MR Contrast Agents
Understanding and Embracing Change

Kristan Harrington, MBA, RT (R) (MR) (ARRT)

Why Use Contrast Agents in MRI?

- Improve disease detection and characterization
- Increase sensitivity to extent of disease
- Increase differentiation between normal and abnormal tissues
- Track enhancement patterns
- Demonstrate pathophysiology
- Perfusion
- Clearance

US Agents

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Trade Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gadopentetate dimeglumine</td>
<td>Magnevist</td>
</tr>
<tr>
<td>Gadoteridol</td>
<td>ProHance</td>
</tr>
<tr>
<td>Gadodiamide</td>
<td>Omniscan</td>
</tr>
<tr>
<td>Gadoversetamide</td>
<td>OptiMARK</td>
</tr>
<tr>
<td>Gadobutrol</td>
<td>Gadavist</td>
</tr>
<tr>
<td>Gadoterate meglumine</td>
<td>Dotarem</td>
</tr>
<tr>
<td>Gadobenate dimeglumine</td>
<td>MultiHance</td>
</tr>
<tr>
<td>Gadoxetate disodium</td>
<td>Eovist</td>
</tr>
<tr>
<td>Gadofosveset trisodium</td>
<td>Ablavar</td>
</tr>
</tbody>
</table>
Gd-Based Contrast Media

**Variable Properties**
- Chelate design - Clinical Safety
- Ionic/Non-Ionic - Clinical Safety
- Excretion - Renal or Biliary
- Molar concentration - Volume Delivery in ml based on Dose
- Relaxivity - Effectiveness based on Dose

**Question**

**Mechanism of Action**

**TR (Time of Repetition)**

**T1-Relaxation**

![Diagram of T1-Relaxation](image)
Molecular tumbling-rate slows

T1-relaxation time shortens

\[ \Delta \frac{1}{T_1} = r_1 \{\text{Gd}\} \]

Relaxivity \( r_1 \) is a measure of the effect on the T1-relaxation rate

**Brain**

- Intra-axial
- Extra-axial

**Low-Grade Lesion**

Pre vs Post
Intraindividual Crossover Comparison

**Gadopentetate vs. Gadobenate: Timecourse**

![Graph showing time course comparison between Gadobenate (MultiHance) and Gadopentetate (Magnevist).](image)

*Lesion contrast significantly higher after MultiHance administration (N = 24)

Data from Essig M. Appl Radiol 2003; April (suppl):92-100

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**Increasing Signal (Contrast)**

- Reduce background (MTC)
- Increase dose
- Increase concentration (1.0 molar vs 0.5 molar)
- Increase Relaxivity

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**Concentration**

- 1.0 Molar
- 0.5 Molar

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**Dosing**

Dose is determined by **amount of gadolinium** not volume of the agent

<table>
<thead>
<tr>
<th>ProHance 0.5 molar concentration</th>
<th>Standard dose: 0.1 mmol/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient weight: 80 Kg (approx 180 lbs)</td>
<td></td>
</tr>
<tr>
<td>$80 \times 0.1 = 8$ ml</td>
<td></td>
</tr>
</tbody>
</table>

**Same for:**
- Magnevist
- MultiHance
- Omniscan
- Optimark

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**Dosing**

Dose is determined by **amount of gadolinium** not volume of the agent

<table>
<thead>
<tr>
<th>Gadavist 1.0 molar concentration</th>
<th>Standard dose: 0.1 mmol/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient weight: 80 Kg (approx 180 lbs)</td>
<td></td>
</tr>
<tr>
<td>$80 \times 0.1 \neq 8$ ml</td>
<td></td>
</tr>
</tbody>
</table>

**Lower Volume**

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No data to support increased safety due to reduced volume but same dose

Increased concentration in the bottle does not translate to increased concentration in tissues.

Increasing Relaxivity

**Standard**

- Benzylxymethyl chain
- Gd$^{3+}$ & H$_2$O

**Gd-BOPTA**

- 2-fold increase in relaxivity (r1, r2)
- Weak / Transient Interaction w/ Proteins


**Qualitative Measures**

- Lesion Border Delineation
- Extent of Lesion
- Internal Morphology
- Degree of Enhancement

Quantitative Measures


Additional References (partial list)


**CONCLUSION:** Gadobenate dimeglumine at a dose of 0.1 mmol/kg is comparable to gadopentetate dimeglumine at 0.2 mmol/kg for contrast-enhanced renal MRI angiography.

