CAPM) between January 2009 and December 2011. The TDM of isoniazid was initiated 3 h after its administration and for rifampicin 2 h after its administration. The TDM was performed by the High performance liquid chromatography. A descriptive analysis of the ADRs to AT was undertaken, then a correlation between ADR and the plasmatic level of drugs was discussed.

Results: The analysis revealed that 73.5 % of the specimens received by the laboratory during this period concerned AT drugs. A total of 96 patients, 62 women and 40 men, experienced an ADR. The mean age of these patients was 46.3± 21.5 years. Liver and biliary disorders represented 64 % of the ADRs described in the patients. The drugs involved include isoniazid, rifampin and pyrazinamide and in some cases ethambutol and streptomycin.

The TDM underlined that a proportion of 61.5 % of isoniazid plasma concentration was higher than the efficient range of 1 to 2 mg/l (n = 52) whereas only 13.3 % of plasma rifampicin concentration were above the efficient range 6–12 mg/l (n = 31). The average doses of isoniazid administered are relatively higher in patients at high concentration. The higher doses of drug, the slow acetylator phenotype, concomitant disease and enzyme induction by rifampicin represented the risk factors identified in patients who developed ADRs to AT.

Conclusion: Several factors can potentiate the occurrence of ADRs to AT. TDM allows individual adjustment of the dose to be taken by the patients in order to minimize the potential risk of ADRs occurrence.

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Abstract Code: ISP3490-44

Risk of Major Bleeding with Dabigatran Versus Active Controls: a Systematic Review and Meta-analysis of Randomised Clinical Trials

S. Antoniazzi[1], D. Berdai[2], V. Conti[3], P. Robinson[4], F. Scaglione[5], S. Radice[1], E. Clementi[1], N. Moore[4], A. Pariente[4], F. Salvo[4]

(1) Department of Biomedical and Clinical Sciences, Unit of Clinical Pharmacology, University Hospital "Luigi Sacco", Università di Milano, Milan, Italy, (2) CHU Bordeaux, Bordeaux, France, (3) Regional Centre for Pharmacovigilance, Lombardy Region, Milan, Italy, (4) Univ Bordeaux, Bordeaux, France, (5) Department of Medical Biotechnology and Translational Medicine, University of Milan, Milan, Italy

Introduction: The direct thrombin inhibitor dabigatran is approved for atrial fibrillation (AF) and for prophylaxis of venous thromboembolism (VTE) as a therapeutic alternative to warfarin and enoxaparin, respectively. The standard dabigatran dose is 300 mg/day for AF and 220 mg/day for VTE. As for other anticoagulants, major bleeding represents a safety issue of this drug. Several meta-analyses have evaluated risk of major bleeding related to dabigatran exposure, but not for both approved indications and according to dose.

Aim: To evaluate major bleeding risk of dabigatran in AF and VTE, stratifying by dose.

Methods: A systematic review and meta-analysis was conducted applying keywords related to *Dabigatran* and *Randomised Controlled Trials* (RCTs) in Medline, SCOPUS, and Cochrane database. Actively controlled RCTs with at least 100 patients treated with dabigatran, administered at doses approved in clinical practice for AF and VTE, and with Oxford–Jadad score $\geq$3, were included in this meta-analysis. Data were extracted independently by two investigators and verified by a third one. The risk ratio (RR) with 95 % confidence intervals (CI) of major bleeding of dabigatran was estimated for each indication, and stratified by dose. The pooled RRs were computed using fixed-effect models and, in case of significant heterogeneity between studies, using random-effect models. Statistical heterogeneity among studies was evaluated using Q statistic, while publication bias was evaluated with funnel plot and Egger's regression test.

Results: Eight trials (34,078 patients) were included in the quantitative analysis. In AF there was a reduced risk of major bleeding for any dabigatran dose compared to warfarin (RR 0.88, 95 % CI 0.78–0.98); in this indication and compared to warfarin a reduced risk was found for dabigatran 220 mg/day (RR 0.81, 95 % CI 0.71–0.94), while no difference was found for standard 300 mg/day dose (RR 0.94, 95 % CI 0.82–1.07). In VTE prophylaxis there was no difference in risk for dabigatran compared to enoxaparin 40 mg/day, both for any dabigatran dose (RR 1.07, 95 % CI 0.72–1.58), and standard 220 mg/day dose (RR 1.31, 95 % CI 0.85–2.02). No evidence of heterogeneity or publication bias was found.

Conclusions: In AF and prophylaxis of VTE the risk of major bleeding at standard doses of dabigatran was not different to that of active comparators.

Abstract Code: ISP3491-45

Temporal Scan Statistics to Detect a Potential Safety Impact of a Contamination during Vaccine Manufacturing: a Simulation Study

O. Mahaux[1], Z. Zeinoun[2], L. Van Holle[2], V. Bauchau[2]

(1) SGS Life Science Services, Mechelen, Belgium, On Behalf of GlaxoSmithKline Vaccines, (2) Vaccines Clinical Safety and Pharmacovigilance, GlaxoSmithKline Vaccines, Wavre, Belgium

Introduction: Product quality issues can result from incidents in the manufacturing process. They may occur at different steps in the manufacturing process. Some may remain unnoticed but could generate adverse reactions in vaccinated individuals; hence the importance of being able to detect such safety problems from spontaneous reports of adverse events post-vaccination.
Aim: To develop signal detection systems related to product quality issues when no information about the lot number is reported or when the variation in quality is not necessarily at the lot level.
Methods: Considering the actual vaccine manufacturing steps, we simulated a contamination incident occurring early in the vaccine manufacturing process by simulating reports of infection within the usage periods of lots originating from contaminated antigen bottles. These reports were added to existing data from the GlaxoSmithKline Vaccines safety database in increasing proportions (10–200 % of all reports associated with these lots in the database). Signal detection was performed using two versions of the temporal scan statistic based on the log likelihood ratio (LLR) [1]: the classic test, which can detect a cluster of events at any time within the total study period, and the prospective test, which only detects active clusters i.e. clusters reaching the end of the study period. We fixed the total study period to 1800 days and the minimal scan window to 30 days. The relative efficiency of the two methods was measured by (1) the minimum percentage of added simulated reports needed to detect a significant cluster including these simulated reports; and (2) the sensitivity and specificity based on the overlap of the detected cluster with the manipulated period (considered here as a gold standard controlled by simulation).
Results: The prospective method detected a significant cluster including all simulated reports when the proportion of simulated reports was only 10 % (LLR = 3.82). With the classic method, the first significant cluster to include the simulated cluster was detected after increasing the proportion to 30 % (LLR = 7.07). Overall, the classic method detected clusters with more specificity but with less sensitivity than the prospective method.
Conclusions: Both methods could be adapted for signal detection. The specificity of the classic method is an advantage because it enables more focused investigations in the manufacturing process. However, the prospective method is preferable because it presents advantages in the early detection of recent clusters.
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Abstract Code: ISP3492-46

Decision of Diane®35 Withdrawal from the Moroccan Market—Reasons and Constraints

L. Alj[1], G. Benabdallah[1], R. Benkirane[1], R. Soulaymani Bencheikh[1]

(1) Centre Anti Poison et de Pharmacovigilance du Maroc, Rabat, Morocco

In January 2013, the French medicines agency announced its plan to suspend the marketing authorization for Diane®35 for acne treatment within three months.

The French medicine agency considered that Diane®35 and its generics carry a risk of thromboembolism which has been well known for many years, while their effectiveness in treating acne was only moderate and alternative treatments for acne are available.

Following this decision, the health authorities in the United Arab Emirates, Kuwait and Oman suspended marketing of Diane®35. Moroccan health authorities also suspended the drug after analyzing its safety profile as well as the risk-benefit balance of maintaining it.

The analysis of the Moroccan pharmacovigilance database revealed one case of galactorrhea related to Diane®35. The lack of data in our database highlights the under reporting issue within pharmacovigilance centres. Thus, it is likely that adverse drug reactions "ADRs" occurred but were not reported to our pharmacovigilance centre.

In our context, we noticed that Diane®35 is widely used off-label as a contraceptive through self medication. Maintaining this drug might, hence, expose Moroccan women to higher ADRs risk due to an off label use. In addition, women using Diane®35 through self medication might have clinical conditions for which the drug is contraindicated. Other risk factors could increase venous thromboembolism occurrence.

The decision was also influenced by the wide media coverage of drug's withdrawal in France. As a result, women's reaction using Diane®35 revealed that the medicine would not anymore be used even with approved indications.

The decision of withdrawing Diane®35 from the Moroccan market was mainly a preventive action rather than a fully informed one. This situation showed once again the paramount importance of reporting ADRs to pharmacovigilance centres to help them make well informed decisions based on comprehensive ADRs data. A strong regulation could help achieve this objective.

Abstract Code: ISP3493-47

Active Pharmacovigilance of Artemisinin-Based Combination Therapies in Benin

A.C. Allabi[1], D. Kanmandozo[1], A. Massougbodji[2]

(1) Unité de Pharmacologie, FSS, UAC, Cotonou, Benin, (2) Unité de Parasitologie, FSS, UAC, Cotonou, Benin

Artemisinin-based Combination Therapies are widely prescribed in endemic countries to treat uncomplicated malaria. The widespread prescription of these new drugs requires the implementation of a monitoring system for their safety in a real-life prescription. The present study aims to contribute to evaluate the safety profile of Artemisinin-based Combination Therapies including Artemether-Lumefantrine, Artesunate-Amodiaquine and Dihydroartemisinine-Piperaquine in the health district of Cotonou in Benin and to use the results for strengthening the national pharmacovigilance system of Benin. It is a prospective, observational study of active pharmacovigilance held from June to August 2011 in Cotonou. Among the three Artemisinin-based Combination Therapies studied, Artemether-Lumefantrine is the most prescribed. The frequency of patients in whom the diagnosis was biologically confirmed before applying Artemisinin-based Combination Therapy was 57.5 %. The frequency of patients with at least one Adverse Event was 14 %. Main Adverse Events are represented by digestive (3.5 %), neurological (2.5 %) and general (2 %) symptoms. Treatment failures are the only serious Adverse Events reported by patients. All treatment failures are experienced by patients

under Artemether-Lumefantrine, with an overall incidence of 3.82 with 3.18 % for Early Treatment Failures. The implementation of pharmacovigilance is a challenging for Benin. But the implementation of this study and preliminary results obtained demonstrate its feasibility. The occurrence of a considerable number of treatment failures under Artemether-Lumefantrine requires periodic assessment of the effectiveness of Artemisinin-based Combination Therapy in Benin.

Abstract Code: ISP3494-48

The Positive Impact of Pharmacovigilance Integration in the HIV/AIDS Program

H. Farouk[1], R. Benkirane[1], R. Soulaymani Bencheikh[1]

(1) Centre Anti Poison et de Pharmacovigilance du Maroc, Rabat, Morocco

Background: Data on adverse drug reactions "ARDs" related to antiretroviral drugs "ART" in public health program are few, indicating the need for ART safety surveillance in clinical care. In Morocco, the integration of pharmacovigilance HIV/AIDS program started in 2012 with the support of the global fund.
Objective: To evaluate the impact of pharmacovigilance integration in HIV/AIDS program on the ADR reporting rate.
Method: Descriptive analysis of the rate of ADRs in relation to ART registered in the Moroccan pharmacovigilance Database before and after implementing pharmacovigilance in VIH/AIDS program.
Results: From 2007 to 2011, 17 adverse drug events were reported. It concerned essentially skin (45. 6 %) and hepatobiliary (37.5 %) adverse reactions. About one third of these reactions were "serious" (35.1 %) leading to the interruption of the medication (s) suspected (s) in (82.1 %). The evolution was favourable in 95 %.

After the pharmacovigilance integration in HIV/AIDS program, 395 adverse effects were reported. The hematological and neurological side effects are the most common reactions registered with respective (35.4 %) and (30.4 %) frequencies. The nucleoside and nucleotide reverse transcriptase inhibitors were the top drugs incriminated (59.8 %) followed by the combination therapy (23.6 %).the Serious ADRs requiring hospitalization accounted for 89 % and (11.33 %) have sequelae and two deaths.
Conclusion: The adverse drug reactions were for the most reported in the literature. However, their frequency and their seriousness underline the interest of a post marketing monitoring to reassess the drugs risk-benefit balance.

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How Logistic Regression Can Combine the Two Causality Criteria of Strength of Association and Temporality into a Signal Detection Method

L. Van Holle[1], V. Bauchau[1]

(1) Vaccine Clinical Safety and Pharmacovigilance, GlaxoSmithKline Vaccines, Wavre, Belgium

Background: In spontaneous report databases, safety signals can be detected for vaccine-event pairs presenting a number of reports higher than expected (disproportionate reporting) [1, 2]. Safety signals can also be detected when the time-to-onset (TTO) distribution of a vaccine-event pair deviates from the expected pattern of reported TTO within a given time period. In this TTO method [3], a first Kolmogorov–Smirnov (KS) test compares the TTO distribution of a vaccine-event pair of interest with the distribution for the same event following other immunizations for a "between vaccines" comparison (KS_{BV}); a second KS test compares the TTO distribution of a vaccine-event pair of interest with the distribution for events, other than the one of interest, following immunization with the same vaccine (a "between events" comparison, KS_{BE}). Disproportionality and time-to-onset methods are complementary tools, quantifying two causality criteria: the strength of association and temporality [4].
Objective: To evaluate the use of logistic regression to weight the quantified causality criteria based on spontaneous report data, to predict the probability of a vaccine-event pair being an adverse reaction (AR).
Methods: We used the GlaxoSmithKline vaccine spontaneous report database and derived proportional reporting ratio estimates (PRR_E), the 95 % lower confidence limits (PRR_{LL}) and p-values for the two KS tests within a time period of 60 days following immunization. We subsequently selected eight vaccines and used their listed events as proxies for ARs. Three different logistic regressions modelling ARs were built: model 1, based only on PRR_E and PRR_{LL}; model 2, based only on the two KS test p-values and model 3 based on PRR_E, PRR_{LL} and KS test p-values. The performance measures of fit statistics, explained variability (Nagelkerke R^2), calibration (Hosmer–Lemeshow test) and discrimination (c statistic) were measured on 100 bootstrap samples for reducing bias in the measure of performance [5].
Results: Model 3, which uses two causality criteria, provided the best model for predicting ARs, for all performance aspects. The p-value of the "between vaccines" KS test was the most significant factor. Model 1, based only on disproportionality measure, had the poorest model performance.
Conclusions: Within the scope of this study, the most significant causality criterion was the unexpectedness of the TTO distribution quantified by a "between vaccines" KS test. The logistic regression framework allowed the weighting of two quantified causality criteria for estimating the probability of a vaccine-event pair being an AR. As such, logistic regression could play a role in the pharmacovigilance toolkit.

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Abstract Code: ISP3496-50

Tyrosine Kinase Inhibitors—Associated Ischemic Events in Patients Treated for Chronic Myeloid Leukemia

P. Quillet[1], D. Bourneau-Martin[1], G. Drablier[1], L. Lagarce[1], P. Lainé[1], R. Pharmacovigilance Centers[2]

(1) Pharmacovigilance, University College Hospital of Angers, France, (2) French Pharmacovigilance Network, France

Introduction: Chronic myeloid leukemia (CML) has long been associated with poor prognosis. Since early 2000s, the development of tyrosine kinase inhibitors (TKI) has dramatically improved the survival of patients. However, while imatinib is an older and better known drug, knowledge about the second generation of TKI dasatinib and nilotinib is more limited. Among post-marketing surveys, ischemic events (IE), including myocardial infarction and arteriosclerosis, have been reported with nilotinib. Therefore, we decided to study the IE reported with imatinib, dasatinib and nilotinib, since their introduction into France.
Objectives: Compare the reporting rate of IE between the three TKI.
Methods: We performed an analysis of IE reported in the French Pharmacovigilance database with imatinib, dasatinib and nilotinib prescribed to treat CML, from Nov. 7, 2001 to Dec. 31, 2012. We used the Fisher's exact test to compare the reporting rates.
Results: (1) Coronary IE represent 6.3 % of adverse effects reported with nilotinib (median time of onset lower than 1 year). They affect only men with cardiovascular risk factors. These events are less reported with imatinib and dasatinib ($p < 0.001$) and occur later (median time of 3 and 6 years). (2) Peripheral IE, mainly represented by the peripheral artery occlusive disease (PAOD), represent 7.2 % of adverse effects reported with nilotinib. The notification of peripheral IE is respectively 6 and 8 times less common with dasatinib and imatinib ($p < 0.001$). These events affect both men and women, without known risk factor in a third of cases. (3) Cerebral IE are more rare (0.3 to 1.2 %) and the reporting rate is statistically independent from treatment ($p = 0.198$). (4) The reporting rate of all IE is statistically higher with nilotinib ($p < 0.001$) (Table 1).
Conclusion: Comparatively with imatinib and dasatinib, this study suggests an association between IE and nilotinib treatment, especially for coronary and peripheral IE.
Discussion: Two mechanisms are suggested to explain the rate of IE reported with nilotinib: (1) metabolic disorders promoting the formation of atherosclerotic plaques, (2) inhibitory activity on the hERG potassium channel promoting the coronary vasoconstrictor effect. Thus, careful monitoring of patients treated with nilotinib, especially with cardiovascular risk, should be recommended pending further pharmaco-epidemiological studies.

Table 1

	Imatinib	Dasatinib	Nilotinib
Angina	1	0	1
Acute coronary syndrome	0	0	2
Myocardial infarction	3	2	4
PAOD	0	1	6
Peripheral ischemia	4	1	2
Raynaud's disease	2	0	0
Transient ischemic attack	0	2	0
Ischemic stroke	2	0	1
IE/total adverse effects	12/669 = 1.8 %	6/161 = 3.7 %	16/111 = 14.4 %

Abstract Code: ISP3497-51

Epidemiological Characteristics of Stevens–Johnson Syndrome to Drug: A Retrospective Analysis of the Moroccan Pharmacovigilance Centre

S. Belamaalem[1], R. Ouled Errkhis[2], A. Tebaa[2], A. Khadmaoui[1], A. Soulaymani[1], R. Benkirane[2], R. Soulaymani Bencheikh[2]

(1) Laboratory of Genetics and Biometry, Faculty of Sciences, University IbnTofail, Kenitra, Morocco, (2) Centre antipoison et de Pharmacovigilance, Rabat, Morocco

Background: The Steven Johnson Syndrome (SJS) is among the most serious cutaneous adverse drug reaction. The average reported mortality rate for SJS is varying between 1 to 5 % [1]. Prevention of this pathotology requires knowledge of drugs involved and better management of risk factors.
Aim: To describe the SJS cases reported to the Moroccan Pharmacovigilance Centre in order to ascertain the therapeutic classes most involved.
Methods: Retrospective analysis of the Moroccan Pharmacovigilance center database from January 2010 to December, 2012.
Results: During this period, 23 SJS cases have been reported. This represents 2 % of all cutaneous adverse drug reactions collected during this period and 9.5 % of serious adverse drug reactions. The average age of the patients was 45.1 ± 15.3 years. The sex ratio (F/M) was 2.2 with a highly significant difference ($P < 0.001$) for females with χ^2 (5 %): 89. The highest SJS rate (83 %) was found in the adult age group, and the lowest SJS rate was found in children (6 %). The most involved drugs include allopurinol (21 %), ethambutol (5 %), paracetamol (5 %), recombined isoniazid/rifampicin (5 %), sulfamethoxazole associated with trimethoprim (5 %) and pyrazinamide (5 %). 60.9 % of patients had taken one drug. Polymedication was noticed in 39.1 % of the cases (44.4 % two drugs, 55.6 % more than 2). The median time to onset after drug therapy was 18.4 days, with a range from 1 day to 63 days. The hospitalisation rate was in 95 % cases. The Causality assessment according to the WHO method revealed that the relationship was scored in 62 % as "probable" and in 38 % cases as "possible". The outcome was favourable in 86 % of the cases, fatal in 5 % and unspecified in 9 % of cases.
Conclusion: In the light of this analysis, we found that allopurinol was the top drug associated to SJS (with 8 exposed patients). This is in concordance with the literature [1].

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Abstract Code: ISP3498-52

A Case-Series of Metformin-Associated Lactic Acidosis in the German Spontaneous Reporting System–Time to Remember This Serious ADR!

T. Stammschulte[1], J. Spranger[2], A. Daul[3], U. Gundert-Remy[1]

(1) Drug Commission of the German Medical Association (DCGMA), Berlin, Germany, (2) Department of Endocrinology, Diabetes and Nutrition, Charité-Universitätsmedizin, Berlin, Germany, (3) Clinic for Nephrology and Dialysis, St. Marien-Hospital, Mülheim, Germany

Background: Metformin is the first-line drug in the treatment of type 2 diabetes mellitus. In Germany prescriptions have increased substantially since 1990, with the highest rates of increase in patients >75 years. A concomitant increase of spontaneous reports of metformin-associated lactic acidosis (MALA) since 1990, with a cluster in 2012, has prompted us to reassess reports from recent years.
Objective: To investigate patient characteristics, outcome and possible risk factors in spontaneous reports of MALA.
Methods: We included cases from the German spontaneous reporting database from 2001–2012 with available original reporting documents (report form, medical letters, laboratory findings). We reviewed data on patient characteristics, medical history, laboratory findings and outcome.
Results: 99 of 221 reports of MALA were eligible. 5 reports were excluded because neither pH nor serum lactate was documented, or pH was >7.35. Table 1 displays the clinical characteristics of the remaining 94 cases.

Table 1

No. of cases	94
Sex	34 m/60 f
Mean age (range)	71.7 years (50–87)
Mean BMI (range)	30.3 (16–67)
Medical history	Hypertension 63 (67.0 %)
	Coronary artery disease 20 (21.3 %)
	Cerebrovascular disease 10 (10.6 %)
	Peripheral artery disease 8 (8.5 %)
	Chronic heart failure 24 (25.5 %)
	Chronic renal failure 26 (27.7 %)

78 patients had acute renal failure (ARF) at diagnosis of MALA (mean serum creatinine 7.7 mg/dl); most commonly (n = 25) caused by dehydration due to gastrointestinal symptoms (vomiting, diarrhea). In 47 patients (50 %) concomitant cardiovascular diseases other than hypertension were reported (Table 1). 28 patients (29.8 %) also took other antidiabetes drugs including insulin (7) and exenatide (1). Mean serum pH was 6.93 (range 6.5–7.35), serum lactate 15.7 mmol/l (3.4–34). In 22 cases serum metformin concentration was available and highly elevated (mean 38.4 mg/l, therapeutic range 0.1–1.3 mg/l). Renal replacement therapy was performed in 59 (63 %) cases. 44 patients (46.8 %) died.
Discussion: Our data suggest that an age above 70 years and concomitant cardiovascular or renal disease are risk factors. We cannot clearly distinguish between vomiting/diarrhea as a cause for dehydration inducing MALA or a symptom of beginning lactic acidosis. Nevertheless gastroenteritis in elderly patients treated with metformin should be considered as a potential risk factor for MALA. Regular monitoring and informing of patients and caregivers about the risks of metformin in acute illness seems crucial, especially in patients at high risk of renal function deterioration.

Abstract Code: ISP3499-53

Management of Medication Errors Associated with the Use of Delivery Devices for Orally Ingested Liquid Drugs—The French Drug Agency

M. Dahani[1], D. Durand[1], F. Cardona[1], P. Maison[1], E. Falip[1]

(1) French National Drug and Health Products Safety Agency (ANSM), Saint Denis, France

Introduction: The French Agency (ANSM) has set up in 2005 a department to collect and manage medication errors or potential errors related to medicinal products, and perform the follow up of those likely to present a Public Health risk. The "Medication errors' Guichet" enables healthcare professionals and patients to report medication errors (ME) without adverse effect (AE) or near misses, in addition of reports with AE collected through the Pharmacovigilance System. In 2011 and 2012, respectively 1734 and 1589 ME have been collected.
Aim: To quantify and analyse medication errors due to the use of Delivery Devices (DD) and establish recommendations to reduce this risk.
Methods: We performed a retrospective analyse of medication errors (risk, near misses and patent) reported in the ANSM medication error database for the period of May 2005 to February 2013.
Results: 26 reports of risk of ME and 109 reports of patent errors resulting in patient administration associated with the use of DD for orally ingested liquid drug products have been identified. Of the 109 errors:

- 46 % without an AE, 37 % with AE (half serious), 17 % with no available information.
- 94 % of the patients belong to the paediatric population, 4 % were adults, age unknown in 2 %
- 85 % occurred at home, 10 % in hospitals, 5 % with no available information.

Two major causes of errors were identified: those directly attributable to DD (e.g. DD deficiency, lack of drugname on DD, inappropriate measure for low dosages, different units between leaflet or prescriptions and DD etc.), the others attributable to human errors of utilization (e.g. drug given with DD from an other drug, DD provided not used, inadequate doses taken by habits etc.)

Some of these reports led in the past to corrective measures on a case by case basis at the request of ANSM, e.g. adding a DD when none was available, adding table of equivalence or warnings in the SPC, labelling and leaflet etc.
Conclusion: This analyse highlights that given the number of specialities involved and the number of reports, implementing general measures to minimize this kind of medication errors is essential.

ANSM decided in accordance with the medication errors working group to set up minimization risk measures including:

- Recommendation to MAH for safer DD
- Communication to healthcare professionals highlighting the risk of medication error related to DD
- Educational materials for patients and caregivers to raise awareness concerning this issue.

Abstract Code: ISP3500-36

Aminoglycosides and Ageing: Still an Issue? A Prospective Monocentric Survey

S. Dinane[1], C. Woloch[2], V. Poinsignon[2], K. Maley[3], C. Minozzi[4], S. Kernéis[5], A. Novara[6], A. Guinvarch[7], A. Lillo-Le Louet[1], E. Billaud[8]

(1) Pharmacovigilance, Hôpitaux Universitaires Paris Ouest, AP-HP, Paris, France, (2) Pharmacologie, Hôpitaux Universitaires Paris Ouest, AP-HP, Paris, France (3) Gériatrie, Hôpitaux Universitaires Paris Ouest, AP-HP, Paris, France, (4) Hygiène Hospitalière, Hôpitaux Universitaires Paris Ouest, AP-HP, Paris, France, (5) Unité mobile de Microbiologie clinique, Hôpitaux Universitaires Paris Ouest, AP-HP, Paris, France, (6) Réanimation Médicale, Hôpitaux Universitaires Paris Ouest, AP-HP, Paris, France, (7) Réanimation Chirurgicale, Hôpitaux Universitaires Paris Ouest, AP-HP, Paris, France, (8) Pharmacologie, Hôpitaux Universitaires Paris Ouest, AP-HP, Paris, France

Introduction: A pluridisciplinary morbidity-mortality review was initiated in our centre, following cases of adverse drug reaction related with aminoglycosides use, with one fatal issue in an elderly patient. The French recommendation for aminoglycosides favours a once daily dosing for these concentration-dependant antibiotics (Cmax/mic >8) in Gram-infections*. Due to both renal elimination and nephrotoxicity, the achievement of non-detectable residual concentration has to be evaluated, especially in elderly patients and/or kidney failure.

Aim: The aim of our study was to update our local recommendations to improve aminoglycosides' prescription, therapeutic drug monitoring and patients care.

Methods: A prospective non-interventional survey was carried out to describe aminoglycosides use in all patients treated by gentamicin(G), amikacin(A) and tobramycin during July 2012, together with pharmacokinetic profile (peak and trough immunoassay concentrations) in elderly (aged over 80 years) and/or intensive care patients over a 6 months period.

Results: In 2169 hospitalized patients, 129 (5 %) had received aminoglycosides. Main sites of infections were pulmonary (26 %), bacteraemia (16 %) and surgical site infection (15 %). Acquisitions were mostly nosocomial (55 %) and healthcare-associated infection (31 %), few community-acquired infections (9 %) and some without infection (5 %). Aminoglycosides were prescribed for identified infection (53 %), empiric therapy (43 %) and prophylaxis (4 %).

80 % had a renal function follow up: 30 % already had a renal failure. 18 % worsened their renal function (2/3 pre-existing renal impairment), therefore 1/3 needed dialysis. 2 % had a change in dosage and/or modification of the administration scheme.

93 % of patients received a once daily dose: 40 % on a 30 min drip in accordance with recommendations, 30 % were still in 1 h drip (30 % unknown).

Pharmacokinetics was documented in 31 A and 23 G first administrations, and in respectively 8 and 8 elderly patients. Peak endpoints were more easily achieved, even in ICU, for A (75 % >60 mg/L) than G (19 %), in agreement with recommended G targets at 32–40 mg/L established for *Pseudomonas* and not achievable with the recommended 3–8 mg/kg/day. However peak G >15 mg/L acceptable for other species was achieved in 84 %. On the contrary, reinfusion at 24 h (35 %/A; 19 %/G) was usually not possible in ICU and elderly due to impairment of renal function.

Conclusion: No further dose of aminoglycoside should be administrated until undetectable residual concentration, especially in elderly en/or in patients with renal failure. Even mild increase in residual level should be considered as a surrogate for renal failure installation. Systematic early prescription of residual dosages is to be improved in common practices in these patients.

Abstract Code: ISP3501-37

Management of Medication Errors Associated with the Intrathecal Administration Instead of Intravenous Administration at the French Agency (ANSM)

N. Martin-Brisac[1], N. Grene-Lerouge[1], F. Cardona[1], P. Maison[1], E. Falip[1]

(1) French National Drug and Health Products Safety Agency (ANSM), Saint Denis, France

Introduction: The French Agency (ANSM) has set up in 2005 a department to collect and manage medication errors or potential errors related to medicinal products, and perform the follow up of those likely to present a Public Health risk. The "Medication errors' Guichet" enables healthcare professionals and patients to report medication errors (ME) without adverse effect (AE) or near misses, in addition of reports with AE collected through the Pharmacovigilance System. In 2011 and 2012, respectively 1734 and 1589 ME have been collected.

Aim: Following errors due to intrathecal administration instead of intravenous administration, ANSM has already published recommendations for a safe administration of vinca alkaloid in 2007 and 2009.

The aim of this study is to quantify and analyse ME due to this type of error and establish recommendations to avoid this risk.

Methods: A request in the French Pharmacovigilance Database was performed on 11 April 2013 on all cases reporting a drug (suspect or interaction) administered by intrathecal route, during the period from January 1985 to 10 April 2013. Then, a retrospective analysis was made.

Results: 28 reports of patent errors resulting in inadvertent administration by intrathecal route instead of intravenous route were retrieved, including:

- 33 % during a chemotherapy protocol, 21 % during rachianesthesy, 21 % during myelography, 11 % in patient with external ventricular drains. No information was available for the 14 % remaining cases.
- 100 % lead to an adverse effect, 96 % were serious and 4 % no serious.
- 39 % (n = 11) of the cases had a fatal outcome (100 % for errors during a chemotherapy protocol)

On the basis of those cases, three main situations were observed:

1. during chemotherapy when an intravenous drug (vinca-alcaloid for example) is associated with an intrathecal drug (methotrexate or cytarabine, for example)
2. IV medication administered in the tubing of external ventricular drains.
3. Confusion of the drug selected (Hexabrix® instead of Omnipaque®)

Conclusion: This analysis highlights that given the number of fatal issue due to inadvertent intrathecal administration, implementing general recommendations to minimize these medication errors is essential. Furthermore, this error belongs to the French "Never Events" list.

ANSM decided in accordance with the medication errors working group to set up minimization risk measures including:

- General recommendation for all intrathecal drugs,
- Communication(s) to healthcare professionals highlighting this risk of medication error

Abstract Code: ISP3502-38

Modelling Relative Rates of Hospitalisation for Febrile Convulsions and Severe Varicella Under Combined MMRV Compared to Separate MMR+V Vaccination

V. Bauchau[1], L. Van Holle[1], C. Cohen[1]

(1) GlaxoSmithKline Vaccines, Wavre, Belgium

Background: Compared to separate MMR (Measles, Mumps, Rubella) and V (Varicella) injections, quadrivalent MMRV vaccines increase convenience and compliance of vaccination. Febrile convulsions (FC) were previously known to be triggered by fever in the first 2 weeks after MMR vaccination. Recent studies have also shown that the risk of

developing FC within 5–12 days post vaccination in children was about two times higher when vaccinated with MMRV as a first dose of measles-containing vaccine compared to separate injections for MMR and V. Therefore in a population vaccinated with MMRV there will be a number of additional cases of FC compared to a population vaccinated with MMR (+/−V) and a proportion of these will be hospitalised. On the other hand, use of combination vaccines has been shown to increase vaccination coverage. In a vaccination program utilising MMR+V (separate injections), some children will receive MMR but not V and will therefore be at risk of developing varicella later in life, in some cases with severe consequences leading to hospitalisation.

Objectives: To estimate and compare the relative number of hospitalisation days for FC and severe varicella under combined MMRV compared to separate MMR and V vaccination.

Methods: We developed a model and sensitivity analysis to integrate parameters from various sources. Hospitalisation duration was chosen as a proxy for the most significant burden of both FC and varicella infection.

Results: For parameter values compatible with Germany, where MMRV was introduced in 2006, the model suggests that transitioning from MMR+V to MMRV for the first dose of measles-containing vaccine would reduce the cumulated total number of hospitalisation days: although there may be an additional 180 days of hospitalisation from vaccine-related FC, close to 2,000 hospitalisation days due to severe varicella could be averted per year in this country. Expected outcome in other countries and other situations can be derived from the sensitivity analysis based on their respective vaccination coverage and hospitalisation probabilities.

Conclusions: The model suggests that the use of MMRV instead of MMR+V may substantially reduce the number of hospitalisations despite the observed increased risk of FC when MMRV is used as a first dose of measles-containing vaccine. This is one of the trade-offs between the two vaccination schemes that needs to be considered when making decisions on their use in immunisation programs.

Abstract Code: ISP3503-39

Compliance with Pregnancy Prevention Recommendations and Pregnancy Outcomes in 7406 Women of Reproductive Age: Case of the Highly Teratogenic Acitretin

F. Raguideau[1], M. Mezzarobba[2], M. Zureik[1], A. Weill[2], P. Ricordeau[2], F. Alla[2], H. Allemand[2]

(1) Agence nationale de sécurité du médicament et des produits de santé, Saint-Denis, France, (2) Caisse nationale de l'assurance maladie des travailleurs salariés, Paris, France

Background: Acitretin is a retinoid treatment for severe psoriasis. It is teratogenic up to 2 years after treatment cessation. A care and contraception agreement has thus been implemented, as in France, where women must undergo serum pregnancy tests (PT) 3 days before the first drug dispensing (D-3 to D0), every 2 months during treatment and regularly during the 2 years following treatment cessation.

Aim: To assess compliance with the acitretin French recommendations in a cohort of women of reproductive age initiating acitretin therapy, by estimating (1) the rate of serum PT, (2) the rates and outcomes of pregnancy.

Methods: Using SNIIRAM (reimbursement data) and PMSI (hospitalisations) French databases, a cohort of fertile women aged 15–49 years initiating an acitretin treatment in January 2007–September 2012 was identified. Women were monitored up to 2 years after treatment cessation, end-September 2012, death, hysterectomy or bilateral oophorectomy, whichever came first. Pregnancies were identified based on hospitalisations and medical abortion outpatients. The pregnancy outcomes assessed in 2007–2011 were deliveries or abortion or ectopic pregnancies. Reimbursed serum or urine PT were used to assess the rate of PT.

Results: From 2007 to September 2012, 7406 women, mean age 39.5 years (±8.3) were newly prescribed an acitretin treatment. Only 11 % of women underwent PT during the recommended period i.e.: between D-3 to D0 (21 % between D-10 and D+3, 18 % between D-7 and D+3). About 65 % of women under treatment never had a PT and this rate reached 78 % of women in the 2 years after treatment cessation.

From 2007 to 2011, of the 6461 women included, 271 pregnancies were identified, an incident pregnancy rate of 2.4 per 100 person-years considered at teratogenic risk. For these 271 pregnancies the last acitretin reimbursement was recorded: during pregnancy in 45 cases, during the four last months before the pregnancy in 63 cases and between one and 2 years before pregnancy in 74 cases; 157 pregnancies occurred in women with only one acitretin reimbursement.

Of the 271 pregnancies, 157 resulted in childbirth (58 %) with one stillborn baby, 106 had a medical or spontaneous abortion (39 %) and eight ectopic pregnancies (3 %).

Conclusion: This real-life study showed that the pregnancy prevention recommendations in France for acitretin treatment were not complied. It is vital that physicians, pharmacists and patients are alert to the risks of acitretin use. New stricter restrictions on prescribing and dispensing were implemented in October 2012 and their impact will have to be assessed.

Abstract Code: ISP3504-40

Causality of Drugs Involved in Acute Liver Failure Leading to Transplantation: Results from SALT Study (Study of Acute Liver Transplant)

S.E. Gulmez[1], N. Moore[1], G. Pageaux[2], S. Lignot[1], Y. Horsmans[3], B. Stricker[4], J. Bernuau[5], F. Bissoli[6], D. Thorburn[7], J. Montastruc[8], S. Micon[1], F. Hamoud[1], R. Lassalle[1], J. Jové[1], P. Blin[1], D. Larrey[2]

(1) Department of Pharmacology, University of Bordeaux, Bordeaux, France, (2) CHU Hôpital Saint-Eloi, INSERM1040-IRB, Montpellier, France, (3) Département d'Hépatogastroentérologie, Bruxelles, Université Catholique de Louvain, Belgium, (4) Department of Epidemiology, Erasmus Medical Centre, Rotterdam, The Netherlands, (5) Hepatology Department, Beaujon Hospital, Clichy, France, (6) Department of Internal Medicine and Cardiology, Clinica San Gaudenzio, Novara, Italy, (7) Liver Transplantation Hepatobilliary Unit, Royal Free Hampstead NHS Trust, London, UK, (8) Pharmacologie médicale et clinique, Faculté de Médecine de Toulouse, INSERM 1027, Toulouse, France

Background: Several methods have been proposed to assess causality in drug-induced liver injury but none have been tested in the specific context of acute liver failure leading to transplantation (ALFT).

Objectives: We took the advantage of SALT (Study of Acute Liver Transplant), a European case-population study of ALFT, to test different causality scales.

Methods: Causality was assessed by experts in SALT, a 7-country case-population study from 2005 to 2007 of adult otherwise unexplained ALFT, for all drugs found within 30 days prior to the date of initial symptoms of liver disease (index date), using information content, causality scales and data circuit determined from a pilot study, Salome.

Results: The consensus points from Salome were to provide full data on drugs including INN and doses except for NSAIDs and to use the WHO causality scale. In SALT, among the 9479 identified patients, 600 (6.3 %) were cases of ALFT, of which 187 had been exposed to drugs within 30 days, without overdose. In 130 (69.5 %) of these the causality score was *possible*, *probable* or *highly probable*.
Conclusion: In ALFT cases, once other clinical causes have been excluded and drug exposure established within 30 days, the main discriminant characteristic for causality will be previous knowledge of possible hepatotoxicity.

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Abstract Code: ISP3505-41

Knowledge Based Method for Automated Generation of New MedDRA Groupings

C. Bousquet[1], G. Declerck[2], J. Souvignet[1], M.C. Jaulent[2]

(1) Département de Santé publique et information médicale, Université de Saint Etienne, Saint Etienne, France, (2) INSERM U872, Eq 20, Centre de Recherche des Cordeliers, Paris, France

Introduction: MedDRA preferred terms can be grouped in High level terms or Standardized MedDRA Queries (SMQ) [1]. These groups of terms aim to define medical conditions and are intended to support retrieval of case reports in pharmacovigilance databases. But these groupings do not cover all drug related medical conditions or may not have the required specificity.
Objective: To implement a knowledge-based method in order to support the generation of new groupings of MedDRA terms.
Methods: We developed a semantic model of adverse drug reactions (OntoADR). As reference grouping, we manually selected terms related to the upper part of the gastrointestinal tract from the 'Gastrointestinal hemorrhage' SMQ (27 out of 50). We then defined these terms using the web ontology language (OWL-DL). Two queries were developed to match the reference grouping.

Query 1:
hasFindingSite some 'Upper gastrointestinal tract structure'
AND *hasAssociatedMorphology* some 'Hemorrhage'
Query 2:
interprets some 'Evaluation of stool specimen'
AND *hasAssociatedMorphology* some 'Hemorrhage'

Results: Table 1 shows the comparison of precision, recall and F-Measure for the different groupings. The best results were observed with Query 1 + 2 versus the reference grouping (RefG).
Conclusion: We already replicated similar results on 'Anaphylactic Shock' and other safety topics [2, 3]. Selecting terms is an important step before performing signal detection in a pharmacovigilance database. Our results demonstrate that this method can efficiently support the realization of automated ADR groupings. This is a promising result, because MedDRA terms groupings for pharmacovigilance (mainly SMQs) are so far achieved manually, and an automation of the process, even partial, could allow an important saving of time.

Table 1

Results of precision, recall and F-measure for each query versus the Upper Gastrointestinal Bleeding reference grouping

	Query 1 vs RefG	Query 1 + 2 vs RefG
Precision	83.3 %	86.2 %
Recall	74.1 %	92.6 %
F-Measure	78.4 %	89.3 %

Acknowledgments: The research was conducted as part of the PROTECT consortium. It has received support from the Innovative Medicine Initiative Joint Undertaking (www.imi.europa.eu).

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Abstract Code: ISP3506-42

Suspension of Anti EGFR Therapy for Skin Toxicity and Reporting of Suspected Adverse Reactions

E. Tenti[1], A. Casadei Gardini[2], I. Stanganelli[3], M. Medri[3]

(1) Pharmacy unit, IRCCS IRST Cancer Center, Meldola, Italy, (2) Medical Oncology Unit, IRCCS IRST Cancer Center, Meldola, Italy, (3) Skin Cancer Unit, IRCCS IRST Cancer Center, Meldola, Italy

Introduction: The targeted therapies are used in the treatment of various malignancies such as non-small cell lung cancer, colorectal cancer, pancreatic cancer, head neck cancer and hepatocellular carcinoma. Among these there are the anti-EGFR (Epidermal Growth Factor Receptor) agents, which are characterized by a particular skin toxicity known as like-acneiform rash. The most frequent localizations of skin lesions are the face, chest and back, and appears a few days after the therapy reaching a peak at 23 weeks and then gradually disappears. Despite the increase in knowledge about the treatment of these toxicities, there is uncertainty about the extent of the severity of the relative toxicity of EGFR [1].
Aim: The aim of this study was to identify the cases of patients who interrupt therapy due to skin toxicity and for which reporting was made with the pharmacovigilance system.
Methods: Adult patients in treatment with cetuximab, panitumumab, gefitinib, erlotinib and sorafenib from 1 December 2012 to 1 May 2013 have been investigated with pharmacy management software database; among these the patients who interrupted treatment for skin toxicity identified in the Common Toxicity Criteria for Adverse Events scale as grade(**G**)2 and G3 have been selected. For these patients the path of pharmacovigilance has been followed and the suspected adverse reaction's form was completed.

Results: In the 6 months period 142 patients have been treated with anti EGFR. Specifically, 37.3 % had a first-line treatment, 41.5 % second-line, 17.6 % third-line and 2.8 % fourth-line. 8.5 % of the patients had skin toxicity of grade 2 and 1.4 % of patients interrupted treatment due to grade 3 toxicity. In particular, the two patients who had toxicity G3 were doing, respectively, a treatment of II-line with erlotinib and a treatment of IV-line with cetuximab. For both cases it there has been an improvement in the outcome of skin toxicity. Number 14 forms of suspected adverse drug reaction (ADR) have been completed and included in the national network of pharmacovigilance

Conclusions: Dermal toxicity is an important critical factor in the course of therapy with anti EGFR and its management is very important for the well being of the patient. The pharmacovigilance activities and the monitoring of toxicity data of drugs so it is important for the effectiveness of any measures.

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Abstract Code: ISP3507-43

Electronic Platform Supporting Implementation of Additional Risk Minimization Measure: Assessing Success and Penetration

S.T. Kaehler[1], J. Freeman[2], R. Bwire

(1) Celgene Europe Limited, Uxbridge, UK, (2) Celgene Corporation, Summit, NJ, USA

At the beginning of 2013 an electronic solution was implemented in an EU country, replacing a paper based additional risk minimization measure that was in place for the previous 5 years to support the thalidomide and lenalidomide Pregnancy Prevention Programs (PPP). The main objective of the implementation of an electronic solution was to improve adherence of participants to the PPP requirements and to reduce the paper work burden. The development of such an electronic solution needs to involve all stakeholders. Adequate Business Requirements for the electronic solution must be developed and success rates defined. How can the success rate of an electronic solution for additional risk minimization measures be defined?

To measure success we utilized two concepts—the basic mandatory requirement and the added value that is uniquely attributable to the electronic component, examined the following factors were taken into consideration. The mandatory part refers to the requirement as stipulated in the conditions and obligations of the marketing authorization. Success in the mandatory part requirement is reflected through an increase in compliance and data quality (completeness, consistency and plausibility). The added value part success is reflected in reduced burden in paper work for the participants and should result in increased time for patient communication and reduction in the number of contacts due to incomplete, inconsistent or implausible data.

The penetration rate on the other hand can be defined by percent of prescribers and other stakeholders utilizing the electronic system on a day by day basis but also by the number of patients and amount of transactions covered by these prescribers.

Abstract Code: ISP3508-44

Distinguishing Important Identified Risks, Important Potential Risks and Important Missing Information: A Newly Developed Decision Tree

S.T. Kaehler[1], J. Freeman[2], R. Bwire[2]

(1) Celgene Europe Limited, Uxbridge, UK, (2) Celgene Corporation, Summit, NJ, USA

In Europe a new guideline on good pharmacovigilance practices (GVP) 'Module V – Risk Management Systems' was issued and came into effect on 2nd July 2012. The guideline describes in detail the risk management plan, which is a detailed description of the risk management system itself. Managing risks to an active ingredient is a global activity. However, because of differences in authorized indications or pharmaceutical forms the target population may be different across the world and risk minimisation activities will need to be tailored to the particular country or global region. The terms 'identified risk', 'potential risk' and 'missing information' are commonly used in pharmacovigilance and are key concepts in global risk management plans (RMPs) safety concerns.

The term identified risk includes adverse reactions for which there is adequate evidence. For adverse reactions you need an active ingredient (extrinsic moiety) which encounters an intrinsic moiety (i.e receptor) and the outcome is an adverse effect (i.e. immunological response) with a clinical manifestation (adverse reactions: noxious and unintended response). The term potential risk includes adverse events for which there is some basis for suspicion of an association with an extrinsic moiety but which is not confirmed. This means the outcome is an adverse experience (i.e. immunological response) with or without a clinical manifestation (adverse event: noxious and unintended sign).

There are distinct differences between identified and potential risks, and a decision tree to support classification is proposed. This tool should improve harmonization of risk assessment and minimise inter-RMP variability in the presentation of safety concerns. Further, the tool provides factors to take into consideration when re-classifying a risk as more information becomes available during the product's lifecycle.

Abstract Code: ISP3509-45

A Pilot Study on the Feasibility of Using P-Plots for Signal Detection in Pharmacovigilance

M. Hauben[1], C. Zou[2], W. Wang[2], L.H. Zhang[2]

(1) Worldwide Safety and Regulatory, Pfizer Inc., New York, USA, (2) Research and Development, Pfizer Inc., Shanghai, China

Background: Pharmacovigilance signal detection algorithms commonly involve the calculation of observed/expected (O/E) reporting frequencies, ratios or odds calculated from 2×2 contingency tables [1]. Frequentist and Bayesian implementations each have strengths and limitations. No single approach has emerged as universally superior. P-plots are a graphically oriented frequentist statistical methodology based on the distributional properties of p-values as random variables under the null versus alternative hypothesis [2, 3].

Aim: Assess the feasibility/performance of P-plots as a novel signal detection methodology.
Methods: A public release version of US FDA AERs data was analyzed after preprocessing to mitigate duplicate reporting and redundant drug nomenclature. A convenience sample of six pharmacologically/therapeutically diverse drugs was selected. χ^2 and corresponding p-values were calculated for all reported DECs for each drug from the corresponding 2×2 contingency tables. P-value rank was plotted against 1-p. Piecewise regression determined break points in p-plots (transition from null to alternative hypothesis). Alternative hypothesis segments of plots were considered to represent statistical signals.

For each drug 180 drug-event combinations (DECs) were randomly selected and classified by three experienced safety reviewers as reference positive/negative events based on product information and scientific knowledge and judgment. Twenty additional reference positive events were selected/drug.

P-plots were compared to three legacy algorithms/metrics (MGPS, PRR and RR) for the 1200 DECs sampled for testing. For each, multiple performance parameters were calculated: sensitivity, specificity, positive/negative predictive value, F1 score, Matthews correlation coefficient (MCC) and AUC with corresponding confidence intervals calculated via asymptotic formulas and bootstrapping.
Results: Overall P-plots were superior to other algorithms on multiple performance measures including sensitivity, NPV, F1 score, MCC and AUC but demonstrated inferior PPV and specificity.
Conclusions: P-plots may provide an alternative statistical signal detection method. Advantages include simple and graphical rationale and attractive performance characteristics. Prescriptive statements about a preferred algorithm are precluded because of the limited scope of analysis, absence of an accepted calculus of cost and utilities of misclassification errors in pharmacovigilance, and uncertainty that performance gradients in data mining exercises translate to real-world pharmacovigilance.
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Abstract Code: ISP3510-37

Quality of Label Information on QT-Interval Prolongation of Medicinal Products Registered in the EU

M. Warnier[1], F. Holtkamp[2], F. Rutten[3], A. Hoes[3], A. De Boer[1], P. Mol[2], M. De Bruin[1]

(1) Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht University, Utrecht, The Netherlands, (2) Medicines Evaluation Board (CBG-MEB), Utrecht, The Netherlands, (3) Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, The Netherlands

Background: The summary of product characteristics (SPC) is the most important (indirect) source of information for healthcare providers (HCP) to gain information on QT prolonging properties of drugs. However, we have noticed that information regarding QT prolongation varies between different products, which may hamper the uptake of the information.
Objective: To systematically assess the number of products reporting an impact on QT interval in the SPC, and the variation in nature of the observed QT prolonging effect described and recommendations given to the HCP.
Methods: The SPCs of products centrally approved in Europe between 1.1.2006 and 1.5.2012 were screened. Of those mentioning 'QT', we examined in which sections of the SPC 'QT prolongation' was mentioned. The nature of the message on QT prolongation and the advice on cautionary measures related to QT prolongation was examined as well as the relation between both.
Results: Of the 172 screened products, 44 products contained information on QT in the SPC. QT related issues were most commonly reported in section 4.4 (special warnings and precautions, 66 %) and section 4.8 (undesirable effects, 57 %). In almost half of the products, the main message was that either the drug prolongs the QT interval (18 %), or *potentially* prolongs the QT interval (20 %). The SPC contained a negative message (the drug *does not* prolong the QT interval) in 23 % and no clear positive or negative message on QT prolongation in 39 % of the SPCs. Sixty-two percent of the SPCs gave the advice to act with caution in patients with QT related risk factors ($n = 25$), and 16 % explained the association of QT prolongation with ventricular arrhythmias ($n = 27$). The advice on monitoring of patients was given in 34 % of the SPCs ($n = 15$). Products that were more likely to have QT-prolonging properties according to the SPC provided more information on QT prolongation in the SPC.
Conclusion: We observed that products, that were more likely to have QT prolonging properties according to the SPC, provided more information on QT prolongation in the SPC. We advise the development of a more extensive guideline concerning reporting on QT prolonging in SPCs, in order to guide prescribers more clearly.

Abstract Code: ISP3511-38

Does Media Attention Affect Impact of Regulatory Warnings in The Netherlands?

P. Mol[1], V. Damoiseaux[2], K. Reber[3], J. Wieringa[3], S. Straus[4], F. Haaijer-Ruskamp[5]

(1) Clinical Pharmacology, University Medical Center Groningen, Groningen and Dutch Medicines Evaluation Board, Utrecht, The Netherlands, (2) Clinical Pharmacology, University Medical Center Groningen, Groningen, The Netherlands, (3) Marketing, University of Groningen, The Netherlands, (4) Medical Informatics, Erasmus University, Rotterdam, The Netherlands, (5) Clinical Pharmacology, University Medical Center Groningen, The Netherlands

Background: A third of Direct Healthcare Professional Communications (DHPCs) has been shown to have a long-term impact on drug use in the Netherlands. It is suggested that impact of these regulatory warnings may be affected by attention of the lay media, as illustrated by papers on the 'pill scare' and SSRI risks. However, no empirical data are available supporting this assumption for a wider range of drug safety issues.
Objectives: To explore if lay media affect the impact of DHPCs on drug use in the Netherlands.
Methods: DHPCs issued in the Netherlands (2001–2007) and monthly dispensing data (2000–2008) were obtained. Lay media articles (2000–2008) reporting on the drug safety issues communicated in the

DHPCs were retrieved from Lexis Nexis Academic. We performed a multiple linear regression analysis to examine the impact of media attention (number of articles) and as an interaction term the number of articles with a clearly negative tone (3-rater consensus classification of the tone as 1 (very) negative on a 5-point Likert scale that ranged from 1 (very) negative to 5 (very) positive). We corrected for determinants that we earlier showed to be significant determinants for the impact of a DHPC; i.e. specialist drugs, availability of a DHPC template, and DHPCs conveying risk of death or disability. The outcome variable was defined as the relative change in new drug use (change in use/median use 12 months pre DHPC) post DHPC as determined in interrupted time series ARIMA models for each drug and DHPC pair.

Results: In our study period 58 DHPCs for 46 drugs were issued, of which 20 (34.5 %) DHPCs resulted in a mean long-term decrease in drug use of 26.7 % (95 % CI: −15 % to −38 %). Lay media reported on 23 (39.7 %) drug safety issues that were reported in the 58 DHPCs. In those cases a median of 3 (IQR 2 to 9) articles reported on the issue, of which in 40 % (SD39 %) the tone was (very) negative. In the multiple linear regression model lay media coverage was not associated with impact of the DHPC ($p = 0.928$), nor was the number articles with an outspoken negative tone (1 on Likert-scale, $p = 0.830$), nor was the interaction term of the two ($p = 0.872$).

Discussion: In this first systematic evaluation of how lay media coverage affects impact of DHPCs, we found no association between coverage and impact of DHPCs on drug use. Any impact seems limited to high profile cases only.

Abstract Code: ISP3512-39

Bayesian Measures of Signal Detection with Dabigatran in the FDA Database

C. Bousquet[1], J. Souvignet[1], M.N. Beyens[2]

(1) Department of Public Health and Medical Informatics, CHU University of Saint Etienne, Saint Etienne, France; INSERM U872, Eq. 20, Paris, France, (2) Regional Pharmacovigilance Centre, CHU Saint-Etienne, Saint-Etienne, France; EA3065, Research Group on Thrombosis, Jean Monnet University, Saint-Etienne, France

Introduction: Dabigatran is a novel oral anticoagulant prescribed for stroke prevention in patients with atrial fibrillation. Compared to clinical trials haemorrhagic or thromboembolic risk may be higher than in clinical practice, especially in elderly patients with renal failure [1]. The Food and Drug Administration (FDA) approved only a higher dose (150 mg) of dabigatran which is more efficient than the lower dose (110 mg) but causes more bleedings.

Aim: To apply Bayesian measures of signal detection on dabigatran in FDA's Adverse Event Reporting System (AERS) pharmacovigilance database.

Method: We applied the MGPS (Multi-item Gamma-Poisson Shrinker) measure of disproportionality for the period from first-quarter 2004 to third-quarter 2012. We considered the lower limit of the 95 % confidence interval (Empirical Bayes Geometric Mean; EB05 >1, a Bayesian estimate for the ratio of observed versus expected number of cases). Then we compared the proportion of bleedings according to anatomical sites relative to the total number of cases reporting a hemorrhage.

Results: Most adverse drug reactions (ADR) highlighted by MGPS were related to bleeding. When site of bleeding was documented, the most frequent sites were gastrointestinal tract (74.90 %), intracranial (31.83 %), genitourinary (10.50 %), epistaxis (7.33 %), and intrathoracic (5.90 %). Total was superior to 100 % as bleeding could be observed in different sites within the same case report. Dabigatran was reported as non-efficient in several case reports (e.g. embolic stroke, ischemic stroke, cerebral accident or deep vein thrombosis). Myocardial infarction was also observed quantitatively but was not detected as a signal.

Conclusions: Most signals highlighted in the AERS database were bleedings especially a predominance of gastrointestinal bleedings. The FDA reported that "the rate of reported incidents was unusually high and was greater than the concurrent rate of reported bleeding incidents with warfarin" [2]. Such rate may be explained by reporting biases in pharmacovigilance, especially for new drugs (Weber effect). However, one must take into account the possibility that case reports related to dabigatran may describe different situations than clinical trials (possibly older population, major renal failure, or prescription for other indications than atrial fibrillation).

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Abstract Code: ISP3513-40

Medication Related Problems in Cardio-Metabolic Disease Management in Sub-Saharan Africa: A Systematic Review

A. Berhe[1], P. Mol[2], K. Taxis[3]

(1) Pharmacotherapy and Pharmaceutical Care, University of Groningen, The Netherlands and Pharmacy, University of Mekelle, Ethiopia, (2) Clinical Pharmacology, University Medical Center Groningen, The Netherlands, (3) Pharmacotherapy and Pharmaceutical Care, University of Groningen, Groningen, The Netherlands

Background: The burden of cardio-metabolic diseases is growing rapidly in Sub-Saharan Africa, but little is known about medication related problems in these patients.

Objective: To review frequency and type of medication related problems in the management of diabetes and cardiovascular diseases in Sub-Saharan Africa.

Methods: We performed an electronic search of embase.com (MEDLINE and EMBASE), WHO library database (WHOLIS) and INRUD bibliography for original studies on medication related problems in patients with diabetes and cardiovascular diseases in Sub-Saharan Africa following PRISMA guidelines.

Results: A total of 40 relevant articles were included out of 4097 studies. Most of the studies came from Nigeria ($n = 25$). Tertiary care ($n = 21$) was the most common setting and hypertension patients ($n = 24$) were studied frequently. Methods included cross-sectional surveys ($n = 14$) and retrospective reviews of case notes ($n = 12$). Non-adherence ($n = 19$) and inappropriate prescribing ($n = 10$) were studied most frequently.

Medication non-adherence ranged between 15 % and 59 %. Reasons for non-adherence included: supply problems because of long distances, forgetting, side effects, illiteracy and high cost of drug therapy. Inappropriate prescribing was due to physicians not following treatment guidelines (e.g. underutilization of the most cost effective medication, inappropriate polypharmacy), not recording diagnoses, not prescribing by

brand names as well as not considering drug–disease and drug–drug interactions.
Conclusions: Overall few studies are available outside Nigeria. Non-adherence seems to be a common problem in Sub-Sahara Africa as elsewhere, but some reasons are specific for resource restricted settings. More research is needed, especially on inappropriate prescribing and interventions which improve medication related problems.

Abstract Code: ISP3514-41

Cases of Materiovigilance Collected by the Centre Anti Poison et Pharmacovigilance du Maroc

F. Abadi[1], G. Benabdallah[1], R. Benkirane[1], R. Soulaymani Bencheikh[1]

(1) Centre Anti Poison et de Pharmacovigilance du Maroc, Rabat, Morocco

Introduction: Medical devices (MD) are essential for the prevention, diagnosis, treatment of diseases and rehabilitation of the patients. These MD should be evaluated to ensure their effectiveness and safety. In 2010, a unit of materiovigilance was launched in the Centre Anti Poison et Pharmacovigilance du Maroc to monitor MD on the national market.
Objectives: To determine the type of MD implicated, the nature of the incidents related to MD and to highlight the difficulties and limitations of this activity across Morocco.
Materials and Methods: Retrospective review of case reports of incidents or incidents related to the risk of MD collected in The Centre Anti Poison et de Pharmacovigilance du Maroc from January 2010 to December 2012.
Results: We received 378 notifications of MD (less than 2 % of pharmacovigilance notifications), divided into requests for information in 60 % of cases and incidents in 40 % of cases. The collection is done by phone call in 59.2 % of cases, followed by mail (19.8 %). The public is the first reporter with 65.1 % of the cases followed by the pharmacist (21.1 %). According to the MD risk classification, MD class III (high level of risk) are the most involved (65.3 %). Among 154 cases with an incident, almost half of them reached the patient. The impact on the patient was variable, ranging from local allergy to life-threatening.
Conclusion: Our study highlighted the low volume of notifications of incidents related to the use of MD compared to the important volume of MD on the market, and highlighted the need to raise the awareness of all users of MD to report incidents related to the use of MD, in order to reduce the recurrence of such incidents.

Abstract Code: ISP3516-43

A Description of the Content of Risk Management Plans for Initial Centrally Authorised Medicines in the European Union

C. Boidin[1], L. Prieto[1], A. Hidalgo-Simon[1], P. Arlett[1]

(1) European Medicines Agency, London, UK

Introduction: Once a marketing authorisation is granted for a pharmaceutical product some new risks can arise [1] from their use in real practice. In Europe, Risk Management Plans (EU-RMPs) are set up since 2005 and are mandatory for all centrally authorised products (CAPs) since 2012 [2] in order to monitor the outcome of a drug in post approval. EU-RMPs include the safety specification for a product (i.e: identified, potential, missing) with the planned routine and additional pharmacovigilance activities (PhV) and risk minimisation activities (RMin).
Aim: To describe the content of EU-RMPs.
Methods: EU-RMPs for initial marketing authorisations for CAPs with a positive CHMP opinion between 2010 and 2012 were selected. The summary tables of the EU-RMPs were inspected regarding the content of the safety specification and their additional PhV and RMin activities. The variables of interest for each product were the safety issues, the risk category (identified risks, potential risks and missing information) and the additional activities: clinical studies, observational studies, active surveillance and assessment of effectiveness of risk minimisation for additional PhV; patient education and Healthcare professional education for additional RMin. Data were pooled in a spreadsheet. Univariate and bivariate descriptive analysis were performed.
Results: In total, 1972 safety issues were identified from 121 EU-RMPs. The average number of safety issues per product was 16. The minimum number of safety issues per product was 4, with a maximum of 36. The distribution of activities was: 98 products with additional PhV activities (81 % of the total), 38 with additional RMin activities (31 % of the total). Additional PhV activities are designed to investigate what is not well characterised, so there were more additional PhV activities for missing information (38 %) and for potential risk (36 %) than for identified risk (26 %). The opposite trend was observed for additional RMin as these activities are planned to minimise risk already known: there were more additional RMin activities for identified risk (49 %) and potential risk (30 %) than for missing information (21 %).
Conclusions: This study provides description of the trends in the content of the EU-RMPs which may inform future decisions for risk management activities.
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Abstract Code: ISP3517-44

Results of a Pharmacovigilance Unit: Review and Analysis of 3676 Notifications Received

G.A. Keller[1], M.L. Ponte[2], R.A. Diez[3], G. Di Girolamo[1]

(1) Pharmacovigilance Unit, Second Chair of Pharmacology, School of Medicine, Universidad de Buenos Aires, Buenos Aires, Argentina (2) Hospital General de Agudos Cosme Argerich, Ciudad Autónoma de Buenos Aires, Argentina, (3) Second Chair of Pharmacology, School of Medicine, Universidad de Buenos Aires, Buenos Aires, Argentina

Objectives: In Argentina, pharmacovigilance program was created in 1993 centered in the national regulatory agency with peripheral nodes. Our node has used a proactive approach since 2006, in addition to the registration of spontaneous reports.
Methods: The notifications are incorporated into a database (SQL), in addition to being sent to Regulatory Agency. We describe the notifications

received (demographics and types of events reported; side effects, ineffectiveness or failure of quality) [1] and the result of the intervention of analysis, when it was required.

Results: From November 2004 to May 2013, 3676 notifications were received. There was no difference between sex, with a low proportion of pediatric patients (<2 %) and high proportion of elderly (>60 years) patients (1463, 40 %). Most notifications corresponded to adverse effects (3499, 95 %), followed by cases of lack of efficacy (149, 4 %) and quality failure (28, <1 %). The degree of severity was mild in the majority (2591, 74 %), followed by severe (612, 17 %) and moderate (296, 9 %). The largest categories of drugs involved in adverse effects were antimicrobials (29 %), drugs for cardiovascular disorders (23 %), drugs for CNS disorders (15 %), non-sexual hormones (9 %), antineoplastics (8 %), NSAIDs (6 %), hematopoietic drugs (4 %) and drugs for lung diseases (3 %). Among all (3499) adverse event notifications, 672 (19 %) were serious adverse events, including cases of 528 (15 %) hospital admissions, 98 (2 %) prolonging an existing hospitalization, 41 (1 %) life-threatening diseases, 4 (<1 %) deaths, and 1 (<1 %) persistent incapacity. Among cases of lack of efficacy the most frequently involved were neurological drugs (28 %), cardiovascular drugs (17 %), antimicrobials (19 %), and NSAIDs (11 %). All samples of products involved in notifications of failure of efficacy or quality were sent to the National Institute of Medicines (INAME).

Conclusions: The presence of old people and groups involved in drug side effects is consistent with data from other Pharmacovigilance studies [1, 2]. Possible causes of lack of notification by the health professionals seem to include ignorance, fear, lack of time, lack of incorporation of the drug, and lack of necessary data, among others. The proactive approach allows the systematic inculcation of side effects and effectiveness evaluation as part of the activity.

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Abstract Code: ISP3518-45

Assessment of Serious Adverse Events in Academic Clinical Trials: Concordance Between Investigator and Sponsor

J. Bezin[1], G. Miremont-Salame[2], F. Haramburu[2], N. Moore[3], A. Gimbert[4]

(1) Unité de vigilance et de sécurité des essais cliniques, CHU Bordeaux, Bordeaux, France; INSERM U657, Univ. Bordeaux; CIC-P0005, CHU Bordeaux, Bordeaux, France, (2) INSERM U657, Univ. Bordeaux; CIC-P0005, CHU Bordeaux; Centre Régional de pharmacovigilance et d'addictovigilance, Bordeaux, France, (3) INSERM U657, Univ. Bordeaux; CIC-P0005, CHU Bordeaux, Bordeaux, France, (4) Unité de vigilance et de sécurité des essais cliniques, CHU Bordeaux, Bordeaux, France

Background: Assessment of the relatedness of the research in the occurrence of a serious adverse event (SAE) is realized by both investigator and sponsor in accordance to current regulations and study documents.

Objective: To assess the concordance between investigators and the sponsor (Bordeaux teaching hospitals) in the judgment of a possible causality of the research in the occurrence of SAE during academic clinical trials (CT).

Methods: All SAE reported by the investigators to the sponsor, wich occurred during academic CT between September 2007 and October 2012, and recorded in the Safety database of the sponsor were included in this study. The concordance was calculated using SAS® software.

Results: 1194 SAE from 63 CT, were included in this study. A difference of assessment between investigator and sponsor was observed for 244 SAE (20 %). In CT concerning medicinal products 24 % of SAE were assessed differently, in CT on cellular therapy product, 21 %, in CT on medical devices, 18 % and in CT not on health products, 14 %; 136 SAE (56 %) were considered related to the research by the sponsor contrary to the investigator and 42 SAE (17 %) were considered not possibly related by the sponsor contrary to the investigator. The assessment of the investigator was missing for 54 SAE (22 %) when they were assessed by the sponsor and 12 (5 %) were not assessed by the sponsor when an assessment by the investigator was given.

Discussion: Fewer than a quarter of SAE were assessed differently. Assessment of the relatedness of the research in the occurrence of a SAE seems to be quite homogeneous between the investigator and the sponsor and independent of the type of the CT. The sponsor seems to relate more frequently the SAE to the research than investigators, who might not assess the SAE at all. Regulations require to assess rapidly the possible relatedness between the CT and SAE. Clinical information available at the time of notifying of the SAE are often limited. Information about regulation requirements and definitions of suspicious adverse events must be reinforced for the investigator to improve information exchange. A study of causes of discrepancies must be made to assess if the sponsor concludes to a relationship by excess and the investigator by default, or not.

Abstract Code: ISP3519-46

Tumor Lysis Syndrome in Off-label Lenalidomide-treated Chronic Lymphocytic Leukemia Patients: Effectiveness of the TLS Educational Outreach Program

L. Weiss[1], D. Gary[1], J. Freeman[1], R.J. Delap[2], R.D. Knight[3], J.B. Zeldis[4]

(1) Drug Safety, Celgene Corporation, Summit, NJ, USA, (2) Office of the CMO, Global Clinical Research, Celgene Corporation, Summit, NJ, USA, (3) Clinical Development, Celgene Corporation, Summit, NJ, USA, (4) Office of the CMO, Celgene Corporation, Summit, NJ, USA

Background: Lenalidomide (Revlimid) was added to the DrugDex compendia listing for Chronic Lymphocytic Leukemia (CLL) in October 2008. Medical insurance providers and the US Centers for Medicare & Medicaid Services limit cancer drug coverage for off-label indications to indications listed in certain compendia. Each compendia recommendation is supported by a level of evidence category. Limited data on the tumor lysis syndrome (TLS) risk in lenalidomide-treated CLL patients was available at time of compendia listing.

In a 2007 Celgene safety database review, TLS occurred in 3 % (7/260) of CLL patients receiving 10 mg or 25 mg lenalidomide, including 2 with fatal outcome; all cases developed during the first 15 days of treatment [Moutouh-de Parseval L 2007]. With other therapies typically

utilized in CLL including fludarabine, cyclophosphamide, rituximab, pentostatin, or 2-chlorodeoxyadenosine, the incidence of TLS is less than 5 % [Blum 2011]. The potential for TLS and strategies for prevention/management have been considered for CLL patients who are candidates for lenalidomide in clinical trials and under compendia for off-label indications. Upon FDA notification in 2008, a prescriber education outreach program was initiated to minimize TLS occurrence when prescribed off-label for CLL. Each prescriber requesting a dispense of lenalidomide for a patient with CLL receives a call and faxed letter with safety data and guidance on recommended prophylactic and management measures for TLS.

Method: Effectiveness of this educational outreach program was evaluated by comparing number and severity of TLS reports in lenalidomide-treated CLL patients in the year before and after implementation of the program.

Results: Effectiveness of the Prescriber Education Outreach Program in US lenalidomide-treated CLL patients (off-label use only)

Year and exposure	% (n/N)	Fatal
Before program (2007–2008): 2.0 % (11 reports/556 treated) all reports; 5 fatal, 4 occurred outside Celgene clinical trials		
2007 (260)	3.5 (9/260)	3 (CST 1, IIT 2)
2008 (296)	0.7 (2/296)	2 (Off-label 2)
After program (2009–2012): 0.2 % (3 reports/1293 treated) US spontaneous reports; **no fatal**		
2009 (268)	0.0 (0/268)	0
2010 (252)	0.0 (0/252)	0
2011 (352)	0.0 (0/352)	0
2012 (421)	0.7 (3/421)	0

Conclusion: The prescriber education outreach program has been beneficial in reducing severity of TLS. There were no fatal reports of TLS with off label use of lenalidomide in CLL since introduction of the program. While physicians may prescribe lenalidomide off-label for use in CLL based on compendia listings, it is the Celgene position that investigational use of lenalidomide should be confined to controlled clinical trial settings.

Abstract Code: ISP3520-38

The Preventability of Adverse Drug Reactions Occurring With Antineoplastic Drugs—An Evaluation of Spontaneously Reported Cases

I. Barata[1], C. Alves[1,2], D. Mendes[3], C. Fontes Ribeiro[4], F. Batel Marques[5]

(1) School of Pharmacy, University of Coimbra, Portugal, (2) Central Regional Pharmacovigilance Unit, AIBILI. Health Sciences Research Centre, University of Beira Interior, Portugal, (3) Central Regional Pharmacovigilance Unit, AIBILI., Portugal, (4) Central Regional Pharmacovigilance Unit, AIBILI, School of Medicine, University of Coimbra, Portugal (5) Central Regional Pharmacovigilance Unit, AIBILI, School of Pharmacy, University of Coimbra, Portugal

Background: Antineoplastic drugs have narrow benefit/risk ratio and are associated with serious adverse events. The extent to which adverse drug reactions (ADRs) could be avoided or prevent deserves careful evaluation.

Objective: This study is aimed to assess the predictability and the preventability of ADRs in patients on oncologic chemotherapy.

Methods: ADRs associated with antineoplastic drugs which have been spontaneously reported to the Central Portugal Regional Pharmacovigilance Unit (UFC) between January 2001 and December 2012 were selected. Suspected drugs were classified as antineoplastics if they were included in first level anatomical main group of the Anatomical Therapeutic Chemical (ATC) "Antineoplastic and Immunomodulators Agents". Only ADRs classified as certain or probable and as serious, causing death or being life-threatening, were included in this study. Causality was assessed according the global introspection method. Seriousness of ADRs was assessed according to the WHO-UMC criteria. The ADRs which frequency has been described as very common ($\geq$1/10), common ($\geq$1 /100 to <1/10) or uncommon ($\geq$1/1,000 to <1/100), according to the SmPCs of suspected drugs, were assessed as predictable. ADRs were assessed as preventable if preventive measures were proposed in the SmPCs.

Results: A total of 202 ADRs associated with antineoplastic drugs were received by UFC. Fifteen ADRs met the inclusion criteria, out of which 11 (73 %) were assessed as certain and 4 (27 %) as probable. None had death as an outcome. Twelve ADRs were assessed as predictable (80 %) and 3 as not predictable (20 %). Of the 15 ADRs, 9 (60 %) were assessed as being simultaneously predictable and preventable, 3 (20 %) were assessed as being predictable but no preventable and 3 (20 %) as being neither predictable nor preventable. Preventive measures were applied before suspected drug being administered in 6 (40 %) patients, yet ADRs occurred. Preventive measures were not applied in 3 (20 %) cases despite their recommendation in SmPCs.

Conclusions: Despite preventive measures being described for the majority of the antineoplastic drugs included in this study, life-threatening ADRs still occur even when such measures were applied.

Abstract Code: ISP3521-39

Data Sources by Regulatory Agencies on the Generation of Drug Safety Alerts

C. Alves[1], A.F. Macedo[2], F. Batel Marques[3]

(1) School of Pharmacy, University of Coimbra. Centre for Health Technology Assessment and Drug Research, AIBILI. Health Sciences Research Centre, University of Beira Interior, Portugal, (2) Health Sciences Research Centre, University of Beira Interior, Portugal, (3) School of Pharmacy, University of Coimbra. Centre for Health Technology Assessment and Drug Research, AIBILI, Portugal

Background: Evidence on the benefit/risk ratio of drugs during their lifetime was found to be provided by different sources. Therefore, the study of the grounds on which data supporting regulatory authorities' decisions on drug safety evaluations is an important clinical and public health issue.

Objective: This study was aimed at identifying, reviewing and signalling the publication status of data sources leading to label changes due to safety alerts, as conducted by four major drug regulatory authorities, between January 2010 and December 2012.

Methods: A website search was carried out in order to identify all safety alerts published by the US FDA, Health Canada, EMA and the Therapeutics Goods Administration. Safety alerts were included if the causal relation between a suspected drug exposure and the occurrence of an adverse event have been evaluated for the first time between January 2010 and December 2012. The type of data sources evaluated by authorities, its publication status and the drug label section updated were retrieved.

Results: A total of 59 safety alerts were included in this study, 5 issued by TGA, 13 issued by Health Canada, 16 issued by US FDA and 25 issued by EMA. Thirty-three (56 %) safety alerts issued by authorities supported their regulatory decisions on post-marketing spontaneous reports (SR), 24 (41 %) evaluated RCT, 16 evaluated cohort studies (27 %), 13 case-control studies (22 %) and 11 evaluated case report/case series (17 %). The regulatory decisions of twelve (20 %) safety alerts were based exclusively on post-marketing SR and 8 (14 %) based exclusively on RCT. Twenty three safety alerts (39 %) were issued based on unpublished evidence, corresponding mainly on post-marketing SR. Warnings and precautions section was the drug label section most frequently updated (n = 40; 68 %).
Conclusion: Despite the different lengths of time to take similar decisions on the same issues between regulatory agencies, which seems to deserve further harmonization, post-marketing SR have supported most of the B/R ratio reevaluations due to safety reasons, between January 2010 and December 2012, confirming its value in detecting unknown adverse events, especially those which were described as rare and serious.

Abstract Code: ISP3522-40

Statin Therapy and Incidence of Cataracts: A Meta-Analysis

C. Alves[1], A.F. Macedo[2], D. Mendes[3], C. Fontes Ribeiro[4], F. Batel Marques[5]

(1) Centre for Health Technology Assessment and Drug Research, AIBILI. School of Pharmacy, University of Coimbra. Health Sciences Research Centre, University of Beira Interior, Portugal, (2) Health Sciences Research Centre, University of Beira Interior, Portugal, (3) Centre for Health Technology Assessment and Drug Research, AIBILI, Portugal, (4) Centre for Health Technology Assessment and Drug Research, AIBILI. School of Medicine, University of Coimbra, Portugal, (5) Centre for Health Technology Assessment and Drug Research, AIBILI. School of Pharmacy, University of Coimbra, Portugal

Background: The association between statin use and the development of cataract has been evaluated in several studies with inconsistent results. The risk for cataract development associated with the use of statins should be clarified, as well as a possible dose-response relationship.
Objective: This study was aimed at identifying the risk of developing cataracts in patients exposed to statins, according to the published evidence from both experimental and observational studies.
Methods: A meta-analysis was carried out pooling data from studies identified on a Medline and on a Cochrane Library search. Studies were eligible for inclusion if they were prospective, observational or controlled clinical trials (RCT), evaluating any statin and reporting data on cataracts incidence. Odds ratios (OR) were estimated using random-effects models and statistical heterogeneity was estimated with I^2 statistics.
Results: One RCT, two case-control and three cohort studies were included. Statins use was not associated with an increased risk for cataract development (OR 1.10 [95 % CI 0.88–1.37], $I^2 = 52$ %). The sensitivity analysis according different study designs did not change the results.
Conclusion: Despite the statistically significant heterogeneity between included studies, particularly length of drug exposure, drug dose and the associated comorbidities precludes definitive conclusions.

Abstract Code: ISP3523-41

Combined Oral Contraceptives and Risk of Pulmonary Embolism, Stroke and Myocardial Infarction: A Cohort Study of 4 Million French Women

A. Weill[1], M. Dalichampt[1], F. Raguideau[2], P. Ricordeau[1], F. Alla[1], H. Allemand[1], M. Zureik[2]

(1) French National Health Insurance (CNAMTS), Paris, France, (2) The French National Agency for Medicines and Health Products Safety (ANSM), Saint-Denis, France

Background: Among combined oral contraceptives (COC), those containing levonorgestrel combined with the lowest possible dose of ethinylestradiol (EE) are recommended by many authors. However, the magnitude of venous and arterial thromboembolism risk associated with intake of other COC, particularly gestodene or desogestrel, remains highly controversial. To address this issue, a large population-based study was requested by French medical authorities.
Aim: To assess absolute and relative risks (RR) of pulmonary embolism (PE), ischaemic stroke (IS) and myocardial infarction (MI) according to the type of COC.
Methods: This historical cohort included all women aged 15–49 years, living in France, with at least one COC reimbursement between July 2010 and December 2011, identified in the French national health insurance system (SNIIRAM). This database covers the entire population and is linked to the French hospital discharge database (PMSI), in which PE, IS, and MI outcomes are identified. Exclusion criteria included a history of cancer or venous or arterial thrombotic event before the study period. RR were estimated using Poisson regression and estimates were adjusted for age, deprivation index and status with respect to complementary Universal Health Insurance for the poorest women (12 % of the study population), hypertension, diabetes, smoking (nicotine substitute reimbursement or hospital diagnosis related) and a visit to a private practice gynaecologist.
Results: A total of 4,327,579 women with a mean age 27.9 years (±8.6) contributed to 2,972,772 person-years of COC exposure. Women on so-called third-generation COC were more socially advantaged, younger, with a lower cardiovascular risk, usually monitored by a community gynaecologist and most often taking a 20 μg EE dose (54.2 % vs 16.8 %). A total of 967 PE, 475 IS and 208 MI were observed with incidence rates of 3.3, 1.6 and 0.7 per 10,000 person-years, respectively. Adjusted RR (and 95 % confidence intervals) for PE (levonorgestrel/20 μg EE as reference) were: 2.06 [1.50–2.90] for desogestrel/20, 1.74 [1.09–2.73] for gestodene/20, 1.36 [1.02–1.87] for levonorgestrel/30–40, 2.97 [2.17–4.17] for desogestrel/30–40 and 1.77 [1.00–3.00] for gestodene/30–40. Adjusted RR for MI/IS were 1.14 [0.76–1.74] for desogestrel/20, 0.55 [0.25–1.09] for gestodene/20, 1.35 [0.97 to 1.95] for levonorgestrel/30–40, 1.05 [0.67–1.65] for desogestrel/30–40 and 1.35 [0.69–2.50] for gestodene/30–40.
Conclusion: This study reports similar results to those of recent large observational studies despite the limitations of database studies. We found a significantly lower risk with levonorgestrel combined with EE at a dose of 20 μg, a combination not previously assessed in the Danish cohort.

Abstract Code: ISP3524-42

Neuroleptic Malignant Syndrome: Case Report and Underdiagnosis Considerations

G.A. Keller[1], M.L. Ponte[2], R.A. Diez[3], G. Di Girolamo[1]

(1) Pharmacovigilance Unit, Second Chair of Pharmacology, School of Medicine, Universidad de Buenos Aires, Buenos Aires, Argentina, (2) Internal Medicine Department, Hospital General de Agudos Cosme Argerich, Ciudad Autónoma de Buenos Aires, Buenos Aires, Argentina, (3) Second Chair of Pharmacology, School of Medicine, Universidad de Buenos Aires, Buenos Aires, Argentina

An 24-year-old man consulted to the emergency department presenting general rigidity, sedation, fever, and muscle pain. A chest X-ray and general laboratory showed no abnormalities. The patient had progression of symptoms in 6 hours, reaching unconsciousness, Glasgow 8/15 (M4O3V1). A new laboratory showed signs of rhabdomyolysis (CPK 4328) and leukocytosis (18000). A lumbar puncture was performed finding a Normal cerebrospinal fluid. Adminido The patient was in intensive care and required mechanical ventilation. An examination showed a relative that the patient had a history of schizophrenia and was using haloperidol and lorazepam. The patient improved in intensive care and was extubated 8 days later and discharged after 12 days. Neuroleptic malignant syndrome (NMS), are a rare but potentially fatal complication of neuroleptic medications (e.g., antipsychotics, sedatives and antinauseants), is characterized by hyperthermia, muscle rigidity, an elevated creatine kinase level and autonomic instability (1, 2). The syndrome often develops after a sudden increase in dosage of the neuroleptic medication or in states of dehydration (3). Treatment is mainly supportive and includes withdrawal of the neuroleptic medication and, possibly, administration of drugs such as dantrolene and bromocriptine (3). Clinicians must increase awareness of this clinical syndrome as it is often overlooked and underdiagnosed and consider the relationship between dopamine D2 receptor occupancy rates and haloperidol dose. Investigations have suggested that patients with >80 % D2 receptor have a higher chance of experiencing side effects. Studies have demonstrated that 2–20 mg/day of haloperidol saturate 60–80 % dopamine D2 receptors (1–4). Increased awareness, early recognition of NMS and use of lowest dose of neuroleptics with gradual are escalation needed.

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Abstract Code: ISP3525-43

Risk of Infections and Tuberculosis Associated With Adalimumab, Etanercept and Infliximab: Analysis of Spontaneously Reported Adverse Drug Reactions in Portugal

D. Mendes[1], C. Alves[2], F. Batel Marques[3]

(1) Centre for Health Technology Assessment and Drug Research, AIBILI, Portugal, (2) Centre for Health Technology Assessment and Drug Research, AIBILI. School of Pharmacy, University of Coimbra. Health Sciences Research Centre, University of Beira Interior, Portugal, (3) Centre for Health Technology Assessment and Drug Research, AIBILI. School of Pharmacy, University of Coimbra, Portugal

Background: Although the effectiveness of biologics in the treatment of rheumatoid arthritis (RA), they have been associated with an increased risk of infections, including tuberculosis.
Objectives: This study is aimed at evaluating the rate of all infections and tuberculosis associated with the three most consumed biologics in Portugal for treating RA: adalimumab, etanercept, and infliximab.
Methods: Suspected adverse drug reactions (ADR) spontaneously reported to the Portuguese Pharmacovigilance System (PPS) between January 2009 and December 2011 were included. Suspected ADRs were classified according to MedDRA® version 12.0 in the primary System Organ Class (SOC) and in the Highest Level Term (HLT). The reporting odds ratio (ROR) and its 95 % confidence interval (CI) were calculated to each biologic regarding suspected ADR classified at the SOC 'Infections and infestations' and at the HLT 'Tuberculous infections'. Microsoft Excel 2010® was used to perform all the calculations.
Results: The PPS received 992 suspected ADR. Two hundred and seven suspected ADR (20.87 %) were reported for adalimumab, 199 (20.06 %) for etanercept, and 586 (59.07 %) for infliximab. Of 127 (12.80 %) suspected ADR classified in the SOC 'Infections and infestations', 43 (33.86 %) were reported for adalimumab, 15 (11.81 %) for etanercept, and 69 (54.33 %) for infliximab. The ROR (95 % CI) for 'Infections and infestations' was 2.19 (1.63, 3.28) for adalimumab, 0.50 (0.38, 0.87) for etanercept, and 0.80 (0.57, 1.16) for infliximab. Of 23 (2.32 %) suspected ADR classified in the HLT 'Tuberculous infections', 13 (56.52 %) were reported for adalimumab, 2 (8.70 %) for etantercept, and 8 (34.78 %) for infliximab. The ROR (95 % CI) for 'Tuberculous infections' was 5.19 (2.46, 12.02) for adalimumab, 0.47 (0.21, 1.61) for etanercept, and 0.36 (0.19, 0.86) for infliximab.
Conclusions: In the PPS, the majority of the infections and, particularly, tuberculosis reported for the three biologics have been associated with adalimumab. Further studies comprising head to head comparisons of biologics are needed to clarify the relative risk of infections among all biologics.

