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Adverse reactions to ultrasound contrast agents: Is the risk worth the benefit?

P.A. Dijkmans*, C.A. Visser, O. Kamp

VU University Medical Center, Amsterdam, The Netherlands

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Abstract The introduction of ultrasound contrast agents has led to a marked improvement in diagnostic capabilities in echocardiography. As no serious adverse events were seen during the preclinical development phase, ultrasound contrast agents were thought to be safe. Recently, three fatal and 19 severe, non-fatal adverse reactions were reported in a post marketing analysis of more than 150,000 studies of Sonovue®, which has led to the addition of several contra-indications for the use of this ultrasound contrast agent. Although a strong relationship was established between the non-fatal cases and administration of Sonovue, a causal relationship between the fatal cases and the use of Sonovue is debatable. Therefore, the risk associated with the use of this ultrasound contrast agent should be judged carefully, taking into consideration the prevalence of adverse effects of other contrast media and diagnostic procedures used in cardiology.

The widespread introduction of ultrasound contrast agents (UCAs) a few years ago has led to a marked improvement in diagnostic capabilities in echocardiography. As only minor adverse events (AEs) were seen during the preclinical development phase of several currently registered second generation contrast agents, the general belief is that UCAs were safe. Recently, post marketing analysis of 157,838 studies of Sonovue® brought to light 19 cases of severe, non-fatal (0.012%) and three cases of fatal AEs (0.002%) after the use of this UCA [1]. This has led to a restriction for the indication of the use of Sonovue®. Although it is generally assumed that there was a strong relationship between administration of Sonovue and the non-fatal cases, a causal relationship between these fatal AEs and the use of this UCA is uncertain. Therefore, the risk which arises from the use of UCAs should be judged carefully, taking into consideration the additive value of UCAs, and the risks

* Corresponding author. Department of Cardiology 6N-120, VU University Medical Center, PO Box 7057, 1007 MB Amsterdam, The Netherlands. Tel.: +31 (0) 20 4442244; fax: +31 (0) 20 4442446.
E-mail address: pa.dijkmans@vumc.nl (P.A. Dijkmans).

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and prevalence of adverse effects of other contrast agents and diagnostic tests used in cardiology.

The use of contrast agents is widely spread in nuclear medicine, radiology, and cardiology. Intravenous administration of contrast agents in general is, although relatively safe, known to cause side effects. Several studies investigating the prevalence of adverse reactions to nuclear radiopharmaceuticals, magnetic resonance agents, and ionic/non-ionic radiological contrast media have shown that adverse drug reactions are, although present in only a few percent of the population, inevitable and can be serious. The prevalence of AEs after the use of Gd-GTPA, a magnetic resonance imaging (MRI) contrast agent, was studied by Niendorf et al. in a phase IIIb–IVa study in 13,439 patients [2]. Serious or fatal AEs were not reported (Table 1). In this study, postmarketing surveillance data included over 2,000,000 applications, in which 39 (0.002%) serious AEs occurred. Seven deaths were seen following administration of Gd-GTPA, however, no causal relationship could be established in the fatal cases that occurred in temporal coincidence of administration of this contrast agent. Similar results were shown by Katayama et al. in a large comparative study of ionic and non-ionic contrast agents used in urography, contrast enhanced computed tomography, and digital subtraction angiography [3]. Although the prevalence of serious AEs was relatively high, i.e. 0.22% in ionics and 0.04% in non-ionics, the number of fatal AEs was limited to 2 in 352,187 (0.0006%). These fatal events could also not be causally related to the administration of the contrast media. This adverse event rate was lower than that was found by Shehadi et al., who reported 18 deaths (0.006%) in a prospective study of 302,083 applications of intravascular contrast media [4]. Adverse reactions in a third large group, namely radiopharmaceuticals used in nuclear medicine were investigated by Silberstein et al. In a prospective study, the prevalence of adverse reactions to 783,524 radiopharmaceuticals and 67,835 nonradioactive drug administrations was studied [5]. In this registration, no serious AEs for radiopharmaceuticals (^{99m}Tc-derivatives most commonly linked to adverse reactions) and one for non-radioactive drugs were reported, while no deaths occurred.

