An Observational Study of the Occurrence of Serious Adverse Reactions among Patients Who Receive Optison in Routine Medical Practice

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Background: Reports of ultrasound contrast agent safety have been derived mainly from retrospective databases rather than from studies specifically designed to assess safety. The purpose of this study was to prospectively determine the safety of Optison in routine medical practice.

Methods: Patients referred for routine rest or stress two-dimensional echocardiography who had indications for contrast were enrolled. Vital signs were obtained at baseline and at intervals up to 1 hour after dosing of Optison. Patients were followed for the development of any serious adverse event (SAE), defined as an event that causes death, is life threatening, requires or prolongs hospitalization, or causes another important event, for 24 hours after Optison administration.

Results: A total of 1,039 patients were enrolled, and 76% had 24-hour follow-up. The median age was 60 years (range, 20–97 years), and 62% were men. The mean body mass index was 33 $\pm$ 9 kg/m^2. Patient comorbidities included hypertension (73%), hyperlipidemia (64%), smoking (52%), and diabetes (37%). There were significant increases in systolic blood pressure, heart rate, and respiratory rate between the baseline, 5- to 15-min, 30-min, and 60-min time points after the administration of Optison in patients undergoing stress studies but none in those undergoing rest studies. There was a total of six SAEs during the study, which were felt to be related not to Optison but rather to the stress test itself or to the patient's underlying pathology. Although two events were classified as SAEs because of hospitalization, the hospitalizations were appropriate for pathology that would have been missed without Optison use.

Conclusions: In this large, prospective safety study of Optison during routine resting and stress echocardiography, no SAEs related to Optison developed. Optison helped define abnormalities that required appropriate hospitalization for further management. (J Am Soc Echocardiogr 2014;■:■-■.)

Keywords: Echocardiography, Contrast agents, Safety

The use of ultrasound contrast agents (UCAs) has been found to be safe during rest and stress echocardiography in large single and multicenter studies.[1-10] The use of UCAs has also been shown to be safe in even the sickest hospitalized patients.[11-13] It is in the most compromised and critically ill patients that contrast use often provides the greatest benefit, because these patients have the most limited echocardiographic windows. Reducing the number of uninterpretable studies, improving the assessment of left ventricular (LV) function, and defining unsuspected pathology help alter cardiac diagnoses and patient management and decrease downstream resource utilization.[14]

Since receiving approval, Optison (GE Healthcare, Princeton, NJ) has been administered to >1 million patients worldwide. Rare but serious cardiopulmonary reactions were reported in postmarketing surveillance, but because these events were reported voluntarily from a population of uncertain size, it was not possible to accurately estimate the true frequency of these reactions or to establish a causal relation to the drug. Reports of UCA safety have been derived from retrospective databases, but again, these data were not derived from studies designed to assess safety. In one retrospective analysis that included >76,000 subjects, the incidence of anaphylactoid reactions to UCAs was estimated to be one in 15,000.[3] During the time period in which these data were collected, however, Optison was not readily available.

Because of these limitations, the US Food and Drug Administration mandated a large multicenter postmarketing surveillance study, with the enrollment of 1,000 subjects, to determine prospectively the occurrence of serious adverse events (SAEs) in patients who received Optison during routine clinical care. This report summarizes the findings of this study.

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Presented in part at the American Heart Association Annual Scientific Sessions, Orlando, Florida, 2009.

The study was sponsored by GE Healthcare (Princeton, NJ).

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0894-7317/$36.00

http://dx.doi.org/10.1016/j.echo.2014.04.020

Abbreviations
AE = Adverse event
LV = Left ventricular
SAE = Serious adverse event
UCA = Ultrasound contrast agent
VT = Ventricular tachycardia

METHODS

The study was performed at 18 centers in the United States (see the Appendix). The study was an open-label, prospective, postmarketing surveillance study. Any patient >18 years of age referred for routine clinically indicated outpatient resting or stress echocardiography with an approved indication for ultrasound contrast administration was eligible to participate. Consecutive patients who met enrollment criteria were approached to participate in the study. Each center obtained approval from its respective human investigation committee or institutional review board, and informed consent was obtained from all patients.

Optison vials were stored and prepared for use in accordance with the package insert. The dose and method of administration of Optison were based on each institution's own protocols and were not specified by the study protocol, but the recommended dose was 0.5 mL of Optison injected peripherally, followed by a slow flush of 0.9% sodium chloride at a rate not to exceed 1 mL/sec. The maximum total dose was not to exceed 5 mL in any 10-min period or 8.7 mL in any individual study.

