"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
"The clinical safety of a gadolinium chelate is to a large extent dependent upon the stability of the chelate in vivo"
- Dr. Val Runge

Stability Metrics

Table 21: Stability Measurements, Excess Ligated, and Elimination Times of Gadolinium-based Contrast Agents

<table>
<thead>
<tr>
<th>Direct Name</th>
<th>Gd Dose (mg)</th>
<th>Low (mg)</th>
<th>Medium (mg)</th>
<th>High (mg)</th>
<th>Mean Elimination Time (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omnipaque</td>
<td>10.0</td>
<td>6</td>
<td>5</td>
<td>1.3</td>
<td></td>
</tr>
<tr>
<td>Gadovist</td>
<td>10.0</td>
<td>5</td>
<td>6.5</td>
<td>1.7</td>
<td></td>
</tr>
<tr>
<td>MultiHance</td>
<td>15.4</td>
<td>Medium</td>
<td>6.5</td>
<td>1.5</td>
<td></td>
</tr>
<tr>
<td>Epix L.</td>
<td>15.4</td>
<td>Medium</td>
<td>6.5</td>
<td>1.5</td>
<td></td>
</tr>
<tr>
<td>Fortivist</td>
<td>15.4</td>
<td>High</td>
<td>6.5</td>
<td>1.5</td>
<td></td>
</tr>
<tr>
<td>Gadovist</td>
<td>15.4</td>
<td>High</td>
<td>6.5</td>
<td>1.5</td>
<td></td>
</tr>
</tbody>
</table>

*Not currently available in the United States
Increase zinc excretion

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

Compared Omniscan, Magnevist and ProHance

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.

Increase zinc excretion

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

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.

Prince MR, et al.

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.”

Increase zinc excretion


Compared Omniscan, Magnevist and Dotarem

Retention in bone marrow

White GW, Gibby WA, Tweedle MF, Invest Radiol 2006 Mar;41(3):272-8

Comparison of Gd(DTPA-BMA) (Omniscan) versus Gd(DOTAPDO3A) (Prohance) relative to gadolinium retention in human bone tissue by inducibly coupled plasma mass spectrometry.
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])."

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

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

Renal Function

ACR Grouping

Only agents with labeled contraindications
Omniscan, OptiMARK, Magnevist
MultiHance (Linear Ionic)

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

Gadobenate Dimeglumine Administration and Nephrogenic Systemic Fibrosis: Is There a Real Risk in Patients with Impaired Renal Function?

Teodoro SF, Arsenio CL, Giresse Y, Serrano A, Goñi JL.

Objective: To determine the incidence of nephrogenic systemic fibrosis (NSF) in patients with renal disease who received gadobenate dimeglumine at a single medical center. Materials and Methods: This was an institutional review board-approved IRB-approved retrospective study with review of medical records of 401 patients who received gadobenate dimeglumine at a single medical center from January 2002 to December 2013. The eGFR range was from 6 to 41. Results: 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. T Spera, 2015.
Study links gadolinium MR contrast to brain abnormalities
By Wayne Forrest, AuntMinnie.com staff writer
December 17, 2013--Japanese researchers have found a connection between gadolinium-based MRI contrast and abnormalities in two regions of the brain, which could represent a reaction to gadolinium's toxicity, according to a study published online December 17 in Radiology.

The findings from Teikyo University School of Medicine in Tokyo suggest the possibility that a toxic component of the contrast agent may remain in the body long after it is injected, even in patients with normal renal function.

High signal intensity is common in the dentate nucleus and globus pallidus regions of the brain on unenhanced T1-weighted MRI scans, noted lead author Dr. Tomonori Kanda, PhD, and colleagues. Previous research has shown that high signal intensity in the dentate nucleus is associated with a history of brain irradiation or multiple sclerosis, while high signal intensity of the globus pallidus has been linked to a number of conditions, including hepatic dysfunction, calcification, and neurofibromatosis.

