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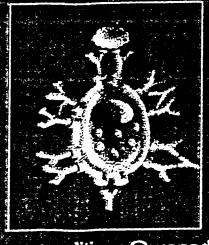

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NASAL AND BRONCHIAL TOLERABILITY OF ROFECOXIB IN PATIENTS WITH ASPIRIN INDUCED ASTHMA

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SUMMARY: Aspirin (ASA) and several other nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit cyclo-oxygenase (COX) enzyme both isoforms 1 and 2, and can precipitate asthmatic attacks in aspirin-induced asthmatics. Rofecoxib (R) is a novel and specific COX-2 inhibitor which is caracterized by an highly selective COX-2 inhibition, and can be presumed as non cross-reactive with ASA.

Aim of the study was to assess the bronchial and the nasal response to R in AIA.

Materials and methods: Nineteen subjects with AIA (21-54 years, 7 m, mean FEV_1 85.1% pred. ± 5.4 sd) performed two oral provocation tests: one with increasing doses of ASA and one other of R at a time interval of 2 weeks, according to a randomized, cross-over design. The bronchial and the nasal responses were measured by serial measures of FEV_1, and of nasal resistences by acoustic rhinomanometry, respectively.

Statistics: Anova for trends was used, and $p<0.05$ accepted.

Results: Mean ASA PD_{20} was 68.3 mg ± 12.4 sd. ASA induced a significant broncho-constriction in all patients with AIA: basal FEV_1 dropped from 88.9% pred. ± 6.2sd to 70.1% pred. ± 6.9sd after 60min. (Anova $p = 0.001$). Despite ASA, R was well tolerated: basal FEV_1 remained unchanged during the period of observation following the R 25mg ingestion. ASA also precipitated a significant nasal response with increased nasal resistances (anova $p < 0.001$) and reduced volumes (anova $p < 0.001$). The nasal function was unchanged following R 25mg.

Conclusions: Despite ASA, Rofecoxib, largely due to its highly specificity for COX-2, proved a drug particularly safe in treating patients with AIA.

Key words: aspirin induced asthma/COX-2 specific inhibitors/Rofecoxib.

Aspirin-induced asthma (AIA) is known as a syndrome characterised by acute asthma attacks often related to nasal symptoms which are usually worsen by oral administration of aspirin (ASA) and other non-steroidal anti-inflammatory drugs (NSAID) (1). Chronic nasal congestion is the major clinical manifestation of AIA. Watery rhinorrhea and nasal obstruction, which lead to frequent development of nasal polyps, precede the appearance of asthma and ASA intolerance for months or years (2). ASA administration in these individuals is followed by the onset of bronchospasm within 30 to 90 min. Moreover, up to 90 % of AIA subjects challenged with provocative doses of ASA demonstrate also a nasal response heralded by rhinorrea and nasal obstruction (3).

Aggressive nasal polyps and asthma run a protracted course, despite the avoidance of ASA and cross-reacting drugs. Blood eosinophil counts are raised, and eosinophils are present in nasal mucosa and bronchial airways (4). AIA is difficult to treat and frequently the patients require a treatment with systemic corticosteroids to control symptoms.

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The precise mechanism behind this non-immunological hypersensitivity remains unclear, however it has been hypothesised that the capability of these agents to provoke asthma is related to their potent action as inhibitors of cyclooxygenase (COX) (5-6). Arachidonic acid, released from cell membrane phospholipids by the action of phospholipase A_2, may be metabolized by the COX pathway to prostaglandins and thromboxane A_2, or by the 5-lipoxygenase pathway to sulfidopeptide leucotrienes (LTs): LTB_4, LTC_4, LTD_4, LTE_4. The recent discovery that COX could be present in cells in both a constitutive (COX-1) and an inducibile form (COX-2) led to new roads in the interpretation of these phenomena (7). Both isoforms contribute to the inflammatory process, but COX-2 is of higher therapeutic interest as it is induced, and resulting in an anhanced formation of prostaglandins during both acute and chronic inflammation. Conventional NSAID inhibit both isoforms to a similar extent and in an approximately equal dose and concentration range.

Celecoxib and Rofecoxib are COX-2 inhibitors which are about 100-1000 times more selective on the COX-2 than on the COX-1 isoform, and, due to their selectivity, no cross reactivity between ASA and Rofecoxib was described in ASA sensitive subjects (8).

