CaRES (Contrast Echocardiography Registry for Safety Surveillance): A Prospective Multicenter Study to Evaluate the Safety of the Ultrasound Contrast Agent Definity in Clinical Practice

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Background: Definity (perflutren lipid microsphere) is an ultrasound contrast agent approved for use in patients with suboptimal echocardiograms to opacify the left ventricular chamber and to improve the delineation of the left ventricular endocardial border. This prospective, open-label, nonrandomized, multicenter, phase 4 surveillance registry study was conducted at 15 clinical sites in the United States and was designed to assess the risk for adverse cardiopulmonary events occurring during or within the initial 30 min after Definity administration in routine clinical practice.

Methods: Patients with suboptimal baseline images were consecutively approached regarding study participation. Safety monitoring including vital sign measurements, continuous electrocardiographic monitoring, and continuous oxygen saturation was initiated at baseline before Definity administration and then at regular intervals for 30 min after Definity injection. Patients were assessed for adverse events at 30 min after Definity administration and then contacted by telephone at 24 $\pm$ 4 hours to record any subsequent adverse events.

Results: A total of 1,060 patients were enrolled at 15 clinical sites. Of these, 1,053 (99.3%) received at least one dose of Definity and completed the study. No deaths, serious adverse events, or other significant adverse events occurred during this study. The overall adverse event rate was 10.8% (4.5% in patients undergoing rest echocardiography, 13% in patients undergoing rest and exercise stress echocardiography, and 27.7% in patients undergoing rest and pharmacologic stress echocardiography). The overall drug-related adverse event rate (patients with at least one adverse event reported by the principal investigator as related to Definity) was only 3.5%, and most of these (110 of 114 [96.5%]) were reported by the investigator as mild or moderate in intensity.

Conclusions: Definity is well tolerated in routine clinical practice in patients with a high prevalence of cardiopulmonary disease. (J Am Soc Echocardiogr 2012;25:790-5.)

Keywords: Ultrasound contrast agents, Contrast echocardiography, Safety

Echocardiography is the first-line imaging method of choice for evaluating patients with suspected cardiac disorders because of its ease of use, widespread availability, portability, lack of ionizing radiation exposure, and high diagnostic utility. However, largely because of patient-related factors such as obesity and chronic obstructive pulmonary disease, $\geq$10% to 15% of patients are technically difficult to image, which results in reduced image quality and lower diagnostic accuracy.[1] This percentage is as high as 30% in critically ill patients[2] and 33% in patients undergoing stress echocardiography.[3]

Definity (perflutren lipid microsphere for injectable suspension; Lantheus Medical Imaging, Inc., North Billerica, MA) is an ultrasound contrast agent consisting of phospholipid-encapsulated octafluoropropane microspheres.[4] In a multicenter, randomized, placebo-controlled trial evaluating the efficacy and safety of Definity in patients with suspected cardiac disease and suboptimal baseline echocardiograms, improvement in left ventricular endocardial border delineation was demonstrated in patients who received Definity in comparison with those who received placebo.[4] Definity has been approved in the United States since 2001 for "use in patients with suboptimal echocardiograms to opacify the left ventricular chamber and to improve the delineation of the left ventricular endocardial border."[4]

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Abbreviations
AE = Adverse event
BMI = Body mass index
SAE = Serious adverse event

In October 2007, the US Food and Drug Administration issued a "black box warning" for the commercially available ultrasound contrast agents, including Definity, after reports of serious adverse events (SAEs) that occurred in close temporal relationship to contrast administration.[5] Since then, multiple postmarketing studies have confirmed a highly favorable risk-benefit profile for ultrasound contrast agents in clinical practice.[6-16] In addition, in 2008, the Food and Drug Administration requested a three-study risk assessment program for ultrasound contrast agents after a meeting of the Cardiovascular and Renal Drugs Advisory Committee convened to evaluate "safety considerations in the development of ultrasound contrast agents."[17] The three studies were (1) an invasive hemodynamic assessment of pulmonary artery pressure and resistance in patients receiving Definity, (2) a large retrospective assessment of mortality in critically ill hospitalized patients undergoing echocardiography with or without Definity, and (3) the present study, a prospective registry of approximately 1,000 patients receiving Definity in routine clinical practice, to determine its safety. It is important to note that two large retrospective registry studies have concluded that the incidence of life-threatening anaphylactoid reactions associated with ultrasound contrast agents is approximately 1:10,000 doses. These data would indicate that the current study size is insufficiently powered to detect these rare events.[7,8]

