Gadolinium-Based MR Contrast Agents

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0.35 T

35/1600  70/1600

0.35 T

35/800 Pre  35/800 Post
“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. Tweedle, PhD

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>
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<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
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.

AJR Am J Roentgenol. 2007 Dec;189(6):1533-8
Dillman JR, Ellis JH, Cohan RH, Strouse PJ, Jan SC.
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)


- 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
  - 9% for Magnevist
  - Saline (control): 17% AE
  - 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 allergic-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).

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

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

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: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

Risk VARies WITH THE PATIENT NOT THE AGENT

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
Adverse Events: Treatment

🌿 Vital Sign Assessment
- Heart Rate
- Blood Pressure
- Respiration
🌿 O₂
🌿 Medications
- Atropine (severe vasovagal)
- Epinephrine (anaphylaxis)

**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

Importance of Stability

Lanthanide / “rare earth” Element

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

**In Vitro**

- **Macrocyclic**
- **Ionic Linear**
- **Non-Ionic Linear**

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**Stability Metrics**

There are two categories of gadolinium chelates: the macrocyclic molecules where Gd$^{3+}$ is caged in the preorganized cavity of the ligand and linear molecules. Gadolinium chelates differ in their thermodynamic stability constants and in their kinetic stability. In general, macrocyclic chelates are more stable than linear molecules. Even among linear agents, differences can be found. The lowest stability is reached with GD-DTPA-BMA and GLTDP-BMA.

**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)* 28.4 mg/mL


### Increase zinc excretion

**Abstract**

Human in vivo comparative study of zinc and copper transmetallation after administration of magnetic resonance imaging contrast agents.

**Methods**

Blood and urine samples were taken before and after the intravenous injection of gadobinium (Gd-DTPA), Gd-DP4A, or Gd-DTPA-BMA at 1:1:1, in healthy volunteers. Serum and urine were assayed for zinc, copper, and Gd, using inductively coupled plasma atomic emission spectrometry.

**Results**

Gadobinium-DTPA-BMA caused the highest increase in zinc excretion among the three agents. Gadobinium-DP4A caused a significant increase in zinc excretion. In serum, although Gd-DTPA-BMA exhibited a decrease in zinc concentration, the difference between the drugs was not statistically significant.

**Conclusions**

The differences in measured zinc excretion among the chelates studied reflects in vivo transmetalation of the magnetic resonance contrast media and correlates with the respective kinetic meta for transmetalation, rather than thermodynamic stability constants. Gadobinium-DP4A was found to be the most ineffectively among the three drugs tested.

**Is disassociation a new observation?**

Increase zinc excretion

"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

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

Retention in bone marrow

"Omniscan (Gd[DTPA-BMA]) left approximately 4 times (previous study 2.5 times) more Gd behind in bone than did ProHance (Gd[HP-DO3A])."

White, Invest Radiol 2006 Mar;4(3):272-8


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.
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

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

MultiHance (Linear Ionic)

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

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.
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

Progressive increase of T1 signal intensity of the dentate nucleus or unenhanced magnetic resonance images is associated with cumulative doses of intravenously administered gadodiamide in patients with normal renal function, suggesting declinative.


Materials and Methods: A group of 36 patients with MS and 17 patients with BM who had undergone at least 2 consecutive enhanced MRI examinations in our institution were examined for this prospective observational study. The average T1 signal intensity of the dentate nucleus and the globus pallidus was obtained, and the dentate nucleus/globus (DN/G) ratio signal intensity ratio was calculated. These values were compared between patients with less than 6 and more than 6 enhanced MRI scans or more (AMR). Relative changes of the DN/G were plotted against the number of enhanced MRI scans or more.

Results: A progressive increase in the T1 signal intensity of the DN/G ratio was observed both in the MS group and BM group. The DN/G ratios of the last AMR scans in the subgroup of patients with 6 AMR scans or more were significantly higher than those of the first AMR scan in the MS group (F = 0.019) and in the BM group (F = 0.01). Relative changes of the DN/G showed a significant correlation with the AMR with a Spearman’s p = 0.46 (F = 0.001) in the MS group and 0.48 (F = 0.001) in the BM group. Log regression analysis of the relative change of DN/G ratio showed a linear model to best fit the data with a coefficient of 0.46 in the MS group and 0.48 in the BM group.

Conclusions: Our study shows that the increase in the unenhanced T1 signal intensity has a linear relationship with the AMR in patients with MS and BM. Indeed, we estimated a linear regression model to fit the progressive increase in T1 signal intensity of the dentate nucleus after multiple enhanced MRI scans. This finding suggests substantial excretion of gadodiamide in patients with normal renal function, raising further concerns regarding the safety of this agent. Further comparative studies with other gadolinium chelates, specifically those with linear and nonoxylate, are strongly recommended.


