Ultrasound in Med. & Biol., Vol. 32, No. 9, pp. 1369–1375, 2006

0301-5629/06/$–see front matter

ELSEVIER

doi:10.1016/j.ultrasmedbio.2006.05.031

● *Original Contribution*

THE SAFETY OF SONOVUE® IN ABDOMINAL APPLICATIONS: RETROSPECTIVE ANALYSIS OF 23188 INVESTIGATIONS

FABIO PISCAGLIA and LUIGI BOLONDI ON BEHALF OF THE ITALIAN SOCIETY FOR ULTRASOUND IN MEDICINE AND BIOLOGY (SIUMB) STUDY GROUP ON ULTRASOUND CONTRAST AGENTS[1]

Division of Internal Medicine, Department of Internal Medicine and Gastroenterology, University of Bologna, Bologna, Italy

(*Received* 28 *February* 2006, *revised* 17 *May* 2006, *in final form* 23 *May* 2006)

Abstract—The aim of the present retrospective study was to assess the incidence of adverse events (AE) of a second-generation ultrasound contrast agent in real clinical practice. A total of 28 Italian Centres provided data on the postmarketing use of SonoVue® (Bracco Spa, Milan, Italy) in abdominal examination performed between December 2001 and December 2004. A total of 23 188 investigations were reported. No fatal event occurred. AEs were reported in 29 cases, of which only two were graded as serious; the rest, 27, were nonserious (23 mild, three moderate and one severe). The overall reporting rate of serious AE was 0.0086%. Overall, only four AEs required treatment (two serious, two nonserious including one moderate and one severe AEs). In conclusion, the present large-scale retrospective analysis showed that SonoVue has a good safety profile in abdominal applications, with an AE reporting rate lower than or similar to that reported for radiologic and magnetic resonance contrast agents. (E-mail: Piscagl@med.unibo.it)

Key Words: **Adverse effect, Contrast agents, Contrast-enhanced ultrasonography, Ultrasound.**

INTRODUCTION AND LITERATURE

Extraordinary progress has been made in the diagnostic potential of ultrasonography in recent years, due to the combination of ultrasound contrast agents and contrast-specific imaging techniques. Dedicated ultrasonography using low acoustic energy emission (mechanical index <0.3) applied to highly flexible contrast microbubbles, the so-called second-generation contrast agents, produce reduced intravascular microbubble destruction, allowing prolonged *in vivo* circulation time of the contrast agents and real-time continuous scanning (Albrecht et al. 2004; Gaiani et al. 2004; Hohmann et al. 2003; Piscaglia et al. 2003). SonoVue® (Bracco Spa, Milan, Italy) is one of the second-generation ultrasound contrast agents, constituted by stabilised microbubbles containing sulphur hexafluoride, an echogenic, poorly soluble gas (Schneider et al. 1995) approved for abdominal imaging including microvasculature enhancement, *e.g.*, for liver lesion characterisation (Bartolotta et al. 2005; Gaiani et al. 2004; Hohmann et al. 2003; Piscaglia et al. 2003; Quaia et al. 2004), commercialised in Italy since the end of 2001. Other organs are also occasionally investigated (Quaia et al. 2003) since more new indications are being investigated and established. Based on the available data, SonoVue has been considered safe and utilised in both in- and out-patient clinics. No fatal adverse event (AE) related to SonoVue has been reported in the clinical trials used to obtain marketing authorisation (EMEA 2005a). However, in May 2004, Bracco informed the European Medicines Agency that the United States Food and Drug Administration (FDA) had placed their ongoing SonoVue clinical studies in liver imaging and myocardial perfusion imaging on clinical hold in April 2004, based on safety data derived from spontaneous post-marketing surveillance reports in Europe (EMEA 2005b). Three serious events with fatal outcomes in patients with coronary artery disease were of particular concern, due to their close temporal relationship to SonoVue administration for cardiac imaging. After the subsequent reassessment of the risk-safety profile of SonoVue by experts and the cat-

Address correspondence to: Fabio Piscaglia, Div. of Internal Medicine, Via Albertoni 15, 40138 Bologna, Italy. E-mail: Piscagl@med.unibo.it