METHODS

This was a prospective, open-label, nonrandomized, multicenter, phase 4 surveillance registry study conducted at 15 echocardiography clinical sites in the United States between February 20, 2008, and April 26, 2009. Although average enrollment was only five subjects per site per month, as in most multicenter studies, enrollment was competitive and rolling, with some sites not active until relatively late because of contractual issues or delays in attaining local institutional review board approval. The study was approved by respective institutional review boards, and all patients gave written informed consent before study participation. Patients aged $\geq$ 18 years who had undergone unenhanced echocardiography yielding suboptimal images and for whom contrast-enhanced echocardiography was indicated were invited to participate in the study and subsequently screened for eligibility. Exclusion criteria were pregnancy; known intracardiac shunts; known hypersensitivity to perflutren, Definity, or any other ultrasound contrast agent; or a prior SAE associated with perflutren, Definity, or any other ultrasound contrast agent. Patients with pulmonary hypertension were eligible to participate.

Patients entered into the study received commercially available Definity. Definity was administered as a diluted bolus at all sites, and dosing guidelines as detailed in the product insert were followed. Safety monitoring included vital sign measurements (heart rate, respiratory rate, systolic and diastolic blood pressure), continuous electrocardiographic monitoring, and continuous cutaneous oxygen saturation measured by pulse oximetry, initiated before Definity administration and then at regular intervals for up to 30 $\pm$ 5 min after Definity injection. Four categories of adverse events (AEs) were collected over the study period: AEs, defined as any new untoward medical occurrences or worsening of preexisting medical condition in a patient administered Definity that did not necessarily have a causal relationship with Definity (moderate-intensity AEs were defined in the protocol as introducing a "low level of inconvenience or concern to the patient and may interfere with daily activities but are usually ameliorated by simple therapeutic measures"); treatment-emergent AEs, defined as those AEs that appeared for the first time during or after Definity administration or were exacerbations of pretreatment conditions; life-threatening cardiopulmonary events (i.e., cardiac or respiratory arrest, acute myocardial infarction, or life-threatening arrhythmias); and other SAEs, defined as those AEs that resulted in death, were life threatening (defined as an event in which the patient was at risk for death at the time of the event), required inpatient hospitalization or caused prolongation of existing hospitalization, resulted in persistent or significant disability or incapacity, jeopardized the patient, or required intervention (e.g., medical, surgical) to prevent any other serious outcome. Patients were assessed for death and life-threatening AEs for 30 $\pm$ 5 min after the completion of Definity administration and for any AEs and SAEs subsequently by phone at 24 $\pm$ 4 hours. AE and electrocardiographic adjudication was performed at the clinical sites by the investigators. In addition, detailed information was collected from all patients regarding cardiac history, pulmonary history, central nervous system history, other significant conditions and both prior and concomitant cardiac medications by drug class.

All statistical analysis was performed using SAS release 9.1.3 or higher (SAS Institute Inc., Cary, NC). All statistical tests of comparisons were based on a 5% level of significance. Safety summaries were produced for all patients receiving at least one dose of Definity and subsequently by subgroup on the basis of the following medical conditions: history of percutaneous coronary intervention or coronary artery bypass grafting, heart failure, chronic obstructive pulmonary disease, mechanical ventilation, diabetes mellitus, hepatic impairment, renal impairment, and obesity (defined as a body mass index [BMI] $>$ 30 kg/m^2). No adjustments for multiple comparisons were made in statistical tests of significance. To address factors affecting the incidence of AEs, a multivariate logistic regression analysis was performed separately for patients given single rest doses and for patients given rest and stress doses to determine which variables were associated with AEs. The primary purpose was to determine if there is a dose-response relationship in AEs adjusted for patient factors and stress testing. Covariates included Definity dose, age, gender, BMI in the rest-only model, and the same variables plus stress type in the rest-plus-stress model. In the rest-plus-stress model, age and gender were significant factors in AE incidence, with the proportion of AEs higher in female stress patients.

RESULTS

A total of 1,060 patients were enrolled at 15 clinical sites in the United States. Of these enrollees, 1,053 (99.3%) received at least one dose of Definity and completed the study. A total of 1,013 patients (95.6%), all of whom received Definity, completed the 30 $\pm$ 5 min safety assessments. A total of 599 patients (56.5%) received only rest doses of Definity, 32 (3.0%) received only stress doses of Definity, and the remaining 422 (39.8%) received both rest and stress doses.

Of the 1,053 patients who completed Definity administration, 1,021 patients received Definity at rest imaging, with a mean dose of 0.5 $\pm$ 0.3 mL, and 454 patients received Definity as part of stress imaging, with a mean dose of 0.5 $\pm$ 0.3 mL.

Overall, demographic and baseline characteristics were similar across the rest-only and rest-plus-stress groups (Table 1), except for a slightly lower mean age in patients undergoing rest and stress