FDA's Ultrasound Contrast Warning Draws Heat

BY BRUCE K. DIXON
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Black box restrictions imposed by the Food and Drug Administration on the use of ultrasound contrast agents have caused consternation among cardiologists and radiologists who fear that the agency's decision will have a chilling effect upon the use and further development of these "microbubble" agents.

Efforts at getting the FDA to reconsider the label change, which was issued in October (CARDIOLOGY NEWS, November 2008, p. 20), may have borne fruit in December, when a delegation of four cardiologists met with Dr. Rafel D. Rieves, acting director of the FDA's Division of Medical Imaging and Hematology Products, and his staff in Silver Spring, Md. The cardiologists were Dr. Steven B. Feinstein of the Rush Medical College, Chicago; Dr. Jonathan H. Goldman of the University of California, San Francisco; Dr. Paul A. Grayburn of the Baylor University Medical Center, Dallas; and Dr. Michael L. Main of the Mid-America Heart Institute, Kansas City, Missouri.

The emissaries represented an international group of 160 cardiologists, radiologists, and other medical imaging professionals who had earlier signed a letter to Dr. Rieves asking that the FDA division convene a panel of cardiologists to assess fully the adverse events that have been attributed to the contrast agents and determine the most appropriate corrective actions.

The letter, dated Nov. 10, 2007, said the black box warning ignores the proven efficacy and established safety of perflutren gas microspheres for use as echocardiographic contrast agents, as well as the potential risks of alternative procedures and the likely confounding effect of pseudocomplications that may be pertinent to some of the deaths associated with use of the ultrasound contrast agents.

"Our presentation to the division of medical imaging focused on the critical role that ultrasound contrast agents play in the diagnosis and management of patients with acute coronary syndromes, decompensated heart failure, and respiratory failure," Dr. Main said in an interview.

"These are patient groups [that] must now undergo more invasive alternative testing when their baseline echocardiographic imaging is inadequate. We were encouraged that the FDA seemed receptive to the basic premise, which was that the risk-benefit ratio of ultrasound contrast is so favorable that the new contraindications will result in more harm than good," said Dr. Main, medical director of the echocardiography laboratory at the Mid America Heart Institute of St. Luke's Health System.

Dr. Main has received research support from and has a consultant relationship with, POINT Biomedical Corp., Acusphere Inc., and Bristol-Myers Squibb Medical Imaging Inc. Dr. Goldman is a POINT Biomedical shareholder and has a consultant relationship with Bristol-Myers Squibb Medical Imaging. Dr. Grayburn has received grant support from Acusphere, POINT Biomedical, Medtronic Inc., and Guidant Corp.

Two ultrasound contrast agents, Definity (Bristol-Meyers Squibb) and Optison (GE Healthcare), are approved for use to improve suboptimal echocardiograms. Both consist of injectable, perflutren-filled lipid microspheres. Optison is back on the market following a 2-year hiatus attributed to a manufacturing recall.

In issuing the warning, the FDA said it had received reports of serious cardiopulmonary reactions following contrast injection, including 10 deaths following the administration of Definity and 1 death following an Optison injection. Of those 11 deaths, 4 were caused by cardiac arrest and occurred during or within 30 minutes of infusion; the remaining 7 deaths occurred within 12 hours of administration.

In addition, about 190 nonfatal serious reactions were reported in the United States following administration of Definity and Optison.

The boxed warning states that "serious cardiopulmonary reactions, including fatalities, have occurred during or within 30 minutes" after administration of Definity or Optison. Referring to contraindications described on the label, the warning requires that all patients be assessed for the presence of any condition that precludes administration of the contrast agent. In addition, patients are to be monitored during, and for 30 minutes following, contrast administration, including vital sign measurements and electrocardiography in all patients and cutaneous oxygen saturation in patients at risk for hypoxemia. Resuscitation equipment and trained personnel should be readily available.

Additional pressure on the FDA has come from the 12,000-member American Society of Echocardiography (ASE). In late November, ASE President Thomas Ryan wrote a letter to Dr. Andrew C. von Eschenbach, the FDA Commissioner, requesting an opportunity to engage in a dialogue with the agency regarding its decision to issue the black box warning.

"The risk of an adverse event resulting from the administration of a contrast agent must be weighed against the value of a correct diagnosis," said Dr. Ryan, who noted that he has no conflicts of interest related to the topic. "Because contrast agents improve accuracy and reduce the need for additional downstream testing, we believe their continued use in appropriate cases is justified and consistent with the mission of both the FDA and the ASE," wrote Dr. Ryan, who is the John G. & Jeanne Bonnet McCoy Chair in Cardiovascular Medicine and the director of the Ohio State University Heart Center in Columbus.

A spokesman for the FDA said, "the letter has been received, and the agency is working on a response." The agency had no further comment on the issue.

"The near-term result of this black box warning, in my opinion, will be a dramatic drop in the use of ultrasound contrast agents, and as a result, the quality of echocardiograms will go down until this scare wears off," Dr. Peter S. Rahko said in an interview.

