Gadolinium-Based Contrast Media

Wm. Faulkner, B.S., R.T.(R)(MR)CT, FSMRT, MRSO (MRSC™)
Kristan Harrington, MBA, R.T.(R)(MR), MRSO (MRSC™)

Gadolinium ($^{64}$Gd)
7 un-paired electrons

[chelate](http://www.britannica.com/EBchecked/topic/108427/chelate), any of a class of coordination or complex compounds consisting of a central metal atom attached to a large molecule, called a ligand
Purpose

Shorten the T1- and T2-relaxation rates of water-based hydrogen protons

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
### 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>
</tbody>
</table>

### Dose

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Trade Name</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gadopentetate dimeglumine</td>
<td>Magnevist</td>
<td>0.1 mmol/kg</td>
</tr>
<tr>
<td>Gadoteridol</td>
<td>ProHance</td>
<td>0.1 mmol/kg</td>
</tr>
<tr>
<td>Gadodiamide</td>
<td>Omniscan</td>
<td>0.1 mmol/kg</td>
</tr>
<tr>
<td>Gadoversetamide</td>
<td>OptiMARK</td>
<td>0.1 mmol/kg</td>
</tr>
<tr>
<td>Gadobutrol</td>
<td>Gadavist</td>
<td>0.1 mmol/kg</td>
</tr>
<tr>
<td>Gadoterate meglumine</td>
<td>Dotarem</td>
<td>0.1 mmol/kg</td>
</tr>
<tr>
<td>Gadobenate dimeglumine</td>
<td>MultiHance</td>
<td>0.1 mmol/kg</td>
</tr>
</tbody>
</table>

### Molar Concentration

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Trade Name</th>
<th>Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gadopentetate dimeglumine</td>
<td>Magnevist</td>
<td>0.5 molar</td>
</tr>
<tr>
<td>Gadoteridol</td>
<td>ProHance</td>
<td>0.5 molar</td>
</tr>
<tr>
<td>Gadodiamide</td>
<td>Omniscan</td>
<td>0.5 molar</td>
</tr>
<tr>
<td>Gadoversetamide</td>
<td>OptiMARK</td>
<td>0.5 molar</td>
</tr>
<tr>
<td>Gadobutrol</td>
<td>Gadavist</td>
<td>1.0 molar</td>
</tr>
<tr>
<td>Gadoterate meglumine</td>
<td>Dotarem</td>
<td>0.5 molar</td>
</tr>
<tr>
<td>Gadobenate dimeglumine</td>
<td>MultiHance</td>
<td>0.5 molar</td>
</tr>
</tbody>
</table>
Calculating Volume Delivered

Dose is determined by amount of gadolinium, not volume of the agent.

Dose: 0.1 mmol/kg
80 kg patient

0.5 molar agent
(80 x 0.1) x 2 = 16 ml

1.0 molar agent
(80 x 0.1) = 8 ml

Lower volume, not lower dose.

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 (needed for greater effect).

Relaxivity

\[ \Delta \frac{1}{T_1} = \gamma_1 \text{[Gd]} \]
Increasing Relaxivity

Standard

Gd-BOPTA

1. Benzyloxymethyl chain
2. Gd^{3+} & H_2O
3. Weak / Transient Interaction w/ Proteins

Gd^{3+} & H_2O

2-fold increase in relaxivity (r1, r2)

Protein

Effectiveness

Signal intensity vs TR

Higher Signal

from the lesion = improved visualization

T1 = 1/(R_1 + r_C)

Relaxivity and Molecular Design

MultiHance

Eovist (Primovist)

Gadavist

Ablavar

Courtesy Dr. E. Kanal
Protein Interaction

Relaxivities in Protein-Containing Solutions (1.5 T)

Interaction w/ Protein

Comparative Study Gadavist vs. ProHance

Phase III data

Relaxivity

- MultiHance (~100% higher ~8)
- Gadavist (~17% higher ~5)
- Magnevist, OptiMARK, Omniscan, ProHance (~4)
- Dotarem (~4)

*Relaxivity is defined as L/mmol/sec
Reducing Dose

“The lowest possible dose of GBCA required to obtain the needed clinical information should be used, and it should generally not exceed the recommended single dose. (Note: the lowest diagnostic dose has not been thoroughly investigated for many indications and caution should be exercised so as not to administer a dose that is too low to provide the diagnostic information sought from the examination).”