**Clinical Safety**

- Adverse Events
- Stability

**Gadolinium**

- Rare Earth Metal
- Toxic to Mammals if delivered alone
- Paramagnetic

http://en.wikipedia.org/wiki/Gadolinium
**Adverse Events**

Rare and most are mild (Idiosyncratic)

No difference between any of the agents available in the US today

Sites should be prepared to treat a reaction just as they would with iodinated contrast media

Dillman, et. al.: AJR:189 Dec 2007
Murphy, et. al.: AJR:196 Oct 1996
Runge VM: Invest Rad 2001 Vol 36, Num 2, 65-71
Shellock FG, et. al.: Invest Rad 2006 Vol 41, Num 6, 65-71

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**Contrast Media Adverse Events**

**Then**
- Happened every day
- We expected it
- We were prepared
  - Ammonia capsules
  - Benedryl
  - Epinepherine
  - Atropine
  - O₂
  - BP cuff
  - IV sets

**Now**
- Rarely happens
- We don’t expect it
- We are not prepared
  - Patients not well monitored
  - Drugs locked up
  - Where’s the key?
  - Physician available?
  - Just call 911

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**Assessment of Adverse Reaction Rates to a Newly Approved MRI Contrast Agent: Review of 23,553 Administrations of Gadobenate Dimeglumine**

Andrew Bleicher, Emanuel Kanal
AJR: 191, December 2008

13 hospitals and associated imaging centers
13 months and 23,553 doses of MultiHance

Data recorded by technologists included dose, related adverse reactions (type and treatment)

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**13 months and 23,553 doses of MultiHance**

- 178 Reactions (0.76% of CE examinations)
- 22 Required treatment (13% of reactions)
- 8 (5%) qualified as serious

**CONCLUSION:** With the introduction of the most recent MR contrast agent approved for use in the United States, our interest in its substantial potential clinical benefits that would result from its increased relaxivity was balanced by concern that the rate of adverse effects may increase. This concern has been ameliorated with the findings of rates of adverse reactions that are comparable to those published for other MR contrast agents.

Chelate
Any of a class of coordination or complex compounds consisting of a central metal atom attached to a large molecule, called a **Ligand**

http://www.britannica.com/EBchecked/topic/108427/chelate

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**GBCM Make-up**

- **Linear Ionic**
- **Linear Non-Ionic**
- **Macroyclic**

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**Stability and Transmetalation**

**Concerns regarding stability of chelates are NOT NEW..**


Laurent S, Elst LV, Muller RN Contrast Media Mol Imaging. 2006 May;1(3):128-37

Nephrogenic Systemic Fibrosis

Syndrome:
- Skin
- Joints
- Eyes
- Internal Organs

Screening Questions:
- Kidney Disease
- Acute Kidney Trauma
- Sickle Cell
- Chemotherapy recently
- Liver Transplant
- Kidney Transplant

Glomerular Filtration Rate

Estimation Calculation Based On:
- Serum Creatinine Level
- Age
- Sex
- Race

NSF is believed to occur more commonly in patients who have received high doses of GBCM as well as in patients who have received higher cumulative lifetime doses of


