Gadolinium-Based MR Contrast Agents

Wm. Faulkner, BS, RT(R)(MR)(CT), FSMRT, MRSO (MRSC™)
Kristan Harrington, MBA, RT(R)(MR) ARRT, MRSO (MRSC™)


INITIAL CLINICAL EVALUATION OF GADOLINIUM DEPA FOR CONTRAST-ENHANCED MAGNETIC RESONANCE IMAGING

Val M. Runge, M.D. * Wolfgang Schweske, M.D. **
Jane Pfeif Nieding, M.D. *** Michael Laxer, M.D. ***
D. Reinier, M.D. **** C. Couhans, M.D. ****
D. Reznikov, M.D. *****

*Department of Radiology and Biomedical Sciences, Stanford University Medical Centre, Stanford, CA 94305, USA
**Department of Radiology and Biomedical Sciences, University of California, San Francisco, CA 94143, USA
***Department of Radiology, University of Alabama, Birmingham, AL 35294, USA
****Department of Radiology, University of California, San Francisco, CA 94143, USA
*****Department of Radiology, University of California, San Francisco, CA 94143, USA

Gadolinium DEPA was evaluated in in-vivo human subjects for magnetic resonance imaging at 3 T. This study was a retrospective, non-randomized, controlled trial comparing gadolinium-depenetrated DEPA with non-contrast-enhanced T1-weighted images in 20 patients with a variety of abnormalities. Gadolinium DEPA was evaluated as an intravenous contrast agent for magnetic resonance imaging in 20 patients with a variety of abnormalities. Gadolinium DEPA was evaluated as an intravenous contrast agent for magnetic resonance imaging in 20 patients with a variety of abnormalities. Gadolinium DEPA was evaluated as an intravenous contrast agent for magnetic resonance imaging in 20 patients with a variety of abnormalities.

Keywords: Contrast-enhanced MRI, Gadolinium DEPA, Magnetic resonance imaging.
Gadolinium-based contrast agents (GBCAs) have been used internationally for more than a quarter century in more than 100 million patients. They are indispensable adjuncts to magnetic-resonance (MR) imaging in a broad spectrum of diseases for detection and therapeutic guidance.

Emanuel Kanal, MD, Michael F. Evron, PhD
### US Agents

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Trade Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gadopentetate dimeglumine</td>
<td>Magnesvist</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>

### Gadolinium: Clinical Safety

- Adverse Events / Patient Tolerance
- Stability

To mitigate risks you have to know and understand the risks.
Have you or has your site ever experienced a significant anaphylactoid reaction following a GBCA injection?

An anaphylactoid reaction due to Gd-DTPA was observed in a patient who had disposition of asthma bronchiale. Five minutes after injection of Gd-DTPA, the patient developed laryngeal edema and erythema over the whole body. The patient recovered after treatment. It may be advisable to tighten indications for Gd-DTPA study on patients with allergic disposition. Gd-DTPA should be used with the same care against the anaphylactoid reaction as iodinated contrast media.

CONCLUSION: Adult and pediatric acute allergic-like reactions to i.v.-administered gadolinium-containing contrast media are rare. Most of these reactions are mild; however, moderate and severe reactions that require immediate management do occur.
There were no discernible differences in any of these studies noted between the different contrast agents in terms of the incidence or type of adverse events reported. Headache, nausea, taste perversion, and urticaria (hives) are typically the most frequent adverse events reported. It should be noted that anaphylaxis and death, although very rare, are known following gadolinium chelate administration.

ACR

According to the ACR Guidance on MR Safe Practices (pg 15), adverse events after the 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.

Patients with asthma 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 (approx 2 - 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)

\[ threw \]


- 287 patients enrolled in intraindividual crossover trials
- Received MultiHance and Magnevist in 2 separate studies within 14 days
- Adverse events rate in these patients was comparable
  - 8% for MultiHance
  - Saline (control): 17% AE
  - 9% for Magnevist
  - Post Marketing survey: 0.05%
“The most important factors in the production of contrast media reactions are the patient’s fear and apprehension.”

