MRI Contrast Agents for Cardiovascular Imaging: Risks and Benefits

Martin R. Prince, MD, PhD, FACR – Cornell & Columbia, NY

- Anaphylaxis
- Loss of consciousness
- Hives
- Swelling of tongue, inability to swallow
- Rapid swelling of throat tissues
Nephrogenic Systemic Fibrosis (NSF)

- Papular morphology
- Dimpling

Disclosures
Patent Agreements: GE, Siemens, Philips, Hitachi, Toshiba, Bayer, Bracco, Mallinckrodt, Medrad, Nemoto, Topspins, Epix, Lantheus
Outline

• Gd Toxicity
• Gd interference with serum testing
• Gd → triggers fibrosis (NSF)
• Gd → triggers adverse reactions
  – Interferes with study
  – May be life threatening
  – Death ~ 1/ million injections
75 year old female with hypertension and renal insufficiency

Creatinine = 2.1 mg/dl

"Life-threatening" low calcium
Colorimetric Ca Measurement

OCP + Ca → OCP-Ca → color change

Gadodiamide Interference

Gd-DTPA-BMA → Gd + DTPA-BMA
OCP + Gd → OCP-Gd
Ca + DTPA-BMA → Ca-DTPA-BMA

↓[Ca] → ↓color

Jing Lin et al. Guerbet
Effect of renal insufficiency & Gadodiamide dose

-2 -1 1 2 3 4

serum calcium (mg/dl)

Gadodiamide injection

Cr< 1.5 0.1 mmol/k
≥0.2 mmol/k

Cr>1.5 0.1 mmol/k
≥0.2 mmol/k

Clinician Response to Lab Error

# of patients with drop ≥ 2    42 (4.6%)
Attributed to MR contrast agent 2 (0.2%)
Treated with po Ca             12 (1.3%)
Treated with iv Ca             7* (0.8%)

* Life threatening

<table>
<thead>
<tr>
<th>Chelate</th>
<th>Thermodynamic Stability $\log[K_{eq}] @ pH=7.4$</th>
<th>Kinetic half-life</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Macrocyclic:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gd-DOTA (Gadoterate)</td>
<td>25.8</td>
<td>1 mo</td>
</tr>
<tr>
<td>Gd-HP-D03A (Gadoteridol)</td>
<td>23.8</td>
<td>3 hour</td>
</tr>
<tr>
<td><strong>Linear:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gd:Bopta</td>
<td>22.6</td>
<td></td>
</tr>
<tr>
<td>Gd-DTPA (Gadopentatate)</td>
<td>22.5</td>
<td>10 min</td>
</tr>
<tr>
<td>Gd-DTPA-BMA (Gadodiamide)</td>
<td>16.9</td>
<td>30 s</td>
</tr>
</tbody>
</table>

Gd-OCP unknown but believed to be in this range

Kinetics vs. Thermodynamics

Kuo JACR 2008; 5:29-3
Chelate Stability

Macrocyclic > Linear Ionic > Linear Nonionic

Gadoteridol > Gd:DTPA > Gadodiamide
Interferences related to Gd stability

Proctor AJCP 2004;121:282-92

- Calcium
- Zinc
- Magnesium
- Iron/Total iron binding
- ACE
NSF
major risk factors

• GFR < 30ml/min
• high dose
• pro-inflammatory
  • thrombosis
  • surgery
  • trauma
  • SLE
• inpatient >> outpatients

Biopsy site
NSF – key points

To prevent NSF

- Identify at-risk patients: GFR < 30 ml/min, acute
- For these at-risk patients
  - verify Gd is necessary
  - avoid high Gd doses (use 0.1mMol/kg or less)
  - hand inject, experienced technologists
  - For dialysis patients do MRI just before dialysis appt
  - Do not use Omniscan, OptiMark or Magnevist.
  - Allow sufficient time for elimination before re-administration.

Virtually no new cases since 2008

- Nonionic linear Gd more reports of NSF
  - fewer reports of death (anaphylaxis)
Cases of NSF by Date of Onset*

Gadodiamide
Gd:DTPA

FDA & EMEA warnings
Skin thickening

Peau D’orange

Skin thickening
Joint Contractures

NSF

Jeunevile Rheumatoid Arthritis
80 papers → 292 NSF cases  
all biopsy confirmed

• 64 papers had data on the relationship of GBCA and NSF involving 243 patients.
  – History of Gd exposure 220
  – Gd looked for but not found 23

• Gd not discussed (16 papers) 49

Total = 292

(These AE rates are specific to the experience at the institutions studied in this publication.)

