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Anaphylactic reaction on sulphur hexafluoride

Introduction

Sonovue[®] (sulphur hexafluoride) is a second-generation ultrasound contrast agent consisting of phospholipid-stabilized microbubbles filled with sulfur hexafluoride and was granted a marketing authorisation via the centralised registration procedure in the European Union on May 16th 2001. Sulphur hexafluoride is for use with *ultrasound imaging to enhance the echogenicity of the blood, which results in an improved signal to noise ratio. Specific indications include echocardiography Doppler of macrovasculature and microvasculature.*

In echocardiography SonoVue is a transpulmonary contrast agent for use in patients with suspected or established cardiovascular disease to provide opacification of cardiac chambers and enhance left ventricular endocardial border delineation [1]. Contraindications for use include: known hypersensitivity to sulphur hexafluoride or to any of the components of the product, patients with right-to-left shunts, severe pulmonary hypertension, uncontrolled systemic hypertension or patients with adult respiratory distress syndrome. The recommended dosage is 2.4 ml intravenous, twice if necessary.

Section 4.8 does not mention any allergic reaction nor hypotensive reaction.

This report discusses possible anaphylactic reactions caused by sulphur hexafluoride use.

Reports

Up to 15 March 2004 Lareb received three reports on sulphur hexafluoride, all concerning anaphylactic reactions. Two of these reports were received from the MAH.

Case A reported by a specialist doctor, concerns a 59-year-old female who experienced an anaphylactic reaction with probably rash, myoclonic jerks, loss of tension, subsequently followed by myocardial infarction immediately after administration of sulfur hexafluoride for cardiac ultrasound. As concomitant medication she used: clopidogrel, selektine, metoprolol, piperazine. Relevant medical history: not reported. The anaphylactic shock was treated and the patient recovered. An intracutaneous test for sulphur hexafluoride was positive whereas 5 control subjects showed no reaction.

Case B concerns a report from the MAH about an 80-year-old male who received a 1.5 ml bolus sulphur hexafluoride, followed by 7 ml of glucose solution prior to a scheduled stress echocardiography with dobutamine. After 30 seconds he complained of dizziness, developed shortness of breath, sweating, drop of systolic blood pressure from 140 mmHg to 70 mmHg, but no heart rate or ECG abnormality. Anaphylactic reaction was diagnosed and the patient was treated with prednisone injections, clemastine, and oxygen. In the next 30 minutes skin redness developed and ST segment depression became visible in the ECG. He was observed in the ICU for several hours. The patient recovered and was dismissed from hospital the next morning. No prior exposure to sulphur hexafluoride had occurred and dobutamine had not been administered yet. Concomitant medication included carbasalate calcium, clopidogrel, and pantoprazol.

Case C was reported by the MAH. According to a cardiologist a 70-year-old female experienced an anaphylactic reaction 0.5 minutes after a bolus IV injection of 10 ml sulphur hexafluoride, prior to left ventricular opacification. The patient experienced at first sneezing and itching. She was treated with hydrocortisone and clemastine IV and recovered on the same day. Additional dermatological examination did not reveal signs of an allergic reaction. It was assumed that the anaphylactic reaction to sulphur hexafluoride, most probably occurred via a not specific immunologic mechanism.

All patients reported to Lareb used clopidogrel as concomitant medication which contains macrogol 6000 while sonovue contains macrogol 4000 as carrier.

Other sources of information

Literature

Sulfur hexafluoride is an inert gas used mainly as a test gas in respiratory physiology. Other uses include its injection in vitreoretinal surgery to restore the vitreous chamber and as a tracer in monitoring the dispersion and deposition of air pollutants. As a sonographic agent about 20 articles in Medline are present.

Only two studies mention safety of sulfur hexafluoride. In a study by Navin *et al.* 22 (15.9%) of 138 patients reported mild adverse reactions, while no markers of anaphylaxis and no evidence of antibody production or complement activation were found [2]. A second study, sponsored by Bracco, showed 144 nonserious events (10.4%) of which the majority was mild and 'recovered without consequence' in 1406 patients [3]. Allergic reactions on sulphur hexafluoride have not been reported in literature.

Databases

The WHO Uppsala Monitoring Centre received 10 reports about sulfur hexafluoride in 2003 and 2004 (see table 1). All of these reports could be cases of anaphylactic reactions with (anaphylactic) or without (anaphylactoid) immunological mechanisms on sulfur hexachloride.

Table 1. All reports on sulphur hexafluoride in the WHO database

Patient, Sex, age	country	Suspected adverse drug reaction	Concomitant medication	Dosage	Outcome
A M, 21	de	headache, abdominal pain, hypotension, tachycardia, flushing	levofloxacin, pantoprazole, heparin, itraconazole, xylometazoline		recovered
B M, 66	se	anaphylactic shock	felodipine, captopril, acetylsalicylic acid, clopidogrel sulfate	2.4 ml	not recovered
C M, 40	it	sweating increased, ocular hyperaemia, vomiting, nausea, hypotension, bradycardia	none reported	3 ml	unknown
D M, 62	es	dyspnoea, oedema mouth	heparin fraction, enalapril maleate, omeprazole	5 ml	recovered
E F, ?	de	anaphylactoid reaction	none reported		
F M, 72	uk	hypotension, bradycardia	none reported	4 ml intraocular	recovered
G F, 48	se	urticaria	none reported	2.5 ml	recovered
H F, 80	de	anaphylactoid reaction	none reported	1 ml	recovered
I 49, M	de	coma	none reported	1 ml	fatal

Mechanism

Mechanisms of hypersensitivity to sulfur hexafluoride were not found in literature. As an inactive gradient Sonovue contains polyethylene glycol (Macrogol 4000) of which rare cases of hypersensitivity reactions and anaphylaxis have been reported [4].

Conclusion

Severe anaphylactic and anaphylactoid reactions on sulphur hexafluoride as contrast agent have been reported to Lareb and the WHO-UMC. No other reactions on this drug have been reported which makes it impossible to estimate disproportionality. Little information on this product is available in literature.

References

1. European Public Assessment Report SonoVue. (version date 18-5-2001) EMEA.
2. Nanda NC, Wistran DC, Karlsberg RP, Hack TC, Smith WB, Foley DA, Picard MH, Cotter B. Multicenter evaluation of SonoVue for improved endocardial border delineation. *Echocardiography*. 2002;19(1):27-36.
3. Bokor D. Diagnostic efficacy of SonoVue. *Am.J Cardiol*. 2000;86(4A):19G-24G.
4. Fisher AA. Immediate and delayed allergic contact reactions to polyethylene glycol. *Contact Dermatitis* 1978;4(3):135-8.