- Dr. Anthony LF Lalli

After gadobenate dimeglumine was substituted for gadopentetate dimeglumine, a significant transient increase occurred in the frequency of reported allerg-like reactions that demonstrated a temporal pattern suggestive of the Weber effect (a transient increase in adverse event reporting that tends to peak in the 2nd year after a new agent or indication is introduced)

Radiology: Volume 266: Number 3—March 2013

Adverse Events: Bottom Line

Rare and most are mild
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

Dilmun, et. al., AJR 1997 Dec
Murphy, et. al., AJR 1986 Oct
Runge VM, Invest Radiol 2001 Vol 36, Num 2, 65-71
Shellock FG, et. al., Invest Radiol 2006 Vol 41, Num 6, 65-71
Adverse Events: Bottom Line

You can change agents due to adverse events
BUT... you don’t reduce the risk of adverse events

Dillman, et. al.: AJR 19 Dec 2007
Murphy, et. al.: AJR 1996
Runge VM: Invest Radiol 2001 Vol 36, Num 2, 65-71
Shellock FG, et. al.: Invest Radiol 2006 Vol 41, Num 8, 65-71

Adverse Events: Treatment

$ Vital Sign Assessment
  - Heart Rate
  - Blood Pressure
  - Respiration
$ O₂
$ Medications
  - Atropine (severe vasovagal)
  - Epinephrine (anaphylaxis)
Importance of Stability

Lanthane / “rare earth” Element

**chelate**, any of a class of coordination or complex compounds consisting of a central metal atom attached to a large molecule, called a ligand

“...the clinical safety of these agents is to a large extent dependent upon their metabolic stability in vivo.”

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

In Vitro

- Macroyclic
- Ionic Linear
- Non-Ionic Linear


Stability Metrics

In Vitro

- **Kinetic Stability**: Rate/speed at which the gadolinium dissociates (reported at a pH 1)
- **Thermodynamic Stability**: Energy required to release the Gd\(^{3+}\) ion (reported at a pH 1 or pH 7 as "conditional stability")

Excess Chelate

- **MultiHance** (gadobenate dimeglumine): 0.0 mg/mL
- **ProHance** (gadoteridol): 0.23 mg/mL
- **Magnevist** (gadopentetate dimeglumine): 0.4 mg/mL
- **Omniscan** (gadodiamide): Linear, 12 mg/mL
- **OptiMARK** (gadoversetamide): no molecular charge, 28.4 mg/mL
Is disassociation a new observation?

Increase zinc excretion

Puttagunta, Invest Radiol 1996 Dec;31(12):739-42

“Gadolinium-DTPA-BMA caused the highest increase in zinc excretion among the three agents.”

“Gadolinium-HP-DO3A was found to be the most kinetically inert among the three drugs tested.”

Compared Omniscan, Magnevist and ProHance

Gadodiamide administration causes spurious hypocalcemia.

CONCLUSION: Gadodiamide administration causes spurious hypocalcemia, particularly at doses of 0.2 mmol/kg or higher and in patients with renal insufficiency.

Retention in bone marrow

Comparison of Gd-DTPA-BMA (Omniscan) versus Gd-HP-DO3A (ProHance) relative to gadolinium retention in human bone tissue, as measured by inductively coupled plasma mass spectrometry.

White, Invest Radiol 2006 Mar;41(3):272-8

Using Radiotracers to Characterize Magnetic Resonance Imaging Contrast Agents

Michael P. Tweddle, PhD
Risk increases with decreasing renal function, decreasing agent stability, increasing dose (mmol/kg) and repeat dose.

Incidence has been greatly reduced by screening patients and selection of agents with higher stability.
Renal Function

ACR Grouping

Only agents with labeled contraindications

Omniscan, OptiMARK, Magnevist

Renal Function

Published data: frequency of NSF not equal among all agents

(Radiology 2008, 10.1148/radiol.2483072093)

Only agents with no unconfounded cases of NSF

MultiHance, ProHance, Dotarem

Radiology. 2015 Apr 15:142423. [Epub ahead of print]

MultiHance (Linear Ionic)
Radiology. 2015 Apr 15;142(4):23. [Epub ahead of print]

MultiHance (Linear Ionic)

Retrospective Study
401 Patients
303 Dialysis Dependent
eGFR range: 6 - 41
Mean Contrast Amount: 24 ml

Conclusion
No patients undergoing peritoneal dialysis, hemodialysis, or nondialysis who experienced renal failure developed NSF after administration of gadobenate dimeglumine after more than 2 years’ mean follow-up. Gadobenate dimeglumine may be safe in this population.

