Gadolinium-Based MR Contrast Agents

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

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Gadolinium-DTPA was evaluated on an interchangeable scanner for magnetic resonance imaging of 10 patients with various diseases and abnormalities. Images were obtained on a 0.35 T superconductive magnet. The range of administered doses was 0.1 mg/kg to 3 mg/kg; the range of imaging times was 10 min to 60 min. A control group was scanned without administration of the contrast material. The control group was scanned without administration of the contrast material. The results clearly demonstrated the usefulness of gadolinium-DTPA as a contrast agent for 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. 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>OptiMARK</td>
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<tr>
<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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<tr>
<td>Gadofosveset trisodium</td>
<td>Ablavar</td>
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</tbody>
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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.
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.

Contrast Agents: Safety Profile
Val M. Runge MD
Scott and White Clinic and Hospital Texas A&M University Health Science Center
Temple, Texas USA

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 199 Dec 2007
Murphy, et. al.: AJR 198 Oct 1996
Runge VM: Invest Radiol 2001 Vol 36; Nune 2, 65-71
Sherlock, T. 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 199 Dec 2007
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Runge VM: Invest Rad 2001 Vol 33; Num 2, 45-71
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

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
- OptIMARK
- Magnevist
- Omniscan
- MultiHance
- Eovist (Primovist)

Macro cyclic
- Gadavist
- Dotarem
- ProHance

**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

*Excess Chelate*  

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


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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 microg Gd/g bone (n=9) for Omniscan and 0.477+/-0.271 microg Gd/g bone (n=10) for ProHance measured by ICP-MS. These findings confirm previous results from a previous study, which found 2.5 times more Gd in bone tissue with Omniscan compared to ProHance.

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]).

PN: 7751910 [PubMed - indexed for MEDLINE]

In humans, a comparative study of zinc and copper translocation after administration of magnetic resonance imaging contrast agents.

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."

Increased copper and zinc excretion

Puttagunta, Invest Radiol 1996 Dec;31(12):739-42
Another Case Study
Increase zinc excretion

“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.”

Compared Omniscan, Magnevist and Dotarem


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

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, ProfHance, 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.
For Patients with low eGFR

“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).”
**Relaxivity**

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

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

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**Relaxivity**

**No unconfounded cases of NSF**

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*Relaxivity (r1) in units of L/mmol/sec*
Stability of Gadolinium-Based Contrast Agents

Is NSF the only concern?

“Gadolinium Retention”

Increased T1 Signal in the Dentate Nucleus on Non-Contrast MRI
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 suggest 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 (Macroyclic)

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 (Macroyclic 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 precursor interacting agents tested also deposit Gd in brain as well as in bone and skin tissue. Analysis of multiple depositions suggests that the macrocyclic gadobenate signals that deposit Gd in brain at a lower level versus the Gd-1 agents gadoxeline and gadopentetate. This study also shows deposition in bone that occurs at much higher levels compared to brain. Further studies are needed to determine the form(s) of Gd deposited for various GBCAs and implications for any possible adverse health effects.
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 13)

“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

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 radio-pharmaceuticals 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 Physicians 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.