Rad Tech 4623 Advanced MRI Procedures and Safety
Contrast Agents
(Chapter 11 MRI In Practice)

Rex T. Christensen MHA RT (R) (MR) (CT) (CIIP)
Weber State University
Gadolinium (atomic # 64 – Heavy Metal)
Chelates

The word chelate derives from the Greek word “chel”, meaning a crab’s claw, and refers to the pincer-like manner in which the metal is bound.

Eliminates toxicity of Gad by neutralizing the Ion
Gd-DTPA (Gad + Chelate)

Gadolinium + Diethylenetriaminepentaacetic acid-chelate

The gadolinium chelates are 100% renally excreted, with the exception of two agents with combined renal and hepatobiliary excretion (MultiHance and Primovist)
Gadolinium Chelates

- Clear, colorless fluids, formulated without bacteriostatic additives for intravenous administration.
- The standard dose (excluding use in MR angiography) is 0.1 mmol/kg, which corresponds to 15 mL for a 75-kg patient.
- The distribution of the agents is to the extracellular space.
Lesion enhancement occurs by one of two mechanisms:

- disruption of the bloodbrain barrier (for intraaxial brain lesions)
- lesion vascularity

The gadolinium ion is strongly paramagnetic, leading to a reduction in both T1 and T2, which is visualized on T1-weighted images as an increase in signal intensity. Due to relaxivity.
Gadolinium Chelates

Chelation of Metal Ions

- Improves biologic tolerance
- Controls biodistribution
- Prevents intracellular deposition
- Facilitates rapid and complete excretion

Gd-DTPA
Relaxivity

The ability of magnetic compounds to increase the relaxation rates of the surrounding water proton spins.
Relaxivity
Relaxivity – How does it work?

- T1-relaxation is dependent on the molecular tumbling rate. (T1 weighted exams)
- The gadolinium molecule is a “big tumbling magnet”
- The slower a molecule tumbles, the shorter the T1-relaxation time of the hydrogen molecule (the greater the relaxation rate).
Relaxivity – How does it work?

- When the gadolinium molecule gets next to the water molecule, it effects the rate at which the water molecule tumbles, slowing it down.
Relaxivity – So what is the big deal?

• Shortening the TR or increasing the relaxivity increases the signal.

• Signal can be increased in other ways:
  - Increase the molar concentration
  - Increase the dose
Paramagnetic Contrast Agents

- Gadolinium chelates shorten both T1 and T2 values
- T1 effects predominate at clinical doses

T1 shortening = increased signal on T1-weighted images
T2 shortening = decreased signal on T2-weighted images
Gadolinium Considerations

- Efficacy
- Safety
- Cost
Efficacy

• The gadolinium chelates currently available for clinical use can be differentiated on the basis of:
  • charge (ionic or nonionic)
  • structure (linear or cyclic)
  • stability
Charge (Ionicity)

Given that the gadolinium ion carries a 3 charge, if the ligand, for example, is HPDO3A (that for ProHance, with a charge of 3), the metal chelate itself will carry a net charge of zero, and thus be nonionic.

In the U.S. market, considering only the gadolinium chelates with 100% renal excretion, there are three nonionic agents (ProHance, Omniscan, and Optimark) and one ionic agent (Magnevist).
MRI Contrast Agents

Non-Ionic

Ionic

Non-Ionic

Ionic

Non-Ionic

Ionic

Linear

Macroyclic
Structure (Linear or Cyclic)

- The structure of the chelate can be linear or macrocyclic (ring-like), with the cyclic chelates demonstrating higher in vivo stability and thus an improved safety margin. ProHance is the only macrocyclic chelate available in the United States.

- Internationally, two other extracellular gadolinium chelates are in widespread use, both macrocyclic: Dotarem (ionic) and Gadovist (nonionic).
MRI Contrast Agents

Non-Ionic

Ionic

Non-Ionic

Ionic

Non-Ionic

Ionic

Non-Ionic

Linear

Macro cyclic
Stability

• Stability is related to structure of the chelate. Gadolinium Chelates differ in their thermodynamic stability constants and their kinetic stability.

• Macro cyclic chelates are more stable than linear molecules.

• Even among linear agents there are differences in stability.
Stability

<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>

• **Thermodynamic stability** occurs when a system is in its lowest energy state, or chemical equilibrium with its environment.