NSF

Risk Varies with the Patient and the Agent
Increased T1 Signal in the Dentate Nucleus on Non-Contrast MRI

Also Seen in the Globus Pallidus
T1 hyperintense basal ganglia in a cirrhotic patient


Omniscan was the only agent given

Postmortem neuronal samples from 13 patients with at least 4 CE MR exams (Omniscan)

Postmortem neuronal samples from 10 patients without Gad

Gadolinium deposition observed in capillary endothelium and neural interstitium

No neuronal damage seen

40-year-old female
7 prior administrations of Omniscan (Linear)

27-year-old female
15 prior administrations of ProHance (Macroyclic)
Increased T1-signal seen with Magnevist but not with Dotarem

What happens when Gd$^{3+}$ dechelates?

1. Invivo Ligand Competitors: Fe$^{3+}$, Mg$^{2+}$, Cu$^{2+}$, Zn$^{2+}$, Ca$^{2+}$
2. Invivo Gd$^{3+}$ Competitors: Phosphate, Carbonate and Hydroxide

How a GBCA works
Relaxivity ($r_1$) is a measure of the effect on the T1-relaxation rate

Relaxivity ($r_2$) is a measure of the effect on the T2-relaxation rate

In order for us to see the T1-shortening effects the Gd has to be interacting with water
So if we don’t see T1-shortening, does that mean there is no Gd retention?
TABLE 2: Level of Gd Deposition by Tissue Type

<table>
<thead>
<tr>
<th>Tissue Type</th>
<th>GdCA 125+95% MRS Along kristaxis</th>
<th>GdCA 95-5% MRS Along kristaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal Brain</td>
<td>0.18</td>
<td>0.20</td>
</tr>
<tr>
<td>Cerebral Cortex</td>
<td>0.16</td>
<td>0.20</td>
</tr>
<tr>
<td>Cortex</td>
<td>0.14</td>
<td>0.18</td>
</tr>
<tr>
<td>White Matter</td>
<td>0.12</td>
<td>0.15</td>
</tr>
<tr>
<td>GdCA 125+95% MRS Along cornu ammonis</td>
<td>0.16</td>
<td>0.18</td>
</tr>
<tr>
<td>GdCA 95-5% MRS Along cornu ammonis</td>
<td>0.14</td>
<td>0.15</td>
</tr>
</tbody>
</table>

In conclusion, this study documents that the macromolecular and linear protein interacting agents tested also deposit Gd in brain as well as in bone and skin tissue. Analysis of multiple decedents receiving the macromolecular gadodiamide suggests that deposits Gd in brain at a lower level versus the Group I agents gadodiamide and gadopentetate. The study also shows deposition in bone that occurs at much higher levels compared with brain. Further studies are needed to determine the form(s) of Gd deposited for various GSCAs and implications for any possible adverse health effects.
Increased T1-Signal (Brain)

<table>
<thead>
<tr>
<th>Yes</th>
<th>Magnevist</th>
<th>Omniscan</th>
<th>MultiHance</th>
<th>Gadavist</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>ProHance</td>
<td>Dotarem</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Conclusion:** In the presence of ascholestasis, a transmuralization mechanism may be set off between feric iron and gadoxetate disodium. Desferrioxamine appears capable of binding to gadoxetate iron. Further studies of the safety of GBCAs in severe ascholestasis are warranted. Cholestasis should be considered in patients with iron overload and a history of cirrhosis.
Increased signal intensity in the dentate nucleus on unenhanced 1H-Whipplard images after Gd-DTPA administration: an in vivo study of HD in the mouse model.

Materials and Methods

The present study was approved by the local institutional review boards of the University of California, San Francisco, and the University of California, Davis. All animals were cared for according to the guidelines of the Animal Care and Use Committee of the University of California, San Francisco. For the purpose of this study, 12 60-day-old female HD transgenic mice were used. The mice were anesthetized with pentobarbital (60 mg/kg, i.p.) and placed in a stereotaxic frame. A 3 T magnetic resonance imaging (MRI) system was used to acquire images. The images were acquired using a T2-weighted, T1-weighted, and diffusion-weighted sequence. The T2-weighted images were acquired using a spin-echo sequence (TR/TE = 4000/100 ms, flip angle = 90°), and the T1-weighted images were acquired using a gradient-echo sequence (TR/TE = 300/15 ms, flip angle = 15°). The diffusion-weighted images were acquired using a diffusion-weighted echo-planar imaging sequence (b-values of 0, 100, and 800 s/mm², TR/TE = 5000/90 ms, flip angle = 90°). The images were analyzed using ImageJ software (National Institutes of Health, Bethesda, MD). The signal intensity in the dentate nucleus was measured using a region of interest drawn around the dentate nucleus on the T2-weighted images. The signal intensity was measured at multiple time points after the administration of Gd-DTPA. The results were analyzed using a one-way analysis of variance (ANOVA) followed by a post-hoc Tukey's test.