Abstract Code: ISP3526-44

Benzodiazepine Use and Risk of Dementia: A Case Control Study Using the Quebec Claims Database

S. Billioti De Gage[1], Y. Moride[2], T. Ducruet[3], T. Kurth[4], H. Verdoux[1], K. Peres[5], A. Pariente[1], B. Begaud[1]

(1) Pharmacoepidemiology INSERM U657, Universite Bordeaux Segalen, Bordeaux, France, (2) Faculty of Pharmacy, University of Montreal, Montreal, Canada, (3) Research Centrer, University of Montreal Hospital Center, Montreal, Canada, (4) Neuroepidemiology INSERM U708, Universite Bordeaux Segalen, Bordeaux, France, (5) INSERM U897, Universite Bordeaux Segalen, Bordeaux, France

Background: We recently conducted a prospective cohort study in France, which highlighted an increased risk of dementia among incident users of benzodiazepines (BZDs). Because of the high incidence of dementia and the widespread chronic use of BZDs in the elderly, such findings, if reproduced, would have a major public health impact.
Objectives: To conduct a population-based study in order to evaluate the association between BZD use and risk of dementia in the community-elderly population of Quebec (Canada).
Methods: A nested case-control study was undertaken using the Quebec medical services and prescription claims databases (RAMQ) between 2000 and 2009. The main cohort consisted of a random sample of elderly members (age 66+) with at least 6 years of follow-up. Dementia cases were identified through a diagnosis (index date) of Alzheimer's disease (ICD-9). For each case, 4 controls were matched on sex, age and duration of follow-up (incidence density sampling). Past exposure to BZDs was categorized into: past use: last BZD claim >5 years before index date/ recent use: first BZD claim <5 years before index date/continued use: BZD claim >5 years before and last claim <5 years before index date/ never use. The association between BZD use and dementia was assessed using multivariate conditional logistic regression.
Results: A total of 1,796 cases and 7,184 controls were identified. BZD use was associated with an increased risk of dementia in all time windows considered: odds ratio (OR) 1.94 (95 % CI: 1.44–2.61) for past use, 2.00 (1.68–2.37) for recent use and 2.00 (1.76–2.26) for continued use. Adjustment for anxiety, depression and other psychotropic drugs did not change the results: OR 1.75 (1.30–2.38) for past, 1.55 (1.30–1.86) for recent, and 1.46 (1.28–1.67) for continued use.
Conclusions: BZD use was associated with an increased risk of dementia even after adjusting for anxiety, depression and other psychotropic use, which confirms our previous findings. Hence, we consider that BZDs are a major public health issue in the elderly.

Abstract Code: ISP3527-45

Evaluation of Effectiveness of Risk Minimisation Activities for Vandetanib in Canada

Y. Moride[1], F. Salvo[2], M. Kozmenko[3], S. Frise[3]

(1) Faculty of Pharmacy, Université de Montréal, Montreal, Canada, (2) Department of Pharmacology, University Bordeaux Segalen, Bordeaux, France, (3) AstraZeneca Canada, Mississauga, Canada

Background: Vandetanib (CAPRELSA) has been approved in Canada for the treatment of medullary thyroid cancer. Important safety concerns consist of QTc prolongation (QTP)/Torsade de Pointes (TdP), Diarrhea and Rash. The risk minimisation interventions (RMIs) include communications to health care professionals, restricted product distribution through a centralised pharmacy, and mandatory prescriber education and certification.
Objectives: To evaluate the effectiveness of the vandetanib RMIs through a prospective drug utilisation study (DUS) and a knowledge and understanding survey (KAU) of prescribers.
Methods: All patients who initiated treatment with vandetanib during the first year post-launch were invited to participate in the DUS. Appropriate prescriber's actions related to concomitant use of QT prolonging drugs was evaluated at treatment initiation, 3 months, 6 months and 12 months after treatment initiation. Data sources for concomitant drug usage and medical history included: (i) Oncologist case report form; (ii) home pharmacy records; (iii) patient questionnaire. Assessment of appropriateness of concomitant drug usage was assessed against the product label and the Arizona Centre for Education and Research on Therapeutics (CERT) lists. All prescribers who have undergone the mandatory web-based training were eligible to participate in the KAU survey conducted at 12 months post launch. The results of KAU were used to determine understanding of key safety messages and a root cause analysis for results of the DUS.
Results: At 12-month post-launch, 11 patients were prescribed vandetanib of which, 8 provided data for the DUS (73 %). Two patients (25 %) developed QTP that was chronologically related to vandetanib use. All QTP events led to discontinuation of vandetanib with a re-introduction at a lower dosage. In general, drugs that were clearly associated with QTP or TdP, (i.e. listed in the product label and included in the Arizona CERT lists) were discontinued or not prescribed. When referencing the product label, two occurrences of sub-optimal prescribers' actions were found with respect to concomitant drugs; these were related to use of CNS (Central Nervous System) medications, including opioids, antidepressants, and anxiolytics.
Conclusions: Overall, risk minimisation interventions were found effective. It is difficult to assess whether continued concomitant prescription of at-risk medications was due to the fact that the physician did not consult the product label, or read the label but decided that the benefits outweighed the risks. A root cause analysis of sub-optimal prescribing obtained from the KAU will be presented.

Abstract Code: ISP3528-46

A Comparison of the Quality and Accuracy of Information Available on the Internet for Warfarin and Dabigatran

R. Andev[1], A. Anand[2], A. Blaggan[1], H. Amar[1], H. Sooch[1], A. Chowdhury[1], J. Hodson[2], S.E. Mcdowell[2], S.K. Thomas[3], J.J. Coleman[3]

(1) College of Medical and Dental Sciences, University of Birmingham, Birmingham, UK, (2) University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK, (3) College of Medical and Dental Sciences, University of Birmingham, Birmingham, UK, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK

Introduction: The Internet is now regarded as one of the major sources for accessing health-related information [1]. Internet usage has given rise to a new type of patient; one who is encouraged to be proactive and use available information to form a shared health decision with their

healthcare provider [2]. However, the quality and accuracy of drug information available on the Internet may vary and is not widely studied.
Aim: We wished to analyse and evaluate the quality and accuracy of drug information available on the Internet, in the form of web pages and videos, for warfarin and dabigatran.
Methods: We performed a search of Google.com in May 2013 using the text words warfarin and dabigatran. The quality and accuracy of the sources were assessed using a modified scoring system that incorporated criteria from the Health Related Web Evaluation Form (HRWEF), the Health on the Net Foundation Code of Conduct (HONcode), the DISCERN instrument, and the drug monographs from the British National Formulary. Two reviewers scored each source in pairs and any discrepancy was resolved by discussion. Each source was also categorised as official, professional, user generated, or no source provided. Mean score values were compared between the two drugs using independent samples t-tests. Multivariable analyses were then performed using general linear models.
Results: We analysed 120 web pages and 103 videos for warfarin and 120 web pages and 46 videos for dabigatran, after exclusion of sources based on language, restricted access to the source, or for repeated web pages/videos. The proportions of sources within each category differed significantly between the two drugs ($P < 0.001$), with a higher percentage of dabigatran sources in the official and professional categories than warfarin (81.9 % compared with 61.4 %; $P < 0.001$). In a multivariable model, dabigatran sources had a significantly higher total mean score (difference = 5.18 points, $P = 0.002$) and drug information score (difference = 2.18 points, $P = 0.009$) than warfarin. As the sources progressed from result 1 to 120 on Google, the total score decreased by 0.19 per link ($P < 0.001$) and the drug information score decreased by 0.027 per link ($P = 0.028$).
Conclusions: The quality of information presented on web pages and videos is of a higher calibre for dabigatran compared with warfarin. Websites of official origin and those with a higher position on Google.com provided the highest quality sources with increased accuracy of information.

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Abstract Code: ISP3529-47

Prevalence and Preventability of Adverse Events in the Medical Intensive Care Unit of Ibn Sina Hospital: Preliminary Results

N. Badrane[1], K. Berechid[2], S. Benchekroun[2], T. Dendane[2], K. Abidi[2], A.A. Zeggwagh[2]

(1) Moroccan Poison Control and Pharmacovigilance Centre, Rabat, Morocco, (2) Medical Intensive Care Unit, Ibn Sina University Hospital, Rabat, Morocco

Introduction: In developing countries, the relative importance of adverse events (AEs) in terms of morbidity and mortality remains poorly assessed. One report, in eight developing or transitional economies in the Middle East and Africa, has demonstrated the high prevalence of AEs and their high preventability [1]. In addition, the intensive care unit represents a high-risk area for AEs that could occur due to the complexity of care, the large number of interventions performed, and the patients' fragile medical condition [2].
Aim: The aim of our study was to assess the frequency, cause, and preventability of AEs in Medical Intensive Care Unit (MICU) in Ibn Sina hospital in Morocco.
Methods: We conducted a prospective observational study in the MICU of the University Hospital Ibn Sina since August 2012 to determine the frequency, cause, preventability and outcome of AEs related to drugs, mechanical ventilation and central venous catheterization, performed in consecutive ill patients admitted over a 6-months period. We used the world health organization preventability scale
Results: A total of 154 patients in our unit were studied during 6 months. We found 66 adverse events in 42 patients (27.3 %), including 35 (53 %) non preventable and 31 (47 %) preventable. Among all the reported AEs, 69.7 % referred to drug adverse event, 28.8 % to central venous catheterization AEs and 1.5 % to mechanical ventilation AEs. The frequency of medication errors were prescription: 5/13 (38.5 %), administration: 4/13 (30.8 %), no respect of precautions and contraindications: 3/13 (23 %) and others: 1/13(7.7 %). The anticoagulants were the most common drugs in drug adverse events. Self-extubation was the most common accident of mechanical ventilation. Among adverse events, 33.3 % (22/66) were fatal; and among serious errors (15/66), 60 % (9/15) were potentially life-threatening. The most common causes of error included failure in communication and lack of procedures and protocols.
Conclusions: This preliminary study has identified the high prevalence of AEs in our unit. From these results we will formulate preventive strategies including better implementation of protocols, better formal quality monitoring and better education and training.

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Abstract Code: ISP3530-39

Incidence of Adverse Drug Reactions Identified Using Health Insurance Claims Database in South Korea

N.K. Choi[1], Y.J. Kim[2], J. Lee[1], B.R. Yang[2], B.J. Park[3]

(1) Medical Research Collaborating Center, Seoul National University Hospital, Seoul, Korea, (2) Department of Preventive Medicine, College of Medicine, Seoul National University, Seoul, Korea, (3) Korea Institute of Drug Safety and Risk Management, Seoul, Korea

Introduction: The adverse drug reaction (ADR) is one of the leading causes of morbidity and mortality and considerable health-care related economic burden. Using large administrative database is efficient way to produce reliable estimates for ADR incidence.
Aim: To estimate the incidence and demographics of ADR-related hospital visits in South Korea using Health Insurance Review and Assessment Service (HIRA) claims database in Korea between 2008 and 2010.
Methods: We performed a retrospective analysis using health insurance claims records from HIRA database for the year 2007–2010. We selected

patients recorded as ADR-related diagnosis based on International Classification of Diseases, 10th revision (codes containing the words 'causing adverse effects in therapeutic use', 'drug-induced' or 'due to drug'). Incident cases were defined as patients who were not diagnosed same code in the year before the index date. We evaluated the average incidence rate of ADRs during the 3-year period based on total number of hospital visits in HIRA database (N = 134,550,389 from 2008 to 2010). The age- and gender-specific person-time incidence rates of ADRs were presented in the number of events per 1,000 person-years with their 95 % confidence interval (CI). The most frequently ADR-related diagnoses were analyzed in hospital admission and ambulatory care settings.

Results: A total 545,913 ADR-related hospital visits were identified in HIRA database between 2008 and 2010. The overall 3-year incidence rates of ADR-related hospital visits were 4.06 (95 % CI: 4.05–4.07) in all hospital visits, 4.77 (95 % CI: 4.73–4.80) in hospital admission, and 3.63 (95 % CI: 3.62–3.64) in ambulatory care setting. The greatest ADR incidence rate was in patients aged 70 years or older (7.65, 95 % CI: 7.59–7.71) in both men and women. The ADR incidence rate in women (4.72, 95 % CI: 4.70–7.73) was slightly higher than the incidence rate in men (3.36, 95 % CI: 3.35–3.38). The most frequently ADR-related diagnoses were generalized skin eruption due to drugs and medicaments (L270, 16.9 %) and other drug-induced secondary parkinsonism (G211, 10.9 %) in hospital admission, allergic contact dermatitis due to drugs in contact with skin (L233, 17.0 %) and generalized skin eruption due to drugs and medicaments (L270, 12.7 %) in ambulatory care setting.

Conclusions: The nationwide incidence of ADR-related hospital visits in the Korean population was 4 per 1,000 person-years. While our results must be viewed with circumspection because the estimates could be a smallest level of incidence of ADRs considering the fact that not all ADRs recognized or recorded in claims database.

Abstract Code: ISP3531-40

New Oral Anticoagulants (Dabigatran, Rivaroxaban, Apixaban) and Vitamin K Antagonists: Incidence and Treatment Patterns in 2012 in France

G. Maura[1], C. Billionnet[1], A. Weill[1], P. Ricordeau[1], F. Alla[1], H. Allemand[1]

(1) Caisse Nationale de l'Assurance Maladie des Travailleurs Salariés, Paris, France

Background: Since 2011, the new oral anticoagulants (NOAC) have been licensed in France as alternatives to Vitamin K antagonists (VKA) for the prevention of stroke and systemic embolism in patients at risk with non-valvular atrial fibrillation. NOAC are also licensed for thromboprophylaxis in patients following total knee or hip replacement.

Aim: To investigate the prescribing trends for NOAC and VKA drugs in France in 2012.

Methods: A retrospective, drug utilization study was conducted. Reimbursement data from the French national health insurance system (SNIIRAM) covering the entire French population (65.3 million inhabitants in 2012) was searched for patients newly prescribed NOAC or VKA drugs and with no prescription during the previous 6 months. NACO treatment patterns, including the prescribing physician's speciality, names of NACO products and switches from VKA, were identified.

Results: In 2012, 207,900 patients initiated NOAC therapy: 49 % were female, with a mean age of 71 years (±13.2) and 28.8 % were 80 years and older. At the same time, there were 347,200 new users of VKA therapy: 51.3 % female, mean age: 70.9 years (±15.9) and 36.0 % were 80 years and older.

The yearly incidence was 3.2 per 1000 persons and 5.3 per 1000 respectively.

Among news users of NOAC, 30.2 % switched from VKA to NOAC (36.3 % were 80 years and older), 6 % discontinued the NOAC drugs and resumed VKA within 2 months. Most of NOAC therapy initiations were recorded in the second half of 2012 (74 %). Among those patients who had switched from VKA to NOAC during this period, 42.2 % had received a maximum of 12 VKA deliveries during the previous 2 years.

Dabigatran 110 mg (38 %) and rivaroxaban 10 mg (21 %) were the two NACO drugs most commonly prescribed. General practitioners prescribed 33 % of the NACO drugs, and private practice cardiologists prescribed 26 % of NACO drugs.

Conclusion: An increasing prescription incidence of NOAC therapy was observed over the second half of 2012, especially in patients older than 80 years. Further evaluations are therefore ongoing to characterise this patient cohort, especially patients at risk of bleeding, and to assess whether NOAC are a safe alternative to VKA in real life.

Abstract Code: ISP3533-42

Fatigue and its risk factors in Lenalidomide-Treated Relapsed Refractory Multiple Myeloma (RRMM) and Myelodysplastic Syndrome (MDS) Patients: Postmarketing Surveillance

D. Gary[1], L. Weiss[1], N. Minton[1], J. Freeman[1]

(1) Drug Safety, Celgene Corporation, Berkeley Heights, NJ, USA

Background: 80 % of cancer patients report fatigue as the most distressing symptom associated with cancer treatment [1]. Celgene Drug Safety signal monitoring revealed higher rate of early treatment discontinuation due to fatigue in postmarket-versus-trial settings. In three lenalidomide (LEN) RRMM and MDS pivotal trials, fatigue was reported frequently (RRMM: LEN-Dex 44 % vs Pbo/Dex 42 %; MDS: LEN 18 % vs Pbo 8 %). Grade 3/4 severity was: RRMM (LEN-Dex 7 % vs Pbo/Dex 5 %) and MDS (LEN1.2 % vs Pbo 1.5 %). Few patients discontinued treatment due to fatigue, 1 % in each arm of RRMM and none in MDS. In RRMM trials, time to response was reached with median treatment duration of 11 cycles. For MDS, discontinuation of LEN is indicated for patients without a minor erythroid response after 4 cycles [2].

Aim: To understand, characterize and mitigate events of fatigue in patients treated with LEN in real life setting.

Methods: Celgene Drug Safety's database was searched for spontaneous reports received from 27 Dec 2005 to 26 Jun 2012 utilizing MedDRAv15 HLT Asthenic Conditions. Proximity analysis, events reported ±30 days to fatigue, was applied to better understand associations with fatigue.

Results: 5 % (11,339/182,672) of patients reported fatigue and of those, 14 % (1,588/11,339) discontinued treatment due to fatigue. There were differences in reporting and discontinuation rates by region: US- 10 % and 13 %, EU- 1 % and 30 %, respectively. Median time to onset was 60 days (range 1–2,555), and discontinuation 56 (RRMM: 1–2,221) and 53 (MDS: 1–2,293) days. Proximity analysis identified decreased appetite, diarrhea, nausea, muscle spasms and cytopenias as top risk factors.

Conclusion: Cancer or treatment related fatigue can be debilitating, leading to decreased quality of life and less than optimal outcome due to premature treatment discontinuation. The majority of reported fatigue occurred in the first 2 months of treatment and was accompanied by risk

factors that could lead to poor nutritional intake and sleep disturbances, having an additive effect on fatigue. NCCN guidance for assessment, education/counseling and treatment of fatigue recommends continuous patient assessment and monitoring from diagnosis and throughout management of the disease [1]. Other causes including comorbidities and anemia should be considered when assessing and treating fatigue. Health care professionals should empower patients and caregivers with information about activity management, exercise, optimizing sleep quality, relaxation, and massage therapy [1]. Available resources include NCNN guidelines, patient/caregiver informational leaflets and websites (cancer clinics/cancer foundations).

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Abstract Code: ISP3534-43

Pharmacovigilance of Biotechnological Therapies: How the Brazilian Public Pharmaceutical Industry Have Been Preparing Itself?

P.R.G. Dos Santos[1], P.M.N. De Oliveira[1], H.G.T. Defendi[1], M.L.F. Leal[1], M.L.S. Maia[1]

(1) The Immunological Technology Institute Bio-Manguinhos, Oswaldo Cruz Foundation, Ministry of Health, Rio de Janeiro, Brazil

Introduction: The Immunological Technology Institute Bio-Manguinhos has been leading original and follow-on biologics joint development and technology transfer processes in order to attend the increasing demand of the Ministry of Health, guaranteeing non-charged access of the Brazilian population to effective and safe drugs, including cutting edge biotechnological therapies. Alongside this, new challenges have arisen: the establishment of higher regulatory standards for post-authorisation monitoring in due to the concern regarding the risk-benefit balance of biologics and biosimilars; and theirs acceptance by the organized civil society and scientific community in replacement of known brands that have been sold for more than a decade in the pharmaceutical market.
Aim: To evaluate the current methods and propose new approaches for optimize the efficacy and safety assessment system, envisioning debates and partnerships for the development of the pharmacovigilance activities on account of the specificities of the biopharmaceuticals.
Methods: Considering the incorporation of drugs to the institute portfolio and its commitment with innovation, quality, efficacy and safety; also the Brazilian, European and North American present regulations and initiative projects, a situational analysis of the pharmacovigilance activities have been developed. The current assessment methods for products that have been marketed since 2004 (epoetin alfa and interferon alfa-2b) have been indicated. Confronting these, most adequate methodologies for the products that will be launched on the following years (epidermic growth factors, monoclonal antibodies and pegylated molecules) have been sought.
Results and Discussion: As expected, post-authorisation efficacy and safety studies of paramount importance for public health have been conducted for validating signals from spontaneous reports and active surveillance programs by clinical research and observational studies. Nevertheless, given the nature of the new products, it has been found that the use of existing practices would not be sufficiently effective for detecting adverse events. The most proactive and cost effective strategies should be included on the pharmacovigilance activities. Especially the ones that approach the industries to the opinion former professionals based in health education, research and service institutions: drug utilisation studies, intensive monitoring schemes, prescription event monitoring, registries and sentinel system, according to the outcome, could be placed in partner teaching hospitals.
Conclusion: Breaking out of paradigm and invest in new pharmacovigilance approaches is essential before the regulatory requirements and the public opinion about follow-on biologics. Such innovative practices must be shared with involved Brazilian public pharmaceutical industry in a collaborative partnership, assuring the efficacy and safety of the biopharmaceutical therapies.

Abstract Code: ISP3535-44

Veterinary Pharmacovigilance—A Pilot Study in Tamil Nadu, India

S. Ghadevaru[1]

(1) Pharmacovigilance Laboratory for Animal Feed and Food Safety, Directorate Centre for Animal Health Studies, Tamilnadu Veterinary and Animal Sciences University, Chennai, India

Introduction: Veterinary Pharmacovigilance monitors the safety of veterinary medicines, including vaccines (VAC) used for the prophylaxis, diagnosis or treatment of diseases in animals once they reach the market after authorization (1). The task of veterinary Pharmacovigilance is to ensure the protection of the environment as well as the safety of veterinary medicines in animals, animal-derived food and people in contact with veterinary medicines (2) The reporting of adverse drug events (ADE)/reactions is a key part of the process of ensuring the safety of medicines, and plays a part in keeping existing medicines in the market and its availability (3). In India, there is no Pharmacovigilance programme/monitoring of adverse drug events in veterinary medicine. Essential data on the frequency, severity of the treated animal ADE remains unreported in India.
Aim: The study was conducted to assess for the first time the ADEs in treated livestock of Tamil Nadu, India
Methods: A 12-month period pilot study was conducted to monitor the ADE for frequently used drugs (labeled/extra labeled drugs). A survey protocol (3) consisting of questionnaire about used drugs in livestock was developed; the questionnaire was distributed to 300 veterinarians of Tamil Nadu state. The veterinarians were instructed to voluntarily report on the various types of drugs used and the ADEs, if any observed.
Results: More than 37 % ADEs were related to antimicrobials, ant parasitic and anti-inflammatory agents. A further 27 % of ADEs were due to vitamins and feed additives. Two cases of ADEs observed in FMD vaccination in cattle and canine Parvo vaccine in dogs. In poultry, tiamulin and salinomycin ADEs induced serious mortality
Conclusions: The present study warrants for the need of sustained veterinary Pharmacovigilance programmes in livestock for timely ADEs presenting drug detections and drug safety improvement

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Abstract Code: ISP3536-45

Hospital Readmission Rate Related to Adverse Drug Reactions in Patients >65 years: A Study in a French University Hospital

L. Hauviller[1], V. Garnault[2], V. Rousseau[1], J.L. Montastruc[1], H. Bagheri[1]

(1) Service de Pharmacologie Médicale et Clinique, Centre Midi-Pyrénées de Pharmacovigilance, de Pharmacoépidémiologie et d'Informations sur le Médicament, Faculté de Médecine, Toulouse, France, (2) Département d'Informations Médicales, CHU Toulouse, Toulouse, France

Introduction: Adverse Drug Reactions (ADRs) are responsible of around 3 % to 6 % of hospitalizations (1) (2). Despite its importance in terms of patient care, readmission to hospital due to ADRs remains less documented (3) (4).
Aim: To assess readmission rate for ADRs of patients older than 65 years previously admitted for ADR in Toulouse University Hospital (South Western, France).
Methods: Standardized hospital discharge summaries were provided by the Hospital Department of Medical Information. Our population included inpatients older than 65 years admitted during 2010 in medical units of Toulouse University Hospital with diagnosis codes (according to International Classification of Diseases) included the terms describing a possible ADR as main or related diagnoses (ICD10-ADR). Among these patients, we identified all readmissions to Toulouse University Hospital (all wards) within the year of discharge from the index admission. Data of patients readmitted with ICD10-ADR were completed using medical files.
Results: A total of 1,000 patients admitted in 2010 with ICD10-ADR 2010 were included. Among the 553 patients (55.3 %) readmitted, 143 had an ICD10-ADR code. Median age was 74.2 years (SD: 6.15). The mean number of admission with ICD10-ADR was 2.75 (range 2–11). Complementary data extracted from medical files allowed to exclude 56 cases (error of code, history of ADR) and then to identify 87 cases of hospital readmission corresponding to 257 ADRs. Blood and lymphatic (63 %) and nervous system (11 %) ADRs were the most frequent ADRs related to 244 suspected drugs. According to ATC classification, antineoplastic and immunomodulating agents (78.7 %), blood and blood forming organ drugs (8.2 %) and nervous systems drugs (4.9 %) were the most involved.
Conclusions: This study found a readmission rate for hospitalization due to ADRs in patients older than 65 years around 9 % (87/1,000 patients-years). Analysis of characteristics of the cases could allow to determine their preventability and undertake appropriate corrective actions.

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Abstract Code: ISP3537-46

Do Different Refill Adherence Patterns Influence the Reporting of Adverse Drug Reactions and Sub-Therapeutic Effects? A Population-Based Study

K. Hedna[1], S. Hagg[1], K. Andersson Sundell[2], M. Petzold[3], K. Hakkarainen[4]

(1) Department of Drug Research/Clinical pharmacology, Linköping University, Linköping, Sweden, (2) Unit of Social Medicine, University of Gothenburg, Gothenburg, Sweden, (3) Centre for Applied Biostatistics, University of Gothenburg, Gothenburg, Sweden, (4) Nordic School of Public Health NHV, Gothenburg, Sweden

Introduction: Suboptimal medication refill adherence among individuals with chronic conditions is a significant clinical problem 1. However, evidence on actual self-reported medication-related morbidity due to non-refill adherence to long-term medications in clinical practice is limited. Such evidence is useful for planning interventions to improve the management and outcomes of medication therapies 2.
Objective: To investigate whether the percentages of self-reported adverse drug reactions (ADRs) and sub-therapeutic effects (STEs) differed for medications refilled adherently, oversupplied and undersupplied.
Method: A survey was administered to a random sample of adults ($\geq$18 years) drawn by Statistic Sweden from the Total Population Register. Survey responses on self-reported ADRs and STEs were linked to data from the Swedish Prescribed Drug Register. Refill adherence to antihypertensive, lipid-lowering and oral anti-diabetic medications was measured using the continuous method of medication acquisition (CMA). The percentages of self-reported ADRs and STEs were compared between medications refilled adherently (CMA 0.8–1.2), oversupplied (CMA >1.2) and undersupplied (CMA <0.8).
Results: The study included 1827 individuals aged 19–96 years (mean 68 years). Overall, 1655 individuals refilled 3014 antihypertensive, 817 individuals refilled 839 lipid lowering and 205 individuals refilled 235 oral anti-diabetic medications. The percentages of self-reported ADRs and STEs for medications refilled adherently, oversupplied and undersupplied were respectively 2.6 %, 2.7 % and 2.1 % ($p > 0.5$) for ADRs, and 1.1 %, 1.6 % and 1.5 % ($p > 0.5$) for STEs.
Conclusion: The ADRs and STEs were, unexpectedly, equally commonly reported for long-term medications refilled adherently, oversupplied and undersupplied, which was probably contributed by the lower percentages of self-reported ADRs and STEs than found in studies using medical record data. These results indicate a need for improved understanding of patients' behavior to refill long-term medications and patients' perceived and diagnosed adverse outcomes of medications, in order to improve medication management. The impact of individual and healthcare factors that may influence the association between refill adherence and medication-related adverse outcomes should be investigated in future studies.

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Abstract Code: ISP3538-47

Evaluation of Compliance and Level of Knowledge of Patients Treated with Vitamin K Antagonists

J. Bene[1], M. Auffret[1], A.E. Dubart[2], C. Senis[3], S. Gautier[1]

(1) Centre Régional de Pharmacovigilance, Lille, France, (2) Centre Hospitalier de Béthune, Service des Urgences, Béthune, France, (3) Centre Hospitalier de Béthune, Pharmacie, Béthune, France

Introduction: The behaviour and the knowledge of patients on their oral anticoagulant are factors that can influence strongly iatrogenia of these treatments. Improving the understanding of patients on their therapies is a source of good compliance and thus better balance in their anticoagulation.
Aim: To evaluate the compliance and the knowledge of patients treated with vitamin K antagonists.
Method: Patients were identified from the emergency department of a secondary hospital (Bethune Hospital, France). All patients admitted in the emergency department from 2012 March, 1st to May, 31st for a hemorrhagic or a thrombotic accident related with their vitamin K antagonist treatment were selected. All patients were contacted by phone call. Questions asked concerned the respect of the compliance, conditions of taking the treatment and their knowledge about it.
Results: Forty two patients were contacted. Among them, 40 (95 %) reported to have a good compliance and 41 (98 %) reported to regularly performed their International Normalized Ratio (INR). When INR was not in the normal range, 71 % (n = 30) of the patients changed the dosage of their vitamin K antagonist with the advice of their general practitioner.

Thirteen patients (31 %) considered the treatment such as constraining (most of them considered that the need to perform laboratory tests was the most restrictive aspect of the treatment). Ten patients (24 %) were in possession of a booklet. Only two patients (5 %) reported having benefited from therapeutic education.

Concerning the knowledge of the patients on their anticoagulant treatment, over 80 % of them knew the name of their anticoagulant, the hemorrhagic risk inherent in these treatments, can cite the name of the laboratory test regularly done to evaluate their anticoagulation level (i.e. INR) and the normal range of the INR. Less than 80 % knew the consequences of the anticoagulant treatment and the indication of this treatment.
Conclusion: These good results are the consequences of 10 years of educational program and encourage early education in patients treated with vitamin K antagonists and, soon, new oral anticoagulants, across therapeutic education.

Abstract Code: ISP3539-48

Risk Factors for Hemorrhagic and Thrombotic Accidents in Patients Treated with Oral Anticoagulants: A Case-Control Study

J. Bene[1], A.E. Dubart[2], M. Auffret[1], C. Senis[3], S. Gautier[1]

(1) Centre Régional de Pharmacovigilance, Lille, France, (2) Centre Hospitalier de Béthune, Service des Urgences, Béthune, France, (3) Centre Hospitalier de Béthune, Pharmacie, Béthune, France

Introduction: With a follow of more than 60 years, data concerning the iatrogenia of vitamin K antagonists are large, but hospitalisations for hemorrhagic or thrombotic events nevertheless persist.
Aim: To identify the risk factors for hemorrhagic and thrombotic accidents in patients treated with oral anticoagulants and admitted in an emergency department.
Methods: All patients admitted in the emergency department of a secondary hospital (Bethune Hospital, France) from 2012 March, 1st to May, 31st and treated with oral anticoagulants (vitamin K antagonists or new oral anticoagulants) were consecutively selected.

Two case-control studies were performed to identify risk factors for hemorrhagic and thrombotic accidents. Cases were patients admitted for a hemorrhagic or a thrombotic accident and controls were patients admitted for any other reason. Each case was matched with two controls on age (+/− 5 years) and gender. Conditional logistic regression was carried out.
Results: In 3 months, 240 patients were identified (59 cases, 181 controls). Most of them were treated with fluindione (89 %). Among cases, 40 (68 %) were admitted for a hemorrhagic accident and 19 (32 %) for a thrombotic accident. Atrial fibrillation was the main indication of the anticoagulant therapy (68 %). Among patients admitted for a hemorrhagic accident, 55 % had a normal INR (range 2–3) and 37 % of patients admitted for a thrombotic accident had a normal INR.

In the case-control study concerning risk factors for hemorrhagic accidents in patients treated with vitamin K antagonists, no risk factors were significantly associated with the occurrence of a hemorrhagic accident. Main drug interactions which may have favored hemorrhagic events were precautions for use between vitamin K antagonists and hypolipemiants or amiodarone. In the case–control study concerning risk factors for thrombotic accidents, only chronic respiratory diseases tended to be associated with the occurrence of a thrombotic accident in patients treated with vitamin K antagonists ($p = 0.055$).
Conclusion: Even if avoidable adverse reaction related to vitamin K antagonists have diminished during the last years it is important to continue to improve the utilisation of these therapies despite the increasing use of new oral anticoagulants.

Abstract Code: ISP3540-40

Evaluation of Safety Information in Drug Labelling in Products Containing St. John's Wort

H. Lebanova[1], I. Getov[1], E. Grigorov[1]

(1) Medical University-Sofia, Sofia, Bulgaria

Background: Depression affects people from all ages and backgrounds. Accessing the frequency varies widely but in most countries 8–12 % (mainly women) of the population suffers from depression at some point in their lives [1]. There are a lot of herbal medicines and dietary supplements indicated for treatment of depression. Most popular ones contain St. John's Wart and are widely available [2]. Due to the different regulatory status of the products extended assessment of the safety profile is needed. One of the valuable sources for safety information is labeling.
Objective: The aim of the study is to assess the safety information in outer and inner labelling of different products containing St. John's Wart (Hypericum sp).
Methods: Data collection and analysis of the herbal products authorized for sale on Bulgarian market was performed. Products were classified according to trade name, quantity of active substance, type of the extract, presence of other active substances and legal status. Second phase was to analyze and compare safety data in Summary of Product Characteristics and/or product labelling with literature sources. Adverse reactions were assessed by frequency and seriousness according WHO and Benichou.

Results: The study shows that the most frequent adverse effects related to the use of St. John's Wort-containing products are photosensitivity, skin reactions, gastro-intestinal disorders, allergic reactions, tiredness, anxiety. However there are discrepancies and missing information among the labels of products with different legal status.
Conclusion: Classification and assessment of adverse reactions related to the use of Hypericum-containing products and enhanced control on the safety information in the labelling could support daily practice, encourage reporting of suspected cases and would have positive impact on herbal pharmacovigilance.
Discussion: The missing and sometimes contradictory information could be a thread to patients' safety and lead to the occurrence of serious adverse drug events.
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Abstract Code: ISP3541-41

Preliminary Results for Reporting of Problems Associated with Medications in Spain. The yo notifico (I notify) Project

G. Manso[1], M.E. Salgueiro[1], F.J. Jimeno[1], C. Aguirre[2], M. Garcia[2], A. Etxebarria[2], A. Carvajal[3], M. Sainz[3], C.J. Lamela[1], L. Ordonez[1]

(1) Departmento de Medicina, Area de Farmacologia, Universidad de Oviedo, Oviedo, Spain, (2) Unidad de Farmacovigilancia del País Vasco, Hospital de Galdakao, Galdakao, Spain, (3) Centro de Estudios sobre la Seguridad de los Medicamentos, Universidad de Valladolid, Valladolid, Spain

Introduction: The new European legislation on pharmacovigilance establishes the obligation for member states to implement, at the least, a system for the electronic reporting of suspected adverse reactions for patients, leaving open the initiative for the development of complementary (or wider) systems to the reporting by patients.
Aim: To explore the feasibility of a scheme intended for patients to report both adverse reactions and other problems related to medications.
Methods: Under the slogan *"yo notifico"* (I notify) we have developed: (1) a web page: www.yonotifico.es. This page is linked to the web page of the Spanish Agency of Medicines and Health Products for reporting adverse reactions by patients and (2) a paper formulary: "the blue card", to report adverse drug reactions and other problems related to medications. In addition to the formulary, the web page includes information about why, what and how to report. In January 2013, we began a promotional campaign of the Project in collaboration with consumer organizations, pharmacists, town associations, patient associations and local communication media.
Results: From January to May 2013 we have received 29 reports from patients (adverse drug reactions, 23; other problems related to medications, 5; adverse reaction associated with a health product, 1). Pharmacological groups most frequently involved were: psychotropic drugs (n = 12), non-steroidal anti-inflammatory drugs (n = 4), antihypertensive drugs (n = 3) and antineoplastic agents (n = 3). The organs and systems most frequently involved in the adverse reactions reported were: nervous system (n = 10; 21 %), skin and subcutaneous tissue (n = 7; 15 %), gastrointestinal (n = 7; 15 %) and general disorders (n = 6; 13 %). Other problems reported were: 3 related to the purchase of the medication, 1 regarding the information included in the leaflet and 1 concerning difficulty in the oral administration of a drug.
Conclusions: Our first reports are in line with those previously obtained in other countries [1, 2] and show the ability of the Spanish population to provide valuable information about different problems associated with the consumption of medications.
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Abstract Code: ISP3543-43

Spontaneous Reporting of Toxic Epidermal Necrolysis, Stevens–Stevens–Johnson Syndrome Johnson Syndrome and Erythema Multiforme associated with Antineoplastic and Immunomodulating Agents

L. Ordonez[1], M.E. Salgueiro[1], F.J. Jimeno[1], G. Manso[1]

(1) Departamento de Medicina, Area de Farmacología, Universidad de Oviedo, Oviedo, Spain

Introduction: Toxic Epidermal Necrolysis (TEN), Stevens–Johnson Syndrome (SJS) and Erythema Multiforme (EM) are frequently associated to pharmacological groups such as anti-epileptic and non-steroidal anti-inflammatory drugs. However, the knowledge of reported cases as well as the increased number of antineoplastic drugs and immunomodulating agents authorized suggests the advisability of analyzing the association of these drugs with the development of TEN, SJS and EM.
Aim: To study the involvement of antineoplastic drugs and immunomodulating agents in the development of TEN, SJS and EM.
Methods: Spontaneous reports of TEN, SJS and EM associated with antineoplastic drugs and immunomodulating agents and registered in the Spanish Pharmacovigilance System database from 01/01/1980 to 30/09/2009 were analyzed. Pharmacological groups and drugs involved were studied and classified according to the date at which they were approved. Reporting odds ratio (IC 95 %) were calculated for each drug and previous knowledge of the association between the drugs and adverse reactions were also evaluated by the analysis of the Summary Product Characteristics.
Results: Reports associated with 32 drugs included in the group of antineoplastic drugs and immunomodulating agents were identified. Of these, 15 drugs, mainly monoclonal antibodies, had been on the market for less than 15 years. The distribution of frequencies for the different pharmacological subgroups was: antineoplastic drugs (34, 57.6 %), immunosuppressants (14, 23.7 %), immunostimulants (7, 11.9 %) and endocrine therapy (4, 6.8 %). The highest reported odds ratio was found to leflunomide [2.9 (1.2–7.0)], followed by rituximab [2.7 (1.0–7.2)] and imatinib

[2.6 (0.8–8.2)], these being adverse reactions mentioned in the Summary Product Characteristics of the three drugs.

Conclusions: Some antineoplastic drugs and immunomodulating agents seem be associated with the development of TEN, SJS and EM. This association has not been observed in previous post-authorization studies [1, 2] perhaps due to the short time some drugs have been in the market and to the low incidence of these adverse reactions.

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Abstract Code: ISP3544-44

Bleeding and Thrombosis With New Oral Anticoagulants (Noacs): Analysis of Four Years of Spontaneous Reports in France

A. Lillo-Le Louet[1], P. Laine[2], T.F.N. of Pharmacovigilance[3]

(1) Pharmacovigilance, Hôpitaux Universitaires Paris Ouest, AP-HP, Paris, France, (2) Pharmacovigilance, Centre Hospitalier Universitaire, Angers, France, (3) The French network of Pharmacovigilance, Marseille, France

Introduction: Dabigatran and rivaroxaban are NOACs that respectively inhibits thrombin and activated Factor X (FXa). They are used in prevention of thromboembolic event after orthopedic surgery and in patients with non valvular atrial fibrillation with one or more other risk factor. More recently, rivaroxaban was approved in treatment and prevention of deep venous thrombosis, pulmonary embolism. In France, the European management plan was completed by a national survey whose results corresponding to a 3–4 year-following are now available.

Material and Methods: all French AR notified spontaneously to the pharmacovigilance network and to the firms between the launch date and December 31st 2012 were analyzed.

Main Results:

1. Dabigatran: haemorrhagic and thromboembolic AR represent respectively 36 % (n = 669) and 15.5 % (n = 279) of all AR analysed (n = 1841) during the survey. The most frequent bleeding sites were gastrointestinal tract (n = 279), urinary (n = 85), epistaxis (n = 57), intracranial (n = 50). Thromboembolic AR were mainly of venous origin (n = 179). The more serious thromboembolic effects were pulmonary embolism (n = 61 cases) and arterial thrombosis mainly ischemic stroke and myocardial infarction (n = 71). Fifty eight patients died from bleeding, twelve from thromboembolic events.
2. Rivaroxaban: haemorrhagic and thromboembolic AR associated with rivaroxaban represented respectively 44 % (n = 421) and 22 % (n = 207) of all analyzed patient-cases (n = 957). These AR were major in 37 % of cases. The most frequent bleeding sites were surgical site (n = 117), gastrointestinal tract (n = 83), ORL (n = 59), urinary (n = 42 %), and intracranial (n = 31). Thromboembolic AR were mainly of venous origin (n = 180). The more serious effects were pulmonary embolism (57 cases) and ischemic stroke (16 cases). Eighteen patients died from bleeding, and fifteen from thromboembolic event.

Conclusion and Perspective: Most analyzed AR are serious according to OMS criteria and expected, regarding the anticoagulant activity. Bleeding and thrombosis represent half of the cases analysed in this survey. The bleeding sites are in accordance with what was observed during clinical trials. Unfortunately missing information such as weight, renal function, dose and measure of specific anticoagulant activity does not allow an accurate analysis of the majority of cases. Some cases Misuse can't be evaluated with these spontaneous reports. Other database such reimbursement database must be used in this purpose. After recent alerts about haemorrhagic risk with NOACs, the notification rates are reassuring. The pharmacovigilance survey is still ongoing in France as more patients are expected to be treated.

Abstract Code: ISP3548-48

Bleeding Reports with Rivaroxaban in Turkey

Y. Kasap[1], N. Durmus[1], C. Babacanoglu[1], E.C. Basgut[1], G. Artiran[1], S. Kerman[1], D. Aydinkarahaliloglu[1]

(1) Turkish Medicines and Medical Devices Agency, Ankara, Turkey

Introduction: Rivaroxaban is a new oral anticoagulant, a highly selective direct Factor Xa inhibitor. Rivaroxaban, as other novel anticoagulant drugs, are mostly associated with an increased risk of bleeding [1].

Aim: To discuss the reports especially bleeding reports of rivaroxaban received by summary reports, a part of national rivaroxaban risk management plan.

Methods: Summary reports are part of national rivaroxaban risk management plan, contains all serious and non-serious spontaneous adverse drug reactions (ADRs), to review of all ADRs. This reports were sent by marketing authorization holders to Turkish Pharmacovigilance Risk Management Unit. Summary report, between 3 June 2011 and 3 March 2013, was reviewed. Adverse events, coded to MedDRA PT terms and MedDRA System Organ Classes (SOC) was used in ADR classification. The total package sales of rivaroxaban (all dosages) since the beginning of marketing were received by Intercontinental Medical Statistics (IMS) database.

Results: 50 reports had received related to the use of rivaroxaban from summary report. Reports date range was 3 June 2011 to 3 March 2013. These reports contained a total of 98 ADRs from spontaneous sources including 33 (33.6 %) bleeding cases. Of these 33 bleeding reports, 26 were classified as serious and 7 as non-serious. Overall, the distribution of the most frequent reported bleeding events, contain non-serious and serious, were ecchymosis/epistaxis (18.2 %), wound bleeding (12.1 %) and haematoma/gastrointestinal haemorrhage (9.1 %). Two fatal bleedings were received during this period. The total package sales of rivaroxaban (all dosages) from June 2011 to February 2013 were 40751 units. Distribution of SOCs and patient demographics were explored as well.

Conclusions: Rivaroxaban 10 mg was approved in Turkey in 2011 and 20 mg/15 mg was approved in 2012. There is currently no antidote available for this drug. Rivaroxaban, as other novel anticoagulant drugs, are mostly associated with a risk of bleeding. Thus, bleeding cases will remain under close observation. For this observation national rivaroxaban risk management plan, rivaroxaban web-based prescription and adverse reaction monitoring system should be used from doctors for all prescriptions.

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Abstract Code: ISP3549-49

Evaluation of Adverse Effects of Lenalidomide in Turkey

E.C. Basgut[1], C. Babacanoglu[1], N. Durmus[1], Y. Kasap[1], G. Artiran[1], S. Kerman[1], D. Aydinkarahaliloglu[1]

(1) Turkish Medicines and Medical Devices Agency, Ankara, Turkey

Introduction: Lenalidomide is an immunomodulator that has potent anti-tumor and anti-inflammatory effects [1] which has been marketed since 2010 in Turkey and is indicated for the treatment of multiple myeloma in adult patients [2] of which treatment causes undesirable effects such as infections and infestations, blood and lymphatic system disorders, metabolism and nutrition disorders, endocrine disorders, nervous system disorders, vascular disorders, respiratory disorders [3].
Aim: To evaluate the adverse reports of lenalidomide treated patients in Turkey between June 2011 and March 2013.
Methods: Lenolidomide has been marketed since 2010, also used in compassionate use (CU) program and clinical studies in Turkey. For the evaluation of data, we performed the reports between June 2011 and March 2013 by using monthly adverse event lists for lenalidomide which are sent to our Pharmacovigilance Risk Management Unit. The data sources were CU program, marketing authorization holder sponsored-clinical studies and spontaneous reports. System organ class was used in adverse drug reactions (ADR) classification.
Results: Data from monthly adverse event lists included 46 reports and totally 94 ADRs. Eighteen (19.1 %) of ADRs were from CU program, 6 (6.4 %) from clinical studies and 70 (74.5 %) from spontaneous reports. Forty-six (48.9 %) reports were from male and 47 (50 %) from female. The most adverse event caused by lenalidomide were benign, malign and unspecified neoplasms 13 (13.8 %), vascular disorders 13 (13.8 %) and cardiac disorders 11 (11.7 %). Forth-four (46.8 %) of the patients with ADRs were 65 years old and above, 42 (44.7 %) were under 65. The most outcome after these adverse events were recovered/resolved 30 (31.9 %), not provided 23 (24.5 %) and death 17 (18.1 %).
Conclusions: These data support that physicians should be aware of the potential for lenalidomide-associated adverse events especially benign, malign and unspecified neoplasms, vascular and cardiac disorders especially in 65 years of age and above.

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Abstract Code: ISP3550-41

ADR on the Skin, Analysis of Results Collected by the Drug Agency of Bosnia and Herzegovina from 2006 to 2012

D. Djuric[1], K. Ilic[2], J. Balaban[3], J. Aralica[4], N. Grubisa[5]

(1) Altiora doo, Banja Luka, Bosnia and Herzegovina, (2) Faculty of Pharmacy, Belgrade, Republic of Serbia, (3) Clinical Center, Banja Luka, Bosnia and Herzegovina, (4) Altiora doo, Zagreb, Republic of Croatia, (5) Agency for Medicinal Products and Medical Devices of Bosnia and Herzegovina, Banja Luka, Bosnia and Herzegovina

Purpose: The main aim of this study was to analyze all reported adverse drug reactions (ADRs) in Pharmacovigilance Department (PD) of Agency for Medicinal Products and Medical Devices of Bosnia and Herzegovina. Additionaly, adverse drug reactions that were expressed in the skin are specially analyzed.
Methods: Retrospective observational study of spontaneously reported ADRs collected in Agency for Medicinal Products and Medical Devices of Bosnia and Herzegovina from October 2006 to July 2012 was done. The Medical Dictionary for Regulatory Activities (MeDRA) was used to identify all cases and specially cases of disorders of the skin and subcutaneous tissue. Drugs were classified using the Anatomical Therapeutic Chemical (ATC) classification of World Health Organisation (WHO).
Results: Among the 267 reports of ADRs recorded in the Agency for Medicinal Products and Medical Devices of Bosnia and Herzegovina 58 cases (22 %) were referred to the disorders of the skin and subcutaneous tissue. Drugs most frequently associated with disorders of the skin and subcutaneous tissue were antibiotics, nonsteroidal antiinflammatory drugs, proton pump inhibitors, cardiovascular drugs, citostatics (27.6 %, 26 %, 17.8 %, 14.7 %, 7.3 % respectively). There was one case of severe skin changes, Steven Johnson Syndrome, with complete recovery of patients as outcome.
Conclusions: There are under-reporting of adverse drug reactions in Bosnia and Herzegovina. Antibiotics, nonsteroidal antiinflammatory drugs, proton pump inhibitors, cardiovascular drugs, citostatics were the most common drug groups reported for disorders of the skin and subcutaneous tissue. There is need for additional education and cooperation among all health professionals in the field of improvement of pharmacovigilance. It is necessary to investigate the cause of insufficient reporting of adverse drug reactions.

Abstract Code: ISP3551-42

Necessity of Quantity Limiting Per Package For Oral Olanzapine Preparations to Minimize the Suicide Risk

C. Babacanoglu[1], E.C. Basgut[1], Y. Kasap[1], N. Durmus[1], G. Artiran[1], S. Kerman[1], D. Aydinkarahaliloglu[1]

(1) Turkish Medicines and Medical Devices Agency, Ankara, Turkey

Introduction: Olanzapine is an antipsychotic displaying nanomolar affinity at D_1–D_4, serotonergic (5-$HT_{2,3,6}$), muscarinic (subtypes 1–5), adrenergic (α_1), and histaminergic (H_1) binding sites [1] which was approved in Turkey in 2004 for the treatment of schizophrenia, moderate

to severe manic episodes and the prevention of recurrence in patients with bipolar disorder. The most common effects of olanzapine toxicity are central nervous system depression, which may progress to coma, delirium and hypotension. This drug potentially has effects to induce suicidal intent [2].

Aim: To discuss the risk of taking whole dose in a package of oral olanzapine preparation, and to determine the necessity of quantity limiting per a package as a risk minimization activity.

Methods: Literature screening, database search and evaluation of data from periodic safety update reports (PSURs) are accomplished to assess the suicide risk and olanzapine. Suicide reports that were reported to Turkish Pharmacovigilance Center (TUFAM) since 2004 and suicide attempt cases via taking high dose olanzapine were determined. System organ class (SOC) was used in ADR classification.

Results: No definite lethal dose for human is detected. Although there are many cases of suicide attempt that olanzapine is used. In these cases olanzapine toxicity is seen with survivals as well as deaths and hospitalizations with different doses of olanzapine, with or without any other drug. There are five suicide attempt reports and one completed suicide report that were submitted to TUFAM since 2005.

Conclusions: The incidence of suicidal intent with olanzapine is 0.1 %–1 % [2]. Evaluation of all these data indicate that quantity limiting per package as a risk minimization activity is not enough to prevent suicide attempt by using olanzapine. Therefore no quantity limiting per oral olanzapin preparation packages is accomplished.

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Abstract Code: ISP3552-43

Assessment of "Dear Doctor Letters" Delivered in Turkey Since 2006

N. Durmus[1], Y. Kasap[1], E.C. Basgut[1], C. Babacanoglu[1], G. Artiran[1], S. Kerman[1], D. Aydinkarahaliloglu[1]

(1) Turkish Medicines and Medical Devices Agency, Ankara, Turkey

Introduction: Serious safety issues relating to drugs are communicated to health-care professionals via Direct Health-Care Professional Communications usually called as "Dear Doctor Letters" (DDL) which are describing the safety problems [1,2]. These letters alert the prescribing community of drug labeling changes that contain new contraindications, warnings, adverse reactions, and precautions. The most important point for the effectiveness of these letters is to get the letters off to all target health care professionals.

Aim: To summarize the number of DDLs between 2006 to May 2013 and, the subject of these letters and the number of communicated Health-Care Professionals between January 2012 and May 2013 in Turkey.

Methods: When an important safety issue about a drug has been diagnosed, this issue is discussed in Pharmacovigilance Consulting Commission and DDLs are published if needed. We performed DDLs published by Risk Management Department of Turkish Pharmaceuticals and Medical Devices Agency (TITCK) since 2006 and also the reports about the delivery of these letters by MAHs between January 2012 and May 2013, retrospectively.

Results: Eighty-three DDLs have been published by TITCK since 2006. Most of the letters were published in 2009 (22.9 %), 2011 (21.6 %) and 2012 (16.8 %). Summary of Product Characteristics and Patient Information Leaflets update (43.3 %), safety warnings and updates (32.5 %), and quality problem warnings are the most cause of these letters. There was a significant difference between the numbers of health care professionals delivered by different MAHs between January 2012 and May 2013.

Conclusions: Delivering DDLs is one of the mostly used and effective methods to warn the health care professionals for the safety problems about any pharmaceutical. In conclusion, Turkey is a developing country in economics and also in all areas like pharmacovigilance and risk management. Turkish Risk Management Department is aware of all kinds of pharmaceutical safety problems, follows and shares safety problems internationally and takes measures by letters or other risk management methods successfully.

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Abstract Code: ISP3553-44

Strengthening Pharmacovigilance System in Community

Y. Oppamayun[1], W. Rungapirumnun[1], W. Suwanakaesawong[1], S. Preechataveekit[2]

(1) Health Product Vigilance Center, Food and Drug Administration, Thailand, (2) Technical and Planning Division, Food and Drug Administration, Thailand

Introduction: Searching treatment via internet may lead to using wrong medicines. Not only buy them from internet, but patients also buy from drugstores. If we strengthen vigilance system in community, we can early detect problems or minimize risks effectively.

Objective: To extend a pharmacovigilance system in community.

Methods: We developed the drugstores' vigilance system module by combining the conceptual frameworks of stakeholder-participation, which provides practices for learning, with the extended parallel process of hospitals' vigilance model, which provides best practices for patient safety by adverse drug reactions' reports management. The prototype was tested concept by a group of experts (from ThaiFDA, The Community Pharmacy Association (Thailand), Faculty of Pharmaceutical Sciences, Chulalongkorn University), and end-users (drug stores' pharmacists), and feasibility issues were identified in collaboration with a large work setting.

Results: Vigilance system was identified to 4 parts; (1) Having basic tools (guideline), (2) Continuing education (training), (3) Risk communication mechanism (committee), and (4) Implementation (reporting). There are 5 topics in the guideline; introduction to an important of pharmacovigilance

by drug stores' pharmacists, risks in focus, risk management for drugs, risk management for irrational drug use, How to submit reports. After 1 day training course for pharmacists, 50 % of targeted group had participated with fruitful recommendations. For sustainable development of drug stores' vigilance, the committee responsible for these tasks has been appointed by ThaiFDA, which annual plan and regular meetings will be prepared. A month after reporting-guideline was implemented in drugstores, 6 reports from 2 drugstores were received by Health Products Vigilance Center (HPVC), ThaiFDA. Of these, were classified to 3 drug groups; genito urinary system and sex hormone, central nervous system, and general antiinfectives, which ADRs were atrial flutter, abdominal pain, and rash.

Conclusions: These finding suggest that the system; guideline should be used widely, and regular reviewed. Training courses are expected to organize by ThaiFDA for better quality and quantity reports. Furthermore, any modern communication tools and social networks will be used to promote and higher reach new targeted drugstores. The monthly committee meeting should be held. Finally, the project should be integrated into drugstores' routine jobs.

Abstract Code: ISP3554-45

Characteristics of Use and Comparative Effectiveness and Safety of Filgrastim Compounds in the Biosimilar Era

O. Lavon[1]

(1) Clinical Pharmacology and Toxicology Unit, Carmel Medical Center, Haifa, Israel

Background: A biosimilar compound of Filgrastim named Tevagrastim® was approved recently for routine clinical use. The original Filgrastim compound Neupogen® is in use for many years. Both are registered for the reduction of neutropenia duration and febrile neutropenia incidence in patients treated with cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukaemia and myelodysplastic syndromes) and for the reduction of neutropenia duration in patients undergoing myeloablative therapy followed by bone marrow transplantation.

Aim: To evaluate the characteristics of use and compare the clinical effectiveness and safety of Filgrastim compounds after the approval of the biosimilar compound.

Methods: Single center on-going comparative cohort study of hospitalized adult patients treated with either one of the Filgrastim compounds.

Results: Preliminary results of the period between January to October 2012 are presented. During this period of 10 months 48 hospitalized adult patients were treated with Filgrastim compounds; 21 patients were treated with Neupogen and 27 with Tevagrastim. Age range and average were 40 to 80 and 68 years, respectively, for the Neupogen treated, and 52 to 84 and 65 years, respectively, for the Tevagrastim treated. Female gender was predominant in both treatment groups; 12 (57 %) in the Neupogen group and 21 (77 %) in the Tevagrastim group. All the patients were administered subcutaneously doses of 300 mcg. Indications for Neupogen and Tevagrastim were febrile neutropenia in 18 (85.7 %) and 22 (81.4 %) cases, respectively, and neutropenia without fever in 3 (14.3 %) and 5 (18.6 %) cases, respectively. Causes for neutropenia in the Neupogen group were chemotherapy for different malignancies (19 cases) and immune-modulating medications for cirrhosis and sarcoidosis. Causes for neutropenia in the Tevagrastim group were chemotherapy for different malignancies (22 cases), immune-modulating medications for ulcerative colitis and biliary cirrhosis, and secondary to sepsis and to medications. Neutrophil count at the start of the treatment with Neupogen and Tevagrastim was less than 600 and 700 /μL, respectively. Duration from the initiation of treatment to a neutrophil count of over 1000 /μL was similar between the groups)unpaired t-test, two-tailed p value = 0.408(; approximately half the patients improved their neutrophil count to over 1000 /μL 24 h after the first dose. No adverse drug reactions were documented in any patient.

Conclusion: The use of Filgrastim compounds is diverse and exceeds its regulatory registration. Overall the treatment was effective within one to several days. There was no significant difference in the clinical effectiveness and safety between the two compared compounds.

Abstract Code: ISP3556-47

Pregnancy Outcomes in Women Using Antiepileptic Drugs

W. Kaabi[1], S. El Aidli[1], S. Kastalli[1], G. Lakhoua[1], A. Zaiem[1], S. Srairi[1], R. Daghfous[1]

(1) National Center of Pharmacovigilance of Tunis, Tunisia

Objective: The aim of this study is to assess neonatal effects after in utero antiepileptic drugs exposure.

Patients and Methods: We report 19 pregnancies exposed to antiepileptic drugs (AED) during pregnancy about which the Tunisian National Center of Pharmacovigilance has been questioned during the year 2010. Pregnancy-outcome ascertainment was obtained through subsequent follow-up with the reporting health care provider or through mails and telephone calls to women enrolled in the study.

Results: Women involved in the study have an age ranging from 24 to 40 years, with a mean of 32 years.

Ten women were prescribed AED for epilepsia, eight for psychiatric disorders and one for neurological pain.

Fifteen women were treated with monotherapy: VPA (7 cases), CBZ (5 cases), PB (2 cases) and phenytoin (PHT) (1 case).

Four women were exposed to polytherapy of AED. Associations of valproic acid (VPA) with carbamazepine (CBZ) and Phenobarbital (PB) with CBZ were used equally.

Clonazepam and levetiracetam were used each one in 2 associations.

Exposure period had been, during the 3 trimesters of pregnancy in 10 cases, during the first trimester in 6 cases, during the first and second trimester in 2 cases and during the third trimester in 1 case.

There were 3 cases of abortions (2 of them were spontaneous) and 3 cases of prematurity (15 %). Birth weight in the 13 healthy full-term newborn varied from 2.75 kg to 4.5 kg with a mean of 3.5 kg.

There was one case of birth defect (bilateral hydronephrosis) after exposure to VPA and one case of hypotonia and growth retardation after exposure to PB.

Discussion: In literature, there is some evidence to support an increased risk of preterm birth in mother under AED. It is well recognized that VPA is the most teratogenic AED.

In our study, prematurity was noted in 15 %. The only case of birth defect was associated to VPA.

Growth retardation is exceedingly uncommon with PB. We reported, in our study, one case of growth retardation after exposure throughout the pregnancy to PB.

Abstract Code: ISP3557-48

Spiramycin-Induced Acute Generalized Exanthematous Pustulosis Confirmed by a Positive Patch-Test

W. Kaabi[1], A. Zaiem[1], S. El Ferjani[1], R. Daghfous[1], S. El Aidli[1]

(1) National Center of Pharmacovigilance of Tunis, Tunisia

Introduction: Spiramycin is a macrolide that is widely prescribed for ear, nose and throat diseases, bronchitis and stomatitis. Gastroinestinal disorders are the main side effect of spiramycin. Acute generalized exanthematous pustulosis (AGEP) is reported with macrolides, but rare cases are described with spiramycin. We report a case of (AGEP) induced by spiramycin and confirmed by a positive patch-test.
Observation: A 29-year-old man, with no medical history, was prescribed spiramycin at the dose of 3 MUI twice a day to treat a dental infection. He had no personal or family history of skin disease or cutaneous adverse drug reactions. Seven days later, he developed acute, tender, erythematous and pustular eruption beginning in the folds, quickly spreading to involve the entire body. The patient reported malaise and fever to 39 °C. The case was notified to the pharmacovigilance center and analysed according to Naranjo score of imputation. Total resolution was observed within 3 days after discontinuation of the drug. Patch tests were performed 2 months later and showed an intense positive result at 48 h.
Discussion: AGEP is a severe manifestation of drug sensitivity. Its diagnosis is based on the temporal relationship incriminating the presumed causative agent, an often short interval between administration of the drug and the skin reaction, and exclusion of other pustular dermatoses, especially pustular psoriasis. The role of spiramycin was retained with a Naranjo score of 5 (probable). Euroscar Group has proposed a score for AGEP. In our case Euroscar score was valued as 6 (probable). The use of patch test in AGEP is very helpful to precise the responsible drug and to avoid the need of provocation test, that is potentially dangerous. In our case, the positivity of this test helped to confirm the responsibility of spiramycin.
Conclusion: This study reported an exceptional case of AGEP induced by spiramycin, which was confirmed by a positive patch-test.

Abstract Code: ISP3558-49

Concomitant Drug Use as a Contributing Factor for Developing Cardiovascular Adverse Reactions with Trandolapril/Verapamil Combination

G. Ozcan[1], E. Aykac[1], Y. Kasap[1], E. Sen[1], N. Nemutlu[1], G. Artiran[1], S. Kerman[1], N.D. Aydinkarahaliloglu[1]

(1) Turkish Medicines and Medical Devices Agency, Republic of Turkey Ministry of Health, Ankara, Turkey

Introduction: Trandolapril/Verapamil combination is commonly used for the treatment of hypertension especially in cases do not benefit from monotherapy. Bradycardia, Atrioventricular Block (AV Block) and Hypotension are expected adverse drug reactions (ADRs) related to its individual components [1]. Accordingly this combination has a high disproportionality rate in Turkish Pharmacovigilance Database for mentioned ADRs.
Aim: To identify factors that may contribute for developing Bradycardia, AV Block or Hypotension during the use of Trandolapril/Verapamil combination.
Methods: A retrospective observational study was conducted on the Trandolapril/Verapamil combination related ADRs, reported to Turkish Pharmacovigilance Center from January 2005 up until May 2013.
Results: There were 180 adverse reactions in 98 cases reported in the study period. Majority of the ADRs were under the Cardiac Disorders (n = 77, 42.8 %) and Vascular Disorders (n = 29, 16.1 %) System Organ Classes. Most common of all ADRs were Bradycardia (n = 34, 18.9 %) and AV-Block (n = 26, 14.4 %) constituting 77.9 % of Cardiac ADRs together and Hypotension (n = 24, 13.3 %) constituting majority (82.7 %) of the Vascular ADRs. In Bradycardia, AV Block and Hypotension groups there was female predominance (71 % to 77 %). Another prominent factor in each group was the use of one or more concomitant drug(s) observed approximately in 50 % of the cases. Nearly half of the concomitant drugs in all groups had Beta-adrenergic receptor blocking activity.
Discussion: It is known that concomitant use of Calcium channel blockers and Beta-Blockers can cause marked suppression of sinus node activity, and prolongation of atrioventricular conduction leading death in some cases [2]. Concomitant use of Beta-Blockers with Trandolapril/Verapamil combination possess the same risk due to its calcium channel blocker component Verapamil. Despite the presence of information about this risk in related Summary of Product Characteristics (SPCs) and Patient Information Leaflets (PILs), we observed a high rate of concomitant Beta-Blocker use with Trandolapril/Verapamil combination. As a measure, revision of the SPCs and PILs with additional warnings was planned and information about the risk is conveyed to health professionals by Dear Doctor Letters.
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Abstract Code: ISP3559-50

The Webreporting Format to Report Adverse Drug Reactions in Latin-American Countries—an Affordable Way to Overcome the Underreporting

M. Tarapués[1], G. Cereza[2], A. Figueras[3]

(1) Pharmacology Unit of Biomedical Center, Universidad Central del Ecuador, Quito, Ecuador, (2) Fundació Institut Català de Farmacologia, Barcelona, Spain, (3) Pharmacology, Therapeutics and Toxicology Department, Universitat Autònoma de Barcelona, 08193, Bellaterra, Spain

Introduction: Underreporting is a major limitation of the pharmacovigilance (PV) systems. Generally speaking PV is poorly known in Latin-American (LA) region; a study carried out in Venezuela showed that >60 % of health-professionals was unaware of PV-program [2]. Moreover, a systematic review showed that unavailability of yellow cards or suitable forms was a justification for not reporting in 3/4 of the participants [1]. National PV websites could help to overcome these limitations.
Aim: To review the availability of webreporting of adverse drug reactions (ADRs) in LA countries.
Methods: The availability of webreporting and the PV-information were sought and analyzed in eleven LA websites in April 2013.
Results: The LA countries affiliated to the World_Health_Organization program are Costa Rica, Cuba, Argentina, Venezuela, Chile, Mexico,

Brazil, Uruguay, Peru, Guatemala and Colombia. Availability of webreporting was observed in only four countries: Argentina, Venezuela, Brazil and Colombia. Furthermore, Chile and Peru are building up their webreporting site. Safety alerts were observed in 5 countries, however in another 4 countries this information were not consider because they were out-of-date (CR,C,V,M). Website characteristics are in Table 1.

Conclusions: A third part of LA countries has webreporting format. However PV information and its updating process is scarce in LA websites. To encourage the webreporting and to improve PV information in websites could be an affordable way to overcome underreporting.

Table 1

Website information	Total N = 11	Webreporting of ADR available	
		Si = 4*	No = 7
Description of national pharmacovigilance program	8(CR,C,A,V,Ch,M,B,Col)	4	4
Instructions to fill out ADR report form	7(CR,C,A,Ch,M,B,U)	2	5
Printable version of ADR report form	10(CR,C,A,Ch,M,B, U,P,G,Col)	3	7
Information about causality assessment and processing of reports	4(C,A,V,M)	3	1
Periodic analysis or data summaries of ADR reports	4(CR,C,A,P)	1	3
Summary of Product characteristics (independent information)	1(C)	1	10
Links or additional sources of pharmacovigilance information	6 (C,A,Ch,M,B,P)	3	3
Current safety alerts	5(A,Ch,B,P,Col)	3	2
On-line subscription for drug safety information (bulletins, alerts, etc)	1(C)	0	1
Access to website using Google search: "farmacovigilancia" + "country"	9(CR,C,A,Ch,M,B, U,G,Col)	3	6

CR = Costa Rica (since 1991), **C =** Cuba (1994), **A =** Argentina (1994), **V =** Venezuela (1995), **Ch =** Chile (1996), **M =** Mexico (1999), **B =** Brazil (2001), **U =** Uruguay (2001), **P =** Peru(2002), **G =** Guatemala (2002), **Col =** Colombia (2004). *Countries with webreporting = A,V,B,C

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An Assessment of the 2006–2013 Voluntary REVLIMID Patient Knowledge Surveys

E. Adams[1], S. Colman[2], N. Brandenburg[3], R. Bwire[3], J. Freeman[3], F. Houn[3], P. Sheehan[3]

(1) Covance Market Access Services Gaithersburg, MD USA,
(2) Covance Market Access Services, Sydney, Australia,
(3) Celgene Corporation, Summit, NJ USA

Background: In the United States REVLIMID® (lenalidomide) is indicated to treat myelodysplastic syndromes and multiple myeloma, the latter in combination with dexamethasone. REVLIMID is only available through a Risk Evaluation and Mitigation Strategy (REMS) called the REVLIMID REMS™ program (formerly known as RevAssist®) [1]. A key component of this program was conducting voluntary patient surveys, a requirement that was removed in 2013.

Objectives: To review data from the voluntary patient surveys during the observational period February 2006 through February 28, 2013.

Methods: During the registration process, patients indicated willingness to participate in a voluntary survey conducted by a sampling of patients across 5 groups: Adult Males ≥18 years old (yo), Males 12–17 yo, Females of Child Bearing Potential (FCBPs), Adult Females Not of Childbearing Potential, and Children <12 yo. Evaluation comprised 2 phases: initial surveys of newly prescribed patients, and follow-up surveys of patients receiving REVLIMID for ≥3 months. Key measures include knowledge that REVLIMID can cause birth defects, compliance with birth control, not sharing medication, or giving blood. This report describes the results of the initial and follow-up surveys among adult males and FCBPs since 2006. Data are presented on measures of patient understanding of key risks, compliance with the contraception requirement, and knowledge retention of the key risks associated with REVLIMID.

Results: Since the survey's inception, 27,780 patients were sampled with 22,167 (79.8 %) completing the initial and 82.6 % (22,432/27,143) completing the follow-up survey. Response rates were similar across all patient groups. Based on data from the initial surveys, respondents represent an older population (mean age of adult males, ~67 yo; mean age of FCBPs, ~45 yo). Eighty-seven percent (87.2 %) of FCBP and 90.3 % of all respondents reported receiving the educational brochure and generally read it (97 and 96 % respectively). Similarly, ~98 % of patients who received the information from the pharmacist reported understanding it. In the initial survey, between 95 and 99 % of patients reported understanding the key risk messages. Importantly, 92.7 % of FCBPs were compliant with birth control requirements. Among those taking REVLIMID for ≥3 months, knowledge of key risks associated with REVLIMID ranged from ~95 to 98 %.

Conclusion: The REVLIMID REMS™ program has demonstrated that REMS that incorporate consistent and repeated educational messages can be successful. Key risk messages were understood, contraceptive compliance rates were high and those messages were retained for ≥3 months. These results have remarkably consistent since the survey initiation in 2006.

Abstract Code: ISP3561-43

An Assessment of the 2005–2013 Voluntary THALOMID Patient Knowledge Surveys

E. Adams[1], S. Colman[2], N. Brandenburg[3], R. Bwire[3], J. Freeman[3], F. Houn[3], P. Sheehan[3]

(1) Covance Market Access Services Gaithersburg, MD USA, (2) Covance Market Access Services, Sydney, Australia, (3) Celgene Corporation, Summit, NJ USA

Background: In the United States THALOMID® (thalidomide) is indicated for the acute treatment of the cutaneous manifestations of moderate to severe erythema nodosum leprosum (ENL), and in combination with dexamethasone for the treatment of patients with newly diagnosed multiple myeloma (MM). THALOMID is only available through a Risk Evaluation and Mitigation Strategy (REMS) called the THALOMID REMS™ program (formerly *S.T.E.P.S.*®) [1]. The *S.T.E.P.S.*® program included voluntary patient surveys that were reported to the FDA quarterly and following REMS approval, annually. The requirement for the voluntary surveys was removed in 2013.

Objectives: The paper reviews data from the voluntary patient surveys during the observational period from 2005 through February 28, 2013.

Methods: During the registration process, patients indicated willingness to participate in a voluntary survey that was conducted in a sample of patients reported across 5 patient groups: Adult males ≥18 years old (yo), Males 12–17 yo, Females of Child Bearing Potential (FCBP), Adult Females Not of Childbearing Potential, and Children <12 yo. Evaluation included: surveys of newly prescribed patients, and surveys among patients receiving THALOMID for ≥3 months. Key measures included knowledge that THALOMID can cause birth defects, compliance with birth control, and not sharing medication, or giving blood. This report focuses on the results of the initial and follow-up surveys among adult males and FCBPs.

Results: Since inception, a total of 29,214 patients were sampled for the initial surveys and 22,123 (75.7 %) completed it. Response rates for the follow-up surveys were (16,534/20,895) 79.1 %. Respondents to the initial survey represent an older population (mean overall age, 63.5 yo; mean age of FCBPs, 41.6 yo). Overall 89.6 % report receiving the THALOMID brochure, almost all who received it reported reading it (19,330/19,820). In addition, 3,516 patients reported watching the video. Over more than 7 years of evaluation, respondents clearly understood the key risks associated with THALOMID with knowledge exceeding 95 % on all risk measures. For example among FCBPs, 99.3 % knew that THALOMID can cause birth defects, 98.5 % responded that women should not get pregnant, and that FCBPs need to use two different types of birth control (96.5 %) while taking THALOMID. Compliance among FCBP was 92.8 % and exceeded 95 % among males. Results for the follow-up/retention surveys were similar.

Conclusion: The THALOMID REMS™ program is effective as measured by knowledge of the key messages and compliance with birth control measures. Importantly, knowledge of these key messages was retained at 3 months.

Abstract Code: ISP3564-46

Healthcare Providers and Population's Knowledge Regarding the Risks Related to Medicinal Products Use: A Cross-Sectional Study in Laos.

C. Caillet[1], L. Syhakhang[2], C. Delpierre[3], C. Manithip[4], M. Mayxay[5], F. Quet[6], Y. Buisson[6], M. Lapeyre-Mestre[1], P. Newton[5], A. Roussin[1]

(1) Pharmacoépidémiologie, UMR1027 INSERM-Université de Toulouse III, Toulouse, France, (2) Food and Drug Department, Ministry of Health, Vientiane, Lao PDR, (3) Cancer et Maladies chroniques, UMR1027 INSERM-Université de Toulouse III, Toulouse, France, (4) Faculty of Pharmacy, University of Health Sciences, Vientiane, Lao PDR, (5) Wellcome Trust-Mahosot Hospital-Oxford Tropical Medicine Research Collaboration, Microbiology Laboratory of Mahosot Hospital, Vientiane, Lao PDR, (6) Institut de la francophonie pour la médecine tropicale, Vientiane, Lao PDR

Introduction: Besides promoting access to medicines, the rapid expansion of health markets in developing countries [1] also creates issues with drug safety. In Laos, as in numerous developing countries, health problems due to adverse drug reactions (ADRs) could arise from insufficient knowledge on drug safety of healthcare providers (HPs) of different educational backgrounds. In addition, whereas self-medication is very common in developing countries, there is a lack of data on the perception and knowledge of the population regarding the risks.

Aim: To assess the knowledge of Lao HPs and citizens regarding the potential risks induced by the use of medicinal products in Vientiane Capital.

Methods: We performed a cross-sectional study, using face-to-face interviews with pre-tested structured questionnaires of HPs and citizens in randomly selected health structures and villages, respectively. General and in-depth knowledge of HPs and citizens about the risks related to medicinal products use (including modern, counterfeits and traditional medicines) and the risks of drugs associations were investigated. Comparisons were performed between HPs of three different educational backgrounds: (i) Medical doctors, pharmacists; (ii) Nurses, mid-level medical/pharmacist assistants; (iii) Midwives, Village Health Volunteers, primary level medical/pharmacist assistants.

Results: We interviewed 219 HPs and 144 citizens. Most of HPs (91.8 %) had already heard about ADRs, significantly ($p = 0.0033$) more frequently among group (i). Thirty-eight percent of HPs did not think that ADR occurrence can be associated with normal doses and normal use of a medicine. Approximately 40 % of HPs had never heard about pharmacodynamic and pharmacokinetic interactions with a significant difference between the three educational backgrounds ($p = 0.0178$) in favor of group (i). For most of the citizens, modern and traditional medicines were thought not to induce harm at normal doses and with appropriate use (90.3 and 57.6 %, respectively). Only 36.8 % ($n = 53$) and 47.2 % ($n = 68$) citizens had already heard about ADR and low quality/counterfeits, respectively.

Conclusion: These results highlight the need to adapt the training of HPs and to inform the population about risks related to medicinal products in

order to promote the rational and appropriate use of medicinal products in Laos. A special focus on the possible occurrence of ADR with an appropriate use and on consequences of drugs associations is needed. A deeper understanding of local and national values and beliefs that drive risk perception is important in many countries to increase the level of public Health, especially in the developing world.

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Abstract Code: ISP3565-47

Evaluation of Re-Administration of Drugs Registered on Alert System

Y.R. Lee[1], J.W. Jung[2], B.W. Choi[2]

(1) Department of Pharmacy, Chung-Ang University Hospital, Seoul, Korea, (2) Department of internal medicine, Chung-Ang University Hospital, Seoul, Korea

Introduction: Just the same as collecting information of adverse drug reaction (ADR) and to monitor them, it is very important to prevent to re-prescribe the drugs through the ADR alert system. It is necessary to check the information about ADR of patient during prescription, because re-administration of the same drug may cause the more serious reactions. The ADR monitoring center in Chung-Ang University Hospital has evaluated the severity and causal relationship since October 2011. The ADR records were registered on EMR classified into two categories of severe/mild reaction and displayed with coloring on patient list according to severity.

Aim: To evaluate the influence of ADR alert system on doctors' prescribing decision.

Methods: The 741 patients who were registered in alert system from May 2012 to October 2012 were enrolled. According to the review of medical records, re-administration of causal drugs was investigated and tendency of re-dosing was evaluated.

Results: In 302 outpatients and 399 inpatients, 26 ADRs were severe reactions, which were with anti-neoplastic drugs (11), antibiotics (7), antituberculosis drugs (3), radiocontrast agents (1) and others (4). The causal drugs with mild reactions were antituberculosis drugs (198 cases, 27.7 %), opiate (114 cases, 16 %), antibiotics (99 cases, 13.9 %), anti-neoplastic agents (86 cases, 12 %), anti-inflammatory analgesic drugs (60 cases, 8.4 %), respiratory agents (31 cases, 4.7 %), radiocontrast agents (19 cases, 2.7 %), cardiovascular agents (15 cases, 2.1 %), gastro-intestinal agents (10 cases, 1.4 %), anticonvulsant (7 cases, 1 %) and others (72 cases, 10.1 %) respectively.

In the 707 cases who re-visit the hospital after the occurrence of adverse reaction, the anti-neoplastic agent with the reduced dosage were re-prescribed in 6 patients with previous severe ADR to same drugs.

In the mild cases, 156 cases of anti-tuberculosis drug have been re-used without replacing with the other drug and add the proper drug in order to alleviate ADR since antituberculosis drugs were limited. In the case of opiate it was mainly used for PCA (Patient-controlled analgesia) and there were 7 cases of re-dosing and the other dosage form of same ingredient.

Conclusions: In this study, it is estimated that the alert system can prevent to re-dose the drugs inducing ADR and it is also believed that the system was more effective in the case of causing the severe reactions. It is highly recommended that ADR alert system should be widely advertised to the medical staff and technique to assess the combination drug should be established.

Abstract Code: ISP3566-48

Validation of Sequence Symmetry Analysis as a Tool for Rapid Safety Signal Detection: A Simulation Study of Newly Marketed Medicines

N. Pratt[1], I. Wahab[1], L. Kalish[1], E. Roughead[1]

(1) Centre of Research Excellence in post-market surveillance of medicines and medical devices, QUMPRC, University of South Australia, Australia

Introduction: Sequence Symmetry Analysis (SSA) is a tool to generate medicine safety signals. The statistic of interest is the sequence ratio (SR), which estimates the risk ratio of events in exposed compared to unexposed person-time. The SR is robust to patient specific confounders but may be sensitive to underlying medicine utilisation trends. SSA utilises data from computerised claims databases and offers advantages over spontaneous report databases due to its computational speed and its minimum data set requirement. To date, power and sample size requirements for SSA as a rapid signal detection tool have not been investigated.

Aim: To evaluate the validity and sample size requirements of SSA as a signal detection tool for newly marketed medicines.

Methods: Randomly simulated prescription supplies for a population of one million were generated for two medicines, DrugA (medicine of interest) and DrugB (adverse event). Scenarios were created by varying utilization trends for a newly marketed medicine (DrugA). The magnitude of association between DrugA and DrugB were varied from no association to a two-fold increase in the risk of receiving DrugB after DrugA. 1,000 simulations were generated for each scenario. Average Adjusted Sequence Ratios [1] (ASR) were calculated to account for time trends in utilization and standard errors were generated using 100 bootstrap replications. To evaluate the performance of SSA approach, relative bias and coverage probabilities (percentage of CI's which contained the expected ASR) were calculated. Sample size calculations were performed by varying the prevalence of medicine use in the population.

Results: In scenarios where DrugA and DrugB were associated (ASR = 2), unadjusted SR's ranged from 1.90 (95 % Confidence Interval 1.68–2.15) for no trend in DrugA to 1.57 (95 % CI 1.42–1.74) for a steeply increasing trend. After adjustment ASR estimates were 1.90 (95 % CI 1.67–2.14) and 1.87 (95 % CI 1.69–2.07) respectively. For increasing trends in DrugA, 85 to 89 % of CI's contained the expected ASR. Sample size calculations suggests that 1,800, 800, 400 pairs are required to achieve an 80 % power to detect a 20, 50 and 100 % increased risk of an adverse event respectively.

Conclusions: Adjustment for underlying medicine utilization patterns effectively overcomes potential under-ascertainment of signals in SSA analyses. SSA has a place as a complementary post-marketing surveillance tool for newly marketed medicines in sufficiently large claims databases.

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Abstract Code: ISP3568-50

One Year Experience of Spontaneously Reported Adverse Drug Reactions in A Tertiary University Hospital

C.W. Kim[1], J.Y. Kang[2], M.R. Eom[2], S.H. Gong[2], H.G. Lee[2]

(1) Department of Internal Medicine, Inha University Hospital, Incheon, Korea, (2) Inha Regional Pharmacovigilance Center, Inha University Hospital, Incheon, Korea

Background: Adverse drug reactions (ADRs) frequently occur in hospital setting and affect negatively patient outcomes. The number of self-reported ADRs has been rapidly increased in Korea. This study was conducted to investigate the clinical characteristics of ADRs in a single university hospital, and to evaluate the features of ADRs to anti-asthma or anti-allergic drugs in patients with allergic diseases.
Methods: ADRs reported to Hospital Pharmacovigilance Center were collected from Jan 2012 to Dec 2012. Assessment was performed for causality and severity. Clinical information was also collected from electronic medical records.
Results: The total number of ADRs through spontaneous reporting system was 2,673. Among them, 1,693 (63.3 %) were reported from female, and 35.4 % were reported from patient aged 60 and over. ADRs were reported by doctors (36.5 %), nurses (39.7 %), and hospital pharmacists (23.8 %). Central nervous system (CNS) agents and anti-infective agents (AIA) were the drug class most commonly involved, and NSAIDs and cephalosporin antibiotics were the most frequently offending subclass. The most frequently reported system-organ class was GI system disorders (33.9 %), and skin and appendages disorders (22.1 %) were the next. Serious adverse events (SAE) were developed in 109 cases (4.1 %), severe cutaneous adverse reaction (SCAR) such as DRESS syndrome and Stevens-Johnson syndrome were noted in 17 cases. About 6.9 % of total ADRs were severe in severity. Compared to ADRs reported from doctor or pharmacists, severity of ADR reported from nurses was more mild form ($p < 0.01$). 85 ADRs (3.2 %) were developed against anti-asthmatic or anti-allergic drugs. Most of them were mild (71.8 %) and moderate (24.7 %) in severity. Anti-histamines (29 of 85) were the most commonly involved drugs in these classes. ADRs to inhaled steroids with/without LABA (9) and LTRA (4) were also reported.
Conclusion: Nurses report relatively mild ADRs, however, doctors and pharmacists may have tendency to report more severe cases of ADRS. Anti-infective drugs and NSAIDs can elicit ADRs most frequently. Although the severity is usually mild or moderate, ADRs to anti-asthmatics or anti-allergic drugs are not uncommon in patients with allergic diseases in university hospital setting.