ACR Manual on Contrast Media Version 9 2015
MultiHance
0.1 mmol/kg

Dotarem
0.1 mmol/kg

Dotarem
0.05 mmol/kg

MultiHance
0.1 mmol/kg

Relaxivity and Dose

Clinical Safety

§ Adverse Events
- Acute: Idiosyncratic / Anaphylactoid
- Chronic: NSF
§ Gadolinium Retention

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.

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)
"...the clinical safety of these agents is to a large extent dependent upon their \textit{metabolic stability in vivo}.”

- Val Runge, MD

<table>
<thead>
<tr>
<th>Linear</th>
<th>Macrocyclic</th>
</tr>
</thead>
<tbody>
<tr>
<td>OptMARK</td>
<td>Gadavist</td>
</tr>
<tr>
<td>Magnevist</td>
<td>Non-ionic</td>
</tr>
<tr>
<td>Omniscan</td>
<td>MultiHance</td>
</tr>
<tr>
<td>Ionic</td>
<td>Eovist (Primovist)</td>
</tr>
<tr>
<td>Ionic</td>
<td>ProHance</td>
</tr>
</tbody>
</table>

*Fundam Clin Pharmacol. 2006 Dec;20(6):563-76*
Stability Metrics

In Vitro

- Macroyclic
- Ionic Linear
- Non-Ionic Linear


- Kinetic Stability: Rate/speed at which the gadolinium dissociates (reported at pH 1)
- Thermodynamic Stability: Energy required to release the Gd^{3+} ion (reported at pH 1 or pH 7 as "conditional stability")
Is disassociation and retention of gadolinium a new observation?

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

Increase zinc excretion

Compared Omniscan, Magnevist and ProHance

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

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

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

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

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

Compared Omniscan, Magnevist and ProHance

Increase zinc excretion

Compared Omniscan, Magnevist and ProHance

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

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

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

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

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

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

“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;41(3):272-8

Using Radiotracers to Characterize Magnetic Resonance Imaging Contrast Agents

MICHAEL F. TWEDELL, MD
Tweedle ME. Using Radiotracers to Characterize MRI Contrast Agents. Invest Radiol 2002;37:107–113
In conclusion, this study documents that the macrocyclic and linear proton 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)

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

Pull linear MRI contrast from market, European group says

*By Brian Casey and Wayne Forrest, AuntMinnie.com staff writers.*

March 10, 2017 — In a stunning development, a European Union regulatory body on March 16 recommended that four gadolinium-based contrast agents (GBCAs) for MRIs be pulled off the market due to concerns about gadolinium remaining in the body years after scans occur. The agents affected include some of the most widely used contrast products in medical imaging.

The recommendation was issued by the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA), the primary body in the European Union responsible for regulating pharmaceuticals. The committee met this week to review gadolinium safety in response to a request made by the European Commission last year.
Intracranial gadolinium retention only recently reported but known for over 10 years some chelates not completely stable

Indisputable evidence amount of gadolinium deposited after a single dose is incredibly small

Although gadolinium accumulation appears to be dose dependent, no evidence of cellular toxicity nor is there credible evidence of neurologic sequelae after > 300 m human doses worldwide

Observing increased signal on T1-weighted images is not a sensitive way to detect retained gadolinium

Sensitive quantitative mass spectrometry data from multiple sources show that deposition occurs even with macrocyclic agents (albeit at lower levels)

Deposition rates for linear and macrocyclic agents vary with a given class
Retrospective Study
50 patients (mean age 8 yr)
- normal renal function
- ≥ 6 administrations of Dotarem
Control: 59 age-matched never having received Gd
Measured:
- globus pallidus-to-thalamus SI ratio
- dentate nucleus-to-pons SI ratio
Conclusion Quantitative analysis evaluation of globus pallidus/ thalamus and dentate nucleus/pons of the pediatric brain demonstrated an increase after serial administrations of macrocyclic GBCA. Further research is necessary to fully understand GBCA pharmacokinetic in children.
Retained Gadolinium

- All agents have some level of retention
  - Bone, tissues, brain, etc
- Stratifies similar to what we see regarding NSF
- Clinical implications unknown (except for NSF)
- Radiologists should review orders for gadolinium to ensure they are clinically necessary (FDA statement July 2015)
- Document: Agent, dose, route and rate (if applicable) for ALL patients (ACR pg 13)

NSF

- 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
- Now generally accepted that GBCA exposure is a necessary factor in the development of NSF (ACR)

ACR Grouping
NSF

ACR Grouping

Only agents with labeled contraindications
Omniscan, OptiMARK, Magnavist

NSF

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)
Retrospective Study
401 Patients
303 Dialysis Dependent
eGFR range: 6 - 41
Mean Contrast Amount: 24 ml
1423 patients with eGFR <30
MultiHance
No cases of NSF
One More Thing