[1] L. Aiani, M. Luigi Angeli, V. Arienti, L. Barozzi, R. Basilico, M. Bertolotto, E. Biasini, P. Busilacchi, F. Calliada,* M. Caremani, E. Caturelli, N. Celli, A. Colecchia, L. Cova, M. Assunta Cova, L. Crocetti, I. de Sio, F. Drudi, G. Ferraioli, C. Filice, F. Fornari, S. Gaiani, F. Giangregorio, A. Giorgio, T. Ierace, R. Lencioni, T. Livraghi, F. Magnolfi, A. Martegani, F. Meloni, G. Menozzi, G. Pelosi, M. Pompili, L. Riccardi, P. Ricci, L. Rubaltelli, D. Sacerdoti, G. Serafini, C. Serra, L. Solbiati, D. Tacconi, M. Valentino, G. Vidili and F. Vitali

egorisation of fatal events as idiosyncratic hypersensitivity reactions, not unusual for injectables (Neugut et al. 2001), Europe's Committee for Human Medicinal Products (CHMP) removed the safety restriction for SonoVue (EMEA 2005c) in August 2004, extending contraindications to patients with acute coronary syndrome or other unstable cardiac conditions.

Following these regulatory measures, concerns for the safety of SonoVue temporarily limited the use of this contrast agent. However, information exchanged among the most experienced centres revealed excellent performance data on SonoVue safety in abdominal ultrasound. Hence, the Italian Society for Ultrasound in Medicine and Biology (SIUMB) decided to promote an independent retrospective analysis in Italy on the AE rate in SonoVue-enhanced abdominal ultrasound in clinical practice to access data from a large case series.

MATERIALS AND METHODS

A total of 29 Italian centres were selected because of their experience in liver imaging studies and/or affiliation with the SIUMB. The study was in agreement with the declaration of Helsinki and subsequent amendments and was approved by the hospital Ethics Committee in Bologna. A letter was sent to the responsible person(s) at each of these centres in August 2004, presenting the background of the study and inviting the participants to provide: 1) the total number of investigations in which SonoVue was administered for abdominal imaging and 2) more in detail for investigations of the liver or for other abdominal organs (specifying for which); 3) the dosages of SonoVue most commonly used in each centre and the range of dosages utilised (from the minimun to the maximum for each bolus); 4) the percentage of investigations during which repeat injections were performed; 5) the type of equipment(s) and dedicated protocol used (high or low, threshold 0.2, mechanical index for black and white harmonic imaging or Doppler investigations); and 6) the number and type of AEs occurred (with a description of each event, which had to be graded according to the rules of the Italian Ministry of Health for reporting drug-related adverse events, see below). Patients involved in sponsored SonoVue investigational clinical trials were excluded.

All the AEs were classified into either serious or nonserious, according to the classification of the Italian Ministry of Health for reporting drug-induced reactions. According to this classification, an AE is considered serious if it meets any of the following criteria: 1) resulted in death, 2) involved or prolonged hospitalisation, 3) involved persistent or significant disability or incapacity, 4) was life-threatening and 5) caused congenital anomaly/birth defect; or 6) was a medically important event or reaction.

Nonserious AEs were also graded according to their severity (mild, moderate or severe). Mild AEs were those not resulting in disability/incapacity and resolved without treatment. Moderate AEs were those not resulting in disability/incapacity, but required treatment or assistance. Severe AEs were those resulting in temporary and mild disability/incapacity and required treatment.

The centres were asked to provide descriptions of the reported AEs, if any, and the course, management and outcome of the AEs. After reading the description, the authors also contacted by telephone the physicians providing the report, to go into details of each event and guarantee an homogeneous assessment among the various centres according to the classification reported above. The period of data collection ranged from December 2001 to 31 December 2004, which was the last limit allowed for performed examination that could be included in the study.

RESULTS

A total of 28 out of 29 centres submitted the requested information to the coordinating centre in Bologna. The specialties of the 28 centres involved in the present safety data collection were radiology 13, internal medicine six, gastroenterology five and infectious disease four.