Abstract Code: ISP3569-51

Utilization of ADR Reporting forward to Safety Laws and Regulations

P. Pokhagul[1], W. Suwannakaesawong[1], P. Sriphiromya[1]

(1) Food and Drug Administration, Nonthaburi, Thailand

Introduction: For a period of time, there were some spontaneous adverse drug reactions (ADRs) have been reported to Thai National Health Product Vigilance Center (HPVC). Some safety signals were discovered from Thai national ADR database (Thai Vigibase) such as barakol—acute hepatitis and andrographolide—hypersensitivity. Thai Vigibase will be very useful data for HPVC to improve their laws and regulations of safety.
Aims: To identify and minimize the potential risks from Thai Vigibase.
Methods: Suspected ADRs reported to the Thai Vigibase between 1984 and 2011 were reviewed and analyzed by descriptive statistics. The meetings were arranged to evaluate and discuss on the safety issues.
Results: For a total of 463,067 suspected ADR cases were reported to HPVC. Skin and appendages disorders divided by system organ class were mostly found, of which 8,394 cases (15.08 %) were serious skin adverse reactions as Stevens-Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN). And 242 fatal cases had these severe side effects. The first ten suspected medicines which were categorized in eight groups were co-trimoxazole (sulfonamide group), allopurinol (antigout), carbamazepine, phenobarbital, phenytoin (antiepileptic), ibuprofen (NSAIDs), nevirapine containing products (NNRTI), amoxicillin (penicillin group), rifampicin (antimalarial) and dapsone (sulfone group). Though SJS and TEN were already known ADRs for each drug, the safety label warning of these serious side effects has not been shown yet. It was submitted to the Developing Vigilance System and Risk Management Working Group and the Drug Safety Advisory Committee. The safety issues and risk communication were evaluated and the Safety News was launched. Giving advices to the Drug Committee, the safety laws and regulations were developed. Nowadays these medicinal products have the label warning about serious skin adverse reactions to communicate with public and health care professionals to enhance the safety level from drug use.
Conclusion: There are many benefits of ADR reporting, a crystal clear one is the safety laws and regulations development.

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Abstract Code: ISP3570-43

Pharmacovigilance at The University Hospital "Dr. José E. González": 2012 Report

L. Garza-Ocanas[1], S. Paz-Manifacio[1], E. Perez-Rodriguez[1], S. Guzman-Lopez[1]

(1) Medicine School and University Hospital "Dr. Jose E. Gonzalez", UANL, Monterrey, Mexico

Introduction: Hospital-based monitoring and reporting programmes aim to identify and quantify the risks associated with the use of drugs provided in hospital setting. This information may be useful for identifying and minimizing ADRs and medication errors (ME) and may enhance the ability of prescribers to manage ADRs more effectively.
Aim: The main objective of this study was to evaluate spontaneous ADRs and ME reports at the University Hospital "Dr. José E. Gonzalez (HU) in Monterrey, Nuevo León, México.
Methods: A prospective study was conducted, from January to December 2012. This observational, descriptive study was based on an analysis of spontaneous ADRs and ME reports. The parameters evaluated for ADRs, including: patient demographics, drug and reaction characteristics, and

reaction severity and outcomes. For ME the type, consequences, and stage of medication process were the ME occurred were evaluated.
Results: A total of 39 ADRs and 99 ME were reported. The highest ADR rate was found in the adult age group 15 to 60 years and gender was not found to be a risk factor. The nurse team (70 %) reported the most ADRs, most likely due to the job responsibilities of nurses. As expected, the most noticeable ADRs occurred in skin tissues, with such ADRs are more obvious to medical staff, with rashes being the most common reactions. The drugs responsible for most ADRs were paclitaxel, carboplatin, heparin, vancomycin, levofloxacin and warfarin. The majority of ADRs had moderate severity (60 %), thus requiring intervention. Type A reactions were the most common. Most of the ME were in doses (preparation process) and administration and were caused by missing actions. A common types of error throughout the medication process were: unordered drug, and omission of drug/dose. We assume that the number of spontaneous reports does not correspond with the total number of ADRs and ME of the studies period and there is a lack of reporting.
Conclusions: The results obtained will contribute to the development of strategies for the pharmacovigilance service at the HU, which will improve the quality of ADR and ME reporting and ensure safer drug use.

Abstract Code: ISP3571-44

Drug Induced Anaphylaxis in Korean: Data from the Adverse Drug Reaction Reporting System to the Korea Food and Drug Administration

J.W. Jung[1], H.R. Kang[2], Y.R. Lee[3]

(1) Department of Internal medicine, Chung-Ang University College of Medicine, Seoul, Korea, (2) Department of Internal Medicine, Seoul National University College of Medicine, Seoul, Korea, (3) Department of Pharmacy, Chung-Ang University Hospital, Seoul, Korea

Introduction: Adverse drug reactions occur in 10–20 % of hospitalized patients, 2 to 3 % experience allergic drug reactions and 1 in every 2,700 suffers drug-induced anaphylaxis. Incidences of drug-induced anaphylaxis from all drug types are reportedly rising.
Aim: We investigate causal drug and clinical manifestation of the drug induced anaphylaxis in Korean by using data from the adverse drug reaction (ADR) reporting system to the Korea Food and Drug Administration (KFDA).
Methods: Data were extracted from spontaneous ADR reporting system to KFDA from July, 2009 to December, 2010. The data were established by a pharmacovigilance research network including 15 regional pharmacovigilance centers. The data included reported date, patient's age, gender, and initials, as well as suspected drugs, concomitant drugs, and adverse event. We extracted and analyzed data about drug induced anaphylaxis.
Results: A total of 1,047 cases and 1,187 causal drug of drug induced anaphylaxis were identified. Male was 493 (47.7 %) and mean age was 50.84 ± 21.80 years. 138 cases (13.2 %) had grade 2 anaphylaxis, 242 (23.1 %) had grade 3, and 667 (63.7 %) had grade 4. Hypotension was presented in 596 patients (56.9 %) and dyspnea was in 392 (37.4 %). Most common causal drug was antibiotics (270, 22.7 %), 2nd was aspirin and NSAIDs (249, 21.0 %) and 3rd was contrast media (246, 20.7 %) and 4th was anticancer drug (115, 9.7%). Intravenous injection was most common administration rout (68.4 %) and next was oral administration (29.0 %). The rate of grade 4 anaphylaxis was significantly higher in males than in female (67.5, vs. 60.0 %, OR = 1.443, 95 % CI: 1.134–1.834, P = 0.003), in patients ≥60 years than in patients <60 years (70.8 vs. 59.0 %, OR = 1.482, 95 % CI: 1.297–1.694, P < 0.001) and in intravenous injection than in oral administration (67.9 vs. 50.9 %, P < 0.001). Anaphylaxis to propionic acid derivatives was 53 cases and had high risk for grade 4 anaphylaxis (OR = 2.071, 95 % CI: 1.077–3.985
Conclusion: Antibiotics and aspirin and NSAIDs were common causal drug for drug induced anaphylaxis in Korean. More than half of drug induced anaphylaxis was grade 4 and male and old age were risks for severe anaphylactic reaction.

Abstract Code: ISP3572-45

Drug-Induced Torsade de Pointes: Review of the National Adverse Drug Reactions Reporting System in Taiwan

W. Chen[1], L. Chen[2], W. Ke[1]

(1) Taiwan Adverse Drug Reactions Reporting Center, Taiwan Drug Relief Foundation, Taipei, Taiwan, (2) National Taiwan University, College of Pharmacy, Taipei, Taiwan

Background: Torsade de Pointes (TdP) is a rapid form of polymorphic ventricular tachycardia which is related to evidence of delayed ventricular repolarization with long QT interval or prominent U waves showed on electrocardiogram (ECG). Although the prevalence of drug-induced TdP remains unknown, associated risk factors and potential risky drugs have already been well studied. However, discrepancies of prescribing patterns, lifestyles, and prevalence of cardiovascular diseases between Taiwan and other countries may result in different patterns of relevant drugs and risk factors of TdP. The main purpose of this study was to review the patterns of drug-induced TdP in Taiwan.
Methods: The data of this study was derived from the database of National ADR Reporting System and Standardised MedDRA Queries (SMQs, MedDra: Medical Dictionary for Regulatory Activities) were used to define drug-induced TdP when retrieving the associated adverse drug reaction (ADR) cases up until February, 2013.
Results: A total of 135 TdP cases were identified under the definition of Standardised MedDRA Queries. Most of the cases were female (57.0 %). 110 cases (81 %) were considered as serious. The average age was 60.6 ± 18.6 years old and 83 cases (61.5 %) were older than 55 years old. Amiodarone, moxifloxacin and digoxin were most frequently reported. The onset of drug-induced TdP was within 2 weeks in most cases (56.3 %). 61 cases (45.2 %) were recovering or resolving from the ADR. As for the outcome of the ADR, 81 % (110 cases) were defined as serious per reporter. Left ventricular ejection fraction (4.4 %), serum magnesium (17.8 %), heart rate (21.5 %), and QTc interval (27.4 %) were seldom recorded in the case report.
Conclusion: Female and elderly counts for majority of the cases analyzed which was in consistency with the risk factors being well-studied. Prescribers should consider the risk of QT prolongation which can be fatal when weighing the risks and benefits for at-risk groups upon prescribing drugs with known TdP risk. Parameters of risk factor including left ventricular ejection fraction, serum magnesium, heart rate, QTc interval, and etc. should be assessed and recorded for better case evaluation.

Abstract Code: ISP3573-46

Medicines in the Paediatric Area: Recommendations for Safer Use and Improvement of Adverse Drug Reactions Reporting

F. Locchi[1], M. Morotti[1], D. Fedele[2], F. Rossi[3], M. Barotto[4], M. Falvo[5], S. Corradi[6], C. Puggioli[1], F. Bernardi[7]

(1) Clinical Pharmacy, Azienda Ospedaliero-Universitaria Policlinico S.Orsola-Malpighi, Bologna, Italy, (2) Pharmaceutical Department, Arcispedale S. Anna, Azienda Ospedaliero-Universitaria di Ferrara, Ferrara, Italy, (3) Pharmaceutical Department, Azienda USL di Ravenna, Lugo, Italy, (4) Pharmaceutical Department, Azienda USL di Ferrara, Ferrara, Italy, (5) Pharmaceutical Department, Istituto Ortopedico Rizzoli, Bologna, Italy, (6) Pharmaceutical Department, Azienda Ospedaliero-Universitaria Policlinico di Modena, Modena, Italy (7), Pediatric Unit, Azienda Ospedaliero-Universitaria Policlinico S.Orsola-Malpighi, Bologna, Italy

Introduction: Because of the limited number of clinical trials, the safety of drug use in children has not been well established and the consequence of such a lack of research is that many children are prescribed off label drugs [1]. Several studies suggest that the percentage of unlicensed and off-label drug use is significantly associated with the risk of Adverse Drug Reactions (ADRs) [2–4].
Aim: To improve both the off-label drug use clinical evidence based and the ADRs reporting in pediatric population.
Methods: It is a multi-center project, started in January 2012, involving the specific pediatric units and pharmacy services of six healthcare settings of Emilia-Romagna-Italy, with two main goals:

- editing an hospital formulary of drugs with evidence of safety and use in children to support prescribers
- promoting ADRs reporting and implementing a system of active pharmacovigilance in paediatric area

We analysed all drugs used in the pediatric units of the healthcare settings involved during one year (March 2011–2012) in terms of authorization/evidence of use in clinical practice.

We collected all ADRs reported from the six centres (period 2005–2012) and stored them into an Access database for analysis.

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Abstract Code: ISP3575-48

Colchicine Side Effects'

G. Lakhoua[1], S. Kastalli[1], A. Zaiem[1], S. Srairi[1], R. Daghfous[1], S. El Aidli[1]

(1) Centre National de Pharmacovigilance, Tunisia

Introduction: Colchicin is usually prescribed in gout, its side effects' are often gastro-intestinal symptoms (GIS) such as diarrhea, nausea or vomiting. Hematological troubles or cutaneous eruptions are rarely described.
Aim: The aim of our study is to precise the nature, the severity and circumstances of occurrence of the colchicin's side effects.
Methods: This is a retrospective study which has concerned all cases of adverse reactions where colchicine has been suspected. All the cases have been reported to the Centre National of Pharmacovigilance during the period 2009–2011. The imputability of colchicine was made according to the French method of imputability.
Results: Thirteen cases were retained: 6 women and 7 men. Their age varied from 24 to 82 years. Three cases were aged over 65 years. The nature of adverse side effects was hematological in 4 cases, hepatic in 3 cases, cutaneous in 3 cases, digest if in 2 cases, and an effect on reproduction (oligospermia) in one case. The score of imputability was likely in one case, possible in 6 cases and doubtful in six cases.
Discussion/Conclusion: Three elderly were retrieved among the 13 patients. Colchicin pharmacokinetic varies with age. In elderly, colchicine intestinal absorption is slowed, the volume of distribution of colchicine is reduced, so as the total corporal clearance, resulting in colchicine accumulation in body. This explains the frequency of toxic side effects in elderly.

GIS are the most frequent side effects with colchicine. In our series, we retrieved 2 cases of diarrhea and hematological reactions were the most frequent (4 cases). Those reactions are often associated with overdose, so as hepatic reactions.

In our study a case of cytolysis was retrieved with a high score of imputability (I3).

In our study, we have found three cutaneous eruptions (bullous eruption, fixed bullous drug eruption, and maculopapular eruption), they are probably due to an immunoallergic mechanism of colchicine. Those types of cutaneous eruption are rare and colchicine side effects' are mainly due to overdoses.

Azoospermia due to the antimitotic effect of colchicine, evolve favorably after drug discontinuation. That was also true in our case.

Abstract Code: ISP3576-49

Direct Cost of Severe Cutaneous Adverse Reaction in a Tertiary Hospital in Korea

S. Lee[1], J.Y. Koh[2], T. Kim[2], J. Lee[2], M. Yang[3], S. Cho[1], H. Kang[1]

(1) Department of Internal medicine, Seoul National University College of Medicine, Seoul, Korea, (2) Drug Safety Monitoring Center, Seoul National University Hospital, Seoul, Korea, (3) Department of Internal medicine, SMG-SNU Boramae Medical Center, Seoul, Korea

Introduction: There were several reports on the epidemiologic data on severe cutaneous adverse reactions (SCARs) in Korea. However, analyses on the direct cost of SCARs in Korea have never been reported.
Objective: To evaluate the direct cost of drug reaction with eosinophilia and systemic symptoms (DRESS) and Stevens-Johnson syndrome (SJS)/ toxic epidermal necrolysis (TEN) in a tertiary hospital in Korea
Method: Seventy-seven SCAR patients who admitted to Seoul National University Hospital from 2005 to December 2010 were included in this study. Patients who acquired SCARs during their admission due to other medical condition were excluded. Clinical data of the patients were reviewed. The direct cost for the hospitalization and the outpatient department (OPD) visits for the patients was collected and calculated.
Result: There were 40 DRESS and 37 SJS/TEN patients. Thirty six (46.8 %) were males. Median age was 47 years old. About 2.57 billion KRW [The Korean won (KRW) is the currency in South Korea. 1 United State Dollar = 1,109 KRW in May 15, 2013] was spent on the medical care for the study population. For inpatient care, 2.54 billion KRW (743 million for DRESS vs. 1.8 billion for SJS/TEN) was spent and 38 million (7.6 million for DRESS vs. 30 million for SJS/TEN) for the OPD visits. Median cost per person for the hospitalization was 7 million KRW for DRESS vs. 11 million for SJS/TEN. However, 6 SJS/TEN patients with ocular sequelae had to pay additional medical fee from 100 thousand to 16 million KRW for the ophthalmologic care. Additionally, 19 SJS/TEN patients who received intravenous immunoglobulin (IVIG) had a tendency to pay more money than 18 IVIG non-users [p = 0.08, 19.7 million KRW (2.1 million, 644 million] for IVIG users vs. 6.4 million KRW (1.3 million, 315 million) for IVIG non-users].
Conclusion: The management of SCARs requires considerable direct medical costs. SCARs in Korea are not only a public health problem but also a significant economic burden.

Abstract Code: ISP3577-50

Attention-Deficit/Hyperactivity Disorder Drug Prescribing Trend is Increasing Among Children and Adolescents in Hong Kong: 2001–2012

K. Man[1], P. Ip[2], E. Chan[1], C. Chui[1], M. Lam[1], W. Wong[2], C. Chow[2], A. Yung[2], I. Wong[1]

(1) Centre for Safe Medication Practice and Research, Department of Pharmacology and Pharmacy, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong SAR, (2) Department of Paediatrics and Adolescent Medicine, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong SAR, China

Introduction: Methylphenidate and atomoxetine are drugs available in Hong Kong that are recommended in the UK by the National Institute for Health and Clinical Excellence (NICE) guideline in treating Attention-Deficit/ Hyperactivity Disorder (ADHD) when drug intervention is considered appropriate in the management of ADHD symptoms. In the past few decades, ADHD prescribing trends rapidly increased in many Western countries. Of the scant published local studies in Hong Kong, the focus has been on the prevalence of ADHD among children and adolescents, but none have investigated prescribing of ADHD medication.
Aim: To investigate the prevalence of ADHD medication prescribing of children and adolescents in Hong Kong from 2001–2012 and to compare local prescribing patterns to those in other countries.
Methods: An observational study was conducted using Hong Kong Hospital Authority Clinical Data Analysis and Reporting System (CDARS) to investigate the epidemiology of children and adolescents receiving ADHD medication. Records of children and adolescents aged between 3–19 years who were prescribed either methylphenidate or atomoxetine from 2001–2012 were retrieved. The prevalence of children and adolescents prescribed ADHD medication was calculated. Microsoft Excel and Statistical Analysis System (SAS) v9.3 (SAS Inc., United States) were used for data manipulation and analysis.
Results: Prevalence of children and adolescents on ADHD medication increased from 0.066 % in 2001 (95 % confidence interval [CI] 0.062 to 0.070 %) to 0.819 % (95 % CI 0.802 to 0.836 %) in 2012. The prevalence demonstrated an increasing trend throughout the study period ($P < 0.05$). The prevalence of ADHD medication prescribing in females increased at a faster rate than that in males. The prescribing trend in kindergarten children (3–5 year-old) was relatively steady from 2001–2008 [0.012 % (95 % CI 0.007 to 0.017 %)] until a marked increase from 2009–2012 [0.051 % (95 % CI 0.039 to 0.062 %)].
Conclusion: The prevalence of ADHD medication prescribing in Hong Kong is increasing but still lower than most western countries. However, the prevalence of ADHD medication prescribing for kindergarten children has increased in recent years. It is important to continue to monitor the prescribing in this group of vulnerable patients.

Abstract Code: ISP3578-51

Safety of Tofacitinib in the Treatment of Rheumatoid Arthritis: a Systematic Review and Meta-Analysis

Y. He[1], A. Wong[1], E. Chan[1], W. Lau[1], K. Man[1], C. Chui[1], A. Worsley[1], I. Wong[1]

(1) Centre for Safe Medication Practice and Research, Department of Pharmacology and Pharmacy, The University of Hong Kong, Hong Kong SAR, China

Introduction: Tofacitinib is a disease-modifying antirheumatic drug (DMARD) which was recently approved by US Food and Drug Administration (FDA). There are several randomised clinical trials (RCTs) conducted on the efficacy and safety of tofacitinib in adult patients with rheumatoid arthritis (RA). A systematic review with a meta-analysis of RCTs was undertaken to investigate the safety of tofacitinib in treating patients with RA.
Aim: To compare the incidence of infections, immunological or haematological adverse events (AE), laboratory findings and the incidence of withdrawal from the trials in patients receiving tofacitinib versus placebo.
Methods: Electronic and clinical trials register databases were searched for published RCTs of tofacitinib between 2009 and 2013. Outcomes of interest include infections, immunological/haematological AEs, laboratory results (hepatic, renal, haematological tests and lipoprotein level) and incidence of withdrawal.

Results: Eight RCTs (n = 3,791) were reviewed. Patients in the tofacitinib group had significantly lower mean neutrophil counts, higher serum creatinine, higher percentage change of LDL/HDL and a higher risk of ALT/AST >1 ULN (upper limit of normal) versus placebo. There were no statistically significant differences in patients receiving tofacitinib versus placebo in the incidences of infections, neutropenia and withdrawal due to AEs. However, significantly fewer patients withdrew from tofacitinib than placebo (RR 0.60; 95 % CI 0.45, 0.78).
Conclusion: Haematological, liver function tests and lipoproteins should be monitored when patient is prescribed with tofacitinib. Long-term efficacy and pharmacovigilance studies are recommended.

Abstract Code: ISP3579-52

Antibiotics and Liver Injury in Paediatric Primary Care: a Case–Control Study using Healthcare Database Network

C. Ferrajolo[1,2], K.M. Verhamme[2], G. Trifirò[2,3], B. Stricker[4], G. Picelli[5], C. Giaquinto[6], C. Cricelli[7], F. Rossi[1], A. Capuano[1], M.C. Sturkenbooom[2,4]

(1) Campania Regional Centre of Pharmacovigilance and Pharmacoepidemiology, Experimental Medicine, Second University of Naples, Naples, Italy, (2) Medical Informatics, Erasmus MC University, Rotterdam, The Netherlands, (3) Clinical and Experimental Medicine and Pharmacology, University of Messina, Messina, Italy, (4) Epidemiology, Erasmus MC University, Rotterdam, The Netherlands, (5) Pedianet-Società Servizi Telematici SRL, Padua, Italy, (6) Paediatrics Department, University Hospital, Padua, Italy, (7) Società Italiana di Medicina Generale, Florence, Italy

Background: Antibiotics have been associated with hepatotoxicity but the comparative risk of liver injury among antibiotics needs to be better evaluated in the pediatric population.
Objective: To assess the association between antibiotic use and liver injury in children and adolescents.
Methods: We performed a population-based case-control study combining three European electronic primary care databases over the years 2000–2008: The Integrated Primary Care Information database (Netherlands), and PEDIANET and Health Search/CSD Longitudinal Patient Database (Italy) covering overall 450,000 children and adolescents (<18 years old). Cases of liver injury in this paediatric population were identified according to CIOMS criteria and validated in each database, retaining only idiopathic events. Up to 100 controls were matched to each case by age, sex and index date. Antibiotic exposure was classified as current if a prescription for the antibiotic of interest lasted until index date or ended within 15 days prior to the index date. Odds Ratios (OR, plus 95 % of confidential interval, CI) of liver injury following antibiotic use were estimated using conditional logistic regression.
Results: Overall, 938 liver injury cases were matched to 103,306 controls. Current use of any antibiotic was associated with an increased risk for hepatotoxicity compared to past use [OR adj. 2.8 (95 % CI 2.3 to 3.6)]. In comparison to past use of antibiotics, statistically significant ($p < 0.05$) associations were identified for current use of the following agents: rokitamycin (16.6, 6.9–39.9) and clarithromycin (3.5, 2.0–6.4) among macrolides; ceftriaxone (14.9, 6.1–36.7), cefaclor (3.9, 1.8–8.1), and cefixime (3.6, 1.7–7.7) among cephalosporins; co-trimoxazole (12.6, 5.5–28.6); amoxicillin/clavulanic acid (2.5, 1.6–4.0) and amoxicillin (1.9, 1.1–3.1), among penicillins. When restricting the analysis to the cases diagnosed by specialists, the associations remained for all of these antibiotics, except for rokitamycin and amoxicillin. When using current use of amoxicillin as comparator, the risk of liver injury increased only for current use of rokitamycin, ceftriaxone, and co-trimoxazole.
Conclusions: The risk of liver injury in children and adolescents is three-times higher for current users of antibiotics as compared to those who were previously exposed. Among antibiotics belonging to different therapeutic subclasses, heterogeneity of the associations was observed ranging from 16.6 for rokitamycin to 1.9 for amoxicillin. Several analyses were applied to control for confounding factors, although some residual confounders due to unmeasurable covariates, such as severity of infection, cannot be ruled out.

Abstract Code: ISP3580-44

Antidepressant Use in Italian Elderly Patients: a Nationwide Population Based-Study

J. Sultana[1], D. Italiano[1], E. Spina[1], C. Cricelli[2], F. Lapi[2], S. Pecchioli[2], G. Trifirò[1]

(1) University of Messina, Messina, Italy, (2) Italian College of General Practitioners, Florence, Italy

Introduction: Despite the high use of antidepressants (ADs) among the elderly there is limited information about the use of these drugs in this population.
Aims: To analyse the patterns of AD prescribing in the Italian elderly population, and specifically to evaluate rate and predictors of AD treatment discontinuation.
Methods: The general practice Health Search Database (HSD) was used to identify AD users aged over 65 years old from 2003–2009. ADs were categorised as (1) selective serotonin reuptake inhibitors (SSRIs); (2) serotonin-norepinephrine reuptake inhibitors (SNRIs); (3) tricyclic antidepressants (TCAs); (4) noradrenergic and specific serotonergic antidepressants/norepinephrine reuptake inhibitor (NaSSAs/NRIs); (5) other ADs. Prevalence of AD use per 1,000 inhabitants was calculated by drug class and single compound. We also measured the numbers of continuous and intermittent users and 'switchers' and identified rate and predictors of AD discontinuation (i.e. treatment gap of ≥60 days).
Results: Overall, 39,560 AD users over 65 years (3.4 % of the total HSD population) were included in the study. SSRIs were increasingly and most frequently prescribed ADs (102.7–195.3 per 1,000 over 7 years). The most common indications for AD use were depression and anxiety. Overall, 14 % of AD users continued their AD medication without treatment gaps, 27 % were intermittent AD users and 58 % discontinued their ADs during the first year of follow-up. In depressed AD users, concomitant use of ≥5 drugs was more likely to predict discontinuation (IRR = 1.22, CI 1.1–1.34). The use of NaSSas/NRIs, TCAs and 'other ADs' was also more likely to predict discontinuation, as were the patients' origins in Southern Italy.
Conclusion: ADs, especially SSRIs, are widely and increasingly prescribed in elderly Italian patients. High AD discontinuation rates, especially for TCAs and 'other ADs' are likely to impact the achievement of a therapeutic endpoint. Predictors of drug discontinuation as explored in this study have the potential to identify populations at risk of low adherence a priori and improve the clinical efficacy and economic efficiency of treatment plans.

Abstract Code: ISP3581-45

Creation of the Chapter ISOP ISRAEL and its Program Tailored to the Specificities of Israeli Healthcare System

I. Fermont[1], L. Brezka[2], M. Marcus-Kalish[3], H. Voliovitch[4], Y. Wexler[5], D. Cohen[6]

(1) Advisory Board and Safety Strategic Consulting, Jerusalem, Israel-Plaisir, France, (2) Advisory Board and KAMADA, Kibbutz Beit Kama, Israel, (3) Advisory Board and International Research Affairs and Interdisciplinary Center for Technology Analysis and Forecasting (ICTAF), Tel Aviv University, Israel, (4) Advisory Board and TEVA, Petah Tikva, Israel, (5) Advisory Board and BIOFORUM, Ness Siona, Israel, (6) School of Public Health, Sackler Faculty of Medicine, Tel Aviv University, Israel

Introduction: According to OECD, in 2013, Israel has "*one of the best healthcare systems in the world*". Since 1995, Israel has set up original mechanisms dedicated to patient's protection:

- **The Health Management Organizations** have developed extensive computerized health records and databases on the Israeli population for the last 20 years, allowing signals detection and analysis, risk factors identification and the quick, harmonized implementation of prevention/minimization actions in case of a safety concern.
- **The Risk Management Units** in hospitals detect and analyze safety concerns arising from healthcare products or disease management, and implement correction actions, such as the remarkable Medical Simulation Center of Tel Hashomer in Ramat Gan.

Since 2012, the Ministry of Health underwent a wide re-organization with a new Pharmacovigilance regulation, inspired by the European one, requiring for instance a Qualified Person for Pharmacovigilance. EU Advanced Therapies regulation has been adopted earlier to answer the development of Cell and Gene Therapy products

Methods: The project of an Israeli Chapter of ISOP started in January 2013 and is committed to join forces with the Ministry of Health toward the implementation of the new regulation.

ISOP ISRAEL has the mission to mobilize all strengths to improve Pharmacovigilance for the benefit of all:

- Academia, through research, developing tools and education,
- Industry, through identifying their needs and providing their experience
- The Regulatory Agency through the evaluation of all regulations and their environment.

ISOP ISRAEL objectives are:

- Improve and harmonize Pharmacovigilance systems in Israel
- Increase awareness on patient's safety
- Gather all stakeholders
- Be a think tank
- Support a mechanism for data sharing between all stakeholders and Ministry of Health
- Use and develop new Pharmacoepidemiologic tools and databases

ISOP ISRAEL will achieve this goal through:

- An educational program:
  - For Healthcare professionals and General Public
  - Integration of Pharmacovigilance courses in medical, paramedical and pharmacist studies
  - Academic specialization course
  - Professional continuing education
- Sharing experience with other regions through multidisciplinary workshops and publications

Results: After several meetings, an Advisory Board was created. The Tel Aviv University supports this project as well as an increasing number of pharmaceutical companies.

The 1st ISOP ISRAEL Conference is planned in November 2013 with expected speakers from ISOP, EU and US Authorities.

Conclusion: ISOP ISRAEL is raising a great interest among industry and academy and has the ambition to foster a unique and original Pharmacovigilance system to be shared with the international community.

Abstract Code: ISP3582-46

Systematic Review and Meta-Analysis of the Safety of Perampanel in the Treatment of Partial-Onset Epilepsy

W. Hsu[1], C. Sing[1], Y. He[1], A. Worsley[1], I. Wong[1], E. Chan[1]

(1) Centre for Safe Medication Practice and Research, Department of Pharmacology and Pharmacy, The University of Hong Kong, Hong Kong SAR, China

Introduction: Perampanel is a highly selective and noncompetitive antagonist of the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) glutamate receptor. AMPA receptors are found on the excitatory synapses in the central nervous system. These receptors mediate fast synaptic signaling by the binding of glutamate, which is an excitatory neurotransmitter. Overexpression of AMPA receptors plays a crucial role in the forming and spreading of seizures. Therefore, as an AMPA receptor antagonist, perampanel produces an anti-epileptic effect. The European Medicines Agency (EMA) and the United States Food and Drug Administration (FDA) approved perampanel under the trade name Fycompa® in July 2012 and October 2012 respectively. It is a first-in-class AED approved for adjunctive treatment of partial onset seizure in patients aged 12 years old or older. A meta-analysis of the safety of parampanel was warranted to combine evidence from currently available RCTs to investigate the safety of perampanel.

Aim: To systematically review the safety of perampanel in the treatment of partial-onset epilepsy.

Methods: Electronic and clinical trials databases were searched for randomised controlled trials (RCTs) of perampanel published up to March 2013. Outcomes of interest were treatment-emergent adverse events (TEAEs) and incidence of withdrawal. Meta-analysis was performed to investigate the outcomes of interest.

Results: Five RCTs with a total of 1,678 subjects were included. Dizziness, somnolence, headache, fatigue and nasopharyngitis were included in this meta-analysis. The association between perampanel and TEAEs was assessed using 95 % confidence intervals of the RRs. There was no evidence of a statistically significant association between the use of 4 mg perampanel and the five TEAEs. Of the five commonly reported TEAEs included, both dizziness and somnolence were statistically associated with 8 mg perampanel, whilst dizziness was statistically associated with 12 mg perampanel. Incidences of withdrawal due to adverse events were significantly higher in 8 and 12 mg perampanel groups versus placebo.
Conclusion: Perampanel is well tolerated at 4 mg and reasonably tolerated at 8 and 12 mg. Further clinical and pharmacovigilance studies are required to investigate the long-term efficacy and safety of perampanel.

Abstract Code: ISP3583-47

Working to Improve the ADRs Reporting in Oncology: An Example of Cooperation Between Pharmacists and Clinicians

R. Bona[1], P. Mero[2], D. Piccioni[2], I. Barbato[2], P. Graziano[3], A.M. Toffano[3], M. Colombo-Gabri[3], F. Testore[4], S. Martinetti[2]

(1) School of Clinical Pharmacy, University of Turin, Turin, Italy, (2) Pharmaceutical Care Service, Asti Local Health Unit, Asti, Italy, (3) Hospital Pharmacy, Asti Local Health Unit, Asti, Italy, (4) Oncology, Asti Local Health Unit, Asti, Italy

Introduction: Under-reporting is recognized as the main limitation of the Pharmacovigilance System, particularly in the field of oncology. The development of pharmacovigilance activity is particularly urgent to monitor drug effects in oncologic patients.

In Italy innovative cancer drugs were included in National Registry of Cancer Drugs subject to intensive monitoring to evaluate its safety and effectiveness.

In Asti Local Health Unit (ASL AT) are active part of the process a Clinical Pharmacist, working on the Oncology ward, and a Pharmacist Responsible for Pharmacovigilance, working on the Pharmaceutical Care Service. The Pharmacist Responsible for Pharmacovigilance reports the ADRs to the National Network of Pharmacovigilance.

The Oncology Clinical Pharmacist has a substantial role in Adverse Drug Reactions (ADRs) reporting to the National Registry, but these ADRs are not automatically reported in the National Network of Pharmacovigilance. Fundamental is the cooperation between the two Pharmacist functions, to promote the transmission of ADRs reports.
Aim: The primary aim of this research was to define a process of cooperation between the Oncology ward, the Hospital Pharmacy and the Pharmaceutical Care Service, to improve reporting of adverse drug reactions (ADRs) in the National Network of Pharmacovigilance.

The secondary aim was to analyze the ADRs that happened in Piedmont and in ASL AT, particularly concerning cancer drugs.
Methods: The way of cooperation was defined through multidisciplinary meetings, including Pharmacists and Oncologists.

The data concerning the ADRs were extracted from the National Network and analysed with MSExcel.
Results: The Clinical Pharmacist works beside the Oncologist, in order to improve and optimize the reporting of ADRs. Later, the Clinical Pharmacist, in cooperation with the Responsible for Pharmacovigilance, report the ADRs to the National Network. The number of ADRs reported for anticancer drugs in ASL AT has increased from 10 in 2011 to 56 in 2012.

A total of 2,353 ADRs occurred in Piedmont in 2012; 130 ADR reports were collected in ASL AT. From 130 reports, 43 % concern anticancer agents: 12.5 % taxane, 30.4 % protein kinase inhibitors, 12.5 % multitargeted antifolate, 33.9 % monoclonal antibodies.
Conclusion: The project demonstrated the importance of the Pharmacovigilance activities, to increase reporting of ADRs and the knowledge about security and efficacy of anticancer agents. A great opportunity exists for Pharmacists to contribute in area of Pharmacovigilance. Pharmacists have the knowledge and responsibility to contribute to ADR reporting programs.

Abstract Code: ISP3584-48

Leukotriene Receptor Antagonists and Suicide: a Self-Controlled Case Series Study

N. Iessa[1], M. Murray[1], I. Wong[2], K. Man[2], B. Frank[3], P. Santosh[4], A. Sutcliffe[5]

(1) Centre for Paediatric Pharmacy Research, UCL School of Pharmacy, London, (2) Department of Pharmacology and Pharmacy, Li Ka Shing Faculty of Medicine, The University of Hong Kong, (3) Mid Beds Clinic, CAMHS-LD SEPT: South Essex Partnership University NHS Foundation Trust, Grove Place, Bedford, United Kingdom, (4) Department of Child and Adolescent Psychiatry, Institute of Psychiatry, King's College London, UK, (5) General and Adolescent Unit, Institute of Child Health, University College London, London, UK

Background: In March 2008 the suicide of a 15 year old boy captured media attention. The suicide was attributed to exposure to montelukast, a leukotriene receptor antagonist (LTRA) used to treat asthma and allergies. Existing observational studies fail to provide evidence of a link between suicide behaviour and LTRAs, and further investigations are needed. The presence of unknown and unmeasured confounders are limitations in observational studies, particularly in the study of suicide which has several risk factors. The self-controlled case series (SCCS) method automatically controls for fixed confounders.
Objectives: To investigate the association of suicide and LTRAs using the SCCS method in the UK.
Method: Electronic healthcare records of patients with a record of suicide attempt (including suicide and self -harm, poisoning-self-inflicted, injury–self inflicted, cause of overdose-deliberate) and exposure to LTRAs during the period of 1st January 1998 to 1st January 2011 were extracted from the Health Improvement Network (THIN) database of anonymised records from contributing UK general practices. A risk period within thirty days of exposure to LTRA and control periods within the observation time of each patient were identified. A Poisson analysis conditioned on the event was used to calculate the Incidence Rate Ratio (IRR).
Results: A total of 370 cases of first attempts of suicide were identified. The IRR for a risk period of 30 days after the start of treatment with LTRA was 1.69 (95 % CI 0.80–3.58; $P = 0.167$).
Conclusion: Our study does not support the association between the use of LTRA and suicide attempts within the first thirty days of exposure to LTRA. Further studies with larger number of cases are needed.

Abstract Code: ISP3585-49

An Investigation of The Association Between Retinal Detachment and Oral Fluoroquinolones: A Self-Controlled Case Series Study

C.S. Chui[1], K.K. Man[1], C. Cheng[2], E.W. Chan[1], W.C. Lau[1], V.C. Cheng[3], D.S. Wong[4], Y. Yang-Kao[2], I.C. Wong[1]

(1) Centre for Safe Medication Practice and Research, Department of Pharmacology and Pharmacy, Li Ka Shing Faculty of Medicine, The University of Hong Kong, (2) Institute of Clinical Pharmacy and Pharmaceutical Sciences, College of Medicine and Health Outcome Research Center, National Cheng Kung University, (3) Department of Microbiology, Li Ka Shing Faculty of Medicine, The University of Hong Kong, (4) Department of Ophthalmology, Li Ka Shing Faculty of Medicine, The University of Hong Kong

Introduction: Fluoroquinolones (FQ) are a commonly prescribed class of broad-spectrum antibiotics and retinal detachment (RD) is a medical urgency where surgical intervention is needed. Etminan et al recently reported that patients who took oral FQ were at a higher risk of developing RD when compared with nonusers. However, it is not clear whether the analysis adequately controlled for the effect of variations in the severity of myopia, as risk of RD increases with the severity of myopia. Further, no existing studies have ever reported the absolute risk of experiencing RD while on FQ treatment.

Aim: To investigate the association between oral FQ and RD and to estimate the absolute risk of developing RD in patients exposed to oral FQ.

Methods: We performed a self-controlled case series study on the Hong Kong, Taiwanese and British patients who had prescription(s) of oral FQ (exposure) and procedure code(s) of RD (event) during 2001–2012; 2000–2010; and 1994–2012 respectively. Records were retrieved from the Hong Kong Clinical Data Analysis and Reporting System database, the Taiwan National Health Insurance Research Database and the United Kingdom IMS Disease Analyzer Database. Incidence rate ratios (IRR) are derived, by comparing the rate of events during exposed periods (on-medication), with the rate during all other observed non-exposed periods (off-medication). Microsoft Excel and Statistical Analysis System (SAS) v9.3 (SAS Inc, United States) were used for data manipulation and the analyses.

Results: A total of 1,516,566 FQ prescriptions were prescribed to 836,249 patients. There were 417 cases in Hong Kong, 1,002 cases in Taiwan and 861 cases in United Kingdom. A total of 13 events were found during the FQ exposed period; and 2,268 during the non-exposed period. The adjusted IRR for patients in Hong Kong was 1.35 (95 % confidence interval 0.41–4.41), 1.70 (0.84–3.46) for patients in Taiwan and 0.65 (0.16–2.63) for patients in United Kingdom. In the combined model, there was no statistically significant association with an adjusted IRR of 1.30 (0.75–2.27). The crude absolute risk of experiencing RD whilst on oral FQ was approximately 1 per 150,000 prescriptions.

Conclusions: Our study does not support the association between the use of FQ and the development of RD. Therefore, the use of FQ should not be precluded based on the current evidence on the risk of RD. However, in view of the current debates, a further study is warranted to investigate this controversial association.

Abstract Code: ISP3586-50

Dipeptidyl Peptidase-4 Inhibitor Use and Risk of Acute Pancreatitis in Patients with Type 2 Diabetes

J. Seong[1], N. Choi[2], J. Kim[3], J. Lee[2], Y. Kim[4], B. Park[1]

(1) Korea Institute of Drug Safety and Risk Management, Seoul, Korea, (2) Medical Research Collaborating Center, Seoul National University College of Medicine/Seoul National University Hospital, Seoul, Korea, (3) Department of Family Medicine, Seoul National University Bundang Hospital, Seoul, Korea, (4) Department of Preventive Medicine, Seoul National University College of Medicine, Seoul, Korea

Background: There is uncertainty about whether use of dipeptidyl peptidase-4 (DPP-4) inhibitors is associated with the risk of acute pancreatitis in a clinical practice setting.

Objectives: To evaluate the risk of acute pancreatitis in patients treated with the combination of a DPP-4 inhibitor plus metformin compared with a sulfonylurea (SU) plus metformin or a thiazolidinedione (TZD) plus metformin.

Methods: This was a retrospective, population-based cohort study using the 2006–2010 national health insurance claims database from the Health Insurance Review and Assessment Service (HIRA), Republic of Korea. Patients aged 20–99 years with type 2 diabetes who initiated a DPP-4 inhibitor, SU or TZD plus metformin were included between December 1, 2008 and December 31, 2009. Patients with acute pancreatitis in the 2.5 years prior to cohort entry were excluded. Incident acute pancreatitis was assessed using incidence rates by study therapies and relative ratio (RR) estimated from Cox proportional models and propensity score (PS) analyses for a DPP-4 inhibitor plus metformin, compared with a SU or TZD plus metformin.

Results: A total 376,208 patients were included in the cohort, including 78,712 treated with a DPP-4 inhibitor plus metformin, 266,875 with a SU plus metformin, and 30,621 with a TZD plus metformin. Incidence of acute pancreatitis in a DPP-4 inhibitor, SU, and TZD plus metformin users was 1.16, 1.21 and 1.04 cases per 1,000 person-years, respectively. Neither multivariable nor PS-adjusted Cox models demonstrated an association between the use of a DPP-4 inhibitor plus metformin and acute pancreatitis. In PS-stratified models, the RR for a DPP-4 inhibitor plus metformin compared with a SU plus metformin was 1.03 (95 % confidence interval (CI), 0.77–1.37) and compared with a TZD plus metformin was 1.14 (95 % CI, 0.69–1.88).

Conclusions: The risk of acute pancreatitis in patients receiving DPP-4 inhibitor plus metformin was not significantly different from that in patients receiving a SU or TZD plus metformin.

Abstract Code: ISP3587-51

The Analysis of the Special Situations and the Product Technical Complaints Associated with Adverse Reactions Received by Bayer Turk

B. Unal[1], E. Arslan[1], B. Ozturk[1], O. Korkmaz[1]

(1) Bayer Turk Kimya San. Ltd. Sti., Istanbul, Turkey

Background: The current Turkish Pharmacovigilance Guideline is effective since 2005, whereas the new pharmacovigilance legislation has come into effect across the EU in 2012. The term "dose" is removed in the new definition of adverse reaction (AR) and extended including the uses outside terms of Marketing Authorisation (including misuse and abuse), medication error, overdose, occupational exposure by EMA.
Aim: To compare the reporting requirements of *special situations* (use of a medicinal product during pregnancy or breastfeeding, overdose, abuse, off-label use, misuse, medication error, occupational exposure, lack of therapeutic efficacy) between the current Turkish Pharmacovigilance Guideline and EMA regulation; additionally to assess the cases received by Bayer Turkey during a 5-year period.
Methods: The regulation in Turkey is compared with the new EU reporting requirements in terms of *special situations*. The number of spontaneous, literature reports and the reports which are related to product technical complaints (PTCs) were investigated during 2008–2012.
Results: Most of the reporting requirements are the same in terms of *special situations*; however positive/negative experiences during breast-feeding should be only mentioned in Periodic Safety Update Report in Turkish regulation whereas suspected ARs which occur in infants following exposure to a medicinal product from breast milk should be reported in the new EMA regulation. Medication error (ME) and occupational exposure are not mentioned in Turkish regulation whereas it is stated in the new EMA regulation.

Based on our yearly review, there is an increase in the number of *special situations* between 4 and 117 % per year. The observed increase in the number of PTCs associated with an AR is between 4 and 83 % per year. There is a significant increase (117 %) of the *special situations* from 2008 to 2009, resulting from the literature reports. The most frequently reported reaction is lack of therapeutic efficacy followed by use of a medicinal product during pregnancy and ME. Occupational exposure has not been reported at all.
Conclusions: Our investigation points out that the current regulation in Turkey is align with Vol 9A in terms of reporting *special situations*. When the awareness of reporting ARs is increased, the reports of *special situations* are increased in parallel. Most of the MEs have been received while asking a medical inquiry about the possible consequences.

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Abstract Code: ISP3588-52

The Observational Safety Evaluation of Asenapine (OBSERVA) Study: Rationale and Design

D. Layton[1], F. Mitchell[2], S.A. Shakir[1]

(1) Drug Safety Research Unit, Southampton, UK; University of Portsmouth, Portsmouth, UK, (2) Drug Safety Research Unit, Southampton, UK

Background: Specialist Cohort Event Monitoring (SCEM) post marketing studies (registries) are designed to monitor the use and safety of new drugs prescribed by specialists. Thus SCEM studies complement primary care based studies by monitoring use and safety in the more complex patient population seen by specialists.

OBSERVA is being conducted as part of the Risk Management Plan to monitor the short-term (<12 weeks) safety and utilisation of asenapine (Sycrest®) as prescribed by psychiatrists in a mental health care setting in England and Wales.
Objectives: To describe the rationale, challenges and study design choice of OBSERVA
Methods: A single exposure observational cohort study of >1,000 patients identified over 2 years with no specific exclusion criteria. Important considerations in the design include facilitating recruitment of patients with mental health conditions who may have difficulty in providing consent/participation in research, risk estimation in the absence of a counterfactual comparator cohort, external factors (prescribing guidelines) influencing drug availability and case definition of outcomes often subject to mis-ascertainment (adherence, reported misuse/diversion).
Results: OBSERVA has been adopted by the Mental Health Research Network who will collaborate in: enrolment of investigative sites where asenapine is on the drug formulary; patient recruitment and help maintain psychiatrist engagement. Thus potential obstacles affecting recruitment are likely to be minimised. For estimating strength of association between exposure to asenapine and acute events associated with administration in such a diverse study population and lack of comparator cohort, the self controlled case series method will be employed. Since December 2012, 9 investigative sites have engaged.
Conclusions: Well designed observational studies/registries are an important and valuable approach to monitoring the post-marketing safety

of new treatments. Identifying appropriate strategies during study design may help overcome recruitment challenges. This is anticipated to be of particular value given increasing legal demands for post-authorisation Pharmacovigilance.

Abstract Code: ISP3590-45

Great Case Reports, Where Do They Come From?

T. Bergvall[1], G.N. Norén[1], M. Lindquist[1]

(1) Uppsala Monitoring Centre, WHO Collaborating Centre for International Drug Monitoring, Uppsala, Sweden

Background: Individual case reports are fundamental to post-marketing surveillance. Their value is directly proportional to the amount of clinically relevant information they include. The Uppsala Monitoring Centre has developed a completeness measure for the amount of clinically relevant information in structured format, without consideration of whether the information establishes causality between the drug and adverse event.
Objective: To identify predictors of well-documented individual case reports, globally.
Methods: Completeness (C) starts at 1 for reports with information on *time-to-onset*, *age*, *sex*, *indication, outcome, report type, dose, country*, *primary reporter*, and *case narrative*. For each missing information item, a penalty of 50 % (*time-to-onset)*, 30 % (*age*, *sex*, *indication, outcome*) or 10 % (*report type, dose, country*, *primary reporter*, *case narrative*) is detracted. The penalty varies with clinical relevance, as determined by three UMC pharmacovigilance experts with medical training, through consensus. We classified reports with $C > 0.8$ as well-documented and identified all such reports in the WHO Global ICSR Database, VigiBase, from 2007 to Jan. 2012. We utilized shrinkage odds ratios to identify countries, reporter categories and report formats with unexpectedly high proportions of well-documented reports if the lower limit of the 99 % credibility intervals exceeded 0.5.
Results: Altogether, 430,000 (13 %) of the studied reports achieved $C > 0.8$ in VigiBase. Two out of three well-documented reports come from Europe, and two out of three from physicians. Among the countries with more than 1,000 reports in total, the highest rate of well-documented reports is 65 % in Italy. Tunisia, Spain, Portugal, Croatia, and Denmark each have rates above 50 %, and another 20 countries have rates above 30 %. On the whole, 24 % of the reports from physicians are well-documented compared to only 4 % for consumers/non-health professionals. Notably, Denmark and Norway have more than 50 % well-documented reports from consumers/non-health professionals and higher rates for consumers/non-health professionals than for physicians. The rate of well-documented reports for the E2b format is 11 % compared to 22 % for INTDIS. However, for E2B reports entered via the WHO programme's e-reporting system VigiFlow, the rate is 29 %.
Conclusion: Overall, only one in ten reports provide the desired level of information, but much higher proportions are observed for individual countries. Physicians and e-reporting tools also generate greater proportions of well-documented reports overall, whereas reports from consumers/non-health professionals in specific regions have excellent quality, which illustrates their potential for the future.

Abstract Code: ISP3591-46

High-Versus-Low-Dose Histamine-2 Antagonists for the Prophylaxis of Non-Steroidal Anti-Inflammatory Drug-Associated Gastrointestinal Ulcers

Y. He[1], W.C. Lau[1], E.W. Chan[1], K.K. Man[1], V.C. Cheng[2], I.C. Wong[1]

(1) Centre for Safe Medication Practice and Research, Department of Pharmacology and Pharmacy, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong SAR, China, (2) Department of Microbiology, Queen Mary Hospital, Hong Kong West Cluster, Hong Kong SAR, China

Introduction: Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most commonly prescribed drugs, which are widely used in the treatment of pain, fever and rheumatic disorders. However, their potential to cause gastrointestinal ulcers (GIUs), including peptic and duodenal ulcers, remains a major concern. Acid-suppression drugs such as histamine-2-receptor antagonists (H2RAs) or proton pump inhibitors (PPIs) are commonly prescribed together with NSAIDs for the treatment or prevention of GIUs. A previous Cochrane review showed that high-dose H2RAs were more effective compared to placebo in preventing NSAID-associated endoscopic GIUs while standard-dose H2RAs were statistically no more effective than placebo. To date, there was no study which has investigated the effectiveness of H2RAs in the primary prophylaxis of NSAID-associated clinical GIUs.
Aim: To compare the effectiveness of high-dose versus low-dose H2RAs in the primary prophylaxis of NSAID-associated clinical GIUs in Hong Kong during 2011–12.
Methods: A retrospective cohort study was conducted using Hong Kong Hospital Authority Clinical Data Analysis and Reporting System. Both records of incident adult patients (18 years or older) who had prescription(s) of NSAIDs + H2RAs (exposure) and diagnosis code(s) of GIUs (event) during 2011–12 were retrieved. Patients who were ever diagnosed with at least one of: GIUs, *Helicobacter pylori* infection, or who had ever received NSAIDs + H2RAs or NSAIDs + PPIs or had gastrointestinal endoscopy procedures in the previous two years before the index year were excluded. The high dose of H2RAs was defined as double the standard dose or higher, and the low dose was defined as lower than double dose (according to British National Formulary 63). The adjusted odds ratio of GIUs during NSAIDs + high-dose H2RAs versus NSAIDs + low-dose H2RAs exposure was calculated. Microsoft Excel and Statistical Analysis System (SAS) v9.3 (SAS Inc., United States) were used for data manipulation and analysis.
Results: A total of 782,056 NSAIDs + H2RAs prescriptions were prescribed to 204,957 patients. There were 148 GIUs events during 2011–12. A total of 26 events were found during the NSAIDs + high-dose H2RAs; and 122 events were found during the NSAIDs + low-dose H2RAs. The adjusted odds ratio for patients receiving NSAIDs + high-dose H2RAs versus NSAIDs + low-dose H2RAs was 0.70 (95 % CI 0.46–1.07).
Conclusion: Our study does not support superior effectiveness of high-dose versus low-dose H2RAs in preventing NSAID-associated endoscopic GIUs. The available literature does not adequately support the routine use of high-dose H2RAs as prophylaxis of GIUs in patients receiving NSAIDs. Further study involving international patient data will further inform on the place of high-dose H2RAs in clinical management.

Abstract Code: ISP3592-47

Case Series of Patients with Reported Renal Events in a Prescription Event-Monitoring (PEM) Study of Aliskiren

C. Doe[1], C. Fogg[1], D. Layton[1], S.A. Shakir[1]

(1) Drug Safety Research Unit, Southampton, UK; University of Portsmouth, Portsmouth, UK

Background: The direct renin inhibitor aliskiren (Rasilez(R)) was launched in the UK in Aug 2007 for essential hypertension. The SPC at market launch listed renal events (REs) as uncommon and reversible. In 2011 the ALTITUDE study was stopped due to events including REs. This case series is a post hoc analysis in response.
Objectives: To describe the characteristics of patients with renal events suspected to be related to aliskiren in a PEM study in England.
Methods: This study used an observational single exposure cohort design. Exposure data were collected from dispensed aliskiren prescriptions issued by general practitioners (GPs) from Feb 2008 to Nov 2010. Outcome data were collected from questionnaires sent to GPs 6 months after each patient's first prescription. Drug relatedness assessments were performed where relevant. Patients with REs probably or possibly related to aliskiren were categorised using reported laboratory values according to the RIFLE classification, (a spectrum of renal insults.) Characteristics of these patients were described.
Results: The final cohort consisted of 6,385 patients of which 120 (1.9 %), reported 183 REs; 78.1 % (143/183) renal function test (RFT) decline, 21.9 % (40/183) renal failure. REs in 20.0 % of the RE patients (24/120), were assessed as probably or possibly related to aliskiren. Reported characteristics of this subset: female 58.3 % (14/24); median age 75 years (IQR 68–81); RIFLE categories (Acute Renal Failure (ARF) 16.7 % (4/24), Renal Injury (RI) 12.5 % (3/24), Risk of renal injury (Risk RI) 45.8 % (11/24), RFT decline (below RIFLE) 25.0 % (6/24); Chronic Kidney Disease (CKD) 79.2 % (19/24); Diabetes Mellitus (DM) 62.5 % (15/24); Concurrent ACE inhibitor (ACEi)/angiotensin blocker (ARB) use 45.8 % (11/24). CKD, DM or ACEi/ARB use present in 95.8 % (23/24). In 'Risk RI' and 'RFT decline' 100 % (17/17) had CKD. In ARF 75.0 % (3/4) had both DM and ACEi/ARB use.
Conclusions: REs were commonly reported but not always related to aliskiren. Where relatedness suspected, majority of ARF group, had DM and ACEi/ARB use, (as per ALTITUDE study). Majority with CKD were in less severe RE groups. Possibly RFTs were more closely monitored in CKD.

Abstract Code: ISP3593-48

Using the RIFLE Classification System to Categorise Severity of Adverse Renal Events in a Prescription Event-Monitoring Study

C. Doe[1], D. Layton[1], S.A. Shakir[1]

(1) Drug Safety Research Unit, Southampton, UK; University of Portsmouth, Portsmouth, UK

Background: Renal events (REs) range from minor changes in renal function tests (RFTs) up to acute renal failure (ARF). Categorising RE severity in drug safety studies may improve clinical relevance. In acute hospital care REs are considered on a spectrum of severity. The RIFLE classification system uses change in RFT from baseline to categorise severity and aid management.
Objectives: To investigate whether the application of the RIFLE classification system can improve discrimination of reported REs, within a Prescription Event-Monitoring (PEM) study of a direct renin inhibitor.
Methods: This study used an observational single exposure cohort design. Exposure data were collected from dispensed prescriptions issued by general practitioners (GPs) from Feb 2008 to Nov 2010. Outcome data were collected from questionnaires sent to GPs 6 months after each patient's first prescription. Drug relatedness assessments identified patients with REs probably or possibly related to the study drug. In these patients, reported baseline and event estimated glomerular filtration rate or creatinine were used to calculate change in RFT and apply a RIFLE category; Risk of renal injury (RiskRI), Renal Injury (RI), ARF, Renal Loss (RL), End Stage Kidney Disease (ESKD). The distribution of reported renal events was described.
Results: Of 6,385 patients in the final cohort, 24 patients had a reported RE probably or possibly related to study drug. Reports involved Renal Failure 16.7 % (4/24) and RFT decline/renal impairment 83.3 % (20/24). RIFLE categories; RiskRI 45.8 % (11/24), RI 12.5 % (3/24), ARF 16.7 % (4/24). RFT decline (below lowest RIFLE criteria); 25.0 % (6/24). Of the 4 patients reported as renal failure, 3 had suspected ARF by RIFLE and 1 had RFT decline. The 4th patient with ARF by RIFLE, was reported by GP as RFT decline.
Conclusions: GP reports of REs may not indicate severity. In this study, RIFLE suggested most REs were at less severe end of the spectrum. The forthcoming Acute Kidney Injury NICE guideline will disseminate RIFLE concepts. Further work is required to explore the validity of this tool, and application to other pharmacoepidemiological study designs.

Abstract Code: ISP3594-49

Preventability Analysis of Adverse Drug Reactions to Oral Anticoagulant Therapy

A. Farcas[1], A. Sinpetrean[2], C. Bucsa[1], C. Mogosan[1], D. Dumitrascu[2]

(1) Drug Information Research Center, School of Pharmacy, University of Medicine and Pharmacy "Iuliu Hatieganu", Cluj-Napoca, Romania, (2) 2nd Medical Department, University of Medicine and Pharmacy "Iuliu Hatieganu", Cluj-Napoca, Romania

Background: Oral anticoagulant therapy has proved through years its benefits, being widely used for thromboprophylaxis and stroke prevention in atrial fibrillation. Although recommendations for management of anticoagulation were proposed, bleeding events due to anticoagulant therapy are still between the most reported adverse drug reactions (ADRs) in pharmacovigilance studies [1]. In a prospective study conducted in internal medicine in Romania, anticoagulants were responsible for 21 % of the ADRs detected [2].
Objectives: To analyze the causes of ADRs to anticoagulants in order to target adequate future interventions for prevention.
Methods: A series of 37 cases of ADRs detected for acenocoumarol at the Drug Information Research Center was analyzed for preventability. Data on age, gender, main reason for hospitalization, diagnoses, renal/hepatic function, history of alcohol intake, all drugs administered (including self-medication) with respective doses and duration of therapy, clinical and

biological data, dechallenge and rechallenge, ADR treatment and outcome were all available for analysis. Contraindications, off-label use, drug-drug interactions, inadequate dose according to SmPC and Thomson Micromedex, aside inadequate monitoring, self-medication, or non-adherence to therapy were the factors assessed for preventability.

Results: 78 % of the adverse reactions to acenocoumarol (29 ADRs out of 37) were considered preventable (pADRs). 93 % of the pADRs to acenocoumarol were serious, leading to hospitalization or to prolongation of the hospitalization. Mean age of patients with pADRs to acenocoumarol was 63 [39–80] and 62 % were female. Multiple site hemorrhages, hematomas including a colonic hematoma, hematuria, gastrointestinal bleeding and a serious intracerebral hemorrhage were among the bleeding events secondary to acenocoumarol with at least a probable causality relationship. Drug interactions that increase the risk of bleeding (82 %) were the most frequent cause for pADRs, followed by inadequate monitoring (21 %). There were patients were 2 or even 3 drug associations that interact with the risk of bleeding were prescribed.

Conclusion: The high percentage of drug-interactions responsible for pADRs to acenocoumarol indicates a clear target for interventions for better prescribing in order to achieve an optimal anticoagulation management.

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Abstract Code: ISP3595-50

Haematological Toxicity of PPIs: Analysis of Spontaneous Reporting of Adverse Drug Reactions in S. Orsola-Malpighi Hospital of Bologna

S. Restuccia[1], C. Sacripanti[1], M. Morotti[1], E.R. Cosentino[2], M. Kolletzek[2], A. Cicero[2], C. Borghi[2], C. Puggioli[1]

(1) Hospital Pharmacy, S.Orsola-Malpighi Hospital, Bologna, Italy, (2) Internal Medicine, S.Orsola-Malpighi Hospital, Bologna, Italy

Introduction: Proton Pump Inhibitors (PPIs) consumption in Italy between years 2007 and 2012 is more than doubled [1]. However, together with the increased use, pharmacovigilance signals (s. a. hypomagnesaemia, alopecia and impotence) about PPIs toxicity also emerged [2]. Recent studies identified a potential etiopathological mechanism underlying hematotoxicity from PPI, such as the development of self-reactive antibodies with cytotoxic effect on leukocytes and their precursors [3,4].

Aim: To collect data of hematotoxicity from PPIs through spontaneous ADRs (Adverse Drug Reactions) reporting system in S. Orsola-Malpighi Hospital of Bologna.

Methods: From hospital pharmacovigilance database, where we registered all ADRs recorded in the National Pharmacovigilance Network, ADRs from PPIs (ATCIV: A02BC, period 2007–2012) were extracted. The reports about hematotoxicity from PPIs (leukopenia, anaemia and thrombocytopenia) were analyzed. To exclude that haematological disorders depend from underlying disease, we checked all cases reported only after differential diagnosis for concomitant myelosuppressive diseases.

Results: Seventy-two percent (n = 26) ADRs to PPIs concerned haematological toxicity. The distribution of cases was similar in both gender, 54 % female (F) and 46 % male (M), while average age was higher in F (83 years) than in M (72 years). All cases concerned elderly patients with concomitant cardiovascular diseases. The number of reported cases increased with the duration of treatment with PPI and the average duration of therapy was 644 days (min 49–max 3,540). Lansoprazole was used in 42 % (n = 11) of cases, omeprazole 27 % (n = 7), pantoprazole 19 % (n = 5) and esomeprazole 12 % (n = 3). The ADRs concerned leukopenia (64 %, n = 21), anemia (30 %, n = 10), and thrombocytopenia (6 %, n = 2). Some cases reported both anemia/leukopenia (n = 4), anemia/thrombocytopenia (n = 1) and leukopenia/thrombocytopenia (n = 1). Almost all cases (96 %) were evaluated as "not severe", except one case that resulted in patient hospitalization. However, the values of haematochemical parameters reported were: Hb 4.08–12 g/dl, RBC 2.37–4.33x10^6/μl, WBC 1.000–3.890/mm^3 and PLTS 60.000–78.000/μl. After haematological toxicity, PPIs treatment were discontinued in all cases. In 65 % (n = 17) of cases a resolution and in 12 % (n = 3) an improvement were reported; in 23 % (n = 6) of cases data was not available.

Conclusions: PPIs are widely used in clinical practice with a positive benefit-risk profile. However, spontaneous reporting system of suspected ADRs allowed to highlight potential risks of this class of drugs. The case series collected could support the hypothesis that haematological toxicity could be considered as PPIs effect class. Therefore, further analysis are needed to evaluate a potential association [5] between PPIs and haematological toxicity and to identify possible risk factors in particular population [6].

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Abstract Code: ISP3596-51

Ecopharmacovigilance in Africa—The Future?

Y. Esseku[1], A. Dodoo[2]

(1) Rapha Develoment Institute, Accra, Ghana, (2) WHO Collaborating Centre for Advocacy and Training in Pharmacovigilance, Accra, Ghana

Ecopharmacovigilance (EPV) is the area of pharmacovigilance concerned with adverse events due to the persistence of pharmaceuticals in the environment and its attendant effects and consequences on humans, other animals and the overall ecosystem [1]. EPV has been formally defined as the science and activities associated with the detection, evaluation, understanding and prevention of adverse effects of pharmaceuticals in the environment [2]. Though EPV is a new science, there has been a reasonable amount of research conducted globally. However, very little has

been done in EPV in Africa despite the tons of medicines consumed on the continent and the acknowledged weakness in infrastructure including sanitation systems and the known pollution of water bodies. There is currently very little knowledge on the types of pharmaceuticals which are present and persisting in various media on the African continent and their effect on the health of individuals as well as the ecosystem. There is really a stark and startling dearth of needed information on the impact of medicines on the environment in Africa, how ecosystems are being affected and what species are being lost as a result of the presence of medicines in the environment. There is also little knowledge of what medical conditions may be worsening as a result of inappropriate exposure to medicines and what economic impact these environmentally induced health conditions may bring up. Since environmental effects can occur far afield from the sources of the problem, it is important that Africa is not left behind with all knowledge and understanding of these effects taking place in other areas. Some of the areas in which research is crucially needed in the African continent include, but are not limited to:

- Assessment of the environmental impact of the presence and persistence of pharmaceuticals in Africa;
- The significance of engineered landfills and treatment of leachate from these landfills;
- Waste water treatment and EPV;
- Proper handling of dispensed, unused and expired medicines;
- The role of green pharmacy in EPV in Africa;
- The role of education and behavioural change in EPV

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Prescribing Medication Errors: 2nd Generation Sulfonylureas

M. Lesicar[1], K. Gvozdanovic[1], M. Dimov Di Giusti[1], D. Krnic[1], B. Dolinic[1], Z. Margan Koletic[1], V. Maciolic Sarinic[1]

(1) Agency for Medicinal Products and Medical Devices, Zagreb, Croatia

Introduction: Medication errors are unintentional errors in the prescribing, dispensing, or administration of a medicine while under the control of a healthcare professional, patient or consumer. They can cause a serious harm to patients but are preventable in most cases. By reviewing WHO ADR database (VigiBase), a small number of medication errors reported by Croatian healthcare professionals was noticed.
Aim: To identify the frequency and types of medication errors among prescriptions for 2nd generation sulfonylureas.
Methods: A retrospective data collection of medication errors was performed by analysing prescriptions for 2nd generation sulfonylureas (glimepiride, gliclazide, gliquidone, glibenclamide). A notice was posted on HALMED (Agency for Medicinal products and Medical Devices) website with the invitation to community pharmacists to report any prescription medication error for 2nd generation sulfonylureas found within their pharmacies' database from February 1st to February 28th 2013. Any deviation from approved prescribing information stated in Summaries of product characteristic was considered medication error. Medication error notification form was filled in for any noticed medication error, indicating type of prescribing medication error: wrong indication, wrong dose, wrong drug dosing time, dividing of dose, wrong route prescribing error and lack of prescribing information.
Results: One pharmacist responded to our invitation and searched database of two pharmacies. Among 7,784 prescriptions, 1.45 % (113) were for 2nd generation sulfonylureas. Out of 113 prescriptions, 45.1 % (51) had medication errors. The most common prescribing medication error was dividing of dose which was noticed in 54.4 % (31/57) prescriptions for glimepiride, 28.6 % (7/32) for gliquidone and 21.9 % (4/14) for gliclazide. Drug overdose was noticed in 8.8 % (5/57) prescriptions for glimepiride and 6.3 % (2/32) prescriptions for gliclazide. Wrong indication was the most frequent error for gliquidone (42.9 %; 6/14). No medication errors were reported for glibenclamide.
Conclusions: Although the studied sample was small, it showed quite alarming frequency of different types of medication errors among prescriptions for 2nd generation sulfonylureas. These results will be used as a starting point for further projects with larger sample of medication errors which will include different type of reporters, more therapeutic classes and clinical outcomes of medication errors. Better understanding of trends in medication errors will help us to prevent them and thus improve patient safety.

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Ten Years of Pharmacovigilance in Italy: the Experience of Emilia-Romagna Region in the Monitoring of Drug's Safety Profile

M. Melis[1], S. Lo Bianco[1], C. Biagi[1], E. Buccellato[1], N. Montanaro[1], A. Vaccheri[1], D. Motola[1]

(1) Department of Medical and Surgical Sciences, Pharmacology Unit, University of Bologna, Bologna, Italy

Background: Spontaneous reporting of suspected adverse drug reactions (ADR) is considered the cornerstone of pharmacovigilance as it allows to assess the risk/benefit ratio of all marketed drugs. Regional health service has arranged numerous initiatives aimed at promoting the culture of pharmacovigilance and the participation of all health care professionals.
Aim: To describe the evolution of spontaneous reporting in the Emilia-Romagna Region (ERR) in the period 2001–2010 through qualitative (e.g. proper compilation of the report form) and quantitative indicators (number of annual reports for Local Health Authority, source of the report, etc).
Method: Data of regional spontaneous reporting 2001–2010 were extracted from the National Network of Pharmacovigilance of the Italian Drug Agency (AIFA). Drugs were classified according to the ATC classification (Anatomical Therapeutic Chemical Classification System). For the analysis of adverse drug reactions the dictionary of terminology of Regulatory Agencies MedDRA was used.

Results: The contribution of the Region in the decade was approximately 10 % of the national amount (9,633 out of 99,321), with 8 reports per 100 physicians and 230 per million inhabitants. The number of national and regional reports progressively decreased from 2001 onwards and then returned to grow in recent years. Strong differences between the individual Local Health Authorities were identified. The reports concerned more females than males (F/M ratio 1.3:1) and age classes 0–2 and 60–80 years. Hospital doctors were the main source of reports, followed by general physicians while it is still negligible the contribution by nurses and pharmacists. 2,556 reports (26.5 %) were classified as serious and 125 cases were lethal (4.9 % of serious ADRs and 1.3 % of all regional reports). Iomeprol, amoxicillin/clavulanic acid, lenalidomide and ticlopidine were the most reported suspected drugs. Several serious cases involved vaccines.
Discussion: ERR contributes most to the national pharmacovigilance system. Several initiatives launched in recent years allowed to involve in the spontaneous reporting system nurses and pharmacists who in the past underestimated the importance of monitoring the safety of drugs, but there is considerable room for improvement. General practitioners lost their major role in spontaneous reporting, probably due to the loss of patents of drugs and also for the marketing of new drugs made for hospital use only.
Conclusion: The pharmacovigilance system of ERR participates in the periodic signal analysis, therefore the quality of the data and the number of reports are essential for the emergence of these signals that allow to re-evaluate the safety profile of marketed drugs in the primary interest of public health.

Abstract Code: ISP3599-54

Comparison of Biosimilar Guidelines: Impact on Patient Safety

S. Kong[1], A. Worsley[1], S. Dufay[1]

(1) Department of Pharmacology and Pharmacy, The University of Hong Kong, Hong Kong

Background: Innovator biopharmaceutical patents are expiring therefore biosimilars are continuously entering the market. Minimizing healthcare cost is important because many of these biologics are used to treat chronic illnesses costing tens of thousands of dollars per patient annually. However, biosimilars are not generic medicines due to factors such as protein molecule complexity, manufacturing process and immunogenicity issues. Many countries have formed or are pressured to form guidelines to review biosimilars to ensure their safety, quality and efficacy.
Aim: To compare guidelines of biosimilars with regards to parameters evaluated in terms of safety, efficacy and quality.
Methods: Extensive literature review on Pubmed®, and Department of Health websites of each government between September 2011–March 2012.
Results: A total of 17 guidelines were found including Australia, Canada, China, Cuba, EU, India, Iran, Japan, Jordan, Malaysia, Mexico, Saudi Arabia, Singapore, South Korea, Turkey, USA, and WHO of which 15 were reviewed. China and Jordan was excluded from the review due to a language barrier and an identified need for a guideline but unavailable draft version respectively. Different countries use different terms when referring to biosimilars and not one name or definition is accepted worldwide. Most countries require a reference product for comparison to be registered in their own country. However some countries (Cuba, India, Iran, Malaysia, Saudi Arabia, Singapore, South Korea, and Turkey) accept references from reputable countries. India's guideline did not include comparability testing. In guidelines from Cuba, India, Iran and Japan, details for the amount of safety, efficacy, pharmacokinetic and pharmacodynamic data were not provided. Immunogenicity evaluations were not mentioned in India and Mexico's guidelines nor did Mexico's guideline address pharmacovigilance plans.
Discussion: Biosimilar guidelines can be divided into four categories depending on the individual characteristics of each country and their access to the original product including Mature Market, Developing Market, Futuristic Market and Following Market. Even with guidelines trying to ensure quality, safety and efficacy, there are still issues such as immunogenicity of biological that are related to the discrepancies of assay methods, patient, disease etc. Furthermore, it would be difficult to trace these issues if biosimilars were used interchangeably with their reference product.
Conclusion: The comparison of guidelines showed that copies of innovator biologics are not evaluated in the same way even if biosimilar guidelines have been put in place, which highlights the importance of reporting the country of origin of the copy when declaring adverse reactions.

Abstract Code: ISP3600-37

Contribution of Therapeutic Monitoring in the Assessment of Toxic Adverse Effects of Mitotane

N. Jebabli[1], E. Gaies[1], I. Salouage[1], H. El Jebari[1], R. Charfi[1], S. Trabelsi[1], M. Lakhal[1], A. Klouz[1]

(1) Centre National de Pharmacovigilance, Tunis, Tunisia

Introduction: Mitotane, is a compound derived from the insecticide dichloro-diphenyl-dichloroethane, having a potent adrenotoxic effects and is able to block cortisol synthesis. It is widely used in the treatment of adrenocortical cancer (ACC). At doses varying between 6 and 10 g mitotane provided serious side effects and low doses (1–3 g) seemed to be tolerated [1–2]. We report herein a case of toxic plasma levels with low doses of mitotane
Case Report: A 47 years old man treated with mitotane for ACC administered orally at a starting dose of 3 g daily and progressively increased to 3.5 g for reached the therapeutic range (defined as mitotane plasma levels between 14–20 μg/mL) while monitoring drug plasma levels. One year after the initiation of mitotane the patient presented adverse reaction such us asthenia, gastrointestinal disorders (nausea and vomiting) and abdominal bloating. These side effects seemed due to mitotane and so therapeutic monitoring of this drug was been required. Plasmatic levels measured by High Performance Liquid Chromatography HPLC showed a concentration about 42 μg/ml. Mitotane was stopped and after 1 and 2 months, concentrations decreased respectively to 29–20 μg/ml. Therapeutic drug monitoring of mitotane is useful even with low doses in order to avoid drug toxicity witch can be observed in some cases.

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Abstract Code: ISP3601-38

General Physician Therapy Review and Polypharmacy in Elderly Outpatients

S. Ussai[1], A. Casetta[2], M. Bresigar[3], F. Barbone[1], F. Pisa[1]

(1) Institute of Hygiene and Clinical Epidemiology, University Hospital of Udine, (2) Department of Medical and Biological Sciences, University of Udine, (3) Infostruttura Research Organization, Gorizia, Italy

Background: Polypharmacy has been associated with functional decline and adverse outcomes in vulnerable populations, particularly in the elderly patients with complex medical conditions.

General Physicians (GPs) play a relevant role in reviewing the therapy of fragile outpatients.

Aim: To evaluate the relation between:

- a last therapy review (LTR), made by General Physician (GP), more than 6 months before the baseline, and the number of medications (NOMs) and Drug–Drug Interactions (DDIs) during the follow up;
- the Charlson Comorbidity Index age adjusted (CCI) and the NOMs.

Methods: A cohort of outpatients of age ≥65 years was identified through a closed loop, fully automated system that records and updates all the drugs taken during therapy cycle/s by specifically designed software interfaces loaded on Information and Communication Technology programs.

The record of each patient was linked through her/his tax code to all prescription/OTC drugs from November 2012 to April 2013, generating a personal pharmacological profile. Data on age, sex and comorbidity, last therapy review, NOMs and DDIs was recorded.

The Mann–Whitney test was used to assess the relation between LTR and NOMs/DDIs and between CCI and NOMs.

Results: In this cohort of 180 patients, mean age 76.6 ± 9.4, 57.3 % women, 47.2 % (N = 85) received LTR over six months before the baseline and 36.1 % (N = 65) had at least one DDI, from 1 to 74 DDIs per person (5.9 % high, 60.4 % moderate).

Overall, 4.4 % of patients were affected by cancer, 14.4 % diabetes, 3.9 % depression, 33.9 % cardiovascular disease.

According to CCI, 70 patients (38.8 %) had a ten-year survival probability <25 %.

Overall, 67.2 % of the cohort took ≥2 drugs (from 2 to 114 drugs per person) and 95 patients were in polypharmacy, managing ≥5 drugs.

The median and interquartile range (IQR) of the NOMs and DDIs were: 4 (IQR 0–15); 5.5 (IQR 3–11.5) and 7 (IQR 1–18); 6 (IQR 2–15) respectively for < and ≥6 months from LTR.

Neither difference was statistically significant.

No difference was seen in the 10-year survival probability between those patients who managed <5 or ≥5 drugs (p = 0.827).

Discussion: More studies are needed to evaluate the impact of GPs monitoring of therapy on health outcomes of elderly people.

Conclusion: Outpatients ≥65 years of age receiving a LTR < or ≥6 months before the baseline do not differ significantly with respect to NOMs and DDIs.

The probability of a 10-year survival does not correlate with the number of medications.

Abstract Code: ISP3602-39

Implementing a Pharmacovigilance Program to Evaluate Adverse Drug Reactions in HIV-Infected Patients: the Role of Clinical Pharmacist

L. Apolloni[1], F. Locchi[1], M. Morotti[1], L. Calza[2], V. Colangeli[2], R. Manfredi[2], E. Vanino[2], C. Puggioli[1], P. Viale[1]

(1) Clinical Pharmacy, Policlinico S. Orsola-Malpighi, Università di Bologna, Bologna, Italy, (2) Department of Clinical Infectious Diseases, Policlinico S. Orsola-Malpighi, Università di Bologna, Bologna, Italy

Introduction: The use of Highly Active Antiretroviral Therapy (HAART) as the main option for the management of people living with HIV, is associated with decreased morbidity and mortality. Notwithstanding its effectiveness in inhibiting viral replication, HAART is correlated with several adverse effects. The monitoring and evaluation of adverse events related to HAART represents an essential aspect for optimal management of patients with HIV.

Aim: The aim of our study is the monitoring of Adverse Drug Reaction (ADR) of the outpatients of an HIV referral centre (department of Clinical Infectious Diseases, Policlinico S. Orsola-Malpighi, Bologna).

Methods: It is an active pharmacovigilance surveillance project started in February 2012 at the Department of Clinical Infectious Diseases. The pharmacist became active part of the management group, in order to directly provide the distribution of antiretroviral drugs, give information about proper storage, usage and possible interactions associated with treatment.

The pharmacist hands out a questionnaire (10 questions about adherence, co administered drugs, adverse events) to each patient to complete and return at the following visit. These information were reported into a specific database for analysis. Furthermore, the clinical pharmacist co-operates with physicians in order to observate and record adverse events due to therapy and implement ADR reporting.

Results: Our outpatients in treatment with antiretroviral therapy were N.1,252 (Female = N.280; Male = N.690; average age = 48 years). N.26 adverse drug reactions were reported (period February 2012–2013), regarding 46 active pharmaceutical substances. Compared to past year, there has been a significant increase in the number of reported adverse drug reactions (n.2 in 2011 vs n.26 in 2012). N.8 reports (31 %) have been reported by the pharmacist: n.3 of them were serious. With regard to the outcome, improvement or resolution of the ADR occurred in 58 % of cases. The most reported active suspects were related to emtricitabine/tenofovir (n.12; 26 %), efavirenz (n.9; 20 %), and ritonavir (n.5; 11 %). Serious adverse reactions included: suicidal ideation; eosinophilic pneumonia; cutaneous adverse drug reactions; loss of attention, fatigue, insomnia, and gastrointestinal disorders. We analysed the medical records of outpatients who changed therapy during 2012 (N.75; 6 %), to retrieve the related causes: toxicities 27 % (N.20), (ADRs not reported) 24 % (N.18), simplifications of the previous regimen 6 % (N.5), failure 2 %, (N.1), pregnancy, 41 % (N.31), not identified.

Conclusions: The pharmacist may support physicians in monitoring adverse events related to HAART and may implement ADR reporting in order to improve antiretroviral safety knowledge in the post-marketing phase.

Abstract Code: ISP3603-40

Early Drug Induced Liver Injury After Intensive Phase of Tb Treatment in Indonesia: Primary Care Centers and Lung Hospital Study

J. Atthobari[1], U. Adhie Mulyani[2], D. Perwitasari[3], I. Darwis[4]

(1) Department of Pharmacology and Therapy, Faculty of Medicine, Universitas Gadjah Mada, Yogyakarta, Indonesia, (2) Institute of Research and Development, Ministry of Health Office, Jakarta, Indonesia, (3) Faculty of Pharmacy, Universitas Ahmad Dahlan, Yogyakarta, Indonesia, (4) Department Pharmacology, Faculty of Medicine, Universitas Lampung, Lampung, Indonesia

Background: Tuberculosis are still a problem for emerging countries such Indonesia. The program for controlling and eliminations had been addressed on the use of antituberculosis medicines. The safety profile of those drugs, particularly drug-induced liver injury (DILI), has been studied, however, this information on local or Indonesian capture is still minimum.

Objectives: To assess the proportion of early drug-induced liver injury (eDILI) due to tuberculosis treatment (TBT) among Indonesian's TB patients during the intensive phase of treatment.

Methods: Prospective cohort study in 10 primary care centers and 2 lung hospitals based setting from 2 provinces (Yogyakarta and Lampung Provinces, Indonesia) were conducted in TB patients who used standard fixed combination regimens during the intensive phase of treatment. Patients with abnormal baseline AST and ALT level, lower hemoglobin level and HIV positive were excluded. The AST and ALT level were measured before treatment and after two months intensive phase of treatment. Early DILI (eDILI) was defined if the AST/ALT increasing above the upper normal limit.

Results: One hundred and fifteen subjects were followed, 58.3 % were male, age 38.6 years (±16.6), and 58.3 % were underweight BMI. The baseline of AST and ALT were in normal range value, 20.4 (±1.4) and 16.7 (±1.7), respectively. After intensive phase of treatment, 7.5 % patients were considered as eDILI. This group has significantly higher percentage of increase AST and ALT after intensive treatment compared to non-eDILI (63.3 (±0.22.4) vs. 39.1 (± .3.8), $p < 0.001$, respectively for AST, and 191.1 (± .67.6) vs. 78.1 (± .7.5), $p < 0.001$, respectively for ALT. This changed has still significantly difference after adjusting of age and BMI.

Conclusions: The incidence of drug-induced liver injury is around 10 % among Indonesian's TB patients who used standard fixed combination regimens. The TB program need to increase awareness on this potential liver injury related to TB drugs. Prospective studies are needed to know the DILI among these after continuation phase of treatment

Abstract Code: ISP3604-41

Autoimmune Disease Induced by Anti-TNF Agents and Tocilizumab: An Analysis of the Italian and English Pharmacovigilance Database

A. Marra[1], A. Bin[1], C. Cazzorla[2], G. Fresca[3], D. Fedele[1], R. Carletti[1]

(1) Dipartimento Farmaceutico Interaziendale, Azienda Ospedaliero-Universitaria di Ferrara, Ferrara, Italy, (2) Facoltà di Farmacia, Università degli Studi di Ferrara, Ferrara, Italy, (3) Dipartimento Farmaceutico Interaziendale, Azienda USL di Ferrara, Ferrara, Italy

Introduction: Anti-TNF agents are increasingly being used for a rapidly expanding number of rheumatic and systemic autoimmune disease. As a result of this use, and of the longer follow-up periods of treatment, there are a growing number of reports of autoimmune processes related to anti-TNF agents and tocilizumab, ranging from asymptomatic immunological alteration to life-threatening systemic autoimmune disease.

Aim: The aim of this study was to make a comparison between the Italian and the English pharmacovigilance database on ADR reports of autoimmune disease related to anti-TNF agents: adalimumab, certolizumab, etanercept, golimumab, ustekinumab, infliximab, and tocilizumab.

Methods: We used both the Italian Rete Nazionale di Farmacovigilanza (RNF) and the English MHRA (Medicines and Healthcare Products Regulatory Agency) databases to extract ADR data. We analyzed ADR reports till March 13th 2013.

Results: Over the study period, the incidence of autoimmune ADR related to those biological agents on the total of ADR is, respectively, 6.23 % in RNF and 4.06 % in MHRA. System organ classes majorly involved in autoimmune ADR are: muscle and tissue disorders (13.47 % RNF, 31.97 % MHRA), skin disorders (35.92 % RNF, 30.7 % MHRA) and nervous system disorders (14.3 % RNF, 10.63 % MHRA). Most representative autoimmune ADR reported in RNF are: psoriasis (17.5 %), pustular psoriasis (7.75 %), Lupus erythematosus and vasculitis (5.3 %), Crohn's disease (4.9 %), noninfectious pericarditis (4.1 %), sarcoidosis and uveitis (3.6 %). In the MHRA database, instead, most representative autoimmune ADR reported are: rheumatoid arthritis (18.62 %), psoriasis (18.44 %), Crohn's disease (7.18 %), lupus-like syndrome (6.18 %), pustular psoriasis (5.36 %), vasculitis (5.18 %) and Lupus erythematosus (4.45 %). Anti-TNF agents mostly involved in autoimmune disease are adalimumab (7.27 % RNF, 3.96 % MHRA), etanercept (6.49 % RNF, 4.06 % MHRA), infliximab (6.59 % RNF, 3.98 % MHRA), ustekinumab (5.88 % RNF, 11.15 % MHRA), the less involved both in the two databases is the tocilizumab (1.55 % RNF, 2.25 % MHRA).

