Is the Safety of Ultrasound Contrast Agents a Concern?

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Disclosures: Research grant from GE
Post-marketing Survey Events

1. 6 patients had “cardiac arrest” within 30 min of Definity administration (out of approximately 2 million doses)

2. Acute anaphylactoid reactions reported: hypotension, bronchospasm, urticaria, pruritus (approximately 1 out of 10,000 for Definity, unknown with Optison)
FDA-mandated Prescribing Information

October 10, 2007

**Warning**: serous cardiopulmonary reactions and fatalities within 30 min of contrast administration

**Contraindications**: any ACS, unstable CHF, ventricular arrhythmias, pulmonary hypertension, right-left shunt, known allergies, arterial injection

**Administration guidelines**: 30 min observation period with vital signs, ECG and O$_2$ monitoring
Contraindications for Contrast Ultrasound use as of May 14, 2008

- Known right to left intracardiac shunt
- Known allergy to ultrasound contrast agent component
- Intra-arterial injection

30 min observation in patients with Pulmonary Hypertension or unstable cardiopulmonary condition.
FDA participates in seminar at ASE scientific sessions in June 2008.

May 2011 FDA invites 2 advisory panels: Cardiorenal and Safety to study the results.

FDA now in the process of setting up special advisory panel for all of imaging.
DEFINITY® Prescribing Information

• October 2011
  – DEFINITY specific label changes
    • Post administration monitoring period recommendation removed
    • Statement added indicating that “most serious reactions occur within 30 minutes of administration”
    • Previous statement that “the safety and efficacy of DEFINITY with exercise stress or pharmacologic stress have not been established” deleted from label
ASE Multicenter Registry

- Retrospective 13 site registry (January 1, 2001-September 30, 2007)
- 66,164 doses of Definity and 12,219 doses of Optison (5% of transthoracic/28% stress)
- Severe adverse reactions in 8 patients (0.01%)
- Anaphylactoid reactions in 4 patients (0.006%)
- No deaths
- No SAE in hospitalized patients

Conclusions: The incidence of severe adverse reactions to ultrasound contrast agents is lower than, or similar to, that reported for contrast agents commonly used in other cardiac imaging tests.

18,671 patients
- 12,475 unenhanced
- 6,196 Definity

In-patient echocardiography between January 2005 and October 2007

Vital status at 24 hours available for all patients
**Conclusion:**
No difference in 24 hour mortality in hospitalized patients undergoing echocardiography with or without contrast administration despite those receiving contrast being sicker.
Acute Mortality in Hospitalized Patients Undergoing Echocardiography with and without an Ultrasound Contrast Agent: Multicenter Results in 4,300,966 Consecutive Patients

Multivariable logistic regression analysis: patients receiving Definity were 24% less likely to die within 1-day than patients not receiving a contrast agent (adjusted odds ratio=0.76 (95% CI =0.70-0.82).

Main ML et al. Am J Cardiol 2008;102:1742-6
Intraoperative Contrast Echocardiography with Intravenous Optison Does Not Cause Hemodynamic Changes During Cardiac Surgery

Joachim M. Erb, MD, DEAA, and Jack S. Shanewise, MD, Berlin, Germany, and Atlanta, Georgia

Background: The echocardiographic contrast agent Optison may be useful in patients undergoing cardiac surgery. This study investigates its effects on hemodynamics, cardiac performance, and oxygenation in this group of patients.

Method: Parameters of hemodynamic stability, cardiac performance, and oxygenation were measured in 57 patients by transesophageal echocardiography, electrocardiography, invasive arterial blood pressure and central venous pressure monitoring, capnography, pulseoximetry, and pulmonary artery catheter before and 5 and 10 minutes after intravenous bolus of 0.3 ml of Optison.

Results: No statistically significant differences in ST-segment changes, heart rate, arterial and central venous pressure, peripheral oxygen saturation, cardiac index, left ventricular ejection fraction, and regional wall motion were seen 5 and 10 minutes after injection of Optison compared with baseline parameters.

Conclusion: Optison did not cause clinically important changes in parameters of hemodynamic stability, cardiac performance, and oxygenation in our patients. The intraoperative use of intravenous Optison appears to be safe in patients undergoing cardiac surgery, including in the use of cardiopulmonary bypasses. (J Am Soc Echocardiogr 2001;14:595-600.)