Furthermore, Rofecoxib proved well-tolerated in patients with AIA in different trials (9-11).
Aim of this study was to assess both the bronchial and the nasal effects of Rofecoxib in patients with AIA

MATERIALS AND METHODS

Subjects

Nineteen patients with AIA entered for the study after their informed consent (tab1). Patients were selected on the basis of a clear past history of significant reactions to inadvertent ingestion of ASA, with features of naso-ocular symptoms and severe bronchospasm. All patients suffered also from chronic rhinosinusitis, and four had also nasal polyps.
Before oral challenge, patients stopped their medications: oral antihistamines for 7 days; nasal cromolyn sodium and nasal or inhaled corticosteroids for 1 week; nasal antihistamines for at least 48 hours before the test, short acting inhaled β2-adrenergic for at least 6 hours; and long acting inhaled β2-adrenergic for at least 12 hours.
The study was a randomised, double-blind, placebo controlled, cross-over study, consisting of two 5-day challenge periods: every morning, patients assumed a drug (ASA or R); on the first challenge day all patient assumed placebo.

age	21-54 ys
sex	7 m, 12 f
FEV_1 (% predicted)	85.1 ± 5.4sd
Nasal Req (mmH_2O/l/min)	0. 9 ± 0.2sd
Nasal volume (cm^3)	11.1 ± 3.2sd
Minimal cross sectional area (cm^2)	5 .9 ± 2.2sd

Table 1. Demographic and basal (lung and nasal) characteristics of subjects.

■ **Oral challenge test with ASA;** Oral challenge was carried out on two consecutive days (12). On the first day, five tablets of placebo were administered every 2 hours, and FEV_1 changes < 15% from baseline were tolerated. If greater falls in FEV_1 occurred, patients were considered clinically instable and then excluded from further analysis. On the second day, subjects ingested 10mg of ASA, and serial measurements of FEV_1 were performed at 30, 60, and 120 min. If the FEV_1 drop was <20%, 30mg of ASA were given and FEV_1 measured. Increasing doses of ASA (50,100, 250 and 500 mg) were further given at 2-hour intervals until reaching a > 20% fall in FEV_1.
Pulmonary function (forced vital capacity, FVC; forced expiratory volume in 1 sec, FEV_1; and mean maximal expiratory flow, MMEF) were measured by means of a computerized pneumotachograph (Masterlab, Jaeger). The provocative dose which caused a 20% fall in FEV_1 was calculated and recorded as PD_{20} ASA oral, and derived by linear interpolation from the respective log_{10} cumulated dose-response curves.

■ **Oral challenge with Rofecoxib:** At a two-week interval from the ASA-challenge, Rofecoxib was administered in progressively increasing doses. On day two, subjects ingested initially 12.5 mg of R, with serial measurement of FEV_1 after 30, 60, and 120 min. If the decrease in FEV_1 was <20%, R 25mg was given and FEV_1 measured at the same time intervals. If the decrease in FEV_1 was <20%, R 50mg was given and FEV_1 was measured for other two hours.

■ **Acoustic rhinomanometry:** At the same experimental times, also nasal function was assessed by means of acoustic rhinomanometry (13). This method involves the measurement of acoustic reflections from the nasal cavity of a sound pulse created by a spark in a sound tube connected to the nasal cavity via a nosepiece. Unlike traditional rhinomanometry, acoustic rhinomanometry does not require generation of nasal flow and therefore its use is less limited by the presence of nasal polyps and nasal obstruction (14). The response was evaluated by Eccovision Acoustic Rhinomanometry System (TM Hood Laboratories, USA), and the indices measured were:
1) calculated resistance, based on a tube with the same area and laminar flow (Req, mmH_2O/l/min);
2) total volume of the nostril (cm^3) represents the nasal cavity volume in the analysis segment;
3) minimal cross sectional area (cm^2) and its distance from the nosepiece.
Rhinometric measurements were performed while the subject was in apnoea after a non- forced expiration. The rhinomanometer was calibrated daily with a calibration tube provided by the manufacter. Data were calculated using the Kwikstat program (TM Texasoft).
Clinical symptoms scored included rhinorrhea; nasal congestion; itching or burning of the nose, ear, palate or throat; sneezing and lacrimation. The intensity of these symptoms were expressed with the following scale: 0, none; 1, mild; 2, moderate; 3, severe. Total nasal score at each time interval was calculated as a sum of the above individual scores, being the maximal score = 15 points.
Basal nasal function was assessed while subjects in sitting position.