JMRI December 2009;30:1298-1308
Infancy and Old Age may be protective

NSF Case Reports
Columbia Gd MR GFR < 30

JMRI December 2009;30:1298-1308
Youngest NSF case → 6 years old

• Neonates have immature kidneys → low GFR
• Sick neonates with congenital heart disease get multiple high dose MR exams.
• No reported NSF case less than 6 years old
• Therefore: infants and toddlers may be protected from NSF
• In USA there is no contra-indication in infants
Type of MRI scan (n=112)

- MRA 57
- Brain 7
- Pelvis 2
- Liver 1
- Abdomen 9
- Lower extremity 4
- MRCP 5
- Spine 2
- Cardiac 1
- Multiple 23
- DSA txp renal art. 1

JMRI December 2009;30:1298-1308
<table>
<thead>
<tr>
<th>Gadolinium dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard Dose (0.1mmol/kg):</td>
</tr>
<tr>
<td>High Dose (&gt;0.15mmol/kg):</td>
</tr>
<tr>
<td>Dose not specified:</td>
</tr>
<tr>
<td>Total</td>
</tr>
</tbody>
</table>

(These AE rates are specific to the experience at the institutions studied in this publication.)

JMRI December 2009;30:1298-1308
Typical NSF Presentations
(collected from 292 reported cases)

• Dialysis: 208/292 → 71%
  • Not specified 17
  • Hemodialysis 150
  • Peritoneal dialysis 37
  • CVVH 4

• Renal transplant: 57/292 → 20%

• Failing renal transplant: 34 → 12%

(These AE rates are specific to the experience at the institutions studied in this publication.)

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JMRI December 2009;30:1298-1308
“some patients with NSF (estimated at 5% or less) have an exceedingly rapid and fulminant disease course....

Cowper et al  www.icnfdr.org
Is Dialysis Protective?

Broome et al AJR 2007; 188:586-592

4 patients – acute hepatorenal syndrome ➔ unstable
   ➔ high dose omniscan
   ➔ dialysis on 3 consecutive days
   ➔ developed NSF

Initial interpretation: dialysis does not prevent NSF

Correction:
“daily low intensity hemodialysis on 3 consecutive days does not prevent NSF.”
“immediate post-MRI dialysis is STRONGLY advised”
Transmetallation \( (\text{Zn}^{2+}, \text{Cu}^{2+}, \text{Ca}^{2+}, \text{Fe}^{2+} \ldots) \)
**Transmetallation Potency**

<table>
<thead>
<tr>
<th>Cation-DTPA-BMA</th>
<th>Log $K_{\text{therm}}$</th>
<th>Transmetallation Potency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium</td>
<td>$10^{7.2}$</td>
<td>+</td>
</tr>
<tr>
<td>Zinc</td>
<td>$10^{12}$</td>
<td>++</td>
</tr>
<tr>
<td>Copper</td>
<td>$10^{13}$</td>
<td>++</td>
</tr>
<tr>
<td>Gadolinium</td>
<td>$10^{16.9}$</td>
<td>–</td>
</tr>
<tr>
<td>Iron</td>
<td>$10^{21.9}$</td>
<td>++++</td>
</tr>
</tbody>
</table>

$K_{\text{therm}}$ is a thermodynamic stability constant. The plus and minus symbols refer to the degree of potency. +, mild; ++, moderate; ++++, strong; –, n/a.