"The reaction of the FDA and the rules they imposed seem to be excessive," said Dr. Rahko of the departments of medicine and public health and director of the adult echocardiography laboratory at the University of Wisconsin, Madison.

But Dr. Rahko does agree with the FDA's expressed concerns that an unknown proportion of patients may suffer allergic reactions to the microsphere contrast agents, which has occurred on a few occasions at Wisconsin.

When the black box warning was issued, the use of contrast-enhanced ultrasound ceased at the University of Wisconsin and other centers. The Wisconsin team developed a two-stage screening protocol for stable and critically ill patients (see box), said Dr. Rahko, who was one of the original investigators in the Definity trials but has no financial conflicts related to the topic. ■

Adjusting to the Black Box Alert

After the FDA issued its warning on ultrasound contrast agents, Dr. Rahko and his colleagues at the University of Wisconsin halted their practice of automatically ordering contrast following a bad-quality echocardiogram.

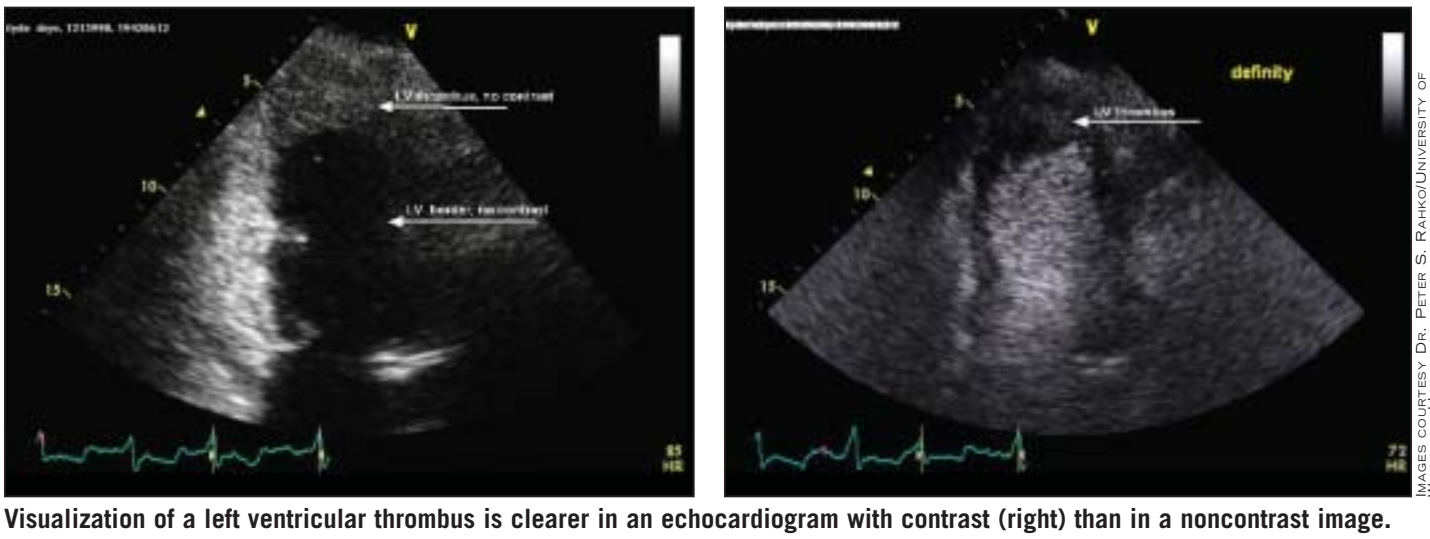
Previously, "If the patient was appropriate, then the contrast could be administered in the intensive care unit with the assistance of nursing personnel and others taking care of the patient," Dr. Rahko said.

The hospital now operates with a more costly and time-consuming two-tiered protocol that is tailored to stable and unstable patients undergoing echocardiography.

For an unstable hospitalized patient, the baseline sonogram is read by a cardiologist; if it's of poor quality and a redo with Definity seems appropriate, the cardiologist recommends that the study should be repeated with contrast. "The patient care team now becomes the responsible party ordering the contrast."

The protocol for stable patients scheduled for echo in the inpatient or outpatient setting shifts responsibility for the final decision to the patient and includes screening for conditions that might contraindicate the use of the microspheres. "Our nurses—in the echo lab or at other sites—screen the patients using oxymetry to make sure that oxygen saturation levels are appropriate and that patients don't have significant hypoxia or lung disease," Dr. Rahko explained.

Patients who are stable and cleared for a contrast injection are given an information sheet that explains the procedure, why it's being done, and the risks it poses. The patient then decides whether or not to proceed. And "we keep the patient under direct observation for 30 minutes, in case of an allergic reaction," he said.



IMAGES COURTESY DR. PETER S. RAHKO/UNIVERSITY OF WISCONSIN HOSPITAL

Visualization of a left ventricular thrombus is clearer in an echocardiogram with contrast (right) than in a noncontrast image.

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