Use of SonoVue

A total of 23188 investigations were available for this safety data collection, ranging in the various centres from 50 to 2930 (Table 1). The vast majority of abdominal contrast-enhanced US scans (about 92%, Table 1) were performed on the liver. Investigations of spleen, kidneys and major abdominal vessels were performed only occasionally and, more often, in Radiology Units than in the other specialties, whereas intestinal walls were studied in some gastroenterology centres. SonoVue has rarely been employed to improve visualisation of large abdominal vessels or to increase signals in color Doppler investigations of liver lesions, these two applications together corresponding to less than 1% of the total investigations. All the remaining were contrast B-mode grey-scale investigations. More than 99% of the latter were performed with a low-mechanical index continuous imaging mode. The dose utilised varied between the various centres and the drug accountability was not feasible in this retrospective data collection. In some centres, a full dose (4.8 mL) was utilised for nearly all examinations, whereas, in others, more than 50 to 60% of the examinations had been performed with a dosage of 2.4 mL (or as low as 1.2 mL). Repeat injections were reported to have been used in about 15% (range 5 to 30%) of the patients.

Table 1. Contrast studies included the in analysis and equipment used at each centre for the present contrast investigation

Centre	Manufacturer and equipment used	Total no. of studies	No. of liver studies	Total no. of AEs	Total no. of serious AEs
1	Siemens - Acuson Sequoia	300	260	5	0
2	Esaote Esatune + Technos MPX	998	844	0	0
3	Esaote Esatune + Aloka 5500	201	195	0	0
4	Esaote Esatune + Technos MPX	1212	1148	3	0
5	Esaote Esatune + Philips ATL5000	1806	1624	1	0
6	Esaote Esatune + Technos MPX	552	490	3	0
7	Philips ATL5000	198	109	0	0
8	Siemens - Acuson Sequoia + Esaote Technos MPX	2930	2630	0	0
9	Philips ATL5000	645	550	2	1
10	Siemens - Acuson Sequoia + Esaote Esatune	1831	1598	0	0
11	Esaote Esatune + Technos MPX	120	104	0	0
12	Aloka 5500 PHD Extended	1521	1498	0	0
13	Philips ATL5000	155	155	0	0
14	Esaote Esatune	160	158	1	0
15	Esaote Esatune MPX + Philips ATL IU22	2135	2115	3	0
16	Toshiba Aplio	360	328	2	1
17	Hitachi H21	74	69	1	0
18	Esaote Esatune + Technos MPX	1163	1047	1	0
19	Philips ATL5000	623	598	0	0
20	Esaote Esatune + Technos MPX	830	760	1	0
21	Esaote Esatune	317	317	0	0
22	Esaote Esatune	780	764	2	0
23	Esaote Technos MPX + Esatune, Toshiba Aplio, Aloka 550 PHD Extended	352	278	0	0
24	Esaote Technos MPX	50	3	0	0
25	GE Logiq 9	307	298	1	0
26	Philips ATL5000 + Esaote Esatune	767	726	0	0
27	Siemens - Acuson Sequoia	2689	2587	0	0
28	Esaote Esatune	112	93	3	0
Total		23188	21346 (92.1%)	29	2

Adverse events (AE)

The number of AEs reported varied from centre to centre. Several centres had no complaints of any AEs reported (Table 1), while others had more. The total number of reported AEs was 29, among which two were serious and 27 were nonserious (23 mild, three moderate, one severe) (Table 2a and 2b), with an overall reporting rate of 0.125% for all AEs and 0.0086% for serious AEs. All AEs took place after the first and only contrast injection for a given session. None of the late AEs occurred in patients being administered multiple boluses during their last investigation.