### Effect of Renal Function on Gd Excretion

<table>
<thead>
<tr>
<th>Gd chelate</th>
<th>Normal</th>
<th>Mildly Reduced (GFR=60 to 90 mL/min)</th>
<th>Moderate (GFR = 30 to 60 mL/min)</th>
<th>Severe (GFR &lt;30 mL/min)</th>
<th>Dialysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Magnevist</td>
<td>1.6</td>
<td>2.6</td>
<td>4.2</td>
<td>11</td>
<td>68%</td>
</tr>
<tr>
<td>Gadavist</td>
<td>1.8</td>
<td>5.8</td>
<td>5.8</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Omniscan</td>
<td>1.3</td>
<td>no data available</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prohance</td>
<td>1.6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multihance</td>
<td>1.2</td>
<td></td>
<td>6.1</td>
<td>9.5</td>
<td></td>
</tr>
<tr>
<td>Eovist</td>
<td>0.9</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ablavar</td>
<td>16</td>
<td></td>
<td>49</td>
<td>70</td>
<td>47%</td>
</tr>
</tbody>
</table>
Protein Binding Ionic Agents

Higher T1 Relaxivity $\rightarrow$ lower Gd dose
Biliary excretion $\rightarrow$ alternative elimination path
Intravascular retention $\rightarrow$ reduces tissue exposure

Gadofosveset trisodium (Ablavar)* 10% bile, 5xR1
Gadoxetate trisodium (Eovist)* 50% bile, 2xR1
Gadobenate Dimeg.. (MultiHance)** 5% bile, 1.5xR1

*No reported cases of NSF
**No unconfounded cases of NSF
Why are nonionic linear agents still available?
# Acute Adverse Reactions to Gd in CMR

**JACC Cardiovascular Imaging 2011;4:1171-6**

17767 high dose GBCA cardiac MR exams

<table>
<thead>
<tr>
<th>Agent</th>
<th>Adverse Reaction type</th>
<th>Agent</th>
<th>Adverse Reaction type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gadodiamide</td>
<td>0.06%</td>
<td>Gd:DTPA</td>
<td>0.20%</td>
</tr>
<tr>
<td></td>
<td>nonionic linear</td>
<td>Gadobutrol</td>
<td>0.23%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gd:DOTA</td>
<td>0.25%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gadoteridol</td>
<td>0.39%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gadobenate</td>
<td>0.47%</td>
</tr>
</tbody>
</table>
### RSNA 2010: Ayako Taketomi-Takahashi et. al.

13,252 GBCA enhanced exams

<table>
<thead>
<tr>
<th>Agent</th>
<th>Adverse Reaction</th>
<th>type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gadodiamide</td>
<td>0.14%</td>
<td>nonionic linear</td>
</tr>
<tr>
<td>Gd:DTPA</td>
<td>0.55%</td>
<td>ionic linear</td>
</tr>
<tr>
<td>Gd:DOTA</td>
<td>0.34%</td>
<td>macrocyclic ionic</td>
</tr>
<tr>
<td>Gadoteridol</td>
<td>2.32%</td>
<td>macrocyclic myelod</td>
</tr>
</tbody>
</table>

History of Gd rxn 21% pooled
Immediate Anaphylaxis in 141,623 patients for Gd MR

Whal Lee et al
MRA Workshop BANFF 9/2011

Nonionic: Gadodiamide: 0.00013

  p<0.001

Ionic:     Gadobenate:  0.00221
Adverse Reactions - 105 MRI centers
Murphy et al. Academic Radiology 1999;6:656-664
(These AE rates are specific to the experience at the institutions studied in this publication.)

<table>
<thead>
<tr>
<th>Contrast Agent</th>
<th>n</th>
<th>AE Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gadoteridol</td>
<td>64005</td>
<td>0.27% nonallergic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.14% allergic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.02% severe</td>
</tr>
<tr>
<td>Gd:DTPA</td>
<td>68755</td>
<td>0.067% total</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.001% severe</td>
</tr>
<tr>
<td>Gadodiamide</td>
<td>74275</td>
<td>0.031% total</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.00% severe</td>
</tr>
</tbody>
</table>

These AE rates are specific to the experience at the institutions studied in this publication.
### Adverse events in 158,796 GBCA administrations