* No NSF

- MultiHance
- Eovist
- Ablavar

* Not commercially available at this time

---

July 2017

**EMA endorse chrysochrome use in liver gadolinium agents**

By Philip West, AuntMinnie.com staff writer

July 21, 2017 - No official: After months of intense testing and weighing the use of some liver gadolinium contrast agents in MRI will be permitted, and others are to be phased from the market. Following confirmation on Friday by the European Medicines Agency (EMA) that chrysochrome agents are safe to use as a contrast agent in MRI, this morning EMA has recommended restrictions for some intravenous liver agents in order to prevent any risks that could potentially be associated with gadolinium based contrast agents. This is the first time in the EMA's history that it has recommended restrictions for some intravenous liver agents.

The intravenous liver agents, gadopentate dimeglumine (Primovist in Europe, Evist in the US, Bayer Healthcare Pharmaceuticals and gadobenate dimeglumine or Multihance, Bracco), will remain available to these agents under the same updated and can be used for imaging poorly vasculatured regions, especially in delayed phase imaging, but cannot be adequately studied with other agents.

---

**European Medicines Agency recommendations**

<table>
<thead>
<tr>
<th>Product</th>
<th>Type (contrasted)</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ablavhan (gadobenate dimeglumine)</td>
<td>Micronized (BIV)</td>
<td>Manual</td>
</tr>
<tr>
<td>Ablavhan (gadobenate dimeglumine)</td>
<td>Micronized (BIV)</td>
<td>Manual</td>
</tr>
<tr>
<td>Gadovist (gadobenate dimeglumine)</td>
<td>Micronized (BIV)</td>
<td>Manual</td>
</tr>
<tr>
<td>Magnevist (gadopentetate dimeglumine)</td>
<td>Linear (pre-contrast)</td>
<td>Manual</td>
</tr>
<tr>
<td>Magnevist (gadopentetate dimeglumine)</td>
<td>Linear (post-contrast)</td>
<td>Manual</td>
</tr>
<tr>
<td>Multihance (gadoversetamide)</td>
<td>Linear (IV)</td>
<td>Residual use to three doses</td>
</tr>
<tr>
<td>Omniscan (gadopentate dimeglumine)</td>
<td>Linear (IV)</td>
<td>Manual</td>
</tr>
<tr>
<td>Optiray (gadobenate dimeglumine)</td>
<td>Linear (IV)</td>
<td>Manual</td>
</tr>
<tr>
<td>Peramist (gadoversetamide)</td>
<td>Linear (IV)</td>
<td>Manual</td>
</tr>
<tr>
<td>ProHance (gadobenate dimeglumine)</td>
<td>Micronized (BIV)</td>
<td>Manual</td>
</tr>
</tbody>
</table>
July 2017

However, the time-educational formulations of the linear agents gadopentetic acid will continue to be available because the dose of gadolinium that is required for these scans is very low. ESR explained.

Another area of gadolinium agents, monocrystalline agents are more stable and have a lower propensity to release gadolinium than linear agents. These products can still be used in current indications but in the latest showed that some reactions that are rare are not consistent with the data. These include the following:

- Gadobutrol (Gadovist®)
- Gadobenate dimeglumine (Gadavist®)
- Gadoterate meglumine (Dotarem®)

Lifting of suspensions/market withdrawals

The suspension or withdrawals on these agents can be filed. The companies can provide evidence of harm but an identified patient specific that over the last decade of these companies can modify their products so they do not release gadolinium significantly or closer to elevated in water, the agency noted.

July 2017

Conclusions and future directions

Convincing evidence available for the deposition of gadolinium in the deep tissue and the brain, particularly after repeated exposure to GBCAs. Although differences in deposition are observed between agents and between agents’ class, some data are contradictory. Additionally, no data are available regarding gadolinium deposition for some contrast agents. The detection of gadolinium deposition in the brain is concerning; however, there is no reliable data regarding its clinical or biological implications. If any, these implications appear to be small. In general, the risk may be balanced against the potential benefits associated with the use of GBCAs. Further research is needed to elucidate the mechanisms and implications of gadolinium deposition in the brain. This research should focus on the clinical and biological implications of these findings on patients who have been exposed to GBCAs and will continue to be a priority.

The ISMNM supports rigorous research in all aspects of MRI, and will continue to urge aggressive research and discussion on this subject at scientific meetings, workshops, academic journals, and through pilot grants and funding. As shown in this newsletter, several papers remain unaddressed and unsolved, and which should be updated in future editions.
“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