• **Conditional stability constant** is the equilibrium reaction of a metal cation and a ligand to form a chelating mononuclear complex; the absolute-stability constant is expressed by the product of the concentration of products divided by the product of the concentrations of the reactants.
# Contrast Agents

## Osmolality, Ionicity, Viscosity

<table>
<thead>
<tr>
<th>Compounds</th>
<th>Osmolality (mOsm/kg)</th>
<th>Ionicity</th>
<th>Viscosity 37°C (cP)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Magnevist</td>
<td>1960</td>
<td>Ionic</td>
<td>2.9</td>
</tr>
<tr>
<td>MultiHance</td>
<td>1970</td>
<td>Ionic</td>
<td>5.3</td>
</tr>
<tr>
<td>Omniscan</td>
<td>789</td>
<td>Nonionic</td>
<td>1.4</td>
</tr>
<tr>
<td>OptiMARK</td>
<td>1110</td>
<td>Nonionic</td>
<td>2.0</td>
</tr>
<tr>
<td>ProHance</td>
<td>630</td>
<td>Nonionic</td>
<td>1.3</td>
</tr>
</tbody>
</table>
Osmotic (Ion) concentration. An indicator of fluid balance in the bodies tissues.

The term "osmolal" describes an ion concentration of a solution in moles per kilogram of solvent (mol/kg), while "osmolar" describes an ion concentration in moles per liter (mol/L).
Viscosity

Resistance of fluid. Measured in *centipoise* ($cP$)
Viscosity

Osmolality, Ionicity, Viscosity

<table>
<thead>
<tr>
<th></th>
<th>Viscosity 37.5°C (cP)</th>
<th>MR contrast agents can safely be administered at injection rates from 1-4 ml/sec</th>
</tr>
</thead>
<tbody>
<tr>
<td>Magnevist</td>
<td>2.9</td>
<td></td>
</tr>
<tr>
<td>MultiHance</td>
<td>5.3</td>
<td></td>
</tr>
<tr>
<td>Omniscan</td>
<td>1.4</td>
<td></td>
</tr>
<tr>
<td>OptiMARK</td>
<td>2.0</td>
<td></td>
</tr>
<tr>
<td>ProHance</td>
<td>1.3</td>
<td></td>
</tr>
</tbody>
</table>
### Ionicity and Osmotic Load

#### Osmolality, Ionicity, Viscosity

<table>
<thead>
<tr>
<th></th>
<th>Ionicity</th>
<th>Total Osmotic Load (mOsm)</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Magnevist</td>
<td>Ionic</td>
<td>27</td>
<td>Ionic and nonionic MR contrast agents both have high safety profiles</td>
</tr>
<tr>
<td>MultiHance</td>
<td>Ionic</td>
<td>39</td>
<td></td>
</tr>
<tr>
<td>Omniscan</td>
<td>Nonionic</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>OptiMARK</td>
<td>Nonionic</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>ProHance</td>
<td>Nonionic</td>
<td>9</td>
<td></td>
</tr>
</tbody>
</table>
## Contrast Agents

<table>
<thead>
<tr>
<th>_contrast agent</th>
<th><strong>Osmolality (mOsm/kg)</strong></th>
<th><strong>Injection Volume (mL)</strong></th>
<th><strong>Total Osmotic Load 37 1/4 C (cP)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Magnevist</td>
<td>1960</td>
<td><strong>14</strong>*</td>
<td>27</td>
</tr>
<tr>
<td>MultiHance</td>
<td>1970</td>
<td><strong>14</strong>*</td>
<td>39</td>
</tr>
<tr>
<td>Omniscan</td>
<td>789</td>
<td><strong>14</strong>*</td>
<td>11</td>
</tr>
<tr>
<td>OptiMARK</td>
<td>1110</td>
<td><strong>14</strong>*</td>
<td>16</td>
</tr>
<tr>
<td>ProHance</td>
<td>630</td>
<td><strong>14</strong>*</td>
<td>9</td>
</tr>
<tr>
<td>Hypaque 370</td>
<td><strong>2100</strong></td>
<td><strong>150</strong></td>
<td><strong>315</strong></td>
</tr>
<tr>
<td>(HOCM)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Omnipaque 350</td>
<td><strong>844</strong></td>
<td><strong>150</strong></td>
<td><strong>127</strong></td>
</tr>
<tr>
<td>(LOC)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Volume of contrast typically administered to a 70kg patient based on a 0.1 mmol/kg dose.
Molar Concentration

Gd-HP-DO3A (ProHance)

0.1 mmol/kg  0.3 mmol/kg

1.0 molar concentration

10 cc Gadovist
2 cc/sec
Flush 25 cc
Low osmolar contrast media (LOCM) are less nephrotoxic than high osomolar contrast media (HOCM).
Nephrotoxicity

Contrast-induced Nephrotoxicity

- Contrast-induced nephrotoxicity may be related to total osmotic load
- Little or no nephrotoxicity at clinical doses

