Safety of Contrast Enhanced Ultrasound

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Society of Pediatric Radiology
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No disclosures
Background

• Children more sensitive to radiation effects
• Medical imaging
  – CT, radiographs, nuclear medicine
• Ultrasound as cornerstone of pediatric imaging
  – No radiation
  – Safe, low-cost, portable, dynamic
  – Diverse applications

Ultrasound Contrast Agents

• Biocompatible
• Improve quality of ultrasound images
• No dye or radioactive material
• Routes of administration:
  – Intravascular
  – Intravesical (VCUG)
  – Intracavitary
Ultrasound Contrast Agents

• Highly reflective on ultrasound
• Unlike gadolinium and iodinated CT contrast...
  – Not metabolized by kidneys
  – No labs required
  – No renal damage
Ultrasound Contrast Agents

• Use and advances
  – Europe
  – Adult cardiology
    • Improved visualization of endocardial borders during echocardiography

• In United States
  – Echocardiography
  – Off-label clinical uses
  – Research

History/Development of Agents

- Concept emerged in late 1960s—adult cardiology
  - Gramiak and Shah: “clouds of bubbles” during saline injection into intra-aortic catheter
  - Bove, Kremkau
  - Meltzer, Reale
  - DeMaria, Ong, Armstrong, Sakamacki, Feinstein

History/Development of Agents

• Observations >> development of first generation US contrast agents
  – Agitated saline, hydrogen peroxide, others
  – Cardiology applications
    • Large particles did not pass through pulmonary circulation
    • Unstable
    • Limited clinical utility

History/Development of Agents

• First commercial contrast agents
  – Europe, Japan, Canada:
    • Echovist™ (1982)
    • Levovist™ (1985)
  – US:
    • Albunex™ (1994)
History/Development of Agents

• Nitrogen as gas component
  – Diffusible
  – Did not stay in intravascular compartment
  – Decreased efficacy

• Led to development of “second generation” agents

Second Generation Agents

- Insoluble, stable gas encapsulated by protein, lipid, or polymer shell
  - Biologically inert
  - Gas: perfluorocarbon, sulfur hexaflouride, others
    - Approximately size of a red blood cell
    - Remain in intravascular space
    - Exhaled by lungs within minutes
    - Larger than CT/MRI contrast agents

Wilson SR, Burns PN. Radiology. 2010; 257:24-39
http://radiologykey.com/microbubble-ultrasound-contrast-agents
Technique—IV

- Suspension of contrast “bubbles” in water
- Injected into central line or PIV
- Dose depends on agent used
- Dynamic imaging
  - Low MI, contrast specific software/settings
Ultrasound Contrast Agents

• Cardiology
  – Improved echo image quality
  – Increased diagnostic confidence
• Decreased additional testing for inadequate studies
  – 10-30% transthoracic echo studies suboptimal
  – TEE, angiography
• Safety/efficacy data>>FDA approval
  – Adult cardiology

Parker et al. Am J Cardiol 2013;112:1039-1045
Black Box Warning

- October 2007
- Applied to perflutren-based UCAs Optison and Definity
- Prompted by reports of four patient deaths and ~190 serious cardiopulmonary reactions
  - Temporally but not definitively caused by UCA
    - “Pseudocomplication” related to underlying illness?

Main ML, et al. JACC 2007; 50: 2434-7
Black Box Warning

• All four deaths < 30 min after UCA
  – **Seriously ill patients:**
    • 67 yo male ischemic cardiomyopathy, cardiac arrest 1 min after beginning exercise stress test
    • Elderly male in CVICU, recent MI, severely dec LVF
    • 70 yo male S/P CABG, heart failure, DVT, massive PE as cause of death
    • 34 yo morbidly obese female, ventilator, severe pneumonia, postpartum cardiomyopathy, sepsis, PE

Main ML, et al. JACC 2007; 50: 2434-7
Black Box Warning

• Required additional warning labels
  – New contraindications
    • Acute coronary syndromes, acute MI, worsening or clinically unstable heart failure
  – Required 30 minute postinjection monitoring
    • Optison, Definity

Main ML, et al. JACC 2007; 50: 2434-7
Physician Response

• Swift and strong
• Publications supporting safety and efficacy
  – Pooling of data
• Lobbying by physicians
• Editorials highly critical of FDA’s action
Review of Ultrasound Safety Data

• Main ML, et al
• Reviewed safety data
  – Published March 2008 to 2009
    • Following the black box warning
• 7 large scale retrospective reviews
  – 188,748 patients