Description of serious AE cases

Two AEs were reported as serious in this study (Table 2a). One was reported from a 71 y male patient, previously operated on for prostate cancer, being investigated to characterise a liver lesion suspected of metastasis. Within 1 min after SonoVue administration (1.2 mL), the patient complained of dyspnoea with signs of bronchospasm (whistles) at auscultation. Slight hypotension and bradycardia also appeared. The anaesthesiologist on call in the hospital was urgently contacted and promptly intervened. The patient was given hydrocortisone injection twice (1 g each), due to poor response

Table 2a. Description of the two serious adverse events (AEs) reported in the present series

Case no.	Description of AE	Severity	AE onset time after SonoVue injection	AE duration, outcome, treatment applied and other comments
1	Dyspnoea, bronchospasm, slight hypotension and bradycardia	Severe	<1 min	<30 min; recovered after 2 g of i.v. corticosteroids + antihistamines
2	Clouding of consciousness, dursolumbar pain, severe hypotension, cutaneous rash	Severe	2 min	Hypotension lasted 30 min and slowly recovered after administration of 1 g of hydrocortisone and vasoactive amines. CT examination performed 6 h after the reported events showed occlusion of the stent previously positioned in the right renal artery.

Table 2b. Description of the 27 nonserious adverse events (AEs) reported in the present series

Case no.	Description of AE	Severity	AE onset time after SonoVue injection	AE duration, outcome, treatment applied and other comments
3	Dizziness	Mild	7–10 min. The onset occurred at the time of standing after the exam.	<2–3 min. Fully resolved after lying down.
4	Dizziness	Mild	7–10 min. The onset occurred at the time of standing after the exam.	<2–3 min. Fully resolved after lying down.
5	General sensation of warmth	Mild	2–3 min	<1 min. Spontaneously resolved.
6	Paresthesia at the upper limbs	Mild	2–3 min	<1 min. Spontaneously resolved.
7	Paresthesia at the upper limbs	Mild	2–3 min	4–6 min. Spontaneously resolved.
8	Erythematous rash at the forearms; dysesthesia (pain) at the lower limbs	Mild	30–60 min	12 h. Spontaneously resolved.
9	Aspecific malaise; erythematous rash at the forearms	Mild	2 min	<2 min. Spontaneously resolved.
10	Aspecific malaise	Mild	2 min	<2 min. Spontaneously resolved.
11	Aspecific general malaise and very mild dspnoea	Mild	1 week	12 h. Spontaneously resolved.
12	Aspecific general malaise and very mild dispnoea	Mild	3 h	2–3 h. Spontaneously resolved.
13	Itching; a specific general malaise	Mild	Around 18–20 h	Around 12 h. Resolved.
14	Itching	Mild	Hours	One day. Spontaneously resolved.
15	Itching	Mild	Around 18–20 h	Around 12 h. Resolved.
16	Itching	Mild	10 s	5 min. Spontaneously resolved.
17	Itching and generalized oedema, more intense at the perioral region; itching	Moderate	20 h	6 d, treated with steroids and antihistamines with complete resolution.
18	Sensation of warmth with erythema of the face; itching and generalized oedema, more intense at the perioral region	Mild	1–2 min	2–3 min. Spontaneously resolved.
19	Sensation of warmth with erythema of the face; sensation of warmth with erythema of the face	Mild	1–2 min	2–3 min. Spontaneously resolved.
20	Generalized feeling of warmth; sensation of warmth with erythema of the face	Mild	15 s	1 min. Spontaneously resolved.
21	One episode of biliary vomit in a patient with a Klatskin tumour and endobiliar prosthetic tube	Mild	5 min	Restoration of the usual baseline conditions after the episode of vomiting (which had also occurred previously).
22	Retching	Mild	20 s	1 min. Spontaneously resolved.
23	Nausea and vomiting	Mild	20–30 s	4 min. Spontaneously resolved.
24	Nausea and vomiting	Mild	10 s	3 min. Spontaneously resolved.
25	Bitter taste in the mouth	Mild	15 s	5 s. Resolved.
26	Mild dyspnoea with bronchospasm	Severe	1 min	Duration 4 min; regression with 1 g of hydrocortisone. Resolved.
27	Icy sweating, dizziness, palpitations	Mild	2 min	5 min. Resolved after lying down.
28	Hypotension with cold sweating	Moderate	2–3 min	20 min. Spontaneously resolved. Very anxious environment. Probably vasovagal reaction.
29	Hypotension	Moderate	1–2 min	15 min, resolved after lying down with both legs raised. Probably vasovagal reaction.

after the first one (persisting dyspnoea), and intravenous (IV) chlorophenamine once. No intubation was required. Dyspnoea and objective findings gradually resolved and the patient recovered completely within 30 min.