Conclusion: Data suggest that the type of autoimmune ADR reported are more or less the same in the two databases as the agents involved;

paradoxically for many of these autoimmune processes current treatment indications include the very biological agent producing the adverse event.

The lowest number of reported ADRs for tocilizumab is probably due to the different mechanism of action of this agent. Post-marketing studies are required to evaluate the risk of developing autoimmune disease in patients receiving TNF-targeted and tocilizumab therapies.

Abstract Code: ISP3605-42

Interactions between Warfarin and Other Drugs: a Known but Neglected Problem

G. Vighi[1], L. Prestini[1], F. Rotondo[1], F. Di Sessa[1]

(1) Unity of pharmacovigilance and clinical pharmacology, Niguarda Hospital, Milan, Italy

Introduction: Warfarin is the drug most widely used in the prevention and treatment of thromboembolic accidents; the efficacy and safety of this drug must be considered to avoid the risk of bleeding. Many factors[1] may potentiate the action of warfarin. Though interactions between warfarin and other drugs are known, their contemporary use is frequently associated with elevated risk of bleeding, due to metabolic competition that produces INR increasing.

Aim: To verify the incidence of ADRs caused by the interaction between warfarin and drugs known to potentiate the anticoagulant effect.

Methods: We used data collected in the national project MEREAFAPS (epidemiological monitoring of adverse drug reactions and events in the emergency department). We only considered ADRs recorded as bleeding in 2010 and 2011 in Lombardy and we studied if warfarin was associated with one of the drugs increasing its effects with high probability, as reported in Holbrook's study [1].

Results: We collected 712 bleedings caused by warfarin out of 8,983 total ADRs (7.93 %); in 27 % warfarin was associated with a drug increasing the anticoagulant effect. In 84.38 % warfarin is associated with a single interacting drug, while in 15.62 % was associated with two or three interacting agents. We detected nine of all the 22 reported interacting agents (Table 1). Amiodarone was the single drug most frequently prescribed together with warfarin, while omeprazole was most frequently associated with other interacting agents .We noticed a relevant increase of serious ADRs when warfarin was associated with interacting drugs; indeed the proportion of severe reactions changes from 52.50 % without interacting agents, to 63.54 % with their association.

Table 1. Principal Warfarin interacting agents

	Single association	Double or triple association	Total
Amiodarone	71	17	88
Omeprazole	52	23	75
Diltiazem	13	8	21
Propafenone	8	5	13
Citalopram	10	2	12
Sertraline	5	7	12
Fenofibrate	2	0	2
Piroxicam	1	0	1
Ciprofloxacin	0	1	1

Conclusions: It is important to improve control of patients in TAO with warfarin to prescribe drugs with lower interaction activities and perform more frequent INR controls in order to optimize warfarin prescription and to avoid risk of bleeding.

Reference

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Abstract Code: ISP3606-43

ADRs in Emergency Department: Incidence and Characteristics of Serious Reactions

G. Vighi[1], L. Prestini[1], F. Rotondo[1], F. Di Sessa[1]

(1) Unit of Pharmacovigilance and Clinical Pharmacology. Niguarda Hospital, Milan, Italy

Introduction: Emergency room has always been considered a privileged observatory for ADRs that occur in outpatients. Elderly (≥65 years) are the population most affected by serious ADRs both for frequency and severity.

In the literature, it is estimated that older people have a 6.2 times greater risk of hospitalization from the emergency room as a result of ADRs. Severe reactions cause harm to the patient and high costs for the national health system involving hospitalization [1].

Aim: To identify the medications and drug classes provoking serious adverse reactions in different age groups in order to recognize the drugs that should be better supervised by physicians in these different populations.

Methods: We used data collected in the national project MEREAFAPS (epidemiological monitoring of adverse drug reactions and events in emergency department). We considered only ADRs recorded in 2010 and 2011 in Lombardy region.

All drugs were classified using the Anatomical Therapeutic Chemical (ATC) classification code system. Clinical conditions were coded by medDRA Dictionary. ADRs were considered serious according to EMA criteria: life threatening or death, hospitalization, severe or permanent disability, congenital deficiency of the newborn.

Results: Between 2010 and 2011 8,983 reports were collected in Lombardy and 45.07 % were classified as serious. The elderly was the age group with the highest percentage of serious reactions: 55 %, while in pediatric patients only 15 % of the ADRs were classified as serious. Also the distribution of drugs responsible for severe reactions was different in elderly compared with other age groups; in pediatric patients and adults (<65 years) antibiotics and NSAID are the most frequent cause of ADRs, while in elderly population the most frequent drugs provoking ADRs were anticoagulants and antiplatelet agents. The skin and subcutaneous tissue disorders were the most frequent reactions in adults and children, followed by gastrointestinal disorders, while the latter were the most frequent in elderly followed by respiratory diseases.

Conclusions: Our data suggest that ADRs are due to different drugs and cause different clinical pictures in the different age groups. For this reason, the different populations should be monitored and studied separately for what concerns the ADRs.

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Abstract Code: ISP3607-44

Best Evidence to Support Regulatory Decision-Making

K. Blake[1], H. Fitt[1], A. Hidalgo-Simon[1], P. Arlett[1]

(1) European Medicines Agency, London, UK

The European Medicines Agency (EMA) has developed an initiative termed 'best evidence to support regulatory decision-making' for the timely gathering of scientific evidence to inform regulatory decision-making. Sources for such evidence include analyses of EudraVigilance (EV) and in-house data from The Health Improvement Network (THIN) and Intercontinental Medical Statistics (IMS); review of the literature; and liaison with the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP). This liaison may take the form of requests to the network for relevant findings, direct commissioning of ENCePP studies and interaction with the consortia funded under the European Commission DG-RTD 7th Framework Programme.

The overall objective of this initiative is to enhance the complementary role of pharmaceutical industry, academic research centres and the EMA itself in conducting and evaluating timely, high quality, scientifically robust and transparent research to support the EMA and its committees, in particular the Pharmacovigilance Risk Assessment Committee (PRAC) in decision-making to benefit public health.

An internal EMA 'best evidence' meeting is held each month in the week following the PRAC meeting. From September 2012 until March 2013 (inclusive) a total of 36 issues were discussed. Major outputs in terms of best evidence activities include the conduct of 8 EV, 6 THIN and 3 IMS analyses that have supported assessments by the relevant PRAC Rapporteurs/PRAC. As of 31 March 2013, the 'best evidence' activities undertaken since September 2012 have been reflected in a total of 17 discrete PRAC outcomes. These will be discussed in detail and updates provided..

Abstract Code: ISP3608-45

Cold preparations Use in Turkey: a Large Descriptive Study of SGK — Medula Database

S. Kalaca[1], M. Dogukan[2], H. Gok[2], S.E. Gulmez[3], F. Ozcan[2], B. Donertas[4], A. Kaptanoglu[5], M. Yer[2], A. Akici[4]

(1) Marmara University, School of Medicine, Department of Public Health, Istanbul, Turkey, (2) Social Security Institution, General Directorate of Universal Health Insurance, Department of Health Insurance, Istanbul, Turkey, (3) INSERM CIC-P 0005 Pharmacoépidémiologie, Service de Pharmacologie, Université Bordeaux Segalen, France, (4) Marmara University, School of Medicine, Department of Pharmacology, Istanbul, Turkey, (5) Marmara University, Faculty of Health Sciences, Health Management Division, Department of Health Economy, Istanbul, Turkey

Introduction: The inappropriate use of medicines (IUM) is not only widespread; it is costly and extremely harmful both to the individual and the whole population. In Turkey, one of the important aspects of the IUM is cold preparations oversupply.

Aim: To investigate patient profile and drug utilization indicators for the prescriptions containing drugs with R05X code (*other cold preparations*) in the Medula System of Social Security Insurance in Turkey (SGK-Turkey).

Methods: SGK has the Medula system containing all reimbursed prescriptions. A total of 6,206,970 prescriptions that were recorded during the five workdays from 4–8 February 2013 were drawn. Among them, 737,605 prescriptions (11.9 %) containing drugs with R05X code according to Anatomical Therapeutic Chemical Classification System (ATC) were retrospectively analyzed.

Results: The median age of the patients was 18 and 53.4 % of them were female. More than one third of the prescriptions were issued to patients aged below 6 years; where 13.6 % of them were under 2. The average number of drugs per prescription was 3.1 ± 1.2. Among prescriptions, 59.6 % contained an "antibacterial for systemic use", 23.5 % contained an "anti-inflammatory and anti-rheumatic products, non-steroids", 7.7 % contained "paracetamol".

Conclusion: Almost 13 % of the all prescriptions contained cold preparations. Results indicate a polypharmacy and possible drug interaction problem based on the fact that more than 1/3 of those prescriptions contain an additional analgesic. In addition, cold preparation use in children should be carefully considered in Turkey.

Abstract Code: ISP3609-46

Delayed Myelosuppression Induced by Azathioprine: a Report of Four Cases Having Inflammatory Bowl Diseases

M. Ben Sassi[1], E. Gaies[1], I. Salouage[1], N. Jebabli[1], S. Trabelsi[1], R. Charfi[1], H. El Jebari[1], M. Lakhal[1], A. Klouz[1]

(1) Centre National de Pharmacovigilance de Tunis, Tunis, Tunisia

Introduction: Azathioprine (AZA) is an immunosuppressant agent widely used in inflammatory bowl diseases. Because of its pharmacokinetics variability, its narrow therapeutic window, therapeutic drug monitoring of this drug is essential. Myelosuppression is an important and potentially lethal side effect of AZA. This toxicity appears generally during the first months (1) and is due to methyltransferase deficiency. Delayed myelosuppression seems less frequent and correlated with high AZA blood concentration.

We report herein four cases of delayed bone marrow toxicity after the use of AZA for inflammatory bowl diseases

Case Report: Four patients treated by AZA (three for Crohn's disease and one for hemorrhagic rectocolitis). The median age was 48 years. The average dose was 2 mg/kg/day. No other medication was associated. Hematologic toxicity happened from 1 to 10 years after the start of AZA. All patients developed bicytopenia. Three of them had leucopenia and a decrease in red blood cells count and one of them developed thrombopenia. Concomitant AZA monitoring showed an average concentration of 589 pmol/8*10^8GR [230–450 pmol/8*10^8GR]. AZA doses was reduced in one case and stopped in another case. Biological improvement is obtained after 20 and 15 days, respectively.

Conclusion: Myelosuppression induced by AZA can be observed many years after the beginning of the treatment and seems to be frequent even after the use of recommended doses and in the lack of comedication. This is explained by the large variability of the pharmacokinetics parameters of AZA. So, it is interesting to continue biological and AZA monitoring in the long term, especially when drug interaction is suspected.

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Abstract Code: ISP3610-38

Management of Dermatologic Toxicities Associated with Monoclonal Antibody Epidermal Growth Factor Receptor Inhibitors: a Case-Review

C. Leporini[1], F. Saullo[1], P. Rende[1], M. Patanè[1], M. Lucia[2], L. Gallelli[1], E. Russo[1], G. De Sarro[1], U. Univigil Cz Research Group[3]

(1) Department of Science of Health, School of Medicine, University of Catanzaro, Catanzaro, Italy; Pharmacovigilance's Centre Calabria Region, University Hospital Mater Domini, Catanzaro, Italy, (2) Oncology Unit, "S. Francesco di Paola" Hospital, Paola (CS), Italy, (3) Pharmacovigilance's Centre Calabria Region, University Hospital Mater Domini, Catanzaro, Italy

Introduction: The epidermal growth factor receptor (EGFR) inhibitors, cetuximab and panitumumab, represent an effective treatment option for patients affected by metastatic colorectal cancer (mCRC); furthermore, they are relatively devoid of systemic toxicities which are commonly observed with standard cytotoxic chemotherapy. However, the majority of patients treated with these monoclonal antibodies (mAbs) will experience dermatologic toxicities, most notably the papulopustular skin rash, which can impact quality of life and affect adherence to therapy [1, 2].
Aims: To review the most recent practices in the management of skin rash related to anti-EGFR mAbs cetuximab and panitumumab in the treatment of mCRC; to underline the importance of a proactive and early management strategy of skin toxicity in order to ensure adherence to therapy and maintain quality of life.
Methods: A computer-aided search of Medline, PubMed, Embase, Cochrane library databases, American Society of Clinical Oncology (ASCO) Meetings and European Society for Medical Oncology (ESMO) Congresses was performed to identify relevant literature regarding the signs and symptoms, assessment of severity, and best strategies available to prevent and manage dermatologic toxicities associated with the anti-EGFR mAbs, cetuximab and panitumumab, especially in mCRC.
Results: Two case reports were presented to show how skin rash could hamper mAb EGFR inhibitors use in clinical practice, underscoring the need of implementing a comprehensive management strategy of skin toxicity in order to promote patients' compliance with anti-EGFR therapy and maintain quality of life. Based on randomized data, recent guidelines established by the Multinational Association for Supportive Care in Cancer (MASCC) Skin Toxicity Study Group suggest that prophylactic use of oral doxycycline or minocycline reduces the risk and severity of skin rash, improving clinical outcomes.
Conclusions: At the start of treatment with cetuximab and panitumumab, the proper patient education about the rash associated with these mAbs and the implementation of a pre-emptive, comprehensive skin toxicity program significantly contribute to improve adherence to therapy, optimize anti-EGFR therapy and maintain quality of life.

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Abstract Code: ISP3612-40

Drug Interaction between Two Generic Formulations of Immunosuppressant Drugs in Tunisian Renal Transplant Patients: Mycophenolic Mofetil (MMF®) and Cyclosporine (Equoral®)

E. Gaies[1], M. Ben Sassi[1], I. Salouage[1], R. Charfi[1], N. Jebabli[1], S. Trabelsi[1], H. El Jebari[1], M. Lakhal[1], A. Klouz[1]

(1) Centre National de Pharmacovigilance de Tunis, Tunis, Tunisia

Introduction: Mycophenolate mofetil (MMF, Cellcept®) is a prodrug of mycophenolic acid (MPA) that is used as an immunosuppressant in transplant patients. In Tunisian renal transplant recipients, MMF®, a generic formulation of Cellcept®, is largely prescribed in combination with calcineurin inhibitors. Its therapeutic drug monitoring is essential because of its pharmacokinetics variability and its narrow therapeutic range. Pharmacokinetics of MPA can be modified by drug interaction. Drugs may interfere with MPA clearance by different mechanisms such us the suppression of the enterohepatic recycling pathway by cyclosporine (CsA).
Aim: The aim of this study is to investigate pharmacokinetics parameters of MPA when associated to calcineurin inhibitors (CsA or tacrolimus) in Tunisian renal transplant patients.
Methods: It consists on a retrospective study (2009–2013). A total of 75 renal transplant patients were evaluated. These patients were treated by (MMF®) associated to tacrolimus (Prograf®) or a generic of CsA (Equoral®). The median age was 37 years. The sex ratio (M/F) was 55/20. The average weight was 70 kg. Full MPA pharmacokinetics profiles were made. Therapeutic drug monitoring was carrying out by HPLC.
Results: Our results show a mean AUC_{0-12h} of MPA of 37.39 h*mg/L (therapeutic interval: 30–60 h*mg/L). The mean AUC_{0-12h} of MPA when associated to CsA was 30.5 h*mg/L and it was about 42.9 h*mg/L in combination with tacrolimus ($p = 0.02$). 48 % of patients have an infratherapeutic concentration, among these patients, 63 % were treated by CsA with an MPA dose of 1,600 mg/d and 37 % by tacrolimus with an MPA dose of 1,450 mg/d ($p < 0.02$).
Conclusion: Our results confirm data reported previously. We demonstrate that the rate of patients having an infratherapeutic AUC_{0-12h} and treated by CsA is superior to those treated by tacrolimus although the dose of MPA was superior in patients treated by tacrolimus although the dose of MPA was superior in patients treated by CsA. We demonstrate also that the significant reduction of MPA AUC_{0-12h} remains the same in a different population and with a generic drug formulation.

Abstract Code: ISP3613-41

Use and Perception of Phytoestrogens in Postmenopausal Women: Result of a Questionnaire-Based Survey

C. Piccinni[1], E. Poluzzi[1], E. Raschi[1], B. Vitamia[1], A. Koci[1], F. De Ponti[1]

(1) Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy

Background: Use of food supplements containing phytoestrogens among postmenopausal women is rapidly increasing, especially after the WHI

(Women's Health Initiative) trial publication suggesting an unfavorable risk-benefit profile of prolonged Hormone Replacement Therapy. Although phytoestrogens are often perceived safe, evidence for overall positive risk-benefit profile is inconclusive. Moreover, the chance to buy them by user's initiative does not facilitate surveys on their prevalence and pattern of use.

Objective: To describe pattern of use and self-reported positive and negative perceptions of phytoestrogens in post-menopause.

Methods: A questionnaire was administered to women who were buying food supplements containing phytoestrogens in 22 pharmacies located in the Bologna area (400,000 inhabitants). Questionnaire was structured into 3 sections: (a) socio-demographic; (b) pattern of use (e.g., duration and frequency of therapy), (b) perceived benefits and adverse events. Differences in positive and negative perceptions, between short-term (<1 year of treatment) and long-term users (≥1 year of treatment) were assessed by standard chi-square test ($p < 0.05$).

Results: Data on 190 post-menopausal women (aged 38–77) were collected. Out of these, 35 % reported high level of cholesterol, 18 % hypertension, 11 % circulation disorders, and 4 % breast cancer diagnosis, before starting phytoestrogens. Women stated to use phytoestrogens to reduce hot flashes (79 %), insomnia (15 %), mood disturbances (14 %) and prevent osteoporosis (15 %). The majority (59 %) took phytoestrogens routinely, whereas 28 % in 3-month cycles. In terms of therapy duration, 47 % of women were considered short-term and 53 % long-term users. Among positive perceptions, no difference was found between groups for palpitation reduction (37 % of cases, $p = 0.96$) and mood improvement (51 %, $p = 0.75$); a slight difference was reported for hot-flashes relief (68 % in short-term vs. 81 % in long-term users; $p = 0.05$). Negative perceptions were reported more frequently in the long-term group, but this difference was statistically significant only for edema (6 % in short-term vs. 17 % in long-term users; $p = 0.03$), and not for other effects: swelling sensation (10 vs. 21 %; $p = 0.08$), somnolence (7 vs. 10 % $p = 0.60$), fatigue (4 vs. 11 % $p = 0.13$).

Conclusions: In the Bologna area, the pattern of use of phytoestrogens for menopausal symptoms is heterogeneous, and women overall find these substances to be beneficial, especially for relief of hot-flashes. Other positive perceptions, instead, seem to decrease with a long-term use. Negative perceptions with long-term therapy appear as estrogen-like effects. Physicians should routinely ascertain the use of phytoestrogens in post-menopausal women, in order to recognize possible adverse effects and interactions.

Abstract Code: ISP3614-42

Adverse Reactions Associated with Interferon Beta in Multiple Sclerosis

R. Sahnoun[1], G. Lakhoua[1], S. El Ferjani[1], S. Kastalli[1], M. Lakhal[1], R. Daghfous[1], S. El Aidli[1]

(1) National Centre of Pharmacovigilance, Tunis, Tunisia

Introduction: Interferons beta (INF ß) are widely used as the first line in the treatment of relapsing remitting multiple sclerosis. These immunomodulators drugs are associated with miscellaneous side effects, such as flu-like syndrome, headache, increased spasticity, and psychological changes. Local skin reactions are common after subcutaneous injection of INF ß (1). The aim of this study was to report adverse reactions associated with INF ß in multiple sclerosis notified to the Tunisian National Centre of Pharmacovigilance.

Methods: It was a retrospective study involving all adverse reactions associated with INF ß, notified to Tunisian National Centre of Pharmacovigilance between January 2008 and December 2012 and valued with a French method of imputation of Begaud et al. We considered the cases in which INF ß had the most important imputation score alone or in association with other drugs.

Results: There were 16 patients including 12 women and 4 men. The age varied from 19 to 53 years. Ten patients received subcutaneous injection of Rebif® (INF ß1a), 4 patients received intramuscular injection of Avonex® (INF ß1a), and 2 patients received subcutaneous injection of Betaferon® (INF ß1b). INF ß was prescribed alone in 10 cases and associated with other drugs in 6 cases. The adverse reaction type was cutaneous effect (8 cases), liver abnormalities (2 cases), pancreatitis (1 case), hematologic disorder (3 cases), cardiovascular disorder (1 case), and Flue like syndrome (1 case). Cutaneous reactions were localized at the injection site in 5 cases (in one case, the localized reaction was severe: Panniculitis), and generalized in 3 cases (allergic dermatomyosite in 1 case, pruritus in 1 case, and psoriasis in 1 case). The imputation score was likely (I3) in 2 cases, possible (I2) in 8 cases and doubtful (I1) in 7 cases.

Discussion: In our study, cutaneous effects were the most common adverse reactions and represented the half of cases (8/16). In the literature, the most frequent adverse reactions associated with INF ß are flu like syndrome, fever, chills, headache, malaise, asthenia and inflammatory skin reactions at the injection site. This can be explained by underreporting of flu-like syndrome, fever, asthenia, since they represent classic adverse effects.

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Abstract Code: ISP3615-43

Levofloxacine Induces Rhabdomyolysis: a Case-Report

O. Charfi[1], S. Kastalli[1], R. Sahnoun[1], M.H. Loueslati[1], R. Daghfous[1], S. El Aidli[1]

(1) National centre of Pharmacovigilance, Tunis, Tunisia

Background: Fluoroquinolones have been widely used to treat various bacterial infections because of a broad spectrum of antimicrobial activity. *Common side effects of fluoroquinolones include gastrointestinal, central nervous and allergic reactions.* Adverse effects of these drugs on the musculoskeletal system such as myalgia, arthralgia and tendon disorder have been rarely reported. Few cases of fluoroquinolones induce rhabdomyolysis have been published.

Herein we report a case of rhabdomyolysis that occurred after the patient began taking levofloxacin. The case were analysed according to Begaud's method of imputation.

Case Report: A 50-year-old woman with no medical history was prescribed levofloxacine (1,000 mg/day) for pulmonary infection. On the 2nd day of treatment, 36 h after the first intake, she developed general musculoskeletal pain then facial and feet swelling. Laboratory investigation, realized on the 3rd day, shows these results: Aspartate aminotransferase (AST) 180 IU/L [5–34], Creatine kinase 451 IU/L [29–168], creatinine 113 µmol/L [53–97]. Levofloxacine was stopped. Clinical symptoms disappeared progressively and spontaneously on the 10th day (7 days following treatment withdrawal). Laboratory parameters returned to normal 9 after levofloxacin was discontinued. The intrinsic imputability relating the possible drug-effect relationship between levofloxacin and the occurrence of rhabdomyolysis was valued as I1 (doubtful).

Discussion: The responsibility of Levofloxacine was suspected in front of the close time relationship between drug administration and the development of symptoms and the suggestive outcome: recovery after drug withdrawal. A variety of muscle syndromes have been rarely reported in association with fluoroquinolone use, ranging from mild myalgias to life-threatening rhabdomyolysis [1]. In the literature, fluoroquinolone induces rhabdomyolysis have been mainly reported with levofloxacin (29 cases) and less often with ciprofloxacin, ofloxacin, gatifloxacin, norfloxacin and moxifloxacin. These case-reports include at least four with a fatal outcome [1]. Symptoms usually occur within 1 week after initiation of fluoroquinolone treatment and often resolve within 1–4 weeks after discontinuation of the medication. Our patient, although normal renal function, developed symptoms shortly, 36 h after the drug intake. The mechanisms of fluoroquinolone-induced myotoxicity are unknown. Fluoroquinolones appear to have a pathological influence on intracellular calcium handling. A pre-existing impairment of the calcium homeostasis, however, seems to be necessary for this effect.

Conclusion: Although levofloxacin-induced rhabdomyolysis seems to be rare, patients with myalgia, or weakness during therapy should be aware for this adverse effect.

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Abstract Code: ISP3616-44

Lichenoid Eruption During Chronic Hepatic C Treatment with Interferon-Alpha 2 a Plus Ribavirin

R. Sahnoun[1], S. Kastalli[1], O. Charfi[1], A. Zaiem[1], M. Lakhal[1], R. Daghfous[1], S. El Aidli[1]

(1) National Center of Pharmacovigilance, Tunis, Tunisia

Introduction: The association between pegylated interferon alpha and ribavirin is widely used in the treatment of chronic hepatitis C. The main side effects are fatigue, muscular and articular pains, humor disturbance, insomnia, depression, anemia and leucopenia (1). We report a case of lichenoid eruption during the 5th month of interferon plus ribavirin treatment in a patient with chronic hepatitis C infection. This case was evaluated according to the French method of imputation of Begaud et al. (2).

Case Report: A 59-year-old man was treated by Pegasys® (pegylated interferon alpha 2a) 180 mcg weekly and Copegus® (ribavirin) 1,200 mg/day for chronic hepatitis C virus (HCV) infection. He was anti-HCV (+), and her serum HCV RNA level was 687,000,000 UI/ml (6.82 log), genotype Ib. Her physical examination was completely normal. Her blood count was in the normal range (hemoglobin 14 g/dl). After 4 months, hemoglobin, was 8.5 g/dl, and HCV RNA level was negative. Ribavirin dose was decreased to 800 mg/day and her hemoglobin increase to 10.5 g/dl. During the follow-up, no further modifications in drug doses were required. At the 5th month of treatment, shiny flat violaceous polygonal papules appeared, scattered the upper limbs and neck without mucosal lesions. These lesions suggest a lichenoid eruption. During this time, a serum HCV RNA level was negatif. Lichenoid eruptions regressed after symptomatic treatment (Local corticosteroid ointment plus oral antihistaminic). Lichenoid eruptions had completely resolved 1 month after completing a 48-week treatment period. The control of the viral load was still negative. The imputation score was plausible (I2).

Discussion: Lichenoid eruption and especially oral lichen planus is frequently seen in patients with HCV infection and was reported to be an extra hepatic manifestation of HCV. In lichenoid drugs eruptions, the mucosal lesions are exceptionally reported.

In our case, the responsibility of the antiviral treatment was retained in the genesis of these lichenoid eruptions with an intrinsic score of I2 (plausible) mainly because of:

- a suggestive delay of onset on the symptoms (5 months);
- the appearance of skin lesions when HCV RNA level was negative;
- a suggestive evolution: lesions disappeared after one month of stopping treatment;
- absence of mucosal lesions.

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Abstract Code: ISP3617-45

DRESS Syndrome Associated with Lamotrigine in a Child

O. Charfi[1], S. Kastalli[1], S. El Ferjani[1], M.H. Loueslati[1], R. Daghfous[1], S. El Aidli[1]

(1) National Center of Pharmacovigilance, Tunis, Tunisia

Background/Aim: Drug reaction with eosinophilia and systemic symptoms (DRESS) is an adverse drug-induced reaction. It has been well described with aromatic anticonvulsant drugs and rarely associated with non aromatic antiepileptic like lamotrigine.

Herein, we are presenting a seven-year-old boy, who developed DRESS syndrome due to Lamotrigine with aggravation after the first intake of phenobarbital.

Case Report: A 7-year-old boy with a history of seizure was treated by valproic-acid for six years. Because of obesity and hyperactivity, it was decided to switch to lamotrigine. On the 5th days after starting lamotrigine, he developed fever. On the 10th day, fever persisted, a general rash with edema and lymphadenopathies appeared. On the 20th day, the patient was admitted in the primary care because of impairment of consciousness with fever 41°, seizure, general erythema and edema. Lamotrigine was discontinued and discharged on clonazepam. He was treated by corticosteroid. Laboratory parameters showed hypereosinophilia, and elevated liver enzymes. In front of skin condition improvement on the 5th following lamotrigine withdrawal, the patient was authorized to leave the hospital. He was prescribed phenobarbital 50 mg/day and corticosteroid was continued at the same dose. Few hours following Phenobarbital intake, he developed a severe general edema and his skin condition worsened with extensive detachment of the epidermis involving hands, feet and the face. Phenobarbital was discontinued. The symptoms resolved within 15 days. Patch tests were positive for lamotrigine.

Discussion: The responsibility of lamotrigine in the genesis of DRESS syndrome was retained in front of a suggestive delay, a recovery after drug withdrawal, and a positive patch test.

Patch testing is a safe and useful procedure in patients with antiepileptic drug induced DRESS, where the proportion of relevant and specific positive patch tests is high [1]. However, a negative patch testing doesn't exclude the responsibility of the tested drug in the genesis of DRESS syndrome.

In our case, the worsening of the skin condition after the first intake of phenobarbital allowed us to suspect a possible cross-reactivity between lamotrigine and phenobarbital, despite the negative patch testing to this drug.

Conclusion: This case report a lamotrigine induced DRESS and the possible cross-reaction with an aromatic anticonvulsant.

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Abstract Code: ISP3618-46

Adverse Effects of Oxytocin and Misoprostol Reported to the National Pharmacovigilance Centre After Induction of Labor in Term Parturients

N.T. Mpiempie[1], M.O. Mboma[1], K.C. Kilandamoko[1], N.Y. Lula[1], L.B. Mvete[1], B.M. Makila[1], K.A. Bapite[1], K.L. Mesia[2], N.C. Nsibu[3], L.G. Tona[1]

(1) Unite de Pharmacologie Clinique et Pharmacovigilance, Faculte De Medecine, Universite De Kinshasa, RD Congo, (2) Hospital Saint Joseph, Service de Gynecologie Obstretrique, RD Congo, (3) Service de Pediatrie, Cliniques Universitaires de Kinshasa, Faculte de Medecine, Universite de Kinshasa, RD Congo

Background: Labour induction is common in obstetrics, usually oxytocin or prostaglandins analogues are used in some protocols. However, the risk of uterine hyperstimulation which can be fatal for both foetus and mother is relatively frequent and life-threatening reactions can accompanied their use. Labour induction with misoprostol is so controversial, its formal indication is peptic ulcer. The oxytocin infusion and misoprostol orally, rectally or vaginally are the medicines administered in DR Congo which is accounted among the most-affected countries with maternal mortality.

Objective: The main objective of this study is to determine adverse events pattern following oxytocin and misoprostol administration for labour induction in DR Congo and their impacts on delivery process.

Methods: All individual case safety reports (ICSRs) received by National Pharmacovigilance Centre from 1st January 2011 to 31st December 2012 related to use of oxytocin and misoprostol for labour induction were analyzed. Adverse events were coded using the World Health Organization Adverse Reaction Terminologies (WHO-ART).

Result: Oxytocin infusion was most used (14 cases), 8 parturients were administered misoprostol (3 vaginally, 4 rectally, 1 orally) and in 2 cases both oxytocin and misoprostol were used.

The most common adverse effect reported was foetal distress (70.8 %) expressed by foetal bradycardia, foetal tachycardia or meconium-stained amniotic fluid. Others adverse events reported include failure of induction (20.8 %) attributed mainly to ocytocin, fetal death in utero occurred in to 2 cases (8.4 %). 13 women (54.2 %) were primipara. Caesarean section was required in all cases of foetal distress.

Conclusions and Discussions: Potential risks associated to administration of oxytocin and misoprostol are of more concern. Primipara seems to be on high risk than multipara. Adequate studies are needed to determine accurately which substance, dose, route of administration must be used for labour induction, protocols of their use made available to large audience of healthcare professionals. Risk minimization plan especially during pregnancy must be clearly known for these medicines

Abstract Code: ISP3619-47

Poison Control Data as Source of Information for Pharmacovigilance: the Italian Experience

L. Settimi[1], F. Davanzo[2], F. Giordano[3], G. Milanesi[2], E. Urbani[1], L. Cossa[1], F. Sesana[2], M. Ferruzzi[2], R. Borghini[2], I. Rebutti[2]

(1) National Institute of Health (Istituto Superiore di Sanità), Rome, Italy, (2) National Poison Control Center in Milan, Niguarda Cà Granda Hospital, Milan, Italy, (3) "Sapienza" University of Rome, Italy

Objectives: In early 2000s, the Italian National Institute of Health and the National Poison Control Centre in Milan (NPCCM) implemented a surveillance system based on data collected by PCCs, denominated National System for Surveillance of Toxic Exposures and Poisonings (NS-STEP). Aim of the present contribution is to provide a preliminary characterization of toxic exposures to pharmaceuticals identified by NS-STEP and to highlight the relevance of this source of information for pharmacovigilance activities, as required by EU legislation.

Methods: Descriptive analysis of cases exposed to pharmaceuticals in 2007–2010 notified to NS-STEP by NPCCM.

Results: In the period under study NS-STEP identified 78,012 human cases of exposure to pharmaceuticals, accounting for 40 % of all cases of exposure notified to the system. Reason for exposure was unintentional for 56 % of cases, intentional for 38 %, and unknown for 2 % of cases. About 3 % of cases developed an adverse reaction. Among unintentionally exposed cases, 78 % were young children aged <6 years, 8 % were aged 6–19 years, 16 % >19 years. About 70 % of unintentional exposure were caused by uncontrolled access to pharmaceutical products, while 30 % of cases were victims of medication error. Pouring from the original container caused 3 % of unintentional exposures. Among intentionally exposed cases, 88 % were >19 years old, 87 % attempted suicide, 12 % were victims of abuse or intentional misuse.

The most common pharmaceutical categories involved in human exposures reported to NS-STEP included: Sedative/Hypnotic/Antipsychotics (26 % of cases); Analgesics (15 % of cases); Antidepressants (12 % of cases); Cardiovasculars (7 % of cases); Hormone and Hormone antagonists (7 % of cases); Antimicrobics, Anticonvulsants, and Topical preparations (6 % of cases, respectively).

Conclusions: Directive 2010/84/EU clarifies that pharmacovigilance of medicinal products should also include noxiuos and unintentional effects resulting not only from the authorised use of a medicinal product at normal doses, but also from medication errors, misuse and abuse. PCCs can provide a relevant contribution to identify this kind of effects and to monitor the safety use of authorised medicinal products.

Abstract Code: ISP3620-39

Adverse Drug Reactions During Antibiotics Administration in Hospitalized Children and Doctors' Attitudes and Beliefs in ADRs Reporting

A. Toska[1], M. Geitona[2], C. Demetzos[3]

(1) Doctoral candidate, Department of social and Educational Policy, University of Peloponnese, Korinthos, Greece, (2) Associate professor, Faculty of social and Educational Policy, University of Peloponnese, Korinthos, Greece, (3) Professor, Faculty of Pharmacy, University of Athens, Greece

Introduction: Adverse drug reaction (ADRs) is a significant problem in children. Systematic reviews show that almost 1 out of 10 children in hospital experience ADRs[1] with antibiotics being among the leading causes[2].

Aim: The aim of this study was the assessment of adverse reactions (ARs) incidence experienced by doctors during the administration of antibiotics in pediatric patients, as well as the assessment of doctors' attitudes and beliefs in ADRs reporting.

Material and Methods: A cross sectional study was conducted in 2012 in all Pediatric Hospitals and Pediatric Departments in the general hospitals in Greece. A self-administrated questionnaire was given to pediatricians and intern doctors in pediatrics.

Statistical Analysis: Statistical analysis was performed by using SPSS statistical software 17.0.

Results: From the 400 questionnaires distributed to all doctors, 275 were returned fully completed given a response rate of 68.75 %. Overall 23.6 % of responders answered that adverse reaction (AR) in antibiotics use occur often/ very often during their clinical practice. The majority (80.4%) reported that rush was the most common ARs following by diarrhea (60.4 %). Regarding the classes of antibiotics involved with ARs, 45 % of doctors reported amoxicillin/clavoulanic acid as the responsible antibiotic with the most frequent adverse reactions. Overall 32.7 % of respondents answered that they had never reported adverse drug reactions, whereas the percentage of non-reporting was higher for intern doctors in comparison with pediatricians ($p = 0.033$). Qualified doctors also, believed less that the ADRs reporting is more important in pediatrics ($p = 0.024$).

Conclusions: Lack of sufficient data in the pediatric due to the limited clinical trials, make exigent the necessity of post marketing epidemiological studies in order the safety profile of the drugs to be ensured. This could be achieved by ensuring the active surveillance of ADRs in children with the participation of all health professionals. The rational drugs' use and especially the antibiotics use, is also essential, given that ADRs depends on the prescribing attitudes.

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Abstract Code: ISP3621-40

Fatal Multi-Organ Toxicity Induced by Low-Dose of Methotrexate for Evacuate an Ectopic Pregnancy

I. Salouage[1], M. Ben Sassi[1], E. Gaies[1], R. Charfi[1], S. Trabelsi[1], N. Jebabli[1], H. El Jebari[1], M. Lakhal[1], A. Klouz[1]

(1) Centre National de pharmacovigilance de Tunis, Tunis, Tunisia

Introduction: Methotrexate is an antifolate that inhibits dihydrofolate reductase, an enzyme crucial in the metabolism of a folic acid. It is used to treat some blood cancers and autoimmune diseases. These side effects are hematological, hepatic, renal, skin, gastrointestinal. These effects usually occur at high doses but also at low doses.

We report a case of multi-organ toxicity induced by low-dose of methotrexate in a patient with an ectopic pregnancy.

Case Report: A 32-years-old woman with a history of penicillin allergy. She was treated by 75 mg of methotrexate (day 1) to evacuate an ectopic pregnancy.

Forty-eight hours after, she developed mucositis grade 2, odynophagia, dysphagia, and a fever (40 °C) and skin lesions (diffuse erythema, macular lesions, hyperpigmentation).laboratory findings showed pancytopenia (hemoglobin count 7.7 g/dL, leukopenia count 300/mn3 and thrombocytopenia count 14,000/mn3), renal failure (creatinine 204 umol/ml), hepatic cytolysis was 3 times normal upper limit (3 N), cholestasis (PAL = 1.5 N, GGT = 3 N), C-reactive protein was 335 mg/L. Neurological examination, chest X-ray and urine culture were normal. The plasma level of methotrexate (day 11) showed a toxic concentration equal to 0.05 μM. She was treated by folic acid 60 mg/day, hydration, urine alkalinization and an empirical antibiotic therapy. The outcome was marked by the persistence of pancytopenia and hepatic cytolysis with the appearance of a mucoid-bloody diarrhea. Concentration of méthotrexte (day 13) was 0.03 μM. She developed a severe bone marrow aplasia and she died after a severe septic shock.

Conclusion: Side effects related to low-dose methotrexate are uncommon but life-threatening disorder. Methotrexate toxicity can be detected by therapeutic drug monitoring of plasmatic concentration.

Abstract Code: ISP3622-41

Therapeutic Drug Monitoring of Sirolimus

M. Ben Sassi[1], I. Salouage[1], E. Gaies[1], S. Trabelsi[1], R. Charfi[1], N. Jebabli[1], H. El Jebari[1], M. Lakhal[1], A. Klouz[1]

(1) Centre National de Pharmacovigilance de Tunis, Tunis, Tunisia

Introduction: Sirolimus is an immunosuppressant agent used mainly as a second line for organ transplantation. The therapeutic drug monitoring (TDM) is essential because of the narrow range and the use of several drugs in combination in this population (enzyme inducer or inhibitor). Several studies have reported variability of pharmacokinetics parameters of sirolimus and that adverse effects of this drug are more closely correlated with sirolimus blood concentration rather than the dose.

Aim: To investigate the interindividual variability of pharmacokinetic parameters of sirolimus and evaluate the correlation between blood levels of sirolimus and its adverse effects.
Methods: This is a retrospective study (March 2010–April 2013) conducted in the department of clinical pharmacology with patients treated with sirolimus. The residual concentrations were made by enzyme-linked immunoassay. The therapeutic range is between 4 and 12 ng/mL.
Results: We collected 93 samples from 36 patients. The sex ratio (M/F) is 3.5, and the median age was 32 years. 91 % of these patients are followed for kidney transplant. The average dose is 2.3 mg/kg/day. The mean concentration found was 12.43 ng/mL. In our study, 61 % were in the therapeutic range, 6.5 % infratherapeutic concentration, 31.5 % supratherapeutic concentration. Mean concentrations of each interval are 8 ng/mL, 2.91 ng/mL, 23.25 ng/mL respectively. 43 % of patients developed adverse effects (hematological, renal and gastrointestinal) and 25 % of them have a supratherapeutic concentration. The study of the correlation between dose and blood concentration showed a correlation coefficient of 0.648.
Discussion: The interindividual variability of biodisponibility of sirolimus needs a therapeutic drug monitoring for improved therapeutic efficacy and fewer side effects especially in front the correlation between blood levels and adverse effects.

Abstract Code: ISP3623-42

ABCG2 Gene Variant as Predisposition for Developing Atorvastatin Adverse Drug Reactions: Case–Control Study

N. Mirosevic Skvrce[1], N. Bozina[2], L. Pejnovic[2], I. Barisic[2], L. Zibar[3], V. Macolic Sarinic[1], I. Simic[4]

(1) Agency for Medicinal Products and Medical Devices, Zagreb, Croatia, (2) University Hospital Centre Zagreb, Zagreb, Croatia, (3) Clinical Hospital Centre Osijek, Osijek, Croatia, (4) University Hospital Centre, Zagreb, Croatia

Background: The mechanisms by which statins cause myotoxicity and hepatoxicity remain unknown, but appear to be related to statin concentrations in the blood. Consequently, factors inhibiting statin catabolism are associated with increased myotoxicity and hepatoxicity risk including advanced age, hepatic or renal dysfunction, perioperative periods, multisystem diseases, small body size, untreated hypothyroidism and concomitant use of drugs that diminish statin catabolism. Newly identified risk factors for statin induced toxicity are genetic variants of drug metabolizing enzymes and membrane transporters. The ABCG2 efflux transporter is expressed in multiple tissues and plays an important role in the disposition of different drugs including statins. The functional 421C>A polymorphism in the ABCG2 that reduces transporter activity has been found to be associated with increased systemic exposures to certain statins, including atorvastatin.
Aim: The aim of this case–control study is to show the contribution of ABCG2 gene variant to the development of dose-related atorvastatin ADRs.
Materials and Methods: Fifty patients who experienced atorvastatin ADRs and 50 controls matched for age, gender, dose and concomitant therapy were enrolled in the study.
Methods: Genotyping of the ABCG2 421C>A polymorphism was performed using the TaqMan allele-specific PCR assay (Applied Biosystems).
Results: Thirteen patients that experienced atorvastatin induced ADRs were carriers of 421CA genotype and one of 421 AA genotype. Seven patients that did not experience atorvastatin induced ADRs were carriers of 421CA genotype and none of 421 AA genotype. ABCG2 421CA and AA genotype (taken together) were significantly more prevalent in the patient group with ADRs ($p = 0.0145$).
Conclusion: We found out that A allele carriers of ABCG2 421C>A (421CA and 421AA genotypes), responsible for reduced transport activity, were at greater risk for developing ADRs to atorvastatin therapy comparing to non carriers of this polymorphism. This is first study showing association between ADRs caused by atorvastatin and ABCG2 variant. Result of our study is of special importance for patients with multiple risk factors for developing atorvastatin toxicity and genotyping for ABCG2 could help them in minimizing risk.

Abstract Code: ISP3624-43

Determinants for Predicting Serious Adverse Event (SAE) Rates Across Study Duration in Selected Rheumatology Indications

D. Coleman[1], C. O'halloran[2], D. Murphy[1], S. Dobo[3]

(1) Quintiles, Dublin, Ireland, (2) Quintiles, London, UK, (3) Quintiles, Raleigh Durham, USA

Objective: When planning a study, it is necessary to accurately predict the volume of SAEs. We examined the relationship between randomization, study duration and SAE numbers.
Method: Three Rheumatology indications; Rheumatoid Arthritis (RA), Gout and Osteoporosis, were selected for review. Numbers of patients randomized were compared to SAE numbers for study duration.
Results: The rate at which SAEs accumulate differs according to the indication. For RA and Osteoporosis studies, the rate of SAEs appears to be a function of time and does not correlate closely with enrollment. There is a plateau for SAE accumulation at the end of the RA studies. The SAE rate for Osteoporosis is very linear and does not plateau at the study end. SAEs in gout are more closely related to subject enrollment and increase as more subjects enter study. The duration of the study was an additional factor. For Gout, length of study duration had no clear impact on the overall rate of SAEs (where rate is calculated as the number of SAEs per randomized subject expressed as percentage); while for RA and Osteoporosis, the longer study duration led to a substantial increased rate. The decline in new SAEs at study end in RA may be explained by increased discontinuations. Additionally, the surviving population may be healthier, have had more efficacy, therefore eliminating SAEs due to progression or worsening of disease, and may also have good tolerance of the study drug. In osteoporosis, the lack of consistent confounding comorbidities (other than age) may explain the very linear relationship of SAEs with time. Although there are well documented co-morbidities with gout, there are too few SAEs and studies are of shorter duration limiting the ability to make meaningful conclusions.
Conclusion: The review suggests that it may be possible to determine SAE rate profiles for specific indications. If the volume or pattern of SAEs deviates from what is expected for the population, an earlier trigger of a safety issue for the study drug may be detected rather than waiting for study end and unblinding. For future consideration, the impact of the inclusion of AEs into the population profile may also be considered as well as comparison with extension or open label studies where the patient population is preselected due to perceived efficacy of study drug, and tolerance of it, and where study drug received by the patient is known and placebo element is eliminated.

Abstract Code: ISP3625-44

Fixed Drug Eruption to Paracetamol and Diagnostic Tools

S. El Ferjani[1], S. Kastalli[1], O. Charfi[1], M. Lakhal[1], R. Daghfous[1], S. El Aidli[1]

(1) National Centre of Pharmacovigilance, Tunis, Tunisia

Introduction: Fixed drug eruption (FDE) is one of the most typical cutaneous drug adverse reactions. It has mainly been reported with non steroidal anti-inflammatory drugs (NSAIDs). Paracetamol-induced FDE has also been reported. The diagnosis of FDE is mainly clinical. However, identification of the culprit drug requires the practice of allergy tests such as patch-testing or oral rechallenge.
Aim: To describe the clinical characteristics of fixed drug eruption and to identify diagnostic tools.
Methods: We performed a retrospective observational study of all the cases of FDE in patients who received paracetamol, reported to the Tunisian national centre of pharmacovigilance, for the period from January 2010 to March 2013. We retained 11 cases where paracetamol has the most important imputation score alone or in association with other drugs. Patch-tests to paracetamol were performed in all patients. Oral rechallenge was proposed to the patients with negative patch-tests.
Results: Among the reported cases (n = 11), 5 were women and 6 were men. The age varied from 12 to 72 years. The number of lesions ranged between 3 and several lesions. FDE had multiple locations in all cases. In 6 cases the diagnosis was established after several reactivations. Two patients benefited from cutaneous biopsy which confirmed the diagnosis. The delay varied between few minutes to 3 days. In all cases, the outcome was characterized by residual hyper pigmentation. Patch-tests on pigmented lesions (n = 11) were reactive in two cases. Oral rechallenge was positive in one patient. In the 8 other cases, this test was refused.
Discussion: In our study, two patch-tests to paracetamol were positive. In literature, a retrospective analysis in a 20-year period has shown that patch-tests can be positive in 40.4 % of cases of fixed drug eruption mainly with NSAID. However, in this study, no positive patch-test to paracetamol (n = 8) was observed even under conditions of high clinical suspicion (n = 2) [1]. Patch-tests are safe and simple to perform. However, their negativity cannot exclude liability of inducing drug. In our study, oral rechallenge was performed for only one patient and was positive. Oral rechallenge remains the only way to confirm the diagnosis. However, it exposes the patient to the reactivation of old lesions and the possible appearance of new lesions [1].
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Abstract Code: ISP3626-45

Fixed Drug Eruption to Quinolones

S. El Ferjani[1], S. Kastalli[1], W. Kaabi[1], M. Lakhal[1], R. Daghfous[1], S. El Aidli[1]

(1) National Centre of pharmacovigilance, Tunis, Tunisia

Introduction: Fixed drug eruption (FDE) is a common adverse drug reaction. Among antibiotics, trimethoprim/sulfamethoxazole and tetracyclines are most commonly associated with FDE. FDE has been rarely reported with quinolones.
Aim: To analyse the observations of patients who experienced quinolones-induced fixed drug eruption (FDE) and to identify diagnostic tools.
Methods: We performed a retrospective observational study of all the cases of FDE in patients who received quinolones, reported to the Tunisian national centre of pharmacovigilance (CNPV), for the period from December 1990 to March 2013. We retained 4 cases where quinolones have the most important imputation score. We collected the age, the sex, the medical history, the clinical characteristics of the FDE, the drugs administered in association, the delay, the outcome, the results of patch-tests and the imputation score of quinolones.
Results: Observations concerned 2 men aged respectively 49 and 65 years and 2 women aged respectively 29 and 65 years. The quinolones implicated in the genesis o FDE were ciprofloxacin, ofloxacin and levofloxacin. Patch-tests to quinolones in pigmented lesions were performed in the 3 first patients and were positive. Cross reactivity between levofloxacin, ofloxacin, and ciprofloxacin has been demonstrated in the first patient. On the fourth patient, the practice of patch-test was not possible because of the location in the penis and oral rechallenge was refused. The intrinsic imputation score according to Bégaud et al. varied from I3 to I4.
Conclusions: Our study collected only 4 cases of quinolones-induced FDE reported to the CNPV over a period of 22 years. Only second and third generation quinolones (ciprofloxacin, ofloxacin and levofloxacin) were implicated in the genesis of FDE. In literature, FDE to quinolones has mainly been reported with ciprofloxacin, ofloxacin and rarely with levofloxacin [1, 2]. In our study, a cross reactivity between second and third generation quinolones has been demonstrated with positive patch-tests. In literature, cross reactivity between 2nd and 3rd generation quinolones has previously been reported [3].
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Abstract Code: ISP3627-46

Phenobarbital Therapeutic Drug Monitoring After Loading Dose in Children

M. Ben Sassi[1], R. Charfi[1], S. Trabelsi[1], I. Salouage[1], E. Gaies[1], N. Jebabli[1], H. El Jebari[1], M. Lakhal[1], A. Klouz[1]

(1) Centre National de Pharmacovigilance de Tunis, Tunis, Tunisia

Introduction: Phenobarbital is the recommended drug for the treatment of seizures and neonatal asphyxia in neonates. Because of its pharmacokinetics variability in children especially in neonates and its risk of toxicity, therapeutic drug monitoring (TDM) of phenobarbital is recommended specially after a loading dose.
Aim: We aimed through this study to emphasize the interest of the phenobarbital TDM after a loading dose.
Methods: It consisted on a retrospective study made in the National Centre of Pharmacovigilance from January 2012 to April 2013. We

collected 46 samples from 30 infants and neonates who took one or more boluses of Phenobarbital.

The samples were analyzed by an automated chemiluminescence immunoassay. We considered the therapeutic range as 20–40 μg/mL.

Results: A total of 30 children were included in our study comprising 37 % of neonates. Among the children, 21 were followed for seizures, 5 for neonatal asphyxia and 4 for meningitis. The sex ratio (M/W) was 0.9. The median age was 0.33 years old [0.008–12 years old], the mean weight was 9 kg [1.6–60 kg]. Seven children used one other anticonvulsant drug and 3 used 2 others.

The children received one (33 %) or two boluses (67 %) with a maintenance dose in 46 % of them. The mean loading dose was 19 mg/kg/day and the maintenance dose was 5 mg/kg/day. The TDM was made 1–7 days with a mean of 2 days after. The mean concentration was 20 μg/mL [4–59 μg/mL]. In our study, 38 % of the children had an infratherapeutic concentration, 51 % had a concentration in the therapeutic range and 11 % had a supratherapeutic concentration. Statistical analysis showed a low correlation between mean doses and phenobarbital concentrations in infants ($r = 0.28$) and no correlation in neonates ($r = 0.06$).

Five children presented a side reaction: 4 developed drowsiness (comprising 3 neonates) and the last one developed excitation TDM allowed dose adjustment within one to 16 days after the drug onset.

Conclusion: Close TDM is recommended to ensure therapeutic efficacy and to avoid adverse drug reactions due to phenobarbital in this particular population.

Abstract Code: ISP3628-47

Adverse Events Associated with Emergency Contraceptive: Comparing the Results of a Follow Up Study with Those Coming from Spontaneous Reporting

A. Carvajal[1], M. Sainz[1], I. Salado[1], L. Garcia Sevillano[1], M. Pellon[1], L. Martin Arias[1], V. Velasco[1], P. Garcia Ortega[1], C. Treceno[1]

(1) Centro de Estudios Sobre la Seguridad de los Medicamentos Universidad de Valladolid, Spain

Background: The emergency contraceptive pill (ECP) is dispensed without a prescription in Spain since 2009. An easy access could diminish unwanted pregnancies; however, there is a risk of misuse and of developing some adverse events. The aim of the present study is to further learn the adverse effects of the ECP.

Methods: A follow-up study has been performed in three community pharmacies in a city of Central Spain (Valladolid). The sample was composed of those women asking for the ECP and who agreed to participate; they were interviewed by telephone after at least a month since the last intake of the ECP. Information was collected by using a structured questionnaire. Additionally, data from spontaneous reporting in Spain were used. A descriptive analysis was performed and most of the results are expressed in frequencies and percentages; 95 % confidence intervals were calculated for proportions of adverse reactions. The two-tailed Chi-square test was used to analyze differences in proportions.

Results: During the period of the study (June 2011 to September 2012), 256 different women asked for the ECP in whichever pharmacy. Overall, 139 women were surveyed, the age ranged from 14 to 50 years (mean age 26.2 ± 7.4); most had university studies (54.1 %). There were 311 reactions detected in the follow-up study, none of them was considered severe; the most common being menstrual disturbances (26 %; $n = 81$). Spontaneous reporting yielded 45 reactions; a third of the reactions were considered severe; the most common was unwanted pregnancy (24.4 %; $n = 11$).

Conclusions: The most common reactions with the ECP are mild; nevertheless, attention must be paid to the factors which may account for efficacy failures. Combining an ad-hoc follow-up study with spontaneous reporting the whole safety profile of a given medication can be obtained.

Abstract Code: ISP3629-48

Vancomycin Therapeutic Drug Monitoring in Renal Failure

M. Ben Sassi[1], R. Charfi[1], I. Salouage[1], S. Trabelsi[1], E. Gaies[1], N. Jebabli[1], H. El Jebari[1], M. Lakhal[1], A. Klouz[1]

(1) Centre National de Pharmacovigilance de Tunis, Tunis, Tunisia

Introduction: Vancomycin is a glycopeptide antibiotic mainly used in the treatment of Staphylococcus infections. Vancomycin has a bactericid time-dependent activity.

The therapeutic drug monitoring (TDM) is recommended in patients with renal failure because of a decreased vancomycin clearance resulting in a higher risk of toxicity.

Aim: We aimed through this study to assess sampling modalities for the TDM and the influence of sex, age and hemodialysis on the vancomycin concentrations in case of a renal failure.

Methods: It consists on a retrospective study from January to April 2013 made in the National Centre of Pharmacovigilance. From 29 patients with a renal failure, we collected 55 samples, which were analyzed by an automated fluorescence polarization immunoassay. We considered the therapeutic ranges (TR) for the trough concentrations (C0) as 10–12 μg/mL and for a continuous infusion concentration (CCI) as 20–30 μg/mL.

Results: Sex ratio M/W was 4. Median age was 45 years old (1–80). Nine patients were older adults (≥65 years old).

Among our patients, 38 % were treated for a sepsis and mainly addressed from intensive care units. In our patients, 45 % were receiving haemodialysis: 56.5 % of the men and 50 % of the women. The average creatinine concentration was 459 mmol/L. Aminoglycosides were associated to vancomycin in 3 patients.

The vancomycin mean dose was 820 mg/day (10 mg/kg/day). A mean of 5 days between vancomycin onset and the first TDM (1–9 days) and of 2 samples per patient (1–6) were noted.

Vancomycin concentrations in the haemodialysis patients versus the others were as following: the mean C0 was 15 μg/mL versus 14.18 μg/mL and the mean CCI was 32.5 μg/mL versus 23.3 μg/mL. Supratherapeutic concentrations were noted in 59 % of the hemodialysis patients and in 89 % of the women's ones (Table 1).

Conclusion: Supratherapeutic concentrations were mainly noted in case of hemodialysis and in women. Vancomycin doses should be adjusted after a TDM drawn every 4–7 days to ensure therapeutic efficacy and to prevent toxicity.

Table 1 Percentage of concentrations in the TR and above in function of the sex, the age and the hemodialysis on the vancomycin concentrations in case of a renal failure

	Concentrations in the TR (%)	Concentrations > TR (%)
Men	21.5	55
Women	11	**89**
Age ≥65 years	13.5	53
Age <65 years	22.25	55.5
Hemodialysis patients	21	**59**
No hemodialysis	17	50

Abstract Code: ISP3630-40

Fixed Drug Eruption to Non Steroidal Anti Inflammatory Drugs (NSAID)

G. Lakhoua[1], R. Sahnoun[1], A. Zaiem[1], S. Ferjani[1], M. Lakhal[1], R. Daghfous[1], S. El Aidli[1]

(1) Centre National de Pharmacovigilance, Tunisia

Introduction: NSAID belong to the most frequently prescribed drugs in the developed countries. They are also used currently by self-medication. Their side effects are various: digestive, renal, hepatic, hematological, and cutaneous. Fixed drug eruptions (FDE) are rare with NSAID.
Aim: The aim of this study was to identify and to analyze all the cases of FDE related to NSAID notified to the Centre National of Pharmacovigilance of Tunisia between January 2008 and December 2011.
Methods: We underwent a retrospective study. We included all the cases of FDE where the NSAID had the highest score of imputability or shared the same highest score with other drugs. Data collection precised age, sex, pathological history, drugs administrated, delays, evolution, score of imputability, and recommendations. We analyzed these cases with the French method of imputability.
Results: Fourteen cases were retained, among them 9 men and 5 women. Their age varied between 12 and 60 years old. Three patients have a history of FDE; two among them have developed a FDE with piroxicam. The other eleven cases were inaugural FDE. Only three patients used a NSAID alone, for the eleven other the NSAID was used with one to eight drugs. Piroxicam was taken by eleven patients, mefenamic acid by 3 patients and niflumic acid by one patient. FDE was bullous in 3 cases. The delay of onset of lesions varied between few hours to ten days in 13 cases, in one case the delay wasn't précised. The score of imputability was very likely and likely in 5 cases each, possible in 4 cases. The contraindication of the NSAID was recommended in 14 cases.
Discussion/Conclusion: FDE to NSAID is rare in literature. It was mainly reported with piroxicam. It seems exceptional with mefenamic and niflumic acid. In a Tunisian series of cases of 56 FDE, salycilate acid and piroxicam were retrieved in 2 cases each. FDE was bullous in three cases, among them piroxicam was responsible in two cases. In literature, oxicams are considered as the NSAID most bullous eruption purveyors. In our study, the delay varied between few hours to ten days. It's known in literature, that the delay become shorter with the recurrence of episodes. The score of imputability was high in ten cases reflecting a specific drug related semiology.

Abstract Code: ISP3631-41

Evolving Vigilance Landscape in Ghana: Review of Safety Reporting in Regional Hospital Bolgatanga in 2012

A.R. Al-Abdneger-Issifu[1]

(1) Regional Hospital Bolgatanga, Bolgatanga, Ghana

Introduction: Spontaneous reporting of ADRs has been shown to be an important method to increase drug safety knowledge [1].The Food and Drugs Authority (FDA) monitors the safety of medicines to contribute to a better understanding of their possible adverse effects when they are used outside the controlled conditions of clinical trials. The FDA depends on health professionals to solicit ADRs on their behalf through spontaneous reporting. The aim of this study was to evaluate if one-page ADR information letters affect the reporting rate of ADRs and the quality of the ADR reports.
Methods: Data was collected from the Regional Hospital Bolgatanga (RHB) and the intervention consisted of circulation of one page ADR newsletter to all health professionals. The ADRs solicited and reported to the FDA were assessed for quality based on completion and causality assessment by the Technical Advisory Committee (TAC) of the FDA.
Results: In 2012, 196 adverse reactions were recorded at the RHB and 23 (11.74 %) were submitted to the FDA for causality assessment. Overall, 190 of the adverse reactions were drugs related, 3 were vaccine related, 2 were blood related and one was device related. The number of quality reports was 23 (11.74 %) and that of high quality was 21 (10.72 %). Pharmacists accounted for 65.22 % of the reports submitted to the FDA, followed by Nurses 21.74 % and Physicians 13.04 %.
Conclusions: This study suggests that one page ADR newsletter to Health professionals improved the number of adverse reactions reported by the RHB to the FDA.

Table 1 Quality of adverse reaction reports submitted by the Regional Hospital Bolgatanga in 2012

Parameters	Drugs	Blood	Devices
Total number of reports	193	2	1
Total number of quality reports (% of vigilance category)	20 (10.4)	2 (100)	1 (100)
Total number of quality reports (% of quality reports)	20 (87)	2 (8.70)	1 (4.35)
Total number of high quality reports (% of vigilance category)	18 (9.3)	2 (100)	1 (100)
Total number of high quality reports (% of the total high quality reports)	18 (85.7)	2 (9.52)	1 (4.76)

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Abstract Code: ISP3632-42

Contribution of Patient Reporting by Phone Call to Spontaneous Reporting and Signal Detection: Case of Antimalarial Drugs

N.Y. Lula[1], N.P. Ntamabyaliro[1], Y.J. Liwono[1], K.G. Mesia[1], N.C. Nsibu[2], L.G. Tona[1]

(1) Clinical Pharmacology and Pharmacovigilance Unit, University of Kinshasa, Kinshasa, DR Congo; National Pharmacovigilance Centre, Kinshasa, DR Congo, (2) Clinical Pharmacology and Pharmacovigilance Unit, University of Kinshasa, Kinshasa; National Pharmacovigilance Centre, Kinshasa; Paediatrics Department, University of Kinshasa, Kinshasa, DR Congo

Background: In many countries, spontaneous reporting system remains one of the most important means of monitoring the post-marketing safety of medicines [1]. However, underreporting is a well-recognized concern. There is increasing interest to use various means such as telephone, fax, electronic mail or internet in reporting system and, consumer reporting is encouraged as a complement to reports from health-care professionals (HCPs) and can contribute to the signal detection.
Objectives: To evaluate the contribution of patient reporting using a mobile phone technology to collect Artemisinin-based Combination Therapies (ACTs) adverse events (AE).
Methods: The study was conducted in 3 health facilities of Kinshasa (DR Congo) during a 3-month period. A specific questionnaire was designed for this purpose and investigators were trained in Pharmacovigilance basics and antimalarial adverse effects. Outpatients diagnosed for uncomplicated malaria and treated with ACTs were asked to report any AE via phone mobile interviews with investigators. Informed consent was obtained previously from each selected patient. At the time of treatment, each patient was monitored for AE experiences during 7 days.
Results: 140 patients were interviewed and 87 of them (62 %) experienced a suspected ADR. Two hundred and eighteen AEs were experienced. Forty point seven percent (40.7 %) of them were associated with Amodiaquine w/Artesunate, 32.1 % with Artemether w/Lumefantrine and 15.7 % with Dihydroartemisinin w/Piperaquine. Higher incidence rate of ADRs was observed with general disorders (35.4 %, asthenia among 69 patients), central and peripheral nervous disorders (29.8 %, dizziness and headache mainly) and gastrointestinal disorders (20.7 %, especially anorexia and vomiting). Reactions led to treatment interruption in 11 cases (7.9 %).
Conclusions and Discussions: This active surveillance shows a higher rate of antimalarial AE than spontaneous reports recorded from HCPs, but ADRs profile seems to be similar [2]. The results suggest that patient reporting may have a valuable contribution to Pharmacovigilance system or signal detection and facilitate medicines monitoring in low-income countries.

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Abstract Code: ISP3635-45

Incretins-Associated Pancreatitis: Evidence from the Italian Spontaneous ADR Reporting Database

M. Delfino[1], V. Monda[2], A. Benini[1], D. Motola[3], G.P. Franzè[4], M. Barotto[1], A. Campi[1]

(1) Department of Pharmacy, Hospital and Community Pharmaceutical Assistance, Local Health Authority of Ferrara, Italy, (2) Department of Internal Medicine, Division of Diabetology "S.S. Annunziata" Hospital of Cento (FE), Local Health Authority of Ferrara, Italy, (3) Department of Medical and Surgical Sciences, Unit of Pharmacology, University of Bologna, Italy, (4) Chemical-Clinical Analysis Laboratory and Microbiology, "S. Anna" University Hospital of Ferrara, Italy

Background: Recent studies on the safety profiles of the new drugs for diabetes glucagon-like peptide-1 analogues (such as exenatide and liraglutide) and dipeptidyl peptidase-4 inhibitors (such as sitagliptin, vildagliptin and others) showed an increased risk of hypersensitivity reactions, renal failure, infection, thyroid and pancreas cancer, and acute pancreatitis. These factors contribute to uncertainty about the safety profile of these new drugs.
Aim: To contribute to risk assessment of pancreatic damage associated with these drugs by evaluating the spontaneous ADRs reporting in Italy.
Methods: Reports of suspected adverse drug reactions associated with new antidiabetic drugs were selected from the Italian Spontaneous ADR Reporting Database and analyzed starting from the marketing date of the exenatide. We described the characteristics of the subjects and of the drugs reported for all cases. Only for a subgroup of these cases belonging to the Local Health Authority (LHA) of Ferrara laboratory parameters (level of pancreatic enzymes, amylase and lipase) were available, before and after the therapy with the incretin mimetics (GLP-1 analogues and DPP-4 inhibitors).
Results: At the end of December 2012, 2443 reports of suspected ADR associated with hypoglycaemic drugs (excluding insulin), 1169 (47.85 %) concerned new incretin-mimetics. Ninety reports out of 1169 described pancreatitis (44) and elevated pancreatic enzymes (46). Twenty-six out of 44 reports concerned the analogues of GLP-1, whereas among the 46 reports describing elevated pancreatic enzymes (amylase and lipase), 20 were associated with analogues of GLP-1. Acute pancreatitis and increase in pancreatic amylase resulted in the hospitalization of 19 and 2 subjects, respectively. Among the cases from the LHA of Ferrara the finding of increased values for amylase and lipase caused the discontinuation of the drugs and the monitoring of patients. Subsequent laboratory data showed a decrease, and in some cases normalization of the values of amylase and lipase after the dechallenge.
Conclusion: Our data add up and confirm the information available on the association between incretin-mimetics and pancreatic damage and suggest caution in the prescribing of these new drugs. In patients already using drugs, special careful should be reserved to signs and symptoms of early occurrence of pancreatitis, with the precautionary suspension of the treatment and the adoption of another appropriate therapy.

Abstract Code: ISP3638-48

Use of Antibiotics and Risk of Ventricular Arrhythmia: A Nested Case–Control Multi-Database Study in 5 European Countries

A. Oteri[1], M. De Ridder[1], S. Pecchioli[2], I. Bezemer[3], E. Garbe[4], T. Schink[4], M. Clò[5], S. Pilgaard Ulrichisen[6], M.C. Sturkenboom[1], G. Trifirò[7]

(1) Department of Medical Informatics, Erasmus University Medical Center, Rotterdam, The Netherlands, (2) Health Search, Italian College of General Practitioners, Florence, Italy; Regional Agency for Healthcare Services of Tuscany, Florence, Italy, (3) PHARMO Institute for Drug Outcomes Research, Utrecht, The Netherlands, (4) Leibniz Institute for Epidemiology and Prevention Research, BIPS GmbH, Germany, (5) Department of Pharmacology, University of Bologna, Bologna, Italy, (6) Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark, (7) Department of Medical Informatics, Erasmus University Medical Center, Rotterdam, The Netherlands; Department of Clinical and Experimental Medicine and Pharmacology, University of Messina, Messina, Italy

Background: Some antibiotics (i.e. macrolides or fluoroquinolones) are known to be associated with cases of ventricular arrhythmia (VA). A recent study showed an increased risk of cardiovascular death in association with azithromycin, confirming the arrhythmogenic potential of macrolides.
Objective: Aim of this multi-database nested case–control study was to evaluate the risk of VA in current users of antibiotics (especially those known to be torsadogenic) as compared with no-use, in a large population from 5 European Countries.
Methods: All data were retrieved from 7 health care databases (AARHUS/Denmark, GEPARD/Germany, HSD and ERD/Italy, PHARMO and IPCI/The Netherlands, and THIN/UK), covering a population of 27 million individuals. A cohort of incident antibiotic users from 1996 to 2010 was identified from the 7 databases. Cases of VA were selected through harmonized DB-specific and validated, coding-algorithm, including validated diagnostic codes or free-text search. Up to 100 controls were matched to each case by index-date, sex, age and database. Exposure to antibiotics was categorized into 4 mutually exclusive groups: (a) current (if the exposure period covered the index-date plus a 7 day carry-over period); (b) recent (if the exposure period ended between 7 and 90 days before the index-date); (c) past (if the exposure period ended between 90 and 365 days before the index-date); and (d) no-use (if there was no exposure within 365 days prior to index-date). Drugs with at least 5 exposed cases were included in the analysis. The odds ratio (OR) of current use for individual antibiotics relative to no-use was estimated using multivariate conditional logistic regression, while adjusting for confounders.
Results: Overall, 25,952 cases and 2,594,738 matched controls were identified. Among cases, 2,298 (8.9 %) were current users of antibiotics. Current use of beta-lactam antibiotics and macrolides showed higher risk of VA as compared with no-use. Current use of azithromycin (OR_{Adj} 2.12 [1.62–2.77]), clarithromycin (OR_{Adj} 2.12 [95 % CI 1.72–2.61]) and erythromycin (OR_{Adj} 1.66 [1.28–2.13]) was associated with significantly increased risk of VA ($p < 0.05$). ORs from single database and meta-analyses of database-specific estimates were in line with results from the pooled analysis. Among fluoroquinolones, current use of ciprofloxacin (OR_{Adj} 1.43 [1.14–1.79]) was associated with a statistically significant increased risk of VA, while moxifloxacin showed an increased, although non-significant, risk of VA (OR_{Adj} 1.54 [0.94–2.77]).
Conclusion: A large database-network from 5 European Countries allowed for investigation of the arrhythmogenic potential of several antibiotics. The recently documented increase in the risk of VA in current users of azithromycin was confirmed in our study.

Abstract Code: ISP3639-49

Use of Antipsychotics and Risk of Ventricular Arrhythmia: A Nested Case–Control Multi-Database Study in 5 European Countries

A. Oteri[1], M. De Ridder[1], S. Pecchioli[2], I. Bezemer[3], E. Garbe[4], T. Schink[4], A. Puccini[5], S. Pilgaard Ulrichsen[6], M.C. Sturkenboom[1], G. Trifirò[7]

(1) Department of Medical Informatics, Erasmus University Medical Center, Rotterdam, The Netherlands, (2) Health Search, Italian College of General Practitioners, Florence, Italy; Regional Agency for Healthcare Services of Tuscany, Florence, Italy, (3) PHARMO Institute for Drug Outcomes Research, Utrecht, The Netherlands, (4) Leibniz Institute for Epidemiology and Prevention Research, BIPS GmbH, Germany, (5) Department of Pharmacology, University of Bologna, Bologna, Italy, (6) Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark, (7) Department of Medical Informatics, Erasmus University Medical Center, Rotterdam, The Netherlands; Department of Clinical and Experimental Medicine and Pharmacology, University of Messina, Messina, Italy

Background: In the last years, some antipsychotic drugs (APDs), such as thioridazine or haloperidol, have been associated with an increased risk of serious ventricular arrhythmias (VAs) leading to regulatory actions.
Objective: Aim of this multi-database nested case–control study was to evaluate, in a large population from 5 European Countries, the risk of VA in association with individual APDs as compared to no-use.
Methods: All data were retrieved from 7 healthcare databases (AARHUS [Denmark], GEPARD [Germany], Health-Search/Thales (HSD) and Emilia-Romagna Regional Database (ERD) [Italy], PHARMO and IPCI [The Netherlands], and THIN [UK]), covering a total population of around 27 million individuals. A cohort of incident users of APDs from 1996 to 2010 was identified from the 7 databases. Cases of VA were selected through harmonized DB-specific coding algorithms including validated diagnostic codes or free-text search. Up to 100 controls were matched to each case by index-date, sex, age and database. Exposure to APDs was categorized into mutually exclusive groups of current (if exposure period covered the index-date plus a carry-over period of 30 days), recent (if exposure period ended between 30 and 90 days before the index-date), past (if the exposure period ended between 90 and 365 days before the index-date), and no-use (if there was no exposure within 365 days prior to index-date). Only those drugs with at least 5 exposed-cases were included in the analysis. The odds ratio (OR) of current use for individual APDs relative to no-use was estimated using multivariate conditional logistic regression while adjusting for confounders.
Results: Overall, 1,676 cases and 164,968 matched controls were identified. Of all cases, 629 (37.5 %) were currently exposed to APDs. Current use of levosulpiride (OR_{Adj} 12.90 [95 % CI 5.41–30.68]), haloperidol (OR_{Adj} 2.70 [2.10–3.47]),chlorprothixene (OR_{Adj} 1.81 [1.11–2.93]), thioridazine (OR_{Adj} 1.75 [1.06–2.89]), levomepromazine (OR_{Adj} 1.61 [1.02–2.55]), flupentixol (OR_{Adj} 1.61 [1.10–2.38]), quetiapine (OR_{Adj} 1.53 [1.18–1.98]) and olanzapine (OR_{Adj} 1.33 [1.05–1.70]) was associated with a statistically significant increased risk of VA ($p < 0.05$). ORs from single

database and meta-analyses of database-specific estimates were in line with those observed in the pooled analysis.
Conclusion: A large database network from 5 European Countries allowed for investigation of the arrhythmogenic potential of individual APDs. Current use of several APDs was associated to an increased risk of VA. The risk was higher for drugs with known torsadogenic potential.

Abstract Code: ISP3641-42

Causality and Preventability of Adverse Drug Reactions of Analgesics

I. Cazacu[1], G. Miremont-Salame[2], H. Geniaux[2], A. Benard-Laribiere[2], A. Daveluy[2], H. Theophile[2], A. Farcas[1], C. Mogosan[1], F. Loghin[3], F. Haramburu[2]

(1) Drug Information Research Center Cluj-Napoca, Romania, (2) Regional Pharmacovigilance Centre of Bordeaux, France, (3) Department of Toxicology, Faculty of Pharmacy, "Iuliu Hatieganu" University of Medicine and Pharmacy, Cluj-Napoca, Romania

Introduction: Analgesics are among the most used drugs worldwide for the treatment of various types of pain and can induce adverse drug reactions (ADRs). A significant proportion of these ADRs are or may be preventable.
Aim: To assess the causality and the preventability of analgesics ADRs spontaneously reported.
Methods: A retrospective, descriptive study was conducted on analgesics adverse effects spontaneously reported to a French regional pharmacovigilance centre, between January 2011 and June 2012. Cases where analgesics-antipyretics (N02B), opioid analgesics (N02A), but also non-steroidal anti-inflammatory drugs (NSAIDs, M01A), treatment for acute migraine (N02CC), anticonvulsants (N03AF, N03AX) or antidepressants (N06AA, N06AX) had an approved indication for pain and were suspected to be linked to the ADR were included. For NSAIDs, those used for rheumatic diseases were excluded. The causality of ADR cases had already been assessed by the team of the centre (Bégaud et al. 1985). The preventability was assessed by two clinical pharmacologists and a pharmacist (Olivier et al. 2005).
Results: A total of 127 ADR cases was reported in 57 men and 70 women, with a mean age of 58.6 years (median 61, range 14–94) (age unknown for 2 cases). There were 194 adverse effects (1.5 per case), for which 153 analgesics (1.2 per case) were suspected. Tramadol, paracetamol, morphine, pregabalin, fentanyl, oxycodone and ibuprofen accounted for the majority of ADR cases. Causality of analgesics was assessed as certain in 2 % of cases, probable in 28 %, possible in 27 % and doubtful in 42 %. In 8 % of cases, the ADRs were unlabelled or only seldom published. ADRs were assessed as preventable in 30 % of cases, potentially preventable in 12.6 % and not preventable in 28.3 % of cases (preventability not assessable in the other cases). For almost 26 % of the cases, the recommendations for use were neglected, for 30 % of the patients risk factors were not taken into account and for almost half of the cases (46 %) there was an alternative therapy that could have been used with a better risk/benefit ratio. Out of the preventable ADR cases, 15 (39.5 %) were medication errors of administration, prescription, compliance or self-medication.
Conclusions: An important number of ADRs of analgesics could be prevented. There is a continuously need of detecting the drug related problems and preventive strategies should be implemented to avoid the harm that drugs could bring to the patients.

Abstract Code: ISP3643-44

Development of an Integrated Torsadogenic Score: The Experience of the ARITMO Project with a Focus on Antipsychotics

E. Raschi[1], F. Salvo[2], E. Poluzzi[1], U. Moretti[3], A. Chiarolanza[1], M. Suling[4], L. Hazell[5], M. Sturkenboom[6], A. Pariente[2], F. De Ponti[1]

(1) Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy, (2) Department of Pharmacology, Université Bordeaux Segalen, Bordeaux, France, (3) Pharmacology Unit, University of Verona, Verona, Italy, (4) Bremen Institute Of Prevention Research and Social Medicine, University of Bremen, Bremen, Germany, (5) Drug Safety Research Unit, Southampton, UK, (6) Erasmus Medical Center, Rotterdam, The Netherlands

Background: Novel automated approaches are under development to support signal detection and to complement case-by-case analysis, but they are usually performed on a single database and, most importantly, do not take into account other variables such as extent of consumption and time on the market of the analyzed drugs.
Objective: Within the ARITMO project (http://www.aritmo-project.org), we developed a pharmacovigilance score with the aim of improving the efficacy of traditional disproportionality approaches for prioritization of torsadogenic signals.
Methods: 11 criteria were defined and weighted through a Delphi-like approach to detect torsadogenic signals for antipsychotics, H1-antihistamines and anti-infectives. They were calculated using FAERS, EudraVigilance, France, German and Italian databases. These scores, previously normalized to the 0-1 range, were aggregated calculating the mean value to obtain an integrated torsadogenic score. We also separately computed information on (1) drug consumption (DDD/TID obtained from various European Countries, as a measure of drug exposure), (2) time on the market (in years, from year of first marketing to 2011), (3) consistency among archives (mean difference across scores). These three continuous parameters were converted to the 0–1 range and aggregated to obtain a measure of the uncertainty (from low to high).
Results: Out of 482 analyzed agents, 169 received an integrated score. Thirty drugs were retrieved only in one single database (54 in FAERS, 12 in Eudravigilance, 6 in Italy, 5 in France, and 3 in Germany). Eighteen of the top-50 ranked agents are labelled by AZCERT lists as being potentially torsadogenic (http://www.azcert.org, as of May 15th 2013). Thirty-eight antipsychotics received a score, with 28 ranked among top-50 drugs. Pimozide showed the highest score (score = 0.47; uncertainty = 0.63), followed by chlorprothixene (0.30; 0.49) and ziprasidone (0.30; 0.65); haloperidol showed intermediate score (0.16; 0.42), clotiapine the lowest (0.02; 0.93). Among the other studied classes, first-ranked drugs were rupatadine (H1-antihistamines; score = 1; uncertainty = 0.64), halofantrine (antiprotozoals; score = 0.63; uncertainty = 0.71), ganciclovir (antivirals; score = 0.51; uncertainty = 0.84), cefalotin (antibacterials; score = 0.26; uncertainty = 0.81), and posaconazole (antimycotics; score = 0.24; uncertainty = 0.56).
Conclusions: This score attempts to integrate different indicators of torsadogenic risk through multiple sources and provides initial elements to provisionally rank drugs for their torsadogenic potential by highlighting inter- and intra-class differences. Calibration is required to identify optimal thresholds for signal prioritization, both in terms of score and its uncertainty.
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Comparison of Torsadogenic Events Extracted from National Pharmacovigilance Databases: An Overview from the ARITMO Project

E. Raschi[1], F. Salvo[2], E. Poluzzi[1], U. Moretti[3], A. Koci[1], M. Suling[4], L. Hazell[5], M. Sturkenboom[6], A. Pariente[2], F. De Ponti[1]

(1) Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy, (2) Department of Pharmacology, Université Bordeaux Segalen, Bordeaux, France, (3) Pharmacology Unit, University of Verona, Verona, Italy, (4) Bremen Institute Of Prevention Research and Social Medicine, University of Bremen, Bremen, Germany, (5) Drug Safety Research Unit, Southampton, UK, (6) Erasmus Medical Center, Rotterdam, The Netherlands

Background: Spontaneous reporting systems (SRSs) represent a valuable source to detect rare events with high drug-attributable component such as Torsades de Pontes (TdP). National databases cover different patterns of reporting (influenced by habits in drug prescription and market penetration) and offer access to detailed information on patient's medical history (i.e. narratives).
Objective: To compare the distribution of torsadogenic events recording antipsychotics, H1-antihistamines and anti-infectives as suspects, by using a common search strategy in 3 national pharmacovigilance databases: Italy, Germany and France SRSs.
Methods: Within the ARITMO project (http://www.aritmo-project.org), a protocol was developed to extract torsadogenic events by creating 4 groups in decreasing order of drug-attributable risk: (1) TdP, (2) QT abnormalities, (3A) Ventricular/Cardiac Fibrillation, (3B) Ventricular Tachycardia/Arrhythmia (fatal/serious), (3C) Ventricular Tachycardia/Arrhythmia (non-fatal/serious), (4A) Sudden Cardiac Death/Cardiac Arrest, (4B) Syncope (fatal/serious) [1]. Full access was possible in France (2000–2010) and Italy (1989–2010), including free-text search through narratives; restricted access in Germany (2005–2010 without narratives).
Results: Overall, the highest number of ARITMO events was recorded in Germany, followed by France and Italy (4,837, 4,350 and 3,294, respectively). TdP was most frequently reported in France, followed by Germany and Italy (85, 45 and 19, respectively). France and Germany detected very similar number of events for the three drug classes, as compared to Italy (1,372, 1,330 and 744, respectively). The highest number of cases was retrieved for group 3C in Germany and Italy (906 and 405, respectively), whereas France recorded a large proportion of cases in group 3A (469) and 4A (326). Antipsychotics were highly reported in Germany (854 cases), whereas anti-infectives in Italy and France (684 and 659, respectively).
Conclusions: Substantial differences were found in case distribution, for event type, but also for pharmacological classes. Reasons may be ascribable to peculiarities in types of access, processing of the original report (drug/event codification, causality assessment, case validation), type of reporter and prescribing patterns. This confirms that multiple database analysis is informative when studying torsadogenic events.
Acknowledgments: The research leading to these results has received funding from the European Community's Seventh Framework Programme (FP7/2007-2013) under grant agreement n° 241679—the ARITMO project.
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Pharmacovigilance and Drug Safety in Calabria (Italy): 2012 Adverse Events Analysis

C. Leporini[1], C. Giofrè[1], F. Scicchitano[1], C. Palleria[1], L. Gallelli[1], E. Russo[1], G. De Sarro[1], U. Univigil Cz Research Group[1]

(1) Department of Science of Health, School of Medicine, University of Catanzaro, Italy and Pharmacovigilance's Centre Calabria Region, University Hospital Mater Domini, Catanzaro, Italy

Introduction: Pharmacovigilance (PV) is designed to monitor drugs continuously after their commercialization, assessing and improving their safety profile. The main objective is to increase the spontaneous reporting of adverse drug reactions (ADRs), in order to have a wide variety of information [1]. The Italian Drug Agency (Agenzia Italiana del Farmaco, AIFA) is financing several projects to increase reporting. In Calabria a PV Information Centre has been created in 2010. We report the results obtained during the 2012 in Calabria.
Methods: Data were obtained through the database of the national New Health Information System (NSIS) AIFA relatively during the 2012. Anova test was used for statistical analysis.
Results: 461 ADRs have been recorded in 2012 with a 234 % increase respect to 2011 (138 reports). Female gender (61.83 %) and the age group "41–65 years" (39.07 %) and "over 65" (27.9 %) were mostly affected. Hospital doctors represent the main source of this reporting (51.62 %). Sorafenib, amoxicillin/clavulanic acid and ketoprofen represent the drugs most frequently involved in ADRs.
Conclusions: In Calabria we recorded an increase in ADRs reported number, although the gold standard (GD) set by World Health Organization (WHO) (about 600 reports) has not reached. The data have showed that PV culture is making inroads in this region; in this light, PV projects stimulating and increasing PV knowledge are needed.
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Abstract Code: ISP3651-43

Dosage Adjustment Practice in Hospitalized Patients with Chronic Kidney Disease in a Teaching Hospital in Nepal

S. Shrestha[1], S.P. Lohani[1]

(1) Department of Pharmacy, Institute of Medicine, Tribhuwan University, Maharajgunj, Nepal

Introduction: Patients with chronic kidney disease (CKD) have a high risk of developing adverse effects due to reduced drug elimination and multiple drug therapy. Impaired renal function results in dose adjustment of a number of pharmacologic agents to avoid unwanted drug effects and to ensure optimal outcomes. Several studies have been conducted to assess dosage adjustment practices in renal failure patients [1–2]. However, such study has not been previously conducted in Nepal.