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients receiving contrast</th>
<th>Objective</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kusnetzky et al. [38]</td>
<td>6,196</td>
<td>Short-term mortality versus non-contrast</td>
<td>No increase in crude mortality in hospitalized patients undergoing contrast echocardiography compared to controls</td>
</tr>
<tr>
<td>Main et al. [39]</td>
<td>58,254</td>
<td>Short-term mortality versus non-contrast</td>
<td>No increase in crude mortality in hospitalized patients undergoing contrast echocardiography compared to controls; lower risk-adjusted mortality in patients receiving contrast</td>
</tr>
<tr>
<td>Herzog [40]</td>
<td>16,025</td>
<td>SAE rate</td>
<td>Serious nonfatal reactions in 0.03%</td>
</tr>
<tr>
<td>Wei et al. [41]</td>
<td>78,383*</td>
<td>SAE rate</td>
<td>Serious nonfatal reactions in 0.01%</td>
</tr>
<tr>
<td>Dolan et al. [42]</td>
<td>34,447</td>
<td>Short and intermediate events in rest and stress echocardiography</td>
<td>No short-term adverse events with contrast; No increase in MI or mortality compared to control group</td>
</tr>
<tr>
<td>Gabriel et al. [43]</td>
<td>4,786</td>
<td>SAE in stress echocardiography</td>
<td>No increase in SAE rate with contrast</td>
</tr>
<tr>
<td>Shaikh et al. [44]</td>
<td>5,069</td>
<td>SAE in stress echocardiography</td>
<td>No increase in SAE rate with contrast</td>
</tr>
</tbody>
</table>

*Includes 14,412 patients also reported on in [40].
MI: Myocardial infarction; SAE: Serious adverse event.
• Conclusions:
  – Ultrasound contrast agents safe
    • ~1-3:10,000 risk of serious adverse events
    • Many SAE’s likely acute allergy phenomenon
  – No evidence of increased mortality
    • Even with high baseline clinical acuity
FDA Modifications

- May 2008
  - Disease state contraindications reduced to warnings
  - 30 minute monitoring period removed for most patients
    - Except pulmonary hypertension or critically ill

Current Labeling

• Adverse reactions
  – Minor—vary by agent but infrequent
    • Headache, nausea, altered taste, flushing, dizziness

• Warnings/Precautions
  – Serious cardiopulmonary reactions, including fatalities
  – Hypersensitivity reactions
Current Labeling...until recently!

- **Contraindications**
  - Known or suspected right-to-left, bi-directional, or transient right-to-left cardiac shunt
    - Also called into question
  - Known hypersensitivity to any ingredient
Current Labeling...until recently!

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Safety of UCAs in Shunts

- Parker et al.
- 2013
- Review of current peer-reviewed research
Safety of UCAs in Shunts

• Known or suspected shunts
  – 10-35% of population
  – Contraindication to UCAs
    • Based on limited data
    • Speculation
      – MAA particles in nuclear medicine VQ scans
  – Restriction of UCAs
    • Impact on patient care

Parker et al. Am J Cardiol 2013;112:1039-1045
<table>
<thead>
<tr>
<th>Agent</th>
<th>Particle Sizes</th>
<th>Potential Occlusion Level</th>
<th>FDA Label</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAA</td>
<td>10–150 μm (90% from 10 to 70 μm), maximum 150 μm</td>
<td>Arterioles (size 20–30 μm)</td>
<td>Precaution</td>
</tr>
<tr>
<td>Optison</td>
<td>Mean 3–4.5 μm (95% &lt;10 μm), maximum 32 μm</td>
<td>Capillaries (size 5–10 μm)</td>
<td>Contraindication and box warning</td>
</tr>
<tr>
<td>Definity</td>
<td>Mean 1.1–3.3 μm (98% &lt;10 μm), maximum 20 μm</td>
<td>Capillaries (size 5–10 μm)</td>
<td>Contraindication and box warning</td>
</tr>
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Studies since 2001 in routine echocardiography practice across wide range of patient conditions—no increased risk in patients with R>>L cardiac shunts

Parker et al. Am J Cardiol 2013;112:1039-1045
FDA approves label changes for GE’s Optison

OCTOBER 3, 2016 BY SARAH FAULKNER — LEAVE A COMMENT

GE Healthcare (NYSE:GE) announced today that the FDA approved label changes for its ultrasound contrast agent Optison, removing contraindications for use in patients with cardiac shunts and for administration by intra-arterial injection.

Optison is the 1st contrast agent available in the U.S. to receive this label change, according to GE.

“Up to one-third of our patients have known or suspected cardiac shunts and, thanks to this important FDA decision, they too will now have access to ultrasound contrast agents, which offer an inexpensive and radiation-free option for diagnostic imaging,” International Contrast Ultrasound Society co-prez Dr. Steven Feinstein said in prepared remarks. “The International Contrast Ultrasound Society applauds the FDA for its decision, and believes it will benefit individual patients as well as our healthcare delivery system.”
Optison now has an FDA-approved labeling change!

- The FDA has moved the contraindications for use in patients with cardiac shunts and for administration by intra-arterial injection to the Warnings and Precautions section.
- Please see the Full Prescribing Information for details.
Do I need to do an echo before CEUS to rule out cardiac shunt?