Another event was reported from a 65 y female patient who suffered from atherosclerotic vasculopathy and had a stent positioned in the right renal artery for a severe ostial stenosis. The stent became occluded the following day, with complete thrombosis of the entire right renal artery tree. Following local thrombolytic therapy, a second stent was placed and recanalisation of the right renal artery was obtained. After that, two SonoVue-enhanced abdominal US scans were performed with no reported AEs.

On the day of the event, about two weeks after the first stent placement, the patient underwent a low-mechanical index contrast–enhanced ultrasound examination due to a suspected in-stent restenosis, which could

Table 3. Incidence of serious/severe adverse events (in percent of total number of studied cases) with radiologic contrast agents in various series reported in the literature. The corresponding rate with SonoVue in the present series was −0.009%.

Author/year	NO. of cases	Ionic radiologic contrast agents	Nonionic radiologic contrast agents	MR gadolinium chelates
Katayama et al. 1990	337647	0.22%	0.04%	
Cochran and Bomyea 2002	>56000		0.015%	
Wolf et al. 1991	≈15000	0.25%	0.1%	
Palmer 1988	109546	0.09%	0.02	
Thomsen and Bush 1998	>21000			0.01%
Kirchin et al. 2001	2540			0.2%
Kirchin et al. 2001	>100000			<0.005%

not be adequately visualised with conventional colour and spectral Doppler imaging. Shortly after SonoVue administration, the patient experienced clouding of consciousness followed by dursolumbar pain. The pulse accelerated first and then quickly became immeasurable. The patient was administered 0.5 g of hydrocortisone by the radiologist, while the anaesthesiologist on call in the hospital was urgently contacted and promptly arrived. A second dose of 0.5 g of hydrocortisone was administered a few minutes later. Severe hypotension lasted over 30 min despite further medical treatment with vasoactive amines and later returned to 110/70 mmHg, when the patient finally recovered full consciousness. About 15 min after contrast medium administration, a cutaneous rash occurred. A contrast-enhanced CT performed 6 h after the reported event did not show opacification of the lumen of the stent. The function of the kidney did not recover. The temporal relationship between the stent occlusion and the reported serious AE could not be precisely assessed, since the exact time of stent occlusion, whether before or at the time of the examination, could not be determined. The liver was not under investigation in this patient.

Description of nonserious AEs

The majority of nonserious AEs (Table 2b) were mild and resolved completely without any medical intervention and not all of them could be classified as definitively related to the administration of SonoVue.

The nonserious AEs observed included itching (five cases, four were mild and one moderate); mild dizziness (two cases); moderate hypotension (two cases, resolved spontaneously) and other AEs such as headache, sensation of warmth, nausea and vomiting etc. similar to symptoms reported in randomised controlled clinical trials following IV injection of placebo (Nanda et al. 2002).

The only nonserious, but severe, event was reported in a patient who underwent liver ultrasound investigation to confirm a diagnosis of haemangioma. The patient reported mild dyspnea, starting around 1 min after SonoVue administration. The patient was immediately treated with 1 g of IV hydrocortisone by the radiologist performing the examination and both dyspnea and associated auscultatory findings of bronchospasms (mild whistles) immediately improved up to disappearing completely within 3 to 4 min.

The overall clinical impact of this case did not appear to have reached any of the levels required to classify it as a serious event to the physician in charge. This might also be due to the very prompt medical intervention, which likely was so rapid because it was managed by a physician already experienced in such a problem, since he was present also during the occurrence of the serious case number 1. It remains impossible to establish whether this patient would have proceeded to a serious condition if she had not been assisted so rapidly.

No relationship was apparent between dosage of SonoVue used and incidence and severity of AEs.

DISCUSSION

In general, it is accepted that US contrast agents are safe with a low incidence of side effects (Jackobsen et al. 2005). They are neither nephrotoxic nor cardiotoxic and do not require renal function tests before their administration (Jackobsen et al. 2005).