INTRODUCTION

Although the first reported use of an echocardiographic contrast agent dates back to 1968, when Graziani and Shah1 observed an ultrasound contrast effect after injection of hand-gauged indocyanine green during coronary angiography, contrast echocardiography was confined to the research laboratory for many years. A more widespread use of contrast echocardiography as a diagnostic tool in daily clinical practice became possible with the introduction of a method of sonication2 in 1984 and the availability of commercially produced contrast agents. The first available FDA-approved echocardiographic contrast agent in the United States was a suspension of air-filled albumin microspheres (Albunex, Mallinckrodt Inc, St Louis, MO). Since 1998, a second-generation echocardiographic contrast agent consisting of a suspension of octafluoropropane-filled albumin microspheres (Optison, Mallinckrodt Inc, St Louis, MO) has been available and approved by the FDA to improve endocardial border delineation with 2-dimensional echocardiography after intravenous injection. Optison has an average microsphere size of 2.0 to 4.5 μm and a concentration of 5 to 8 x 10⁸ microspheres/ml. Compared with Albunex, the smaller size and greater stability of the microspheres allow for improved transpulmonary passage with less decrease of the microsphere concentration caused by destruction or filtering in the pulmonary capillary bed.

Because this development improves the practical application of echocardiographic contrast agents, their intraoperative use in patients undergoing cardiac surgery may become more frequent. Studies have shown that Optison can improve the quality of echocardiographic images with significant decrease in acoustic noise. However, the potential impact on hemodynamic function has not been studied. The following study was therefore performed to assess the hemodynamic effects of Optison when administered in clinically relevant doses.
# Meta-Analysis of Adverse Cardiovascular Events Associated with Echocardiographic Contrast Agents

**Table 4**

Incidence of allergic/anaphylactic reactions with echocardiography contrast agents

<table>
<thead>
<tr>
<th>Studies</th>
<th>Patients Receiving Contrast Agent (n)</th>
<th>Allergic Reactions (n)</th>
<th>Anaphylactic Reactions (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdelmoneim et al(^{10})</td>
<td>10,792</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Gabriel et al(^{13})</td>
<td>4,786</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Dolan et al(^{12})</td>
<td>42,408</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Shaikh et al(^{15})</td>
<td>2,914</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Main et al(^{16})</td>
<td>58,254</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Wei et al(^{17})</td>
<td>78,383</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Kusnetzky et al(^{14})</td>
<td>12,475</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Anantharam et al(^{11})</td>
<td>1,150</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>110,500 (excluding NA studies)</strong></td>
<td><strong>11 (0.009%)</strong></td>
<td><strong>5 (0.004%)</strong></td>
</tr>
</tbody>
</table>

NA = not applicable.

*Khawaja et al. Am J Cardiol 2010;106:742-747*
## Results of the 6 Safety Studies Designed in Conjunction with FDA

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Pulmonary Hemodynamic Study</th>
<th>Critically Ill Propensity Matched Database</th>
<th>Routine Clinical Care Registry</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lantheus Medical Imaging</td>
<td>n=32</td>
<td>n=15,798 propensity matched patients</td>
<td>n=1053</td>
</tr>
<tr>
<td></td>
<td>No change in PA pressure with Definity</td>
<td>HR=0.683 (0.591-0.789)</td>
<td>No deaths or serious adverse events at 24 hours</td>
</tr>
<tr>
<td></td>
<td>No deaths or SAE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GE Healthcare</td>
<td>n=30</td>
<td>N=2884 propensity matched patients</td>
<td>n=1039</td>
</tr>
<tr>
<td></td>
<td>No change in PA pressure with Optison</td>
<td>(HR=1.4 (0.965-2.030)</td>
<td>No deaths or serious adverse events</td>
</tr>
<tr>
<td></td>
<td>No deaths or SAEs</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

[http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/ucm254389.htm](http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/ucm254389.htm)
GUEST EDITORIAL

When you have eliminated the impossible, whatever remains, however improbable, must be the truth

Sanjiv Kaul* and Kevin Wei

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## Major Adverse Events with Common CV Tests

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Adverse Event(s)</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercise stress testing</td>
<td>MI, death</td>
<td>1/2500</td>
</tr>
<tr>
<td>Dobutamine stress testing</td>
<td>MI, VF</td>
<td>1/2000</td>
</tr>
<tr>
<td>Iodinated contrast agents</td>
<td>Potentially or immediately life-threatening reactions</td>
<td>HO 1/500</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LO 1/5000</td>
</tr>
<tr>
<td>Diagnostic cardiac catheterization</td>
<td>Death, MI, arrhythmia, neuro event, vasc complic. contrast reaction</td>
<td>1/500</td>
</tr>
<tr>
<td>Ultrasound contrast agents</td>
<td>Anaphylactoid reaction</td>
<td>1/15,000</td>
</tr>
<tr>
<td></td>
<td>Severe fatal allergic reaction</td>
<td>1/500,000</td>
</tr>
</tbody>
</table>