In the case of Sonovue, preclinical safety studies did not show the occurrence of related serious adverse events. Post-marketing analysis, however, revealed three fatal AEs that occurred in temporal coincidence with the use of this agent (0.002%) [1]. All three patients appeared to have advanced coronary artery disease and were probably in an unstable condition at the time of receiving Sonovue. Although a causal relationship between administration of Sonovue and these events could be established in none of these cases, the close temporal relationship between Sonovue administration and these fatal AEs clearly suggests that Sonovue might be a triggering factor in this high risk population. Besides the three fatal cases, 19 other serious non-fatal AEs have been reported (0.012%), 18 of which were anaphylactoid or vasovagal reactions. Of these 19 serious AEs, 9 were cardiac events (4 bradycardia, 2 tachycardia, 3 myocardial ischemia). Eleven of these 19 patients received Sonovue for the echocardiography indication. The rate of fatal AEs of Sonovue appears to be higher than the AE rate of Optison, another second generation UCA (Table 1). Ten or less cases of serious (<0.002%) and no fatal

Table 1 Studies assessing the safety of several types of contrast media

Author/reference	Type of contrast agent	Number of studies	Serious adverse events (%)	Fatal adverse events (%)	Total serious adverse event rate (%)
Niendorf et al. [2]	Gd-GTPA: phase IIIb–IV	13,439	0 (0)	0 (0)	0 (0)
	PMS	2.000,000	32 (0.002)	{7} (0.0004)	39 (0.002)
Katayama [3]	Ionic contrast media	169,284	370 (0.22)	{1} (0.0006)	371 (0.22)
	Non-ionic contrast media	168,363	70 (0.04)	{1} (0.0006)	71 (0.04)
Shehadi [4]	Intravascular contrast media	302,083	216 (0.07)	18 (0.006)	244 (0.077)
Silberstein [5]	Radiopharmaceuticals	783,525	0 (0)	0 (0)	0 (0)
	Non-radioactive pharmaceuticals	67,835	1 (0.001)	0 (0)	1 (0.001)
Personal communication	Optison	>500,000	≤10 (≤0.002)	0 (0)	≤10 (≤0.002)
EMEA [1]	Sonovue	157,838	19 (0.012)	3 (0.002)	22 (0.014)

PMS: post marketing surveillance; {…} no causal relationship established.

adverse events were reported after the use of this contrast agent until so far, although more than 500,000 studies have been performed in a similar patient population (personal communication, Amersham Health AS/GE Healthcare, 2005).

The AE rate of Sonovue also seems to be relatively high when compared with contrast agents used in MRI, radiology, and nuclear radiopharmaceuticals. However, differences exist between the population in which these contrast media are used. As reported by Katayama et al., the prevalence of (serious) AEs is about twice as high in patients suffering from cardiovascular disease. As UCAs are used for left ventricular opacification or myocardial perfusion in patients with known or suspected cardiovascular disease on a large scale [6], the AE rate is expected to be higher in this patient group. The analysis of the European Medicines Agency (EMEA) shows that a higher AE rate is reported when Sonovue is used for cardiac imaging than for non-cardiac imaging, however, to date, no studies on the safety of UCAs have been published with a solid subgroup analysis to estimate the specific risk of AEs in patients with cardiovascular disease. UCAs have been used in patients suffering from severe cardiovascular disease, unstable coronary syndromes, or heart failure, which increases the risk of a worse outcome of a serious AE. As contrast agents like Gd-GTPA, contrast media used in radiology, and radiopharmaceuticals are probably used less in such a patient population, this can possibly give an explanation for the relatively low rate of fatal AEs of these contrast agents. The lower adverse event rate of Optison compared with Sonovue is remarkable. Shell constituents and shell characteristics (e.g. charge) may account for the difference between these UCAs. As the shell of Sonovue contains polyethylene glycol (macrogol 4000), which is known to be associated with the occurrence of allergic reactions, this chemical may have played a role in the adverse reactions after use of Sonovue [7].