Aim: To assess the dosage adjustment practice and rate of inappropriate dosing in patients with CKD.
Methods: One hundred CKD patients admitted to the medical ward of Teaching Hospital were sampled randomly and a retrospective observational study was conducted. Serum creatinine and age were used as an indicator for the assessment of renal function. Medication chart of patients with renal impairment were reviewed against dosing guideline for prescribing of the renally eliminated medications with or without any dosage adjustment. Jellife equation was used to calculate the creatinine clearance (CrCl). Pearson's chi-square test and odds ratio were applied as statistical tool using statistical software SPSS 16.0.
Results: The number of patients with severe renal failure (CrCl <10 ml/min) was higher in population older than forty years (62.0 %). Out of total 1229 drug prescribed, 290 drugs required dosage adjustment in which antimicrobials, GI drugs and antihypertensive drugs were the most. Of the total drugs requiring adjustment, 47.9 % were adjusted while remaining was in higher dose. There was a significant association between dosage adjustment and renal status of the patients. (odds ratio = 1.96)
Conclusion: The study shows that health care practitioners are showing enough concern about renal function and dose adjustment but still felt the need of strict adherence to dosing guidelines to avoid potential drug toxicity especially with nephrotoxic drugs.
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Characterization of Adverse Reaction Reports Associated with Adulterated Health Products: Analysis of Singapore Pharmacovigilance Database from 1993 to 2012

W.C. Tan[1], Y.K. Puah[1], M.Y. Tham[1], B. Tan[1], S.H. Tan[1], S. Soh[1], D. Toh[1]

(1) Health Sciences Authority, Singapore

Background: Pharmacovigilance has traditionally focused on adverse reactions associated with pharmaceuticals and complementary medicine. However, adulterated health products have increasingly been uncovered through pharmacovigilance [1].
Objective/Aim: To analyse characteristics of adverse reaction reports associated with adulterated health products.
Methods: Data extraction was conducted in Adverse Drug Reaction Database from 1993 to 2012, using search terms of Chinese proprietary medicine, complementary medicine, health supplements, other product types, adulteration, testing and illegal. Reports with suggestive urine/blood toxicology results or confirmatory pharmaceutical analysis for adulterants were analysed with descriptive statistics. Reports with unlikely and unconfirmed causality were excluded.
Results: 392 adverse reports were associated with adulterated health products, accounting for 0.3 % of total 133,126 ADR reports received during the analysis period. Indications include sexual enhancement (73.5 %), pain relief (10.8 %), general well-being (10.4 %), slimming (2.1 %) and others (3.2 %). Most patients were male (83 %) with median age of 53 years old. Ethnicity involved mirrored Singapore population with exception of "Other race" which was attributed to non-residents (Chinese 65 %, Malay 16 %, Indian 9 %, Others 10 %). Most reports were submitted by doctors (96.9 %) and were serious (96.4 %). 30.4 % of the tested products contain more than 1 adulterant. Adulterants detected include glibenclamide (n = 297), sildenafil (n = 73), dexamethasone (n = 35), chlorpheniramine (n = 28), paracetamol (n = 10), phenylbutazone (n = 9), sibutramine (n = 9) and piroxicam (n = 7). Top 3 System Organ Classes involved in adverse reactions were metabolic and nutritional disorders (n = 309), central and peripheral nervous disorders (n = 165) and psychiatric disorders (n = 135). Top 10 WHO-ART Preferred Terms reported include hypoglycaemia (n = 286), coma (n = 99), somnolence (n = 81), dizziness (n = 44), confusion (n = 30), glucocorticoids increased (n = 24), thinking abnormal (n = 21), convulsion (n = 19) and sweating increased (n = 11) and skin cold clammy (n = 11).
Conclusion: When assessing causality of adverse reactions in patients with history of taking products for sexual enhancement, pain relief, general well-being or slimming, possibility of product adulteration should be considered. Majority of the reports received were associated with sexual enhancement products in males with median age of 53 years old and presenting with adverse reactions expected of adulterants detected.
Discussion: Characterization of adverse reaction reports allows health regulators to swiftly tailor detection, communication and enforcement strategies against adulterated health products. With globalization of supply chain, adverse reactions associated with adulterated health products detected in Singapore could similarly be observed in other countries. Pharmacovigilance system can be used to detect and communicate risks of adulterated health products to protect public health and this adds impetus to the development of pharmacovigilance system globally [2, 3].

Abstract Code: ISP3656-48

What Can Safety Engineering Teach Us About Creating Safer Systems to More Effectively Manage Risk?

B. Edwards[1]

(1) NDA Regulatory Science Ltd, UK

Introduction: Safety engineering concerns identifying hazards in a system and preventing transition to an unsafe (hazardous) state. Safety is a control problem not a failure problem so that non-compliance impacting patients results from inadequate control of the system state caused by insufficient constraints on system behaviour. STAMP (Systems Theoretic Accident Model and Process) is a causality model based on systems theory and thinking. Extensive detailed descriptions and applications are available http://sunnyday.mit.edu/.
Aim: The target of STAMP is based on the integration of causal factors such as human-decision making, organizational design into the hazard analysis. STAMP is divided into two parts: STPA System Theoretic Process Analysis (how we find inadequate control in the system) and CAST (Causal Analysis using System Theory to detect inadequate controls that caused non-compliance). By first defining hazards, control actions and safety constraints can be identified. Then scenarios are identified that lead to violation of safety constraints followed by a causal analysis of unsafe control action. If gaps in the system for managing risk appear, actions can be taken to compensate. This means safety is designed into the system rather than added on at the end.

At Birkbeck College in London, a new programme has been established to help pharmaceutical professionals develop such techniques for designing safer systems. This has involved collaboration with other like-minded centres in both the EU and US. This session will present progress with this programme.

Conclusions: Given that STAMP is has been adopted by many different safety critical sectors in society across the world, not only does STAMP offer a standardised approach for the pharmaceutical sector to design safety systems but this will also enable cross-sectoral collaboration and benchmarking with other safety specialists to better define the strengths and weaknesses of STAMP.

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Safety of Trastuzumab Plus Docetaxel Versus Docetaxel Alone in Patients with Breast Cancer: A Cohort Study in a Cancer Centre

E. Sole[1], G. Maura[1], J.B. Rey[2], T. Trenque[1]

(1) Regional Center for Pharmacovigilance and Pharmacoepidemiology, Reims University Hospitals, Reims, France, (2) Institut Jean Godinot, Pharmacy Department, Reims, France

Introduction: Trastuzumab is a recombinant humanized monoclonal antibody directed against HER-2. The combination trastuzumab plus docetaxel is one of the standard treatments for patients with HER-2 positive breast cancer. If monoclonal antibodies are usually well-tolerated in monotherapy, their safety profile in combination with antineoplasic therapy is poorly described in general practice.

Aim: To describe in real-life the safety profile of trastuzumab plus docetaxel versus docetaxel monotherapy in patients with breast cancer.

Methods: An historical cohort included patients with breast cancer and treated by trastuzumab plus docetaxel or docetaxel alone in a French regional cancer centre between March 2009 and March 2012.

The occurrence of ADR during chemotherapy cycles has been assessed from medical and pharmaceutical records including biological analysis carried out by the patients. The seriousness of cases has been defined according pharmacovigilance criteria and ADR classified with MedDRA version 15.0.

Results: 317 patients were included of which 56 patients treated by trastuzumab plus docetaxel (T+D) and 261 patients by docetaxel monotherapy (D). The patient characteristics and the ADR occurrence in each group are presented in the table 1 below:

	T+D n = 56	D n = 261
Age, years ± SD	53 ± 8.8	57 ± 10.7
Sex, n (%)		
Women	56 (100)	258 (99)
Type of cancer, n (%)		
Invasive ductal carcinoma	53 (95)	214 (82)
Other	3 (5)	47 (18)
HER-2 status		
Positive, n (%)	53 (95)	8 (3)
Negative, n (%)	3 (5)	253 (97)
A lest one ADR, n (%)	39 (70)	194 (74)
Cases with serious ADR, n (%)	13 (23)	58 (22)

The first three System Class Organ recorded were skin and subcutaneous tissue disorders (36 % for T+D group versus 41 % for D group), gastrointestinal disorders (36 % T+D versus 37 % D) and blood and lymphatic system disorders (33 % in the both groups).

Conclusion: In this cohort study from clinical practice, ADR observed seemed not increase in the trastuzumab plus docetaxel group relative to docetaxel group. Safety profile of the increasingly used targeted therapies in combination with antineoplasic drugs must be further investigated.

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Identifying Potentially Drug-Induced Acute Liver Injury in Children Using a Multinational Healthcare Database Network

C. Ferrajolo[1,2], P. Coloma[1], K.M. Verhamme[1], M.J. Schuemie[1], R. Gini[3], R. Herings[4], G. Mazzaglia[5], G. Picelli[6], C. Giaquinto[7], L. Scotti[8], P. Avillach[9], L. Pedersen[10], F. Rossi[1], A. Capuano[1], J. Van Der Lei[1], G. Trifirò[1,11], M.M. Sturkenboom[1,12]; On Behalf of EU-ADR Consortium

(1) Medical Informatics, Erasmus MC University, Rotterdam, The Netherlands, (2) Campania Regional Centre of Pharmacovigilance and Pharmacoepidemiology, Experimental Medicine Department, Pharmacology Section, Second University Naples, Naples, Italy, (3) Regional Health Agency of Tuscany, Florence, Italy, (4) PHARMO Institute, Utrecht, the Netherlands, (5) Italian College of General Practitioners, Florence, Italy, (6) Pedianet-Società Servizi Telematici SRL, Padua, Italy, (7) Paediatric Department, University of Padua, Italy, (8) Statistics, University of Milano-Bicocca, Milan, Italy, (9) LESIM, ISPED, University of Bordeaux 2, Bordeaux, France, (10) Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark, (11) Clinical and Experimental Medicine, University of Messina, Messina, Italy, (12) Epidemiology, Erasmus University Medical Centre, Rotterdam, The Netherlands

Introduction: Data mining in spontaneous reporting databases has shown that drug-induced acute liver injury (ALI) is infrequently reported in children [1]. In general, the traditional pharmacovigilance system has limitations due to selective and underreporting which may impair the quality of signal detection. For this reason, the EU-ADR project developed and validated a computerised system combining data from multiple European electronic medical records and claims databases as additional source for early detection of drug safety signals [2]. In EU-ADR, ALI was one of the events under study.

Aims: To identify drugs potentially associated with ALI in children and adolescents using electronic healthcare data and to evaluate the significance and novelty of these associations.

Methods: Using harmonised and database-specific disease codes and free text search, we identified ALI cases occurring during exposure to any prescribed/dispensed drugs for individuals <18 years old and registered in EU-ADR network consisting of seven European population-based healthcare databases in the years 1996–2010 [3]. Several methods for signal detection such as Longitudinal Gamma Poisson Shrinker (LGPS), Self-Controlled Case Series (SCCS), and Longitudinal Evaluation of Observational Profiles of Adverse events Related to Drugs (LEOPARD) [4], were compared to automatically simulate the usual steps in the signal generated from spontaneous reporting system. We used as criteria for statistically significant association a threshold value of lower 95 % CI relative risk >1 for drug associated with ≥3 cases of ALI. Then, we differentiated between potentially new signals and already known

associations concerning ALI (in adults and/or in the paediatric population) through review of published literature and drug product labels.

Results: The study population comprised 4,838,146 individuals <18 years contributing overall 25,575,132 Person-Years (PYs) of follow-up time. Within this cohort, we identified 1,015 cases of ALI. Overall, 20 statistically significant drug-ALI associations were detected. With respect to the literature, the associations between ALI and domperidone, flunisolide, and human insulin were considered as potentially new signals. Citalopram and cetirizine have not been previously described as hepatotoxic in children but only in adults, while all remaining associations were already known in both adults and children.

Conclusions: In this proof-of-concept analysis we demonstrate that data mining of multiple electronic healthcare databases may complement traditional spontaneous reporting systems in the area of paediatric pharmacovigilance. Using the EU-ADR database network, potentially new signals concerning ALI in paediatric population have been identified and now require further investigation.

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Abstract Code: ISP3664-47

Suspected Adverse Drug Reactions in Children: A Descriptive Study of the Italian Spontaneous Reporting System

C. Ferrajolo[1,2], A. Capuano[1], F. Rossi[1], U. Moretti[3], G. Trifiro[2,4], C. Santuccio[5]

(1) Campania Regional Centre of Pharmacovigilance and Pharmacoepidemiology, Experimental Medicine, Second University of Naples, Naples, Italy, (2) Medical Informatics, Erasmus MC, Rotterdam, The Netherlands, (3) Clinical Pharmacology Unit, University of Verona, Verona, Italy, (4) Clinical and Experimental Medicine, University of Messina, Messina, Italy, (5) Pharmacovigilance Office, Italian Medicines Agency, Rome, Italy

Background: Most of the regulatory actions in paediatrics are based on data mining in spontaneous reporting systems (SRS). Suspected Adverse Drug Reactions (ADRs) have been investigated in paediatric international and several national systems.

Objective: To analyse the characteristics of paediatric ADR reports in the Italian SRS over the last decade.

Methods: Reports of suspected ADRs related to children and adolescents (<18 years) were extracted from the Italian SRS over the period 2001–2012. Duplicate, vaccine reports and reports missing information about age were excluded. The Medical Dictionary for Regulatory Activities (MedDRA®) and the WHO-Anatomical Therapeutic Chemical (ATC) classification were used to group ADR reports by suspected drug categories and affected system/organ (SOC). Main characteristics of paediatric ADRs and the most frequently reported drug classes for the MedDRA SOC within specified paediatric age-categories were investigated.

Results: Among 123,129 selected reports over 11-years period, 8,338 (6.8 %) concerned paediatrics. Among them, males were more involved than females (52 vs. 48 %), while this proportion reversed in the 12–17 years age-group. Thirty per cent of paediatric reports were reported as serious and of these, 75 % required hospitalization, mainly in very young children. Most of the reports were issued by hospital physicians (62 %), followed by pharmacists (10 %) and family paediatricians (8 %). Irrespective of the adverse event notified, the most frequently implicated drug categories were anti-infectives for systemic use (n = 3,743, 45 %), drugs acting on nervous system (n = 1,304, 15 %), and anti-inflammatory drugs (n = 849, 10 %). As compared to the total reports for the same ATC category, drugs for respiratory system were most commonly reported for children (22 %), followed by anti-infective agents (15 %) and dermatological agents and drugs for sensory organs (12 %). The distribution of drug classes was comparable among different paediatric age-categories when we looked at skin reactions, gastrointestinal and general disorders, while drug differences occurred when exploring ADR related to nervous and respiratory systems and psychiatric disorders. Over this study period, some recommendations and/or regulatory actions were adopted concerning some drugs such as ibuprofen, ceftriaxone and cefaclor, all of them belonging to the top ten reported single compounds.

Conclusions: This descriptive study of Italian SRS over 11-years reflects real safety concerns for drugs used in paediatrics. Drug safety in children needs to be investigated in age-specific setting, because special characteristics related to the different stage of growth and development could explain the differences in terms of drugs and adverse events observed across age.

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Risk Mitigation of Tumor Lysis Syndrome in Off Label Lenalidomide Treated CLL Patients: Effectiveness of the TLS Educational Outreach Program

L. Weiss[1], D. Gary[1], J. Freeman[1], R. Delap[2], R. Knight[3], J. Zeldis[2]

(1) Drug Safety, Celgene Corporation, Summit, NJ, USA, (2) Office of the CMO, Celgene Corporation, Summit, NJ, USA, (3) Clinical Development, Celgene Corporation, Summit, NJ, USA

Background: Lenalidomide (Revlimid) was added to the DrugDex compendia listing for Chronic Lymphocytic Leukemia (CLL) in October 2008. Medical insurance providers and the US Centers for Medicare & Medicaid Services limit cancer drug coverage for off-label indications to indications listed in certain compendia. Each compendia recommendation is supported by a level of evidence category. Limited data on the TLS risk in lenalidomide-treated CLL patients was available at the time of compendia listing.

In a 2007 Celgene safety database review, TLS occurred in 3 % (7/260) of CLL patients receiving 10 mg or 25 mg lenalidomide, including 2 with fatal outcome; all cases developed during the first 15 days of

treatment (Moutouh-de Parseval 2007). The potential for TLS and strategies for prevention/management have been considered for CLL patients who are candidates for lenalidomide in clinical trials and under compendia for off-label indications. In 2008, upon FDA notification, a prescriber education outreach program was initiated to mitigate a risk of TLS when prescribed off-label for CLL. Each prescriber requesting a dispense of lenalidomide for a patient with CLL receives a call and faxed letter with safety data and guidance on recommended prophylactic and management measures for TLS.

Method: Frequency and severity of TLS reports in lenalidomide-treated CLL patients from all sources in the years before lenalidomide inclusion in the compendia, October 2008, was compared to frequency and severity of TLS reports from off label use after year 2008.

Results: Before risk mitigation outreach program; reports from all sources—2.0 % (11 reports/556 treated); 3 fatal, of which 2 occurred outside Celgene clinical trial.

After risk mitigation outreach program: US off label CLL only—0.2 % (3 reports/1293 treated); no fatal.

Effectiveness of the risk mitigation Prescriber Education Outreach Program in US lenalidomide-treated CLL patients

Year and Exposure	%(n/N)	Fatal
Before program-all sources		
2007 (260)	3.5 (9/260)	3
2008 (296)	0.7 (2/296)	0
After program—US off label only		
2009 (268)	0.0 (0/268)	0
2010 (252)	0.0 (0/252)	0
2011 (352)	0.0 (0/352)	0
2012 (421)	0.7 (3/421)	0

Conclusion: The prescriber education outreach program has been beneficial in reducing severity of TLS. There were no fatal reports of TLS with off label use of lenalidomide in CLL since introduction of the program. While physicians may prescribe lenalidomide off-label for use in CLL based on compendia listings, it is the Celgene position that investigational use of lenalidomide should be confined to controlled clinical trial settings.

Abstract Code: ISP3666-49

Human Factors in Pharmaceutical Safety Systems—Relevance to the New EU PV Legislation

D. Mccarthy[1]

(1) Quintiles Ireland Ltd, Dublin, Ireland

The (so-called) pharmaceutical safety system is struggling with the increased workload arising from changing regulations, under-resourcing, increased costs and serious criticism concerning transparency aggravating underlying mistrust. Many misconceptions and myths still exist about how pharmaceutical companies portray their safety data, which make matters worse. Part of the problem is failure to define the complexity of the system and to design processes which are evidence based and both adaptable and flexible for those who work in them. The lack of training on working and coping in complex systems is notable and the size of the challenge is huge and global.

The changing pharmaceutical regulatory framework is best reflected in the legal requirements for EU PV systems introduced in July 2012. It places increased responsibility on both companies and regulators alike to view the safety of their medicinal products more holistically—in the context of benefit as well as risk. Collection and analysis of benefit and safety information now requires extensive interaction between many additional stakeholders in an organisation. For example the new EU PSUR (prepared in the ICH PBRER format) will require input from and collaboration between PV and other groups such as Clinical, Marketing, Medical Affairs and Pharmacoepidemiology, in order to collect the additional, often more detailed, information necessary to perform an integrated evaluation of the benefit-risk profile. In addition, a much broader definition of an ADR means we now need to look further and wider for relevant safety information.

Key to successful navigation of the new EU PV requirements is an understanding of how 'human factors' impact safety. The key human factors concern DECISION-MAKING, SITUATIONAL AWARENESS, LEADERSHIP, COMMUNICATION, ERROR MANAGEMENT, PERSONALITY AND BEHAVIOUR. The challenges of a system such as the pharmaceutical safety system can only be fully understood with a thorough understanding of the role of people acting within and shaping the system. Human Factors includes examination of competence, decision making, information processing, communication, compliance with procedures and coping with stress and time pressure. These are all key aspects of the human role in the pharmaceutical safety system.

Thus as part of the ISoP UK-Ireland Chapter we are discussing collaboration with the Centre for Innovative Human Systems, Trinity College Dublin http://www.innhf.eu. This Centre focuses on key system considerations such as risk and performance, change, design and competence. This paper discusses the benefit of understanding and managing human factors in modern pharmaceutical safety systems.

Abstract Code: ISP3671-45

Counterfeit Medicines. Some Alarming Stories from Pakistan

N. Khan[1]

(1) Medical Director, Fertility and Gynaecology Centre, Karachi, Pakistan

January 2012 brought devastating news for Pakistan. 150 patients treated at Punjab Institute of Cardiology lost their lives after receiving medicines prescribed by their physicians.

December 2012 a number of deaths reported due to over the counter cough syrup in Pakistan.

Government of Pakistan claims to have an elaborate Extended Program of Immunisation for communicable diseases in neonates and children. Vicious attacks on Polio team had already put childhood immunisation in jeopardy when Pakistani media started reported measles outbreaks in different localities. Several reports of counterfeit vaccines are surfacing.

After deaths in Lahore the Government of Pakistan had a knee jerk response and draft of Drug Regulatory Authority was approved. However these laws and regulations had little impact on actual practices.

It is estimated that more than 40 % medicines available in the market are counterfeit. The packaging of these products is breathtakingly replica

of the original products. A busy physician or health care worker hardly has an eye or training to discern.

Fertility drugs are hormones are expensive products. Apart from those sold in reputed pharmacies, there are several reports of these products smuggled from neighbouring countries over camel back in dry heat. The authenticity of these medicines and their transport conditions are highly questionable. This leads to poorer or no results in sub-fertile patients, leading to financial and emotional strain.

Increasing awareness, education and pressure from various forums may be one way of saving unfortunate lives.

Abstract Code: ISP3673-47

Therapeutic Drug Monitoring of Methotrexate: Assessment of Toxic Concentrations

I. Aouinti[1], I. Salouage[1], E. Gaies[1], R. Charfi[1], N. Jebabli[1], S. Trabelsi[1], M. Lakhal[1], A. Klouz[1]

(1) Centre National de Pharmacovigilance, Tunis, Tunisia

Introduction: High-dose methotrexate (HD-MTX) is indicated in neoplasic diseases. It must be administrated in association with alkaline hyperhydratation and folinic acid in order to interrupt the antifolinic activity of this chemotherapy and avoid toxic concentrations [1, 2]. These are a cause of several toxic side effects as mucosal ulcer, hepatitis and renal impairment [2].

The aim of this study is to assess the toxic concentrations in patients treated by HD-MTX.

Methods: A retrospective study was performed in the Service of Clinical pharmacology from a database of patient's informations between January 2009 and May 2013. We collected all MTX cycles with a concentration at H_{24} greater than 5 μM or those with H_{36} greater than 2 μM (if H_{24} not available).

Results: We identified 730 cycles from 287 patients. The median age was 17 [0.75–70] years and the sex ratio was 2.02. The MTX was administrated for acute lymphoblastic leukemia (ALL) in 17.7 % of patients and for osteosarcoma in 77.1 %. The median dose in ALL was 5 g/m^2 and in osteosarcoma was 12.1 g/m^2. The average H_{24} concentration was 21.1 [5.1–195] μM and the average H_{36} concentration was 7.2 [2.05–96] μM. The concentration at H_{48} was greater than 0.5 μM in 63.4 % of cures and the concentration at H_{72} was greater than 0.05 μM in 61.5 % of cures. Toxic side effects were detected in 11 % of cycles; they were mainly liver cytolysis and renal failure. The rescue treatment was the folinic acid and hydratation.

Conclusions: The MTX therapeutic drug monitoring is essential in administration of HD-MTX because of the high risk of toxicity. It allows to detect precociously toxic levels and to start the rescue treatment with hydratation.

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Abstract Code: ISP3681-46

Agranulocytosis: A Possible Adverse Reaction to Vemurafenib?

G. Hill[1], S. Hult[1], R.H.B. Meyboom[2], R. Bertoli[3]

(1) WHO Collaborating Centre for International Drug Monitoring, Uppsala Monitoring Centre, Uppsala, Sweden, (2) Division of Pharmacoepidemiology, Utrecht University, Utrecht, The Netherlands, (3) Servizio di consulenza sui farmaci e Centro regionale di farmacovigilanza Ospedale regionale di Lugano, Lugano, Switzerland

Introduction: The WHO Global Individual Case Safety Report (ICSR) Database, VigiBase™, which contains over 8 million ICSRs, is routinely screened using disproportionality analysis and triage methods to detect signals of adverse drug reactions. Two combinations concerning vemurafenib and haematological toxicity were identified: vemurafenib/granulocytopenia and vemurafenib/leucopenia. Additional information was requested from National Centres for selected cases and a review of the collected data was undertaken.

Vemurafenib (Zelboraf) is a BRAF serine-threonine kinase inhibitor indicated for the treatment of BRAF V600 mutation-positive unresectable or metastatic melanoma. The recommended dose is 960 mg twice daily [1].

Reports in VigiBase: After exclusion of two probable duplicates, a total of 33 ICSRs (to 29 March 2013) containing the terms leucopenia (17), granulocytopenia (19) and agranulocytosis (7), in which vemurafenib was indicated as the suspected drug, were reviewed. Twenty-four ICSRs contained the terms granulocytopenia and/or agranulocytosis; an additional nine ICSRs contained only the term leucopenia, four of which provided further evidence suggestive of granulocytopenia (infection was co-reported in three cases and one case reported an extremely low white cell count).

The reports came from five countries: United States (22), United Kingdom (6), Austria (3), Switzerland (1), and Germany (1). Age was reported in 14 ICSRs and ranged from 27 to 81 years; there were more females (19) than males (14). Time to onset was available for 14 ICSRs and ranged from 9 to 84 days; onset occurred during the second to fifth week after treatment initiation in over 80 percent of the reports. Dechallenge was positive in 14 ICSRs; re-exposure at a lower dose occurred in three cases but the outcome was not reported. Vemurafenib was the only reported medicine in 19 of the ICSRs and was the only suspected drug in a further 10 ICSRs.

Discussion: Vemurafenib is not known to be haematotoxic. Sudden profound granulocytopenia, as was noted in several of the reported cases, is suggestive of a drug reaction. Lending support to a causal association between vemurafenib and agranulocytosis/granulocytopenia is the relatively consistent time to onset, the number of cases with a positive dechallenge and the consistency of the reports from different countries (several of the US reports were reported as 'foreign source', bringing the total number of countries where the ADR was observed to nine).

Conclusion: The ICSRs contained in VigiBase suggest that agranulocytosis/granulocytopenia may be an adverse reaction to vemurafenib.

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Abstract Code: ISP3683-48

Use of Nephrotoxic Drugs in Patients with Chronic Kidney Disease: A Population-Based Study in Southern Italy

Y. Ingrasciotta[1], F. Giorgianni[1], J. Sultana[1], A.P. Caputi[1], V. Savica[1], V. Arcoraci[1], M. Tari[2], D. Santoro[1], A. Nucita[3], G. Trifirò[1]

(1) Department of Clinical and Experimental Medicine, University of Messina, Italy, (2) Caserta-1 Local Health Service, Caserta, Italy, (3) Department of Cognitive Science, Education and Cultural Studies, University of Messina, Italy

Background: A progressive loss of renal function characterizes chronic kidney disease (CKD). The use of nephrotoxic drugs can further aggravate CKD. It is therefore imperative to explore prescribing practices that can negatively affect patients with renal vulnerability.
Aim: To explore the use of nephrotoxic drugs in CKD patients in the general population of Caserta from Southern Italy during the years 2006–2011.
Methods: The general practice "Arianna" database contains data from 158,510 patients, registered with 123 general practitioners (GPs) of Caserta. CKD patients were identified by searching for: ICD-9CM CKD as cause of hospitalisation; CKD-relevant procedures undergone in hospital (e.g. dialysis); drug prescriptions issued for a CKD-related indication. A list of nephrotoxic drugs was compiled through a literature search using the MESH terms 'nephrotoxic drug', 'chronic kidney insufficiency' and 'drug-induced renal failure', after further revised by nephrologists. Based on the summary of product characteristics, drugs were classified as 'contraindicated' or 'to be used with caution' in CKD. Frequency of use of these 2 categories of nephrotoxic drugs in the year prior, one year after and during the whole period after the first diagnosis of CKD (Index Date) was calculated.
Results: Overall, 1,989 incident CKD patients were identified (1.3 % of total population from Caserta). Of these, 37.4 % received at least one prescription for a contraindicated nephrotoxic drug within one year after ID. A similar proportion (40.5 %) was observed within one year prior to CKD diagnosis. In details, 985 CKD patients (49.5 %) had at least one NSAIDs prescription (most commonly used contraindicated drugs) between ID and end of follow-up. The most common reason for prescribing NSAIDs in CKD patients was bone and joint disorders (76.4 % of NSAIDs CKD users). A large proportion of CKD patients (28 %), were treated with NSAIDs for periods exceeding 90 days. Drugs that should be used with caution in CKD were used more commonly, increasing after ID (79.2 % within one year prior vs. 84.2 % within year after CKD diagnosis). The most frequently used drugs "to be used with caution" in CKD patients were allopurinol (39.6 %) and ramipril (26.7 %).
Conclusions: Contraindicated nephrotoxic drugs were highly prescribed in CKD patients from a general population of Caserta. The CKD diagnosis did not seem to reduce the prescription of potentially harmful nephrotoxic drugs thus, increasing the risk of preventable renal damage. These findings highlight the need to implement healthcare measures that minimise the use of nephrotoxic drugs in CKD patients.

Abstract Code: ISP3684-49

VigiBase and EudraVigilance: Impact on Signal Detection of Myocardial Infarction and Myocardial Infarction Related Events

M. Simunovic[1], Z. Margan Koletic[1], V. Macolic Sarinic[1], D. Krnic[1]

(1) Agency for Medicinal Products and Medical Devices, Zagreb, Croatia

Introduction: Signal is reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously. In July 2012, we received a report of myocardial infarction (MI) in a patient treated with golimumab (human monoclonal antibody) and methotrexate for psoriatic arthropathy. MI is a serious, unexpected and unlisted adverse drug reaction (ADR) of golimumab. We suspected this could be a signal and preformed a search through VigiBase and EudraVigilance.
Aim: To identify how data from VigiBase and EudraVigilance impact on signal evaluation of MI and MI related events associated to golimumab.
Methods: We performed a search through VigiBase, the WHO Global Individual Case Safety Report (ICSR) database by using the ADRs coded to the Preferred Terms (PT) included in the Medical Dictionary for Regulatory Activities (MedDRA, version: 16.0) query Myocardial Infarction (broad) and through EudraVigilance using EudraVigilance Data Source Analysis.
Results: VigiBase contains 26 spontaneous reports of MI and MI related events among 2360 total reports for the drug from 2010 to 2013, while EudraVigilance contains 23 spontaneous reports among 2338 total reports for the drug from 2009 to 2013. Comparing the ICSR's from both databases, we found 9 identical reports (1 report of acute coronary syndrome, troponin increased and 7 reports of MI). There are 2 reports which could possibly be identical, but there is not enough data to confirm that. The IC (Information Component) values are positive for acute coronary syndrome, troponin increased, infarction and electrocardiogram ST segment elevation, indicating that these ADRs are reported more often than expected. PRR values are >1 for all the ADRs mentioned above plus coronary artery occlusion, with the exception of electrocardiogram ST segment elevation.
Conclusions: According to the statistical parameters in both databases, acute coronary syndrome, troponine increased and infarction are potential signals. VigiBase additionally indicates electrocardiogram ST segment elevation, while EudraVigilance additionally indicates coronary artery occlusion as a signal. Search through both databases is more valuable, since resulted in 31 additional reports (17 and 14, respectively) and could contribute to strengthening of signal if they were reported in both databases. Based on these results, further monitoring of MI and MI related events is needed to establish causal relationship between the ADRs and golimumab.

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Abstract Code: ISP3687-52

The Effect of an eLearning Module on Junior Doctors' Knowledge of Adverse Drug Reactions

A.R. Cox[1], C. Anton[2], S.K. Thomas[1], J.J. Coleman[1], R.E. Ferner[2]

(1) School of Clinical and Experimental Medicine, University of Birmingham, UK, (2) West Midlands Centre for Adverse Drug Reactions, City Hospital, Birmingham, UK

Introduction: In 2010 we were involved in setting up a project to raise standards of prescribing competency in foundation (F) year 1 and 2 doctors in the West Midlands—the Standard Computerized Revalidation Instrument for Prescribing and Therapeutics (SCRIPT).[1] This elearning resource has forty interactive web-based modules designed to improve prescribing competency. 'Adverse Drug Reactions (ADRs) and Pharmacovigilance' was one of these. First year (F1) junior doctors in the Region were required to participate. We present data from the module's in-course assessments.

Methods: Junior doctors log in into the system and are presented with a 10-item multiple choice questionnaire of their knowledge on ADRs and pharmacovigilance before viewing the module content, and again afterwards. Our null hypothesis was that that the module would not change the doctors' test scores.

Results: 443 junior doctors completed both the pre- and post-module tests. We excluded from analysis 91 doctors who took only the pre-module test.

The average score in the test pre-module was 8.09/10 and post-module was 9.47/10. The mean change in score was 1.38 [median 1, range −2 to 8; Wilcoxon signed-rank test $P < 0.001$].

Table 1 Pre-module and post-module test scores for first year junior doctors (n = 443)

No. of questions answered correctly	Pre-module	Post-module
1–3	1	0
4	3	0
5	6	1
6	41	1
7	88	6
8	117	47
9	126	111
10	61	277

Conclusions: An eLearning module on ADRs and Pharmacovigilance significantly improved junior doctors' knowledge in the short term. The post-module scores were high, supporting the teaching value of the module. ADR reporting rates to regulatory authorities are low (2). We do not know yet whether the demonstrated increase in knowledge is durable or improves ADR reporting.

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Abstract Code: ISP3693-49

Non Administration of Chemotherapy: A Support for the Identification of Adverse Effects

A. Le-Naour[1], S. Gonnin[2], C. Herrador[2], F. Haramburu[1], S. Pedeboscq[2], G. Miremont-Salame[1]

(1) Département de Pharmacologie, INSERM U657, Université de Bordeaux, CHU de Bordeaux, Bordeaux, France, (2) Service Pharmacie, CHU de Bordeaux, Bordeaux, France

Introduction: Identification of adverse drug reactions (ADRs) is mainly based on spontaneous reporting. However, under-reporting is a known limit of the system; it is therefore necessary to find other tools. Anticancer agents, either cytotoxic or targeted therapies, and biotherapies used in rheumatology, etc. are known to cause frequent ADRs, that are either immediate or delayed effects.

Aim: To identify ADRs of anticancer agents and biotherapies.

Methods: Retrospective study on a 1-year period from the records of the Centralized Chemotherapy Preparation Unit (CCPU), in a 500-bed teaching hospital of Bordeaux.

All prescribed intravenous (IV) anticancer agents and biotherapies are prepared in the CCPU. If not administered to patients, partially or totally, they are returned to the CCPU. Reasons for return are completed by the pharmacists and recorded in a specific file. We identified among returns those caused by ADRs during the year 2012.

Results: 19,787 chemotherapies were prepared by the CCPU corresponding to 7,668 cycles. Only 100 cycles (1.3 %) have resulted in the return of 143 prepared medicines (0.72 %); 49 returns (34 %) were due to ADRs. These returns concerned 29 patients (6 patients had two returns for different courses). We identified 31 ADR cases (2 returns with 2 distinct ADRs with different medicines involved). Seven of these cases (23 %) had already been reported to the regional pharmacovigilance centre. One case had occurred during a clinical trial and was excluded from further analysis.

The median age was 63.5 years (extreme 30 and 84 years). There were as many men than women, 14 of each.

ADRs were either immediate (80 %), hypersensitivity reactions representing 79 % of this group, or delayed effects (20 %) such as infection, cytopenia, etc. Fifteen ADR cases were serious (5, i.e. 33 %, having been reported to the pharmacovigilance centre) and 15 non-serious (2, i.e. 13 %, having been reported).

Suspected medicines, alone or in combination, were: carboplatin (n = 7), oxaliplatin (6), bevacizumab (6), 5-fluorouracil (6), irinotecan (5), cetuximab (5), paclitaxel (2), docetaxel (1), rituximab (1), infliximab (1), capecitabine (1) and etoposide (1).

Conclusions: This method to identify ADRs can be a valuable complement with spontaneous reporting. It allows especially identification of immediate ADRs, such as hypersensitivity reactions. However, it is not well adapted for ADRs that occur after or between treatment cycles. Furthermore, it takes into account mainly ADRs of IV anticancer agents and biotherapies, centrally prepared in the CCPU and rarely ADRs of oral treatment.

Abstract Code: ISP3694-50

The Case-Series Matrix: A Useful Alternative to Individual Case Narratives for Signal Generation?

V. Osborne[1], D. Layton[1], S.A. Shakir[1]

(1) Drug Safety Research Unit, Southampton, UK; University of Portsmouth, Portsmouth, UK

Background: Traditionally, qualitative analyses performed for signal generation purposes include clinical review of individual case narratives, where a causal drug-event association can be inferred. While individual case reports and case-series can be subject to bias in assessing drug-event relationships, the advantage of a collective review is that cases can be evaluated in context using all of the available evidence on important aspects such as unusual features/manifestations, relevant risk factors and clinical course. This may be particularly useful where no suitable comparator is available. Observational post-marketing cohort studies can provide a systematic approach for identifying eligible cases for multiple different outcomes. Data can be reviewed in aggregate form before any conclusions on drug-relatedness are made and hypotheses formulated. If case-series are to be used as a tool to support signal detection, robust quantitative and qualitative approaches for summarising all available data are necessary.
Aim: To identify the essential components of the case-series matrix and evaluate its application within post-marketing observational cohort studies.
Methods: Patient level data were derived from recently completed Modified Prescription-Event Monitoring (M-PEM) studies. Cases were defined for selected events (risks) of interest. Common data fields across individual cases were identified and an algorithm used to obtain summary aggregate information separately for each outcome. The essential components included the total number of cases reported for an event of interest, along with specific details such as distribution of demographic factors (age, gender), exposure duration (time to onset), key event attributes (whether the event was the reason for stopping treatment), and reported risk factors (concomitant medications and co-morbidities).
Results: In the M-PEM studies, we found that the case-series matrix presented concise, relevant information on cases. For example, in a study where weight gain was of interest and 14 cases of increased weight were reported, it could be determined quickly that the median duration of exposure for these cases was 90 days and it was the reason for stopping treatment in 8 cases. The majority of patients were also on other relevant medications (n = 11), though few had other relevant co-morbidities (n = 5).
Conclusions: Overall, we found the case-series matrix to be a useful alternative to case narratives, providing an appropriate level of detail and relevant information whilst minimising the need to review individual case narratives. This could be a complementary method for expediting qualitative analysis in signal generation.

Abstract Code: ISP3695-51

Information on QT-Interval Prolongation Properties of Medicinal Products in the European and American Drug Label

M. Warnier[1], F. Holtkamp[2], F. Rutten[3], A. Hoes[3], A. De Boer[1], P. Mol[2], M. De Bruin[1]

(1) Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht University, Utrecht, The Netherlands, (2) Medicines Evaluation Board (CBG-MEB), Utrecht, The Netherlands, (3) Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, The Netherlands

Background: QT-interval prolongation is one of the most common adverse drug reactions leading to regulatory action. Although the occurrence of QT prolongation is generally rare, it can be potentially fatal by causing ventricular arrhythmia. We have noticed that information regarding QT prolonging properties of drugs varies between different sources.
Objective: To compare the QT prolonging properties described in the European and American drug label.
Methods: The European and American drug labels of products that were centrally approved in Europe between 1.1.2006 and 1.5.2012 were screened. Of those mentioning 'QT', we determined the nature of the message on QT prolongation (no prolongation/unclear drug-QT association/potentially QT prolongation/QT prolongation). The kappa statistic was calculated to estimate the agreement between the message in the European SPC and the American drug label.
Results: Of the 172 selected products approved in Europe, 30 products were not approved by the FDA (44 %). A quarter of the products reported on QT prolongation in both the European and the American drug label (n = 36/142). In one-fifth of the products (n = 28/142), only the American drug label reported on QT prolongation, of which 24 (86 %) contained a negative message (drug *does not* prolong the QT interval). Two products reported only in the European drug label on QT prolongation (1 %). The agreement on the message about QT prolongation between the European and USA drug label was moderate (kappa 0.42). There was a tendency for the FDA drug label to be more explicit on drug-associated QT prolongation than the European SPC (Unclear message on QT prolongation: FDA 6 %, EMA 12 %). One drug had no QT prolonging properties according to the European label of the EMA, while this drug did prolong the QT interval according to the American label.
Conclusion: This study showed that there was moderate concordance between the nature of the QT prolonging effect described in the European and American drug label. The American drug label tended to be more explicit, and more often contained a negative message on QT prolongation than the European drug label.

Abstract Code: ISP3696-52

Pregnancy Outcome in Women Exposed to Dopamine Agonists During Pregnancy: A Study in EFEMERIS Database

C. Hurault-Delarue[1], J. Montastruc[1], A. Beau[1], I. Lacroix[1], C. Damase-Michel[1]

(1) Service de Pharmacologie Médicale, CHU Toulouse, Université de Toulouse, INSERM 1027, Toulouse, France

Background: Dopamine agonist drugs can be prescribed for several indications like hyperprolactinemia or Parkinson's disease. Little is known on the possible effect of dopaminergic agonists on embryo-fetal development.
Objectives: To describe pregnancy outcomes in women having a prescription of dopamine agonists and compare to an unexposed group.
Methods: An "exposed-non exposed" study was conducted using data from EFEMERIS, a cohort of 57,408 pregnant women living in South West France (database of all prescribed and dispensed reimbursed drugs during pregnancy and their outcomes). 183 women (0.3 %) who get at least one dispensation of dopamine agonist drug (bromocriptine, cabergoline, quinagolide, lisuride, piribedil, ropinirole) during pregnancy constituted the "exposed group" (no prescription of levodopa was dispensed to pregnant women). They were individually matched with 2 "unexposed" women according to their age and the month-year of the beginning of their pregnancy. Pregnancy terminations, birth defects, preterm births, low birthweight and psychomotor development were studied. We used a conditional logistic regression to analyse risks for each outcome associated with dispensation of dopamine agonist drugs.
Results: Bromocriptine was the most prescribed dopamine agonist followed by cabergoline and quinagolide. 75 % of dopamine agonist prescriptions concerned the beginning of pregnancy (first trimester of pregnancy). There was no difference between the two groups concerning pregnancy history and demographic data. After adjustment for potential confounders, prescription and dispensation of dopamine agonists was associated with an increased risk of pregnancy termination ($POR_a = 3.7$; 95 % CI 1.8–7.4) and preterm birth ($POR_a = 3.6$; 95 % CI 1.5–8.3). The prevalence of birth defect and low birthweight was not statistically different between both groups. No difference in psychomotor development at 9 and 24 months was observed between the two groups.
Conclusion: The results of this study suggest that situations involving fetal exposure to dopamine agonist drugs are at increased risk of pregnancy termination and preterm birth.

Abstract Code: ISP3697-53

Follow Up of UMC Signals

L. Sallstedt[1], S. Watson[1], R.L. Savage[2], A. Zekarias[1]

(1) WHO Collaborating Centre for International Drug Monitoring, Uppsala Monitoring Centre, Uppsala, Sweden, (2) New Zealand Pharmacovigilance Centre, Department of Preventive and Social Medicine, University of Otago, Dunedin and Department Public Health and General Practice, University of Otago, Christchurch, New Zealand

Introduction: A signal is defined by WHO as 'reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously' [1]. Combinations of drugs and suspected ADRs are filtered out from the WHO Global Individual Case Safety Report (ICSR) Database, VigiBase™, by applying a method that is principally based on Information Component (IC) values [2].
Aim of the Study: To follow up previous UMC signals published in the SIGNAL document, with regards to drug labelling changes and ongoing reporting to VigiBase.
Method: Combinations that were previously identified as a signal were checked in recent versions of the UK Summary of Product Characteristics (UK SPCs) and US FDA labels to identify whether or not the suspected ADR had been labelled [3, 4]. For signals that were found to be labelled, the time of the labelling update was recorded.US DailyMed, was sometimes used to verify when the updated occurred [5].

To follow up ongoing reporting since publication of a signal, IC values and the number of ICSRs in VigiBase were checked during the first quarter of 2013, and compared with the historical values.
Results: Of the 50 signals that were published in the SIGNAL document between 2007 and 2010, 45 had originated from the UMC. Of these 45 signals, 15 were labelled in at least one of the product information sources and 28 were unlabelled [4, 5]. For two of the signals, the drug was not listed in an FDA label or UK-SPC [3, 4]. Review of the VigiBase data showed that the number of ICSRs and the IC value had increased or were stable for eleven signals between the time of publishing and follow up.
Discussion: A signal is an early hypothesis of a potential safety problem. The time required to update product information sources can be long, and some signals may be difficult to confirm. Signals may even be proved false, however, the intention of a signal is to identify a possible causal relationship that needs further investigation. Routine screening of the Global ICSRs database enables the UMC to detect potential ADRs early, often well before they are included in the product safety information label.
Conclusions: The proportion of signals found labelled at the time of follow up, regardless of the time of the update, shows the relevance of the UMC signal detection process.
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Abstract Code: ISP3698-54

Safety of Neuraminidase Inhibitors During Pregnancy: A Comparative Study in the EFEMERIS Database

A. Beau[1], C. Hurault-Delarue[1], J. Montastruc[1], C. Damase-Michel[1], I. Lacroix[1]

(1) Service de Pharmacologie Médicale, CHU Toulouse, Université de Toulouse, INSERM 1027, Toulouse, France

Background: Pregnant women are at increased risk of severe disease and death secondary to influenza infection. During the AH1N1 influenza

pandemic in 2009–2010, recommendations in USA and Europe were to treat pregnant women who are infected with the pandemic (H1N1) 2009 virus, with oseltamivir or zanamivir. However, few data are available concerning these drugs in pregnant women.

Objective: To compare birth outcomes between exposed and unexposed women to the antiviral medications oseltamivir or zanamivir during pregnancy.

Method: This observational cohort study compared 2 groups of exposed and unexposed pregnant women in EFEMERIS. EFEMERIS is a database including prescribed and dispensed reimbursed drugs during pregnancy (data from Caisse Primaire d'Assurance Maladie of Haute-Garonne) and outcomes (data from Maternal and Infant Protection Service and from Antenatal diagnosis Centre). Women who delivered from July 1st 2004 to December 31st 2010 in Haute-Garonne and were registered in the French Health Insurance Service have been included into EFEMERIS database. We compared pregnancy outcomes and newborn health between women exposed to oseltamivir or zanamivir during pregnancy and unexposed women. Unexposed women were individually matched to exposed women by maternal age, month and year of delivery or pregnancy loss. Malformations were classified according to Eurocat classification.

Results: 338 (0.58 % of EFEMERIS women) women exposed to neuraminidase inhibitors were compared with 676 unexposed women. Only 1 pregnant woman received zanamivir and 337 received at least one prescription of oseltamivir. The mean number of drugs taken during pregnancy was higher in the "exposed group" (12.5 ± 7 versus 9.7 ± 6.9; $p < 10^{-4}$). The pregnancies led to 96.4 % vs 93.3 % of live-births ($p < 10^{-4}$) in exposed and unexposed groups respectively. No increased risk of preterm birth associated with these antiviral drugs during pregnancy was found (adjusted OR = 0.67; 95 % CI 0.23–1.80). When exposure during organogenesis was considered, 1/50 case (2.0 %) among those exposed and 1/101 (2.2 %) among the unexposed were observed, no association between exposure and congenital malformations was found (crude OR = 2.0, 95 % CI 0.13–32.00).

Conclusion: We found no significant association between adverse pregnancy outcomes (preterm delivery, low birth weight, neonatal pathology and congenital malformation) and exposure to oseltamivir during pregnancy.

Abstract Code: ISP3699-55

Safety of Influenza AH1N1 Pandemic Vaccination During Pregnancy: A Comparative Study in the EFEMERIS Database

I. Lacroix[1], A. Beau[1], C. Hurault-Delarue[1], J. Montastruc[1], C. Damase-Michel[1]

(1) Service de Pharmacologie Médicale, CHU Toulouse, Université de Toulouse, INSERM 1027, Toulouse, France

Background: Pregnant women are at increased risk of severe disease and death due to influenza infection. During the influenza AH1N1 pandemic in 2009–2010, recommendations in France were to vaccinate pregnant women during the second and third trimester preferably with a non-adjuvant vaccine. However, few data are available concerning this drug in pregnant women.

Objective: To compare birth outcomes between exposed and unexposed women to influenza AH1N1 vaccine during pregnancy.

Method: This observational cohort study compared 2 groups of exposed and unexposed pregnant women in EFEMERIS. EFEMERIS is a database including prescribed and dispensed reimbursed drugs during pregnancy (data from Caisse Primaire d'Assurance Maladie of Haute-Garonne) and outcomes (data from Maternal and Infant Protection Service and from Antenatal diagnosis Centre). Women who delivered from October 21st 2009 to November 30th 2010 in Haute-Garonne and were registered in the French Health Insurance Service have been included. We compared pregnancy outcomes and newborn health between women exposed to a pandemic vaccine during pregnancy and unexposed women. Unexposed women were individually matched to exposed women by month and year of delivery or pregnancy termination. Malformations were classified according to Eurocat classification.

Results: 1645 (13.6 %) women exposed to a pandemic vaccine were compared with 3290 unexposed women. Most were exposed to a vaccine in December 2009 (61 %) and Panenza° was used in 92.7 % of the cases. The average maternal age in the exposed group was 31.4 ± 4.3 and 29.9 ± 5.4 in the unexposed ($p < 10^{-4}$). The pregnancies led to 99.2 % vs 95.2 % of live-births in exposed and unexposed groups respectively, the difference was not significant (adjusted HR = 0.56, 95 % CI 0.31–1.01). When exposure during organogenesis was considered, no increased risk of congenital malformations was found [adjusted OR = 0.73 (0.10–2.34)].

Conclusion: We found no significant association between adverse pregnancy outcomes (pregnancy loss, preterm birth, low birth weight and congenital malformation) and exposure to Panenza° during pregnancy.

Abstract Code: ISP3700-38

Veinotonics in Pregnancy: A Comparative Study in the EFEMERIS Database

I. Lacroix[1], A. Beau[1], C. Hurault-Delarue[1], J. Montastruc[1], C. Damase-Michel[1]

(1) Service de Pharmacologie Médicale, CHU Toulouse, Université de Toulouse, INSERM 1027, Toulouse, France

Background: There are few published data about possible effects of veinotonics in pregnant women. However, many French women use these medications during their pregnancy.

Objective: To investigate potential adverse drug reactions of veinotonics in pregnancy.

Method: EFEMERIS is a database including prescribed and dispensed reimbursed drugs during pregnancy (data from Caisse Primaire d'Assurance Maladie of Haute-Garonne) and outcomes (data from Maternal and Infant Protection Service and from Antenatal diagnosis Centre). Women who delivered from July 1st 2004 to December 31st 2007 in Haute-Garonne (time period when veinotonics were still reimbursed) and were registered in the French Health Insurance Service have been included. We compared pregnancy outcomes and newborn health between women exposed to veinotonics during pregnancy and unexposed women. Malformations were classified according to Eurocat classification.

Results: 9,116 (24.6 %) women exposed to veinotonics during pregnancy were compared with 27,963 unexposed. The most widely used veinotonics were diosmin, hesperidin, and troxerutin. The mean age of the mothers was 31.2 ± 4.8 years in the exposed group and 30.0 ± 5.1 in the unexposed group ($p < 10^{-4}$). The mean number of drugs taken during pregnancy was higher in the exposed group (13.4 ± 8 versus 9.4 ± 7; $p < 10^{-4}$). Pregnancies led to 98.4 % vs 93.6 % of live-births and 0.2 % vs 0.2 % of postnatal deaths in exposed and unexposed groups respectively. When only exposure to veinotonics during organogenesis was considered, 39 (3.4 %) congenital malformation were observed in the

exposed group versus 789 (3.0 %) in the unexposed (p = 0.44). There is no difference in the rate of neonatal pathologies in the exposed group and unexposed (5.7 % vs 6.4 %, adjusted OR = 1.07 (0.95–1.12).
Conclusion: We found no increased risk of adverse pregnancy outcomes (neonatal pathology and congenital malformation) among women exposed to veinotonics compared with unexposed pregnant women.

Abstract Code: ISP3702-40

A Shared Surveillance of Suspected Adverse Reactions to Natural Products: the Italian System

F. Menniti-Ippolito[1], R. Raschetti[1], B. Scarpa[2], S. Dalfrà[2], L. De Iuri[2], F. Firenzuoli[3], A. Valeri[4], G. Mazzanti[5], P.A. Moro[6], G. Calapai[7], G. Zuccotti[8], M.L. Colombo[9], B.M. Bruno[10], C. Santuccio[10]

(1) National Institute of Health, Rome, Italy, (2) Ministry of Health, Rome, Italy, (3) Careggi, University Hospital, Florence, Italy, (4) Italian Society of Homeopathic Medicine, Mirandola, Italy, (5) "Sapienza" University, Rome, Italy, (6) Poison Control Center, Milan, Italy, (7) University Hospital, Messina, Italy, (8) University of Milano, Sacco Hospital, Milan, Italy, (9) University of Turin, Turin, Italy, (10) Italian Medicine Agency, Rome, Italy

Introduction: A wide range of products of natural origin are used by a large and growing number of consumers and there is the need to monitor their use in the population.

Spontaneous reports of suspected adverse events to these products are collected through a system of surveillance complementary to that used for drug monitoring.
Aim: A specific system was implemented in Italy since 2002. The project started as a pilot study but in 2012 the system was enhanced and officially adopted from the Ministry of Health as an alert system.
Methods: The surveillance is based on the collection and evaluation of spontaneous reports of suspected adverse events to: (1) food supplements; (2) herbal preparations and galenic formulations; (3) other preparations of natural origin (e.g. propolis); (4) homeopathic medicines.

A Scientific Committee includes experts in different specialities evaluates severe reactions. A Steering Committee comprising experts of the National Institute of Health, Italian Medicines Agency and Ministry of Health supports the Scientific Committee.
Results: Until March 2013, 819 reports were collected. Most of the reported reactions were severe. The reactions were mainly related to the gastrointestinal tract, the skin, the nervous system. "Botanical" food supplements were the most reported products; 10 % of all reports were related to homepathic medicinal products. In 38 % a concomitant drug was reported. Among others the following signals were pointed out: hepatopathies associated to different products; allergic reactions to propolis containing products; myopathies associated with red yeast rice extracts.
Conclusions: The benefit/risk profile of "natural" medicine is unknown for most of the products on the market, furthermore these products are mostly food supplements, proposed to improve wellbeing and, thus, self administered. Encouraging spontaneous reporting can contribute to improve awareness among health personnel and patients about the risk profile of these remedies.

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Abstract Code: ISP3703-41

Anaphylactic Reactions to Biological Drugs: Data from Spontaneous Reporting in Italy

S. Opri[1], M. Zocca[1], A. Sabaini[1], A. Conforti[1], E. Matarangolo[2], L. Sottosanti[2]

(1) Pharmacology Unit and Pharmacovigilance Centre of Veneto Region, University Hospital, Verona, Italy, (2) Italian Medicines Agency, Pharmacovigilance Office, Rome. Italy

Background: Biological drugs such as monoclonal antibodies have been associated to anaphylactic reactions. Identification of these reports in spontaneous reporting systems is often difficult since the case definition relies upon an accurate analyses of clinical symptoms and signs. Moreover it is based only on the adverse events described by the reporters.
Aim: To analyze reports of anaphylactic reactions caused by biological drugs in the Italian spontaneous reporting database through a search based on the Standardized MedDRA Queries (SMQ).
Methods: According to the European Medicines Agency definition of biological drug and excluding vaccines and allergenic products, we defined biological drugs as drugs with a name ending with the string "mab" or "cept". Case of anaphylactic reactions have been identified through the SMQ "Anaphylactic reaction" using an algorithmic approach which combines a number of anaphylactic reaction symptoms in order to increase specificity. A case should have at least a term in the Category A, representing the "narrow search" in the SMQ and including core anaphylactic reactions, or a combination of a term in the Category B (Upper Airway/Respiratory) and a term in the category C (Angioedema/Urticaria/Pruritus/Flush) or a combination of a term in the Category D (Cardiovascular/Hypotension) with a term in the Categories B or C. The disproportion analysis has been calculated with the Reporting Odds Ratio (ROR) within the biological drugs.
Results: The Italian database up to December 2012 contains 6,565 reports related to the biological drugs. According to selection criteria, a total of 347 cases of anaphylactic reactions, associated to 19 different drugs, were identified: 85 of them (24 %) related to the narrow search of the SMQ and 262 (76 %) identified through the algorithmic approach. Among these the most of the cases (74 %) was identified by association of terms for Category B and C. The most reported drugs associated to anaphylactic reactions were infliximab (142 cases on 824 total reports—17 %), rituximab (72 on 902—8 %), cetuximab (62 on 1035—6 %) and natalizumab (15 on 399—4 %).The disproportion analyses suggests an higher risk for anaphylactic reactions associated to infliximab (ROR 5.6 95 % CI 4.5–7.1) and rituximab (ROR 1.7 95 % CI 1.3–2.2).
Conclusions: Spontaneous reporting is an important source to provide further knowledge on the safety of biological drugs. The algorithmic approach is important to increase the number of the identified cases,

facilitating the search and avoiding the use of the more general "broad search".

Abstract Code: ISP3704-42

Influenza Vaccine Effectiveness Against Severe Cases in Children: Results from Two Influenza Seasons

R. Da Cas[1], G. Traversa[1], C. Santuccio[2], F. Trotta[2], F. Menniti-Ippolito[1], and the Italian Multicentre Study Group of Drug and Vaccine Safety in Children

(1) National Institute of Health, Rome, Italy, (2) Italian Medicines Agency, Rome, Italy

Introduction: Seasonal influenza is a common disease with potentially severe impact in terms of morbidity and mortality. Despite the influenza vaccination is particularly recommended for children with underlying conditions, the vaccine effectiveness in such real life population remains controversial [1, 2].
Aim: To estimate the effectiveness of influenza vaccines in preventing severe cases in children visiting pediatric Emergency Departments (ED).
Methods: The study was conducted in 11 pediatric centers in the 2011-2012 and 2012-2013 influenza seasons. During the influenza epidemic weeks, children with a diagnosis of Influenza Like Illness (ILI) visiting the Emergency Departments were included. Data were collected by interviewing parents during hospital admission (or ED visit) of their children. For the purpose of this study children were considered vaccinated if they had received a dose of flu vaccine at least 15 days before the first symptoms of ILI. A laboratory test for virological confirmation was performed to all children enrolled. Data were analyzed according to a case–control study design. We defined as cases children with ILI positive to confirmatory laboratory test, while controls were children with a negative test. For effectiveness evaluation the exposure to influenza vaccine was compared in cases and controls.
Results: Overall, pooling the two data sets related to the two influenza seasons, 693 children were analyzed. Around 15 % reported an anamnesis of underlying chronic diseases. Children were hospitalized on average for 3 days. Cases were 246 and controls were 447. Seven of the 247 cases and 19 of the 447 controls had been vaccinated in the previous months (between October and December). The OR of developing influenza was 0.7 (95 % CI 0.2–1.7). All positive vaccinated children resulted to be infected with the B virus.
Conclusions: Even though not statistically significant, our findings bring further evidence to support the effectiveness of the influenza vaccine in the pediatric population. The main limitation of the study derives from the low level of vaccination coverage observed in Italy. We deem of interest the results of the study for the possibility to contribute to systematic reviews and meta-analysis.

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Abstract Code: ISP3705-43

Case Definition of Torsades des Pointes and Related Clinical Events in Spontaneous Reporting: The ARITMO Experience

U. Moretti[1], E. Raschi[2], E. Poluzzi[2], R. Lora[1], I. Dienberger[3], M. Sturkenboom[4], F. De Ponti[2]

(1) Clinical Pharmacology Unit, University of Verona, Verona, Italy, (2) Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy, (3) Institute of Cardiology, University of Bologna, Azienda Ospedaliera S.Orsola-Malpighi, Bologna, Italy, (4) Erasmus Medical Center, Rotterdam, The Netherlands

Background: Case definition is a key issue in data mining of spontaneous reporting databases. This process is particularly important for heterogeneous clinical events such as torsade des pointes (TdP), where different symptoms can be reported. Useful tools in this context are the Standardized MedDRA Queries (SMQs).
Aim: To compare results obtained from the case definition within the ARITMO project (http://www.aritmo-project.org) with those based on the SMQ on TdP and QT prolongation.
Method: Based on a consensus process, four groups were created in decreasing order of drug-attributable risk: (1) TdP; (2) QT interval abnormalities; (3) ventricular fibrillation/tachycardia and (4) Sudden Cardiac Death (SCD). Within each group, different subgroups were identified based on the severity of the outcomes. Each medical concept was translated into relevant MedDRA codes; in addition, a list of predefined text strings was used for free-text search through narratives (e.g., in the reported description of the adverse reactions) [1]. The SMQ on TdP and QT prolongation includes narrow and broad search strategies, with different levels of sensitivity/specificity. All MedDRA codes of the SMQ were included in the ARITMO approach, although some of them (e.g., Syncope) only if associated with severe outcomes.
Results: According to the ARITMO definition 3,294 cases were identified in the Italian database (up to December 31st, 2011). The highest number of cases were retrieved for non fatal or life threatening ventricular arrhythmias (2,126 cases, 64 %). About 10 % of cases were identified only through narratives, with higher contribution in some groups. According to the SMQ, 2,996 cases were extracted, 147 (5 %) through the narrow search. Even if the total number of cases was similar in the two approaches, the overlapping was low. Only 928 cases were recorded in both approaches, whereas 2,366 cases were identified only in ARITMO and 2,038 cases were identified only with SMQ.
Conclusion: Case definition is a key issue since it can highlight different groups of patients. The ARITMO approach is different to the current SMQ, leading to a probably more efficient search strategy.
Acknowledgments: The research leading to these results has received funding from the European Community's Seventh Framework Programme (FP7/2007–2013) under grant agreement n° 241679—the ARITMO project.

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Abstract Code: ISP3706-44

Anaphylactic Reactions by Vaccines: Data from the Italian Spontaneous Reporting System

E. Arzenton[1], G. Stoppa[1], U. Moretti[1], P. Felicetti[2], L. Tartaglia[2], R. Opri[3], G. Zanoni[3], C. Santuccio[2]

(1) Pharmacology Unit and Pharmacovigilance Centre of Veneto Region, University Hospital, Verona, Italy, (2) Italian Medicines Agency, Pharmacovigilance Office, Rome; Italy, (3) Immunology Unit, University Hospital, Verona, Italy

Background: Anaphylactic reactions are rarely reported after vaccination. Identification of these reports is often difficult since the case definition relies upon an accurate analyses of clinical symptoms and signs. Moreover it is based only on the adverse events described by the reporters.
Aim: Aim of this study is to analyze reports of anaphylactic reactions associated to vaccines in the Italian spontaneous reporting database.
Methods: In the Italian database adverse reactions are coded with MedDRA. Case of anaphylactic reactions have been identified through the Standardised MedDRA Query (SMQ) "Anaphylactic reaction" using an algorithmic approach which combines a number of anaphylactic reaction symptoms in order to increase specificity. A case should have at least a term in the Category A, representing the "narrow search" in the SMQ and including core anaphylactic reactions, or a combination of a term in the Category B (Upper Airway/Respiratory) and a term in the category C (Angioedema/Urticaria/Pruritus/Flush) or a combination of a term in the Category D (Cardiovascular/Hypotension) with a term in the Categories B or C. Disproportion analysis has been made evaluating the Reporting Odd Ratio (ROR).
Results: Up to March 31 2013 the Italian database contains 27,576 reports related to vaccines. According to the selection criteria, 329 cases of anaphylactic reactions were identified. Only 94 cases were related to the SMQ narrow search, whereas in the algorithmic approach the combination of terms in the categories B and C was the most frequent (203 cases). The MMR (measles, mumps and rubella) vaccine had the highest number of cases (91 cases on 3222 total reports) followed by influenza vaccine (43 on 2129 total reports) and hexavalent vaccine (28 on 5653 total reports). Among vaccines with at least 10 cases the disproportion analyses calculated within the vaccine reports was significantly higher for MMR vaccine (ROR 2.9 95 % CI 2.3–3.7), hepatitis B vaccine (ROR 2.7 95 % CI 1.7–4.1) and influenza vaccine (ROR 1.8 95 % CI 1.3–2.5).
Conclusions: Spontaneous reporting is an important source to provide further knowledge on the reactogenicity of vaccines. In the past years the use of a MMR vaccine was suspended due to allergic reaction, and at that time cases were selected by analysing each report. The algorithmic approach is important to increase the number of the identified cases, facilitating the search and avoiding the use of the more general "broad search".

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Abstract Code: ISP3707-45

Safety Profile of Bevacizumab and Ranibizumab in the Intravitreal Use: Data from Spontaneous Reporting in Italy

E. Viola[1], A. Coggiola Pittoni[1], R. Lora[1], S. Potenza[2], P. Erba[2], L. Sottosanti[2], R. Leone[1]

(1) Pharmacology Unit and Pharmacovigilance Centre of Veneto Region, University Hospital of Verona, Verona, Italy, (2) Italian Medicines Agency, Pharmacovigilance Office, Rome, Italy

Introduction: The intravitreal use of vascular endothelial growth factor (VEGF) antagonists, bevacizumab and ranibizumab, proved effectiveness in the treatment of age-related macular degeneration [1]. Intravitreal ranibizumab is approved for the treatment AMD while intravitreal bevacizumab is used off-label to treat this disease. Several studies have been published to evaluate both efficacy and safety of these two drugs.
Aim: To compare the safety profile of intravitreal injections of bevacizumab and ranibizumab in the spontaneous reporting database in Italy.
Methods: All the cases associated with bevacizumab or ranibizumab, used for intravitreal route, reported up to 28 February 2013 in the Italian database (RNF) were taken into account for this analysis. Adverse reaction were coded in RNF using the MedDRA terminology.
Results: Up to 28 February 2013, 49 and 34 reports of ADRs associated to the intravitreal use of bevacizumab and ranibizumab were identified in the RNF respectively. In the database 1,123 further reports are present associated to bevacizumab used for other indications. Fifty-five per cent of the reports for bevacizumab and 65 % for ranibizumab were classified as serious. The distribution of adverse reactions according to the System Organ Classes shows an higher incidence of Eye disorder (38.2 % vs 26.5 %), Cardiovascular disorders (14.7 % vs 6.1 %) and Nervous system disorders (23.5 % vs 14.3 %) for ranibizumab compared to bevacizumab whereas an higher incidence of General conditions disorders (26.5 % vs 2.9 %) were reported for bevacizumab compared to ranibizumab.

Considering the cardiovascular reactions, three reports of myocardial infarction are present for bevacizumab in RNF, while 1 report of coronary atherosclerosis, 1 fibrillation, 1 heart failure and 2 myocardial infarction for ranibizumab. Six cases of ocular haemorrhage and 4 cases of endophthalmitis for bevacizumab compared to 4 and 8 cases for ranibizumab respectively are identified in RNF.
Conclusions: Data from literature, clinical trials, meta-analysis and observational studies with an overall high number of patients did not shown an higher toxicity linked to the intravitreal administration of bevacizumab compared to ranibizumab.

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Abstract Code: ISP3708-46

Hexavalent Vaccine and Strabismus: Data from the Italian Spontaneous Reporting System

L.A. Gonella[1], L. Magro[1], U. Moretti[1], C. Bonetto[2], R. Opri[3], G. Zanoni[3], C. Santuccio[2]

(1) Pharmacology Unit and Pharmacovigilance Centre of Veneto Region, University Hospital of Verona, Verona, Italy, (2) Italian Medicines Agency, Pharmacovigilance Office, Rome, Italy, (3) Immunology Unit, University Hospital, Verona, Italy

Background: Strabismus is a visual problem in which the eyes are not aligned properly and point in different directions. It is a common condition among children since about 4 % of them have strabismus [1]. It is especially common among children with disorders that may affect the brain and can be caused by palsy of the III, IV, VI cranial nerves responsible for eye movement. Single reports of strabismus associated to palsy of cranial nerves attributed to vaccines have been reported [2], none of them related to hexavalent vaccine. Strabismus is not reported in the Summary Product Information (SPC) of hexavalent vaccine and no case report on strabismus associated to hexavalent vaccine has been published.
Aim: To analyze the spontaneous reports of strabismus associated with administration of hexavalent vaccine in the Italian Pharmacovigilance database (RNF).
Methods: Adverse reaction are coded in the database using MedDRA terminology. Cases of strabismus were defined as cases with at least one event identified through the MedDRA Preferred Term "Strabismus" or with the string "strabism" in the description of the adverse reaction.
Results: Up to March 31 2013 the RNF contains 27,576 reports associated to vaccines, 5,740 of which related to hexavalent vaccine. Twenty-six cases of strabismus are present in the database, 17 of them related to hexavalent vaccine. Among these ten cases were females and the reaction was reported at each dose (7 after the first dose, 6 after the second and 4 after the third dose). Almost all cases reported a time interval between vaccination and the onset of the reaction within 3 days. In two cases the strabismus appeared 11 and 17 days after vaccination. In four cases hexavalent vaccine was co-administrated with pneumococcal vaccine and in two cases concomitantly with meningococcal vaccine. The diagnosis of strabismus was often confirmed by an ophthalmologist. In six cases the reaction recovered and this can suggest a transient involvement of the eye.
Conclusion: The high number of reports suggest an association between strabismus and hexavalent vaccination. However considering the background rate of the disease in children and that almost all the children receive the hexavalent vaccination further analyses are needed to confirm this signal.
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Abstract Code: ISP3709-47

Adverse Drug Reactions Caused by Drug–Drug Interactions Reported in the Italian Pharmacovigilance Network (IPN)

C. Santuccio[1], C. Bonetto[1], A. Cupelli[1], P. Felicetti[1]

(1) Italian Medicines Agency, Pharmacovigilance Office, Rome, Italy

Introduction: Potential drug–drug interactions (DDIs) are frequent in drug prescription but above all clinically significant are those which can result in adverse drug reactions (ADRs). From July 2012, an update to the Italian Pharmacovigilance Network (IPN) made it possible for the reporters to link a Suspected Spontaneous Adverse Drug reaction to a drug–drug interaction (DDI) .
Objective: Describe and analyze all suspected adverse reactions identified by the reporter as potential drug–drug interactions from July 2012 to April 2013.
Methods: Spontaneous reports are collected in Italy in the Pharmacovigilance database. The reporter has currently the opportunity to indicate on a new report format any potential drug–drug interaction. The indentified interactions were then checked by the authors in Micromedex® to confirm them and to verify the strength of the association (major, moderate, minor) and the degree of severity.
Results: From 15 July 2012 to 08/04/2013 IPN received 171 spontaneous reports concerning potential drug–drug interactions.

The authors assessed the distribution by age and by SOCs. The age group most represented was, as expected, the age class patients 65-years (70 %) that had an average of six medications. In therapy class of drug, the ATC most frequently involved was the ATC B (Blood and blood derivatives) with 31 %, followed by ATC J (21 %) and ATC C (10 %). The reported interactions were checked in Micromedex®: 30 % were defined as major interaction, 16 % moderate, 0.6 % minor; for 22 % wasn't revealed any documented interaction even if in 4 cases there was an interaction between drugs listed as concomitant and not suspected, moreover in 3 cases a contraindication to the concomitant use of drugs was highlighted. Remaining reports were not evaluable. The matching between the potential reactions described and data derived from Micromedex® was about 40 %. The percentage of serious reactions among ADR reports involving interactions is higher respect to the total amount of reports in the same period (38 % vs 28 %).

Serious drug–drug interactions frequently involved antiplatelet, anticoagulant and antimicrobics.
Conclusions: Our observation confirmed that the spontaneous reporting database was an useful tool for detecting ADR caused by DDIs. The major interactions are more easily recognized by clinicians and consequently reported. In a consistent number of reports the suspect adverse reaction was indicated as a consequence of a drug–drug interaction not documented in Micromedex®. Further analysis will highlight new and yet unknown drug interactions.

Abstract Code: ISP3710-39

Development and Evaluation of a Voluntary Education Module on Medicine Safety for Preclinical Medical Students

S. Palaian[1], P. Shankar[2], K. Sanjaya[1]

(1) Department of Pharmacology, College of Medical Sciences, Bharatpur, Nepal, (2) Xavier University School of Medicine, Aruba, Dutch Caribbean

Introduction: Often health professionals have a poor understanding of ADR monitoring programs. A possible reason may be poor coverage of medicine safety issues in the curriculum. Teaching students about medication safety thus becomes a matter of priority. College of Medical Sciences is a private medical school in Chitwan, Nepal admitting students from south Asia to the undergraduate medical (MBBS) course.
Aim: To develop and evaluate a voluntary medicine safety module for basic science MBBS students.
Methods: Students' knowledge, attitude and practice (KAP) about medicine safety and pharmacovigilance was studied both before and after the module, and feedback on the module obtained using a questionnaire. A focus group discussion (FGD) was conducted on module completion.

Thirty-one basic science students participated in six one hour sessions over a 3 month period. Their baseline KAP was evaluated. The sessions were 'Sensitization of the medical students on drug use problems and an overview of the proposed module', 'Magnitude of harmful effects caused by drugs and historical aspects of Pharmacovigilance', 'Various causes for ADRs', Strategies to minimize the occurrence of ADRs', 'Safety monitoring systems available in Nepal, South Asia and globally', and 'Politics of medicines with special emphasize on medicine safety'. The small group sessions (7 or 8 students) used group discussions, role plays, activities, elicitation sessions, and facilitator presentations.

The filled KAP questionnaires were evaluated giving a score of '1' for a correct answer or a positive response and '0' for a wrong or negative response. The total baseline KAP scores were compared among different subgroups of respondents using 'Mann Whitney *U* test'. Pre and post interventional scores were compared using Wilcoxon signed ranks test ($p < 0.05$). Feedback questionnaires were analyzed giving a score ranging from 1 to 5 for individual responses. The FGDs were video recorded and analyzed.
Results: Of the 31 respondents, 15 (48.3 %) were male. The baseline total score was 10 (maximum possible score 18). There was no association of baseline scores with age, gender, method of financing, year of study, and nationality. The median (IQR) total baseline scores improved after intervention ($n = 27$) to 12 (11–14) ($p < 0.001$). Respondent feedback ($n = 29$) was positive and the total median (IQR) scores was 81 (73–86), (maximum score 100). The major feedback obtained during FGD related to the 'Venue of the sessions', 'seating arrangements' and 'logistics'.
Conclusions: The authors were successful in designing a module which improved the student KAP, and which was liked by the students.

Abstract Code: ISP3711-40

"Mystery Consumer" Approach as Evaluation of Risk Communication Skills of Community Pharmacists

H. Lebanova[1], I. Getov[1], V. Tsankova[1], G. Momekov[1], E. Grigorov[1], E. Naseva[1]

(1) Medical University Sofia, Sofia, Bulgaria

Background: Community pharmacies are the primary point of care for patients seeking advice for their therapies and adverse drug events. The "mystery consumer" approach gives the chance of monitoring the competence, self-responsibility and empathy in the community pharmacists and in the same time provides feedback for their expertise and skills in risk communication for medicines [1].
Aim: The aim of the study is to assess the community pharmacists' professional competences in risk communication for medicines.
Methods: The study was conducted using the "mystery consumer" approach. 120 community pharmacies were visited for a 1 month period by trained students in pharmacy. Each field interviewer presented in real life conditions a rehearsed pre-selected case and assessed the pharmacist's reaction and behavior caused from it. A standardized score-card validated by a physician and a clinical pharmacologist was used in the survey. Three sections with 11 questions each were included evaluating the pharmacist's behavior, expertise and willingness-to-report an adverse drug event (ADR).
Results: The results show that the majority of pharmacists did not reacted according to the accepted guidelines. Few of them recognized the drug induced adverse reactions and suggested consultation with a physician or change in therapy and no one expressed will to report an ADR.
Conclusion: The "mystery consumer" approach proved to be reliable method for assessment and conducting a study based on observational research technique. Mystery consumers can give researchers objective and quantifiable data that measures specific skills and deportment. Reporting ADRs is essential responsibility of community pharmacists and they must to be more active in the pharmacovigilance system.
Discussion: The results of the survey raise the awareness of the pharmacists' role in the pharmacovigilance system in Bulgaria and should be a subject to further research.
Funding: The study was funded by a research Grant No 46/2012 by the Council of medical sciences in the Medical University-Sofia.
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Abstract Code: ISP3713-42

Adverse Events Following Immunization (AEFI) in Emergency Department: Results of MEREAFaPS Study

A. Saporiti[1], C. Blandizzi[1,2], E. Ruggiero[2], M. Rossi[3], A. Capogrosso Sansone[1], M. Moschini[4], F. Rimoli[5], E. Cecchi[6], A. Vannacci[4], S. Montagnani[1], S. Mantarro[1], N. Lombardi Martelli[4], M. Santini[7], L. Spisni[8], F. Mannelli[9], M.S. Verzuri[10], M. Tuccori[2]

(1) Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy, (2) Unit of Adverse Drug Reaction Monitoring, University Hospital of Pisa, Pisa, Italy, (3) Unit of Pharmacology, University Hospital of Siena, Siena, Italy, (4) Department of Preclinical and Clinical Pharmacology, University of Florence, Florence, Italy, (5) Pharmaceutical Unit, Hospital of Prato, Prato, Italy, (6) Emergency Department Hospital of Prato, Prato, Italy, (7) Emergency Department, University Hospital of Pisa, Pisa, Italy, (8) Emergency Department, Hospital of Pontedera, Pontedera, Italy, (9) Emergency Department, Pediatric University Hospital Meyer-Florence, Florence, Italy, (10) Emergency Department, University Hospital of Siena, Siena, Italy

Introduction: Adverse events following immunization (AEFIs) are untoward events temporally associated with immunization that may have been caused by a vaccine or other immunization processes. AEFIs are generally mild in nature while serious ones are extremely rare [1]. In USA it has been estimated that 15,790 patients every year are admitted to the emergency department (ED) due to vaccine-related problems [2].
Objective: To analyze ED admissions for potential AEFIs in nine EDs involved in the *Epidemiological Monitoring of Adverse Drug Reactions and Events in First Aid* (MEREAFaPS) study from 1st July 2010 to 31st March 2013.
Methods: The MEREAFaPS study is a prospective cohort, observational, multicentre, no profit study, with the aim of investigating admissions to ED for adverse drug reactions (ADRs) and AEFIs. The MEREAFaPS database retrospectively collects data on patients for which the ED admissions for drug or vaccine-related problems have been suspected by the clinicians operating in the ED. ADRs and AEFIs have been coded using the Medical Dictionary for Regulatory Activities (MedDRA).
Results: The study population included 864,046 ED admissions, with 2920 ADR-related (0.34 %) and 166 AEFI-related (0.019 %) admissions throughout the study period; about 1061 ADR-year and 60 AEFI-year. The vaccines most frequently involved in AEFIs were: combined diphtheria-tetanus-acellular pertussis, hepatitis B, poliovirus (15.8 %); combined measles, mumps, rubella and varicella (12.2 %) and conjugate pneumococcal 13-valent (9.3 %). AEFIs involved 81 females (48.8 %) and 85 males (51.2 %). The majority of AEFIs were recorded in children, mainly those belonging to the age group 0–2 years (72.9 %). The MedDRA system organ classes most frequently involved in AEFIs were: injury, poisoning and procedural complications (50.5 %); gastrointestinal disorders (15.9 %); skin and subcutaneous tissue disorders (10.0 %); nervous system disorders (9.0 %) and respiratory, thoracic and mediastinal disorders (4.0 %). AEFI outcomes were distributed as follows: 14 (8.4 %) complete recovery; 63 (38.0 %) improvements; 89 (53.6 %) outcome not available. Among AEFIs, 27 (16.3 % of overall patients with AEFIs) had a serious event, which required hospitalization. Most frequently reported serious AEFIs included: pyrexia (26.9 %); hyperpyrexia (3.8 %); febrile convulsions (3.8 %); sleepiness (3.8 %); rash (3.8 %); ataxia (3.8 %); appetite loss (3.8 %); dyspnea (3.8 %); irritability (3.8 %) and vomiting (3.8 %).
Conclusions: AEFIs seem to represent an uncommon cause of ED admission in Italy, with a small number of them requiring hospitalization. Our results probably underestimate the actual proportion of AEFI-related ED admissions due to potential misclassification bias. ED physicians and nurses should be educated to an appropriate detection and reporting of AEFIs-requiring ED admissions.

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Abstract Code: ISP3714-43

Improving the PhV Knowledge for Medical Staff of SFH During Hajj Time in Makkah City, KSA Toward Reporting of ADRs

N. Alhazmi[1], I. Naylor[1]

(1) Bradford University, Bradford, UK

Pharmacovigilance knowledge for medical staff is of prime importance for reporting of ADRs. The extant literature review suggest that there is a lack of understanding and good command on the Pharmacovigilance knowledge among the medical staff members in the SFH, Makkah, Saudi Arabia. The purpose of this study, to improve the Pharmacovigilance knowledge of the medical staff to report ADRs in SFH during Hajj time. 110 questionnaires have been received from 50 doctors, 10 dentists, 20 pharmacists and 30 nurses. It found that 47.2 % (n = 52) of the respondents were aware of the existence of an ADR reporting and monitoring system in Makkah and 37.2 % (n = 41) were aware of the existence of National Pharmacovigilance Center (NPC) in the Saudi Food and Drug Authority (SFDA). However, only 34.5 % (n = 38) of the respondents had been trained on how to report ADRs and 28.1 % (n = 31) had actually submitted an ADRs report to the Ministry of Health (MOH) in Makkah and 46.3 % (n = 51) thought ADR reporting had benefited their patients by identifying safe drugs. 60 % (n = 66) of the respondents recommended that a mandatory ADR reporting programme was useful. The investigation also teased out factors that affect reporting ADR, which included a lack of reporting forms, the process was too complex, in terms of available resources e.g. no internet, no suitable training for staff on how to report. Overall, the study therefore suggests that, to improve Pharmacovigilance, providing relevant training and education is critical for a required acknowledgment and awareness of ADR reporting among medical staff.

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Abstract Code: ISP3715-44

Attitude and Awareness of Nurses in the Holy City of Makkah Hospital Toward Reporting of Adverse Drug Reactions (ADRs)

N. Alhazmi[1], I. Naylor[1]

(1) Bradford University, Bradford, UK

Objective: To assess the contribution made by Nurses in regard to ADRs reporting in the Holy City of Makkah hospital, Saudi Arabia.
Methods: A face to face structured questionnaire answered by 31 randomly selected nurses of varying professional experience was conducted in hospital in Holy City of Makkah.
Results: The 31 nurses were completed their questionnaires. More than half, 55 % (n = 17), agreed or strongly agreed in stating that ADR reporting should be compulsory and similarly 58 % (n = 18) thought it was a professional obligation. However, concerning specific details as to what should be reported, 58 % (n = 18) were unclear as exactly what to report. One problem in 48.3 % (n = 15) of respondents was said to be the lack of reporting forms. A major limitation to successful reporting was the limited time available in existing clinical practice to make such reports and so the increased workload at the Ummrah time or the Hajj time exacerbated the problem. Furthermore, the clarity of the reporting forms and the time taken to complete these forms were deemed to be major deterrents. Finally, nurses were not dissuaded from reporting by the need to consult a medical colleague or by the absence of a fee. Education and training had a significant influence on nurses' participation in the Yellow Card Scheme.
Conclusions: Makkah's nurses showed a positive attitude and played a valuable part in the improvement of Pharmacovigilance by ADRs reporting and emphasised the education and training was very important so as to both extend and enhance the ADR reporting.
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Abstract Code: ISP3716-45

Adverse Drug Reactions in Odontology: A Retrospective Study in a Teaching Hospital

F. Mouries[1], J. Fricain[2], S. Catros[2], H. Géniaux[1], F. Haramburu[1], G. Miremont-Salame[1]

(1) Département de Pharmacologie, INSERM U657, Université de Bordeaux, CHU de Bordeaux, Bordeaux, France, (2) Odontologie et Santé Buccale, Université de Bordeaux, CHU de Bordeaux, Bordeaux, France

Introduction: Adverse drug reactions (ADRs) affecting the oral cavity are poorly reported to pharmacovigilance. Literature data on ADRs in dental practice are scarce.

Aim: To describe ADRs observed in a dental and oral medicine department.
Methods: Retrospective review of consultation files and picture books in a specialized unit in the dental and oral medicine department, of a teaching hospital, between January 2007 and February 2013. ADR cases were identified through intensive review of consultation files and picture books. Data collection and analysis were performed by a pharmacy resident. All cases were evaluated, regarding seriousness and causality by the pharmacovigilance staff.
Results: During this survey, 1845 consultation files were reviewed. Between January 2007 and February 2013, 67 patients presenting with at least one ADR were identified (total 85 ADRs). Two of these cases (3 %) had already been reported to the regional pharmacovigilance centre. One case had occurred during a clinical trial and was excluded from further analysis.