<table>
<thead>
<tr>
<th>Contrast agents</th>
<th># of Exams</th>
<th>Mild AE</th>
<th>Moderate AE</th>
<th>Severe AE</th>
<th>All events</th>
<th>Events per 1000 injections</th>
<th>Coded</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gadobenate (Multihance)</td>
<td>33,114</td>
<td>31</td>
<td>7</td>
<td>3</td>
<td>41</td>
<td>1.2*</td>
<td>3</td>
</tr>
<tr>
<td>Gd: DTPA (Magnevist)</td>
<td>66,157</td>
<td>26</td>
<td>6</td>
<td>0</td>
<td>32</td>
<td>0.5</td>
<td>0</td>
</tr>
<tr>
<td>Gadodiamide (Omniscan)</td>
<td>55,703</td>
<td>8</td>
<td>1</td>
<td>0</td>
<td>9</td>
<td>0.2</td>
<td>0</td>
</tr>
<tr>
<td>Gadoteridol (Prohance)</td>
<td>3371</td>
<td>8</td>
<td>2</td>
<td>1</td>
<td>11</td>
<td>3.3</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>158,796</td>
<td>73</td>
<td>16</td>
<td>4</td>
<td>93*</td>
<td>0.6</td>
<td>3</td>
</tr>
</tbody>
</table>

*statistically significantly higher than Gd:DTPA and gadodiamide with p < 0.001

AJR 2011;196:138-143
<table>
<thead>
<tr>
<th></th>
<th>AE Patients (n = 94)</th>
<th>Controls (n = 94)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (f/m)</td>
<td>72/22 = 3.3</td>
<td>49/45 = 1.1</td>
<td>&lt; 0.001 (w/Yates)</td>
</tr>
<tr>
<td>Weight (lbs)</td>
<td>157 ± 37</td>
<td>163 ± 42</td>
<td>0.6</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>0.89 ± 0.31</td>
<td>0.97 ± 0.05</td>
<td>0.4</td>
</tr>
<tr>
<td>Mean Gd Dose (mL)</td>
<td>17.0 ± 7.8</td>
<td>18.4 ± 9.3</td>
<td>0.24</td>
</tr>
<tr>
<td>Asthma</td>
<td>8</td>
<td>2</td>
<td>0.1</td>
</tr>
<tr>
<td>Prior Gd exposure</td>
<td>51</td>
<td>48</td>
<td>0.8</td>
</tr>
<tr>
<td>Prior Gd reaction</td>
<td>8</td>
<td>0</td>
<td>0.007 (Fisher’s exact)</td>
</tr>
<tr>
<td>Prior allergic event</td>
<td>38</td>
<td>16</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Inpatient</td>
<td>6</td>
<td>8</td>
<td>0.8</td>
</tr>
<tr>
<td>Steroid pre-treatment</td>
<td>4</td>
<td>0</td>
<td>0.1</td>
</tr>
</tbody>
</table>
## Rate of GBCA adverse events by type* of MRI examination

<table>
<thead>
<tr>
<th>Type of GBCA-enhanced exam</th>
<th># of Exams</th>
<th># of Reactions</th>
<th>Reactions/10,000 Exams</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain</td>
<td>72,756</td>
<td>33</td>
<td>4.5</td>
</tr>
<tr>
<td>Orbit/Face/Neck</td>
<td>3940</td>
<td>3</td>
<td>7.6</td>
</tr>
<tr>
<td>Spine</td>
<td>23,656</td>
<td>8</td>
<td>3.4</td>
</tr>
<tr>
<td>Cardiac</td>
<td>7328</td>
<td>4</td>
<td>5.5</td>
</tr>
<tr>
<td>Breast</td>
<td>4304</td>
<td>4</td>
<td>9.3</td>
</tr>
<tr>
<td>Abdomen</td>
<td>20,992</td>
<td>28</td>
<td>13**</td>
</tr>
<tr>
<td>Pelvis</td>
<td>7328</td>
<td>4</td>
<td>5.5</td>
</tr>
<tr>
<td>Extremity</td>
<td>4492</td>
<td>4</td>
<td>8.9</td>
</tr>
<tr>
<td>MR Angiography</td>
<td>14,000</td>
<td>6</td>
<td>4.3</td>
</tr>
<tr>
<td>Total</td>
<td>158,796</td>
<td>94</td>
<td>5.9</td>
</tr>
</tbody>
</table>

* When > one type of study was performed with a single injection, the study was only counted once based upon the primary reason. **Statistically significantly higher rate compared to brain (p < 0.001)
### US FDA Medwatch Database 2004 to 2009