Data collected from each subject included demographics, cardiovascular and pulmonary histories, risk factors for coronary artery disease, and allergy history. Vital signs (heart rate, respiratory rate, and blood pressure) were obtained at baseline before dosing with Optison and at 5 to 15 min, 30 min, and 1 hour after the administration of Optison. Electrocardiographic monitoring was not required by the protocol, so 12-lead electrocardiograms were obtained at baseline only in patients undergoing stress procedures. The protocol required all subjects to be contacted by telephone for follow-up at 24 hours after the administration of Optison. Patients with known hypersensitivity to perflutren, blood, blood products, or albumin were excluded from the study.

Patients were followed for any cardiopulmonary adverse event (AE) or SAE, defined as an event that causes death, is life threatening, requires or prolongs hospitalization, or causes another important event, for 24 hours after the administration of Optison. A 12-lead electrocardiogram was obtained for any subject who experienced a significant change in vital signs or either a cardiopulmonary AE or an SAE.

Statistical Analysis

No power calculations were used to determine the study sample size, as a sample size of 1,000 subjects was requested by the Food and Drug Administration.

Data are expressed as mean ± SD. Comparisons between continuous variables were performed using repeated-measures analysis of variance. Interstage differences were confirmed using paired Student's *t* tests. Differences were considered significant at $P < .05$ (two sided).

RESULTS

Patient Demographics

A total of 1,039 patients (648 men) were enrolled in the study between June 2008 and March 2009. Patient demographics are shown in Table 1. Body measurements all significantly declined with increasing age: for patients <65 ($n = 671$), 65 to 75 ($n = 227$), and >75 ($n = 141$) years of age, mean weight was 233.6 ± 70.2, 215.0 ± 55.9, and 189 ± 40.9 lb, respectively ($P < .001$); mean height was 67.8 ± 4.1, 67.5 ± 4.3, and 66.8 ± 4.0 in, respectively ($P = .02$); and mean body mass index was 35.8 ± 10.0, 33.4 ± 8.2, and 29.8 ± 5.6 kg/m^2, respectively ($P < .001$).

Table 1 Patient demographics

Variable	Value
Men	648 (62.4%)
Age (y)*	59.9 ± 13.0 (20–97)
Weight (lb)	223.5 ± 65.7 (100–529)
Height (in)	67.7 ± 4.1 (51–78)
Body mass index (kg/m^2)	34.4 ± 9.4 (15–82)
Cardiac risk factors	
Hypertension	751 (72.3%)
Hyperlipidemia	664 (63.9%)
Diabetes	382 (36.8%)
Smoking	543 (52.3%)

Data are expressed as number (percentage) or as mean ± SD (range), except as indicated.
*Median ± SD (range).

Clinical Data

The mean dose of Optison administered was 1.9 ± 1.1 mL (range, 0.2–10 mL). The maximum dose of Optison was exceeded in a single patient who was undergoing resting two-dimensional echocardiography for chest pain. This patient received a total of 10 mL of Optison but developed no AEs. Optison was administered during resting two-dimensional echocardiography in 573 patients, during exercise stress echocardiography in 250 patients, and during dobutamine stress echocardiography in 216 patients. The indications for the echocardiographic examinations are listed in Table 2. As expected, most resting echocardiographic studies were performed to evaluate LV function, while most of the stress echocardiographic studies were ordered for patients with histories of chest pain.

Vital signs data obtained at baseline and at three time points after the administration of Optison are shown in Table 3. No significant changes in any vital signs were noted from before to after the administration of Optison for patients undergoing resting echocardiograms, but as expected, heart rate, respiratory rate, and blood pressure all increased during stress echocardiography but returned to near baseline levels by the 1-hour time point.

Adverse Events

All subjects who received Optison were included in the safety population. Out of the entire population, 790 subjects (76%) were successfully contacted at 24 hours after the administration of Optison for follow-up. No late AEs were reported.

AEs developed frequently in patients undergoing dobutamine or exercise stress testing. Of the 76 patients (35%) who developed AEs during dobutamine stress, 36 (47%) had two or more concurrent symptoms. The symptoms reported included chest pain ($n = 29$); arrhythmias such as premature atrial contractions, premature ventricular contractions, and nonsustained ventricular tachycardia (VT) ($n = 24$); hypertension ($n = 17$); tachycardia ($n = 15$); electrocardiographic changes ($n = 15$); dyspnea ($n = 12$); and other symptoms, including nausea, vomiting, tremor, and dizziness ($n = 16$). None of these AEs were serious, and none were attributed to Optison by