Kanda and colleagues also noticed high signal intensity, or hyperintensity, in these two regions in patients who have had more than one administration of gadolinium-based contrast agents.

"In such patients, the signal intensity on T1-weighted images appears higher with increasing number of exposures to gadolinium-based contrast material," they wrote (Radiology, December 17, 2013).

To further explore this occurrence, the researchers compared 19 patients who had undergone six or more contrast-enhanced brain scans with 16 patients who had received six or more unenhanced scans.

Whole-brain MRI scans were conducted on 1.5-tesla systems (Signa HDxt or Signa Excite Twin Speed, GE Healthcare).

MRI of a 45-year-old woman with glioblastoma treated with surgery, chemotherapy, and radiation therapy. Unenhanced T1-weighted image (above, left) shows high-signal-intensity globus pallidus. Fast spin-echo T2-weighted image (above, right) at same level. Unenhanced T1-weighted image (below, left) shows high-signal-intensity dentate nucleus. Fast spin-echo T2-weighted image (below, right) at same level. Images courtesy of Radiology.

Dec 2013 AuntMinnie.com

A hyperintense dentate nucleus may be seen on unenhanced T1-weighted MR images in some patients and may be associated with a history of brain radiation.

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


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

Roccatagliata, Radiology 2009 May;251(2)503-10

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

Kasahara, Radiology 2011 Jan;258(1):222-8
Patients received either Omniscan, Magnevist or both

Kanda, Radiology 2014 Mar;270(3):834-41

High signal intensity in the dentate nucleus and putamen on unenhanced T1-weighted MR images: relationship with increasing cumulative dose of a gadolinium-based contrast material.

Kanda, Radiology 2014 Mar;270(3):834-41

Patients received either Omniscan, Magnevist or both

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High signal intensity in the dentate nucleus and putamen on unenhanced T1-weighted MR images: relationship with increasing cumulative dose of a gadolinium-based contrast material.


Omniscan was the only agent given


Omniscan was the only agent given


Omniscan was the only agent given

Omniscan was the only agent given

Progressive increase of T1 signal intensity of the dentate nucleus on unenhanced magnetic resonance imaging is associated with cumulative dose of intravascular non-contrast agent gadobenate dimeglumine (Omniscan) in patients with normal renal function receiving at least 4 studies.


“Omniscan was the only agent given”


Analysis of tissue at autopsy shows it is indeed gadolinium in the brain tissues


“Omniscan was the only agent given”
Omniscan in patients with normal renal function receiving at least 4 studies

Electronically published March 2015

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

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

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 (Macrocylic non-ionic)

Increased T1-signal seen with Magnevist but not with Dotarem
SI changes seen with Omniscan but not with MultiHance. However, “rate-of-change” data indirectly suggest deposition with MultiHance.

Conclusions: The present study found an increase in SI in the DN after serial injections of gadobenate dimeglumine. Further studies are needed to clarify the potential of different linear gadolinium-based contrast agents to cause SI increase in the DN.

What we know

- ALL GBCAs have a certain amount retained - never 100% eliminated
  - Includes both macrocyclic and linear
- GBCA exposure is a necessary factor in contracting NSF
  - only about 7% with highest risk agents and patients

MultiHance and Magnevist are similar agents
  - Both linear and ionic
- To date there are no unconfounded cases of NSF with MultiHance even with very high risk patients

Consider this...

- In order to be seen on an MR image, gadolinium must interact with water

Increased signal in the DN and GP on T1-weighted images is observed in some, but not all, patients exposed to multiple administrations of three agents with a linear ligand and one macrocyclic agent

Conflicting studies with MultiHance and Gadovist
What We Don’t Know

- If a GBIA doesn’t cross an intact blood-brain barrier, then why do we see the increased signal? Why is it there?
- Just because you don’t see it does it mean it’s not there?
- In what form is the gadolinium?
- What is the clinical significance of this finding?

YouTube Podcast

Radiology Video Podcast
June 2015

Thanks

William Faulkner & Associates, LLC
www.t2star.com