Warning Issued for Ultrasound Agent Used in Echo

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Microbubble ultrasound contrast agents used in patients with suboptimal echocardiograms have been linked to serious cardiopulmonary reactions and several deaths, according to the Food and Drug Administration.

In October, the agency issued a notice on its MedWatch site alerting health care professionals that the agency had received reports of deaths and cardiopulmonary reactions after ultrasound microbubble contrast agents had been administered to patients undergoing echocardiography. Of the 11 deaths reported, 4 were due to cardiac arrest during the infusion or within 30 minutes of administration, and most of the serious, nonfatal reactions also occurred during this time period.

The manufacturers of Definity (perflutren lipid microsphere) injectable suspension and Optison (perflutren protein-type A microspheres for Injection), the only microbubble ultrasound contrast agents approved in the United States, have agreed to add a black box warning and other warnings to the product labels describing these risks. A contraindication against their use in patients at a particular risk for cardiopulmonary reactions will also be added to the label. These patients include with those with known cardiac shunts, clinically unstable or recent worsening of heart failure, symptomatic arrhythmias, or those at high risk for arrhythmias due to QT prolongation, respiratory failure, severe emphysema, pulmonary emboli "or other conditions that compromise pulmonary arterial vasculature."

These agents are a sterile suspension of perflutren gas microspheres that are indicated for use in patients with suboptimal echocardiograms, and are used to "opacify the left ventricular chamber and to improve the delineation of the left ventricular endocardial border," according to the FDA.

Most of the reports have been associated with Definity, approved in 2001. There have been 10 postmarketing deaths reported with Definity and 1 following the administration of Optison, which was approved in 1997; marketing of Optison was temporarily suspended in 2005. In most of the deaths, the patient had a severe underlying condition: Some patients were on other medications the FDA statement said "could have contributed to their death." Four of the deaths that followed cardiac arrest occurred during administration of Definity or within the 30 minutes that followed; two patients had severe heart failure and one was mechanically ventilated because of respiratory failure.

The FDA received reports of cardiopulmonary reactions and deaths after ultrasound microbubble contrast agents had been administered.

The FDA has also received 190 reports of serious nonfatal reactions following Definity administration and 9 such reports after Optison administration. In many of these cases, the patient had an "acute onset of symptoms suggestive of an anaphylactoid reaction." Other cases described cardiopulmonary reactions with cardiac or respiratory arrest, loss of consciousness, convulsions, symptomatic arrhythmias, cardiac ischemia, hypotension, respiratory distress, and oxygen desaturation "without signs or symptoms of a typical allergic reaction."

The boxed warning and warnings section also will recommend that vital signs, cardiac rhythm, and oxygen saturation be monitored in patients who receive these agents, and that resuscitation equipment and trained personnel be "readily available," in patients who receive these agents, the FDA said.

The indications section will also point out that the safety and efficacy of Definity for use with exercise or pharmacologic stress testing has not been established. (One of the Definity-associated deaths was in a patient undergoing a cardiac stress test.) ■

The full summary is available at: www.fda.gov/medwatch/safety/2007/safety07.htm#bubble. Serious adverse events can be reported to the FDA's MedWatch program at 800-FDA-1088, or on-line at www.fda.gov/medwatch/report.htm.

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