

## Adverse reactions after the use of sulphur hexafluoride (SonoVue) echo contrast agent

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The aim of the present study was to analyse the adverse effects of SonoVue echo contrast in a consecutive series of 352 cardiac patients during a 4-year period. During 352 consecutive cardiac SonoVue studies, seven patients (2.0%) experienced adverse effects. Four patients (1.1%) had mild allergic reactions causing skin erythema and mild sinus tachycardia, and three patients (0.9%) experienced a severe allergic reaction resulting in (nonfatal) shock. The reported incidence of adverse effects of SonoVue echo contrast in this consecutive series of cardiac patients seems markedly higher than those reported in a company postmarketing analysis.

*J Cardiovasc Med* 10:75–77 © 2009 Italian Federation of Cardiology.

*Journal of Cardiovascular Medicine* 2009, 10:75–77

**Keywords:** adverse reactions, contrast agent, sulphur hexafluoride

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Received 11 July 2008 Revised 4 September 2008  
Accepted 18 September 2008

### Introduction

SonoVue (Bracco, Milan, Italy) is a blood pool ultrasound contrast agent that is based on microbubbles, stabilized by a phospholipid shell and filled with sulphur hexafluoride gas [1,2]. It is isotonic to human plasma and claimed to be devoid of antigenic potential, as it does not contain any proteinaceous material. SonoVue has been approved in Europe and other countries for the improvement of endocardial border delineation during echocardiography and other noncardiac applications. However, throughout Europe a number of serious allergic reactions with probable secondary cardiovascular problems have been reported to national and international registry authorities [3,4]. Three of these reports included a fatal outcome soon after the administration of SonoVue in patients with severe coronary artery disease. Despite questions about the causal relationship, the European Medicines Agency (EMA) recently took precautionary measures to limit the use of SonoVue in patients with cardiac disease ([www.emea.eu.int/humandocs/Humans/EPAR/SonoVue/SonoVue.htm](http://www.emea.eu.int/humandocs/Humans/EPAR/SonoVue/SonoVue.htm)). As a result of the EMA interventions, SonoVue is contraindicated in cardiac patients with an (suspected) acute coronary syndrome, recent percutaneous coronary intervention, acute or chronic severe [New York Heart Association (NYHA) class III/IV] heart failure or severe cardiac dysrhythmias. Since mid 2001, we have been using SonoVue in our cardiac department. Because of safety concerns, we systematically reviewed all adverse effects of SonoVue in a consecutive series of patients in our echocardiographic laboratory.

### Mild adverse reactions

During a 4-year period, 352 SonoVue echo contrast studies were performed in 274 patients for a variety of reasons [5,6]. One hundred and ninety-eight patients underwent only one SonoVue study, whereas 77 patients underwent multiple SonoVue studies. Mild adverse reactions, including skin erythema and mild sinus tachycardia, were seen in four patients (1.1%). Three patients were referred for left ventricular (LV) function assessment and one for exclusion of a LV thrombus. These mild reactions were present in two out of the 198 patients (1.0%) who received SonoVue only once, and two out of the 76 patients (2.6%) who received SonoVue twice. All four patients were successfully treated with intravenous clemastine and hydrocortisone.

### Severe adverse reactions

During the same 4-year period an additional three patients (0.9%), who all underwent SonoVue echocardiography for the first time, experienced a severe anaphylactic reaction.

### Case 1 (21 August 2001)

An 80-year-old man, with known hypertension and recent (3 weeks earlier) carotid stenting, was referred to dobutamine stress echocardiography for risk stratification before aortic abdominal surgery. Medical treatment included acetyl salicylic acid, clopidogrel, calcium antagonist,  $\beta$ -blocker and diuretics. The patient was in a stable condition without angina during exercise or symptoms of heart failure. Because of poor quality of

the echo window, SonoVue contrast was used. During recording of the resting echo images (with 0.75 ml SonoVue), the patient developed extensive skin erythema and went into shock with a decrease in blood pressure from 150/70 to 70/30 mmHg. Clemastine 2 mg and hydrocortisone 100 mg were immediately injected intravenously and volume resuscitation (300 ml gelofusine) was applied. After 10 min, the patient recovered fully and his blood pressure returned to a normal level (145/80 mmHg). After an overnight observation in the clinical department, he was discharged the next day. Dobutamine stress technetium-99 m single photon emission computed tomography, performed at the outpatient clinic, did not show reversible perfusion defects and the patient was cleared for vascular surgery.