• No
• Consensus among cardiologists and radiologists who do CEUS
• Supported by data/literature
• Removal of shunt as a contraindication for Optison™
  – Now Warning/Precaution
  – Remains as contraindication for other agents at this time
Safety Literature

• Most in adult cardiology
• Growing body of literature in children
Safety Publications

• Coleman J, et al.
  – 2014

• Prospective

• Pediatric patients <21 y
  – 21 male, 13 female
  – 134 injections
  – 8 mo to 20.7 years (median 8.7 y)

• Rigorous screening and monitoring process

Coleman J, et al. AJR 2014 May; 202(5):966-70
APPENDIX 1: Contraindications to Contrast-Enhanced Ultrasound Performed for Research Purposes at Our Institution

- Worsening or clinically unstable congestive heart failure
- Acute myocardial infarction or acute coronary syndromes
- Serious ventricular arrhythmias or high risk for arrhythmias due to prolongation of the QT interval
- Respiratory failure manifested by signs or symptoms of carbon dioxide retention or hypoxemia
- Severe emphysema, pulmonary emboli, or other conditions that cause pulmonary hypertension due to compromised pulmonary arterial vasculature
- Hypersensitivity to perflutren
- Pregnant
- Lactating
- Right-to-left, bidirectional, or transient right-to-left cardiac shunts
Coleman J, et al.

- Pediatric solid malignancies
- Enrolled on institutional clinical trials
  - June 2003-January 2013
  - Antiangiogenic therapy
- Consent for CEUS
Bolus injection of contrast agent
- Optison™ (GE Healthcare)—126 exams
- Definity™ (Lantheus)—8 exams
- Primary tumor or metastatic site
- Various timepoint during therapy
Coleman J, et al.

- Hemodynamic parameters monitored
  - During and for 30 minutes after injection
- Interview of patient/parent for adverse effects
Results

• Mild transient side effects (3/134, 2.2%)
  – Taste alteration (2/134, 1.5%)
  – Mild transient tinnitus and lightheadedness (1/134, 0.8%)

• Findings support the safety profile of ultrasound contrast agents in children

• Larger studies needed
Safety Literature

- Piskunowicz, M et al.
  - 2015
- Prospective
- Pediatric oncologic patients < 18yo
- 161 studies in 137 patients (83 male, 54 female; mean age: 10.2, range: 0-18 y)
- SonoVue™ (sulfur hexafluoride)
Piskunowicz M, et al.

- Inclusion criteria:
  - Initial assessment and follow-up of solid tumors
  - Alternative to CT
  - Evaluation of residual disease
  - Assessment of adrenal lesions in infants < 1 y
  - Monitoring therapy complications
• Exclusion criteria:
  – Cardiac defect on ECG
  – Active viral or bacterial infection
  – Lack of consent
  – Unknown pregnancy status
  – Allergy/sensitivity
Results

• Adverse events
  – 0.6% (n=1)
  – Severe anaphylactic shock
    • Directly related to the administration of the contrast agent
    • Need rapid access to treatment (epinephrine) due to risk of allergy

Safety in intravesical use

• VCU]:G
  – Minor adverse event rate 3.7%
    • Dysuria, urinary retention, pain, anxiety, perineal irritation
  – Attributed to bladder catheterization

## Commercially Available Agents

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<th>Stabilisation</th>
<th>Approved Applications</th>
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<td>Perfluorobutane</td>
<td>Hydrogenated egg phosphatidyl serine</td>
<td>Abdominal</td>
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<tr>
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<td>GE Healthcare</td>
<td>Perfluoropropane</td>
<td>Albumin</td>
<td>Cardiac</td>
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<tr>
<td>SonoVue™</td>
<td>Bracco</td>
<td>Sulphur hexafluoride</td>
<td>Phospholipid</td>
<td>Cardiac, Vascular, Hepatic, Breast</td>
</tr>
<tr>
<td>Definity™</td>
<td>Lantheus Medical Imaging</td>
<td>Octafluoropropane</td>
<td>Phospholipid</td>
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Also known as **Lumason™**

Applications—Intravenous (most off-label)

• Adult and pediatric echocardiography
• Characterization of focal liver lesions
  – Arterial, portal venous, delayed
• Solid tumor blood flow
• Blunt trauma
  – Solid organ injury

Applications—Intravenous (most off-label)

- Musculoskeletal
  - Synovial thickening in arthritis
  - Revascularization of epiphysis in Legg-Calve-Perthes
- Pyelonephritis
- Inflammatory bowel disease

Applications—Intravesical

- Diagnosis of vesicoureteral reflux
- Contrast-enhanced genitography
  - Ambiguous genitalia
  - Cloacal malformations
April 2016

FDA approval for use in ultrasound of the liver
  – Characterization of focal liver lesions
    • Benign vs. malignant
  – Adult and **pediatric** patients

First agent approved
  – hepatic imaging
  – **pediatric** patients
References