Sunrise Session: CONTRAST ENHANCED ULTRASOUND

SAFETY of Ultrasound Contrast Agents in Children

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Philadelphia
1. US contrast agents: not FDA approved for children
2. No financial disclosure
Objectives

Safety of US contrast agents in CHILDREN

⇒ intravenous

⇒ intravesical
US contrast agents

1. SonoVue®-Lumason®
2. Optison®
3. Definity®
4. Levovist®
Objectives

Safety of US contrast agents in CHILDREN

intravenous

intravesical
Indications

Currently in pediatrics:
1. Tumor
2. Trauma
intravenous US contrast agents

34 patients [0.7-20.8 yr]
134 IV injections
- 126 Optison®
- 8 Definity®

Tumors
Minor transient AEs = 3 [Optison®]
- taste alteration = 2
- lightheadedness+tinnitus = 1

AE=Adverse Events

Comprehensive safety evaluation:

- Continuous electrocardiogram (ECG) monitoring, cardiologist evaluation of an ECG rhythm strip, review of a 12-lead ECG within 4 h after the contrast-enhanced US, pulse oximetry, blood pressure, heart rate and respiratory rate. In addition, children and parents or guardians were interviewed after each injection and 24-48 h later. Focused neurological examinations, cardiac and pulmonary auscultations and fundoscopies.
intravenous US contrast agents

- **137 patients**
- **167 IV injections**
- **Tumor**
- **Severe AE = 1**
  - anaphylactic reaction

- **44 patients**
- **44 IV injections**
- **Focal liver lesions**
- **No AEs**
  - no specific AEs evaluation

AE = Adverse Events
intravenous US contrast agents

- 4 studies
- 110 patients
- 110 IV injections
- Miscellaneous
  - No AEs
    - no specific AEs evaluation

20 patients
- 20 IV injections
- Cardiac
- Minor AEs = 4
  - transient headache = 3
  - taste alteration = 1

AE=Adverse Events
intravenous US contrast agents

- 2010 survey
- 148 questionnaires returned
- 2012 publication

- **30 centers**
- **948 IV injections**
- **Indications:**
  - trauma/tumor/infection
- **Minor AEs = 5 [0.5%]**
  - taste alteration = 3
  - urticaria = 2
  - hyperventilation = 1

AE=Adverse Events
### SUMMARY

<table>
<thead>
<tr>
<th>Category</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of PATIENTS</td>
<td>345</td>
</tr>
<tr>
<td>Number of INJECTIONS</td>
<td>1423</td>
</tr>
<tr>
<td>Number of ADVERSE EVENTS</td>
<td>13</td>
</tr>
<tr>
<td>Percentage of adverse events/injections</td>
<td>0.9%</td>
</tr>
<tr>
<td>Number of SONOVUE injections</td>
<td>1269</td>
</tr>
<tr>
<td>Percentage of SONOVUE injections</td>
<td>89%</td>
</tr>
<tr>
<td>Number of adverse events with SONOVUE</td>
<td>6 [0.5%]</td>
</tr>
</tbody>
</table>

### TYPES OF ADVERSE EVENTS

- **Serious:** 1
  - anaphylactic reaction 1

- **Minor:** 12
  - taste alteration 5
  - taste alteration + urticaria 1
  - transient headache 3
  - lightheadedness + tinnitus 1
  - hyperventilation 1
  - urticaria 1
### Summary of Adverse Events, All Completed Studies Included in Pooled Safety Database (Healthy Volunteers and Patients)