#### Case 2 (24 February 2005)

A 68-year-old woman, with known Pompe's disease (a lysosomal glycogen storage disease due to  $\alpha$ -glucosidase deficiency), was referred for SonoVue contrast echocardiography because of an ongoing study protocol to investigate cardiac function in these patients. Left ventricular end-diastolic diameter was 46 mm and ejection fraction was 83%. Due to Pompe's disease, the patient was in a poor clinical condition with a severely limited exercise tolerance and needed intermittent use of a respirator machine. An intravenous cannula was inserted and the non-contrast-enhanced study images were recorded first. Approximately 20 min later, the contrast study was started. After bolus injection of 0.5 ml and two repeat injections of 0.25 ml of SonoVue, the patient experienced tinnitus and dizziness. Her blood pressure decreased from 140/80 to 70/40 mmHg and sinus rate decreased from 90 to 50 beats per minute, after which the patient became unconscious. Clemastine 2 mg and hydrocortisone 100 mg were immediately injected intravenously and volume resuscitation (150 ml gelofusine) was applied. After 15 min, the patient completely recovered and returned to the neurological department.

#### Case 3 (15 September 2005)

A 34-year-old man, with known familiar non-ischemic dilated cardiomyopathy, was referred for SonoVue contrast echocardiography to exclude non-compaction cardiomyopathy [5]. The patient was in stable NYHA heart failure class I–II for years without evidence of high filling pressures. Medical treatment included angiotensin-converting enzyme inhibitor,  $\beta$ -blocker and diuretics. An intravenous cannula was inserted and the non-contrast-enhanced study images were recorded first. Left ventricular end-diastolic diameter was 69 mm and ejection fraction was 37%. Approximately 15 min later, the contrast study was started. After bolus injection of 0.5 ml and an additional 0.25 ml of SonoVue, the patient experienced a heat sensation with nausea and extensive skin erythema after which sinus bradycardia developed. Despite the immediate intravenous injection of clemastine 2 mg and

hydrocortisone 100 mg, the patient went into shock with extreme bradyarrhythmia (<30 beats per minute), lost conscious and started gasping. After a short-lasting resuscitation procedure (cardiac massage and manual ventilation) of approximately 3 min, the patient recovered fully. The patient was observed in the clinical department from which he was discharged the same day. After 10 h from discharge, the patient experienced pain in multiple joints lasting for 2 days. Immunological analysis revealed a type III allergic reaction without identification of a specific allergen.

#### Discussion

Throughout Europe, a number of serious allergic reactions with probable secondary cardiovascular problems have been reported to national and international registry authorities [3,4]. These allergic reactions may be caused by the SonoVue sulphur hexafluoride gas or the shell component polyethylene glycol (macrogol 4000) [7–9]. In a Bracco company postmarketing analysis of 157 838 patients, 19 non-fatal severe (0.01%) and 3 fatal (0.002%) complications were reported after the use of SonoVue. Obviously, the risks and benefits of SonoVue should be weighed and these should be compared with other diagnostic tests. Unfortunately, clinical outcome studies for SonoVue are not yet published. So, this leaves us with two basic questions. What is the risk of SonoVue and how does this risk compare with other diagnostic modalities? The complication rates in the registry are, although somewhat higher compared with Optison [4], not higher than the complication rates of intravascular contrast media used in radiology [10,11]. This is an important finding because patients referred for a cardiac study are in general at a higher risk to develop secondary cardiovascular problems. We should, however, realize that it is difficult for a postmarketing analysis to define a test as low risk because of potential underreporting of complications. Therefore, it is essential that consecutive series of patients should be prospectively monitored for complications in institutions. In our study population of 352 consecutive cardiac studies, seven patients (2.0%) experienced adverse effects, including anaphylactic shock in three patients (0.9%). None of these patients were known to have a history of allergy, and all had normal liver and renal function. A vasovagal reaction, as a cause for the decrease in blood pressure, is very unlikely as the decrease in blood pressure was preceded by extensive skin erythema, and the delay between intravenous cannula insertion and shock was at least 15 min in two patients. These numbers of adverse effects seem higher than those reported in the registry and await confirmation by others. For this moment, we strongly emphasize the EMEA guideline that recommends keeping the patient under close medical supervision during and for at least 30 min following the administration of SonoVue. Intravenous antiallergic and anaphylactic drugs (H1 and H2 antihistamines, corticosteroids and epinephrine) should

be available in the echo room in addition to standard resuscitation equipment [12]. Apart from the existing contraindications, caution is advised in all patients, and in particular those patients with a compromised cardio-pulmonary status. Finally, we also emphasize that these concerns not only apply to SonoVue but also to other contrast agents, such as Definity or Optison, as has been made clear by the recent black box warning by the American Food and Drug Administration.

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