There were 47 women and 19 men; median age was 63 years (range 23–92 years).

Forty-eight adverse effects affecting the oral sphere were observed in 47 patients. Two patients presented with ADRs affecting also other organs and systems (gastro-intestinal tract, central nervous system); 36 other ADRs (mainly cutaneous, nervous, digestive, etc.) were observed in 19 patients.

Oral ADRs were: oral ulcers and/or swelling (10), osteonecrosis (9), gingival hypertrophy (7), candidiasis (5), xerostomia (3), aphtoses (3), dysgeusia (2), hyposialorrhea (1), hypersialorrhea (1), tongue dysesthesia (1), burning tongue (1), tongue oedema (1), lingual papillitis (1), gingival haemorrhage (1), gingivitis (1), oral pigmentation (1).

Medicines most frequently involved were immunosuppressants (n = 11), biphosphonates (n = 9), calcium antagonists (n = 8), corticosteroids (n = 3), antidepressants (n = 3), benzodiazepines (n = 3), nicotinamide (n = 3), chloroquine (n = 1), etc.

The nine cases of osteonecrosis were the only serious ADR cases.
Conclusions: This retrospective study shows that ADRs are not frequently encountered in dental and oral medicine consultation in a teaching hospital. It has raised awareness among dentists to report ADRs to the pharmacovigilance centre. A prospective ADR collection based on a periodic review of dental and oral medicine consultation files in hospitals would allow identification of oral ADRs, but also other ADRs.
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Abstract Code: ISP3717-46

Evaluation of Valproic Acid Noncompliance and the Interest of the Therapeutic Drug Monitoring

M. Ben Sassi[1], R. Charfi[1], I. Salouage[1], S. Trabelsi[1], E. Gaies[1], N. Jebabli[1], H. El Jebari[1], M. Lakhal[1], A. Klouz[1]

(1) Centre National de Pharmacovigilance de Tunis, Tunis, Tunisia

Introduction: Valproic acid (VPA) is an anticonvulsant drug, used in the treatment of epilepsy, bipolar disorder and major depression. Much attention has been focused on patients' compliance in the treatment of epilepsy [1]. It has been found that poor compliance is a widespread and serious problem, which affects seizures control. So the therapeutic drug monitoring is a useful tool to test patient's compliance.

Aim: We aimed to compare the characteristics of compliant and non-compliant patients to VPA in order to find out the reasons of noncompliance.
Methods: It consisted in a retrospective study made in the National Centre of Pharmacovigilance from January 2013 to May 2013. We collected 499 samples from 422 patients taking valproic acid. The samples were analyzed by an automated chemiluminescence immunoassay. We considered the therapeutic range as 50 to 100 μg/mL [2]. A noncompliant patient was defined as a patient who took irregularly valproic acid based on the questionnaire or who had lower concentrations under the same posology.
Results: In our patients, the sex ratio (M/W) was 1.6. The median age was 8.5 years [0.15–74 years] with 68 % of children (age less than 15 years). Among the patients, 92.5 % were followed for seizures, 3 % for psychiatric disorders and 4.5 % for others diseases. A noncompliance was noted in 8 % of the cases (60 % children) with a sex ratio (M/W = 2.5). The mean dose was 26.65 mg/kg/day. The mean concentration was 67 μg/mL, 30.5 % of the VPA concentrations were infratherapeutic, 55 % were in the therapeutic range and 14.5 % were supratherapeutic. In the noncompliant patients, the average dose was 33.5 mg/kg/day and 100 % of them had infratherapeutic concentrations with a mean of 14.34 μg/mL [0–42 μg/mL]. An adverse drug reaction was noted in 15 % of the patients (among them 9 % were noncompliant). Other anticonvulsant drugs were used in 13.27 % of the patients versus 21.5 % of noncompliant patients.
Conclusion: In this study, noncompliance to valproic acid was noted in 8 % of the cases. The therapeutic drug monitoring of valproic acid is recommended in children and seems necessary even for adults because of the noncompliance.
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Abstract Code: ISP3718-47

Digoxin Therapeutic Drug monitoring in Elderly patients: Retrospective Study and Literature Review

M. Ben Sassi[1], R. Charfi[1], S. Trabelsi[1], I. Salouage[1], E. Gaies[1], N. Jebabli[1], H. El Jebari[1], M. Lakhal[1], A. Klouz[1]

(1) Centre National de Pharmacovigilance de Tunis, Tunis, Tunisia

Introduction: Digoxin is a cardiac glycoside, used to control rapid ventricular rate in patients with atrial fibrillation and to reduce hospitalization in patients with heart failure. The elderly have reduced elimination of digoxin so therapeutic monitoring is needed [1].
Aim: We aimed through this study to assess the influence of age on digoxin C0 and the occurrence of adverse drug reactions in function of the digoxin therapeutic range in patients treated for arial fibrillation and heart failure.
Methods: It consisted in a retrospective study (January 2009 to May 2013) made in the National Centre of Pharmacovigilance. We included 46 samples collected from 41 patients who were treated by digoxin for a heart failure or an atrial arrhythmia. Samples were analyzed by an automated fluorescence polarization immunoassay. We considered the therapeutic ranges (TR) for the trough concentrations (C0) as 0.8 to 2 ng/mL [2] for adult and 0.5 to 0.9 ng/mL for elderly who had atrial fibrillation or heart failure [1].
Results: Sex ratio M/W was 0.7. Median age was 68.5 years old (1.4–86 years). 25 patients were older adults (≥65 years old).

Among our patients, 31 were treated for atrial fibrillation, 10 for heart failure. The digoxin mean dose was 2.2 mg/day (0.197 mg/kg/day). A mean of 31 days between digoxin onset and the first TDM (4–104 days) and of 1 to 2 samples per patient were noted. The average concentration was 1.49 ng/mL [0–7.45 ng/mL].

Table 1 Elderly patients and adverse drug reactions distribution in function of the C0

C0	<TR	=TR	>TR
Number of elderly patients	4	8	15
Adverse drug reactions	1	4	6
Number of the other patients	5	9	5
Adverse drug reactions	2	5	2

In elderly patients, 5 developed gastrointestinal disorders, 2 cardiac disorders, 3 both gastrointestinal and cardiac disorders and one had visual disturbance.

In the other patients, 2 developed gastrointestinal disorders, 4 cardiac disorders, 1 both gastrointestinal and cardiac disorders and 2 had visual disturbance.
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Abstract Code: ISP3728-48

Pharmacovigilance in Northern Region of Zambia

K. Ponshano[1], O. Simooya[1], B. Lunshano[1]

(1) Copperbelt University, Kitwe, Zambia

Introduction: The Copperbelt University Health Services (CBU Health) has been designated by the Pharmaceutical Regulatory Authority (PRA) as its agent for coordinating pharmacovigilance in Copperbelt, Luapula, Northern, North Western and Western Provinces. CBU Health's mandate includes stimulating the reporting of adverse drug reactions (ADRs) as well collecting and collating all ADR reports from health institutions in the five provinces. This report covers our experiences from May 2008.
Methodology: Beginning in early May this year, CBU Health has been visiting on a monthly basis health institutions in the study areas. Activities include holding discussions with health workers, distribution of ADR forms and collection of ADR reports. Once collected these reports are entered into the ADR Register at CBU Health and thereafter causality assessment is done. A report is then prepared for the PRA on quarterly basis. At the PRA, serious ADRs are noted and recommendations made to the Ministry of Health.
Results: Sixty-six (66) ADRs have been collected between May–August 2008. These reports were obtained from twenty-one (21) institutions in the

Copperbelt. The reports have all been documented and assessed using the WHO Causality Method. Most of the ADRs reports were caused by antiretroviral drugs (ARVs) and some by anti-malarial drugs like Artemether/Lumefantrine—Coartem®. The reports have been forwarded to the PRA for further action.
Conclusion: Pharmacovigilance is the science relating to the detection, assessment, understanding and prevention of the adverse effects of drugs. It is an important public health specialty as drug safety awareness can lead to better patient outcomes and reduction in drug related morbidity. Our results show that pharmacovigilance is becoming an integral part of clinical care in Zambia and must be strengthened.

Abstract Code: ISP3737-48

Adverse Drug Reaction in Hospitalised Elderly Patients with Cognitive Impairment: What Drugs are at Risk?

L. Kanagaratnam[1], R. Mahmoudi[2], C. Joachim[2], M. Drame[3], P. Nazeyrollas[3], D. Jolly[3], J.L. Novella[2], T. Trenque[1]

(1) Department of Pharmacovigilance and Pharmacoepidemiology, Reims, France, (2) Department of Geriatrics and Internal Medicine, Reims, France, (3) University of Reims Champagne-Ardenne, EA3797, Reims, France

Background: Elderly patients are particularly vulnerable to adverse drug reaction (ADR). ADR frequently lead to hospitalisation responsible for a decreased autonomy and for an increased morbidity and mortality.
Aims: To identify risk factors for the occurrence of ADR and serious ADR in hospitalised elderly patients with cognitive impairment.
Methods: A longitudinal study was performed in the acute geriatric medicine ward, specialized in the management of dementia disorders, at the University teaching hospital of Reims, France, between May 2010 and November 2011. Sociodemographic characteristics, results of comprehensive geriatric assessment (Mini Mental State Examination (MMSE)) and medication taken were recorded. Occurrence of ADR was recorded at admission and at during the in-hospital phase in all patients, with double assessment (geriatric medicine physician and pharmacovigilance physician). Risk factors for ADR and for serious ADR were identified by logistic regression.
Results: Two hundred ninety three patients aged 82 ± 8 years were included. The MMSE score was 13 ± 8. At admission, 245 (84 %) patients were taking at least 5 different drugs: 160 (54.6 %) patients with an anti-dementiel drug, 157 (53.6 %) an antidepressant, 128 (43.7 %) a sedative, 109 (37.2 %) an Angiotensin-converting enzyme (ACE) inhibitor or Angiotensin-II receptor blockers (ARBs), 106 (36.2 %) an anxiolytic, 93 (31.7 %) a diuretic, 62 (21.2 %) an antipsychotic, 25 (8.5 %) an antiarrythmic class I or III. Seventy patients (24 %) experienced at least one ADR, among the 70 patients, 35 experienced at least one serious ADR. The risk of ADR was significantly higher with an antipsychotic (OR = 2.67; 95 % CI 1.40–5.11) and with an ACE inhibitor or ARBs (OR = 1.86; 95 % CI 1.03–3.4). The risk of serious ADR was significantly higher with an antiarrythmic class I or III (OR = 5.35, 95 % CI 1.72–16.70), with an ACE inhibitor or ARBs (OR = 3.38, 95 % CI 1.55–7.40), and with an antipsychotic (OR = 2.75, 95 % CI 1.21–6.25).
Conclusion: Antiarrythmic class I or III, antipsychotic and ACE inhibitor or ARBs seem to be less well tolerated in elderly patients with cognitive impairment.

Abstract Code: ISP3738-49

Strategy for the Active Surveillance of the Safety of the Pertussis Vaccination in Pregnant Women in the UK

K. Donegan[1], B. King[1], P. Bryan[1]

(1) Medicines and Healthcare products Regulatory Agency, London, UK

Background: In September 2012, following the death of nine infants due to pertussis and a large increase in cases, a temporary vaccination campaign using the dTaP/IPV vaccine Repevax, targeted at pregnant women post-28 weeks gestation, was announced in the UK. This vaccine had not been extensively administered in pregnancy and so the Medicines and Healthcare products Regulatory Agency (MHRA) took a tailored active surveillance approach to pharmacovigilance in order to rapidly obtain robust data on the uptake and safety of the vaccine.
Methods: Prior to the programme, plans were set in place to utilise the primary care data from the Clinical Practice Research Datalink (CPRD) to obtain timely vaccine uptake figures and to rapidly provide relatively robust data on the rates of a range of pre-defined pregnancy-related adverse events which can naturally occur in the third trimester of pregnancy, including stillbirth and pre-term delivery, in women administered the vaccine. Estimates of vaccine uptake were calculated on a monthly basis. At three and six months into the vaccination campaign exposed pregnant women were identified and matched by maternal age, gestational age, and calendar month to unexposed women who were pregnant during 2011. Additional matching by gestational age at outcome was necessary for examining stillbirths. Short-term risks were examined using observed vs. expected methods and overall rates of each pre-defined event were compared using conditional regression.
Results: The first estimate of vaccine uptake was available in the first week of November 2012, within a few days of data release. After three months of the campaign, in January 2013, approximately 12,000 exposed women with short-term follow up were identified. By six months, nearly 6000 vaccinated women, had adequate follow up with a recorded pregnancy outcome providing power to detect an odds ratio for stillbirth of 2.5.
Conclusions: This is the first time the MHRA has conducted this type of comparative analysis for active vaccine pharmacovigilance using the CPRD. It has proved to be a valuable resource for monitoring the uptake and safety of new vaccination campaigns providing robust data on a large number of exposures within a very short time frame. Given the high vaccine uptake the speed with which safety data has successfully become available is particularly important. However, the complexities of the data had to be carefully considered. This active surveillance approach will be further explored for future new immunisation campaigns with new opportunities provided by the expansion of the CPRD.

Abstract Code: ISP3463-44

Perception of Pharmacists' Adverse Drug Reactions (ADRs) Reporting Using the Theory of Planned Behavior (TPB) in Oriental Morocco

Z. Alami[1], S. Ahid[2], A. Naciri[3], P. Gavaza[4], Y. Cherrah[2]

(1) Department of Pharmacology, Medical School, University Mohammed the first, Oujda, Morocco, (2) Pharmacoepidemiology and Research Team, Medical School, University Mohammed the fifth, Morocco, (3) Department of Pharmacy, Al Farabi Hospital, Oujda, Morocco, (4) Department of Pharmaceutical, Social and Administrative Sciences, Appalachian College of Pharmacy, Oakwood, Virginia, USA

Objectives: Spontaneous reporting is the main tool of a pharmacovigilance system. However, under-reporting of adverse drug reactions (ADRs) by health care professionals and specifically pharmacists is a common problem. The purpose of this study was to evaluate pharmacists' perceptions towards ADRs reporting in oriental Morocco and the predictors of pharmacists' intention to report ADRs using the theory of planned behavior (TPB) model.

Methods: A total of 600 surveys were distributed to pharmacists in Oriental Morocco. The survey items included the demographic characteristics of health care professionals and 16 questions exploring their perception towards ADRs reporting based on the TPB. Intention, attitude, subjective norm, and perceived behavioral control were assessed through direct (scale: from 1 to 7) and indirect measures (scale: from −3 to 3) using 7-point bipolar scales.

Results: Eighty-four responses were obtained for a 14 % response rate. Most respondents were male (N = 55, 65.5 %) with a mean age of 41 ± 8 years and work experience of 12 ± 7 years. Respondents dispensed 75 [50–200] medications per day. Fifty nine percent (N = 46) of pharmacists had encountered ADRs in their practice but only 7.1 % had reported them mostly to the medical representative of the pharmaceutical firm. Overall, pharmacists intended to report ADRs (mean 5.12 ± 2.02; range 1–7), perceived that important others wanted them to report (subjective norm [SN] score 2.39 ± 0.95; range −3 to +3), believed that they had control over their reporting behavior (perceived behavior control [PBC] score 4.62 ± 1.65; range 1–7) and had a positive attitude toward reporting (mean 3.97 ± 2.12; possible range 1–7). Pharmacists believed that they had a moral obligation to report ADRs (mean 6.7 ± 3.5; range −9 to +9).The absence of a regional pharmacovigilance center in Oriental Morocco (mean 2.6; range −9 to +9) and the limited provision of clinical information by patients (mean 1.63; range −9 to +9) negatively affected the pharmacists' perception of control over their reporting behavior.

Conclusion: Pharmacists showed a strong positive intent to report ADRs. Many pharmacists in oriental Morocco do not report any ADRs. The development of a regional pharmacovigilance center in this region may be a good strategy to increase pharmacists' intention to report ADRs and change their actual behavior.

Abstract Code: ISP3740-42

Analysis of the ADRs of Medication Error in EudraVigilance: Impact of the Implementation of the New European Union Pharmacovigilance Legislation

V. Cuconato[1], M.C. Cicalese[1], M.L. Casini[1], C. Minore[1], S. Ruggieri[1], M. Di Girolamo[1]

(1) AIFA, Agenzia Italiana del Farmaco, Pharmacovigilance Office, Rome, Italy

Introduction: Medication errors are a major public-health issue. A medication error, as in GVP, refers to any unintended error in the prescribing, dispensing or administration of a medicinal product. Medication errors do not always lead to an ADR but if they do these are considered preventable.

The new pharmacovigilance EU legislation requires the reporting of medication errors that result in ADRs to EudraVigilance (EV). Member States shall ensure that reports of suspected ADRs arising from an error associated with the use of a medicinal product that are brought to their attention are made available to the EV and to any authority, institution, responsible for patient safety.

Aim: To identify the impact of the new pharmacovigilance legislation on the reporting of ICSRs related to the ADR "medication error" in EV.

Methods: Analysis of the number of reports recorded in EV (only serious spontaneous reports, exclusion of duplicated reports, suspect/interacting medicinal products) with particular reference to Italy and associated with the HLGT "medication error", compared to EV cases number. The data refer to a defined range of 10 months before and after the entry into force of the new EU pharmacovigilance legislation. The increase of serious cases reporting has been taken in account as general trend of increase in reporting.

Results: An increase in the number of serious ICSRs of medication error in Europe (22.34 %) and in Italy (110.45 %) was observed.

Table 1 Number of serious spontaneous ICSRs and relative increases (percentages, in brackets)

Medication error (HLGT level): EEA		Medication error (HLGT level): from Italy	
21/09/2011–20/07/2012	21/07/2012–20/05/2013	21/09/2011–20/07/2012	21/07/2012–20/05/2013
3366	4118 (+22.34 %)	67	141 (+110.45 %)
All serious ICSRs: from EEA		**All serious ICSRs: from Italy**	
21/09/2011–20/07/2012	21/07/2012–20/05/2013	21/09/2011–20/07/2012	21/07/2012–20/05/2013
94001	110381 (+17.42 %)	7695	9295 (+20.79 %)

Conclusions: From the entry into force of the new pharmacovigilance legislation (July 2012), the new reporting requirements determined an increase of medication errors case number in EV.

The evaluation of medication errors may result in regulatory actions, in risk minimisation measures (i.e. changes to the labelling, additional warnings in the product information, identification of medication error as a potential risk in the RMP of the drug), aimed to reduce the risk of occurrence of these ADRs.

A strict collaboration among organisations such as patient-safety institutions, pharmacovigilance centres and poison-control centres, would be beneficial to improve medication error detection, reporting and prevention at national and EU level.

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Abstract Code: ISP3741-43

Bisphosphonate-Associated Osteonecrosis of the Jaw: Evidence Coming from the Italian Post-Marketing Surveillance

E. Parretta[1], L. Sottosanti[2], L. Sportiello[1], C. Rafaniello[1], S. Potenza[2], G. Colella[3], F. Rossi[1], A. Capuano[1]

(1) Campania Regional Centre for Pharmacovigilance and Pharmacoepidemiology, Department of Experimental Medicine, Second University of Naples, Naples, Italy, (2) Italian Medicines Agency-AIFA, Rome, Italy, (3) Department of Oral and Maxillofacial Surgery, Second University of Naples, Naples, Italy

Introduction: Bisphosphonate (BP) associated osteonecrosis of the jaw (BONJ) has emerged as an important safety issue [1–3]. Although several cases of BONJ had been described, data from regulatory pharmacovigilance databases have not been taken into account yet.
Aim: To analyze data from the Italian Pharmacovigilance Adverse Event (AE) Spontaneous Reporting System [*Rete Nazionale Farmacovigilanza*] (RNF) to further our knowledge on BONJ.
Methods: From 2004 to 2011, RNF received 723 reports of ONJ or possible ONJ after BP administration. These reports were analyzed for the BP type, the duration of treatment, the dose and how recently the BP was used before ONJ or possible ONJ onset.
Results: The two major patient groups reporting ONJ or possible ONJ after BP administration were those treated with zoledronate for skeletal-related events associated with cancer disease (mainly breast cancer and multiple myeloma) and those treated with alendronate for osteoporosis. ONJ or possible ONJ cases emerged after a long term drug exposure with median time ranged from 1.3 to 6.3 years, depending on BP type. Interestingly, few ONJ cases emerged early with very short BP time exposure never published until now. Moreover, we found that in 178 reports ONJ or possible ONJ occurred after BP therapy cessation. The analysis of these cases, based on how recently the last BP dose was used, showed a great variability in terms of time frame between the last dose and the event onset (from 2 to 80 months).
Conclusion: These new evidences highlight the notion that BONJ is a very complex safety issue whose several questions are still open. National spontaneous reporting databases, which represent one of the major sources of data during the post-marketing phase, can contribute to a better understand of this complex safety issue.

Abstract Code: ISP3742-44

Criteria for Signals of Disproportionate Reporting Prioritization: A Proposal from the ARITMO Project

F. Salvo[1], E. Raschi[2], U. Moretti[3], A. Chiarolanza[2], L. Hazell[4], N. Moore[1], M. Sturkemboom[5], F. De Ponti[2], E. Poluzzi[2], A. Pariente[1]

(1) Université Bordeaux Ségalen, Bordeaux, France, (2) University of Bologna, Bologna, Italy, (3) University of Verona, Verona, Italy, (4) Drug Safety Research Unit, Southampthon, UK, (5) Erasmus Medical Centre, Rotterdam, The Netherlands

Background: Data mining generates large numbers of signals of disproportionate reporting (SDRs), with several false positives. To orientate assessment efforts required to discriminate important SDRs from others, prioritization is essential.
Aim: To elaborate a score for the prioritisation of SDRs generated using automated disproportionality analyses in spontaneous reporting databases.
Methods: Within pharmacovigilance partners of the ARITMO project (http://www.aritmo-project.org) a list of potentially useful criteria for signal prioritisation was defined on the basis of personal expertise; both qualitative and quantitative parameters were included Moreover, a relative weight of each criterion was agreed through a Delphi-like approach. This second step was structured in three rounds, in which all partners in a blind fashion provided a coefficient from 0 to 1 for each criterion, a statistician calculated the median and inter-quartile values and finally a unique coefficient for each criterion was defined.
Results: Five items were identified and included in the score. After running the Delphi-like approach, criteria were as follows: (i) number of cases per 1,000 reports (weight 0.7); (ii) number of cases per 1,000 reports without drugs known to increase the risk of the selected event (weight 0.95), (iii), (iv) and (v) values of the lower limit 95 % CI of the disproportionality measure, using different denominators: the complete database (weight 0.5), reports related to the same 2nd level ATC of the selected drug (0.5), or to the 3rd level ATC (0.7). In the ARITMO project, this score will be refined to take into account the complex clinical entity of drug-induced torsadogenicity, applied separately to different databases and finally integrated also by assessing the degree of uncertainty of the score for each drug class (i.e., antipsychotics, H1-antihistamines and anti-infectives).

Conclusions: This general method will be also applied to SDR prioritisation concerning any type of adverse event and any drug class to test its suitability in routine pharmacovigilance activities. Even if its performance will be demonstrated in signal prioritization, it should however not be considered as an SDR validation tool, which can only be performed by individual cases analysis.

Abstract Code: ISP3743-45

The Individual Feedback Letter Provided by AIFA to Reporters of Suspected Adverse Drug Reaction (ADRs)

S. Potenza[1], R. Gattuso[1], E. Ranucci[2], M. Sottosanti[1], G. Spadaro[1], L. Sottosanti[1]

(1) Italian Medicines Agency Pharmacovigilance Office, Rome, Italy, (2) Department of Haematology, Santo Spirito Hospital, Pescara, Italy

Background: Spontaneous reporting of suspected adverse drug reaction (ADRs) to regulatory authorities plays an important role in providing early signals for detecting new ADRs in the postmarketing surveillance.

In Italy after reporting an ADR, the reporters receive a feedback letter from the local person responsible for pharmacovigilance (LRP), prepared by their regional pharmacovigilance centres (RPC).

For a total of twenty Italian regions without RPC, a feedback letter is provided by the pharmacovigilance office of the Italian Medicines Agency (AIFA).

Objective: Describe the procedure of individual feedback letters provided by AIFA to reporters who belong to those regions without RPC .

Methods: Spontaneous reports are collected through the Italian Pharmacovigilance Database (IPN). Once a report by those regions without RPC has been received by AIFA, it is evaluated, coded and filed in an ad hoc database. This database allows rapid analysis of all ADRs reports sent by those regions.

After the assessment, the individual feedback letter is prepared only for serious cases. This letter contains a description of the main information of the case: number of the same ADR for that drug in IPN, the pharmacodynamic and pharmacokinetics of the drug, data from clinical and epidemiological studies, the published medical literature and potential interaction between one or more coadministered medications verified with the US package inserts (Micromedex®).

Moreover additional information about mechanisms of ADRs, risk groups and prevention issues are also provided.

The causality is assessed on a case by case basis using the Naranjo algorithm. This process is not only focused on providing feedback for the reporter but also on the detection of new signals.

Results: In the first seven months of the activity, AIFA sent 250 individual feedback letters to health care professionals and patients through the LRP of the health peripheral structure to which the reporter belongs.

The reports were sent by 110 different reporters belonging to 35 health peripheral structures, involving 35 LRP.

In total 146 different pairs drug-adverse reaction were examined and two new potential signals of new safety information were identified.

Conclusion: We considered the individual feedback to reporter a useful tool to increase the knowledge and awareness of ADRs reporting. In addition, the provision of personalized information may help to reinforce the relationship between local structures and AIFA, and may be useful in obtaining follow-up information when required.

We also planned a survey to collect the level of satisfaction by reporters regarding the individual feedback letter process.

Abstract Code: ISP3744-46

Adverse Drug Reactions Leading to Hospital Admissions: A Prospective Study

A. Kunchanur[1], G. Parthasarathi[1]

(1) Department of Clinical Pharmacy, JSS College, Mysore, India

Introduction: Adverse drug reactions (ADR) are identified as fifth leading cause of death in USA, and estimated approximately 2.9–5.6 % of hospital admissions are due to ADR [1–2]. ADRs not only increase the morbidity and mortality, adds to the overall healthcare cost.

Aim: To study the nature of ADR-associated hospital admissions and the cost involved in management of ADR.

Methods: The study was conducted in the medicine wards of a tertiary care teaching hospital in Mysore, India from September 2006 to April 2007. Suspected ADRs were collected through spontaneous reporting by healthcare professionals. The causality assessment of suspected ADR was performed using WHO probability scale. Preventability of ADR was assessed using modified Hartwig and Siegel scale. Medications and ADRs were coded using WHO Anatomical, Therapeutic and Chemical classification (WHO ATC) and WHO Adverse Reaction Terminology (WHO ART), respectively. The cost incurred in treating ADR was calculated by considering direct and indirect costs.

Results: During the study period there were 6449 patient admissions to the study medical units. A total of 89 reactions were reported in 82 (1.2 %) patients were attributed to be ADR-related hospital admission. The drug class most commonly implicated was NSAIDs [32 (35.9 %)] followed by antibiotics [30 (33.7 %)]. Diclofenac was the most common drug [13 (14.6 %)] involved in causing ADRs. Most commonly involved WHO-ART system organ classes (SOC) in the reported ADRs were gastrointestinal system disorder [30 (36.5 %)] and dermatological system disorder [26 (31.7 %)]. Most of the reported ADRs were probable [48 (53.9 %)] in their causal association. Most of the ADRs were predictable [60 (73.1 %)] and 70 (85.3 %) ADRs were preventable. Patients admitted with an ADR had an average hospital stay of 9.32 days and the average cost incurred in managing each ADR was found to be Rs. 2,388 per patient.

Conclusion: Our study found that majority of ADRs were predictable and preventable and the average cost incurred in managing each ADR was Rs. 2,388. A successful ADR surveillance system in a country like India can have a greater impact on the medication use system to improve the quality of patient care and in reducing the occurrence of devastating and costly events.

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Abstract Code: ISP3745-47

STOP Pain—Suitable Treatment for Oncologic Paediatric Pain

E. Lucenteforte[1], A. Pugi[1], L. Vagnoli[2], R. Bonaiuti[1], E. Gallo[1], M. Moschini[1], M.C. Lenti[1], N. Lombardi[1], M.L. Coniglio[3], V. Cetica[3], A. Messeri[2], M. Aricò[3], A. Mugelli[1], A. Vannacci[1], V. Maggini[1]

(1) Department of Neurosciences, Psychology, Drug Research and Child Health (NEUROFARBA), CIMMBA, University of Florence, Florence, Italy, (2) Pain Service, Azienda Ospedaliero Universitaria A. Meyer, Florence, Florence, Italy, (3) Department of Pediatric Hematology Oncology, Azienda Ospedaliero-Universitaria, A. Meyer, Florence, Italy

Worldwide cancer incidence in children varies from 100 to 180 per million children under 15 years [1]. All children with cancer reported pain, related to the disease or to chemotherapy medications: over 70 % of them sometimes reported severe pain [2].

Morphine is the first choice opioid for moderate to severe cancer pain and it is generally considered well-tolerated among pediatric patients [2]. Nevertheless physicians often hesitate to prescribe opioids to children because of the risk of side effects [3]. The inter-patient variability in response to opioids is well-known but a specific causality assessment is still lacking [4]. Predictive factors of opioids efficacy and safety have been poorly investigated and, more important, no study to date focused on pediatric population. To the best of our knowledge, no data is currently available on predictors of opioids efficacy and safety in children affected by cancer pain. Therefore, it appears pivotal to determine the risk factors to morphine responsiveness and side effects in order to establish a pharmacogenetic approach as a tool for optimizing and personalizing pain therapy protocols in children.

The present STOP Pain (Suitable Treatment for Oncologic Paediatric Pain) project aims at investigating both clinical and socio-demographic predictors, as well as genetic predisposing traits (single nucleotide polymorphisms of genes involved in opioid transport, target and metabolism) to opioid responsiveness and opioid safety profile in a longitudinal cohort study including at least 100 children receiving an homogeneous pharmacotherapy regimen (i.e. titration of morphine by continuous infusion).

Here we report preliminary results of STOP Pain project; to date fifty patients have been enrolled in Florence A. Meyer Children Hospital, and the recruitment is currently being extended to the Italian Children's Hospital G. Gaslini of Genova.

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Abstract Code: ISP3746-48

A Consortium to Monitor Medicines: The Whole is Greater than the Sum of its Parts

S. Olsson[1], S. Pal[2]

(1) Uppsala Monitoring Centre, Uppsala, Sweden, (2) World Health Organization, Geneva, Switzerland

Introduction: The Monitoring Medicines project, with the full title 'Optimizing drug safety monitoring to enhance patient safety and achieve better health outcomes' was carried out by an 11 partner consortium September 2009–July 2013. It received funding from the Framework Programme-7 (FP-7) of the European Commission. The project was developed by the World Health Organization, Geneva, coordinated by the Uppsala Monitoring Centre, and implemented with partners from Africa, Europe, and the Western Pacific. Knowledge of appropriate & safe medicines has grown. But, there are gaps in what we know and, even where there is sufficient knowledge, brokering of that knowledge is insufficient.

Aims: To bring together relevant stakeholders to strengthen our knowledge of medicine related risks, sharing that knowledge and putting it to better use to prevent patient harm.

Results: The Monitoring Medicines consortium operated in close collaboration with regulatory authorities, patient organizations and public health programmes in and outside Europe. The consortium shared expertise to develop the following areas:

- direct reporting of medicine related harm from the general public
- the role of pharmacovigilance centres in the reporting, learning and prevention of medication errors
- better use of existing ICSR databases in identifying dependence liability and medicines of sub-standard quality
- development of additional methods of pharmacovigilance and risk assessment to complement data from spontaneous reporting systems in public health programmes

Conclusions: The Monitoring Medicines project has driven methodological and technological development in key areas of pharmacovigilance, patient safety and public health. The project results are already in routine use or are in the process of being integrated into models of best practice for patient safety. The project has been instrumental in pulling together a diverse group of experts for a common goal: to create a better knowledge-base for informed policies and therapeutic decisions, and safer patients.

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Abstract Code: ISP3747-49

Overview of the Safety of Biologicals: Data from the Italian Spontaneous Reporting System

P.M. Cutroneo[1], A. Russo[1], C. Sirianni[2], V. Pizzimenti[2], G. D'addetta[2], S. Ruggeri[3], E. Matarangolo[3], L. Sottosanti[3], A.P. Caputi[1], G. Trifirò[2]

(1) Sicilian Regional Pharmacovigilance Center, Messina, Italy, (2) Academic Hospital G. Martino, Clinical Pharmacology Unit, Messina, Italy, (3) Italian Medicines Agency, Pharmacovigilance Office, Rome, Italy

Introduction: Biologicals changed the management of important chronic diseases. These drugs have specific characteristics, which might influence their safety profile. Infections, malignancies and administration reactions have been described for most of biologicals. Furthermore, animated debate exists about both effectiveness and safety of biosimilars. In this context, comparative safety evaluation of biologicals and biosimilars in clinical practice is warranted.

Aim: To provide an overview of safety regarding biologicals and biosimilars from the Italian spontaneous reporting system (SRS).

Methods: We performed an analysis on the Italian SRS database from 2001 to 2012. We selected all the adverse drug reaction (ADR) reports attributed to biologicals, classified in the following mechanistic classes: (a) monoclonal antibodies and fusion proteins; (b) cytokines and antagonists; (c) enzymes; (d) recombinant hormones; and (e) others. Vaccines, toxins, blood derivatives, and radiopharmaceuticals were excluded from the analysis. Frequency analyses for biologicals and, separately, for biosimilars have been conducted.

Results: Overall 165,310 ADR reports have been collected and, of these, 9,196 (5.6 %) were related to biologicals. The mean age of patients with biological-related ADR was 58 years (female/male 1.2). Serious ADRs, including 148 fatal cases, accounted for 38.7 % (N = 3,563) of total reports. Regarding specific mechanistic classes, 6,339 reports (68.9 %) were associated with monoclonal antibodies and fusion proteins, 1,493 (16.2 %) with cytokines and antagonists, 1,213 (13.2 %) with recombinant hormones, 167 (1.8 %) with enzymes, and 76 (0.8 %) with others. Concerning therapeutic classes, two-thirds of all ADR reports involved anticancer monoclonal antibodies (n = 3,562; 38.7 %), TNF-alpha Inhibitors (n = 1,876; 20.4 %) and interferons (n = 1,052; 11.4 %). The most frequently implicated individual biological agents were: bevacizumab (12.1 %), cetuximab (11.2 %), rituximab (9.7 %), and infliximab (8.8 %). Reported ADRs were more frequently "skin and appendages disorders" (17.0 %), "general disorders" (14.1 %), and "gastro-intestinal system disorders" (11.3 %). Moreover, 265 (1.8 %) cases of cancer were reported.

Regarding biosimilars, 138 reports (1.5 % of total biological-related reports) were identified. Among these, 62 (44.9 %) were related to filgrastrim, 42 (30.4 %) to somatotropin, and 34 (24.6 %) to epoetins. Overall, 20 (14.5 %) reports concerned drug ineffectiveness (epoetins = 11 and filgrastrim = 9).

Conclusions and discussion: Most of the ADR attributed to biologicals are immune system-related. Several reports of cancer have been described, which requires further investigation. Concerning different therapeutic classes, anticancer monoclonal antibodies are the most frequently reported biologicals. The registry-based monitoring existing for these and other biologicals in Italy may increase ADR reporting. A low proportion of ADR reports concern biosimilars and a relevant proportion of them indicate drug ineffectiveness.

Abstract Code: ISP3748-50

Allergic Acute Coronary Syndrome (Kounis Syndrome): Report of 3 Cases Secondary to Oral Amoxicillin Use

N. Lombardi[1,2], A. Pugi[1,2], V. Maggini[1,2], M. Moschini[1,2], M.C. Lenti[1,2], E. Gallo[1,2], E. Lucenteforte[1,2], R. Bonaiuti[1,2], A. Mugelli[1,2], E. Cecchi[2,3], A. Vannacci[1,2]

(1) Department of Neurosciences, Psychology, Drug Research and Child Health, Section of Pharmacology and Toxicology, Centre for Molecular Medicine (CIMMBA), University of Florence, Florence, Italy, (2) Tuscan Regional Centre of Pharmacovigilance, Florence, Italy, (3) Prato Hospital Emergency Department, Prato, Italy

Background: The concurrence of acute coronary syndrome with allergy or hypersensitivity as well as with anaphylactic reactions is increasingly encountered in daily clinical practice. Mast cell activation with acute cardiovascular (CV) events is described as Kounis syndrome (KS), an "allergic angina", progressing to "allergic myocardial infarction" [1]. Possible triggers include drugs, foods, animal or insect bites, and even drug-eluting stents or endovascular devices [1].

Description: We present three cases of 57 (1), 58 (2) and 64-year-old (3) men who were admitted to Prato hospital emergency department with thoracic pain and dyspnea. In patients 1 and 2 the symptoms recurred after taking only one pill of amoxicillin/clavulanic acid (875/125 mg) for periodontal disease. The third patient reported being treated with oral amoxicillin (1000 mg) as a preventive measure before dental treatment. He had taken a total of 5 pills and he stopped the medication a day before hospital admission because of intermittent epigastric pain. After the hospitalization, in keeping with analytical parameters (troponin I increase: 3.78 ng/ml (1); 0.14 ng/ml (3)) and electrocardiographic abnormalities (ST segment elevations (1–2)), all patients were diagnosed with unstable angina or acute myocardial infarction during anaphylaxis to antibiotic drug. An emergency coronary angiogram, performed for all patients, showed abnormal coronary arteries only in the 64-year-old man (3). All patients recovered without complications and were discharged on their third, second and sixth day of hospitalization, respectively.

Discussion: From an analysis of medical literature and validated databases (Micromedex®; Farmadati®) emerged that KS due to amoxicillin or amoxicillin/clavulanic acid use is a rare event in the adults [2]. In the present cases the temporal relationship between the event and drug assumption strongly suggested a role of amoxicillin in the occurrence of "allergic angina". The causal relationship of amoxicillin in patients 1 and 2 might be confounded by concomitant use of other drugs (atorvastatin (1); nebivolol/hydrochlorothiazide, doxazosin and tapazole (2)). Therefore the three reports were graded as 'possible' according to the objective causality assessment [3].

Conclusion: The presentation of three cases of Kounis syndrome in a single hospital emergency department during about three months period (between December 2011 and February 2012), suggests that this case might not be as rare as previously believed. Clinicians should be aware of

this contingency when treating patients with acute cardiovascular symptoms taking drugs known to induce allergic reactions.

Abstract Code: ISP3750-43

Open Label, Randomized, Controlled Trial to Study the Effect of Atorvastatin on Peripheral Nervous System

H.S. Rehan[1], S. Sidanas[2], M. Yadav[3]

(1) Department of Pharmacology, Lady Hardinge Medical College and Associated Smt. Sucheta Kriplani Hospital, New Delhi 110 001, India, (2) Intern, Lady Hardinge Medical College and Associated Smt. Sucheta Kriplani Hospital, New Delhi 110 001, India, (3) Professor of medicine, Lady Hardinge Medical College and Associated Smt. Sucheta Kriplani Hospital, New Delhi 110 001, India

Introduction: Atorvastatin is widely prescribed for dyslipidemic drugs. Few case reports suggest that it may be associated with cognitive disorders and polyneuropathy. Hence present work was planned to study the effect of Atorvastatin on peripheral nerves.
Method: Open label, randomized, matched control study was conducted on 75 patients taking Atorvastatin for >3 months. Patients were evaluated for the signs and symptoms of the peripheral neuropathy. Findings were compared with the 75 patients not receiving atorvastatin using fisher test.
Results: Mean dose of atorvastatin used in this study was 14 ± 5.19 mg/day with mean duration of 16.5 ± 20.8 months. In atorvastatin group, patients reported feeling of numbness ($p < 0.001$), burning pain ($p < 0.001$), muscle cramps ($p < 0.001$) prickling feeling ($p < 0.001$) and legs hurt while walking($p < 0.01$) higher than non atorvastatin users. Feeling of weakness and too sensitive to touch was similar in both the groups. None of the patients in the atorvastatin group had ulceration but abnormal appearance of feet was significantly higher ($p < 0.05$). Ankle reflexes was significantly ($p < 0.05$) delayed in 11 and absent in 6 patients; Vibration perception was significantly decreased in 38 ($p < 0.001$) and absent in 11 patients ($p < 0.05$) in atorvastatin group. Monofilament sensation was also decreased significantly in 28 ($p < 0.001$) and absent in 8 patients ($p < 0.05$) in atorvastatin group.
Conclusion: Patients taking atorvastatin should be routinely examined for the signs and symptoms of neuropathy.

Abstract Code: ISP3751-44

Generic Substitution of Antidiabetic Drugs in the Elderly: Does It Affect Adherence?

F. Trotta[1], R. Da Cas[1], M. Maggini[1], M. Rossi[2], G. Traversa[1]

(1) Pharmacoepidemiology Unit, National Centre for Epidemiology, Italian National Institute of Health, Rome, Italy, (2) Unit for Pharmaceutical Governance, General Directorate for Health, The Umbria Region, Perugia, Italy

Background: It is already known that ageing, chronic conditions and polypharmacy may affect treatment adherence [1]. Diabetes treatment includes several drugs available as generics. The effect of switching between different packages of the same substance on treatment adherence has not been previously investigated in the diabetes setting.
Objectives: The aims of this study are: (i) to describe the extent of switches between generics using metformin as a model; (ii) to estimate the association between switches and treatment adherence.
Methods: The prescription database of the Umbria Region (>900,000 inhabitants) was used. All elderly ≥75 years were included if they had received at least two prescriptions of antidiabetics (ATC code A10) either in 2010 or 2011. All prescriptions of other therapeutic categories were also retrieved to identify co-morbidities and polytherapy. The main indicator was the prevalence of drug use. Metformin switchers were identified through the package code (AIC number) at consecutive dispensing. Adherence was determined using the medication possession ratio (MPR).
Results: Overall, 15 964 patients met the inclusion criteria, giving a prevalence of use of antidiabetics of 14.4 % in 2011. 61 % of the DDD of antidiabetics were generics. The most used antidiabetic was the metformin (prevalence of use 6.8 %). Very few patients were prescribed a DPP-4 inhibitor or pioglitazone (prevalence 0.1 % for both). Antihypertensive and anticoagulants were the most frequent drugs concomitantly prescribed to antidiabetics in this cohort (prevalence of use 90.2 and 69.3 % respectively). In addition to antidiabetics, each subject received a median of 10 different drugs and more than 20 % of diabetic patients was treated with at least 15 different drugs. The probability of switching amongst metformin users rises with the increasing number of prescriptions: the 20.1 % of metformin users with at least 11 prescriptions during 2011 received at least 4 switches. The non-switchers were 77.0 % in the group who received 2–3 prescriptions and 57.5 % in case of at least 11 prescriptions. The median treatment adherence (MPR) among non-switchers (78.2 %) was even lower than among patients who experienced at least 5 switches (MPR 85.0 %).
Conclusion: Most diabetic patients received polypharmacy for the treatment of concomitant diseases. There was a high prevalence of use of metformin. The number of switches between metformin packages increases with the number of prescriptions. Overall, the increasing number of switches amongst metformin did not seem to impact on the treatment adherence.
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Abstract Code: ISP3752-45

Comparing ADR Incidence Rates of 7-Valent and 13-Valent Pneumococcal Vaccines Given with Routine Pediatric Vaccination

F. Trotta[1], C. Rizzo[1], C. Santuccio[2], C. Bonetto[2], A. Bella[1]

(1) National Centre of Epidemiology, National Institute of Health, Rome, Italy, (2) Pharmacovigilance Unit, Italian Medicines Agency, Rome, Italy

Background: In mid 2010 the 13-valent pneumococcal conjugate vaccine (PCV13) was introduced in the vaccination programs in Italy replacing the use of 7-valent vaccine (PCV7). In routine immunization PCV7 and PCV 13 were co-administered with hexavalent vaccine. The routine monitoring of spontaneous reports showed higher frequency of serious ADR with PCV13 compared to PCV7 [1].

Objective: To estimate the incidence rate of ADRs following the administration of PCV7 or PCV 13 when coadministered with hexavalent vaccine. Incidence rates of neurological ADRs and convulsions were also calculated.
Methods: Adverse events to both PCV (7 and 13-valent) and to hexavalent vaccine reported from 1 January 2009 to 31 December 2011 were retrieved. The considered timeframe was 2009–2010 for PCV7 reactions and 2010-2011 for PCV13 reactions. The incidence rate of ADRs was calculated using as denominator the doses administered to pediatric population. Data on both ADRs and exposure were available from 4 Italian Regions (Emilia-Romagna, Lombardy, Tuscany and Veneto). Neurological ADRs were identified through PTs leading to primary SOC nervous system disorders according to MedDRA. Convulsion were retrieved according to PTs, verbatim and follow-up information included in each report according a pre-defined case definition. Incidence rates of ADR were expressed per 100,000 administered doses, CI were calculated using Poisson distribution.
Results: Overall 232 ADR reports with PCV7+hexavalent (27/232 were serious) and 305 with PCV13+hexavalent (56/305 were serious) were retrieved. The incidence rate of serious ADRs with PCV7+hexavalent was 6.58 (95 % CI 4.34–9.58) and 11.67 (95 % CI 8.81–15.15) with PCV13+hexavalent. This difference was not statistically significant. No difference in the ADR rates was observed between PCV13+hexavalent and PCV7+hexavalent for the all neurological ADRs (PCV7+hexavalent: 9.75, 95 % CI 6.97–13.28 vs PCV13+hexavalent: 12.92, 95 % CI 9.90–16.56) as well as for serious neurological reactions (PCV7+hexavalent: 3.66, 95 % CI 2.05–6.03 vs PCV13+hexavalent: 8.12, 95 % CI 5.78–11.11). When considering all the convulsions (febrile and afebrile) no difference can be observed in the incidence ADR rates for PCV7+hexavalent (2.93, 95 % CI 1.51–5.11) and PCV13+hexavalent (4.37, 95 % CI 2.71–6.69).
Conclusions: This analysis founds no increased incidence rates for serious reactions, neurological reactions and convulsions following the vaccination with PCV13 compared to PCV7 when used in routine practice vaccination. The effect on the incidence of ADR depending on different vaccination strategies (concomitant vs deferred vaccination of PCV and hexavalent), age at vaccination and comorbidity deserves further investigations.
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Abstract Code: ISP3753-46

Adverse Drug Reactions to Vaccines in a Pediatric Emergency Department

D. Altavilla[1], A. Mecchio[2], R. Antoci[2], F. Menniti Ippolito[3], T. Arrigo[1], P. Cutroneo[2], A.P. Caputi[2]

(1) Department of Paediatric, Gynaecologic, Microbiologic and Biomedical Sciences, University of Messina, Messina, Italy, (2) Department of Clinical and Experimental Medicine, University of Messina, Messina, Italy, (3) National Centre for Epidemiology, Italian National Institute of Health, Rome, Italy

Introduction: Post-marketing surveillance plays an important role in the pediatric population to improve medication safety in pediatrics. We reported a case series of adverse reactions to vaccines that led children to the Pediatric Emergency Department of "Azienda Ospedaliera Universitaria G. Martino" of Messina, over a 11-months period. This report represents a part of a multicentre study on drug safety in children coordinated by the National Institute of Health in Italy.
Aim: To assess the importance and consequences of ADR to vaccines causing admission to a Pediatric Emergency Department.
Methods: This is a retrospective observational study. We selected and then analysed in detail all the case reports of suspected adverse reactions to vaccines collected from June 2012 to April 2013. We included in the study only adverse drug reactions (ADRs) with a probable or possible causality assessment, according to the World Health Organization criteria.
Results: Most ADR occurred in children aged 0–15 months with a slight predominance in males (n = 6) with respect to females (n = 4).

Among the 10 cases of ADRs, all reports were serious and led to hospitalization, complete recovery occurred in all cases. The reported adverse reactions were: dermatological manifestations (3 cases), neurological disorders (5 cases) and various symptoms affecting different organs or systems (2 cases). Two of the dermatological reactions were attributed to Pneumococcal 13-valent vaccine, and one to the Hexavalent vaccine. Among neurological events, three cases were ascribed to coadministered vaccines: Hexavalent vaccine and Pneumococcal 13-valent vaccine, one to Pneumococcal 13-valent vaccine and the last one to concomitant administration of Measles, Mumps, and Rubella Virus Vaccine and Meningococcal Serogroup C Conjugate Vaccine. Moreover, we reported two cases of vomiting, fever and irritability, one to Pneumococcal 13-valent vaccine, while the other to Hexavalent vaccine concomitantly with Pneumococcal 13-valent vaccine.
Conclusions: According to the literature [1–2], vaccines or combination of vaccines represent after antibiotics, the most frequent cause of adverse drug reactions in children. Our reports may be underestimated. The lower number of adverse reactions causing admission to the Pediatric Emergency Department is related to the difficult to achieve patients charts and to the lack of information of these data.
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Abstract Code: ISP3755-48

A Possible Case of Hepatotoxicity due to Pelargonium Sidoides

M.C. Lenti[1], A. Baldini[3], E. Cecchi[2,3], R. Bonaiuti[1,2], E. Gallo[1,2], V. Maggini[1,2], E. Lucenteforte[1,2], M. Moschini[1,2], A. Pugi[1,2], F. Firenzuoli[4], N. Lombardi[1,2], A. Mugelli[1,2], A. Vannacci[1,2]

(1) Department of Neurosciences, Psychology, Drug Research and Child Health (NEUROFARBA), University of Florence, Florence, Italy, (2) Tuscan Regional Centre of Pharmacovigilance, Florence, Italy, (3) Emergency Department, Prato's Hospital, Prato, Italy, (4) Centre for Integrative Medicine, Careggi General Hospital, Florence, Italy

Background: Pelargonium sidoides (PS) is an African herbaceous, perennial plant in the geranium family. Its pharmacological activities include moderate antibacterial and antiviral potencies and immunomodulatory properties. An alcohol extract of PS is popular in Germany as a

treatment for respiratory problems, including acute bronchitis, common cold, sinusitis, pharyngitis and tonsillitis. The chemical composition of PS consists mainly of sesquiterpenes, coumarin and tannins.

Case Presentation: In March 2011, a 46 year-old male patient was admitted to the Emergency Department (ED) of Prato Hospital for severe asthenia associated to a wide complex tachycardia. The patient suffered from epilepsy, mental retardation, hypothyroidism, hypertension and congenital heart disease. He was on well tolerated therapy with furosemide, aspirin, phenobarbital, carbamazepine, olanzapine, valproate, lansoprazole, allopurinol, canrenone, since ten years. On admission, vital signs were normal except for heart rate (108 bpm) and pulse oximetry (oxygen saturation level 91 %). Blood tests, performed about 15 days before, showed normal values (especially ALT, AST and bilirubin). Just before hospital admission, the patient was treated with PS 30 drops three times a day for six days for a common cold. In ED, blood tests showed increased liver enzymes: ALT 2385 IU/I (normal range 1–45) and AST 4072 IU/I (normal range 1–36), with a decrease after three days (ALT 1813 IU/I and AST 1251 IU/I); INR (International Normalized Ratio) was 1.89. The patient died on the 4th day, for acute liver failure and respiratory distress. The PS causality assessment was defined as 'possible' according to Naranjo algorithm, considering the relevant role of numerous concomitant diseases.

Discussion: Adverse drug reactions (ADRs) related to PS are quite rare in clinical trials and generally are of mild severity (mostly gastrointestinal disorders, nervous system, ear and labyrinth disorders). Nevertheless it is known that high concentrations of coumarins and tannins can cause liver toxicity, with 15 cases of suspected hepatotoxicity induced by PS recently published, although they were evaluated as "doubtful" by the authors [1]. Even if in the present case concomitant diseases and drug interactions have probably given a notable contribute to the severe adverse event, this report underlines the importance of further studies to establish the possible association between PS and liver damage.

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Abstract Code: ISP3756-49

The Herbal Supplements in Breastfeeding InvesTigation (HaBIT): Preliminary Results

E. Lucenteforte[1], E. Gallo[2], R. Bonaiuti[1], C. Ravaldi[3], V. Maggini[4], M.C. Lenti[1], N. Lombardi[1], M. Moschini[1], A. Pugi[1], F. Firenzuoli[5], A. Mugelli[1], A. Vannacci[1]

(1) Department of Neurosciences, Psychology, Drug Research and Child Health (NEUROFARBA), University of Florence, Florence, Italy, (2) Department of Neurosciences, Psychology, Drug Research and Child Health (NEUROFARBA), University of Florence; Center for Integrative Medicine, Azienda Ospedaliero-Universitaria Careggi, Florence, Italy, (3) CiaoLapo Charity, Prato, Italy, (4) Department of Neurosciences, Psychology, Drug Research and Child Health (NEUROFARBA), University of Florence, Florence Italy, (5) Centre for Integrative Medicine, Careggi General Hospital, Florence, Italy

Background: Herbal remedies (HRs) are commonly used alone or concomitantly with prescribed medications during pregnancy and breastfeeding [1], a fact that needs to be addressed by pharmacovigilance professionals. Midwives, the main health-care professionals who take care of women during and after pregnancy, represent the more appropriate figure to focus on, in order to address this issue and promote mother and children health.

Aim: The aim of the present study was to evaluate midwives' support for HRs and to investigate use, attitudes, knowledge and beliefs regarding HRs among women during breastfeeding.

Methods: The sample under study was composed of 149 midwives and 204 mothers, investigated using a web-based questionnaire.

Results: About a third of midwives (36 %) had children of whom the most part (96 %) were breastfed. Midwives perceived natural products as safe (63 %) and effective (55 %), and used herbal products (70 %), homemade herbal products (36 %), dietary supplements (44 %), galenic products (15.4 %) and herbal medicines (20 %). About a half (44 %) reported giving information on breastfeeding to more than one women per week, more than half (58 %) believed that mothers followed their advice (mainly on diet or dietary supplements), and a low percentage (25 %) addressed mothers to qualified experts of integrative medicine before suggesting HRs. Moreover, our results indicated a general lack of knowledge about safety, efficacy and therapeutic indication regarding specific products. Similarly to midwives, mothers perceived natural products as safe (71 %) and effective (49 %). About two-thirds (70 %) considered breastfeeding very important, and most of them (59 %) reported receiving information about this issue by midwives. During breastfeeding, about a third (30 %) reported using dietary supplements, herbal products (26 %), homeopathy (16 %) and phytotherapy (13 %).

Conclusions: Our results suggest that an effective information campaign concerning herbal remedies may be fundamental for midwives who take care of women during and after pregnancy. This is particularly important considering the fact that HRs use could be dangerous for mothers and children.

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Abstract Code: ISP3758-51

Surveillance to Herbal Products in Pediatric Patients in Italy

E. Gallo[1], A. Pugi[2], V. Maggini[2], F. Menniti-Ippolito[3], M.C. Lenti[2], N. Lombardi[2], R. Bonaiuti[2], E. Lucenteforte[2], M. Moschini[2], R. Raschetti[3], A. Mugelli[2], A. Vannacci[1], F. Firenzuoli[4]

(1) Department of Neurosciences, Psychology, Drug Research and Child Health (NEUROFARBA), University of Florence; Centre for Integrative Medicine, University of Florence, Florence, Italy, (2) Department of Neurosciences, Psychology, Drug Research and Child Health (NEUROFARBA), University of Florence, Florence, Italy, (3) National Institute of Health, Rome, Italy, (4) Centre for Integrative Medicine, University of Florence, Florence, Italy

Introduction: The use of herbal products (HPs) in pediatric patients is often considered reassuring by parents because promoted to the public as effective and less toxic than conventional drugs. However, some HPs are well known for having adverse effects. A specific knowledge of properties and contraindications of medicinal plants is therefore essential for their clinical use [1]. Aim of the present study was to describe and evaluate the

spontaneous reports of suspected adverse reactions (ARs) associated with HPs in children.

Methods: Spontaneous reports of suspected adverse reactions (ARs) to HPs were retrieved from the database of the Italian National Institute of Health and the Italian Medicines Agency. We analyzed the reports of suspected ARs to the HPs recorded from 2002 to April 2012 selecting those pertaining to patients aged 0–14. Causality assessment was performed and only the reports defined at least as 'possible' were considered in the analysis.

Results: One hundred reports were associated with HPs used for children aged between 0–14 years. Male gender was mainly involved (60 %). The reactions mainly affect skin, gastrointestinal system, respiratory tract, central nervous system and cardiovascular system; 65 % of the reported ARs were considered allergic-like reactions for their clinical manifestations and time of onset. A large portion of ARs were defined as serious (46 %), with patients requiring hospitalization in 91 % of cases; 6.5 % was life-threatening. The presence of concomitant therapies and conditions was reported in the 21 and 27 % of cases, respectively. HPs were used in pediatric patients for treating flu-like symptoms, respiratory diseases, nutritional and vitamin deficiency, infant colic, anxiety and insomnia, musculoskeletal diseases and for immune stimulant properties.

Conclusion: HPs use in pediatrics can be associated with ARs. Safety profile of natural medicines in children has not been deeply investigated. Encouraging HPs spontaneous reporting is important in order to improve awareness and knowledge among health care professionals and parents.

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Abstract Code: ISP3759-52

Direct Health Care Professional Communication Effects on ADR Reporting on Specific Safety Issues Emerged During the Year 2012

E. Marotta[1], E. Matarangolo[1], E. Donnarumma[1], F. Cuppone[1]

(1) Italian Medicines Agency, Rome, Italy

Introduction: Direct Health Care Professional Communications (DHPC) are an important tool for Regulatory Agency and Marketing Authorization Holders to inform Health Care Professional (HPC) of the need to take immediate action or change current practice in relation to a medicinal product. DHPCs are delivered to a target audience: health care professionals are firstly involved to be informed and to be enabled to give clear and useful information to their patients.

Aim: To evaluate the ability of a DHPC in making HPCs and patients aware of new important safety issues related to a medicinal product.

Methods: We performed a comparative analysis relative to ADRs reported in the Italian Pharmacovigilance Network in the 6-month-period before and after the dissemination of a DHPC. In particular we focused on the following safety communications relative to medicinal products belonging to ATC L and J, delivered to HPCs during the year 2012:

- risk of potentially fatal drug–drug interactions between the anti-viral brivudine and anti-neoplastic 5-fluoropyrimidines (5-fluorouracil, capecitabine, floxuridine, tegafur) or anti-fungine 5-fluoropyrimidines (flucytosine).
- The association of panitumumab with life-threatening and fatal infectious complications of severe skin reactions including necrotising fasciitis.
- Potential risks of cardiac events during treatment initiation with fingolimod in patients with relapsing remitting multiple sclerosis.
- Important safety information on bortezomib to avoid fatal inadvertent intrathecal administration.
- Risk of liver disorders associated to lenalidomide in the context of other risk factors.

Results:

Table 1 ADR reports registered in the Italian Pharmacovigilance Network

6-month period before the dissemination of the DHPC		6-month period after the dissemination of the DHPC	
Active substance: reports of safety issue described in the DHPC	Total ADR reports	Active substance: reports of safety issue described in the DHPC	Total ADR reports
Brivudine: –	1	Brivudine: –	7
Panitumumab: 3	5	Panitumumab: 1	14
Fingolimod: 3	5	Fingolimod: 1	14
Bortezomib: 1	47	Bortezomib: –	100
Lenalidomide: –	349	Lenalidomide: –	173

Conclusions: DHPCs seem to have an important role in raising awareness about safety concerns and in enhancing HPCs attention on a specific medicinal product. However, other safety communication tools such as educational materials or press communications should be used together with DHPCs to improve sensitising HPCs in an ADR reporting context while other means for HPCs's sensitization should be considered.

Abstract Code: ISP3760-44

Association Between Paraesthesia and Local Anesthetics: Data Mining of the Public Version of the FDA Adverse Event Reporting System

C. Piccinni[1], D.B. Gissi[2], A. Koci[1], D. Servidio[2], F. Cervellati[2], E. Poluzzi[1]

(1) Department of Medical and Surgical Sciences, Pharmacology Unit, University of Bologna, Bologna, Italy, (2) Department of Biomedical and Neuro-Muscular Sciences, Oral Sciences Unit, University of Bologna, Bologna, Italy

Background: The hypothesis on neurotoxicity of local anesthetics is controversial. The incidence of paraesthesia increased following the introduction of articaine 4 % and frequently dental anesthesia is involved.

Aim: To provide the contribution of spontaneous adverse events reporting analysis on association between paraesthesia and local anesthetics, focusing on those used in dentistry.

Methods: Association between local anesthetics (ATC: N01B) and paraesthesia was analyzed by the case/non-case of spontaneous adverse events recorded in FDA_AERS (Food And Drug Adverse Event Reporting System) between 2004 and 2011. Cases were represented by the reports of

reactions included in the MedDRA high-level term "Paraesthesias and dysaesthesias" for a given local anesthetic; non-cases were all other reports of the same drug. For each anesthetic, the association between such drug and paraesthesia was calculated by using the reporting odds ratio (ROR) with the relevant 95 % confidence intervals (95 % CI). Association was considered statistically significant when: number of cases >3, ROR >1 and lower limit of 95CI >1. To estimate the influence of this association in dentistry, two sensitive analyses were performed: (i) analysis restricted to anesthetics used in dentistry (lidocaine 2 %, bupivacaine 2 %, articaine 4 %, prilocaine 4 % and mepivacaine 2 and 3 %), (ii) analysis focused on the specific adverse reaction "Paraesthesia Oral".

Results: Overall, 528 reports of "Paraesthesias and dysaesthesias" were retrieved, corresponding to 573 drug reaction pairs, with 247 lidocaine 2 %, 99 bupivacaine 2 %, 85 articaine 4 %, 30 prilocaine 4 %, 112 others. The association between drug and adverse reaction was significant for articaine 4 % (ROR 18.38; 95 % CI 13.95–24.21), and prilocaine 4 % (2.66; 1.82–3.90). These associations were confirmed in the sensitive analysis. Indeed, analyzing only anesthetics used in dentistry, articaine 4 % and prilocaine 4 % were significantly associated to paraesthesia. The analysis of the specific term "Oral Paraesthesia" retrieved 90 drug-reaction pairs (37 articaine 4 %, 19 lidocaine 2 %, 14 prilocaine 4 %, 7 bupivacaine 2 %, 13 others), and a statistical significant association for articaine 4 % (58.77; 37.82–91.31) and prilocaine 4 % (8.73; 4.89–15.57).

Conclusion: Our study underlined a stronger association between paraesthesia and articaine 4 % or prilocaine 4 %, rather than other local anesthetics. Data are in agreement with different studies that reported nerve damage after receiving an inferior alveolar nerve block with articaine 4 % or prilocaine 4 % in dentistry. The exact mechanism and the incidence of association remain still unknown. These safety disproportionality signals should stimulate more specific studies to confirm or reject the causality relationship between the 4 % anesthetic solutions and paraesthesia, and to quantify the magnitude of the hazard. In conclusion, health-care professionals, and in specific dentists, should consider risks and complications of articaine/prilocaine administration.

Abstract Code: ISP3761-45

Risk of Perinatal Death After Pandemic Vaccination in Italy

F. Trotta[1], R. Da Cas[1], S. Spila-Alegiani[1], M. Gramegna[2], M. Venegoni[3], C. Zocchetti[4], G. Traversa[1]

(1) Pharmacoepidemiology Unit, National Centre for Epidemiology, Italian National Institute of Health, Rome, Italy, (2) Unit for Preventive Medicine, General Directorate for Health, The Lombardy Region, Milan, Italy, (3) Regional Center for Pharmacovigilance, General Directorate for Health, The Lombardy Region, Milan, Italy, (4) Unit for Local Health Service Governance, General Directorate for Health, The Lombardy Region, Milan, Italy

Background: A systematic review of 120 studies related to the 2009 pandemic influenza infection in pregnancy confirmed an increased risk of morbidity and mortality as well as the worsening of birth outcomes [1]. However, the anecdotal report of fetal deaths and stillbirths following pandemic vaccination also raised the attention about vaccine safety [2]. Few observational studies estimated the risk of pregnancy loss after pandemic influenza vaccination, mainly concerning an AS03 adjuvanted vaccine [3–5].

Objectives: To evaluate the risk of perinatal deaths associated with pandemic MF59 adjuvanted vaccine administered in Italy during 2009.

Methods: We carried out a registry based retrospective cohort study covering the population of the Lombardy Region in the Northern Italy (>9.8 million inhabitants in 2010). All pregnancies of resident women whose delivery occurred between 1 October 2009 and 30 September 2010 were identified through the Regional birth registry. The vaccination status, pregnancy and birth outcomes, and background information of the pregnant women were retrieved by linking Lombardy Regional registries for prescriptions and vaccinations, hospital discharge database and medical birth registry. Stillbirth was defined as a delivery of a dead fetus after 180 days of amenorrhea, while an early neonatal death was defined as a newborn dead in hospital within 7 days after delivery. Perinatal deaths were the sum of stillbirths and early neonatal deaths. A multivariate regression model adjusted by propensity score was adopted to estimate the odds ratios of events in association with the vaccination during pregnancy.

Results: There were 86,171 eligible pregnancies in Lombardy, with 6,246 women exposed to pandemic vaccine (57.9 % were vaccinated in the third trimester and 40.9 % in the second one). Exposure to the H1N1 pandemic vaccination was not associated with an increased risk of stillbirth (adjusted OR 1.1, 95 % CI 0.6–1.9), early neonatal death (adjusted OR 1.0, 95 % CI 0.4–2.8) or perinatal death (adjusted OR 1.1, 95 % CI 0.6–1.7). A sensitivity analysis considering different post-vaccination risk windows did not alter the estimates.

Conclusion: During pregnancy, the administration of MF-59 adjuvanted vaccine against 2009 pandemic influenza virus was not associated with an increased risk of perinatal deaths.

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Abstract Code: ISP3763-47

Development of Safety Concerns Within RMPs After Approval: A Cohort Study of Biologicals

N. Vermeer[1,2], R. Duijnhoven[1,2], S. Straus[2,3], S. Blackburn[4], L. Hoogendoorn[1,2], A. Mantel-Teeuwisse[1], T. Egberts[1], H. Leufkens[1,2], M. De Bruin[1,2]

(1) Utrecht Institute for Pharmaceutical Sciences (UIPS), Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht University, Utrecht, The Netherlands, (2) Medicines Evaluation Board, Utrecht, The Netherlands, (3) Medical Informatics, Erasmus Medical Center, Rotterdam, The Netherlands, (4) European Medicines Agency (EMA), London, UK

Background: Risk management plans (RMPs) form an integral part of the regulatory approval of new drugs in Europe. The RMP details all safety concerns and associated pharmacovigilance activities, facilitating post-approval knowledge increase. The process of knowledge incorporation in the RMP during a medicine's life cycle is currently unknown, and requires study.

Aim: To explore the development of RMPs of biologicals after approval, by quantifying changes in safety concerns over time, and analyzing reasons for change.

Methods: For a cohort of 17 biologicals (approved 11/'05–12/'09) initial RMPs and subsequent updates until 12/'12 were retrieved from EMA.

Information on baseline safety concerns and associated pharmacovigilance activities was extracted from initial RMPs and follow-up information from RMP updates. In RMPs safety concerns are classified as *identified risks*, *potential risks*, and *missing information* (e.g. use in children). Incidence rates of transitions between these three classes, additions after approval and "omissions" (issue resolved or sufficiently studied) were calculated.

Results: The median number of safety concerns was 15 (range 7–23) per product at approval: 3 identified and 6 potential risks, and 5 missing information. Median follow-up was 59 months per product, involving a median of 8 RMP updates.

During follow-up, 43/251 (3/49 identified risks, 29/99 potential risks, 11/103 missing information) of the concerns changed (0.045/year overall, and 0.014/year, 0.084/year, 0.027/year for respective concerns). Among the 43 changes, 20 concerned omissions (3 identified and 9 potential risks, 8 missing information), resulting from completion of committed studies (9/20) or other studies (3/20), no new data (4/20), or unknown (4/20).

59 concerns were newly added (21 identified and 23 potential risks, 15 missing information), originating from studies (20/59), spontaneous reports (10/59), new indications (9/59), or other/combination (20/59).

Conclusion: The observed development of RMPs after approval supports their role in a medicine's life cycle. Five years post-approval, the emphasis seems to be on newly emerged concerns, rather than on changes in baseline concerns.

Abstract Code: ISP3764-48

Adverse Reactions with Antidiabetic Drugs: Results from a Prospective Cohort Study in Sicily

V. Pizzimenti[1], V. Ientile[1], G. Fava[1], I. Lo Giudice[2], C. Bonfiglio[3], U. Alecci[3], A. Russo[4], A. Giandalia[2], P. Cutroneo[4], D. Cucinotta[2], A.P. Caputi[1,2,4], G. Trifirò[1,2]; On Behalf of the Whole Sicilian Antidiabetic Pharmacovigilance Research group

(1) Azienda Ospedaliera Universitaria "G. Martino", Messina, Italy, (2) Department of Clinical and Experimental Medicine, University of Messina, Italy, (3) Società Italiana di Medicina Generale; SIMG, Messina, Italy, (4) Sicilian Regional Pharmacovigilance Centre, Messina, Italy

Background: Antidiabetic drugs are important for preventing complications of type II diabetes mellitus (T2DM). Several safety issues have been recently raised concerning newly-developed antidiabetics (e.g. incretins).

Objective: The aim of this study was: (1) to analyze the type and incidence of adverse drug reactions (ADRs) associated with antidiabetics during a prospective pharmacovigilance study in Sicily; and (2) to estimate the extent of ADR under-reporting.

Methods: In this study, sponsored by Italian Medicines Agency, six diabetologists centers and 60 GPs from Sicily have enrolled and followed for up to one year T2DM patients who started any antidiabetic in the period October 1st 2010–December 31th 2012. Patients' demographic and clinical data were collected through questionnaires administered by GPs or diabetologists at baseline and after 1, 2 weeks, and 1, 2, 3, 6, 8 and 12 months. During the treatment with antidiabetics GPs and diabetologists were asked to report the occurrence of any ADR via questionnaire to the coordinating center as well as via official spontaneous ADR reporting to the Regional pharmacovigilance center. To estimate the extent of under-reporting, we compared the number of antidiabetic drug-related ADR reports in the Sicilian pharmacovigilance center database with ADRs reported to the coordinating center via questionnaire by the study physicians.

Results: Overall, 1.687 T2DM patients (661 (39.2 %) by diabetologists and 1.026 (60.8 %) by GPs) were recruited in the study. After one year of monitoring, 186 (11.0 %) patients experienced at least one ADR. The most frequently involved antidiabetic drugs were biguanides (29.6 %), combinations of oral hypoglycemic drugs (17.6 %) and incretins (16.6 %). Main ADRs were hypoglycemia, especially with insulins, and gastrointestinal events (nausea/vomiting, diarrhea, and abdominal pain) for biguanides and metiglinides.

Despite intensive monitoring prompted the ADR reporting by GPs and diabetologists participating in the study, yet reporting rates of ADRs was low, especially for GPs (42.5 %).

During the first year of follow-up, 138 hypoglycemic episodes have been reported via questionnaire by the study physicians (only 20 have been also reported to the pharmacovigilance regional center). These events were mainly *moderate/mild* (83.3 %). The incidence of hypoglycemia was higher in users of insulin (15.3 %) and metiglinides (6.4 %) than other antidiabetics (2.7 %).

Conclusion: The results of this study confirm the main safety issues of antidiabetics (e.g. gastrointestinal disorder for biguanides and incretins and hypoglycemia for insulins). Intensive monitoring in clinical practice may stimulate ADR reporting, despite a large under-reporting, especially for GPs, has been yet observed.

Abstract Code: ISP3765-49

Severe Intussusception After Administration of Anti-Rotavirus Vaccine: Case Series

A. Pugi[1], M.C. Lenti[1], V. Maggini[1], N. Lombardi[1], E. Gallo[1], R. Bonaiuti[1], E. Lucenteforte[1], M. Moschini[1], A.M. Calvani[2], F. Mannelli[3], L. Innocenti[3], M. Parrilli[4], M. Rossi[2,5], A. Mugelli[1,2], A. Vannacci[1,2]

(1) Department of Neurosciences, Psychology, Drug Research and Child Health (NEUROFARBA), University of Florence, Florence, Italy, Tuscan Regional Centre of Pharmacovigilance of Florence, Florence, Italy, (2) Hospital Pharmacy, Meyer Children's Hospital, Florence, Italy, (3) Emergency Department, Meyer Children's Hospital, Florence, Italy, Tuscan Regional Centre of Pharmacovigilance of Florence, Florence, Italy, (4) Pharmacovigilance Unit, ASL 10, Florence, Italy, (5) Unit of Pharmacology, University Hospital of Siena, Siena, Italy

Background: Rotaviruses are the major cause of gastroenteritis among children of less than 5 years of age and of acute diarrhea in infants. The first rotavirus vaccine was introduced in 1998 but was subsequently withdrawn because of association with intussusceptions. The rotavirus vaccine licensed in 2006 (Rotarix®) is a live attenuated vaccine derived from the human 89-12 strain belonging to G1Ptype, and contains at least 10 median Cell Culture Infective Dose of live, attenuated rotavirus. Post-marketing safety studies assessed rare adverse events (rates <1 in 50,000), such as intussusceptions. Here we report 4 cases of intussusception that may represent an observed value higher than expected, considering an administration of vaccine lower than 7100 doses/year, although the actual exposure to the vaccine and the background intussusception incidence in Italy are unknown.

Description: From February 2012 to April 2013 four ADR reports of anti-rotavirus vaccine (Rotarix®) induced severe intussusception were reported to the Tuscan Centre of Pharmacovigilance. They occurred in four healthy male infants, born at term. The reactions occurred after the first dose in all cases (within 6 days) and all required hospitalization. Clinical manifestations comprised vomiting, melena and abdominal pain. Intussusception was generally diagnosed with ultrasound scan and barium enema, that in one case completely resolved the medical occurrence. In the other three cases surgical interventions were performed with good clinical outcomes. Babies did not assume other medications, but in two cases immunization with Rotarix® was concomitant with the administration of Infanrix Hexa® (DTaP-IPV-HepB/Hib) and Prevenar13® (pneumococcal polysaccharide conjugate vaccine).
Discussion: The cases reported, even if at a preliminary level, suggest that the actual incidence of the syndrome may be higher than expected. Evaluation of the safety of rotavirus vaccines, particularly with respect to the risk of intussusception, is recommended for countries planning to introduce rotavirus vaccines into the National Immunisation Program. However, as prospective studies are costly, require time to conduct and may be difficult to perform in some settings, retrospective studies and healthcare professionals with spontaneous surveillance could be efficacious methods to monitor this medical occurrence.
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Abstract Code: ISP3767-51

Joint Medicines Information and Pharmacovigilance Services Could Improve Detection of New Drug Safety Information

J. Bergman[1], J. Schjott[2]

(1) Regional Medicines Information and Pharmacovigilance Centre (RELIS Vest), Haukeland University Hospital, Bergen, Norway, (2) a. Section of Clinical Pharmacology, Lab. of Clinical Biochemistry, Bergen; b. Regional Medicines Information and Pharmacovigilance Centre (RELIS Vest), Haukeland University Hospital, Bergen, Norway

Introduction: Adverse drug reactions (ADRs) represent the most common category of questions to the Regional Medicines Information and Pharmacovigilance Centres in Norway (RELIS), and represent a substantial part of our question-answer pair (QAP) database (the RELIS database) [1]. RELIS also handle spontaneous ADR reports from healthcare professionals and give individualized feedback which may refer to QAPs. Extensive literature search, pharmacists' and clinical pharmacologists' involvement, and short response time are important in RELIS' communication about ADRs and in encouraging ADR reporting.
Objective: To describe how RELIS could detect new drug safety information through a joint medicines information and pharmacovigilance service.
Methods: We searched the RELIS database for QAPs about ADRs and the Norwegian ADR database for use of QAPs as references in feedback to healthcare professionals in 2003–2012. We selected the example of pregabalin and drug abuse to illustrate RELIS potential to detect new drug safety information through a limited number of QAPs and reports concerning different aspects of drug abuse.
Results: 5,427 (26 %) of 21,071 QAPs in the RELIS database were about ADRs. QAPs were used as references in feedback in 791 (4 %) of a total of 22,090 reports in the Norwegian ADR database. Lyrica (pregabalin) was marketed in September 2004 in Norway, and in July 2005 RELIS received the first question concerning pregabalin abuse. Two subsequent adverse drug reaction reports in January 2006 about drug abuse were followed by a question in March 2006 suspecting a particular problem among patients with opioid addiction and psychiatric diseases. Descriptions of problems with dose escalation, craving, and withdrawal reactions followed through questions and ADR reports during 2007 and 2008. The questions complemented the ADR reports by including a wide specter of behaviors indicating drug abuse, for example the enthusiasm and satisfaction with pregabalin prescriptions shown by former or current drug abusers. Thus, 4 years after marketing in Norway, 13 reports and 11 questions depicted a drug safety problem with pregabalin later described internationally [2].
Conclusions: The synergy of RELIS' joint medicines information and pharmacovigilance services and the quality of our communication about ADRs could improve detection of new drug safety information.
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Abstract Code: ISP3768-52

An Uncommon Steven–Johnson Syndrome Induced A B-Agonist Agent in a 6-Years-Old Child

M.C. Lenti[1,2], N. Lombardi[1,2], B. Faginali[3], V. Maggini[1,2], A. Pugi[1,2], M. Moschini[1,2], R. Bonaiuti[1,2], E. Gallo[1,2], F. Mandò Tacconi[2], A. Mugelli[1,2], M. Parrilli[2], A. Vannacci[1,2]

(1) Department of Neurosciences, Psychology, Drug Research and Child Health (NEUROFARBA), University of Florence, Florence, Italy, (2) Tuscan Regional Centre of Pharmacovigilance of Florence, Florence, Italy, (3) Community Pharmacy, Florence, Italy

Introduction: Stevens–Johnson Syndrome (SJS) is a severe idiosyncratic immune-mediated reaction characterized by extensive cutaneous and mucosal epidermal necrosis and sloughing. Drugs most frequently involved in SJS are antimicrobials, NSAIDs and antiseizure drugs, through a dose-independent mechanism triggered by some kind of immune response. SJS is characterized by mortality rates between 1 and 30 %, depending on the extent of blistering, and up to 35 % of serious sequelae in survivors. The precise incidence of SJS in children is still unknown.
Case Description: A 6-year-old male child was admitted to the Emergency Department (ED) with fever, dyspnea, bilateral purulent conjunctivitis, oral stomatitis, cheilitis, skin and genital blisters. For respiratory tract infection he had been taking amoxicillin/clavulanate and betamethasone 0.5 mg orally and nebulized fluticasone 50 mcg; for dyspnea he had been taking nebulized salbutamol 100 mcg (Ventolin® HFA), 2 sprays 3 times a day for four days. A chest X-ray revealed bronchitis. Therapy given in the first hours of arrival in ED included ophthalmic tobramycin and nebulized salbutamol (4 sprays × 4). Despite these measures his clinical condition worsened, and

he was transferred to the Intensive Care Unit (ICU) where Stevens–Johnson syndrome (SJS) was diagnosed. During hospitalization the patient developed a thrombophlebitis, which was treated for 90 days with low-molecular-weight heparin. Nine months after discharge from the hospital, the patient was hospitalized for a similar event following the re-assumption of inhaled salbutamol for dyspnea and cough. A day before ED admission patient was vaccinated against tetanus, diphtheria, and pertussis. The dermatological consultation confirmed a recurrence of SJS.

Discussion: In a 2009 FDA "Postmarketing Adverse Event Review" two cases of Stevens-Johnson Syndrome were reported after salbutamol assumption, one of these referred to a 10-years-old male child. To our knowledge, no other similar adverse reaction was previously described in literature and databases (Micromedex®; Farmadati®). The contribution from Ventolin® HFA to the occurrence of SJS in the case we described above is strongly suggested by the temporal relationship of the event and the initiation of therapy with this drug. Positive dechallenge/rechallenge episodes are present in patient's history. The causal relationship of Ventolin® HFA in this case is confounded by concomitant use of amoxicillin, which is commonly reported in literature to be associated with SJS; moreover a role of trivalent immunization (Boostrix®) cannot be excluded. Making a final clinical evaluation and in according to the objective causality assessment performed using Naranjo Scale, our case was defined as 'probable'.

Abstract Code: ISP3769-53

Active Pharmacovigilance Monitoring of Treatment Errors in the Tuscan Poison Centre of Florence

C. Lanzi[1], A. Pugi[1,2], P. Botti[3], F. Gambassi[3], M.R. Quaranta[3], M.C. Leo[4], E. Cini[4], E. Masini[1], F. Davanzo[3], A. Vannacci[2]

(1) Department of Neurosciences, Psychology, Drug Research and Child Health (NEUROFARBA), University of Florence, Florence, Italy, (2) Tuscan Regional Centre of Pharmacovigilance of Florence, Florence, Italy, (3) Poison Centre, Toxicology Unit, Careggi General Hospital, Florence, Italy, (4) Hospital Pharmacy, Careggi General Hospital, Florence, Italy

Background: The definition of adverse drug reactions (ADRs) has been recently extended to include "adverse effects and unintended results not only from the authorized use of a medicinal product at normal doses, but also medication errors and uses that do not comply with the terms of marketing authorization, including prescription drug misuse and abuse". To detect those events, an extension of pharmacovigilance systems is needed, with the establishment of networks between pharmacovigilance units and poison centres (Centri Anti Veleno—CAV). Data collected during the consultations are an important source of information to guide public health prevention interventions. The FARVICAV project, supported by Italian Medicine Agency, is already effective in some Italian CAV. Tuscany has joined the project in 2012 with the Poison Centre of Azienda Ospedaliero-Universitaria Careggi.

Objective: The FARVICAV project's objective is to collect and monitor treatment errors (TEs) and ADRs referred to the Tuscan CAV, to classify them for severity and to evaluate the existence of a causal relationship between the drug and the clinical negative effects.

Methods: TEs and ADRs were collected in a specific database from July 2012. Drug use history, clinical and demographic data were collected by a clinical toxicologist. Adverse reactions were classified according to MedDRA dictionary (System-Organ-Class). Causality assessment was performed for each report according to the Naranjo algorithm.

Results: The number of reports from July 2012 accounts for 135 files; 24 cases were ADRs, in 10 cases reactions were caused by therapeutic errors. Psychiatric treatments were involved in 6 ADR reports: 3 cases were due to antipsychotic drugs and one to benzodiazepine. One of these cases was a severe case of neuroleptic malignant syndrome in a woman taking a multidrug therapy that require hospitalization. Analgesics are the other class of drugs mostly involved in ADRs (6 cases, 4 for opioids). Moreover, four cases of amoxicillin induced severe allergy reactions were recorded.

Conclusions: From a Poison Centre point of view, it is interesting to notice how frequently and severely psychiatric drug therapy may be involved in unwanted ADRs. Thus reflecting the complexity of this kind of treatment that rarely is made of a single drug. Pain treatments also seem to be a subject to be focused, especially according to the new EMA directions. Opioid analgesics tend to be abused with ease. In keeping with these results, the phenomenon related to the abuse of prescription opioids is considered a new emergency for which the FDA has implemented life-saving strategies.

Abstract Code: ISP3770-45

Potentially Inappropriate Prescribing in Nursing Homes Residents in Tuscany

E. Lucenteforte[1], F. Collini[2], P. Pepe[2], V. Maggini[1], A. Pugi[1], C. Lorini[3], N. Zaffarana[4], G. Bonaccorsi[3], M. Di Bari[4], M. Cavallini[4], A. Mugelli[1], A. Vannacci[1]

(1) Dipartimento di Neuroscienze, Psicologia, Area del Farmaco e Salute del Bambino (NEUROFARBA), Università degli Studi di Firenze, Firenze, Italy, (2) Osservatorio per la qualità e l'equità, Agenzia Regionale di Sanità della Toscana, Firenze, Italy, (3) Dipartimento di Medicina Sperimentale e Clinica, Health Services Research Unit, Università degli Studi di Firenze, Firenze, Italy, (4) Dipartimento di Medicina Sperimentale e Clinica, Unità di Ricerca di Medicina dell'Invecchiamento, Università degli Studi di Firenze, Firenze, Italy

Background: The occurrence of "Inappropriate Prescribing" (IP) is a well-documented problem in older adults, although its definition in the geriatric population is still debated. The aim of avoiding medications whose risks outweigh benefits in the elderly patients has stimulated the development of different criteria to identify IP. The most known are an American-based screening tool, the Beers criteria [1], and an European physiological system-based screening tool, the "Screening Tool of Older Person's Prescription" (STOPP) criteria [2]. Compared to Beers' criteria, STOPP ones identify an higher proportion of patients requiring hospitalization as a result of IP-related adverse events, and are more suitable for European settings.

Aim: To determine the prevalence of IP in residents of Tuscany Nursing Homes (NHs) using a subset of 10 indicators of STOPP criteria.