<table>
<thead>
<tr>
<th>Category</th>
<th>SonoVue Related</th>
<th>SonoVue All</th>
<th>Placebo/Comparator Related</th>
<th>Placebo/Comparator All</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. (%) of subjects with at least 1 AE</td>
<td>303 (5.7)</td>
<td>572 (10.8)</td>
<td>22 (13.6)</td>
<td>39 (24.1)</td>
</tr>
<tr>
<td>No. (%) of subjects with at least 1 serious AE</td>
<td>3 (0.1)</td>
<td>21 (0.4)</td>
<td>0</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>No. (%) of subjects who discontinued due to AEs</td>
<td>7 (0.1)</td>
<td>16 (0.3)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>No. (%) of deaths</td>
<td>0</td>
<td>8 (0.15)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>No of AEs</td>
<td>491</td>
<td>931</td>
<td>39</td>
<td>63</td>
</tr>
<tr>
<td>No. (%) of subjects with at least 1 non-serious AE by intensity:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild AEs</td>
<td>300 (5.7)</td>
<td>555 (10.5)</td>
<td>22 (13.6)</td>
<td>38 (23.5)</td>
</tr>
<tr>
<td>Moderate AEs</td>
<td>260 (4.9)</td>
<td>446 (8.5)</td>
<td>19 (11.7)</td>
<td>31 (19.1)</td>
</tr>
<tr>
<td>Severe AEs</td>
<td>39 (0.7)</td>
<td>100 (1.9)</td>
<td>3 (1.9)</td>
<td>7 (4.3)</td>
</tr>
</tbody>
</table>

**Notes:**
- Includes definite, probable, possible, doubtful, unknown, and missing relationship.
- Multiple occurrences of the same adverse event in a subject are counted individually.
- If a subject experienced more than 1 non-serious adverse event, the subject was counted only once at the maximum intensity.
- One additional death was reported in 1 patient who died of myocardial infarction before receiving SonoVue.

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**ADULTS**

www.fda.gov
Experience from post-marketing surveillance of the estimated 1,651,451 patients exposed to SonoVue from April 1, 2001 through December 31, 2010 during the market use of this product (including events from observational studies, investigator-initiated studies and publications) shows a total of 217 cases of serious AEs (reporting rate: 0.013%), of which, 213 patients were considered to have AEs with some kind of relationship to the administration of SonoVue (probable, possible or unlikely) and 4 patients were considered to have AEs clearly unrelated to SonoVue administration.

<table>
<thead>
<tr>
<th>System Organ Class / Preferred Term</th>
<th>No. of subjects dose: 5275</th>
<th>Related&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>572 (10.8)</td>
<td>303 (5.7)</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>47 (0.9)</td>
<td>29 (0.5)</td>
</tr>
<tr>
<td>General Disorders/Administration Site Conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chest discomfort</td>
<td>30 (0.6)</td>
<td>16 (0.3)</td>
</tr>
<tr>
<td>Chest pain</td>
<td>33 (0.6)</td>
<td>9 (0.2)</td>
</tr>
<tr>
<td>Injection site pain</td>
<td>26 (0.5)</td>
<td>20 (0.4)</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td>109 (2.1)</td>
<td>59 (1.1)</td>
</tr>
</tbody>
</table>
Safety of Ultrasound Contrast Agents in Patients With Known or Suspected Cardiac Shunts
(Am J Cardiol 2013;112:1039–1045)
Jeremy M. Parker, MD*, Mark W. Weller, JD**, Linda Maiman Feinstein, JD**, Robin J. Adams, BS**, Michael L. Main, MD*, Paul A. Grayburn, MD*, David O. Cosgrove, MD*, Barry A. Goldberg, MD*, Kassa Darge, MD, PhD*, Petros Nihoyannopoulos, MD*, Stephanie Wilson, MD, Mark Monaghan, PhD*, Fabio Fiscaglia, MD*, Brian Fowlkes, PhD*, Wilson Mathias, MD**, Fuminari Moriyasu, MD, PhD**, Maria Christina Chammas, MD, PhD**, Lennard Greenbaum, MD**, and Steven B. Feinstein, MD**

Cardiac shunt [right-to-left or bidirectional] – contraindication

- 10-35% of children/adults intracardiac shunts
- Agitated normal saline used over many decades
- Earlier approvals of US contrast agents no such contraindication
- Incorrect comparison with macroaggregated albumin (nuclear medicine)
- Large safety studies not support contraindication
- International Contrast US Society (ICUS) seeking removal of contraindication
High safety profile with <1% of adverse events, predominantly minor ones
Objectives

Safety of US contrast agents in CHILDREN

- intravenous
- intravesical
Indication

**Intravesical US contrast agent administration for diagnosis of vesicoureteral reflux:**
Contrast enhanced voiding urosonography