**AE outside US and NSF excluded**

AJR 2011:196:w138-143

<table>
<thead>
<tr>
<th></th>
<th>Gadobenate dimeglumine</th>
<th>Gadoteridol</th>
<th>Gd:DTPA</th>
<th>Gadodiamide</th>
<th>Optimark</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Death</strong></td>
<td>8</td>
<td>4</td>
<td>23</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td><strong>Doses (millions)</strong></td>
<td>2.2</td>
<td>2.4</td>
<td>22</td>
<td>12.2</td>
<td>4.5</td>
</tr>
<tr>
<td><strong>Deaths per million doses</strong></td>
<td>3.6</td>
<td>1.7</td>
<td>1</td>
<td>.2</td>
<td>.2</td>
</tr>
</tbody>
</table>

Ionic  
Linear  
Nonionic Linear
blue (a medical emergency in which a team of medical personnel work to revive an individual in cardiac arrest) was called. The patient was transported by ambulance to the hospital and expired. No other details were provided. Information has been requested. 25-Sep-2009: Additional information received from a health professional: This 50-year-old male was a smoker. It is not known which contrast agent he had previously received; concomitant medications were not obtained because he was stated that there was "very little time from injection to death". Anaphylactoid reaction was stated as the autopsy result. Additional information received from a health professional: The patient was injected with contrast and underwent the MRI at 13:56. Immediately after the injection, a code blue was called and the patient was transported to the emergency room (ER) at the local acute care hospital. The patient was administered a serum tryptase of 653 ng/ml (normal range: 0.0-11.4) and underwent an emergent coronary artery bypass graft (CABG) due to radiologic contrast dye characterized by a serum tryptase of 653 ng/ml (normal range: 0.0-11.4) and sudden collapse in the setting of atherosclerosis. A cardiac catheterization revealed severe narrowing of the left anterior descending coronary artery, mild centrilobular emphysema of the lungs, diabetes mellitus, and arteriosclerosis obliterans. Additional information is required.
One in 1 million chance of death

- Driving 78 miles (~100 kilometers)
- One chest X-ray
- Smoking 1.4 cigarettes
- Drinking 1.5 bottles of wine

National Tranportation Safety Board 2008
ACR manual on Radiation Safety
http://tobaccodocuments.org/lor/03732381-2387.html
http://www-nrd.nhtsa.dot.gov/Pubs/811291.PDF
5th Annual Symposium on Nephrogenic Systemic Fibrosis and Allied Systemic Fibrosing Disorders

May 20–21, 2011
Anaphylactoid Reactions Associated With Gadolinium Vs. Iodinated Agents Contrast Media Plus Safety Signal Detection In The FDA's Adverse Event Reporting System

Raisch DW, Garg V, Samaras AT, Saddleton EE, Laumann AE, McKoy JM, Miller F, Restaino J, Belknap SM, West DP

University of New Mexico College of Pharmacy, Albuquerque, NM; Department of Dermatology, Northwestern University Feinberg School of Medicine, Chicago, IL; Department of Radiology, Northwestern University Feinberg School of Medicine, Chicago, IL; Department of Medicine, Division of Geriatric Medicine, Northwestern University Feinberg School of Medicine; Burg Simpson Eldredge Hersh & Jardine

Introduction

- Anaphylactoid reactions (ARs) are associated with gadolinium contrast media (GCM) and iodinated contrast media (ICM).
- In comparison to ICMs, the GCMs are considered to rarely cause allergic reactions.
- The frequency of severe anaphylactoid reactions associated with GCM was found to be 0.01% of the total cases.
- Overall, GCMs are considered to be safer.

Study Aim/Objectives

Aim: To examine the anaphylactoid reactions associated with GCMs and ICMs in the Food and Drug Administration's (FDA) Adverse Event Reporting System (AERS) database.

- Objective 1: To retrieve and compare reports of ARs associated with GCMs and ICMs in the AERS database.
- Objective 2: To compare signal detection results using proportional reporting ratios (PRRs) for ARs associated with GCMs and ICMs.

