Gadolinium-Based MR Contrast Agents

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INITIAL CLINICAL EVALUATION OF GADOLINIUM DEPSI FOR
CONTRAST ENHANCED MAGNETIC RESONANCE IMAGING

0.35 T

35/1600 70/1600
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>
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<tbody>
<tr>
<td>Gadopentetate dimeglumine</td>
<td>Magnevist</td>
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<tr>
<td>Gadoteridol</td>
<td>ProHance</td>
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<tr>
<td>Gadodiamide</td>
<td>Omniscan</td>
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<tr>
<td>Gadoversetamide</td>
<td>OptMARK</td>
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<td>Gadobutrol</td>
<td>Gadavist</td>
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<tr>
<td>Gadoterate meglumine</td>
<td>Dotarem</td>
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<tr>
<td>Gadobenate dimeglumine</td>
<td>MultiHance</td>
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<tr>
<td>Gadoxetate disodium</td>
<td>Eovist</td>
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<td>Gadofosveset trisodium</td>
<td>Ablavar</td>
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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.
Contrast Agents: Safety Profile
Val M. Runge MD
Scott and White Clinic and Hospital Texas A&M University Health Science Center Temple, Texas USA

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
  - 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 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).

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**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.

Dilman, et. al.: AJR:189 Dec 2007
Murphy, et. al.: AJR:198 Oct 1996
Rungo VM: Invest Radiol 2001 Vol 36, Num 2, 85-71
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

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

Adverse Events: Bottom Line

Risk VARIES WITH THE PATIENT
NOT THE AGENT

Runge VM: AJR:189 Dec 2007
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Adverse Events: Treatment

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

Lanthanide / “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

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

Properties of Gd-Based Contrast Media

- Chelate molecule design
- Ionicity
- Biodistribution
- Molar concentration
- Relaxivity
**Properties of Gd-Based Contrast Media**

- **Chelate molecule design**
- **Ionicity**
- **Biodistribution**
- **Molar concentration**
- **Relaxivity**

**Linear**
- OptMARK
- Gadovist
- Omniscan
- ProHance
- Eovist (Primovist)

**Macrocyclic**
- Magnevist
- Omniscan
- MultiHance
- Dotarem
- Gadavist

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

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

White GW, Gibby WA, Tweedle MF. Ernst Felder Laboratories, Bracco Research USA, Princeton, New Jersey 08540, USA. Gregory.White@bru.bracco.com

OBJECTIVE: The objective of this study was to determine the gadolinium (Gd) concentration remaining in human bone tissue after administration of standard clinical doses of 2 Gd-based contrast agents: ProHance and Omniscan. MATERIALS AND METHODS: After administration of 0.1 mmol/kg of Gd chelate to patients undergoing hip replacement surgery, bone specimens were collected and analyzed, and compared with an age-matched control population without a history of Gd chelate administration. Bone specimens were collected fresh, refrigerated, and subsequently frozen. After grinding and freeze-drying, tissue digestion was performed using Teflon bombs and concentrated nitric acid. A method for analysis of Gd in bone specimens was developed and validated using inductively coupled plasma mass spectroscopy (ICP-MS). RESULTS: Results were compared with a previous study using a different technique for analysis of the same tissue specimens. Tissue retention was 1.77±0.704 μg Gd/g bone (n=9) for Omniscan and 0.477±0.271 μg Gd/g bone (n=10) for ProHance measured by ICP-MS. These findings confirmed results from the previous ICP-AES study. CONCLUSION: Omniscan (Gd[DTPA-BMA]) left approximately 4 times (previous study 2.5 times) more Gd behind in bone than did ProHance (Gd[HP-DO3A]).

PMID: 16481910 [PubMed - indexed for MEDLINE]

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.”
Another Case Study

Increase zinc excretion


Compared Omniscan, Magnevist and Dotarem

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

“Gd-DOTA was found to be the most kinetically inert among the three drugs tested.”

Retention in bone marrow

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

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

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.
Renal Function

ACR Grouping

Only agents with labeled contraindications
Omniscan, OptiMARK, Magnevist

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)
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.
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).

For Patients with low eGFR

“...”
Relaxivity

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

*Relaxivity (r1) in units of L/mmol/sec

No unconfounded cases of NSF
Stability of Gadolinium-Based Contrast Agents

Is NSF the only concern?

“Gadolinium Retention”

Increased T1 Signal in the Dentate Nucleus on Non-Contrast MRI

Omniscan was the only agent given
Omniscan was the only agent given

"This finding suggests substantial dechelation of gadodiamide in patients with normal renal function, raising further concerns regarding the stability of this agent."

Analysis of tissue at autopsy shows it is indeed gadolinium in the brain tissues
40-year-old female
7 prior administrations of Omniscan (Linear)

27-year-old female
15 prior administrations of ProHance (Macro cyclic)

Increased signal in the dentate nucleus is seen following repeat doses of Omniscan (Linear non-ionic)
Not seen in patients who had repeat doses of ProHance (Macro cyclic non-ionic)
Increased T1-signal seen with Magnevist but not with Dotarem

Increased T1-signal seen with Gadobutrol (Gadavist)

Linear Agents: Omniscan and MultiHance
In conclusion, this study documents that the macrocyclic and linear perester interacting agents tested also deposit Gd in brain as well as in bone and skin tissue. Analysis of multiple decedents receiving the macrocyclic gadocelbid suggests that deposit 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.
2006
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)

“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

Legal Considerations
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.
CMS and Physician Supervision

CMS has defined supervision in the hospital outpatient setting by drawing on the three levels of supervision defined under the Medicare Physician Fee Schedule (MPFS): general, direct, and personal supervision. Generally, CMS defines these levels of supervision as follows:

- **General Supervision:** Services furnished under the overall direction and control of the physician, but his or her physical presence is not required during the performance of the procedure.
- **Direct Supervision:** The physician is immediately available to furnish assistance and direction throughout the performance of the procedure. The physician need not be present in the same room when the procedure is being performed, and no physical boundary requirement is specified.
- **Personal Supervision:** The physician is present in the room when the service is being performed.

For outpatient therapeutic services, CMS has defined and clarified that “direct supervision” is the default standard for physician supervision.