Criteria for the positivity of challenge tests

The challenge test with ASA or R was interrupted if a FEV_1 drop of at least 20% was observed; or when

nasal resistance increased more than 40% from baseline in at least one nostril and the volume in one nostril decreased more than 10% from baseline (both nasal parameters sustained for at least two consecutive measurements and accompanied by clinical symptoms persisting at least 30 minutes).
Challenge was considered positive also if strong extrabronchial symptoms occurred, such as redness of the face and the upper chest, ocular injection, and/or periorbital swelling, nausea and stomach cramps.

■ **Statistical analysis:** Anova for trends was used for statistics, and $p < 0.05$ accepted.

■ **Results:** Mean ASA PD_{20} was 68.3mg ± 12.4sd. Placebo challenge did not induce any significant change of variables in all subjects. ASA induced a significant broncho-constriction in all patients with AIA, being observed a FEV_1 drop always > 20% baseline. Nasal discharge and/or nasal blockade occurred in all patients, with a nasal resistance increase of more than 40% baseline in at least one nostril, and the nasal volume decrease of more than 10% baseline. Symtpoms were relieved by β2-adrenergics short-acting and only four times oral corticosteroids were used.
A significant broncho-constriction occurred after the provocative dose of ASA: basal FEV_1 changed from 88.9% pred. ± 6.2sd to 84.3% pred. ± 7.3sd after 30 min. from the ASA PD_{20}; to 70.1% pred. ± 6.9sd after 60m,in and 76.1% pred. ± 4.9sd after 120 min (anova p = 0.001). On the contrary, Rofecoxib was well tolerated without any sign of both immediate or delayed reactions: basal FEV_1 changed from 90.1% pred. ± 5.8sd to 87.8% pred. ± 5.3sd after 30 min. from the ingestion of R 25mg to 86.6% pred. ± 6.1sd after 60min, and to 88.3% pred. ± 5.3sd after 120min (anova p = ns). No FEV_1 decrease >20% was observed (tab.2).
ASA also precipitated a significant nasal response: basal nasal resistance changed from 0.78cmH_2O/l/min ± 0.4sd to 0.84cmH_2O/l/min ± 0.6 sd after 30 min from the ASA PD_{20}; to 1.54 cmH_2O/l/min ± 0.59 d after 60 min, and to 1.45 cmH_2O/l/min ± 4.9sd after 120min (anova $p < 0.001$). Furthermore, basal nasal volume changed from 14.78 cm^3 ± 3.59sd to 11.8 cm^3 ± 4.6sd after 30 min from ASA PD_{20}, to 7.54 cm^3 ± 3.6sd after 60min, and to 8.45 cm^3 ± 5.69sd after 120min (anova $p < 0.001$) (tabb. 3-4).
On the other hand, R was particularly safe also in nasal terms: basal nasal resistances changed from 0.81 cmH_2O/l/min ± 0.4sd to 0.86 cmH_2O/l/min ± 0.5sd after 30 min from the ingestion of R 2 mg to 0.85 cmH_2O/l/min ± 0.4sd after 60min, and to 0.82 cmH_2O/l/min ± 0.4sd after 120 min (anova = ns). Basal nasal volume changed from 15.8 cm^3 ± 4.5sd to 15.6 cm^3 ± 4.7sd after 30min from the ingestion of R 2 mg to15.0 cm^3 ± 5.0 sd after 60min, and to 15.8 cm^3 ± 5.4sd after 120min (anova = ns) (tabb.3-4).

DISCUSSION

In about 10 % of adult asthmatics, but rarely in asthmatic children, ASA and other NSAID worsen asthma attacks (1). Most patients with AIA present a peculiar clinical syndrome related to ASA sensitivity, such as bronchial asthma and chronic rhinosinusitis, with nasal polyposis. A recent univariate analyses in the Asthma Foundation cohorts (15) indicated that AIA was associated with more severe asthma, nasal polyposis, atopy, sulfite sensitivity and sensitivity to wine. In AIA patients, the assumption of drugs for the management of common medical conditions, such as pain, fever and inflammation, represents a crucial problem. The choice of safe NSAIDs is very restricted, because the occurrence of adverse reactions can be

	baseline	after 30min	after 60min	after 120 min	p
ASA challenge	88.9 ± 6.2	84.3 ± 7.3	70.1 ± 6.9	76.1 ± 4.9	< 0.001
ROFECOXIB challenge	90.1 ± 5.8	87.8 ± 5.3	86.6 ± 6.1	88.3 ± 5.3	ns

Table 2. Lung function (FEV_1 %pred.) after oral challenge test with ASA (measures after PD_{20}) and after Rofecoxib 25mg.