Methods

Adverse Events Reporting System database (AERS):

- FDAs AERS was queried by creating Event Groups (using preferred terms) and separate Drug Groups for GCMs and ICMs.
- The following preferred terms for ARs from the Medical Dictionary for regulatory Activities (MedDRA), through March 2010:
  - Acute Anaphylaxis
  - Anaphylactoid Reaction
  - Anaphylactic Reaction
  - Anaphylactic Shock
  - Anaphylaxis
  - Systemic Anaphylaxis
  - Type 1 Hypersensitivity
- The two separate cring groups/event queries were performed.
  - One for GCMs and one for ICMs.
  - Based upon data reported to the FDA Adverse Event Reporting System (AERS) through March 2010.

Data analysis and statistical evaluation:

- PRRs were calculated for the combined groups of GCMs and ICMs, as well as individual GCM products, separately.
- Patients' demographics and types of reactions were compared between GCMs and ICMs.

Acknowledgement

Funding for this research was provided by NIH grant number 2 RO1 CA127713-03A2. Research on Adverse Drug Events And Reports (RADAR).

Results and Discussion

- Through March 2010, there were 494 and 2,533 reports for GCMs and ICMs, respectively.
- The data are not confluent since ICM usage preceded GCM usage (first ICM event date: 1943, received by FDA: 1969; first GCM event date: 1983, received by FDA: 1998).
- Mean ages (± standard deviation) were 49.1±18.0, and 57.5±18.5, and % male/female were 38%/62% and 40%/40% for GCMs and ICMs, respectively.
- The ARs for GCMs and ICMs were serious in 91.7%/97.5% and fatal in 7.5%/13.9%, respectively.
- The PRRs were indicative of safety signals: GCMs = 5.9 (CI: 5.4-6.4), ICMs = 7.4 (CI: 7.1-7.7).
- Over 80% of GCM-associated ARs were with linear GCMs and 18% were with a macrocyclic structure GCM.

Table 1. Type of reaction by Product, including cases with ≥1 GCM listed

<table>
<thead>
<tr>
<th>GCMs and ICMs</th>
<th>Clinical</th>
<th>Hospitalization</th>
<th>Other</th>
<th>Life-Threatening</th>
<th>Death</th>
<th>Given Prescription Drugs</th>
<th>Required Intervention</th>
<th>Breaking</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gadodiamide</td>
<td>Low</td>
<td>69.8%</td>
<td>10.1%</td>
<td>18.8%</td>
<td>0.2%</td>
<td>2.2%</td>
<td>0.9%</td>
<td>0.9%</td>
</tr>
<tr>
<td>Gadoversatamide</td>
<td>High</td>
<td>61.5%</td>
<td>20.5%</td>
<td>10.3%</td>
<td>1.5%</td>
<td>5.1%</td>
<td>3.3%</td>
<td>2.6%</td>
</tr>
<tr>
<td>Gadoversatamide/ OptMARK</td>
<td>Low</td>
<td>8.9%</td>
<td>50.0%</td>
<td>50.0%</td>
<td>0.0%</td>
<td>0.0%</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Gadopentetate Dimeglumine/ Magnevist</td>
<td>Low</td>
<td>31.2%</td>
<td>38.1%</td>
<td>21.4%</td>
<td>0.0%</td>
<td>1.4%</td>
<td>1.4%</td>
<td>1.4%</td>
</tr>
<tr>
<td>Gadodextrate Dimeglumine/ Multihance</td>
<td>Low</td>
<td>61.5%</td>
<td>19.4%</td>
<td>16.7%</td>
<td>0.8%</td>
<td>0.8%</td>
<td>0.8%</td>
<td>0.8%</td>
</tr>
<tr>
<td>Gadoveltil Prohance</td>
<td>Cyclic</td>
<td>51.6%</td>
<td>25.1%</td>
<td>18.3%</td>
<td>0.0%</td>
<td>0.0%</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Gadomilte Meglumine/ Dotarem</td>
<td>Cyclic</td>
<td>50.0%</td>
<td>0.0%</td>
<td>0.0%</td>
<td>0.0%</td>
<td>0.0%</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
</tbody>
</table>

*P<0.05 vs. linear, and Gadovist (sodium) did not have ARs reported in AERS.