**ceVUS**
intravesical US contrast agents

<table>
<thead>
<tr>
<th>Studies</th>
<th>n</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levovist</td>
<td>1062</td>
<td>17</td>
<td>1.6</td>
</tr>
<tr>
<td>SonoVue</td>
<td>1889</td>
<td>37</td>
<td>2.0</td>
</tr>
<tr>
<td>Total</td>
<td>2951</td>
<td>54</td>
<td>1.8</td>
</tr>
<tr>
<td>European Survey</td>
<td>4131</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Grand total</td>
<td>7082</td>
<td>54</td>
<td>0.8</td>
</tr>
</tbody>
</table>

- 26 Dysuria
- 15 Transient macrohematuria
- 3 Abdominal discomfort/pain
- 2 Anxiety/crying
- 2 Urinary retention
- 1 Frequency
- 1 Blood/mucous discharge
- 1 Perineal irritation
- 1 Urethral pain
- 1 Urinary tract infection
- 1 Vomiting
### Postprocedural Symptoms in Children Who Undergo Imaging Studies of the Urinary Tract: Is It the Contrast Material or the Catheter?¹

**Radiology 1992; 182:727–730**

**SAFETY**

#### Frequency of Symptoms after VCUG, RNC, and DRS in 61 Boys and 167 Girls

<table>
<thead>
<tr>
<th>Patients</th>
<th>VCUG (n = 100)</th>
<th>RNC (n = 100)</th>
<th>DRS (n = 28)</th>
<th>Total (n = 228)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boys and girls</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptoms</td>
<td>32 (32.0)</td>
<td>37 (37.0)</td>
<td>11 (39)</td>
<td>80 (35.1)</td>
</tr>
<tr>
<td>No symptoms</td>
<td>68 (68.0)</td>
<td>63 (63.0)</td>
<td>17 (61)</td>
<td>148 (64.9)</td>
</tr>
</tbody>
</table>

#### Type and Duration of Symptoms Reported in 228 Children after VCUG, RNC, and DRS

<table>
<thead>
<tr>
<th>Symptom or Duration</th>
<th>Iodinated CA (n = 100)</th>
<th>Radionuclide (n = 100)</th>
<th>No CA (n = 28)</th>
<th>Total (n = 228)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dysuria</td>
<td>29 (29.0)</td>
<td>35 (35.0)</td>
<td>11 (39)</td>
<td>75 (32.9)</td>
</tr>
<tr>
<td>Wetting</td>
<td>1 (1.0)</td>
<td>5 (5.0)</td>
<td>1 (4)</td>
<td>7 (3.1)</td>
</tr>
<tr>
<td>Gross hematuria</td>
<td>5 (5.0)</td>
<td>3 (3.0)</td>
<td>1 (4)</td>
<td>9 (3.9)</td>
</tr>
<tr>
<td>Fever*</td>
<td>2 (2.0)</td>
<td>1 (1.0)</td>
<td>0</td>
<td>3 (1.3)</td>
</tr>
<tr>
<td>Total</td>
<td>32 (32.0)</td>
<td>37 (37.0)</td>
<td>11 (39)</td>
<td>80 (35.1)</td>
</tr>
</tbody>
</table>

#### Symptoms
- **26** Dysuria
- **15** Transient macrohematuria
- **3** Abdominal discomfort/pain
- **2** Anxiety/crying
- **2** Urinary retention
- **1** Frequency
- **1** Blood/mucous discharge
- **1** Perineal irritation
- **1** Urethral pain
- **1** Urinary tract infection
- **1** Vomiting
intravesical US contrast agents

Adverse events are more likely due to bladder catheterization rather than the US contrast agent
Take-Home-Points

CEUS in children
intravenous & intravesical

_ascii_characters

high safety profile

CEUS:
Safety of contrast-enhanced ultrasound in children for non-cardiac applications: a review by the Society for Pediatric Radiology (SPR) and the International Contrast Ultrasound Society (ICUS)

Dohse Radial (2013) 63:1065-1073
DOI 10.1007/s00256-013-2713-0

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THANK YOU