The present analysis confirmed that SonoVue, when used for abdominal imaging, has a favourable safety profile, with a rate of serious AE lower than 1/10 000 patients (0.009%). The ratio would remain practically the same, even in cases that one would classify reactions in minor, intermediate, severe and fatal, as used by most radiologic studies (Ansell et al. 1987). In this case, the rate of serious AEs around 0.01% would correspond to severe reactions since no fatal event did occur. These data are at least comparable, or, in most instances, lower than those reported by others for many contrast agents used for X-ray or magnetic resonance (MR) imaging (Table 3) and for most analgesics and antibiotics.

In the present retrospective analysis, most of the AEs described were reported in the clinical trials (Bokor et al. 2001) and in the SonoVue package insert. Some of

the reported AEs (dizziness, nausea, vomiting, cold sweat, hypotension etc.) may be due to vasovagal reaction. Some (including the two serious AEs and one nonserious and severe AE) had signs or symptoms of anaphylactic-anaphylactoid reactions (Hagan 2004), with an overall reporting rate for this type of reaction of 0.013% (3/23188), lower than that reported for other contrast media and similar to that of some commonly used drugs such as analgesics or antibiotics of common use (0.005 to 0.015%), as reported in large retrospective epidemiologic studies in the USA (Neugut 2001; the ICSSA 2003). Based on these published retrospective studies, analgesics and antibiotics of common use were classified at low risk of inducing severe anaphylaxis (0.013%) (the ICSSA 2003); therefore, according to this classification of the risk of anaphylactic reactions (the ICSSA 2003), SonoVue IV administration should be classified as a procedure at low risk.

Of note, both serious AEs and most nonserious AEs took place within min from contrast administration, before the examination had been finished. To summarise, it is recommended to keep, whenever possible, the IV line patent by continuous saline infusion, not only until the end of contrast administration or the achievement of a diagnosis, but until completion of the examination, both for safety reasons and to allow repeat injections when indicated, which was the case in around 15% of the present series.

A case of moderate AE (case 17, Table 2) occurred at the fourth injection of SonoVue (months apart from the others) in a patient investigated for a suspected focal nodular hyperplasia, indicating that the absence of any reaction during previous administration does not exclude the possibility of any reactions later.

Reactions at the injection site (pain and heat, sometimes requiring repositioning of the needle) were observed by several physicians in the present data collection, but were considered of little clinical significance and not specifically related to SonoVue. Hence, they were not included in the list of AEs. Extravasation of SonoVue due to malposition of the needle was not reported by any centre to have induced specific reactions.

A generalised finding in the use of SonoVue was the difference in the most commonly-used dosages among different centres. Possible explanations might be hypothesised to be: a) experience of the operator: usually, full doses were utilised by operators who were in the earliest learning phase of the contrast-enhanced ultrasonographic technique, whereas skilled operators were able to identify patients in whom a reduced dose would suffice; b) type and quality of equipment that may affect the sensitivity for detecting ultrasound contrast; c) type of lesions to be investigated (studies for metastasis detection benefit from full dosages of contrast providing better exploration of the late phase, whereas, for nodules in cirrhosis, the arterial phase is most important and reduced dosages might suffice).

Limitations of the study

No clinically evident cardiac AE was observed in the present series of 23188 patients. It should be acknowledged, however, that no precise information about the cardiac status was obtained in this retrospective analysis; therefore, the prevalence of cardiac disease in these patients submitted to abdominal imaging with SonoVue is unknown. Furthermore, patients were not routinely investigated for their levels of blood pressure and heart rate before or after contrast injection, nor was electrocardiography carried out after each ultrasonic investigation.

The rate of mild and moderate AEs is likely underestimated in the present retrospective analysis, in which all the investigations were performed in the routine clinical practice, not under research protocols and without specifically addressing AEs and without a systematic recording of minor events in most centres. This might also account for the difference in the reporting rate of AEs among the various centers. It might be that Units which started more recently paid more attention to record any patient's complaint that may have occurred (the same event instead might have been considered not worthy of note in more experienced centres, then not remembered any more at the time of data collection). It does not seem, instead, that the type of equipment and related software for contrast detection had any role since the same models of equipment were used in centres with higher or lower reported rates (Table 1).