Table 2. Signal Detection Results by GCM Product Among Cases with ≥1 GCM Listed

<table>
<thead>
<tr>
<th>GCMs by Product</th>
<th>n</th>
<th>PRR</th>
<th>Upper 95% CI</th>
<th>Lower 55% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gadodiamide/ Omniscan</td>
<td>2</td>
<td>0.16</td>
<td>0.04</td>
<td>0.68</td>
</tr>
<tr>
<td>Gadoversatamide/OptMARK</td>
<td>2</td>
<td>2.248</td>
<td>0.56</td>
<td>5.17</td>
</tr>
<tr>
<td>Gadopentetate Dimeglumine/Magnevist</td>
<td>251</td>
<td>5.03</td>
<td>4.34</td>
<td>5.78</td>
</tr>
<tr>
<td>Gadodextrate Dimeglumine/Multihance</td>
<td>120</td>
<td>11.41</td>
<td>9.67</td>
<td>13.16</td>
</tr>
<tr>
<td>Gadovist/ Prohance</td>
<td>91</td>
<td>5.27</td>
<td>4.30</td>
<td>6.45</td>
</tr>
<tr>
<td>Gadomilte Meglumine/Dotarem</td>
<td>6</td>
<td>18.16</td>
<td>7.60</td>
<td>34.14</td>
</tr>
</tbody>
</table>

Strengths and Limitations

- FDA's MedWatch reports are often incomplete. Our results are based only on the data available in the FDA's AERS.
- Our study only shows the associations between GCMs and ICMs and ARs, not the causal association between these.

Conclusions

- FDA-AERS data indicate that GCM-associated ARs generate a safety signal comparable to ICMs.
- Over 80% of GCM-associated ARs were with linear structure GCMs and 18% were with macrocyclic structure GCMs.

References

Table 2. Signal Detection Results by GCM Product Among Cases with

<table>
<thead>
<tr>
<th>GCMs by Product</th>
<th>n</th>
<th>PRR</th>
<th>Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gadodiamide/ Omniscan</td>
<td>2</td>
<td>0.16</td>
<td></td>
</tr>
<tr>
<td>Gadoversetamide/ OptiMARK</td>
<td>2</td>
<td>2.248</td>
<td></td>
</tr>
<tr>
<td>Gadopentetate Dimeglumine /Magnevist</td>
<td>231</td>
<td>5.03</td>
<td></td>
</tr>
<tr>
<td>Gadobenate Dimeglumine /MultiHance</td>
<td>130</td>
<td>11.41</td>
<td></td>
</tr>
<tr>
<td>Gadoteridol/ Prohance</td>
<td>91</td>
<td>5.27</td>
<td></td>
</tr>
<tr>
<td>Gadoterate Meglumine /Dotarem</td>
<td>6</td>
<td>16.16</td>
<td></td>
</tr>
</tbody>
</table>
**Ionic vs. Nonionic in 337,647 Patients**

<table>
<thead>
<tr>
<th></th>
<th>Ionic</th>
<th>Nonionic</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total</strong></td>
<td>12.66%</td>
<td>3.13%</td>
<td>0.22</td>
</tr>
<tr>
<td><strong>Severe</strong></td>
<td>0.22%</td>
<td>0.04%</td>
<td>0.19</td>
</tr>
<tr>
<td><strong>Very Severe</strong></td>
<td>0.04%</td>
<td>0.004%</td>
<td>0.10</td>
</tr>
<tr>
<td><strong>Death</strong></td>
<td>n = 1</td>
<td>n = 1</td>
<td></td>
</tr>
</tbody>
</table>

*Death rate ~ 6/1 million

Katayama et al Radiology 1990;175:616-8

(These AE rates are specific to the experience at the institutions studied in this publication.)
Suggestions on how to prevent adverse events

• Outpatient center: NSF is rare, code = 911
  – ACLS trained radiologists
  – Crash cart
  – Run Mock codes
  – Consider nonionic Gadolinium if GFR>30 + AE risks
    – prefer hand injection

• Hospital based MRI: code team readily available
  – Ionic and macrocyclic agents for NSF risk patients
  – Nonionic for patients at risk of allergic reactions
Summary

- Gadolinium is extraordinarily safe
- Laboratory interferences are disappearing
- NSF is disappearing due to lower doses, less Gd in renal failure patients, less use of nonionic linear Gd
- Allergic Reactions can be lethal:
  - Most acute reactions are mild
  - Severe reactions can be life threatening
  - Crash Cart, ACLS training, mock codes
  - Nonionic Gd has lowest allergic reaction risk