<table>
<thead>
<tr>
<th>Drug</th>
<th>Total Osmotic Load</th>
</tr>
</thead>
<tbody>
<tr>
<td>Magnevist</td>
<td>27 C (cP)</td>
</tr>
<tr>
<td>MultiHance</td>
<td>39</td>
</tr>
<tr>
<td>Omniscan</td>
<td>11</td>
</tr>
<tr>
<td>OptiMARK</td>
<td>16</td>
</tr>
<tr>
<td>ProHance</td>
<td>9</td>
</tr>
</tbody>
</table>
Nephrotoxicity

Contrast-induced Nephrotoxicity

- Contrast-induced nephrotoxicity may be related to total osmotic load
- Little or no nephrotoxicity at clinical doses
- Triple dose (0.3 mmol/kg) and higher may be problematic in renal impaired patients
Nephrogenic Systemic Fibrosis (NFS)

Development of the disease is due to gadolinium chelate dissociation, with deposition of the free metal, and is thus related to chelate stability, dose, and cumulative (lifetime) dose.
MR Contrast Agents in Dialysis Patients

Precautions

- Avoid double and triple dose, if possible
- Schedule MR shortly before next dialysis session
- Keep intervals short between following 2-3 dialysis sessions
End-Stage Renal Disease

“When a patient with moderate to end-stage kidney disease needs an imaging study, select imaging methods other than MRI or MRA with a gadolinium-based contrast agent for the study whenever possible. If these patients must receive a gadolinium-based contrast agent, prompt dialysis following the MRI or MRA should be considered.”

American College of Radiology Committee on Drugs and Contrast Media. Manual on contrast media, 4.1 ed. Reston, VA; American College of Radiology, 1998
Glomerular Filtration Rate (GFR)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>Glomerular Filtration Rate GFR</th>
</tr>
</thead>
<tbody>
<tr>
<td>At increased risk</td>
<td>Risk factors for kidney disease (e.g., diabetes, high blood pressure, family history, older age, ethnic group)</td>
<td>More than 90</td>
</tr>
<tr>
<td>1</td>
<td>Kidney damage (protein in the urine) and normal GFR</td>
<td>More than 90</td>
</tr>
<tr>
<td>2</td>
<td>Kidney damage and mild decrease in GFR</td>
<td>60 to 89</td>
</tr>
<tr>
<td>3</td>
<td>Moderate decrease in GFR</td>
<td>30 to 59</td>
</tr>
<tr>
<td>4</td>
<td>Severe decrease in GFR</td>
<td>15 to 29</td>
</tr>
<tr>
<td>5</td>
<td>Kidney failure (dialysis or kidney transplant needed)</td>
<td>Less than 15</td>
</tr>
</tbody>
</table>

National Kidney Foundation
Calculating your Glomerular Filtration Rate (GFR)

- Serum Creatine
- Age
- Race
- Gender

Spurious Hypocalcemia

What is Spurious Hypocalcemia?

Omniscan and OptiMARK

- Contrast interference causes a FALSE lowering of serum calcium measurement on colorimetric assay
- More common at higher contrast doses
- Patients with renal insufficiency may have an increased risk due to inadequate elimination of gadolinium
Spurious Hypocalcemia

What is Spurious Hypocalcemia?

Associated only with the colorimetric assay clinical laboratory test
• No interference with other laboratory assays
• Colorimetric assay is the most common assay used in laboratory testing
• No interference with other approved contrast agents (Magnevist, MultiHance, and ProHance)
Spurious Hypocalcemia
Is it a Real Clinical Issue?

TRUE acute hypocalcemia is
• Relatively rare
• Usually associated with clinical symptoms (eg, tetany, arrhythmias, ECG changes)
Spurious Hypocalcemia
Is it a Real Clinical Issue?

Inappropriate treatment and serious adverse events have occurred

- Lack of awareness
- Inappropriate treatment of spurious hypocalcemia
- Untreated hypercalcemia
Spurious Hypocalcemia

Recommendations

- Identify type of assay used
- Educate radiologists, referring physicians, laboratory personnel
- Measure serum calcium 24 hours before or 24 hours after MR exam
- Use ionized calcium assay if blood drawn immediately after MR exam
Safety

MR Contrast Reaction Risk Factors

- Previous reaction to gadolinium
- Previous reaction to iodinated contrast
- Allergic history
Patients with asthma also seem to be more likely to have an adverse reaction to the administration of a gadolinium-based MR contrast agent. Patients with allergies also seemed to be at increased risk (~2.0–3.7 times, compared with patients without allergies). Patients who have had adverse reactions to iodinated contrast media are more than twice as likely to have an adverse reaction to gadolinium (6.3% of 857 patients).