LO, low osmolarity media; HO, high osmolarity media

Lindner and Wei, JACC Cardiovasc Imaging 2008
**Anaphylactoid Reactions**

1. Hypersensitivity reaction, also sometimes called “pseudoallergy”
2. Non-IgE-mediated
3. Does not require prior sensitization
4. Unlike anaphylactic reaction can decrease in severity or even disappear with subsequent exposure.
Anaphylactoid Reactions: Mechanisms

1. Occurs relatively frequently in liposomal drugs (eg: Doxil, Amphotericin); up to 7%

2. Mediated by both complement activation and thromboxane release

3. Ability of lipid particles to produce CARPA (C’ activation-related pseudoallergy) has been studied using liposomes in pig models where it is frequent
Anaphylactoid Reactions: Mechanisms

Liposome

- alternative C’ activation
- classic C’ activation

IgM, IgG

C3a, C5a

Platelets

- TXA$_2$, LTC$_4$
- TNF-$\alpha$, MCP-1
- IL1, IL6, PAF
- Histamine
- Serotonin

Mast cells

Endothelial cells

PMN

Mφ

Platelets
Factors That Influence CARPA

1. Surface charge
2. Lipid dose
3. Rate of infusion
4. Size (surface area)
5. Presence of non-ionic polymer at surface (polaxamer, PEG)
6. Presence of pre-formed anti-lipid antibodies
Microbubble Surface Characteristics

Stearic hindrence

charge

DSPX

PEG stearate

(CH$_2$CH$_2$O)$_{40}$

dFB gas core
C’ Activation by Microbubbles-Flow Cytometry

MB_{neut} PEG^+  

MB_{neg} PEG^-

C’ Activation by Microbubbles: Influence of Composition

## Complement Activation-related Pseudoallergy

<table>
<thead>
<tr>
<th>IgE-mediated Type I</th>
<th>CARPA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reaction arises after repeated exposure to allergen</td>
<td>Reaction may arise at first exposure</td>
</tr>
<tr>
<td>Reaction is stronger upon repeated exposures</td>
<td>Reaction is milder or absent upon repeated exposures</td>
</tr>
<tr>
<td>Reaction does not cease without treatment</td>
<td>Spontaneous resolution</td>
</tr>
<tr>
<td>Reaction rate is low (&lt; 2%)</td>
<td>High reaction rates</td>
</tr>
</tbody>
</table>
**Microbubbles and Pseudoanaphylaxis**

1. All microbubbles (lipid, polymeric, albumin) have the potential to activate complement at their surface.

2. Most commercial lipid microbubbles possess a net charge.

3. Many commercial lipid microbubbles have been designed with non-ionic polymer on the surface (polaxamer, PEG).

4. *CARPA-like syndrome can occur, but rare.*
Pseudoanaphylactic Reactions

MILD REACTION
flank pain, mild dyspnea, malaise

SEVERE REACTION
Lungs: pulmonary edema
Skin: hives, flushing, pruritis, macular rash, facial edema
Neurologic: altered mental status, tremor
GI: abdominal cramps, vomiting, diarrhea
CV: tachycardia, hypotension
# Pseudoanaphylaxis: Treatment in Adults

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage and Route</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epinephrine</td>
<td>0.3-0.5 mL of 1:1,000 by SQ or IM route</td>
<td>Maintain airway and BP</td>
</tr>
<tr>
<td></td>
<td>0.5-1.0 mL of 1:10,000 by IV route</td>
<td></td>
</tr>
<tr>
<td>Diphenhydramine</td>
<td>25-50 mg IV or IM</td>
<td>Anti-histamine</td>
</tr>
<tr>
<td>Albuterol or other beta-2 agonist</td>
<td>0.5 mL of 0.5% soln nebulized in 2.5 mL</td>
<td>Maintain airway</td>
</tr>
<tr>
<td>Cimetidine</td>
<td>200 mg IM or PO</td>
<td>Anti-histamine</td>
</tr>
<tr>
<td>Methylprednisone or other IV steroid</td>
<td>125 mg IV q 6 hr</td>
<td>Late phase reactions</td>
</tr>
</tbody>
</table>
ASE Annual Scientific Sessions
2012- Washington DC
2013- Minneapolis-St. Paul, MN
2014- Portland, Oregon
2015- Boston