Any possible reactions occurring more than 25 to 30 min after the investigation or patients' discharge might also have been missed, especially if they were not deemed so important by the patient as to inform the examining physician, but SonoVue is completely eliminated at that time (Bokor et al. 2001; Morel et al. 2000). However, it should be considered that severe events usually occur early after injection. For instance, surveys on urographic contrast media showed that about 95% of severe/fatal cases started within 20 min from contrast injection (Ansell 1980, 1987). In fact, true late adverse reactions (namely, those occurring between 1 h and 7 d after contrast injection) are reported to be rare and mainly mild or moderate skin reactions, which resolve in 3 to 7 d. Additionally, late reactions do not appear, in most instances, to be agent-related, since they occur with the same frequency in enhanced and nonenhanced CT scans (Beyer-Encke et al. 1993; Schild et al. 1996; Ueda et al. 2001; Yasuda et al. 1998).

Only itching took several hours to develop and several more hours to regress. The underlying mecha-

nism of this reaction is unclear. Given the retrospective nature of this study, these patients were not questioned for other possible causes (*e.g.*, concurrent medication, food and physical contact) or history of previous allergic reactions. Prospective investigations, specifically addressing the potential mechanism of these AEs, are therefore warranted.

In conclusion, given the retrospective nature of the study it is likely that the reaction rate of mild/moderate events is underestimated, but this does not have a major impact on the safety profile of the drug. At variance, it is very unlikely that any serious or severe adverse event, in other words those relevant to the risk-benefit profile of this agent, had been missed.

A prospective analysis would clearly be more precise in classifying and detailing events. However, given their low incidence rate, an extremely large study is necessary and this could be very difficult to be carried out, given the need, not only to keep appropriate records, but, most of all, to follow up patients for one week after the examinations with pertinent investigations.

REFERENCES

Albrecht T, Blomley M, Bolondi L, et al. Guidelines for the use of contrast agents in ultrasound. Ultraschall in Med 2004;25:249–256.

Ansell G, Tweedie MC, West CR, Evans P, Couch L. The current status of reactions to intravenous contrast media. Invest Radiol 1980; 15(Suppl. 6):S32–39.

Ansell G. An epidemiologic report on adverse reactions in urography: ionic and nonionic media. Diagnostic Imaging 1987; (Suppl.):6–10.

Bartolotta T, Midiri M, Quaia E, et al. Benign focal liver lesions: spectrum of findings on SonoVue-enhanced pulse-inversion ultrasonography. Eur Radiol 2005;15:1643–1649.

Beyer-Encke SA, Zeitler E. Late adverse reactions to non-ionic contrast media: a cohort analytic study. Eur Radiol 1993;3:237–241.

Bokor D, Chambers J, Rees P, et al. Clinical safety of SonoVue, a new contrast agent for ultrasound imaging, in healthy volunteers and in patients with chronic obstructive pulmonary disease. Invest Radiol 2001;36:104–109.

Cochran S, Bomyea K. Trends in adverse events from iodinated contrast media. Academ Radiol 2002;9 (Suppl. 1):S65–S68.

European Medicines Agency (EMEA). European public assessment report. Available at: http://www.emea.eu.int/humandocs/pdfs/EPAR/sonovue/005301en1.pdf. Accessed December 22, 2005a.

European Medicines Agency (EMEA). Public statement on SonoVue (Sulpher Hexafluoride). New contraindication in patients with heart disease. Restriction of use in non-cardiac imaging. Available at: http://www.emea.eu.int/pdfs/human/press/pus/021204en.pdf. Accessed December 22, 2005b.

European Medicines Agency (EMEA). Press release. EMEA Committee for Medical Products for Human Use. July 27–29, 2004. Available at: http://www.emea.eu.int/pdfs/human/press/pr/2155004en.pdf. Accessed December 22, 2005c.