Methods: This was a retrospective study on 2527 subjects (72 % female, 78 % 70–94 years old) living in 67 NHs. Database from an ad hoc survey was merged with that from the administrative archives of the Local Health Authority. Data recorded included: all reimbursed drug prescriptions and hospital admissions (from claim databases), current and previous medical conditions and general characteristics (from survey database). We also compared IP criteria before and after NHs admission.

Results: After NHs admission, IP prevalence was less than 5 % for the following indicators: #1 "risk of symptomatic heart block", #2 "risk of bronchospasm", #3 "risk of severe constipation", #4 "likely to worsen extrapyramidal symptoms", #6 "may exacerbate glaucoma", and #10 "risk of

acute exacerbation of glaucoma". The prevalence was 22 % for the #9 "risk of gastrointestinal bleeding" indicator, 23 % for the #5 "may lower seizure threshold", 28 % for the #7 "risk of exacerbation of heart failure", and 34 % for the #8 "risk of deterioration in renal function". These prevalence figures were higher before HNs admission even if statistically significant differences emerged only for few indicators.

Conclusion: Findings of the present study show a generally good appropriate prescribing in the elderly, further improved after NHs admission. There were only few caveats regarding the use of phenothiazines in patients with epilepsy (indicator #5); and the use of non-steroidal anti-inflammatory drug in patients with either heart failure (indicators #7), chronic renal failure (indicators #8), or coexistent warfarin treatment (indicator #9).

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Bio-Tech: An Innovative Approach for Rheumatoid Arthritis, Their Adverse Drug Reactions Constitute Problem

I. Papadopoulos[1], K. Demetzos[1], S. Markantoni-Kyroudi[1], K. Souliotis[2], A. Vozikis[3]

(1) Department of Pharmaceutical Science, Faculty of Pharmacy, University of Athens, Greece, (2) Faculty of Social Science, University of Peloponnese, Tripolis, Greece, (3) Department of Economic Science, University of Piraeus, Piraeus, Greece

Introduction: Biotechnological medicines have improved the treatment of various diseases and the quality of life of patients [1]. The administration of a drug may lead to adverse drug reactions (ADRs) that may or may not be documented. ADRs affect disease progression and health expenditures [2]. Rheumatoid Arthritis (R.A.) is an autoimmune disease for which biotechnological medicines are prescribed. RA has serious economic impact. Especially, the annual cost of RA is 41 billion euros in the USA and 45 billion euros in Europe, which are increasing dramatically with appearance of an ADR [3].

Aims: To record the ADR of biotechnological drugs prescribed for R.A., to assess their possible effects on both patient and health system and to develop a tool aiming the efficient use of biological medicines.

Methodology: A review of existing literature on ADRs of biotechnological medicines for RA and analysis of all available data from Eudravigilinance were conducted. The collection of ADR data from rheumatology clinics of various hospitals will be conducted. Finally, any algorithm/tool currently utilized to guide the selection of the most appropirate treatment will be assessed.

Results: 60 % of patients are female aged 18–65 years. 20 % of reports indicated that an infection has occurred, 15 % highlighted the existence of inflammation at the site of injection and 12.5 % reported a gastrointestinal disorder. The occurrence of musculoskeletal problems, hyperplasia and nervous disorder estimated at 10 % of the reports and the respiratory problems approximately 8 %.

Conclusion: Infection or inflammation at the site of injection is the most common ADR altering microbiological profile of patient. A possible relationships/associations between certain parameters (for example genome and the appearance of an ADR) which will contribute to the safer and efficient use of biological drugs will be examined.

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Abstract Code: ISP3772-47

Pinpointing Key Features of Case Series in Pharmacovigilance—a Novel Method

K. Juhlin[1], K. Star[1], G.N. Norén[1]

(1) Uppsala Monitoring Centre, Uppsala, Sweden

Introduction: When analysing large case series of pharmacovigilance reports, it is valuable to be able to quickly identify their key features, such as patient demographics, type of reporter, drugs and adverse reactions. Differentiating features may reflect variations in reporting practice or patient risk groups. Case series may range from all reports on a drug class such as vaccines, on an adverse reaction such as lack of effect, or from a specific geographic region such as India. If manual, this analysis is time-consuming, and may be difficult to reproduce.

Aim: To propose and evaluate a computational method for pinpointing key features in a case series.

Method: As case study, we evaluated whether the method could reproduce findings from a previously published exploratory analysis of paediatric reports in VigiBase [1]. The proposed method contrasts a selected group of reports, here children, to a reference, here adults. It relies on odds ratios subjected to statistical shrinkage [2] to identify associations across a broad range of covariates, here patient sex, country of origin, type of report and reporter, year of report, number of co-reported drugs, fatality of the reported event, reported drugs (ATC, 1st level) and adverse reactions (MedDRA SOC, HLT). To restrict focus to features with strong enough association and prevalence in the case series, we set the strength of shrinkage to 0.01 times the case series size and require that the lower 99 % confidence interval of the shrunk log2 odds ratio exceed 0.5.

Results: Out of 374 features of VigiBase paediatric reports, the suggested method highlighted 22. In line with the published study, the identified features included higher than expected proportions of paediatric reports for e.g. males, from Asian and South American countries, on anti-infective and respiratory drugs, and on skin disorders. In addition, it flagged higher than expected reporting of erythema multiforme, which had not been highlighted in the published study.

Conclusions: Shrinkage odds ratios can provide a basis for rapid, transparent and reproducible identification of the key features in a case series. The method has the potential to free up time and serve as guidance to direct in-depth expert review.

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Abstract Code: ISP3773-48

Monitoring Program of Adverse Drug Reactions in a Pediatric Emergency Department

M. Moschini[1,2], N. Lombardi[1,2], A. Pugi[1,2], V. Maggini[1,2], E. Gallo[1,2], M.C. Lenti[1,2], R. Bonaiuti[1,2], E. Lucenteforte[1,2], F. Mannnelli[3], L. Innocenti[3], A.M. Calvani[4], M. Parrilli[2,5], F. Mandò Tacconi[2,5], M. Tuccori[2,6], M. Rossi[2,7],A. Mugelli[1,2], A. Vannacci[1,2]

(1) Department of Preclinical and Clinical Pharmacology M. Aiazzi Mancini, Centre for Molecular Medicine (CIMMBA) University of Florence, Florence, Italy, (2) Tuscan Regional Centre of Pharmacovigilance, Florence, Italy, (3) Emergency Department, Meyer Pediatric Hospital, Florence, Italy, (4) Hospital Pharmacy Meyer Pediatric Hospital, Florence, Italy, (5) Department of Pharmacovigilance, ASL 10 Florence, Italy, (6) Unit of Pharmacology, University Hospital of Pisa, Italy, (7) Unit of Pharmacology, University Hospital of Siena, Italy

Introduction: Drug use in pediatric patients requires careful safety evaluation, since many drugs are used in an *off-label* manner, due to the lack of registrative studies in this age group. Moreover, differences in physiological and metabolic functions make children more vulnerable to adverse drug reactions (ADRs). Several studies show that ADRs are a common cause of admission to Emergency Departments (EDs). Thus, in the frame of the national pharmacovigilance project of ADRs monitoring in emergency departments (MEREAFaPS), we focused our analysis on children admitted to a pediatric ED in order to describe the frequency and the features of drug-related ADRs leading to ED visits.

Methods: This prospective and observational study considered patients admitted to ED at Meyer Pediatric Hospital of Florence for a suspected ADR from October 2010 to April 2013. Drug use history, clinical and demographic data were collected by trained monitors. ADRs were classified as serious if they caused or prolonged hospitalization, were life-threatening, resulted in death, or produced permanent malformations or disabilities. Adverse reactions were classified according to MedDRA dictionary (System Organ Class).

Results: The rate of admissions to ED due to ADRs was 0.42 % (488 ADR-related ED admissions). About fifty-two percent of the reports involved male children (mean age 48 months). Serious reactions requiring hospitalization represented 25.6 % of total ADRs, only one being life-threatening; thus, the majority of ADRs were classified as 'not serious' (358). In more than half of cases, it was not possible to define the outcome of the reaction. As expected, the reporters were mainly hospital doctors (82.2 %), followed by other healthcare professionals including nurses (9.6 %) and pharmacists (8 %). The 488 ADR-related ED admissions resulted in 859 adverse events: 21.5 % involved the skin, 17.7 % the gastrointestinal system, 12.4 % were related to general disorders and administration site conditions and 7.8 % to nervous system disorders. Other conditions (respiratory, metabolic and nutritional, musculoskeletal, eye, ear and labyrinth disorders) were also observed. Drugs (n = 794) most frequently involved in the adverse reactions were antibacterials for systemic use (27.7 %) and vaccines (20.4 %), followed by NSAIDs (6.5 %), anticonvulsants (5.4 %), corticosteroids (5.2 %), antipyretic/analgesic agents (3 %) and cough preparations (2.5 %).

Conclusion: Although ADRs are a not very common cause of ED admission among pediatric patients, about a quarter of them was serious. Antimicrobial agents and vaccines were found to be the drugs most frequently associated with ADRs.

Abstract Code: ISP3774-49

Frequency of Expected Drug–Drug Interactions in Emergency Department: Focus on the Elderly

A. Capogrosso-Sansone[1], C. Blandizzi[1], S. Montagnani[1], E. Ruggiero[2], S. Mantarro[1], A. Saporiti[1], S. Felici[2], A. Marino[1], G. Pasqualetti[3], F. Monzani[3], M. Santini[4], M. Tuccori[5]

(1) Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy, (2) Pharmaceutical Unit, University Hospital of Pisa, Pisa, Italy, (3) Geriatric Unit, Department of Clinical and Experimental Medicine, University Hospital of Pisa, Pisa, Italy, (4) Emergency Department University Hospital of Pisa, Pisa, Italy, (5) Unit of Adverse Drug Reaction Monitoring, University Hospital of Pisa, Pisa Italy

Introduction: Drug–drug interactions represent a major concern for elderly people receiving polypharmacy. Although several combinations of drugs are expected to interact, the incidence of those causing an overt pool of adverse symptoms remains unknown.

Aim: To identify potential drug–drug interactions (PIs) in elderly patients admitted to an emergency department (ED) and to evaluate the prevalence of these admissions consistent with an expected drug interaction.

Methods: This study analyzed data collected in the setting of a program of pharmacologic support for elderly patients in an ED, where a pharmacologist and a geriatrist cooperate with ED physicians in the identification of drug-related admissions (including drug–drug interactions). This prospective survey included consecutive patients, ≥65 years-old admitted at the ED of Pisa University Hospital from May 1st, 2012 to May 1st, 2013 (Monday–Friday, 10AM–5PM). Each patient or his/her relatives/tutor was interviewed to collect demographic and therapeutic data. PIs were assessed using Thomson Micromedex®. (http://www.micromedexsolutions.com/home/dispatch), and classified on the basis of clinical relevance (contraindicated, major, moderate, minor). Each ED admission (discharge diagnosis) was evaluated for its consistency with the expected signs and symptoms of PI reported by Micromedex®.

Results: Throughout the study period, 1209 ED admissions (1157 patients, 691 female, mean age 80.2 ± 7.9) were recorded. An overall number of 7235 drugs were evaluated with 2406 PIs. 125 PIs (5.2 % of all PIs) were considered as consistent with ED admission. PIs were classified on the basis of clinical relevance as follow: contraindicated: 17 (4 consistent with ED admission, 23.0 %); major: 672 (37, 5.5 %); moderate: 1627 (84, 5.2 %); minor: 86 (4, 4.6 %). The most frequently recorded PIs were: acetylsalicylic acid + furosemide: 118 (reduction of furosemide diuretic effect); acetylsalicylic acid + ramipril: 78 (reduction of ramipril antihypertensive effect); furosemide + ramipril: 74 (postural hypotension with the first ramipril dose). Among "major" PIs the most frequently recorded were: acetylsalicylic acid + clopidogrel: 23 (bleeding); acetylsalicylic acid + paroxetine: 20 (bleeding); acetylsalicylic acid + sertraline: 15 (bleeding). When considering PIs consistent with ED admission, the most frequently reported were levothyroxine + warfarin: 3 (bleeding); allopurinol + warfarin: 3 (bleeding); lansoprazole + warfarin: 3 (bleeding); and paroxetine + trimipramine: 3 (anticholinergic effects).

Conclusions: Treatments of elderly patients, as recorded in our ED, are associated with a high number of PIs, but only a small proportion of them

is consistent with the cause of admission. Bleeding involving anticoagulants or antiplatelets appears to represent the most relevant issue.

Abstract Code: ISP3776-51

Appropriate Prevention of NSAID-Related Upper Gastrointestinal Injury with Proton Pump Inhibitors at Hospital Discharge

S. Montagnani[1], M. Tuccori[2], A. Testi[3], M. Cristofano[4], M. Filippi[4], D. Benvenuti[4], A. Capogrosso Sansone[1], E. Ruggiero[5], S. Mantarro[1], A. Saporiti[1]

(1) Department of Clinical and Sperimental Medicine, University of Pisa, Pisa, Italy, (2) Unit of Adverse Drug Reaction Monitoring, University Hospital of Pisa, Pisa, Italy, (3) Local Health of Pisa, Italy, (4) Medical Direction, University Hospital of Pisa, Italy, (5) Pharmaceutical Unit, University Hospital of Pisa, Italy

Background: In patient at risk for gastrointestinal (GI) complications requiring treatment with nonsteroidal anti-inflammatory drugs (NSAIDs), guidelines recommend prophylaxis with proton pump inhibitors (PPIs).
Objective: To evaluate the rate of prescriptions of PPI at hospital discharge in the Health District of Pisa, in patients receiving NSAIDs or low dose-acetylsalicylic acid (LD-ASA), with regard for the presence of risk factors of upper GI injury.
Methods: We performed an observational retrospective study on patients discharged with chronic (>3 months) NSAIDs or LD-ASA with or without prescription of PPIs at the University Hospital of Pisa, between 2008 and 2010. Demographic and clinical information where retrieved from hospital discharge records, while information about drug treatments were collected using the Drug Claims database at the Health District of Pisa. Risk factors for NSAID-induced upper GI injuries included: age ≥65 years-old; concomitant therapies with anticoagulants or glucocorticoids; history of GI bleeding or peptic ulcer. Cases of inappropriate prevention of NSAID-related upper GI injuries were considered as follows: (1) any claim of PPIs in patients receiving NSAIDs or LD-ASA lacking at least one risk factor without other authorized indication for PPIs; (2) lack of claims for PPIs in patients receiving NSAIDs or LD-ASA with at least one risk factor.
Results: 6869 patients, discharged with claims of NSAIDs or low-dose ASA during the observation period, were eligible for analysis: 2733 in 2008 [n = 1281 for NSAIDs (mean age 63.5); n = 1452 for LD-ASA (mean age 82.3)]; 1813 in 2009 [n = 575 for NSAIDs (mean age 61.0); n = 1238 for LD-ASA (mean age 80.7)]; 2323 in 2010 [n = 563 for NSAIDs (mean age 60.8); n = 1760 for LD-ASA (mean age 81.7)]. In patients without risk factors receiving chronic NSAIDs or LD-ASA, the rates of claims for PPIs were 15.5 and 37.6 % in 2008, 11.7 and 38.9 % in 2009, 16.5 and 40.0 % in 2010, respectively. In patients with at least one risk factor receiving chronic NSAIDs or ASA, the rates of lack of claims for PPIs were: 36.8 and 42.9 % in 2008, 68.5 and 36.0 % in 2009; 63.9 and 36.1 %, respectively.
Conclusions: Upper GI protection with PPIs in patients receiving chronic NSAIDs or LD-ASA appears to be largely inappropriate, both for the lack of prescription in patients with risk factors and for prescription of PPIs in patients without risk factors. Despite a possible overestimation, due to potential misclassification biases, the trend over the observation period suggests an increase in the inappropriate management of upper GI protection.

Abstract Code: ISP3777-52

Exploring the Reporting of Lack of Effect—An Inventory in VigiBase

G. Karimi[1], K. Juhlin[1], I.R. Edwards[1]

(1) Uppsala Monitoring Centre, Uppsala, Sweden

Background: "Drug ineffective" (MedDRA preferred term (PT)) is one of the top reported terms in the WHO global ICSR database VigiBase [1]. In April 2013, 2.5 % of the eight million reports accumulated in VigiBase contained this very PT. Drug efficacy as measured in clinical trials [2] should be distinguished from lack of effectiveness for a drug in a patient treated in uncontrolled clinical situations, which is referred to as "lack of effect" in this study.
Objective: To pinpoint and evaluate what constitutes and differentiates lack of effect from other ICSR as reported in VigiBase.
Methods: The broad MedDRA SMQ "Lack of efficacy/effect" was reviewed blindly by two researchers and 14 PTs were selected as representatives of the concept. This study was limited to reports entered in VigiBase between years 2000–2012, following the ICH standardization of MedDRA terminology in 1999. Reports containing any of the selected PTs were contrasted against the remainder of the database from the same time period. A number of variables were selected for evaluation: co-reported MedDRA PTs, suspected/interacting drugs, notifier and reporting country. Disproportional reporting of any variable (i.e. log OR with 95 % confidence intervals), applying a shrinkage of 0.5, resulted in lists for further exploration and clinical review.
Results: The most frequently and disproportionally co-reported MedDRA PTs for the concept of lack of effect comprised "Product quality issue", "Insomnia", "Infection" and "Blood glucose increased". These were reflected by the top ten suspected/interacting drugs most frequently and disproportionally reported, including Botulinum toxin type a (Other muscle relaxants, peripherally acting agents), Sildenafil (Drugs used in erectile dysfunction), Eszopiclone (Benzodiazepine related drugs), Docosanol (Antivirals) and Exenatide (Other blood glucose lowering drugs, excl. insulins). Disproportional lack of effect reports mostly came from Consumers/Non health professionals, 94 % of which from the US. The greatest disproportionate reporting of lack of effect was by the US, followed by Canada. South Africa and New Zealand also presented significant disproportionate reporting, if yet of lower degrees. We highlighted "Product quality issue" as the most disproportionally co-reported MedDRA-term. The potential to identify Substandard/spurious/falsely-labelled/falsified/counterfeit medical products by studying spontaneous reports has been previously demonstrated [3].
Conclusion: The top reported drugs for the lack of effect concept represent known problematic treatment areas, e.g. infections and psychiatric disorders. The disproportionate reporting of life style issues may be reflected by the dominance of Consumers/Non health professionals as notifiers of lack of effect.

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Abstract Code: ISP3778-53

Association of Individual Non-Steroidal Anti-Inflammatory Drugs and Chronic Kidney Disease: A Population-Based Study

Y. Ingrasciotta[1], F. Giorgianni[1], J. Sultana[1], M. Muscianisi[1], A.P. Caputi[1], V. Arcoraci[1], M. Tari[2], D. Santoro[1], G. Trifirò[1]

(1) Department of Clinical and Experimental Medicine, University of Messina, Italy, (2) Caserta-1 Local Health Service, Caserta, Italy

Background: Non-steroidal anti-inflammatory agents (NSAIDs) are known to be nephrotoxic drugs. Differences in the risk of chronic kidney disease (CKD) among individual NSAIDs have yet to be better investigated.
Aim: To evaluate the association between the use of individual NSAIDs and the risk of CKD in a general population of Southern Italy.
Methods: The general practice "Arianna" database contains data from 158,510 patients, registered with 123 general practitioners (GPs) of Caserta. We carried out a case–control study in this population. Incident CKD patients were identified in the database by searching for: (1) ICD-9CM coded CKD as cause of hospitalisation; (2) CKD-relevant procedures undergone in hospital (e.g., dialysis); (3) drug prescriptions issued for a CKD-related indication. The date of first diagnosis of CKD was defined as the index date (ID). Up to 4 controls were randomly selected and matched to each case by age ±3 years, sex and ID. Using the prescription data, we classified the exposure to NSAIDs by individual agents, cumulative exposure (≤90, 91–180 and >180 days) as compared to the ID. We defined "current users" patients that used NSAIDs within 90 days before ID. We estimated the risk of CKD associated with NSAIDs exposure, overall and by individual compound, as compared to non-exposure during different risk windows (any time, one year, 6 and 3 months prior to the ID) by calculating odds ratios (ORs) together with 95 % confidence interval (CI). Specifically we conducted multivariate conditional logistic regression retaining in the final model all the potential confounders.
Results: Overall, 1,989 cases and 7,956 matched controls were identified. In detail, 388 (19.5 %) cases and 1,315 controls (16.5 %) were currently exposed to any NSAID.

There is no significant risk of CKD in users of NSAIDs as a whole during the different risk windows; instead, a statistically significant increase in the risk of CKD was observed for those users of ketorolac (OR 2.1; 95 % CI 1.3–3.5) or piroxicam (2.1; 1.4–3.3) within 3 months prior to ID.

The CKD risk substantially increased with increasing cumulative exposure to piroxicam as we estimated an OR = 3.5 (1.2–10.2) for 91–180 days of exposure and OR = 8.5 (2.0–36.3) over 180 days of exposure prior to CKD diagnosis. On the contrary, we did not have enough statistical power to study the cumulative exposure effect among ketorolac users.
Conclusions: Our data demonstrate that the CKD risk changes across different compounds and increases substantially with large cumulative exposure.

Abstract Code: ISP3779-54

Prescriber's Knowledge About the New Oral Anticoagulants When the Marketing Authorization for Atrial Fibrillation Occurred in France

M. Le Bellec[1], S. Fedrizzi[1], J. Lacotte[1], B. Mosquet[1], C. David[1], A. Coquerel[1]

(1) Pharmacovigilance Regional Center, University Hospital, Caen, France

Introduction: Anti-factor II Dabigatran, and anti-factor X Rivaroxaban and Apixaban respectively, are new oral anticoagulants (NOAC) that obtained recently marketing authorization in France to prevent strokes induced by atrial fibrillation. Consequently their prescriptions are dramatically growing since 2012. These new drugs were authorized without any coagulation assay to prevent severe side effects and/or to adjust dosage by contrast to classical anti-vitamins K (AVK) that require INR. Therefore numerous health professional of pharmacovigilance centers are angry about the safety of these NOAC. The aim of the study was to question the knowledge of the potential prescribers in the County of *Basse Normandie* about NOAC and to test whether the risk of side effects of these drugs are clearly felt or not by prescribers. Methods: The Regional Pharmacovigilance Centre of Basse-Normandie conducted a prospective study with general practitioners (GP) and specialized physicians (SP) (cardiologists, anesthetists, surgeons and neurologists) in two counties (Calvados and Orne) which represent about 900,000 inhabitants. The questionnaire was limited to 20 questions with cross answer and few short comments.
Results: 1165 questionnaires were sent. The Pharmacovigilance Centre received 223 answers (answer rate 19.1 %): 175 (78 %) from GP and 48 (22 %) from SP. 53 % of GP and 61 % of SP answered they didn't know anything or they had a bad knowledge about Dabigatran and Rivaroxaban. Among them, 13 and 27 % respectively have already prescribed them. For the physicians who have already prescribed one or the other of these drugs, the safety level didn't seem different that the AVK's (44 and 41 % respectively). Moreover, 69 % of physicians who have answered thought that the absence of biological surveillance is a positive point. Nevertheless 90 % wished to receive independent information on NOAC therapy.
Discussion: It could be supposed that Dabigatran and Rivaroxaban are two underestimated molecules for high risk of serious side effects. The lack of biological surveillance does not seem to worry prescribers. The more or less serious side effects are frequently underestimated and the absence of specific antidotes is ignored by more than 80 %. The risks of interactions and the necessity of creatinine clearance survey of Dabigatran are also widely underestimated. For a better prescription, a particular care seems to be necessary about these new anticoagulants in the promotion of a better knowledge and in the survey and the management of their adverse effects.

Abstract Code: ISP3780-46

The ATHE Score: A New Indicator for Data Quality Management of Spontaneous Reporting in PharmacoVigilance

V. Bres[1], P. Robin[1], V. Pinzani[1], C. Philibert[1], M.A. Bos-Thompson[1], D. Hillaire-Buys[1], J.L. Faillie[1]

(1) Medical Pharmacology Department, Pharmacovigilance Center, CHRU, Montpellier 1 University, Montpellier, France

Introduction: New European practice guidelines have recently been published to improve the execution of PharmacoVigilance activities [1]. They provide guidance for the establishment of quality assurance and highlight the key role of the implementation of quality indicators in the PharmacoVigilance systems. Efficient monitoring of Adverse Drug Reactions (ADRs) by spontaneous reporting is the common way to detect alerts concerning drug safety. If the amount of case reports is recognized as crucial to trigger a signal, there are no fixed indicators to assess reports quality. For this purpose, we analyzed case reports with a qualitative approach by testing an original indicator called "ATHE score".
Methods: We selected the serious ADRs reported in two French risk management plans concerning two recent drugs for the time period from 2008 to April 2013. For each case report, we focused on the availability of four specific items: Associated medication(s), Time to onset, History and Evolution (ATHE). The ATHE score is a score out of 4, according to the availability of each item: '0' if the item is not available, '1' if it is. For the item "Time to onset", the value "1" was given when the delay was estimated in days, '0.5' if the delay was in months and 0 if it was not available or calculated in years. We compared this ATHE score according to the origin of reports: Regional PharmacoVigilance Centres (CRPVs) or manufacturers.
Results: Eight hundred and five reports of serious ADRs were analyzed. Among them, 302 (37.8 %) and 497 (62.2 %) were reported by CRPVs and manufacturers respectively. In total, maximal information score was reached for 32.5 % of reports. Except for time to onset, item availability rate was higher in CRPVs reports compared to manufacturers: respectively, 74 % vs. 64 % ($p = 0.044$) for associated medication(s), 70 % vs. 69 % ($p = 0.528$) for time to onset, 90 % vs. 75 % ($p < 0.001$) for medical history and 89 % vs. 73 % ($p < 0.001$) for evolution. Maximal score (4) was reached for 27 % of CRPVs reports vs. 29 % for manufacturers ($p = 0.49$). ATHE score was higher for CRPVs reports (means): 3.1 vs. 2.7 ($p < 0.001$).
Conclusions: The ATHE score may represent a powerful indicator to evaluate the quality of received reports. By analyzing the information of every serious ADRs of two drugs on a large period, we showed that associated medication(s), medical history and evolution are more documented when they originate from CRPVs.
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Abstract Code: ISP3781-47

Pancreatitis and Use of GLP1 Analogs and DPP4 Inhibitors: A Case/Non-Case Study from the French Pharmacovigilance Database

J.L. Faillie[1], S. Babai[2], S. Crépin[3], V. Bres[1], M. Laroche[3], H. Le Louet[2], J. Montastruc[4], D. Hillaire-Buys[1], F.P. Centers Network[5]

(1) Regional Pharmacovigilance Center Montpellier, France, (2) Regional Pharmacovigilance Center Creteil, Creteil, France, (3) Regional Pharmacovigilance Center Limoges, Limoges, France, (4) Regional Pharmacovigilance Center Toulouse, Toulouse, France, (5) Association Française des Centres Régionaux de PharmacoVigilance (AFCRPV), France

Introduction: Incretin-based therapies have been marketed as a second/third line treatment for type 2 diabetes. Concerns about risks for pancreatitis have raised but have not clearly been demonstrated to date.
Aim: To investigate the association between exposure to incretin-based therapies (GLP-1 analogs and DPP-4 inhibitors) and the occurrence of pancreatitis on the French Pharmacovigilance Database (FPvD).
Methods: A case/non-case method was performed on the FPvD from serious adverse drug reactions (SADRs) reported in type 2 diabetic patients between March 2008 (first marketing of an incretin-based therapy in France) and March 2013. Type 2 diabetes was defined by the presence of at least one antidiabetic drug in the report except for insulin alone. Cases were defined as reports of pancreatitis, all other SADRs were considered non-cases. Disproportionality was assessed by calculating reporting odds ratios (ROR) and corresponding 95 % confidence intervals with adjustment for potential confounders by using a logistic regression model. Notoriety bias was searched by comparing adjusted RORs before and after March 2011 when the first study suggesting a risk of pancreatitis in US FDA adverse event reporting system database was published [1].
Results: 3109 SADRs including 147 cases (4.7 %) were retrieved. Among the 147 reported pancreatitis, 122 (83.0 %) involved incretin based therapies, 55 GLP-1 analogs (GLP1a), 64 DPP-4 inhibitors (DPP4i) and 3 both. After adjustment for age, gender, history of pancreatitis and other drugs associated with pancreatitis, disproportionality was found for all incretin based therapies (adjusted ROR: 15.7, 95 % CI 9.8–24.9), all GLP1a (29.4, 95 % CI 16.0–53.8), exenatide (28.3, 95 % CI 12.8–62.3), liraglutide (30.4, 95 % CI 15.4–60.0), all DPP4i (12.1, 95 % CI 7.3–20.0), sitagliptin (12.4, 95 % CI 7.3–21.0), saxagliptin (15.1, 95 % CI 4.3–52.7), vildagliptin (7.4, 95 % CI 3.1–17.6). Similar adjusted ROR for all incretin based therapies were found before and after March 2011 (respectively 14.3, 95 % CI 7.3–28.2 and 15.3, 95 % CI 8.2–28.7).
Conclusions: Compared with other antidiabetic drugs, use of incretin based therapies is associated with an increased risk of reported pancreatitis, without evidence for notoriety bias. Further pharmacoepidemiological studies are needed to confirm the potential risk of pancreatits associated with these therapies.
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Abstract Code: ISP3783-49

Photosensitivity and Antipsychotic

M. Abou Taam[1], M.P. Roux[1], T. Trenque[1]

(1) Regional Center of Pharmacovigilance and Pharmacoepidemiology, Reims University Hospitals, Reims, France

Introduction: Photosensitivity is abnormal response to sunlight or artificial light due to extreme reactivity of light-absorbing molecules in tissues. It can occur with a wide variety of drugs, including antipsychotics.
Aim: To evaluate associations between exposure to antipsychotic medications and the occurrence of photosensitivity on the French Pharmacovigilance System Database.
Methods: We used the case/non-case method in the French Pharmaco-Vigilance Database (FPVD). Cases were all the observations with the HLT term "Photosensitivity and photodermatosis conditions" registered into the FPVD from January 1985 to Jan 2013. Non-cases were all other reports. Ketoprofen was used as positive control. Data were expressed as odds ratio (OR) with their 95 % confidence intervals.
Results: The results showed that among all the reported photosensitivity reactions (n = 3953), 19 % referred to serious adverse drug reactions (n = 104) and 3.0 % (n = 117) referred to antipsychotic medications. The most frequent antipsychotic medications involved in photosensitivity are cyamemazine (n = 44), risperidone (n = 13) and haloperidol (n = 11). A statistically significant OR was only found with cyamemazine (OR 2.1 [95 % CI 10.7–30.7]). A no statistically significant OR was found with pipotiazine (OR 2.4 [95 % CI 0.9–6.5]) and penfluridol (OR 4.2 [95 % CI 0.6–30.9]). We did not find increased risk of reporting of photosensitivity reactions with the other antipsychotic medications. Taking into account the chemical structure, a statistically significant OR was only found with the aliphatic phenothiazine antipsychotic (OR 1.5 [95 % CI 1.2–2]). Aliphatic phenothiazine antipsychotic group include cyamemazine, levomepromazine and chlorpromazine.
Conclusions: Case/non-case method should be used with caution because under-reporting of the photosensitivity reaction can decrease the odds ratio. The low reporting can be also related to a good prevention of this known reaction. Anyway, physician should be aware of the risk of photosensitivity when prescribing neuroleptics to their patients.

Abstract Code: ISP3784-50

Cancer and Pregnancy: Three Years Experience in a French Regional Pharmacovigilance Center

M. Thompson-Bos[1], P. Boulot[2], G. Cambonie[3], D. Hillaire-Buys[1]

(1) Department of Pharmacologie Médicale et Toxicologie, Lapeyronie Hospital, Montpellier, France, (2) Department of Gynecology-Obstetrics, Arnaud de Villeneuve Hospital, Montpellier, France, (3) Department of Pediatrics II, Arnaud de Villeneuve Hospital, Montpellier, France

Introduction: Treatment of cancer is improving life expectancy and pregnancies can start various times after chemotherapy. Cancer could also be diagnosed during pregnancy, although this is rare. This raises several questions concerning the delay necessary between chemotherapy and the beginning of pregnancy that is safe for the embryo and how best to treat the pregnant woman whilst minimising the risk of toxicity for the embryo and the foetus?
Methods: We report 3 years of experience (2010–2012) in the French Regional Pharmacovigilance Center of Languedoc-Roussillon solicited for counselling for 19 pregnancies in 18 patients.
Results: Of the 19 cases submitted to the Centre, 16 were collected prospectively and 3 retrospectively: 3 for evaluation about chemotherapy used before pregnancy, 8 for counselling before treating during pregnancy, 5 for evaluation about chemotherapy already started during on an ongoing pregnancy and 3 calls after birth for babies monitoring. Chemotherapy was involved in 16 cases, radiotherapy in 1 and tyrosine kinase inhibitor in 2.

Treatments were administered during pregnancy in 12 cases: in 11 cases, between 18 et 33 SA and in one case radioactive iodine was delivered at 5 SA (unknown pregnancy). In 4 cases, treatment was started after abortion or after birth and in 3 cases, pregnancy started 1 at 2 years after chemotherapy).

Outcomes were known in all cases: 2 elective abortions, 4 therapeutic abortions (1 because of fetal risk : radioactive iodine for thyroide cancer with estimated uterus dose (i.e. >200 mGy) during 1st month pregnancy; 1 for maternal risk; 2 because of the need for an aggressive treatment, without specific pregnancy data and poor maternal prognosis), 14 live births (one set of twins), without any congenital anomalies (one colonic duplication but detected before chemotherapy). One baby presented transient thrombocytopenia and increase transaminase level after birth (platelets: 50,000/mm^3 on Day 3 and 5,000/mm^3 on Day 7, without any haemorrhage and recovering on Day 10; Amino Alanine Transferase 88 UI/ml on Day 3), after 6 cycles of FEC therapy (5-fluorouracil, epirubicin and cyclophosphamide), last one 5 weeks before birth).
Conclusion: Until recently, pregnant women with malignant disease have mostly been advised to stop their pregnancies. However, treatments of cancer could in fact be considered for pregnant women after first trimester, with individual counselling, close monitoring and extended follow-up.

Abstract Code: ISP3785-51

Frequency, Severity, Preventability of Drug-Related Visits to the Emergency Department: A Retrospective Cohort Study

V. Perrone[1], V. Conti[2], S. Scotto[2], A.L. Rivolta[2], M. Venegoni[2], S. Radice[1], E. Clementi[1], G. Vighi[2]

(1) Institute of Pharmacology, Sacco Hospital, Milan, Italy, (2) Pharmacovigilance Regional Centre of Lombardy, Milan, Italy

Introduction: Adverse drug reactions (ADRs) are a significant cause of access to the Emergency Department (ED) and hospital admissions with associated resource utilization.
Aim: To evaluate the frequency, severity and preventability of drug-related visits to the ED and economic consequences of ADRs.
Methods: This study is a retrospective cohort analysis conducted in 32 ED of 16 different hospitals of Lombardy Region using the MEREAFaPS (Monitoring Epidemiologic Reactions and Adverse Events of Drugs in Emergency Department) database project and Regional Hospital Discharge (SDO) database. All patients of any age and sex accessing to MEREAFaPS ED, from 1 January 2010 to 31 December 2011, with at least one suspected ADR were included in the analysis. All ADRs were evaluated by a team of experts in pharmacovigilance for severity and preventability.

Results: During the study period 2,561,400 presented to the MERE-AFaPS ED and those ADR-related were 8,983; the incidence rate of ADRs is 3.5 per 1000 ED visits. Serious ADRs were identified in 45.9 % of total sample and among these 14.9 % led to hospitalisation. Death occurred in 9.7 % of total hospitalisation. Severe ADRs occurred more frequently in patients with many concomitant conditions. The SOC class most frequently associated with ADRs were: the skin and subcutaneous tissue disorders, followed by gastrointestinal, nervous system and respiratory, thoracic and mediastinal disorders. The most commonly ATC classes involved in admissions were J (22.2 %), B (18.0 %) and N (17.3 %). The 41.7 % of ADRs were assessed as preventable and this percentage raises to 59.4 and 61.2 % respectively for hospitalised and died patients.

Conclusions: Cooperation between clinicians, clinical pharmacologists and pharmacist is likely to play a key role in preventing ADRs and decreasing ADRs-related costs. Quality improvement efforts and technological advancements aimed to preventing ADRs will require large investments in infrastructure and technology. Therefore, documentation of their effect must be provided to guide administrators, policymakers, and the public in priority setting.

Abstract Code: ISP3793-50

A Paradigm Shift for Screening Individual Case Reports: Accounting for Quality and Content

O. Caster[1], K. Juhlin[1], S. Watson[1], G.N. Norén[1]

(1) Uppsala Monitoring Centre, Uppsala, Sweden

Introduction: Disproportionality analysis is the current state of the art for first-pass screening of collections of individual case reports, as a triage for clinical assessment [1]. This purely quantitative approach naïvely disregards the quality and content of reports, which is essential for determining the relationship between reported drugs and events [2]. Accounting for the amount and quality of information on reports has previously led to much more effective adverse drug interaction surveillance [3].

Aim: To develop a screening algorithm that incorporates report quality and content; and to compare its performance to that of disproportionality analysis.

Methods: The algorithm was developed as a shrinkage regression model for the prediction of emerging safety signals. Training data consisted of reporting patterns in VigiBase on 264 drug-adverse drug reaction pairs for historical European labelling changes [4] and 5280 randomly selected negative controls. Data up until 2004 was used to correspond with the start of the European Medicines Agency's reviews. 13 potential predictors were considered. These capture qualitative aspects, such as the number of well-documented reports ('Informative reports') or the number of reports with a case narrative ('Narrative'); clinical aspects, such as the number of reports with positive de- or rechallenge, or the number of reports without co-reported drugs; and quantitative aspects, such as a disproportional reporting rate ('Disproportional reporting'), the number of contributing countries ('Geographic spread') or the number of reports from the last three years ('Recent reports'). Disproportionality analysis here goes further than what is customary today: it screens for local and global associations and identifies associations unique to e.g. geographic regions or age groups [5]. Predictive performance was measured as area under the receiver operating characteristics curve (AUC), and compared to that of the disproportionality metric IC_{025}, and screening based on raw numbers of reports.

Results: Regression selected the following predictors for inclusion in the algorithm: Informative reports, recent reports, Disproportional reporting, Narrative, and Geographic spread. It obtained a mean AUC of 0.775 in five-fold cross-validation, compared to 0.737 for IC_{025} ($p < 0.001$) and 0.706 for raw numbers of reports. With the same specificity as $IC_{025} > 0$, sensitivity increases from 0.63 to 0.69.

Conclusions: Accounting for quality and content of reports offers clear performance improvement over disproportionality analysis in identifying emerging safety signals. The range of variables and the underlying model should be further refined, but we believe that the shift from plain association analysis to the proposed algorithm represents a paradigm shift for adverse drug reaction surveillance.

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Abstract Code: ISP3794-51

Signals of Drug Abuse and Dependence: An Application of Disproportionality Measures to the French Addictovigilance System

V. Pauly[1], M. Lapeyre-Mestre[2], D. Braunstein[3], X. Thirion[1], J. Micallef[3]

(1) Aix Marseille University, EA 3279, Centre d'Evaluation et d'information sur la Pharmacodépendance, Marseille, France, (2) Centre d'Evaluation et d'information sur la Pharmacodépendance, Service de Pharmacologie Clinique, INSERM 1027, Université de Toulouse, (3) Aix Marseille Université, Centre d'Evaluation et d'information sur la Pharmacodépendance, Service de Pharmacologie Médicale et Clinique, Institut de Neurosciences Timone, Marseille, France

Introduction: Prescription drug abuse and dependence is a widespread phenomenon in many countries [1–2]. The use of disproportionality measures in a drug abuse surveillance perspective is rarely done.

Aims: To compare abuse, dependence and diversion between psychoactive medications in real-life settings.

Methods: Disproportionality analysis applied to a large database specifically constructed for the monitoring of drug abuse and dependence. French national database made up from two annually repeated surveys led on populations seen in care centers or under substitution treatment for drug dependence (the OPPIDUM and OPEMA surveys) [3]. Computation of a Proportional Reporting Ratio (PRR) based on reports concerning suspicion

of abuse/dependence, concomitant alcohol use, illegal acquisition, and diverted route of administration for each psychoactive drug listed and by distinguishing two sub-populations: subjects under an OMT and subjects not under an OMT.

Results: The psychoactive drugs with the highest PRR are, for a large majority, benzodiazepines, particularly flunitrazepam, clonazepam, diazepam, oxazepam, and lorazepam for all the indicators except the diverted route of administration. After benzodiazepines, opioids constitute the class of medicine with the highest signals, in particular morphine sulfate and codeine (only for suspicion of abuse/dependence). In its Opiate Maintenance Treatment (OMT) form, buprenorphine presents significant PRR for all the indicators in subjects not treated with OMT and the highest PRR for the diverted route of administration while methadone presents lower signals. Other psychoactive medications such as ketamine, methylphenidate, trihexyphenidyl present high PRR suggesting that surveillance should be carried on.

Conclusions: This study presents an innovative application of disproportionality measures to drug abuse monitoring based on two cross national and annual studies led in France. Its help to compare magnitude of abuse/dependence behaviours of a large number of drugs and so to prioritize action in a context where such events are usually under-reported

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Abstract Code: ISP3798-55

Adverse Drug Reactions in Children Reported to Croatian Agency for Medicinal Products and Medical Devices from 2005 to 2013

D. Kolaric[1], K. Gvozdanovic[1], V. Macolic Sarinic[1], D. Krnic[1]

(1) Agency for Medicinal Products and Medicinal Devices of Croatia (HALMED), Zagreb, Croatia

Background: Due to limited data from clinical trials in children and significantly different pharmacokinetic profile compared to adults, the data obtained by reporting of adverse drug reactions (ADRs) have been crucial for safe use of drugs in children.

Aim: To identify characteristics of reports and the ADRs reporting trends in children.

Methods: We performed a retrospective analysis of all ADRs related to children reported to HALMED from March 2005 to April 2013. Croatian national ADR database—VigiFlow (version 5.0) [1] was used as data source. Drugs and ADRs were listed according to ATC codes and MedDRA classification. ADRs were analyzed for each year individually by age, gender, ATC classification, system organ classes (SOCs), seriousness, reporter qualification, drug and vaccines ratio; and then mutually compared. Seriousness was assessed using CIOMS V and EMA's Important Medical Events criteria.

Results: Total number of reports in children was 2388 (23.1 % of all reported ADRs to HALMED), with decreasing tendency since 2008. 80.9 % of reports were related to vaccines; the peak (92.0 %; in 2009) and the lowest rate (54 %; in 2012) showing trend of increasing reports related to drugs. In 41.6 % of reports at least one ADR was considered serious and 54.1 % reports were related to men. Although infants aged 1–2 years were most affected by ADRs (33.6 %), significant increase in rate of reports was seen in older age groups. Reporters were mostly health professionals (physician 94.7 %; pharmacist 3.5 %), however the strongly increase in patients reporting was observed in 2012. The most of ADRs were belonged to SOC general disorders and administration site conditions (37.8 %), and to ATC group J (87.4 %).

Discussion: It has been problem of under-reporting of drug related ADRs in children. Croatian National ADR base by giving overview of all ADRs in children, helps to understand reporting trends which contributes to early signal detection.

Conclusion: Although it has been noticed a decline in total number of reported ADRs in children, reveals a greater diversity of reports and significant increase in their quality.

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Abstract Code: ISP3799-56

Transparency Data Regulations and Impact on Pharmacovigilance Communication

S. Tomczyk[1]

(1) Independent Pharmacovigilance Professional, Cambridge, USA

Background: After decades of deliberations, access to Regulators documents, especially safety is now in full effect, with approved and visible regulations and processes for both EMA and FDA.

Objective: To review how the transparency data regulations have/are transforming the landscape of Pharmacovigilance; and the consequences of who are requesting the data, for what purposes and how patients/HCP receive the data.

Methods: An analysis based on case studies, literature review, including EMA and FDA was performed, and feedback collected from different pharmacovigilance stakeholders.

Results: This review, of current and planned Transparency regulations (EU transparency Act and US Freedom of Information) shows the impact, from the acquisition of the data throughout its shaping, interpretation and communication, as well as the constraints resulting from so-called proprietary concepts. The specific safety data requested ranged from toxicology reports to PSUR and Risk management plans, and these requests are mainly made by the pharmaceutical industry and lawyers. The safety information described in these reports is often 'period-based' and hypotheses are discussed, proposed, compared to form a final opinion on the reality of an adverse event related or not to a medication. Sharing such preliminary information is received with divided and mixed feedback, too early for the prescribers, and divided among patients. These requests create cumbersome, delicate processes, possibly profitable for some businesses (law firms) but not necessarily informative and useful for the patient. It brings back the unsolved question of 'when is it a good time to release safety information' and how? Throughout global industry examples and PV practices, we'll show how risk-benefit analysis and evidence-based data as well as transparency among PV stakeholders ultimately benefit the patient.

Discussion/Conclusions: In the age of Renaissance, and transparency of data, it is the time to reflect on traditional good practices of PV sharing safety issues, combined with twenty-first century risk-benefits analysis to bring a healthy exchange truly benefiting the patient, and reflect on the non-medical constraints often preventing this.

Abstract Code: ISP3800-39

Adverse Events Following Yellow Fever Immunization: Reports of 109 Neurological Cases in Brazil

A.L.B. Pavao[1], R.M. Martins[1], V.R. Von Doellinger[1], P.M.N. Oliveira[1], P.R.G. Santos[1], T.G. Noronha[1], M.L.S. Maia[1]

(1) The Immunological Technology Institute Bio-Manguinhos, Oswaldo Cruz Foundation, Ministry of Health, Rio de Janeiro, Brazil

Background: Yellow fever is an acute infectious disease transmitted by arthropods vectors of the genus *Flavivirus*. The prognosis is severe and the symptomatology includes: fever, nausea, vomiting, epigastric pain, hepatitis with jaundice, renal failure, hemorrhage, shock and death in 20 to 50 % of cases. In Brazil, the disease is endemic in the North and Mid-West of the country. There is no specific treatment for yellow fever. However there are two vaccines. Both 17D and 17DD substrains represent independent passage lineages from the original 17D virus developed by Theiler. Although not prevalent, the frequency of neurological serious adverse events following vaccination with the 17DD substrain of YFV (YFV-17DD) has been increasing in the last 10 years in Brazil.

Aim: To describe and analyze the neurotropic and autoimmune adverse events, occurring after the administration of the YFV-17DD in the Brazilian population from 2007 to 2012.

Methods: This is a cross-sectional study based on YFV-17DD neurological adverse events occurring in public health units in Brazil from 2007 to 2012. These notified cases were obtained from the National Immunization Program database in January 31st of 2013 and updated until March 31st. All serious adverse events related to YFV were discussed in a specialized national scientific committee. Rates of YFV associated neurotropic and autoimmune diseases were calculated dividing the number of cases of each neurologic condition temporally associated to YFV by the number of doses distributed to the Brazilian population. National and local analyses were performed, according to age and year.

Principal Results: 109 neurological cases were found between 2007 and 2012 in Brazil. In local analysis, the highest rate of neurotropic disease occurred in the age class from 5 to 9 years (2.66 per 100,000 vaccine doses), whereas the highest rates of autoimmune disease were observed in the lowest age classes: less than 1 year (2.49 per 100,000 vaccine doses) and from 1 to 4 years (2.37 per 100,000 vaccine doses). In national analysis, the highest rates were found in the age class of 5 to 9 years (0.74 and 0.71 per 100,000 doses, for neurotropic and autoimmune diseases, respectively).

Major Conclusions: This is the largest sample of YFV temporally associated neurological adverse events analyzed in Brazil. The number of neurotropic and autoimmune disease found is still significant. However, the vaccine is considered safe as these adverse events tend to have a good prognosis.

Abstract Code: ISP3801-40

Impact on Incorporation of Pharmacobiological Chemist in Prescription of Nephrology Adult service at Civil Hospital of Guadalajara "Fray Antonio Alcalde"

M. Contreras[1], J. Salcedo[1], M. Plascencia[1], P. Navarro[1], A. Jimenez[1], A. Barba[1], M. Avelar[1], M. Gomez Lara[1], B. Becerra[1]

(1) Hospital Civil de Guadalajara, Guadalajara, Mexico

Introduction: In the drug prescription's process are observed the higher incidence of medication errors. For this reason it's a priority implement preventive measures. The incorporation of pharmacobiological chemist, in the validation of prescription makes medication errors be a quasi failures and improved patient safety by reducing the incidence of prescribing errors by medical staff.

Aim: To present the experience of three years of incorporating of pharmacobiological chemist in the medical prescription process in the nephrology department of the Civil Hospital of Guadalajara "Fray Antonio Alcalde"

Material and Methods: We performed a prospective intervention study in which medical prescriptions were validated of patients hospitalized in the Nephrology service by a pharmacobiological chemist for detecting prescribing errors during the period from 2010 to 2012. Was designed a validation format for identifying prescribing errors (Duplication of drugs, trade name instead of the active, adequacy and/or omission of dose, frequency, route of administration and infusion rate).

Results: A total of 22,375 sheets prescriptions validated during the period. In 2010 the average number of prescriptions was 519 ± 127, average prescription errors was 42.3 ± 14.95 with a percentage of error in the prescription of 8.1 ± 1.8 %. In 2011 was 701 ± 45.5, 17.25 ± 13.1, 2.4 ± 1.8 % and for 2012 was 643 ± 82.3, 6.33 ± 4.45 and 1.0 ± 0.62 % respectively, with highly significant when applying ANOVA ($p < 0.0001$), as to the types of errors in prescribing, the wrong dose 153 was the most frequent cause in 2010 and were down significantly in 2011 (15) and 2012 (0).

Conclusions: There was a statistically significant decrease in the percentage of prescription errors and errors of monthly average from the beginning to the end of intervention of pharmacobiological chemist in prescribing.

Our findings are consistent with those reported by the Institute for Safe Medication Practices that the review and validation of the prescription by the pharmacist can detect about 95 % of the errors.

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Abstract Code: ISP3803-42

Suicidal Poisoning with Drugs in Bamako, Mali

H. Hami[1], T. Diallo[2], A. Maiga[2], A. Mokhtari[1], R. Soulaymani-Bencheikh[3], A. Soulaymani[1]

(1) Laboratory of Genetics and Biometry, Faculty of Sciences, Ibn Tofail University, Kenitra, Morocco, (2) Faculty of Medicine, Pharmacy and Odonto-Stomatology, Bamako, Mali, (3) Moroccan Poison Control Center, Rabat, Morocco

Introduction: Suicide is a major hidden public health problem, causing almost half of all violent deaths and resulting in almost one million fatalities every year, as well as economic costs in the billions of dollars, says the World Health Organization (WHO).
Aim: This study was conducted to determine the profile of people who have attempted or committed suicide by voluntary ingestion of drugs in order to identify high risk groups in Bamako, Mali's capital.
Methods: A retrospective analysis of self-poisoning cases, notified between 2000 and 2010 by two University Hospitals (CHU) and six Health Reference Centers (HRC) in Bamako, was performed.
Results: During the period of study, 304 suicidal poisoning cases including 12 cases of successful suicide are diagnosed. Of these, 240 (78.9 %) are females and 75.2 % are unmarried.

Most victims are teenagers and young adults aged 15–24 years (67.2 %). For this age group, the number of suicide attempts is 19 times higher than that for successful suicides. According to recorded data, women make 3.7 times more suicide attempts than men. The most commonly used drug for self-poisoning is chloroquine (59 %). The poisoning effects vary depending on the type of drug consumed, the dose taken and the delay before treatment.
Conclusions: The real number of victims is probably underestimated because of undiagnosed and unreported cases (hidden suicide).

Abstract Code: ISP3805-44

Disease-Related Adverse Events Following Non-Live Vaccines: Analysis of the WHO Global ICSRs Database, VigiBase

G. Roberto[1], G. Zanoni[2]

(1) Department of Medical and Surgical Sciences, Pharmacology Unit, University of Bologna, Bologna, Italy, (2) Immunology Unit, Policlinico G. B. Rossi University Hospital, Verona, Italy

Background: It has been recently suggested the existence of a vaccine-specific reporting bias for which some non-live vaccines may be preferentially reported as the suspected cause of the disease or symptoms/signs related to the disease they should prevent [1].
Aim: To analyze the WHO Global Individual Case Safety Report (ICSR) database, VigiBase [2], in order to explore this newly described reporting bias in greater detail and to verify whether it can generate potentially misleading signals of disproportionate reporting (SDRs).
Methods: Vaccines reports entered into VigiBase between 1990 and 2011 were extracted. Suspected duplicates and vaccination failures were removed. Twelve non-combined non-live vaccines were chosen for the study. A selection of MedDRA preferred terms (PTs) was performed per each of the 12 infectious diseases related to the non-live vaccines tested and two distinct groups of terms were identified: "disease-specific AEFIs" and "disease/organ related conditions". Twenty-four vaccine-events pairs were obtained and referred to as "misleading combinations". The reporting rate distribution of the 24 groups of selected PTs per vaccine included in the study was observed. To verify whether the misleading combinations retrieved could generate SDRs, Reporting Odds Ratio (ROR) and 95 % confidence intervals were calculated as a measure of disproportionality considering all the other vaccine reports as the background [3].
Results: A total of 627,165 reports were analyzed. Among ICSRs containing a "misleading combination", healthcare professionals were the most frequently noted (17 %), though reporter type was unknown in 72 % of the remaining reports. The reporting rate distribution showed that for 16 out of 24 groups of terms tested the highest reporting frequency was reached in association with the vaccine representing the relevant "misleading combination" (in 10 out of 12 cases among disease-specific AEFIs and in 6 out of 12 cases among disease/organ related conditions'). The ROR application resulted in 21 SDRs out of 24 "misleading combinations" tested.
Conclusions: Findings from this study support the existence of a vaccine-specific reporting bias that may result in potentially misleading SDRs. Professionals involved in vaccine safety surveillance should also consider the influence of this bias during the validation of such disproportional associations.

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Abstract Code: ISP3806-45

Hepatic Findings Evaluated by Ecography in a Population Exposed to Paracetamol—A Preliminary Evaluation

A. Cruz[1], J. Joaquim[1], T. Pires[1], C. Matos[1], A. Andre[2]

(1) College of Health Technology of Coimbra, Research Pharmacy Group, Department of Pharmacy, Coimbra, Portugal, (2) College of Health Technology of Coimbra, Department of Radiology, Coimbra, Portugal

Introduction: Paracetamol is the main derivative of para-aminophenol in use and the most sold over-the-counter drug in Portugal however, despite being safely used by millions of individuals worldwide, as analgesic and antipyretic in the last 15 years, this drug has become a major cause of acute liver injury. Alcohol consumption is a daily practice on the part of the adult population and the concomitant use of paracetamol is frequent. For that reason it's important further analyze of the effects of this association, which will target the liver.
Aim: The study intends to evaluate the hepatic changes resulting from consumption of paracetamol and alcohol–paracetamol association through ultrasonography. It's also intended to analyze demographic characteristics, in order to assess the susceptibility to paracetamol adverse effects or liver

damage with worst recovery. Data was supported by a questionnaire to the individuals.

Material and Methods: An observational descriptive correlational study was performed in a primary health care unit, in the central region of Portugal, with all patients attending this primary care center, which consume paracetamol and paracetamol-alcohol concomitantly. Only the first consultation was accounted for each patient.

Results: It's expected to prove the synergistic effect of alcohol on the metabolism of paracetamol, demonstrating that older individuals are more susceptible to the hepatotoxic effects of this association. However, 10 days of treatment with therapeutic doses of paracetamol do not cause clinically significant hepatic injury in moderate consumers of alcohol, when evaluate some hepatic parameters with ultrasound, like echogenicity and dimensions.

Discussion: Ultrasonography is the most widely used imaging tool for hepatic evaluation due to its low cost, excellent profile and wide availability. It's used as noninvasive modality for screening general population and several studies in adults have demonstrated that this technique is highly sensitive and specific for detection of liver alterations.

Up to the present time, abdominal ultrasound accuracy data which concerns to hepatotoxicity detection in patients that consume paracetamol and alcohol are very scarce. In the present study, after paracetamol consumers evaluation some alterations in the echogenicity were observed and classified using a scale (slight, moderate and severe). In this preliminary study were found some patients with slight alterations with association to hepatomegaly.

Conclusion: Abdominal ultrasonography as a non invasive modality for screening general population to detect liver alterations show to be an interesting technique. In this study the alterations observed are very slight so association of hepatotoxicity caused by paracetamol is not conclusive.

Abstract Code: ISP3807-46

Hepatic Findings Evaluated by Ultrasound in Women's Exposed to Oral Contraceptives—A Preliminary Evaluation

S. Cunha[1], J. Joaquim[1], C. Matos[1], T. Pires[1], A. Andre[2]

(1) College of Health Technology of Coimbra, Research Pharmacy Group, Department of Pharmacy, Coimbra, Portugal, (2) College of Health Technology of Coimbra, Department of Radiology, Coimbra, Portugal

Introduction: Since early 1960s, time of first pill approval, several formulations of oral contraceptive pill have been taken by millions of women worldwide, turning it into one of the most consumed drug classes. Continuous use of combined oral contraceptives (OC) may lead to slight hepatocellular dysfunction, through a direct unfavorable effect on liver, either by triggering the disease or by increasing the effects of pre-existing hepatic problems. The most common focal benign alteration in the liver is hemangioma, that could happen predominantly in women between 30 and 50 years old and which can grow with estrogens. Although these lesions are common in young women, most of them are benign and asymptomatic, so they were rarely reported in medical literature by ultrasound evaluation.

Aim: To evaluate the potential harm to the liver of OC trough ultrasound technique.

Methods: Was performed an observational descriptive correlational study in a primary health care unit, in the central region of Portugal, with all women, attending family planning, that consumed OC at least during six years. Only the first consultation will be accounted for each patient. Ultrasound technique was used in all evaluations to find focal alterations or hepatomegaly. A questionnaire was conducted to participants to perceive the pharmacological characteristics of OC.

Results: Possible hepatic findings induced by OC were assessed through ultrasound technique due to great accuracy and specificity for assessing liver. Due to the widely use of OC, benign abdominal tumors are most frequently identified. From preliminary data analysis of 25 women that take OC at least during the last six years, only 1 have an unusual liver tissue, but is not certain yet that is caused by OC.

Discussion: It's expected that the use of oral contraceptives induce hepatotoxicity, dependent by composition, dosage, type and generation of OC and mainly due to duration of therapy. The risk of developing liver disease may be directly proportional to the length of time a woman has been taking OC.

Conclusion: Hemangiomas are asymptomatic, so is important to find, localize and determine the dimensions of the lesion in order to replace contraceptive therapy, generate signal detection concerning to adverse effects of OC and allow faster treatment to hepatic complications. Most consumers of OC would not be subject to adverse hepatobiliary effects. However, due to the high prevalence of the use of these drugs in our society, despite its rarity of these complications, it's expected that these arise.

Abstract Code: ISP3808-47

Characterization of Adverse Drug Reactions Occurred in a Surgical Ward at a University Hospital in Brazil

A.C. Malgueiro[1], K. Dal-Paz[2], P.S.K. Takahashi[2], A.B. Souza[2], N.S. Romano-Lieber[3]

(1) Faculty of Pharmaceutical Sciences, University of São Paulo, São Paulo, Brazil, (2) Pharmacy Service of the University Hospital of the University of São Paulo, São Paulo, Brazil, (3) Faculty of Public Healthy, University of São Paulo, São Paulo, Brazil

Introduction: The direct action of clinical pharmacists and healthcare professionals in the patient pharmacotherapy provides detection of signs of adverse drug reactions (ADR, in order to prevent complications in the patient clinical status [1]. Therefore, characterization of ADRs is of great value, since it is possible to focus on those patients at higher risk of developing them, preventing and decreasing their potential damage.

Objective: We aimed to characterize suspected ADR detected in the Surgical Ward of the University Hospital of the University of São Paulo, Brazil (HU-USP).

Methods: This study was undertaken in Surgical Ward in HU-USP, from January 2012 to March 2013, and suspected ADRs were evaluated from medical. ADRs were characterized by age, sex, time-window, suspected drug, severity, professional notifier, type of ADR, routes of administration and patient evolution.

Results: The study included 34 patients of Surgical Ward, 55.9 % (19) males and 44.1 % (15) females. Most patients affected by the reactions were adults (70.6 %; 24). It was observed 42 episodes of ADR, of which 25.6 % (11) were classified as type A - dose-dependent [2] and 73.7 % (31) as type B-hypersensitivity [2]. Most reactions were considered mild (67.4 %; 28), and in 76.2 % (32) of the cases the patients recovered from the ADRs. 73.8 % (31) of the cases were skin reactions, 19.0 % (8) affected the renal system, 4.8 % (2) the gastrointestinal system and 2.4 % (1) the immunological system. In all cases, the pharmacist was the notifier. We studied 63 medicines suspected of causing ADR: most of them were antimicrobials for systemic use (67 %), and analgesics (21 %). 90.5 % of

these drugs were administered intravenously. The most frequent time-window was 1–7 days (38.1 %; 24). Considering the admissions in the period (2653), the incidence of ADR was 1.29 %, more prevalent in elderly (1.55 %) and men (1.52 %).

Conclusions: The most frequent ADR were mild, dermatological, type B-hypersensitivity, especially in adult males, and with patient recovery. The main suspected drugs were administered intravenously and belong to the class of systemic antimicrobials. Knowing the profile of the most frequent ADRs of Surgical Ward will help to identify patients at higher risk to prevent damage, improve their quality of life and increase the resoluteness of the health service.

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Abstract Code: ISP3809-48

Anaphylactic Shock to cis-Atracurium with Positive Patch Test

A. Zaiem[1], G. Lakhoua[1], R. Sahnoun[1], M. Lakhal[1], R. Daghfous[1], S. El Aidli[1]

(1) Centre National de Pharmacovigilance, Tunis, Tunis, Tunisia

Introduction: Hypersensitivity reaction to anesthetic drugs can occur, especially with neuromuscular blocking agents. However, adverse reactions associated with cis-atracurium remain rare. We report an exceptional case of anaphylactic shock to cis-atracurium with positive patch test.

Case Report: A 56-year-old woman, with no medical history, was anesthetized by cis-atracurium, fentanyl and propofol for an abdominal surgery. Immediately after starting the anesthetic infusions, the patient developed anaphylactic shock with decreased blood pressure at 40 mmHg, associated with bronchospasm and muscle contracture. Anesthetic infusions were stopped and adequate symptomatic treatment (adrenaline, corticosteroid, saline solution) was administered. Six weeks later, prick-test and IDR to anesthetic drugs were performed. Tests were positive to cis-atracurium. The case was notified to the pharmacovigilance and was analyzed according to Naranjo score of imputation. The role of cis-atracurium was retained with a score of 5 (probable).

Discussion: The responsibility of cis-atracurium is mainly retained because of the suggestive chronologic score and the positive allergologic tests to the drug. Anaphylaxis, especially anaphylactic shock, remains a rare but serious complication of anesthesia. The neuromuscular blocking agents are implicated in about 60 % of them. Some differences in the relative risk of an allergic reaction as muscle relaxants have been reported. All cases of anaphylaxis to neuromuscular blocking agents published since 20 years in the international literature, relate, in descending order, the primary responsibility of suxamethonium (39.6 % reactions to neuromuscular blocking agents) followed by vecuronium (25.5 %), rocuronium (13.28 %), atracurium (12.9 %), pancuronium (6.38 %), mivacurium (2.05 %) and cis-atracurium (0.32 %). The allergologic tests (prick and IDR) are very useful to explore anaphylaxis, and to determine the responsible drug. Since histamine and tryptase levels were not performed, the reality of hypersensitivity was confirmed by cutaneous tests.

Conclusions: This case reported an exceptional adverse effect of cis-atracurium which was confirmed by patch tests.

Abstract Code: ISP3811-41

Adverse Reactions Reported with Heparins

A. Zaiem[1], G. Lakhoua[1], R. Sahnoun[1], M. Lakhal[1], R. Daghfous[1], S. El Aidli[1]

(1) Centre National de Pharmacovigilance, Tunis, Tunisia

Introduction: Heparins are prescribed for anticoagulation. We distinguish non fractioned heparins (NFH) and fractioned ones (FH). Heparins are usually well tolerated. However some adverse reactions (ADR) may occur.

Aim: To assess the cases of ADR associated with heparins and notified to the pharmacovigilance.

Methods: It was a retrospective study about all the cases of ADR associated with heparins and notified to the pharmacovigilance between January 2009 and December 2012. We only included the cases where the responsibility of heparins was clearly retained. For each case retained, we collected the sex, the age, the medical history, the delay, the evolution, the seriousness and the imputation score.

Results: We collected 6 cases composed of 3 men and 3 women. The age varied between 2 and 63 years with a median of 24.4 years. The implicated heparins were NFH in 3 cases (sodic heparin) and FH in the other cases (enoxaparin and nadroparin). The type of adverse reactions was cutaneous (2 cases), anaphylaxis (2 cases) and hematologic (thrombocytopenia in 2 cases). The delay varied from few seconds (for the anaphylactic reactions) to 14 days (hematologic reaction). The imputation score varied between I1 (doubtful) and I3 (probable) in 1 case.

Discussion: The most frequent ADR associated with NFH are hematologic effect: thrombocytopenia. In our study, thrombocytopenia was noted in 2/6 cases. Cutaneous effects and anaphylaxis are usually very rare and are exceptionally reported in literature. We reported 4 cases of eruption and anaphylaxis in our population.

Conclusion: Although the number of patients was small, our study reported some exceptional adverse reactions, in addition to the ones usually observed.

Abstract Code: ISP3812-42

Bullous Eruption Induced by dihydropyridines with Cross Reactivity

O. Charfi[1], A. Zaiem[1], G. Lakhoua[1], R. Sahnoun[1], M. Lakhal[1], R. Daghfous[1], S. El Aidli[1]

(1) Centre National de Pharmacovigilance, Tunis, Tunis, Tunisia

Introduction: The dihydropyridine are widely used for the treatment of cardiovascular diseases. The main adverse effects are flushing and ankle edema. Cutaneous reactions can occur and may be serious. Cross reactivity with dihydorpyridine was reported in exceptional papers. We report an exceptional case of bullous eruption in a women treated with dihydropyridines for hypertension, with recurrence of the same eruption when another dihydropyridine was introduced.

Case Report: A 36-year-old woman, with a medical history of hypertension has been taking acebutolol for 10 years. In April 2012, for persistent high levels of blood pressure, lercanidipine was prescribed at the dosed of 10 mg/d. For recurrent peaks of high blood pressure, she also took during this month nicardipine, intermittently. Nicardipine was only

given at the moment of peaks, probably at a rate of once a week. One month later, the patient experienced widespread erythematous papules and plaques that coalesced in areas on the trunk and limbs respecting the face and the upper chest. Some of these papules became bullous. Lercanidipine and intermittent treatment by nicardipine were stopped. A skin biopsy showed spongiotic dermatitis with small focal degeneration of keratinocytes. The lesions healed progressively one month following drug withdrawal. Three months later, the patient was prescribed nitrendipine at the dose of 20 mg/d. A few days later, the same erythematous papules reappeared at the same locations. Nitrendipine was stopped. The patient has been taking instead diltiazem, prazosin and captopril. The lesions healed and there were no further new eruption.

Discussion: The role of the dihydropyridines, lercanidipine and nicardipine, was valued as possible in the genesis of this bullous eruption because of a compatible delay (1 month after starting these two drugs) and a suggestive evolution (regression of symptomatology after stopping these drugs). The histology was in addition for a drug eruption. The recurrence of the eruption, when another dihydropyridine (nitrendipine) was introduced, is strongly suggestive of a cross reactivity between dihydropyridines. Calcium channel blockers are rarely associated with serious cutaneous reactions such as bullous eruptions. Diltiazem, a benzothiazepine different structurally from dihydropyridines, seems to be the calcium channel blocker the most implicated in these reactions. Cross reactivity with calcium channel blockers, even between benzothiazepines and dihydropyridines have been reported in some paper. The patch tests were interesting in these cases.

Conclusions: Dihydropyridine should be considered as possible causative serious cutaneous eruption. Cross reactivity with these drugs is also possible.

Abstract Code: ISP3813-43

Adverse Reactions Associated with Anti-Osteoporosis Treatments

S. El Ferjani[1], A. Zaiem[1], W. Kaabi[1], G. Lakhoua[1], R. Sahnoun[1], M. Lakhal[1], R. Daghfous[1], S. El Aidli[1]

(1) Centre National de Pharmacovigilance, Tunis, Tunis, Tunisia

Introduction: Anti-osteoporosis treatments are effective at limiting the bone loss especially in elderly. Although they are generally well tolerated, potential adverse reactions may occur. The aim of this study was to assess adverse reactions related to anti-osteoporosis treatments and notified to the Tunisian National Centre of Pharmacovigilance.

Methods: It was a retrospective study involving the reports of adverse reaction associated with anti-osteoporosis treatments reported during the last 4 years. We selected 20 cases. We collected the age, the sex, the type of adverse reaction, and the implicated drug. The cases were analyzed according to Begaud method of imputation.

Results: All the patients were women. The age varied from 49 to 77 years, with a median of 62 years. In all cases, anti-osteoporosis therapies were administrated orally. Risedronate was implicated in 9 cases, alendronate in 5 cases, strontium ranelate in 5 cases, and raloxifene in 1 case. There were 3 types of adverse reaction: cutaneous, acute phase reaction and liver injury. Cutaneous reactions (11 cases) consisted of exanthema, oedema, urticaria, erythema multiform, pruritus and mouth ulceration. Acute phase reaction (9 cases) consisted of headache, nausea and dyspepsia. Liver injuries (3 cases) were cytolysis and gamma glutamyl transferase elevation. In 3 cases, there were a combination of cutaneous and acute phase reactions.

Discussion: Our study reported 20 cases of adverse reaction exclusively in old women. The indication of the studied drugs explain these results: osteoporosis treatment is basely prescribed to this kind of population. The cutaneous reactions were the most frequent adverse effect in our study. These reactions are reported with anti-osteoporotic, including bisphosphonates and strontium ranelate. The maculopapular rash, pruritus and urticaria reported in our series, are widely described in the literature. Although serious skin reactions are also described with bisphosphonates and strontium (such as bullous reactions or DRESS syndrome), we have not observed among our patients such reactions. Acute phase reaction, which is usually reported in the literature after IV biphosphonate therapy and less common with oral biphosphonate, was reported in 9 cases in our study. These events are usually mild and reversible. Liver injury is not common with bisphosphonates. However, biological disturbances are described and are generally reversible.

Conclusions: Our study reported 20 spontaneous notifications of adverse reactions related to anti-osteoporosis therapy with a predominance of cutaneous side effects.

Abstract Code: ISP3814-44

Factors Influencing the Disproportional Association Between Triptans and Cerebrovascular Events Within the FDA_AERS Database: Causal Association or Reporting Bias?

G. Roberto[1], C. Piccinni[1], E. Poluzzi[1]

(1) Department of Medical and Surgical Sciences, Pharmacology Unit, University of Bologna, Bologna, Italy

Introduction: Triptans are specific antimigraine drugs. Due to the constriction of the cerebral vessels evoked by triptan intake, in rare cases, these drugs have been associated with cerebrovascular events. Although no epidemiological study suggests an increased risk of stroke [1], our previous analysis of the FDA_Adverse Event Reporting System (FDA_AERS) database found different cerebrovascular events disproportionally reported in association with triptan use.

Aim: To identify factors influencing the disproportional association between triptan and cerebrovascular events within the FDA_AERS database.

Methods: A case/non-case analysis was performed [2] on adverse events reported to the FDA_AERS between 2004 and 2010. *Cases* were reports with at least one event assigned to the MedDRA High Level Terms (HLTs) "Cerebrovascular and spinal necrosis and vascular insufficiency" or "Cerebrovascular aneurisms and dissection", whereas *non-cases* were all the remaining reports. Reporting Odds Ratio (ROR) and 95 % confidence intervals (95 % CI) were calculated. A stratified analysis was performed considering potentially confounding/modifying factors: age (<17, 18–44, 45–64, >64), gender, co-reported estrogens/contraceptives (ATC G03AA, G03AB, G03C, G03F) or cardiovascular drugs (ATC C), and "migraine" (indication of use field).

Results: On a total of 2,131,688 reports, 7808 concerned triptans. Crude ROR for the combination "triptans-cerebrovascular events" (N = 110) was 1.39 (95 % CI 1.15–1.68). Stratification highlighted "age 18–44" (N = 53, ROR = 4.45; 3.38–5.87) and "estrogens/contraceptive use" (N = 12, 2.99; 1.67–5.34) as major modifier factors. In the sensitivity analysis, "estrogens/contraceptive use" also generated a considerable increase of the ROR (N = 12, 3.00; 1.68–5.35) within the "female" stratum. The subset "age 18–44" was further stratified using all the parameters previously considered: ROR values obtained ranged from 2.09 (1.24–3.54) to 5.75 (3.14–10.55).

Conclusion: This study highlighted patient's age between 18 and 44 years and concomitant use of estrogens/contraceptives as major modifier factors

of the disproportional association between triptan and cerebrovascular events within the FDA_AERS database. Current knowledge on stroke occurrence suggest a particularly increased risk in migraineurs aged <45 years and in women treated with oral contraceptives [3]. Results obtained here identify specific subpopulations to be investigated through large scale analytical studies.

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Abstract Code: ISP3815-45

Pharmacovigilance of Anti CD 20 Monoclonal Antibody Biosimilar at the Edgardo Rebagliati Martins Hospital-Peru

L. Aliaga[1], I. Fernandez[1], M. Sanchez[1], H. Saavedra[1], C. Espinoza[1]

(1) Hospital De la Seguridad Social Lima, Lima, Peru

Objective: Detect, classify, and assess causality and factors associated with the onset drug reactions during the administration of anti-CD20 monoclonal antibody in patients biosimilar services Oncology, Hematology, Rheumatology and Dermatology in the Hospital of social security in Peru the months August to November 2012.

Material and Method: Prospective study in patients >18 years of services of Oncology, Hematology, Rheumatology and Dermatology in the Hospital of the Social Security Peru, who received the monoclonal antibody anti-CD20 biosimilar (Dr Reddy's Laboratories) as part of their treatment regimen.

Personalized tracking was developed, information was obtained from the patients through direct interviews and detected the presence of adverse drug reactions (ADRs) during the time of infusion of anti-CD20 monoclonal antibody biosimilar.

Classification by organ system and intensity of ADRs was performed according to Common Terminology Criteria for Adverse Events. Vesion 4.0 (CTAE) and for the assessment of causality was employed algorithm Karch and Lasagna causality modified by Naranjo. The indications used in Oncology and Hematology services were not Hodgkin Lymphoma and Chronic Lymphocytic Leukemia. In Rheumatology and Dermatology were: rheumatoid arthritis, scleroderma and dermatomyositis.

Results: During the study period were monitored in 133 patients treated with anti-CD20 monoclonal antibody biosimilar, which were grouped according to the characteristics of administration and dosage of the drug in two groups: services of Hematology–Oncology (62 %) and Rheumatology–Dermatology (38 %).

Nineteen patients (14.3 % of total) had 30 RAMs during infusion of anti-CD20 monoclonal antibody biosimilar, the most frequent: chills (20.0 %), headache (16.7 %), fever (13 %) and urticaria (10 %).

Also causation of ADRs was: Possible, 66.7 %, probable, and proven 13.3, 20.0 %. The intensity of ADRs were mostly mild (90.0 %), followed by moderate (6.7 %) and severe (3.3 %), there were no deaths in this study.

Additionally, according to the distribution of adverse events according to the classification of organ systems, 73 % of adverse reactions are related to drug administration and which 53 % of patients who present Rams was continuation and 47 % initiator. There were no deaths

Conclusions: The anti-CD20 monoclonal antibody biosimilar proves to be a safe drug (19/133 patients had RAMS, of which 90 % are mild and symptomatic management.) From the RAMs observed, 73 % of them probably occurred to inadequate speed infusion during drug administration.

Abstract Code: ISP3816-46

Metabolic Enzyme CYP2C9 as Predictability Factor of Adverse Drug Reactions (ADRs) of Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

V. Macolic Sarinic[1], N. Bozina[2], N. Mirosevic Skvrce[1], D. Krnic[1], S. Arapovic[1], M. Banovac[1]

(1) Agency for Medicinal Products and Medical Devices (HALMED), Zagreb, Croatia, (2) University Hospital Centre Zagreb, Croatia

Introduction: Polymorphic metabolic enzymes can significantly modulate the pharmacokinetic parameters of drugs and therefore be a reason for the appearance of type A ADRs. The metabolic enzyme CYP2C9 metabolizes some NSAIDs, as for example Aspirin, Diclofenac, Ibuprofen, Naproxen and Indomethacin. The contribution of this enzyme in the total clearance of these drugs is variable, and the results about the relationship between the polymorphism of CYP2C9 and ADRs are not explicit [1].

Aim: To identify the role of polymorphism CYP2C9 in the appearance of ADRs of NSAIDs.

Methods: Based on the collection on ADRs of NSAIDs which are substrates od CYP2C9 from the Croatian National ADR database in the period from 2005 to 2011, 32 subjects with serious ADRs to NSAIDs were selected, who were matched with 40 controls who took the same drugs but didn't develop ADRs to NSAIDs. The genotyping of CYP2C9*2 (rs1799853) and CYP2C9*3 (rs1057910) was performed by the PCR method in real time. Descriptive statistics using IBM SPSS 17.0 were undertaken.

Results: The ratio between serious ADRs in the National database which are reported for NSAIDs and all other drugs is statistically higher for NSAIDs (38.5 % vs. 43.5 %; $p < 0.006$).

Table 1 Frequency of ADRs of NSAIDs in regard to CYP2C9 genotypes

n (%)	Subjects who developed ADRs		Controls		P	Output	OR	95 % CI
Genotype								
wt/wt	5	(15.6)	29	(72.5)	<0.001	0.57	0.07	(0.02–0.23)
wt/mt	25	(78.1)	9	(22.5)	<0.001	0.55	12.30	(4.02–37.68)
mt/mt	2	(6.3)	2	(5.0)	>0.999		1.27	(0.17–9.53)
Total	32	(100.0)	40	(100.0)				

P Fisher's exact test, *OR* odds ratio, *wt* wild, *mt* mutate

Conclusions: The patients receiving NSAIDs and who developed one of the serious ADRs, in comparison to patients without adverse reactions, were more often carriers of mutated alleles that determine reduced enzyme function. As a result of this study the polymorphism of the metabolic enzymes CYP2C9*2 and *3 could be considered a pharmacogenetic predisposition for the appearance of serious adverse reactions. This study shows that these ADRs could be

predicted with the genotyping of CYP2C9 prior to taking NSAIDs, but further research should be undertaken in this direction due the limited number of patients in this study.

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Abstract Code: ISP3817-47

Inadequate Prescription of Medicines Leading to Adverse Drug Reactions in Hospitalized Patients

C. Bucsa[1], A. Farcas[1], C. Mogosan[1]

(1) University of Medicine and Pharmacy « Iuliu Hatieganu », Cluj-Napoca, Romania

Background: Adverse drug reactions (ADRs) are frequently leading to serious outcomes for the patient and for the healthcare system. An important step in preventing the ADRs is identifying the factors leading to their occurrence. As the medicines get closer to the patient in the therapeutic process, the chances of preventing the ADRs are smaller. Since drug prescription is the primary phase of the therapeutic process, an intervention at this stage would probably prevent a large number of ADRs.
Objective: The objective of our study was to determine the incidence of inadequate prescriptions as a factor leading to ADRs in hospitalized patients.
Methods: ADRs identified in two internal medicine departments during 27 consecutive months were registered into Drug Information Research Center's database and analyzed in order to detect the factors leading to their occurrence. An ADR was considered as caused by inadequate prescribing if it was the consequence of drug–drug interactions (DDIs), inappropriate drug recommendation or dosing (according to the Summary of Product Characteristics or to Thomson Micromedex [1]), if the patient had a previous allergy or similar ADRs to a given medicine, and if an inadequate medicine for patient's condition (according to Beers criteria) [2] was prescribed. Descriptive statistic was performed.
Results: A total number of 251 ADRs, identified in 201 patients, were stored in the database and analyzed. In 93 ADR cases (37 % of the total number of ADRs) the inadequate prescriptions were contributing/causing the ADR. The majority of ADRs resulted from inadequate prescriptions (83.87 %) were serious (according to WHO definition).

Factors leading to ADRs	Number (%) of ADRs	Number of serious ADRs
Drug–drug interactions	56 (22.2)	47
Inadequate doses	19 (7.5)	18
Inappropriate drug recommendation	10 (3.8)	9
History of allergy	4 (2)	1
History of similar ADR	3 (1.2)	2
Inadequate drug for patient's condition	1 (0.4)	1

Conclusion: An important percentage of ADRs resulted from inadequate prescription of drugs, most of them being serious. DDIs were the factor most frequently leading to ADRs.

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Abstract Code: ISP3818-48

Ethanol–Drug Interactions: Data from the WHO-UMC Database

M. Petronijevic[1], B. Radojevic[2], K. Ilic[2]

(1) Medicines and Medical Devices Agency of Serbia, Belgrade, Republic of Serbia, (2) Faculty of Pharmacy, Department of Pharmacology, Belgrade, Republic of Serbia

Introduction: Both behind the counter and over the counter (OTC), as well as herbal medicines, can interact with alcohol. While the most ethanol-induced adverse reactions remain unnoticed, more serious ethanol-drug interactions cause hospital admission in about 25 % of cases [1]. Spontaneous reporting of adverse drug reactions (ADRs) is of great importance for the identification of unexpected drug interactions.
Aim: To characterize the reporting of adverse drug reactions associated with ethanol consumption (Et-ADRs).
Methods: The WHO global database (VigiBase) of individual case safety reports was screened for the reports of ethanol suspected for contributing to the onset of the ADRs submitted from January 2003 to December 2012. Search criteria included ethanol as a suspect agent and specified time period. Et-ADRs reports were characterized for the type of ADR, suspected drug, the patient's gender and age, and reporting country. The ADRs were coded with MedDRA terminology. Drugs were classified according to the ATC system. SPSS 16 software (Chicago, IL, USA) was used for statistical analysis.
Results: As of May 2013, VigiBase contained over 8 million ICSRs. There were in total 8,823 reports with 31,100 ADRs associated with use of alcohol submitted from 38 countries. The largest percentage of reports was submitted by the USA (71.7 %), Germany (14.3 %), and Canada (5.5 %). Male gender was overrepresented (4,299 (48.7 %) males vs. 3,680 (41.7 %) females; $p < 0.001$). The mean age of the patients was 40.2 ± 14.0 years. Nearly 900 different drugs or their combinations were suspected in identified cases of Et-ADRs. The highest reporting frequency was observed for oxycodone (1371; 15.5 %), paracetamol (1096; 12.4 %), alprazolam (766; 8.7 %), paracetamol/hydrocodone (650; 7.4 %), diazepam (575; 6.5 %), cocaine (559; 6.3 %), and lorazepam (539; 6.1 %). Out of 1,936 different preferred terms of ADRs, the most commonly reported were: completed suicide (1,890; 21.4 %), intentional overdose (1335; 15.1 %), toxicity to various agents (1079; 12.2 %), overdose (1012; 11.5 %), suicide attempt (970; 11.0 %), cardiac (720; 8.2 %) and respiratory arrest (653; 7.4 %), death (648; 7.3 %), and somnolence (606; 6.9 %). Fatal outcome was reported in 2,452 (27.8 %) individuals, 1,183 (27.5 %) males and 1,018 (27.7 %) females.
Conclusions: Numerous medicines were reported for causing ADRs in association with use of ethanol, while the most frequent were drugs affecting the central nervous system. Wide range of ADRs with significant

proportion of fatal outcome was reported in patients consuming drugs and alcohol.

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Abstract Code: ISP3819-49

Adverse Drug Reaction Reporting of Medicines Under Special Monitoring

C. Santucci[1], R. Papale[1], I. Bignone[1]

(1) Administración Nacional de Alimentos, Medicamentos y Tecnología Médica (ANMAT), Buenos Aires, Argentina

Introduction: Thalidomide and lenalidomide are under special monitoring programs for the prevention of pregnancy to avoid the adverse drug reaction (ADR) of teratogenicity. Currently, there are two drug products for each of these active substances in Argentina. The Intensive Pharmacovigilance Program (IPP) of thalidomide was implemented in 1996 to improve safety measures in its marketing for its uses in discoid lupus erythematosus, relapsing bipolar ulcers, Behcet′s syndrome, among others. lenalidomide is under a Risk Management Plan (RMP) since it was launched in 2009. Although the marketing authorisation holders (MAH) meet the requirement of sending to the ANMAT Pharmacovigilance Department (PD) periodic reports of patients records under treatment with Thalidomide and lenalidomide, the PD only received ADR reports for lenalidomide a but none associated with thalidomide

Aim: To compare the results of the execution of special monitoring programs of thalidomide and lenalidomide.