	baseline	after 30min	after 60min	after 120 min	p
ASA challenge	0.78 ± 0.4	0.84 ± 0.6	1.54 ± 0.4	1.45 ± 4.9	< 0.001
ROFECOXIB challenge	0.81 ± 0.5	0.86 ± 0.6	0.85 ± 0.4	0.82 ± 0.4	ns

Table 3. Nasal function (REQ, mmH_2O/l/min) after oral challenge test with ASA (measures after PD_{20} ASA) and after Rofecoxib 25mg.

	baseline	after 30min	after 60min	after 120 min	p
ASA challenge	14.78 ± 3.4	11.8 ± 4.6	7.54 ± 3.59	8.45 ± 5.5	P<0.001
ROFECOXIB challenge	15.81 ± 4.5	15.62 ± 4.7	15.02 ± 5.0	15.82 ± 5.4	ns

Table 4. Nasal function (VOL, cm^3) after oral challenge test with ASA (measures after PD_{20} ASA) and 25 mg of Rofecoxib.

life-threatening, and are feared by both patients and doctors. Therefore, patients who have adverse reactions to ASA and NSAIDs, need alternative drugs.

ASA precipitates asthmatic attacks in sensitive patients not through an allergic mechanism, but by a pharmacological action, namely by the inhibition of cyclooxygenase. Several observations strongly support the notion that the COX pathway is abnormally regulated in AIA, as reflected by the lowered production of PGE2 (3-5, 16) and the increased production of cysteinyl-leukotrienes (LT)(6). LT are synthesized through the 5-lipoxygenase pathway of arachidonic acid metabolism and are important mediators in AIA (17-19). In particular, LTE_4 concentrations in the urine are basalt elevated in ASA-sentivive asthmatics before ASA challenge, with a mean fourfold increase at 3-6 hours following ASA ingestion, which is coinciding with ASA-induced respiratory reactions (20). The severity of respiratory reactions during the oral ASA challenge was directly related to the extent of baseline LTE_4 synthesis (21), so suggesting that asmatics with asprin-sensitive respiratory disease have a spectrum of reactions in which leukotrienes play a crucial role.

COX enzymes exist in at least two isoforms, COX-1 and COX-2, with similar molecular weights and encoded by distinct genes. COX-1 is a constituent of healthy cells: it is expressed in normal conditions and it is responsible for the physiological production of prostaglandins.

COX-2, the inducible isoform, is the major isoenzyme associated with inflammation, it can be induced by various stimuli, including inflammatory cytokines, resulting in further production of inflammatory substances such as prostanoids (22). ASA, and most NSAIDs, inhibit both isoforms (although at different intensities), being their capability of inhibiting COX *in vitro* and of inducing bronchospasm in sensitive patients directly related (23). The ability of NSAIDs to inhibit COX-2 may explain their therapeutic potentiality as anti-inflammatory drugs, whereas inhibition of COX-1 may account for their unwanted side-effects, such us asthma attacks, nasal obstruction, gastric damage and toxic effects on the kidney (24-25).

This finding has provided a reasonable basis for the development of specific COX-2 inhibitors as a new class of anti-inflammatory agents (26). So, new drugs have emerged that have shown much more specificity: Nimesulide and Meloxicam are known to inhibit COX-2 at a greater extent than than COX-1, and are well-tolerated also by ASA-sensitive asthmatics (27-28). Celecoxib, another COX-2 inhibitor, does not affect basal airway tone, nor afferent airway receptors controlling bronchocostrinction and cough in a group of asthmatics (29-30).

Rofecoxib, a methylsulphonylphenyl derivate, is a novel COX-2 inhibitor with a biochemical and pharmacologic profile that is clearly distinct from that of the NSAIDs currently in use (7). The sole bronchial tolerance of Rofecoxib was already evaluated in ASA-intolerant patients (9-11), but both the spirometric and the nasal response to ingestion of ASA and Rofecoxib were, at our knowledge, never compared previously. Only patients with AIA whose clinical histories of intolerance had been consistently supported by oral challenge procedures, were chosen, and they were included only if also nasal function was deteriorated following the ASA challenge.

The nasal tolerability of these drugs represents a crucial aspect for both patients and doctors: chronic nasal congestion is in fact the major clinical manifestation of AIA. Watery rhinorrhea and nasal obstruction, leading to frequent development of nasal polyps, precede the appearance of asthma and ASA intolerance for months or years (2). Rofecoxib proved free of nasal and bronchial symptoms in patients with AIA also when maximal therapeutical doses were assumed.

Rofecoxib, due to its high COX-2 specificity has to be regarded as particularly safe both in bronchial and nasal terms in patients with AIA.

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