Sadowski, E. A. et al. Radiology 2007;0:2431062144

NSF

http://www.renal.org/eGFRcalc/GFR.pl

Nephrogenic Systemic Fibrosis
## Glomerular Filtration Rate

<table>
<thead>
<tr>
<th>Stage</th>
<th>GFR*</th>
<th>Description</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>90+</td>
<td>Normal kidney function and urine findings or structural abnormalities or genetic trait, point to kidney disease</td>
<td>Observation, control of blood pressure. More on management of Stages 1 and 2 CKD.</td>
</tr>
<tr>
<td>2</td>
<td>60-89</td>
<td>Mildly reduced kidney function, and Observation, control of other findings (see for stage 1) point blood pressure and risk factors. More on management of Stages 1 and 2 CKD.</td>
<td></td>
</tr>
<tr>
<td>3A</td>
<td>45-59</td>
<td>Moderately reduced kidney function</td>
<td>Observation, control of blood pressure and risk factors. More on management of Stage 3 CKD.</td>
</tr>
<tr>
<td>3B</td>
<td>30-44</td>
<td>Severely reduced kidney function</td>
<td>Planning for end stage renal failure. More on management of Stage 4 and 5 CKD.</td>
</tr>
<tr>
<td>4</td>
<td>15-29</td>
<td>Severely reduced kidney function</td>
<td>Treatment choices. More on management of Stages 4 and 5 CKD.</td>
</tr>
<tr>
<td>5</td>
<td>&lt;15 or on dialysis</td>
<td>Very severe, or end stage kidney failure (sometimes called established renal failure)</td>
<td></td>
</tr>
</tbody>
</table>

### ACR: Manual on Contrast Media – Version 7, 2010

**Box 1: Agents associated with the greatest number of NSF cases:**

- **Gadodiamide (Omniscan® – GE Healthcare)**
- **Gadopentetate dimeglumine (Magnevist® – Bayer HealthCare Pharmaceuticals)**
- **Gadoversetamide (OptiMARK® – Coviden)**

As of December 2009, according to data provided by the Food and Drug Administration (FDA) (8), the approximate number of administrations and the number of NSF cases associated with these three agents were as follows:

<table>
<thead>
<tr>
<th>Agent</th>
<th>Approximate # of doses (in millions)</th>
<th># of reported NSF cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gadodiamide</td>
<td>13</td>
<td>162</td>
</tr>
<tr>
<td>Gadopenetetate dimeglumine</td>
<td>23</td>
<td>193</td>
</tr>
<tr>
<td>Gadoversetamide</td>
<td>4.7</td>
<td>35</td>
</tr>
</tbody>
</table>

While various factors may have influenced the number of cases reported with each of these agents, investigators believe that intrinsic properties of these three agents increase the relative likelihood of NSF developing following exposure in at-risk patients.

**Box 2: Agents associated with few, if any, unconfirmed cases of NSF:**

- **Gadodiamide (MultiHance® – Bracco Diagnostics)**
- **Gadodiamide (ProHance® – Bracco Diagnostics)**
- **Gadoteric acid (Dotarem® – Guerbet)**

As of this writing, FDA-approved for use in the United States.

- **Gadobenate (Gadoxin® – Bayer HealthCare Pharmaceuticals)**

**Box 3: Agents which have only recently appeared on the market in the US:**

- **Gadofurisetron (Abravian® – Lanthus Medical Imaging)**
- **Gadobenate (Gadoxin® – Bayer HealthCare Pharmaceuticals)**

There is limited data for these agents, although, to date, few, if any, unconfirmed cases of NSF have been reported.
Stability Measurements

<table>
<thead>
<tr>
<th>Contrast Agent</th>
<th>Thermodynamic Stability Constant ($\log K_{eq}$)</th>
<th>Conditional Stability Constant at pH 7.4</th>
</tr>
</thead>
<tbody>
<tr>
<td>ProHance</td>
<td>23.8</td>
<td>17.1</td>
</tr>
<tr>
<td>Magnevist</td>
<td>22.1</td>
<td>18.1</td>
</tr>
<tr>
<td>MultiHance</td>
<td>22.6</td>
<td>18.4</td>
</tr>
<tr>
<td>Optimark</td>
<td>16.6</td>
<td>15</td>
</tr>
<tr>
<td>Omniscan</td>
<td>16.9</td>
<td>14.9</td>
</tr>
</tbody>
</table>


Summary

- MR contrast agents are an integral part of MR exams
- Gadolinium-based agents act by altering relaxation parameters
- “Enhancement” based on technique, field strength, dose, concentration and relaxivity of the agent

Linear no molecular charge

Summary

- Faster imaging techniques require more efficient MR contrast agents
- Adverse events associated with GBMCAs are rare but occur equally among all agents
- The risk of NSF in patients with poor renal function again demonstrates differences between agents

Thank You!

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