Methods: PD′s database completed with the MAH′s registry of all patients consuming thalidomide and lenalidomide. PD′s data base with the reported ADRs.

Results: In 2012 there were a total of 2298 patients in the IPP of thalidomide: 1174 men, 954 women without childbearing potential and 170 women of childbearing age. The main indications were multiple myeloma (1414, 61.5 %), ulcers (337, 14.7 %), myelofibrosis (101, 4.4 %), oncological (86, 3.7 %), prurigo (77, 3.4 %), lupus (64, 2.8 %), and dermatological diseases (47, 2 %). The PD did not receive any ADR report of thalidomide. In the same year patients receiving lenalidomide under the RMP were 741: 386 men, 343 women without childbearing potential and 12 women with childbearing potential. The indications for lenalidomide were distributed among multiple myeloma (684, 92.3 %), myelodysplastic syndrome (37, 5.0 %), myelofibrosis (10, 1.3 %) and others. 11 ADR reports related to lenalidomide were sent to the PD: acute myeloid leukemia type 5M (possible, serious); tremor, dizziness, bone pain and abdominal pain (possible, non serious); Peyronie's disease and fibrosis in leg (possible, non serious); Peyronie's Disease (not related, non serious); cutaneous hyperpigmentation (conditional, non serious); facial angioedema and dysphonia (conditional, non serious); death (5) (dismissed, not applicable).

Conclusions: There is more interest in ADR reporting of lenalidomide compared with thalidomide. While the main objective of avoiding teratogenicity is reached with the IPP of thalidomide there is under-reporting, perhaps because it is a drug with many years in the market. The PGR of a new drug, such as lenalidomide, promotes ADR reporting allowing to increase knowledge about the safety profile of the medicine.

Abstract Code: ISP3820-41

Anaphylactic Reactions Associated with Diphtheria, Tetanus, Pertussis and Poliomyelitis Combined Vaccine

A. Zaiem[1], G. Lakhoua[1], R. Sahnoun[1], S. Kastalli[1], M. Lakhal[1], R. Daghfous[1], S. El Aidli[1]

(1) Centre National de Pharmacovigilance, Tunis, Tunis, Tunisia

Introduction: Diphtheria, tetanus, pertussis and poliomyelitis can be prevented with an effective combination vaccine DTPP. The Tunisian immunization program provides free DTPP vaccine to children since the age of two months. DTPP is usually a safe vaccine. Some adverse effects can occur and consist usually of local reaction at the injection site or mild general manifestations such as fever. Anaphylactic reaction are rarely reported.

Aim: To assess the cases of anaphylactic reactions associated with DTPP vaccine and notified to the pharmacovigilance.

Methods: It was a retrospective study about all the cases of anaphylactic reactions associated with DTPP and notified to the pharmacovigilance between January 2004 and December 2012. We considered as anaphylactic reaction the following events: generalized urticaria, Quincke edema, anaphylactic shock and bronchospasm. We only included the cases where the responsibility of DTPP was clearly retained. For each case retained, we collected the sex, the age, the delay, the evolution, and the imputation score.

Results: We collected 10 cases composed of 5 males and 5 females. The age varied between 2 months and 43 years with a median of 78 months. There were 6 cases of urticaria, 3 cases of anaphylactic shock and 1 case of Quincke edema. The delay varied from few seconds (immediately after the injection) to 6 h. The issue was favorable in all the case except in one case of anaphylactic shock: the patient rapidly died because of cardio-respiratory arrest. The imputation score varied between I1 (doubtful) and I2 (probable).

Conclusions: Our study reported very exceptional adverse effects of DTPP, especially the anaphylactic shock. Fatalities due to such events were never reported. In one case of our series, the issue was fatal.

Abstract Code: ISP3821-42

Hypotonic-Hyporesponsive Episode Following Immunization

A. Zaiem[1], R. Sahnoun[1], G. Lakhoua[1], S. Srairi[1], M. Lakhal[1], R. Daghfous[1], S. El Aidli[1]

(1) Centre National de Pharmacovigilance, Tunis, Tunis, Tunisia

Introduction: Hypotonic-hyporesponsive episode (HHE), an adverse event following immunization (AEFI), is characterized by sudden onset of reduced muscle tone, hyporesponsiveness and change of skin colour. It has been referred to by various terms including "shock" and "collapse reaction". It has been reported with various vaccines.

Aim: To assess the cases of HHE following vaccination and notified to the pharmacovigilance.

Methods: It was a retrospective study about all the cases of HHE following vaccination and notified to the pharmacovigilance between January 2004 and December 2012. We considered as HHE the association of the

following signs: pallor or cyanosis, hypotonia and hyporesponsiveness. For each case retained, we collected the sex, the age, the delay, the issue and the implicated vaccine.

Results: We collected 9 cases composed of 3 males and 6 females. The age varied between 2 and 36 months with a median of 4 months. The delay varied from one minute (after the injection) to 3 days. The issue was favorable in all the case. The implicated vaccine was in all the cases the combined vaccine of diphtheria, tetanus, pertussis and poliomyelitis (DTPP).

Conclusions: HHE has been documented to occur after immunization with diphtheria, tetanus, *Haemophilus influenzae* type b, and hepatitis B vaccines. In our study all the cases of HHE were associated with DTPP vaccine. The delays found were consistent with literature data. The issue, generally favorable and uncomplicated, was observed in all the cases of our series.

Abstract Code: ISP3823-44

Drug-Induced Stevens Johnson Syndrom (SJS) and Toxic Epidermal Necrolysis (TEN) in DRC Between 2010 and April 2013

B. Mvete[1], P. Ntamabyaliro[1], Y. Lula[1], D. Nzolo[1], F. Makila[1], G. Mesia[1], G. Tona[1]

(1) 1 University of Kinshasa, Clinical Pharmacology and Pharmacovigilance Unit, DR Congo;

Background: Stevens–Johnson Syndrome and Toxical Epidermal Necrolysis are rare, but are the most severe drug-induced skin reactions. They affect people of all ages, all races and of both sexes [1]. The risk of developing SJS or TEN is increased in HIV-infected patients. Drugs are responsible for at least 70 % of cases. Anticonvulsivants (carbamazepine, phenobarbital), antibiotics (sulfonamide derivatives, beta-lactam), Non-steroidal anti-inflammatory drugs, Antiretroviral (Nevirapine) are accounted among most involved drugs [2].

Objectives: The aim of this present study is to determine drugs involved in SJS and TEN cases reported to the DR Congo National Pharmacovigilance (PV) Centre and outcome in patients

Methods: All individual case safety reports (ICSRs) reporting SJS or TEN recorded in the DR Congo PV database from January 2010 to April 2013 were extracted as excel files and analyzed. The age group of the patient is calculated according to the definition of vigiflow.

Results: Out of the 2243 ICSRs in our database, 18 (0.8 %) reported either SJS or TEN. Antibiotics were incriminated in 8 cases, ARVs in 4 and, in 2 case both could be incriminated and Analgesics for 2 case whereas Barbituric, ant antimalarials were incriminated respectively 1 case each.

Individually, cotrimoxazole: an association of sulfamethoxazole and trimethoprim was involved in the highest number of case 7 (38.9 %) followed by nevirapine 6 (33.3 %) and ciprofloxacin 2 (11.1 %).

Table 1 Proportion of death related to the reactions

ADR	Number of cases	Number of deaths	% death
SJS	4	2	50
TEN	14	4	29
TOTAL	18	6	33

Of the eighteen patients, 11 (61.1 %) were female, 7 (38.9 %) male. The relevant age group is divided as follows: 3 (16.7 %) infant; 1(5.5 %) adolescent and 14 (77.7 %) adults. Eight of the 18 cases were HIV positive patients.

Conclusion: SJS and TEN; severe skin reaction constitute 0.8 % of reported ICSRs in DR Congo. Women seem to be more affected than men. Antibiotic and antiretroviral, namely cotrimoxazole and nevirapine are the most commonly incriminated drugs. The reactions are fatal in about one third of the cases. Measures to reduce or avoid these deaths rate need to be put in place.

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Abstract Code: ISP3824-45

Adverse Reactions Associated with Insulins

A. Zaiem[1], R. Sahnoun[1], G. Lakhoua[1], I. Hamza[1], M. Lakhal[1], R. Daghfous[1], S. El Aidli[1]

(1) Centre National de Pharmacovigilance, Tunis, Tunis, Tunisia

Introduction: Various therapies are available for diabetes. The insulin remains the essential treatment in many situations. Its adverse effects are rare, but when they occur, reactions can be severe and can pose a significant risk to diabetes management.

Aim: To assess the cases of adverse reactions associated with insulins and notified to the pharmacovigilance.

Methods: It was a retrospective study about all the cases of adverse reactions associated with insulin and notified to the pharmacovigilance between January 2009 and December 2012. We only included the cases where the responsibility of insulin was clearly retained. For each case retained, we collected the sex, the age, the delay, the evolution, the type of adverse event, the type of insulin and the imputation score.

Results: We collected 24 cases composed of 6 males and 18 females. The age varied between 7 and 80 years with a median of 52. The adverse event were cutaneous in 14 cases, local reaction at the site of injection in 5 cases, anaphylactic reaction in 4 cases and systemic reaction in one case. The delay varied from few seconds (immediately after the injection) to more than 5 years. The issue was favorable in all the cases. The human insulin was implicated in 21 cases and the analogues in 3 cases.

Conclusions: In our series, the adverse effects associated with insulin were mostly skin reaction in 14/24 cases. In the literature, the most common side effects are generally metabolic order: essentially hypoglycemia, electrolyte disturbances and edema. Cutaneous reactions are generally less frequent. Local reactions at the injection sites are often related to the injection technique. A regular variation of injection sites and subcutaneous strict often prevent such adverse effects. The anaphylactic reactions are the most serious events in general, and may be life-threatening.

Abstract Code: ISP3825-46

Impact of Education and Continuous Professional Development in Portuguese Pharmacy Technicians Attitude's to Adverse Drug Reaction Reporting System

J.J. Joaquim[1], T. Pires[1], C. Matos[1]

(1) College of Health Technology of Coimbra, Research Pharmacy Group, Department of Pharmacy, Coimbra, Portugal

Introduction: The phenomenon of the adverse drug reaction underreporting is a field that induced several studies to understand it and it is known the important role played by healthcare professionals in the reporting adverse drug reactions to decrease the underreporting. In Portugal the report of adverse drug reactions traditionally shown to be below of the report average in Europe. Different studies have indentified obstacles to the report of Adverse Drug Reactions and the statistics of ADR report in Portugal show that Pharmacy Technicians (PhT) are away from the National Pharmacovigilance System (NPS).
Aim: To identify the impact of the initial education and the continuous professional development (CPD) in the attitudes and knowledge of pharmacy technicians in the adverse drug reactions (ADR) reporting system in the professional context.
Methods: A descriptive-correlational study is been performed, trough a web-based questionnaire in the Pharmacy Technician's population that works the community, hospital pharmacies or in the OTC-drug stores. The questionnaire was developed and used in a previous study and adapted for this purpose.
Results: They exist about 3000 PhT in Portugal and 478 professionals constituted our sample. This study updates the results of the involvement of PhT in the ADR spontaneous reporting regarding a study conducted in 2009. It is expected that the results show an evolution in the involvement of PhT's with pharmacovigilance observing several aspects like the place and years of professional exercise, initial education and CPD. It is expected that a strong relation between initial education and knowledge of the National System should be confirmed and younger professionals have a better knowledge of the NPS.
Discussion: Portuguese National Pharmacovigilance System was founded in 1992 and after 21 years still have a spontaneous reporting (SR) ratio below of EU average and the goal of WHO. Pharmacy Technician's are qualified professionals with a 4 academic years graduation in pharmacy and should play an active role in the ADR identification and spontaneous reporting. Even if younger pharmacy technicians had a better knowledge of the system they are not linked with an active attitude to the spontaneous report.
Conclusion: Due to the proximity with the patients, PhT's can play a valuable role in the strengthening of the reporting system. It will be important in the future to increase CPD in Pharmacovigilance area and strongly introduce this topic in the initial education and found new and innovative strategies to bring PhT's to the system.

Abstract Code: ISP3826-47

Use of Antihistamines and Risk of Ventricular Arrhythmia: A Nested Case–Control Multi-Database Study in 5 European Countries

E. Poluzzi[1], A. Koci[1], A. Oteri[2], S. Pecchioli[3], I. Bezemer[4], T. Schink[5], T. Froslev[6], M. De Ridder[7], M. Sturkenboom[7], G. Trifirò[7]

(1) Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy, (2) Department of Medical Informatics, Erasmus University Medical Center, Rotterdam, The Netherlands, (3) Health Search, Italian College of General Practitioners, Florence, Italy, (4) PHARMO Institute for Drug Outcomes Research, Utrecht, The Netherlands, (5) Leibniz Institute for Epidemiology and Prevention Research, BIPS, Germany, (6) Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark, (7) Department of Medical Informatics, Erasmus University Medical Center, Rotterdam, The Netherlands

Background: There is appreciable utilisation of systemic antihistamines (AHs) among a number of European countries, principally for the treatment of allergies. They are either prescribed by physicians or directly purchased by patients as self-medications. Arrhythmia caused the withdrawal/restriction of use of some AHs in 90s. No well-defined differences have been identified among single agents so far.
Objective: To estimate the exposure over a 15-year period (1996–2010) in 5 European Countries and evaluate the risk of ventricular arrhythmia associated with AHs.
Methods: Data were retrieved from 7 different healthcare databases; AARHUS [Denmark], GEPARD [Germany], HSD and ERD [Italy], PHARMO and IPCI [Netherlands], and THIN [UK], covering a total population of 27 million individuals. Cases of VA were selected through harmonized DB-specific coding-algorithms including validated diagnostic codes or free-text search. Up to 100 controls were matched to each case by index-date, sex, age and database. Current exposure to AHs was defined when prescription of drugs was within 30 days before the VA event. Only those agents with at least 5 exposed cases were included in the analysis. The odds ratio (OR) of current use for individual AHs relative to no-use was estimated using conditional logistic regression, adjusting for confounders.
Results: Overall, 5,228 cases and 521,596 matched controls were identified. Out of all cases, 759 were currently exposed to antihistamines. Dimetindene (OR_{Adj} 3.08 [1.31–7.27]), promethazine (OR_{Adj} 1.46 [1.16–1.83]) and cyclizine, (OR_{Adj} 5.28 [4.12–6.77]) were associated with a statistically significantly increased risk of VA ($p < 0.05$) in the pooled analysis. No statistically significant associations in AARHUS, ERD, HSD and IPCI were observed, when DB-specific analyses were conducted, except for dimetindene and ebastine in GEPARD, dexchlorpheniramine and promethazine in PHARMO and cyclizine in THIN.
Conclusion: Current use of dimentidene, promethazine, cyclizine ebastine and dexchlorpheniramine was associated with an increase in the risk of

VA. Because of the frequent use of AHs as self-medication, the risk assessment using electronic health care records is very difficult and only an integration of different sources of data (general practice and claim databases) allowed us to do assess the risk of this rare adverse event in the ARITMO project.

Abstract Code: ISP3827-48

Prospective Longitudinal Descriptive Study to Evaluate the Impact of Involves Physician on Training Pharmacovigilance Activities in the Report of AE

C. Galicia-Quintanar[1,2], J.G. Reyes-Garcia[3], C. Fernández del Valle-Laisequilla[1,3]

(1) Productos Medix S.A. de C.V, Mexico City, Mexico, (2) Universidad Nacional Autónoma de México, Mexico City, Mexico, (3) IPN, Escuela Superior de Medicina, Mexico City, Mexico

In Mexico, the pharmacovigilance activities began in 1995. However these activities were mandatory until 2005.

According to the current law, health's institutions and professionals, holders and distributors of medical products, are obligated to report adverse events of which they are aware [1–5].

Unfortunately, the pharmacovigilance norm was published without any previous training or diffusion.

Nowadays, Mexico is facing the underreporting by health professionals especially physicians; this situation, due to the lack of time, unknowing about pharmacovigilance or the fear of a legal sanction. The underreporting may delay signal detection and cause underestimation of the size of a problem. However, in signal detection not only the quantity but also the relevance of case reports and the quality of data are important.

That's why medix® for safety decision-making purposes invited some physicians to participate in pharmacovigilance activities, through training courses on pharmacovigilance which were included:

- What is an adverse event?
- Classifications of adverse events
- Quality information
- How to fill the form adverse events reports?
- Causality assessment

The objective of this training was to increase both the quantity and quality of adverse events reports received during 2012 and compare it to the reports received during 2011.

After the training, were received 607 reports in 2012 vs just 54 reports in 2011, this represents an increase more than 11 times the number of reports received in the laboratory in a year.

All the reports originating by physicians received in the pharmacovigilance unit were classified as quality data more than 2, which give us greater certainty for the data analysis and allows us to establish a risk management plan adequately for our country.

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Abstract Code: ISP3828-49

Economic Impact of Adverse Drug Reactions Leading to Hospital Admission—A Systematic Review

H. Costa[1], J.J. Joaquim[1], T. Pires[1], C. Matos[1]

(1) College of Health Technology of Coimbra, Research Pharmacy Group, Department of Pharmacy, Coimbra, Portugal

Introduction: One of the main drug-related problems are the Adverse Drug Reactions (ADR's) which are often associated to causes of morbidity and mortality and represent a substantial burden on healthcare resources. There are some studies that show obstacles to reporting of Adverse Drug Reactions in hospitals and this is a weakness for the patient's safety that must be improved. Beyond this clinical cost there is a considerable economic impact, that should be minimized.

Objective: To review published papers of Adverse Drug Reactions (ADR's) leading to hospitalization in Emergency Departments (ED) analysing their costs associated.

Methods: Was performed a keyword search on *PubMed* online database for published papers between January 2000 and April 2012. Record data were collected from selected articles and included: Study design, number of patients included and their demographic characteristics, ADR assessment, duration of admissions and estimated costs of ADR-induced hospitalizations. Were only included prospective observational studies available with *abstract* and *full text*. All monetary costs were adjusted and expressed in Euros.

Results: A total of 97 articles were found. Ten prospective observational studies were selected for full text review. The mean of overall ADR incidence found on patients presented to ED was 7.6 % ± 9.3 %. 4.5 % of all admitted patients were hospitalized due to an ADR. The majority of studies indicate that the elderly population is the most affected. Most studies (8 in 10) performed their cost analysis based on associated direct costs, while the other two included all direct and indirect costs.

Discussion: ADR's can have a significantly impact on hospital's budget and, consequently, can lead to important charges to healthcare systems. We estimated that ADR-induced hospitalizations can lead to high expenditures for hospitals up to 4844 € per case. The potential savings for a year can reach up to 706M Euros. Furthermore, associated costs incurred by patients can reach up to 1099 € per severe ADR case.

Conclusion: This review suggests that ADR's are an important cause of hospitalization among patients presented to ED, which incurs several charges on hospital's budget. Measures should be developed to minimize the economic impact of ADR's in healthcare systems.

Abstract Code: ISP3829-50

An Educational Program in Pharmacovigilance for Eastern Europe Countries Developed Within an AUF Project

C. Mogosan[1], O. Vostinaru[1], S. Ghibu[1], C. Pop[1]

(1) Department of Pharmacology, Physiology and Physiopathology, Drug Information Center, University of Medicine and Pharmacy Iuliu Hatieganu, Cluj-Napoca, Romania

«Développement et mise en œuvre d'un programme éducationnel de pharmacovigilance dans la pratique clinique dans les pays francophones de l'Europe de l'Est» ("Development and implementation of an educational pharmacovigilance program in clinical practice in francophone countries from Eastern Europe") is an educational program financed by the Francophone Academic Agency (Agence Universitaire de la Francophonie, AUF), that was scheduled to run over a period of two years, in partnership with the French Pharmacovigilance Centers from Bordeaux University and Rouen University, and Medicine and Pharmacy University "Nicolae Testemitanu" from Chisinau, Moldavia.

During this project, eleven future trainers, both doctors and pharmacists from Romania and Moldavia have been trained in the field of Pharmacovigilance by the French counterparts. These trainers have further organized lectures for 200 doctors and pharmacists in Romania and 100 doctors and pharmacists in Moldavia.

The aim of the project was to create through continuous education a community of specialists that will be able to contribute to the future development of the Pharmacovigilance system and will be able to stimulate spontaneous reporting among doctors and pharmacists, deeply needed in both Romania and Moldavia [1]. Graduate and post-graduate education represents strategic targets for the correction of the underreporting of adverse reactions phenomenon among doctors and pharmacists [2].

In order to serve as course notes, the book "Introducere in Farmacovigilenta" ("Basic Pharmacovigilance") [3] was edited and distributed free of charge to the students. Every course was preceded by a pre-test and finalized by a post-test that tried to evaluate the level of knowledge of the students in the field of pharmacovigilance, the degree of knowledge regarding the spontaneous reporting system and if and how much the students use it. The results of these tests will be presented during the ISOP Congress.

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Abstract Code: ISP3830-42

Drug Exposure During Pregnancy: The Importance of Follow-Up in the Evaluation of Risks

V. Rollason[1], C. Samer[1], K. Ing Lorenzini[1], M. Besson[1], M. Escher[1], V. Piguet[1], J.A. Desmeules[1]

(1) Division of Clinical Pharmacology and Toxicology, University Hospitals of Geneva, Geneva, Switzerland

Background: Pregnant women represent a very special population. The study of drugs in this population faces major issues from a practical and ethical point of view. There is consequently a lack of good quality information on the prescription of drugs in pregnant women. The Division of Clinical Pharmacology and Toxicology of the University Hospitals of Geneva maintains a register for cases of drug exposure during pregnancy. We evaluate the risk of drug exposure for the foetus for each case and provide information to the gynaecologists.

Objective: The aim of this analysis was to characterise the population evaluated in our pregnancy consultations mainly as to the type of patients, the drugs they were exposed to and the outcomes of the pregnancy.

Methods: We performed a retrospective analysis of the requests received in our division relating to drug exposure during pregnancy and the outcome of these from 2007 to 2011. Outcomes were obtained through a follow-up questionnaire sent with the original report and a recall letter sent at the predicted time of delivery.

Results: Between 2007 and 2011, we answered to 529 requests specifically related to drug exposure in an ongoing pregnancy. Amongst these 529 consultations, we received a follow-up for 407 of them (77 %). Mean age of these patients was 31 $\pm$ 6 years, ranging from 14 to 45 years old. These 407 women had taken more than one drug in 55 % of the cases and 8 % had taken five different drugs, for a total of 851 drugs altogether. These drug-exposures occurred mainly during the first trimester When taking into account only the most teratogenic drug, as classified by the FDA, the pregnancy category C was the most represented with 52 % of the consultations followed by pregnancy category D (26 %) and X (16 %). The drugs the most often implicated were psychoactive drugs followed by anti-infectives. As for the outcome of the pregnancies, 281 (69 %) of the women delivered a healthy baby, 50 women underwent elective abortions (12 %), 25 presented with spontaneous abortions (6 %) and there were 50 (12 %) births with neonatal complications, of these 11 malformations (2.7 %).

Conclusion: Our division offers a comprehensive evaluation of drug exposure during pregnancy with a follow-up system that allows an excellent recall rate. This system allows gathering important information on drug-exposure during pregnancy. It does however not replace the need for good quality human studies focusing on the adverse effects of medication use during pregnancy.

Abstract Code: ISP3831-43

Use of Medications, Management of Breastfeeding and Pharmacovigilance: A Mixed-Methods Study on Lactating Women

A. Giusti[1], S. Colaceci[2], M.I. Della Barba[2], A.Y. De Vincenti[2]

(1) National Institute of Health, Rome, Italy, (2) Faculty of Medicine and Surgery, University of Rome Tor Vergata, Rome, Italy

Introduction: A common reason for the cessation of breastfeeding is the use of medication by the nursing mother. Available data suggest that women are often alone in the decision-making process, facing the dilemma to continue breastfeeding their baby giving up the pharmacological treatment or stop breastfeeding [1–2].
Aim: To explore knowledge, attitudes and practice (KAP) and analyze the need and the demand of information of Italian women on medications' use, lactation management and pharmacovigilance during breastfeeding.
Methods: We performed a mixed methods study from May to June 2012. The qualitative phase, based on 2 focus group and 5 semi-structured interviews, involved a theoretical sample of nursing mothers in 3 different community health centers in Rome. The emerging data was used to realize a descriptive study. A KAP questionnaire was administered to pregnant or breastfeeding women (n = 248) in 2 University Hospitals in Rome.
Results: Both qualitative and quantitative data highlight a spread attitude to avoid the use of drugs during lactation as 89.1 % of women consider that they might be risky for the baby. There is a tendency to "bear the pain" (61.3 %), even for minor problems for which a safe treatment is available. In case of doubt, women prefer to suspend breastfeeding basing on their prescriber advice. They also tend to prefer treatments that are perceived as "natural instead of registered medications (74.2 %). These products are often used in form of self-treatment. Women tend to seek information from different sources, often getting discordant opinions. In case of adverse reactions to drugs or natural products, the reference person is the prescriber (83.5 %). Internet is an important source of information (34.8 %), as well as peer-to-peer advice (17.4 %). None of the participants knew the Toxicology Information Services or the Adverse Drug Reaction's reporting system provided by the local and national Pharmacovigilance services.
Conclusions: The security and adequacy of medications' use and lactation management depend to a large extent from the competence of health professionals. Results from this study suggest that there is an urgent need for reliable, accessible and individualized information for health professionals involved in care of breastfeeding women and for women themselves.

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Abstract Code: ISP3832-44

Adverse Drug Reactions to Contrast Agents—An Iopromide Case—Identification, Recording Procedures, Treatment and Pharmacovigilance Improvement—A Pilot Study

J.J. Joaquim[1], T. Pires[1], C. Matos[1], O. Tavares[2], L. Ramos[3]

(1) College of Health Technology of Coimbra, Research Pharmacy Group, Department of Pharmacy, Coimbra, Portugal, (2) College of Health Technology of Coimbra, Department of Radiology, Coimbra, Portugal, (3) Centro Hospitalar e Universitário de Coimbra, Intensive Care Unit, Coimbra, Portugal

Introduction: The Iodine-based contrast agents, such as iopromide, for computed tomography (CT) are accepted as one of the safest injectable drugs, therefore most widely used. It represents an important role in the achievement of image quality with ionizing radiation, consequently improving diagnostic quality. Still there's always a possibility of occurrence of adverse reactions (AR's), with different causality leading to disorders from minor severity to potentially fatal cases.

Iopromide is a molecule used as a contrast agent commonly used in radiographic studies such as computed tomography (CT). The overall rate of ADRs concerning iopromide usage, including tolerance indicators (TI) is about 1.5–2 %. The most frequent AR in iopromide group is headache (4 %), nausea (4 %) and injection/infusion site reaction (3.7 %).
Aim: To classify and characterize the occurred AR's due to a monomeric contrast agent administration, iopromide, for CT in a private hospital of the central region of Portugal.
Methods: It was conducted a six-month retrospective review of records from patients who received contrast for CT, and selected the ones with registered AR. These AR's were categorized as mild, moderate, or severe according to the European Society of Urogenital Radiology (ESUR) guidelines. A recording system was developed by institution healthcare professionals in order to collect and detect the AR's to iopromide. Based in previous studies this record file was created including checklist of most common AR linked to iopromide to evaluate potential AR.
Results: From a total of 3,935 CT performed during the study was administered iopromide in 774 patients. Among these, were found 10 AR's (1.29 %) with the following classification, mild (6), moderate (3) and severe (1). The most used drugs in the immediate treatment of the AR's were hydrocortisone and clemastine. The average age of patients, which expressed AR's, is 58 years old in a interval between 43 and 72.
Discussion: The AR's registered and analyzed in this study were in accordance with published papers. It was possible to achieve it due to the implementation of recording procedures of AR's data, allowing their analysis, in order to improve and accurate patient safety. The support intervention in the patients with AR expression was according to the guidelines of ESUR.
Conclusion: It will be important to follow this study to understand the evolution of AR's to contrast agents in order to improve the safety practices, in spite of the study show a high level of safety in the management of iopromide AR's.

Abstract Code: ISP3833-45

Causality Assessment of Adverse Events—Avoiding Misunderstandings and Disagreements

J. Beckmann[1]

(1) WHO Advisory Committee on Safety of Medicinal Products, Geneva, Switzerland

Background: Causality assessment (CA) of adverse events (AEs) described in individual case harm reports (ICHRs) to detect signals of new adverse drug reactions is often controversial. Various methods have been proposed [e.g. 1–2] but agreement between assessors is usually poor [3–4].
Aim: To develop a sound CA-method with the potential of good inter-assessor accordance.
Methods: Analysis of commonly used methods with respect to sources of controversy and possible solutions.
Results: Substantial discrepancies arise from the following questions: (1) May previous similar ICHRs be taken into account? (2) How to consider other potentially causative factors? (3) Does 'caused' mean 'the drug on its own caused the AE' or 'the drug contributed to the AE'? (4) Should poor quality reports be assessed at all, and how? (5) Which probability is meant by a CA-judgment 'certain' or 'unlikely'? (6) How to rate causality if the diagnosis seems doubtful?
Proposals: (1) Follow established ratings of chronology and pharmacological plausibility with respect to the investigated drug ("D") but do not consider previous similar ICHRs to avoid 'spill over' argumentation from case to case. (2) Consider D together with other potentially causative factors [e.g. 5], classify and where possible rate them as follows: (2a) 'Autonomous' factors, incl. D, which could have actively caused the AE or contributed to it (increased its severity or likelihood). (2b) 'Helping' factors which, dependent on D or other autonomous factors, could have enhanced their effect (e.g. by inhibiting their elimination). (2c) Could autonomous factors, other than D, together with 'helpers', even have been sufficient to cause the AE? (2d) Did such sufficient factors, because of high specificity of the AE (e.g. allergy), make any contribution of D unlikely? (3) Consider 2a–2d and estimate how likely D has contributed to the AE and how big this contribution was. (4) Rate the quality of information about relevant case parameters and define minimum criteria as thresholds to allocate specific degrees of causal relation, e.g. do not rate poor quality reports higher than 'possible'. (5) Use the extreme CA-terms 'certain' and 'unlikely' if you assume that the probability that D contributed to the AE is >95 % or <5 % resp. (6) Grade the certainty of a diagnosis (as proposed e.g. for AEFIs [6]) on a separate scale independently from causality.
Validation: First experience with the method seems promising.
Conclusions: CA should separately take into account different categories of ICHR aspects.
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Abstract Code: ISP3834-46

Nurses Knowledge, Attitudes and Practices Towards the Reporting of Suspected Adverse Drug Reactions (ADR). A Quanti-Qualitative Study

A. De Angelis[1], A. Giusti[2]

(1) Local Health Authority Roma F, Rome, Italy, (2) National Institute of Health, Rome, Italy

Introduction: Nurses play a strategic role in the reporting of suspected adverse drug reactions (ADR) [1–4]. However, in Italy the number of reports of ADRs by nurses is still minor [5].
Aim: To describe what are the attitudes, knowledge and practices (KAP) of nurses in the reporting of suspected ADRs.
Methods: This was a sequential quanti-qualitative study. From May to August 2011 a KAP questionnaire was administered to all nurses working in selected Emergency Departments in 2 main hospitals in Rome and Province. The descriptive study has been followed by a focus group to explore the participants' view of the survey's results.
Results: We retrieved 210 questionnaires, with a response rate of 74.5 %. Out of the respondents, 86.5 % don't know where to find the reporting form and 93.3 % never made a report during their professional career. Those who know the pharmacovigilance system do not consider it as a bureaucratic process (OR = 3.8) and think they have time for reporting (OR = 2.0). Having reported is significantly associated with a higher knowledge of the pharmacovigilance system (OR = 2.0). Nurses having ≤11 years of career don't think that reporting is an exclusive task of the physician (OR = 2.3). Qualitative analysis highlighted a spread misunderstanding of the concept of "reporting". In fact, most of the nurses consider that reporting is to communicate the suspect ADR to the physician or register it in the medical records.
Conclusions: The results show a profile of a nurse that is not fully aware of its active role in ADRs reporting, but with a high interest in this domain. We recommend educational and management intervention aimed to nurses to promote their proactive role within the pharmacovigilance system.
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Drug Interactions with Azole Antifungals in Patients Treated with Hematopoietic Stem Cells

H. Sakly[1], M. Razghallah Khrouf[1], N. Abdejelil[2], M. Turki[1], K. Ben Jeddou[1], A. Mhiri[1], T. Ben Othman[2]

(1) Faculty of Pharmacy of Monastir-University, Monastir, Tunisia, (2) Department of Hematology and Transplant of the National Center for Bone Marrow Transplant, Faculty of Medicine of Tunis, Tunisia

Introduction: The incidence of invasive fungal infections is increasingly important in patients treated with hematopoietic stem cells. These infections are the leading cause of morbidity and mortality in these immunocompromised patients.

Fluconazole and Voriconazole are the main azole prescribed in the service of Hematology and Transplant at the National Center for Bone Marrow Transplant.

These two molecules are both substrates and inhibitors of cytochrome P-450 which is the source of many drug interactions with drugs metabolized by these enzymes.

Aim: The objective is to evaluate the prevalence of drug interactions in patients treated with azole (Voriconazole and Fluconazole) and investigate the possible consequences of these interactions.

Materials and Methods: A retrospective study was performed on 1067 daily drug prescriptions of 38 patients treated with hematopoietic stem cells and hospitalized during 2012 in the service of hematology and transplant

Results: The average number of drugs per prescription is 5 drugs with a minimum of 3 and a maximum of 17.

The average number of interactions is 2 per prescription, ranging from 2 to 18 interactions.

60 % of prescriptions collected contain an azole antifungal, with a slight predominance of Voriconazole 34 % versus 26 % for fluconazole.

74 % of prescriptions containing an antifungal azole have at least one interaction with this antifungal drug.

In one patient (2.63 %), an association was noted against-indicated. This interaction involved the co-prescription of voriconazole and rifampicin (an enzyme inducer responsible for the decrease in the concentration of voriconazole in the blood of more than 95 %).

Also a not recommended interaction was observed in another patient between voriconazole and sirolimus.

The majority of interactions are precautions for use (3rd level of risk):

- Voriconazole: ciclosporine, Loxen et Gaviscon
- Fluconazole: ciclosporine, sintrom et Gaviscon

Azole, by their enzymatic inhibition of CYP3A4, increase plasma concentrations of cyclosporine and thus the risk of nephrotoxicity.

Conclusion: Understanding the mechanisms of drug interactions allows clinicians to avoid certain interactions and develop a possible strategy to minimize iatrogenic events. This is facilitated by the establishment of a computerized system in the service to prevent iatrogenic drug and ensuring patient safety.

Abstract Code: ISP3836-48

Prescribing Trends of Piroxicam in General Practice: How Has Regulatory Action Impacted the Prescribing Demographics of Piroxicam?

J. Wong[1], P. Datta-Nemdharry[1]

(1) Medicines and Healthcare products Regulatory Agency, London, UK

Background: Piroxicam is a non-selective non-steroidal anti-inflammatory drug (NSAID) which has been associated with more gastro-intestinal side effects and more serious skin reactions than other non-selective NSAIDs, resulting in a risk benefit review in June 2007. One of the recommendations that came as a result of the review was that it should not to be used as a first-line treatment and the maximum daily dose should be limited to 20 mg.

Objective: To identify if prescribing demographics for piroxicam differ before and after the EMA risk benefit review.

Methods: Data on patients who received a first prescription for piroxicam during two time periods, July 2005–June 2007 (prior to the review) and October 2007–September 2009 (post-review), were extracted from Clinical Practice Research Datalink (CPRD). Quarterly patient incidence rates by age, sex and location were calculated. The incident doses and the proportion of patients prescribed a daily dose of more than 20 mg were calculated. The median dosage for each cohort was compared using the Mann–Whitney test. The number of previous NSAIDs prescribed in the one-year period prior to their first piroxicam prescription in each cohort was also examined and compared.

Results: There has been a significant reduction in the number of patients being prescribed piroxicam for the first time in the post-review group ($n = 769$) compared to the prior-review group ($n = 2741$). The proportion of patients who were prescribed more than 20 mg daily increased from 3.6 % (pre-review) to 5.6 % (post-review). The median daily dose for each cohort was tested statistically, and it suggested there was weak evidence that the median doses were different from each other ($P = 0.27$). There were very little changes in the proportions of patients per NSAID prior- and post-review. Increases were seen in the prescribing of naproxen and ibuprofen post-review, which suggests that more patients were prescribed these two NSAIDs before they were considered for piroxicam.

Conclusion: There was a decreasing trend in the number of patients being initiated on piroxicam prior to EMA review and it is possible the number of new patients would have eventually dropped to the level that was seen in the post-review cohort without any EMA intervention. Statistical testing suggests there is very weak evidence that the daily

doses in both study groups are different from each other. It is of interest that the number of patients who received more than 1 prescription for meloxicam, another non-selective NSAID, prior to piroxicam has increased.

Abstract Code: ISP3837-49

Multiple Antituberculosis Drug-Induced Adverse Reactions Occurring in the Same Patient: How to Treat?

A. Mhiri[1], M. Turki[2], D. Lahyeni[1], M. Khrouf[2], S. Hammami[1], C. Marrekchi[1], K. Zghal[3], I. Maaloul[1], M. Ben Jemaa[1]

(1) Infectious Diseases Department, Hedi Chaker University Hospital of Sfax, Tunisia, (2) Laboratory of Pharmacology, Faculty of Pharmacy, Monastir, Tunisia, (3) Laboratory of Pharmacology, Medicine University of Sfax, Tunisia

Introduction: The first-line treatment of tuberculosis relies on four essential drugs (isoniazid-rifampicin-pyrazinamide-ethambutol). This association increases the frequency of side effects of each antituberculosis drug [1, 2].
Aim: We report a clinical case in which the patient presented a hepatotoxicity due to pyrazinamide, a peripheral neuropathy due to isoniazid and an ocular toxicity due to Ethambutol.
Patient Presentation: A 19 year-old female, hospitalized hospitalized at the Department of Infectious Diseases for further care for cerebral tuberculosis. Antituberculosis quadruple therapy was initiated and a regular clinical and biological monitoring was established.
Results: One month after the beginning of the treatment, the patient presented a severe anicteric hepatitis. The interruption of antituberculosis drugs one by one leaded to the incrimination of the pyrazinamide on the genesis of this hepatotoxicity. A paresthesia in the lower limbs appeared 70 days after the start of the treatment. The electromyogram (EMG) concluded to a peripheral neuropathy leading to interrupt definitively the isoniazid. Then, the patient reported the notion of blurred vision with decreased visual acuity in the left eye. The ophthalmologic examination completed by a visual field, color vision and Visual Evoked Potentials (EPI) objectified an optic neuritis leading interrupt definitively the ethambutol. These events led to a therapeutic impasse. The patient was treated with rifampicin, levofloxacin and pyrazinamide. The latter, in the absence of therapeutic alternatives, the severity of the neuro-meningeal tuberculosis and despite its liver toxicity previously reported, was taken up with a close monitoring of liver function tests.
Conclusions: The close clinical and biological monitoring [2] of this patient revealed pretty early the adverse effects of antituberculosis drugs, allowing to interrupt the treatment at time, when the adverse effect stills reversible. Thus, this clinical and biological monitoring is very important in the prevention of iatrogenicity.

In such situations, where the patient has several side effects limiting the use of antituberculosis treatment, therapeutic alternatives are minimal.

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Abstract Code: ISP3838-50

Pharmacovigilance and Effectiveness of Emergency Contraception

K. Ilic[1]

(1) Faculty of Pharmacy, Department of Pharmacology, Belgrade, Republic of Serbia

Emergency contraception (EC) has provided women with a viable non-invasive alternative in their effort to avoid an unwanted pregnancy after unprotected intercourse. This revolutionary discovery in medicine allows women to avoid abortion, which is perceived by many to be one of the most traumatic experiences in their life. Abortion can cause short and long-term complications, including the inability to have a healthy pregnancy in the future.

Currently, the most frequently used oral method of EC is levonorgestrel (approved as an over the counter (OTC), behind the counter (BTC), or dual label product) and ulipristalacetate (prescription only pill). EC is often underused, misused or used more frequently than allowed. EC pills must not be used as a regular form of contraception, which occasionally happens amongst young females. As a result, EC pills have been switched from OTC to BTC way of dispensing in some countries.

Given that it takes longer to visit a doctor's office and obtain a prescription versus stopping at a local pharmacy, the BTC status of EC pills may potentially lead to a decrease in its effectiveness. In addition to treatment delay, other factors, such as vomiting, drug interactions, and further intercourse may reduce the effectiveness of EC. If it is properly used, EC pills are much safer than regular contraception. In addition, EC is not an abortifacient and thus, its use could be justified in potential users who are reluctant to take EC due to their religious beliefs.

The most frequent adverse reactions (ADR) identified in the WHO database (VigiBase) were irregular menstruation and unintended pregnancy. This presentation will discuss in-depth factors that can reduce the effectiveness or oral EC as well as the most frequent ADR of EC pills.

Abstract Code: ISP3839-51

Croatian Experience in Communication with Media on Patients' On-line Adverse Drug Reaction Reporting—A Retrospective Observational Study

M. Dimov Di Giusti[1], A. Andric[1], B. Dolinic[1], V. Macolic Sarinic[1]

(1) Agency for Medicinal Products and Medical Devices of Croatia, Zagreb, Croatia

Introduction: An estimated 72 % of Internet users in USA search for health information on-line [1]. A recent study estimated that 70 % of UK patients use the Internet to search for health information [2]. This could be potentially dangerous due to insufficient legislative framework and the large amount of unreliable information available on the internet. On the other hand, for a pharmacovigilance centre, this setting could be used for the communication to the public in a structured and attractive way. In Croatia, Patients' ADR reporting was introduced in 2009 [3]. However,

this was possible only in the paper version and only few reports have been received annually. Since on-line reporting has been introduced in 2012, a significant increase of patients' reports occurred. Because Croatia was the first country in the world to start using Uppsala Monitoring Centre on-line application form for patient reporting, this was communicated to all media (TV, radio, newspapers, internet-portals) with an excellent impact.

Methods: We performed a retrospective observational study of the Patients' ADRs reported to the Agency for Medicinal Products and Medical Devices of Croatia for the period from January 2010 to December 2012. We measured the impact on number of Patients' ADR reports before the communication on possibility of on-line reporting and after the communication which took place in August 2012.

Results: In 2010 and 2011 only 7 and 16 patient reports were received, respectively. In 2012, the number of patient ADR reports has increased to 45. More then 85 % of 2012 reports have been received in a 4 month's time, after the communication on possibility of patients' ADR on-line reporting has been made. This is 5-fold increase compared to 2010 and almost 3-fold increase compared to 2011.

Conclusion: This study has shown how active communication from pharmacovigilance centre, using the large media potential, can be utilized to stimulate patient reporting and to raise awareness on the importance of patient participation in drug safety.

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Abstract Code: ISP3840-43

Prevalence of Some Drug Co-Prescriptions in Antipsychotic-Receiving Elderly Inpatients with or without Hospital-Acquired Pneumonia

F. Westphal[1], C. Nonnenmacher[2]

(1) Regional Agency for Health, Paris, France, (2) Hospital Centre, Strasbourg-Brumath, France

Background: Psychotropic drugs are frequently prescribed in elderly patients but may cause serious adverse effects, e.g., the antipsychotic (AP)-related risk of pneumonia, as recently reported in geriatric outpatients.

The aim of the study was to compare in AP-receiving elderly inpatients with or without hospital-acquired pneumonia the prevalence of some drug co-prescriptions that may increase the risk of pneumonia through drug-induced swallowing disorders.

Methods: 115 consecutive cases of hospital-acquired pneumonia in AP-receiving elderly patients (>65 years) were recorded in the geriatric psychiatry wards of a 600-bed teaching hospital. Clinical data and drug regimens were extracted from the electronic medical records and compared with data from 115 AP-receiving elderly inpatients without history of pneumonia randomly selected through a repeated 1-day cross-sectional recruitment procedure in the same wards. The drug regimens analyzed were those ongoing at the time of pneumonia diagnosis for pneumonia patients (PP) or at the time of discharge for non-pneumonia patients (NPP). Concomitant benzodiazepine (BZ) or non-AP anticholinergic drug (ACh) prescriptions in patients with ongoing AP therapy were examined.

Results: Mean age of patients was 77.2 years (±7.7) and 74.5 years (±7.1) in PP and NPP ($p < 0.01$), respectively. Proportion of patients with at least one chronic co-morbidity was similar in the two patient groups (81 and 87 % in PP and NPP, respectively, $p = 0.20$). Prevalence of dementia did not differ between the patient groups (27 % in PP, 33 % in NPP, $p = 0.31$). The mean number of drugs per drug regimen was 6.0 in PP vs. 6.4 in NPP ($p = 0.20$). Frequency distribution of conventional or atypical single AP treatments did not differ between the patient groups ($p > 0.50$). Mean daily doses of risperidone, olanzapine, and tiapride—the most frequently prescribed AP drugs in this study – were similar in PP vs. NPP. Prevalence of AP polypharmacy was higher in PP (16.3 %) vs. NPP (6.7 %, $p = 0.013$).

While prevalence of either benzodiazepines (BZ) or non-AP anticholinergic drugs (Ach) in drug regimens was similar in PP (24 and 24.5 %, respectively) and in NPP (32.5 %, $p = 0.14$, and 23.5 %, $p = 0.88$), prevalence of combinations of BZ with Ach were two times higher in PP (23.5 %) than in NPP (11.8 %, $p = 0.01$).

Conclusion: AP-receiving patients with hospital-acquired pneumonia were older and more frequently receiving combinations of BZ and ACh drugs at the time of pneumonia diagnosis than AP-receiving patients without pneumonia. These findings should be confirmed by other studies.

Abstract Code: ISP3842-45

Guillain–Barré Syndrome and Influenza Vaccines: Croatian Experience

D. Krnic[1], A. Andric[1], V. Macolic Sarinic[1]

(1) Agency for Medicinal Products and Medical Devices, Zagreb, Croatia

Introduction: Prior the July of 2012 no cases of GBS linked to influenza vaccine have been reported to the Croatian Agency for Medicinal Products and Medical Devices (HALMED). GBS came under the spotlight after the newspaper article which described three patients who were reportedly developed GBS after vaccination with monovalent pandemic flu vaccine. Since then, HALMED received total of ten cases of patients with GBS after vaccination with influenza vaccines.

Aim: Evaluation of 10 cases of GBS reported for influenza vaccines in Croatia.

Methods: We used Brighton collaboration's case definitions for analysing cases of GBS reported to the HALMED for the period July 2012–July 2013. The time window at risk was set at 6 weeks after vaccine administration.

Results: The results showed that among 10 analysed cases, all 10 patients received seasonal influenza vaccines (one patient received seasonal and pandemic influenza vaccine). Overall, 7 cases occurred within 6 weeks from vaccination. Of those 1 fulfilled criteria for level 1, 2 cases fulfilled criteria for level 2 and 4 fulfilled criteria for level 4 of diagnostic certainty.

Conclusions: Following these results, we concluded that benefits of influenza vaccination outweigh potential risks associated with it. Special care should be taken in order to inform patients about benefits and risk of influenza vaccination in order to facilitate informed decision.

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Abstract Code: ISP3843-46

Association of an Antituberculosis Drug-Induced Fulminant Hepatitis and an Omeprazole Drug-Induced Pancreatitis

M.A. Mezghani[1], M. Turki[2], A. Mhiri[1], M. Khrouf[2], I. Maaloul[1], C. Marrekchi[1], S. Hammami[3], E. Elleuch[1], K. Zghal[3], M. Ben Jemaa[1]

(1) Infectious Diseases Department, Hedi Chaker University Hospital of Sfax, Tunisia, (2) Pharmacology Department, Faculty of Pharmacy, Monastir, Tunisia, (3) Laboratory of Pharmacology, Medicine University of Sfax, Tunisia

Introduction: The treatment of the tuberculosis relies on essential drugs used in association (isoniazid–rifampicin–pyrazinamide–ethambutol) for at least 6 months duration [1]. The tolerance of the treatment is crucial to the therapeutic success.

Aim: We report a clinical case in which the patient presented a fatal fulminant hepatitis due to antituberculosis drugs associated with an acute pancreatitis due to omeprazole.

Patient Presentation: A 33 year-old patient, alcoholic weaned since 2000. The diagnosis of neuro-meningeal tuberculosis was established and the treatment was initiated on 07/02/2013. One month later the patient reports the notions of dermal icterus with pale stools and dark urine. When he was admitted on 01/04/2013, he had a low prothrombin at 45.6 %, and an icteric hepatitis. The treatment was immediately interrupted as the clinical and biological signs were alarming.

Results: The evolution was unfavorable with the persistence of the cholestatic icterus and the appearance of hiccups and epigastric pain. The diagnosis of acute pancreatitis was discussed since the patient presented a high level of lipaemia and a hypocalcaemia. The treatment by injectable omeprazole made the pancreatitis worse with a hypereosinophilia (602/mm^3) (day 2 of treatment). The patient develops besides the signs of an acute liver failure with a spontaneous low prothrombin plasmatic level (20 %) and a major hypoproteinemia. The patient died of a hematemesis of big abundance. With such evolution, we concluded to an acute drug-induced hepatitis and pancreatitis. The outcomes of the investigation of the pharmacology department concluded in the very likely implication of antituberculosis drugs, particularly the pyrazinamide, in the genesis of the fulminant hepatitis (score: C2S2I2B3), and the Omeprazole in the genesis of the pancreatitis (score: C2S2I2B2) [2]. In addition, other causes behind the occurrence of pancreatitis that cannot be eliminated.

Conclusions: In patients at risk of developing pancreatitis such as alcoholics, it is necessary administer antituberculosis drugs with precaution and to strengthen the clinical and biological monitoring to avoid serious consequences.

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Abstract Code: ISP3844-47

How Safe is Prucalopride for the Treatment of Chronic Constipation? A Systematic Review and Meta-Analysis

L. Gatta[1,2], C. Scarpignato[2]

(1) Gastroenterology and Digestive Endoscopy Unit, Versilia Hospital, Lido di Camaiore, Italy. Department of Clinical and Experimental Medicine, University of Parma, Parma, Italy, (2) Department of Clinical and Experimental Medicine, University of Parma, Parma, Italy

Background: Available therapies for chronic constipation (CC) have limited efficacy. Gastrointestinal prokinetics represent an attractive option, but both cisapride and tegaserod, the two agents with proved efficacy in CC, have been withdrawn because of cardiac adverse events. Prucalopride is the first selective, high-affinity 5-HT_4 agonist, without any significant activity towards other (5-HT and non 5-HT) receptors or channels (e.g. hERG) at the therapeutic doses.

Aim: To perform a systematic review and meta-analysis of the large clinical trials using prucalopride to treat patients affected by CC in order to assess its safety.

Methods: MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials as well as abstracts from the major American, European and Asian meetings were searched up to November 2012. Large (≥250 patients) randomized controlled trials (RCTs) in adult patients with CC, treated with prucalopride, were included. Relative risks (with 95 % CI) were computed using a random effects model in order to provide a more conservative estimate.

Results: The results, including 5 studies and more than 2500 patients, are shown in Table 1.

Table 1

	Prucalopride 2 mg daily versus Placebo	Prucalopride 4 mg daily versus Placebo	Prucalopride 4 mg daily versus 2 mg daily
Adverse events during the 12 weeks of treatment	**RR: 1.21** (95 % CI 1.06–1.37)	**RR: 1.12** (95 % CI 1.04–1.19)	**RR: 0.98** (95 % CI 0.92–1.04)
Drop-out due to adverse events during the 12 weeks of treatment	**RR: 1.81** (95 % CI 0.82–4.02)	**RR: 2.53** (95 % CI 1.61–3.96)	**RR: 1.61** (95 % CI 0.84–3.09)
Increase of QTcF >450 ms from baseline at week 12	**RR: 1.03** (95 % CI 0.81–1.31)	**RR: 1.01** (95 % CI 0.79–1.30)	**RR: 0.98** (95 % CI 0.77–1.26)
Increase of QTcB >450 ms from baseline at week 12	**RR: 0.88** (95 % CI 0.68–1.30)	**RR: 0.88** (95 % CI 0.60–1.29)	**RR: 0.99** (95 % CI 0.69–1.42)

Conclusions: At the recommended therapeutic doses (2 mg daily), prucalopride is safe for treating CC. The most frequently reported adverse effects were headache and GI events, which occurred mainly on the first day(s) of treatment. Furthermore, there were no significant changes in QT_c interval even when the 4 mg dose was compared to placebo.

QTcF, QT interval corrected with the use of Fridericia's formula; QTcB, QT interval corrected with the use of Bazzett's formula.

Abstract Code: ISP3845-48

Adverse Events Following Mass MenAfriVac™ Vaccination in Ghana, 2012

D. Mimi Darko[1], K. Amponsa-Achiano[2], G. Sabblah[1], K. Odei Antwi-Agyei[2], S.K. Opuni[1]

(1) Safety Monitoring Division, Food and Drugs Authority, Accra, Ghana, (2) Expanded Programme on Immunisation, Ghana Health Service, Accra, Ghana

Background: MenAfriVac™ is a new conjugate vaccine against *Neisseria meningitis* serogroup A. First introduced in Africa's "meningitis belt" in 2010, the vaccine prevents the deadly epidemic meningococcal disease [1, 2] which occurs in outbreaks in this region, with over 8–10 % fatality every 8–10 years. In 2012 as part of the Meningitis Vaccine Project (MVP), Ghana conducted a mass MenAfriVac vaccination campaign in 43 districts in its northern-most regions which lie in the belt [3]. Over three million 1–29 year-olds were targeted. A monitoring system was set up to track adverse events following immunization (AEFI) during and 6 weeks after the campaign.

Objective: To monitor and evaluate adverse events following MenAfriVac immunization in the Ghanaian context.

Methods: We conducted both stimulated passive and active AEFI monitoring. The active monitoring was done for 12 pre-defined clinical syndromes in a sentinel sub-metro (Tamale Central) targeting 152,697 vaccinees. The remaining vaccinated population was monitored through the stimulated passive AEFI system. Focal persons were trained to detect and report any AEFI occurring within 42 days of vaccination using structured guidelines. All serious AEFI cases were submitted for causality assessment by the National Expert Committee (NEC), based at the Food and Drugs Authority.

Results: Of 3,038,393 persons vaccinated, 621 reported at least one AEFI (20.44 cases/100,000 vaccinated; CI 18.86–22.11/100,000). Of these, 572 were classified as non-serious, the commonest being fever/chills, gastrointestinal disorders, headache, and injection site reaction. Of the 49 serious AEFIs, the National Expert Committee assessed vaccine-causal association for 32 cases which had complete documentation. Of these, 20 (62.5 %) were classified as coincidental; seven (21.9 %) unclassifiable; four (12.5 %) indeterminate and one (3.1 %) was classified as immunization error-related. Active monitoring identified 91 cases of the 12 clinical syndromes with breakdown as follows: 23 convulsion, 22 toxidermia; 13 bronchospasm; 10 urticaria; 6 hypotonia; 4 meningitis syndrome and 1 each of anaphylactic shock and local abscess. The attack rates for these conditions were not different from baseline data extracted from clinical records on the same population, over the same month in the preceding year.

Conclusions: Lessons learnt from MenAfriVac AEFI monitoring in Ghana did not identify any new safety concerns. The safety profile is consistent with reports during clinical studies of the vaccine and immunization campaigns carried out in countries in the 'meningitis belt', notably Niger and Burkina Faso [1, 4]. The experience from the system should be used to improve safety monitoring in routine and campaign vaccinations.

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Abstract Code: ISP3848-51

ANVISA'S Pharmacovigilance Office Safety Assessment on Suspected Adverse Events Related to Iron Saccharate

F. Simioni Gasparotto[1], C. Souza Penido[1], G. Silva Calado[1]

(1) Pharmacovigilance Office (GFARM), Brazilian Health Surveillance Agency (Anvisa), Brasília, DF, Brasil

Introduction: When a safety signal is identified, some points are investigated by Anvisa's Pharmacovigilance Office (Gfarm) in order to reach a decision. This research process helps in strengthening a signal in the safety assessment of a drug.

Objectives: The aim of this work is to show which actions were performed in the investigation of suspected adverse reactions related to a specific brand Iron Saccharate (injection) aiming the strengthening of the signal identified and the completion of this process. In Brazil, this drug is distributed by the federal government for the public with a high volume of sales.

Methods: The methodology of Gfarm research process consisted of:

1. Search on Anvisa's Adverse Drug Events databases (NOTIVISA and Sisfarmaco) for reports from health care professionals and consumers.
2. Research on Anvisa's ombudsman systems (SAT and Ouvidori@tende).
3. Analysis of Periodic Safety Updated Reports.
4. Review of scientific literature and updated information on the drug.
5. "Restricted Query" made to institutions of the Sentinel Hospitals Network in order to strength a detected safety signal.

Results: After identification of an alleged increase in adverse reactions related to a specific brand Iron Saccharate, through reports received from consumers on the ombudsman system, a note [1] was published on Anvisa's website to inform that the benefit-risk of this drug was being evaluated. With the purpose of strengthening the signal detected Gfarm conducted its research process and the result of this investigative analysis led to the publication of a new note [2] concluding that most of the adverse events reported were due to administration technique, especially to dilution and infusion, even though a recommendation has already been referred in the drug insert. Actions to inform health care professionals about this risk were necessary, and the marketing authorization holder was requested to submit a Risk Minimization Plan and to prepare a Dear Doctor Letter to Health Care Professionals [3].

Conclusions: A detected safety signal can be strengthened through the implementation of all stages of the investigative process. In the specific case of the drug Iron Saccharate, research has shown that the benefit-risk

profile of the drug remained unchanged, but it was necessary to implement measures to minimize risk and communicate the prescribers of the drug.

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Abstract Code: ISP3853-47

Pharmacovigilance Major Problem is Counterfeit Drugs

S. Gunda[1]

(1) Synowledge PV Services INDIA Ltd., Bangalore, India

All countries around the world have an up growing major problems counterfeit drugs. The present study has information about how to identify counterfeit drugs in drug supply chain and get 100 % accurate data for pharmacovigilance. Most of the pharma companies are data basing the reports from various sources like hospitals, patients, physicians, patient support program and etc. Recent problems noticed by companies were, reports from patients coming due to lack of efficacy as they are using counterfeit drugs. Most of the counterfeit drugs are produced from developing countries like India and China. In recent years all the big pharma companies like Merck, Eli lilly, Ranbaxy, Pzifer, Johnson & Johnson and GlaxoSmithKline alone paid about $13 billons as penalties to different regulatory authorities. This money paid as fine could be used for more clinical studies for development of new drugs. Information about factors encouraging counterfeit drugs and how counterfeit dugs are affecting pharmacovigilance and measures taken to eradicate this problem were mentioned. World health organisation plays a key role in eradication of counterfeit drugs. UK and US had very strong network on controlling counterfeit drugs, and MHRA was one of the development by UK government and USFDA also has very strict rules and procedures to be followed for drugs import in US. Unique Identification Code(UIC) would be one of the measure for getting accurate data from patient or any other source about the company genuine drug. UIC would be most economical technique used in identification of counterfeit drugs in developing countries during drug supply chain. Fake drugs generally resemble like genuine drugs but their percentage of active constituents is always question mark. Because of this reason most of the lack of effect cases are noted in pharmacovigilance. Procedures and methods to be followed to get accurate safety data from patient and other sources. Development in facilities provided to the patient (like toll free no, web email, text services) while reporting a complaint against a company drug. Collecting samples of the company drug from the patient once a complaint was lodged due to lack of effect will make company to be sure about manufacturing defect or supply chain or because of counterfeited drug. Governments and regulatory board of different countries are taking certain steps against companies by increasing penalties and imprisonment duration. So, relentless efforts should be made in developing methods in identification of counterfeit drugs and funds should be increased for R&D, so that 100 % accurate data will be recorded in pharmacovigilance.

Abstract Code: ISP3854-48

The Relationship Between Pharmacovigilance and the Various Media Types: Increasinf Mutual Understanding

P. Bahri[1]

(1) European Medicines Agency, London, UK

Medicines are frequently featured in the media. As pharmacovigilance scientists we fear risk amplification through media, resulting in mistrust in medicines and reduced use with adverse health outcomes. However, we should not allow some negative experiences fostering general negative attitudes towards media. The role journalists play in disseminating news of society's interest and fostering public dialogue is vital to democracy. In addition to journalist-based media, exchanges in internet fora/social media present a new democratic media type, open to equal participation by all, but also fragmenting societies into many sub-communities according to interests, values, lifestyles and media preferences. Even journalist-based media are becoming participatory through using and inviting contributions from people. Computer algorithms and human swarm intelligence are new ways to filter information in the internet. What is publicly discussed on medicines is often triggered by articles in scientific journals, a further media type, involving peer-review. Scientists should present conclusions and rationales in a manner as immune as possible against misinterpretation and make themselves understandable. Regulators communicate about safety actions through own websites/social media channels and should fulfill the public's expected information breadth and depth, as well as conciseness. Given that communication is crucial in pharmacovigilance for kicking off risk minimisation and promoting trust in the safety systems for medicines, we have to increase our understanding of the various media types and possible interactions, as well as cultural contexts. Appropriate interactions will depend on the type of our organisations, e.g. authority or industry. For best evidence, we should review medicines-related communication/media research and evidence on media use. Further, monitoring debates in the media may identify patients' and healthcare professionals' views, concerns and information needs. Health website klick counts and internet rumour monitoring are methods developed most recently to determine spread of infections and vaccine acceptance. Overall, media monitoring may inform scoping risk assessments and planning communications with the public, to ensure that all data on aspects the public wants to know about are assessed. This will also provide for evidence-based incidence management and media crisis prevention. Regulators' visible awareness of public views may contribute to building public trust in regulatory systems. Further, we all can learn from journalists as regards achieving broad/specific reach, audience-specific tailoring, presenting easily accessible text flow and creating motivation for new behaviours, for the purpose of risk minimisation. Finally, we should explore how communication/media research can help evaluating the effectiveness of risk minimisation advice for patients' benefits.

Abstract Code: ISP3855-49

Assessing the Comparative Safety and Tolerability of Antidepressant Drugs

D. Baldwin[1]

(1) Clinical and Experimental Sciences, Faculty of Medicine, University of Southampton, Southampton, UK

Problems abound when assessing the comparative acceptability and safety of antidepressant drug treatments. The findings of double-blind randomized placebo- and comparator-controlled trials (RCTs) can provide a reasonable impression of the relative tolerability of antidepressants in short-term treatment: but less is confidently known about their relative acceptability and safety in continuation and maintenance treatment. In addition the findings of RCTs which are conducted in the homogenous and largely physically healthy samples of trial participants do not necessarily generalize well into the mixed and highly comorbid groups of depressed patients seen in real-world clinical practice. Furthermore, many of the reported adverse effects of antidepressants relate to largely subjective psychological experiences—for example, to reduced sexual desire or emotional indifference—which can make it hard to distinguish the adverse effects of treatment from persistent or emerging symptoms of the underlying condition. Regrettably, the quality of many reports of possible adverse drug reactions with antidepressants is poor and this further hinders the accurate assessment of comparative tolerability and potential toxicity. This talk will include discussion of the role of mixed treatment comparisons in assessing the acceptability of antidepressant treatment; will illustrate current research methodological challenges with the examples of sexual dysfunction and emotional indifference during treatment with selective serotonin reuptake inhibitors; and will consider the quality of case report adverse reactions with the example of the effects of serotonin-noradrenaline reuptake inhibitors on hepatic function.

Abstract Code: ISP3856-50

PASS E PAES for Biosimilar Monoclonal Antibodies

J. Ivanovich[1]

(1) Pharmacovigilance, Department Post Marketing Surveillance, Italian Medicines Agency (AIFA), Rome, Italy

In the near future biosimilar monoclonal antibodies (BmAbs) will represent the major class of biosimilars, with more than 40 BmAbs which have received EMA scientific advice for authorization procedure in last years.

Therapeutic mAbs have proven to be safe and effective pharmaceuticals and BmAbs have to demonstrate similarity to the originator in terms of quality characteristics, biological activity, safety and efficacy. However, the adverse effects of BmAbs and innovators could differ in clinically-important ways.

Most mAbs are indicated for treatment of cancer and inflammatory/autoimmune disease and are designed to directly interact with the immune system. Consequently, mAbs have the potential to induce either immune suppression or immune activation, including immunogenicity, which represents a reason for safety concerns.

While the risk for serious new adverse reactions (ADR) are lower for biosimilars compared to innovator products containing a new substance firstly introduced into the market, some rare but potentially serious safety risks (e.g. unwanted immunogenicity, tumour formation, treatment failure, unwanted tissue formation, ADRs unique to biosimilars and not associated with the innovator) may not be detected during pre-approval clinical testing because the size of the population exposed likely will not be large enough to assess rare events. Moreover, in some cases, spontaneous reporting could be limited by under-reporting as well as by data quality, hindering safety assessment. Thus, the post-marketing program for a biosimilar medicines is tailored taking into account these considerations to best evaluate potential remaining risks and a more proactive approach is required, in particular cases, where safety risks and effectiveness have to be evaluated through post-marketing safety (PASS) and efficacy studies (PAES).

Pharmacovigilance plans and post-authorisation measures should be equally stringent for reference and biosimilar products and the request to conduct an PASS or PAES (during evaluation of the marketing authorisation application or in post-authorisation phase) could be done whenever concerns about the safety or inefficacy risks exist. Another important deliverable of the new European pharmacovigilance legislation is additional monitoring, addressed to detect safety problems and it is introduced for biological medicines, including BmAbs, when there is limited post-marketing experience and for which the marketing-authorisation holder is required to carry out PASS. Those studies could be part of the risk management plan, should ideally be performed in collaboration between marketing authorization holders of reference and biosimilar products and participation of biosimilars in registries should be encouraged. Moreover, assay harmonisation in a post-authorisation setting is desirable to adequately compare spontaneous reports between products.

Abstract Code: ISP3857-51

Patient Support Programs—New EU Regulations and its Challenges for Pharmaceutical Companies

H.A. Oberender[1], P. Koelm[2]

(1) Global Pharmacovigilance, Bayer Pharma AG, Wuppertal, Germany, (2) Global Pharmacovigilance, Bayer Pharma AG, Berlin, Germany

Module VI of the new EU regulations provides a definition for patient support programs (PSPs) and specifies the type of AEs collected as "solicited" [1].

In addition to the rather vague definition examples for PSPs are given [1]. Based on these examples Bayer deduced 3 types of PSPs: (i) Patient Support & Disease Management Programs, (ii) Compensation / Reimbursement Schemes, and (iii) Discount Schemes. Types (i) and (ii) share the direct interaction between the company, the treating physicians and their patients while type (iii) is characterized by at least a patient specific tracking of medicinal products provided by the company.

Due to the fact that the new EU regulations require the collection of all AEs from such PSPs but do not narrow down such AEs to e.g. serious ADRs, this requirement remains a challenge. In addition, companies are requested to conduct an appropriate causality assessment [2] which would include the collection of reporter causality statements.

Besides the challenges for the collection and recording of AEs from PSPs and the timely reporting to the company there exist additional challenges for the Pharmacovigilance organization like the expedited reporting of such cases to Health Authorities outside of the EU where such cases are considered as "spontaneous" reports, the aggregate reporting in periodic benefit risk evaluation reports (PBRERs), and the inclusion of such cases in the signal detection.

From an organizational point of view PSPs provide further challenges for Pharmacovigilance organizations. Usually, PSPs are initiated by the commercial organization within pharmaceutical companies. Thus, a specific training of the new requirements for PSPs has to be organized for the commercial organization. Also, due to the involvement of 3rd parties which are often contracted in for assistance Pharmacovigilance agreements have to be implemented and training to 3rd party staff must be conducted. Finally, a reconciliation process for records of PSPs has to be considered.

Conclusions: Depending on the product portfolio of a pharmaceutical company PSPs may play an important role in the post marketing period. For specific products PSPs may become even more important than non interventional studies (NISs). EU regulators started to set up some rules for such programs. Pharmaceutical companies will have to invest further efforts to accept the challenges and to ensure that PSPs are managed in a robust manner in the near future like it is true for NISs today.

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Abstract Code: ISP3858-52

Assessing the Comparative Safety and Tolerability of Antipsychotic Drugs

E. Spina[1]

(1) Department of Clinical and Experimental Medicine, University of Messina, Messina, Italy

Antipsychotic drugs, conventionally divided into first- and second-generation antipsychotics, are effective in the treatment of psychotic disorders, including schizophrenia and bipolar disorder. The use of antipsychotics is associated with a wide range of potential adverse effects which may impair the quality of life, lead to poor adherence to medication and cause physical morbidity and increased mortality. Assessment of the safety and tolerability of antipsychotics is mainly based on randomized clinical trials, observational studies and post-marketing surveillance. Each of these sources has its own strengths and weaknesses. Moreover, a variety of methodological issues hamper the interpretation of data on antipsychotic tolerability and few studies compare antipsychotics head-to-head. Over the past decade, newer antipsychotics have become the treatment of choice for psychotic disorders due to the perception of a more favourable tolerability profile as compared to traditional compounds. In particular, they tend to be characterized by a lower propensity to produce acute extrapyramidal symptoms and tardive dyskinesia than older compounds. Moreover, with exception of risperidone and amisulpride, newer medications have a weak potential to cause hyperprolactinaemia. There are important differences among second-generation antipsychotics in the relative risk of other adverse effects. In this respect, clozapine and olanzapine tend to be associated with more weight gain and disturbances in lipid and glucose regulation than other newer agents, while ziprasidone appears to carry the higher risk of prolongation of heart rate-corrected QT interval. Sedation, antimuscarinic adverse effects, postural hypotension, seizures and agranulocytosis are more common with clozapine than with other newer antipsychotics. A consistent approach to collecting and presenting side-effect data from studies with antipsychotics would contribute to the development of a more robust evidence base for comparing the safety and tolerability of individual compounds, thus enabling physicians to make more informed decisions about treatment options.

Abstract Code: ISP3861-46

Identification of Risk Factors for Severe Hypersensitivity Reactions in General Anaesthesia

J. Schroeder[1], D. Preziosi[1], C. Mirone[1], C. Stafylaraki[1], A. Mascheri[1], L.M. Losappio[1], L. Farioli[1], M. Michelatti[1], G. Scibilia[1], M.G. Aversano[1], L. Balossi[1], E.A. Pastorello[1]

(1) Allergy and Immunological Unit, Niguarda Ca' Granda Hospital, Milan, Italy

Background: Hypersensitivity reactions to anaesthetic agents are rare but often severe with a mortality ranging from 3.5 to 10 % in IgE mediated events. The knowledge of the risk factors may help reduce the incidence. The aim of the study was to identify the specific risk factors for severe peri-operative hypersensitivity reactions in our study population.

Method: For this study we retrospectively reviewed 128 patients (84 F, 44 M) who presented with suspected drug hypersensitivity reactions during general anaesthesia. The diagnostic protocol consisted of (1) history of the reaction, (2) measurement of serum baseline tryptase (sBT), (3) skin tests for agents received during the anaesthesia and for others likely to be safe for future use, (4) subdivision of our patients on the basis of two criteria: (a) severity of clinical reactions according to Ring and Messmer classification; (b) results of skin tests.

Results: 128 patients (84F, 44M) were evaluated, 54/128 (42.18 %) were atopic, 86/128 (67.18 %) reported hypersensitivity reactions to other drugs, 25/128 (19.53 %) suffered from bronchial asthma. Skin tests were positive in 24/128 patients; 20/24 (11F, 9M) were positives to at least one neuromuscular blocking agent (NMBA), 1/24 atropine, 3/24 ketamine and 3/97 to latex. Women were older than men ($p < 0.00005$). Severe reactions were observed in women more than men (34.5 % vs 27.7 %). No difference was observed between IgE- and non-IgE-mediated reactions when the incidence of atopy, asthma, food hypersensitivity, thyroid diseases and treatment with beta-blockers or ACE-inhibitors were compared. History of hypersensitivity to antibiotics was more frequently reported in IgE-mediated reactions ($p = 0.087$). Treatment with ACE-inhibitors was associated with more severe reactions ($p = 0.016$). We found that a higher basal typtase level was associated with more severe reactions ($p = 0.0277$).

Conclusion: In our study, as reported in the literature, NMBA represented the most common cause of IgE-mediated reactions during general anesthesia. We also found a significant correlation between level of basal tryptase and severity of reaction to general anesthetics opening new prospectives for useful biomarkers of anaphylactic reaction. ACE-

inhibitors treatment is a risk factor for more severe reaction to anaesthetic agents.

Abstract Code: ISP3863-48

Injectable and Oral Contraceptive Use and Cancers of the Breast, Cervix, Ovary, and Endometrium in Black South African Women

M. Urban[1], E. Banks[2], S. Egger[3], K. Canfell[3], D. O'connell[3], V. Beral[4]

(1) NHLS/MRC Cancer Epidemiology Research Group, National Laboratory Services, Johannesburg, South Africa, (2) National Centre for Epidemiology and Population Health, The Australian National University, Canberra, Australia, (3) Cancer Council New South Wales, Sydney, Australia, (4) Cancer Epidemiology Unit, University of Oxford, Oxford, UK

Background: Oral contraceptives are known to influence the risk of cancers of the female reproductive system. Evidence regarding the relationship between injectable progestogen-only contraceptives and these cancers is limited, with the latest assessment from the International Agency for Research on Cancer concluding that there was inadequate evidence in humans for the carcinogenicity of progestogen-only contraceptives. In black South African women injectable contraceptives are almost all progestogen-only preparations and used more commonly than oral contraceptives.

Objective: To investigate the relationship between use of oral and injectable hormonal contraceptives and cancers of the breast, cervix uteri, ovary and endometrium.

Methods and Results: We analysed data from a South African hospital-based case–control study of black females aged 18–79 years, comparing self-reported contraceptive use in patients with breast (n = 1,664), cervical (n = 2,182), ovarian (n = 182), and endometrial (n = 182) cancer, with self-reported contraceptive use in 1,492 control patients diagnosed with cancers with no known relationship to hormonal contraceptive use. We adjusted for potential confounding factors, including age, calendar year of diagnosis, education, smoking, alcohol, parity/age at first birth, and number of sexual partners. Among controls, 26 % had used injectable and 20 % had used oral contraceptives. For current and more recent users versus never users of oral or injectable contraceptives, the odds ratios (ORs) for breast cancer were significantly increased in users of oral and/or injectable contraceptives (OR 1.66, 95 % CI 1.28–2.16, $p < 0.001$) and separately among those exclusively using oral (1.57, 1.03–2.40, $p = 0.04$) and exclusively using injectable (OR 1.83, 1.31–2.55, $p < 0.001$) contraceptives; corresponding ORs for cervical cancer were 1.38 (1.08–1.77, $p = 0.01$), 1.01 (0.66–1.56, $p = 0.96$), and 1.58 (1.16–2.15, $p = 0.004$). There was no significant increase in breast or cervical cancer risk among women ceasing hormonal contraceptive use $\geq$10 years previously ($p = 0.3$ and $p = 0.9$, respectively). For durations of use $\geq$5 years versus never use, the ORs of ovarian cancer were 0.60 (0.36–0.99, $p = 0.04$) for oral and/or injectable contraceptive use and 0.07 (0.01–0.49, $p = 0.008$) for injectable use exclusively; corresponding ORs for endometrial cancer were 0.44 (0.22–0.86, $p = 0.02$) and 0.36 (0.11–1.26, $p = 0.1$).

Conclusions: In this study, use of oral and of injectable hormonal contraceptives was associated with a transiently increased risk of breast and cervical cancer and, for long durations of use, with a reduced risk of ovarian and endometrial cancer. The observed effects of injectable and of oral contraceptives on cancer risk in this study did not appear to differ substantially.

Abstract Code: ISP3864-49

Severe Cutaneous Adverse Drug Reactions

J. Schroeder[1]

(1) Allergy and Immunology Unit, Niguarda Hospital, Milan, Italy

Stevens–Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN) has been defined as the same disease spectrum with different degrees of severity and extent of skin detachment. They are recognized as severe cutaneous adverse drug reactions (SCAR). SJS and TEN are characterized by cutaneous erythema with blister formation of various extent and hemorrhagic erosions of mucous membranes, such as stomatitis, balanitis, colpitis, severe conjunctivitis and blepharitis. Mucositis generally precedes skin lesions by a few days. Frequently fever and malaise are the first symptoms of the disease, which may persist or even increase once the mucocutaneous lesions appeared.

Although rare (1–2/million population/year), SJS and TEN remain of high interest in the field of drug safety because of their high mortality. Death rates vary between less than 10 % in SJS and more than 45 % in TEN, with an overall mortality of about 20–25 %. Precise identification of the causative drug is essential because the mainstay of therapy and future prevention is to discontinue and avoid the use of the suspected inducing drug. In the acute phase, withdrawal of the suspected medication is an urgent requirement for improving the immediate prognosis, whereas other treatments often need to be continued. Many cases occur in patients who are taking multiple medications. Categories of drugs were identified including drugs with a high risk, drugs with a moderate risk, drugs most likely not associated with severe skin reactions, and drugs with a high potential for confounding by indication (LES, infection or fever).

During last years, we fixed a diagnostic and therapeutic protocol in order to give the same treatment to all patients coming to our Burns Unit. We noticed the topical treatment importance, as it is about patients with wide skin alterations, also named acute skin failure, that causes metabolic, kidney, immunological alterations and a thermoregulation imbalance. One of our main goals is the infection decrease, as this represents the first cause of death. Since 2006 we have admitted to our Unit 38 patients with a skin involvement up to 90 % of the body surface. None of the patients had a skin infection. All patients have been treated with intravenous immunoglobulins, followed by a quick and usually complete recovery of the skin. During the period in hospital, a physiotherapy is carried out early. In addition, they are examined several times by ophthalmologists. We also cooperate with the patients association, in order to widespread the pathology information and to gain the rare disease recognition.

Abstract Code: ISP3867-52

Is There Any Additional Value in Mining Electronic Medical Records for Drug Safety Signal Detection? The EU-ADR Experience

G. Trifirò[1,2], P. Coloma[2], M. Schuemie[1], M. Strurkenboom[1], J. Van Der Lei[1], on behalf of EU-ADR Consortium

(1) Department of Medical Informatics, Erasmus University Medical Centre, Rotterdam, The Netherlands, (2) Department of Medical Informatics, Erasmus University Medical Centre, Rotterdam, The Netherlands

The safety profile of medicines requires a continuous monitoring in clinical practice as pre-marketing randomized clinical trials are not sufficient to identify all the potential adverse drug reactions (ADRs). One of the primary aims of pharmacovigilance is to detect drug safety signals, i.e. drug-adverse event associations which are unknown or incompletely documented. Traditionally, both regulators and manufacturers have used computerized data mining techniques on reports of ADR from both healthcare practitioners and consumers to detect signals. However, spontaneous reporting systems (SRSs) have inherent limitations due to extensive under- and selective ADR reporting as well as missing denominator. To overcome these shortcomings, in the last years a number of ongoing international initiatives (FDA's Sentinel, Protect, OMOP, EU-ADR) has started to explore longitudinal observational healthcare data, including electronic health records (EHRs) and claims databases as additional source for signal detection. The ultimate goal of the EU-ADR project was to develop an innovative, computerized system for the automatic detection of drug safety signals. Using a database network of seven databases from three European Countries covering around 30 million inhabitants, EU-ADR developed new methodologies for signal detection and compared the performance of signal detection using either claims data/EHRs or SRS through reference standards. Main findings of the project are that systems such as EU-ADR may not be powered enough to explore infrequently used/captured drugs as well as rare adverse events, while it may have additional value for those adverse events with higher background incidences rate and which are not commonly reported to SRS (e.g. acute myocardial infarction). EU-ADR contributed new evidence about: (a) developing reference standards for testing methodologies; (b) performing methods for signal detection using EHRs and claims databases; (c) minimizing the identification of spurious signals; and d) prioritizing potential signals which require further evaluation. All these methodological issues necessitate further investigations.

Abstract Code: ISP3868-53

Signal Detection Analysis on Vaccines

U. Moretti[1]

(1) Clinical Pharmacology Unit, Regional Pharmacovigilance Centre of Veneto Region, University Hospital of Verona, Verona, Italy

Analysis of spontaneous reports of Adverse Events Following Immunization (AEFIs) is an important way to identify potential problems in vaccine safety. Spontaneous reports related to vaccines are generally collected together with the reports related to all the other drugs in the databases of the European Countries, and all these reports are present in Eudravigilance.

The signal detection process for both vaccines and other drugs is a complex process that include a case by case analyses and the use of statistical tools that look for a disproportionate reporting of specific vaccine-event combinations. Initial signal assessment involves reviewing the reports to characterize clinical features, verify diagnoses, assess other potential risk factors, and evaluate the interval between vaccination and the adverse event. The causality assessment evaluation of the strength of the association between the vaccine and the adverse event is an important issue and this evaluation has different aspect in vaccines compared to the other drugs. Information on dechallenge and rechallenge are often not applicable for vaccine report. Moreover vaccination involves almost the whole paediatric population and it could be very difficult to evaluate whether serious adverse events are causally linked to a specific vaccine or only temporally associated with the vaccine by chance. Knowing the background rates of relevant diseases would assist in deciding when the number of events exceeds the expected count of non-causally linked events.

The statistical tools like the Proportional Reporting Ratio (PRR) or the Bayesian methods are often used in signal detection. Based on the hypothesis that all the reactions are reported in the same proportion for all drugs, the methods used in this context analyze a disproportionate reporting of a vaccine-event pair. Vaccines may require special consideration when applying such tools. Intrinsic differences between vaccines and other medicinal products should be considered, for example frequent reporting of unrelated adverse events in the target population. Furthermore, the safety profile of a vaccine may differ substantially within the target population (e.g. higher risks in the youngest age groups). In order to reduce background noise, estimates of disproportionality should be calculated based on a comparison across groups that have a similar age-specific background risk for illness. A comparison with all medicinal products may result in the detection of reactions specifically related to vaccines. On the other hand, using only vaccine-related reports available in the database may result in signals of age-related reactions (e.g. cardiovascular disorders if the vaccine of interest is used in the elderly).

References

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Abstract Code: ISP3874-50

How to Identify and to Prevent Safety Issues of Newer Antiplatelet and Antithrombotic Treatments

J. Harenberg[1]

(1) Clinical Pharmacology, Medical Faculty Mannheim, University of Heidelberg, Mannheim, Germany

Antiplatelet and antithrombotic drugs are the treatment of choice for arterial and venous thromboembolism, respectively. Specific guidelines define the administration in various diseases. Antiplatelet drugs such as aspirin are indicated for patients with atrial fibrillation and a risk score according CHADS2 (c = cardiac failure, h = hypertension, a = age above 75 years, d = diabetes, s2 = stroke with 2 points) of o and 1,

whereas vitamin-K antagonists (VKA) or oral direct anticoagulants (DOAC) are indicated at risk score >1. Multiple new studies indicate, that for patients with acute coronary syndrome, new antiplatelet agents prasugrel and ticagrelor on top of aspirin and may be more effective and safe than clopidogrel. Other studies indicate that a combination of new antiplatelet and antithrombotic agents have a higher benefit risk ratio compared to standard antithrombotic regimens.

Accordingly, the field of new antithrombotic regimens is developing rapidly. Ticagrelor and prasugrel are approved for treatment of unstable angina. The DOAC dabigatran, rivaroxaban and apixaban are well accepted by practitioners and they are increasingly prescribed for prevention of embolism in patients with non-valvular atrial fibrillation. In addition rivaroxaban is approved in many countries for treatment of acute venous thromboembolism. They have taken over about 20 % of antithrombotic therapy from VKA. The optimism for the new antithrombotic drugs leads to the disadvantage of less screening for side effects by the practitioners. Rare side effects are almost not reported in the literature.

Due to the complex pathophysiology of acute coronary syndrome the DOAC were investigate on top of aspirin and clopidogrel. All studies reported on an increase of major bleeding events. Further development of dabigatran and apixaban is this indication was terminated. Rivaroxaban received recently approval with a very low dose of 2.5 mg bid on top on antiplatelet therapy. The latest developments in clinical studies are the investigation of combinations of prasugrel or ticagrelor with low doses of rivaroxaban for prevention of recurrent events following acute coronary syndrome.

Identification of safety issues requires an increased awareness of practitioners mainly due to the general optimism for DOAC. This group of anticoagulants may increase in every clinical circumstance leading to a reduced renal function. Thus unforeseen accumulation may occur in specific clinical indications. The new antiplatelet therapies also lead to bleeding complications. However, the awareness of practitioners is trained by the other antiplatelet compounds.

Prevention of side effects for new antithrombotic agents requires careful examination and careful prescription of concomitant drugs. Specific attention has to be paid to concomitant use of DOAC with antiplatelet agents. The best option may be to consult a specialist for such therapeutic regimens. Specific test systems may help to identify accumulation of these agents and adherence to therapy.

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