Results

The signal intensity in the dentate nucleus was significantly increased after the administration of Gd-DTPA (P < 0.05). The increase in signal intensity was dependent on the dose of Gd-DTPA administered. The highest dose of Gd-DTPA (5 mg/kg) resulted in the greatest increase in signal intensity (P < 0.01).

Conclusion

The results of this study suggest that unenhanced 1H-Whipplard images can be used to detect changes in signal intensity in the dentate nucleus after Gd-DTPA administration. This finding may have implications for the early detection and monitoring of HD in animal models. Further studies are needed to confirm these findings in larger animal models and in humans.
Retained Gadolinium

- All agents have some level of retention
  - Bone, tissues, brain, etc
- Stratifies similar to what we see regarding NSF
- Clinical implications unknown
- Radiologists should review orders for gadolinium to ensure they are clinically necessary
- Document: Agent, dose, route and rate (if applicable) for ALL patients (ACR pg 15)

Gadolinium Associated Plaques

- A new condition, gadolinium-associated plaques (GAP), is reported in 2 patients. It is related to magnetic resonance imaging with gadolinium-based contrast agents.
- Important: A new condition, gadolinium-associated plaques (GAP), is reported in 2 patients. It is related to magnetic resonance imaging with gadolinium-based contrast agents. GAP may be associated with NSF. Both patients had NSF and only 1 of those patients had renal disease. The patient without renal disease did not have NSF.
- Conclusions and Recommendations: Patients should be aware that NSF can occur with or without GAP and GAP is not associated with the use of gadolinium.
Anthropogenic Gadolinium

Gadolinium Toxicity

Self-reported gadolinium toxicity: A survey of patients with chronic symptoms.

In this study, we describe the self-reported symptoms experienced by patients with chronic renal failure after gadolinium-based contrast agents (GBCA) administration.

METHODS: A cross-sectional survey of 500 respondents was conducted using an online questionnaire. The survey was designed to assess the occurrence and severity of symptoms following GBCA administration.

RESULTS: A total of 500 respondents completed the survey, and 54% reported experiencing symptoms. The most common symptoms included fatigue, headache, and skin rash. The prevalence of symptoms was highest in patients with kidney disease.

CONCLUSIONS: This study underscores the need for further research into the long-term effects of gadolinium in patients with chronic kidney disease. The results highlight the importance of monitoring patients for symptoms following GBCA administration.
“There are things we know that we know. There are known unknowns. That is to say there are things that we now know we don’t know. But there are also unknown unknowns. There are things we do not know we don’t know.”

- Donald Rumsfeld

**Gadolinium Associated Plaques**

<table>
<thead>
<tr>
<th>Gadolinium Associated Plaques</th>
<th>a new, distinctive clinical entity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical</td>
<td>38.3% females, 36.3% males, 25.3% breast 67%</td>
</tr>
</tbody>
</table>

**Authors**

- Image

**HISTORY**

- Image

**CONCLUSIONS AND RECOMMENDATIONS**

- Image

**Anthropogenic Gadolinium**

<table>
<thead>
<tr>
<th>Anthropogenic Gadolinium</th>
<th>a new, distinctive clinical entity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical</td>
<td>38.3% females, 36.3% males, 25.3% breast 67%</td>
</tr>
</tbody>
</table>

**Authors**

- Image
Legal Considerations

ACR Guidance Document 2013

“No patient is to be administered prescription MR contrast agents without orders from a duly licensed physician.”

“Administration of these agents is to be performed as per the ACR policy. 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 or her physician designee who is personally and immediately available, if the practice is in compliance with institutional and state regulations.

“The name of the administered contrast agent, the administered dose, and the route (and, if applicable, rate) of administration as well as any adverse reactions, if any, should be recorded for all contrast agents administered as part of the executed MR examination.”
“All patients with asthma, allergic respiratory histories, prior iodinated or gadolinium-based contrast reactions, etc. should be followed more closely as they are at a demonstrably higher risk of adverse reaction.”
Questions ?