Gaiani S, Celli N, Piscaglia F, et al. Usefulness of contrast-enhanced perfusional sonography in the assessment of hepatocellular carcinoma hypervascular at spiral computed tomography. J Hepatol 2004;41:421–426.

Hagan J. Anaplylactoid and adverse reactions to radiocontrast agents. Immunol Allergy Clin N Am 2004;24:507–519.

Hohmann H, Skrok J, Puls R, Albrecht T. Characterization of focal liver lesions with contrast-enhanced low MI real time ultrasound and SonoVue. ROFO 2003;175:835–843.

Jakobsen J, Oyen R, Thomsen H, Morcos S, Members of Contrast Media Safety Committee of European Society of Urogenital Radiology (ESUR). Safety of ultrasound contrast agents. Eur Radiol 2005;5:941–945.

Katayama H, Yamaguchi K, Kozuka T, et al. Adverse reactions to ionic and nonionic contrast media. A report from the Japanese committee on the safety of contrast media. Radiology 1990;175:621–628.

Kirchin M, Pirovano G, Venetianer C, Spinazzi A. Safety assessment of Gadobenate dimeglumine (MultiHance): extended clinical experience from phase I studies to post-marketing surveillance. J Magn Reson Imaging 2001;14:281–294.

Morel D, Schwieger I, Hohn L, et al. Human pharmacokinetics and safety evaluation of SonoVue, a new contrast agent for ultrasound imaging. Invest Radiol 2000;35:80–85.

Murphy K, Brunberg J, Cohan R. Adverse reactions to gadolinium contrast media: a review of 36 cases. AJR 1996;167:847–849.

Nanda N, Wistran D, Karlsberg R, et al. Multicenter evaluation of SonoVue for improved endocardial border delineation. Echocardiography 2002;19:27–36.

Neugut A, Ghatak A, Miller R. Anaphylaxis in the United States: an investigation into its epidemiology. Arch Intern Med 2001;161: 2046–2047.

Palmer FJ. The RACR survey of intravenous contrast media reactions. Final report. Australas Radiol 1988;32:426–428.

Piscaglia F, Gaiani S, Tamberi S, et al. Liver metastases from colorectal carcinoma: progression of disease in spite of loss of arterial-phase hypervascularity on contrast perfusional angiosonography (CnTI). A case report. J Clin Ultrasound 2003;31:387–391.

Quaia E, Calliada F, Bertolotto M, et al. Characterization of focal liver lesions with contrast-specific US modes and a sulfur hexafluoride-filled microbubble contrast agent: diagnostic performance and confidence. Radiology 2004;232:420–430.

Quaia E, Siracusano S, Bertolotto M, Monduzzi M, Mucelli R. Characterization of renal tumours with pulse inversion harmonic imaging by intermittent high mechanical index technique: initial results. Eur Radiol 2003;13:1402–1412.

Schild H. Delayed allergy-like reactions in patients: monomeric and dimeric contrast media compared with plain CT. European Radiology 1996;6 (Suppl. to issue 5):9–10.

Schneider M, Arditi M, Barrau M, et al. BR1: a new ultrasonographic contrast agent based on sulfur hexafluoride-filled microbubbles. Invest Radiol 1995;30:451–457.

The International Collaborative Study of Severe Anaphylaxis. Risk of anaphylaxis in a hospital population in relation to the use of various drugs: an international study. Pharmacoepidemiol Drug Saf 2003; 12:195–202.

Thomsen HS, Bush WH Jr. Adverse effects of contrast media. Incidence, prevention and management. Drug Saf 1998;19:313–24.

Ueda S, Mori H, Matsumoto S, et al. True delayed adverse reactions to non-ionic contrast media: does it really exist? Eur Radiol 2001;11 (Suppl. 1):377.

Wolf G, Mishkin M, Roux S, et al. Comparison of the rates of adverse drug reactions. Ionic contrast agents, ionic contrast agents combined with steroids and non-ionic agents. Invest Radiol 1991;26: 404–410.

Yasuda R, Munechika H. Delayed adverse reactions to nonionic monomeric contrast-enhanced media. Invest Radiol 1998;33:1–5.