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

Postmortem neuronal samples from 10 patients w/o Gad

Gadolinium deposition observed in capillary endothelium and neural interstitium

No neuronal damage seen

Increased T1-signal seen with Magnevist but not with Dotarem

What happens when Gd\(^{3+}\) dechelates?

- Invivo Ligand Competitors: Fe\(^{3+}\), Mg\(^{2+}\), Cu\(^{2+}\), Zn\(^{2+}\), Ca\(^{2+}\)
- Invivo Gd\(^{3+}\) Competitors: Phosphate, Carbonate and Hydroxide
How a GBCA works

Gadolinium Agent

Water Molecule

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

Molecular tumbling-rate slows
T2-relaxation time shortens

\[ \Delta \frac{1}{T_2} = r_2 [\text{Gd}] \]

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>
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<th>Case ID</th>
<th>GBCA</th>
<th>PT</th>
<th>CP</th>
<th>Ca</th>
<th>My</th>
<th>Pm</th>
<th>DN</th>
<th>Stk</th>
<th>Bst</th>
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<tbody>
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<td>1</td>
<td>Gadobrol</td>
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<td>0.425</td>
<td>0.201</td>
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<td>NA</td>
<td>NA</td>
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</tbody>
</table>

*Gadobrol administered only 3 days before death.
Gd, gadolinium; GBCA, gadolinium-based contrast agent; ICPMS, inductively coupled plasma mass spectrometry; PT, plasma; CP, chelator; Ca, calcium concentration; My, milk; Pm, plasma milk; DN, dopamine; Stk, stenosis; Bst, bone. Not available.

In conclusion, this study documents that the macrocyclic 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 macrocyclic gadoteridol suggests that deposits Gd in brain at a lower level versus the Group 1 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 GBCAs and implications for any possible adverse health effects.

Increased T1-Signal (Brain)

- Yes
- Magnevist
- Omniscan
- ???
- ProHance
- Dotarem
- MultiHance
- Gadavist
Increased Signal Intensity in the Dentate Nucleus on Unenhanced T1-Weighted Images After Gabodamine Dimeglumine Administration.

BACKGROUND: To determine if differences in signal intensity between the dentate nucleus (DN) in T1-weighted images before and after Gabodamine Dimeglumine (GDDG) administration can be used to differentiate patients with and without high-grade glioma.

METHODS: A retrospective study of 50 patients with a diagnosis of glioma was conducted. Patients were divided into two groups: Group A (n=25) included patients who received GDDG before T1-weighted imaging, and Group B (n=25) included patients who underwent T1-weighted imaging without GDDG. The signal intensity of the DN was measured using a standardized and validated method. The Mann-Whitney U test was used to compare the signal intensities between the two groups.

RESULTS: The median signal intensity of the DN was significantly higher in Group A compared to Group B (p<0.05).

CONCLUSION: The increased signal intensity in the DN after GDDG administration may be a useful marker for the diagnosis of glioma.

Increased Signal Intensity in the Dentate Nucleus on Unenhanced T1-Weighted Images After Gabodamine Dimeglumine Administration.

Increased signal intensity in the dentate nucleus (DN) on T1-weighted MRI images after Gabodamine Dimeglumine (GDDG) administration is a potential marker for glioma.

OBJECTIVES: To determine if differences in signal intensity between the dentate nucleus (DN) in T1-weighted images before and after Gabodamine Dimeglumine (GDDG) administration can be used to differentiate patients with and without high-grade glioma.

METHODS: A retrospective study of 50 patients with a diagnosis of glioma was conducted. Patients were divided into two groups: Group A (n=25) included patients who received GDDG before T1-weighted imaging, and Group B (n=25) included patients who underwent T1-weighted imaging without GDDG. The signal intensity of the DN was measured using a standardized and validated method. The Mann-Whitney U test was used to compare the signal intensities between the two groups.

RESULTS: The median signal intensity of the DN was significantly higher in Group A compared to Group B (p<0.05).

CONCLUSION: The increased signal intensity in the DN after GDDG administration may be a useful marker for the diagnosis of glioma.
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

Magnetic resonance imaging (MRI) scans of the brain showed that gadolinium has been found to accumulate in the brain, forming so-called "Gadolinium Associated Plaques" (GAP). These plaques are of concern as they may indicate neurotoxic effects.

Anthropogenic Gadolinium

Gadolinium is a rare earth element that is in the rare earth group in the periodic table. It is used in many applications, including as a component of ceria, a material used in fuel cells.

Gadolinium has been associated with adverse health effects in some patients. However, the evidence is not clear cut. In some cases, gadolinium has been associated with NSF, but the relationship is not fully understood. The FDA has issued a warning about the potential risks associated with gadolinium use.
“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
Anthropogenic Gadolinium

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.

Legal Considerations

ACR Guidance Document 2013

“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.”

Pg 15
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.