For a global evaluation of the risks and benefits of the use of Sonovue, the risks and yield of other diagnostic tests used in cardiology should be considered and compared with the AE rate of this contrast agent. Especially exercise testing and dobutamine stress echocardiography are widely used and the threshold for performing such a study is relatively low. The safety of these tests has been studied extensively for the occurrence of AEs [8,9]. In a survey including 518,448 exercise tests of Stuart et al., a death rate of 0.5 per 10,000 cases (0.005%) was found (Table 2). Although studies with such large numbers are not available for dobutamine stress echocardiography, no deaths have been reported in several cohorts with a total of more than 10,000 studies [10–14]. In these studies, other serious side effects like myocardial infarction or major arrhythmias, are estimated to occur in ~1 of 230 studies (0.43%). These exercise tests are regarded as relatively safe and are performed on a much larger scale than contrast echocardiography, whereas the AE rate seems to be much higher. However, a comparison of the AE rate of on the one side stress testing and on the other side administration of Sonovue cannot be made without recognizing the different profits of different tests. Whereas stress testing is used for detection of ischemic heart disease, UCAs are used as adjuvants in echocardiography. Only in a minority of cases is it used in stress echocardiography, and as no license for myocardial contrast echocardiography has been obtained, a simple comparison of AE event rates is not valid. The risk profile of a contrast-enhanced stress echocardiogram, however, seems to be similar to a conventional stress echocardiogram, and serious AEs have not been reported yet [1]. This raises the question whether the diagnostic value of exercise tests is more important than the diagnostic value of a contrast-enhanced echocardiogram using Sonovue. Another diagnostic procedure which plays an important role in cardiology and should be considered is cardiac catheterization. Although this

Table 2 Studies assessing the safety of several diagnostic procedures in cardiology

Author/reference	Type of diagnostic procedure	Number of studies	Serious adverse events (%)	Fatal adverse events (%)	Total serious adverse event rate (%)
Reference [10–14]	Dobutamine stress echocardiography	11,761	51 (0.43)	0 (0)	51 (0.43)
Noto et al. [15]	Diagnostic catheterization	59,792	956 (1.60)[a]	65 (0.11)	1021 (1.71)
Stuart et al. [9]	Exercise stress test	518,448	~433 (0.084)	~26 (0.005)	~459 (0.089)

[a] Adverse event indicated as major adverse event without specification.

examination is much more invasive than contrast echocardiography, the risk profile of the patient population undergoing these examinations is similar with respect to underlying disease. In a multicenter study, Noto et al. estimated the mortality associated with cardiac catheterization to be 0.11%, which is high compared to the use of any contrast agent or diagnostic test [15]. Also with respect to catheterization, it must be emphasized that a comparison between the AE rate cannot be made directly, but only when considering the difference in diagnostic value of each procedure.

Another important aspect is the circumstance under which a contrast echocardiogram is performed. Intravenous injection of medical products always must be considered as administration of medication. This means that attention should be paid to the possible occurrence of known side effects, and the possibility of severe side effects like an anaphylactic reaction must be kept in mind. As a contrast echocardiogram is relatively simple to perform, negligence of the risk of a contrast injection frequently occurs. Therefore, such a procedure must be carried out under supervision of an experienced doctor and in an environment where facilities for emergency care are immediately available.

After a thorough investigation on the relationship between the 19 non-fatal and three fatal cases and the use of Sonovue, the EMEA has decided to reinstate the echocardiography indication, albeit with addition of several contra-indications. Assuming that the three fatal adverse reactions are indeed related to the administration of Sonovue, the fatal AE rate of this UCA of 0.002% is in between the safe Gd-GTPA, and the fatal AE rate of 0.11% found by Noto et al. of a diagnostic cardiac catheterization. Including serious AEs in this comparison, the AE rate of Sonovue increases to a level which is in between that of Gd-GTPA and non-ionic contrast media. When compared with exercise testing and dobutamine stress echocardiography, administration of UCAs seems to be relatively safe. This comparison stimulates the discussion about which risk is clinically acceptable for the diagnostic value of a specific test. Within this discussion, a central issue is what the clinical importance is of other contrast examinations and diagnostic (exercise) tests, and whether the diagnostic value of these procedures is higher than that of contrast echocardiography. This ethical topic should be discussed not only estimating the risks and the diagnostic values of UCAs, but also the clinical benefit and risks of other contrast agents and diagnostic tests used in cardiology.

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