American College of Radiology Committee on Drugs and Contrast Media, *Manual on contrast media, 4.1 ed.* Reston, VA; American College of Radiology, 1998
Allergy - Prep

Pretreatment Regimen

24 Hours prior to MR examination

- Prednisone 50 mg PO QID
- Benadryl® 50 mg PO BID
The ACR approves of the injection of contrast material and diagnostic levels of radiopharmaceuticals by certified and/or licensed radiologic technologists and radiologic nurses under the direction of a radiologist or his/her physician designee who is personally and immediately available, if the practice is in compliance with institutional and state regulations.
Adverse events after intravenous injection of gadolinium seem to be more common in patients who had previous reactions to an MR contrast agent. In one study, 16 (21%) of 75 patients who had previous adverse reactions to MR contrast agents reacted to subsequent injections of gadolinium.

American College of Radiology Committee on Drugs and Contrast Media. Manual on contrast media, 4.1 ed. Reston, VA; American College of Radiology, 1998
## Adverse Events

<table>
<thead>
<tr>
<th>Contrast Agent</th>
<th>No. of Patients</th>
<th>Headache (%)</th>
<th>Nausea (%)</th>
<th>Taste Perversion (%)</th>
<th>Urticaria (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1,068</td>
<td>3.6</td>
<td>1.5</td>
<td>0.3</td>
<td>0.3</td>
</tr>
<tr>
<td></td>
<td>1,709</td>
<td>0.4</td>
<td>1.1</td>
<td>1.2</td>
<td>0.4</td>
</tr>
<tr>
<td>439/700</td>
<td>1.8/4.4</td>
<td>0.9/3.6</td>
<td>0.9/2.1</td>
<td>0.70.1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1,663</td>
<td>7.5</td>
<td>2.6</td>
<td>5.7</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>2,367</td>
<td>1.9</td>
<td>1.3</td>
<td>1.1</td>
<td>0.3</td>
</tr>
</tbody>
</table>

Adverse Events

Rare and usually mild.

Not specific to any of the agents available today in the US.

Be prepared to treat a reaction just like other contrast media (Iodine)
Pregnancy

• Avoid administering contrast to pregnant patients.

• Article on http://radpacs.weber.edu
Lactating

Use of Gadolinium in Lactating Patients

Standard recommendation

- Suspend nursing for 24 hours post-gadolinium injection
- Pump milk and discard for 24 hours before resuming nursing

Overly Cautious?

- Study with 20 lactating women: 0.04% of maternal gadolinium dose excreted in milk
- < 1% of clinical neonatal dose ingested by infant
- Little risk of adverse events
Feridex

- Iron oxide particulate agent
- Filtered out of the bloodstream by the reticuloendothelial system
- Taken up by the Kupffer cells in the liver, spleen, and bone marrow
- T2 shortening agent
Feridex

Atypical Focal Nodular Hyperplasia (FNH)

- Can be evaluated using gadolinium chelates
- Up to 20-30% of these lesions are atypical
Feridex

Atypical Focal Nodular Hyperplasia (FNH)

Pre-Feridex

Post-Feridex
Focal nodular hyperplasia (FNH) is the second most common tumor of the liver, surpassed in prevalence only by hepatic hemangioma. FNH is believed to occur as a result of a localized hepatocyte response to an underlying congenital arteriovenous malformation.
In symptomatic females, hemorrhagic foci or infarctions may occur within the FNH; these are aggravated by administration of contraceptive agents. The rare complication of a spontaneous rupture into the peritoneum has also been associated with contraceptive use.
Oral Agents

Orally Administered Contrast Agents

- FerriSeltz®
- GastroMARK®
- ImagentGI®
- LumenHance®
GastroMark

GastroMARK
Pancreatic Cancer

Precontrast

Postcontrast
Blood Pooling Agents

MS-325

General characteristics
- Can be injected as a bolus
- Elimination half-life 15 hours
- Excreted by the kidneys
- Osmolality: 717 mOsmol/kg
- Viscosity at 37°C: 1.83 cP
Blood Pooling Agents

MS-325

- Blood pool agents provide two imaging windows

Arterial Phase

Equilibrium Phase
Blood Pooling Agents

Artery-Vein Separation Algorithms

MRA with MS-325

Postprocessing to Remove Veins
Blood Pooling Agents

Potential Applications

- Coronary MRA
- Tumor perfusion
- Gastrointestinal bleeding
- Vessel wall
- Plaque characterization
- Abdominal aortic aneurysm
  - Pre and post stent graft placement
- High resolution MR venography
References

- Jeffrey J. Brown, MD, FACR, MBA
  Mallinckrodt Institute of Radiology, Washington University School of Medicine, St. Louis, Missouri.

- MRI Contrast Media: Willam Faulkner B.S., R.T. (R) (MR) (CT), FSMRT

- Contrast Media: Gd Chelates with Extracellular Distribution

- Magnetic Resonance TIP

- The Free Dictionary by Farlex