EDITORIAL COMMENT

Ultrasound Contrast Agent Safety
From Anecdote to Evidence*

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In October 2007, the U.S. Food and Drug Administration (FDA) mandated significant revisions to product labeling for the commercially available perflutren-containing ultrasound contrast agents (UCA) Definity (perflutren lipid microsphere injectable suspension, Lantheus Medical Imaging, North Billerica, Massachusetts) and Optison (perflutren protein type A microspheres for injectable suspension, GE Healthcare, Buckinghamshire, United Kingdom) after spontaneous reports of 4 patient deaths and approximately 190 “severe cardiopulmonary reactions” occurring in close temporal relationship to UCA administration (1). This 3-part labeling revision included a new “black box” warning (advising of the potential for “serious cardiopulmonary reactions”) and multiple new disease state contraindications to UCA use, including acute myocardial infarction (MI) or acute coronary syndromes, worsening or decompensated heart failure, serious ventricular arrhythmias or patients at high risk for arrhythmias based on QT interval prolongation, as well as respiratory failure, severe emphysema, pulmonary emboli, or other conditions that may cause pulmonary hypertension. Finally, the FDA also required a blanket 30-min monitoring period after UCA injection for all patients, including ambulatory outpatients (1).

Immediate response from the echocardiography community was strongly critical of the FDA action, with clinicians charging that the agency had ignored the previously published safety profile of UCAs in clinical trials at doses exceeding those used in clinical practice, the anecdotal nature of post-marketing safety reports, and the likelihood that deaths and poor outcomes associated with UCA use were in fact “pseudocomplications” (death or complication due to progression of the underlying disease state rather than diagnostic testing or therapeutic intervention) (2,3). Critics also noted the greater potential risks associated with alternative testing procedures such as transesophageal echocardiography and radionuclide ventriculography (which would now be necessary in many patients), the hazards of misdiagnosis or missed diagnosis (due to poor-quality studies without contrast), and the fact that patients with disease state contraindications, including many hospitalized in intensive care units, were the very patients most in need of, and likely to derive significant benefit from, contrast-enhanced echocardiography (2,3).

In July 2008, after intense advocacy by physician experts, publication of exculpatory safety data in hospitalized patients (4), and a better understanding of contrast-enhanced echocardiography efficacy, the FDA partially relaxed product labeling for both Optison and Definity (5). Although a black box warning still exists, the October 2007 disease state contraindications have been replaced by warnings. Additionally, the 30-min monitoring period after injection now applies only to patients with pulmonary hypertension (the severity of which is not defined) and patients with “unstable cardiopulmonary conditions” (who presumably would be hospitalized in intensive care units and subject to continuous rhythm and hemodynamic monitoring) (5).

Since early 2008, multiple UCA safety studies have been published in the peer-reviewed literature (4,6–12). These studies (with experience in
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~200,000 patients receiving UCAs) have established the relative safety of Optison and Definity in a wide range of clinical environments, including hospitalized patients (4,6,7–11), ambulatory outpatients (7–12), and, in a more limited sense, stress echocardiography (7–12). Although the FDA has not expressly approved UCAs for use in stress echocardiography (and UCAs would not have been contraindicated in most patients undergoing stress echocardiography even under the original FDA labeling changes in October 2007), safety of UCAs for this indication is an important issue. Marketing data for the calendar year 2008 indicates that contrast agents were used in approximately 3.2% of stress echocardiographic studies in the U.S. (vs. only 0.4% of resting studies, with both percentages dramatically lower in comparison with 2007 and previous years) (Arlington Medical Resources Imaging Market Guide [USA Edition], unpublished data, 2005–2008), the American Society of Echocardiography recommends use of UCAs for the stress echocardiography indication in “difficult to image patients presenting for echocardiography with reduced image quality” (13), and the recently published Stress Echocardiography Appropriateness Criteria find selective use of contrast (when 2 or more contiguous segments are not seen on noncontrast images) both acceptable and reasonable (with an appropriateness score of 8) (14).

In this issue of JACC, Abdelmoneim et al. (15) extend the growing body of UCA safety literature with a retrospective study in patients undergoing stress echocardiography at the Mayo Clinic in Rochester, Minnesota, between November 2003 and December 2007. A total of 26,774 patients undergoing either exercise or pharmacologic stress echocardiography comprised the study population, including 10,792 patients who received an ultrasound contrast agent (86% Definity and 14% Optison) and underwent either exercise (n = 4,276) or dobutamine (n = 6,516) stress echocardiography. End points included all-cause mortality or MI over the short term (≤72 h) and intermediate term (≤30 days), as well as long-term all-cause mortality or MI in a subgroup of propensity-matched patients (with follow-up extending to 4.5 years). Patients receiving a UCA were older and sicker (with a significantly higher prevalence of diabetes mellitus, systemic hypertension, and symptomatic coronary artery disease in the contrast cohort) and more frequently underwent dobutamine echocardiography, presumably due to inability to exercise. Despite these higher risk features, there was no increase in any of the primary study end points in patients receiving a UCA. These results are reassuring and corroborate previously published data (see Table 5 in Abdelmoneim et al. [15]) which has established an excellent safety profile for UCAs in now 9 large-scale postmarketing studies (4,6–12,15).

An important observation in the present study (and consistent with data from the Hennepin County database [n = 16,025 contrast injections] [7] and the American Society of Echocardiography database [n = 78,383 contrast injections] [8]) is an approximate 1:10,000 incidence of acute anaphylactoid reaction immediately after (generally within several min) UCA injection. These reactions are believed to be secondary to a recently described variant of the type I hypersensitivity reaction (complement activation-related pseudoallergy), and can be life-threatening (16). This risk can be readily mitigated by early recognition of anaphylactoid reactions and prompt treatment with an intramuscular injection of 0.3 mg/1:1,000 dilution of epinephrine (commercially available in the U.S. as an automatic injectable) (EpiPen, Dey, L.P., Napa, California). The risk of anaphylactoid reaction with a UCA appears equal to or lower than that associated with low osmolar noniodinated radiocontrast media (17); individuals with a history of atopy, such as drug, food, or environmental allergy, may be at somewhat higher risk of these reactions with both UCAs and radiocontrast agents (17).

Although it is always easiest (and safest) to conclude that “further studies are warranted,” it is unlikely that additional investigation will significantly alter our current understanding of UCA safety. We now know that UCAs are safe by any reasonable standard, including use in hospitalized patients (4,6,7–10) and ambulatory outpatients (7–12), as well as in patients undergoing rest (4,6–9) or stress echocardiography (7–12,14), and certainly are safe in comparison with competing/complementary cardiovascular testing modalities including coronary angiography, transesophageal echocardiography, nuclear imaging, and physical or pharmacologic stress testing (2). When considered in association with professional society recommendations (13,14), as well as recent efficacy data published in American College of Cardiology journals that have confirmed the critical role UCAs play in enhancing the accuracy of stress echocardiography (18) and in improving the diagnostic utility of transthoracic echocardiography in patients with suboptimal baseline imaging (19), the benefit-to-risk calculation for
contrast echocardiography strongly supports routine use of UCAs in all difficult to image patients.

With these substantial data in support of safety and efficacy, the time is right for the FDA to lift the black box warning, withdraw the disease state and efficacy, and rescind the 30-min monitoring period after contrast injection, all of which discourage UCA use in the patients most likely to derive the greatest benefit from contrast-enhanced echocardiography. In 2007, the FDA questioned the safety of UCAs based on anecdote. These questions have now been answered—with evidence.

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REFERENCES


