Dermatologic and Systemic Effects of Gadolinium-Based Contrast Agents: Nephrogenic Fibrosing Dermopathy (NFD) / Nephrogenic Systemic Fibrosis (NSF)

Core Radiology Rotation
July 2008

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Gadolinium in the Periodic Table

64
Gd
Gadolinium
157.25
[Xe]6s² 4f⁷ 5d¹

For elements with no stable isotopes, the mass number of the most abundant isotope is given in parentheses.
Gadolinium

• Rare earth element from the lanthanide series
• Powerful paramagnetic properties
• Gadolinium ion Gd$^{3+}$ has 7 unpaired electrons
• These unpaired electrons form dipole-dipole interactions with protons in water, resulting in shortened T1 relaxation time, and increased magnetic resonance signal intensity

http://chemistry.about.com
Gadolinium-Based Contrast Agents

• Highly toxic in unbound form
• The first gadolinium-chelate complex approved to be used as a MRI contrast agent in 1988 at a dose of 0.1mmol/kg was magnevist®
• Gadolinium-chelates are also used as contrast agents in MRA, arteriography and venography, but they are not approved by the FDA for these purposes
• Gadodiamide (Omniscan®) has a half life of 1.3hrs in individuals with normal renal function, 34 hrs in pts with stage 5 CKD
<table>
<thead>
<tr>
<th>Gadolinium agents (abbreviation)</th>
<th>Trade name (manufacture)</th>
<th>Approving body (year of approval)</th>
<th>Chemical structure</th>
<th>Charge</th>
<th>Thermo-dynamic stability constant</th>
<th>Excess chelate (mg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gadoversetamide (Gd-DTPA-BMEA)</td>
<td>OptiMARK® (Mallinckrodt; Hazelwood, MO)</td>
<td><strong>FDA</strong> (1999)</td>
<td>Linear</td>
<td>Nonionic</td>
<td>16.6</td>
<td>28.4</td>
</tr>
<tr>
<td>Gadodiamide (Gd-DTPA-BMA)</td>
<td>Omniscan® (GE Healthcare, Chalfont St Giles, Buckinghamshire, JK)</td>
<td><strong>FDA and EMEA</strong> (1993)</td>
<td>Linear</td>
<td>Nonionic</td>
<td>16.9</td>
<td>12</td>
</tr>
<tr>
<td>Gadopentetate dimeglumine (Gd-DTPA)</td>
<td>Magnevist® (Bayer HealthCare Pharmaceuticals; Montville, NJ)</td>
<td><strong>FDA and EMEA</strong> (1988)</td>
<td>Linear</td>
<td>Ionic</td>
<td>22.1</td>
<td>0.4</td>
</tr>
<tr>
<td>Gabobenate dimeglumine (Gd-BOPTA)</td>
<td>MultiHance® (Bracco Diagnostics)</td>
<td><strong>FDA and EMEA</strong> (2004)</td>
<td>Linear</td>
<td>Ionic</td>
<td>22.6</td>
<td>none</td>
</tr>
<tr>
<td>Gadoteridol (Gd-HP-DO3A)</td>
<td>ProHance® (Bracco Diagnostics; Princeton, NJ)</td>
<td><strong>FDA and EMEA</strong> (1992)</td>
<td>Cyclic</td>
<td>Nonionic</td>
<td>23.8</td>
<td>0.23</td>
</tr>
<tr>
<td>Gadobutrol (Gd-BT-DO3A)</td>
<td>Gadovist® (Bayer Schering Pharma; Berlin, Germany)</td>
<td><strong>EMEA</strong> (2001)</td>
<td>Cyclic</td>
<td>Nonionic</td>
<td>21.8</td>
<td>Not available</td>
</tr>
<tr>
<td>Gadoterate meglumine (Gd-DOTA)</td>
<td>Dotarem® (Guerbet; Paris, France)</td>
<td><strong>EMEA</strong> (1989)</td>
<td>Cyclic</td>
<td>Ionic</td>
<td>25.8</td>
<td>none</td>
</tr>
<tr>
<td>Gadoxetic acid disodium salt (Gd-EOB-DTPA)</td>
<td>Primovist® (Bayer Schering Pharma)</td>
<td><strong>EMEA</strong> (2004)</td>
<td>Linear</td>
<td>Ionic</td>
<td>Not available</td>
<td>Not available</td>
</tr>
<tr>
<td>Gadofosveset trisodium</td>
<td>Vasovist® (Bayer Schering Pharma)</td>
<td><strong>EMEA</strong> (2005)</td>
<td>Linear</td>
<td>Ionic</td>
<td>Not available</td>
<td>Not available</td>
</tr>
</tbody>
</table>
Chemical Structures of Gadolinium-Based Contrast Agents

Linear: Magnevist®
Less Stable

Cyclic: Dotarem®
More Stable

Transmetallation

Urinary Zinc Excretion As a Result of Transmetallation

- Linear nonionic gadolinium-chelate complexes are associated with a large increase in zinc excretion in urine.
- The cyclic ionic gadolinium-chelate complex causes no urinary zinc excretion.
- This is consistent with the notion that cyclic and ionic gadolinium compounds are more stable than linear and nonionic ones.
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<th>Gadolinium agents (abbreviation)</th>
<th>Trade name (manufacture)</th>
<th>Approving body (year of approval)</th>
<th>Chemical structure</th>
<th>FDA-reported Gd- NSF cases</th>
<th>Published NSF case reports</th>
<th>VA Market share (05-07, 07)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gadoversetamide (Gd-DTPA-BMEA)</td>
<td>OptiMARK® (Mallinckrodt; Hazelwood, MO)</td>
<td>FDA (1999)</td>
<td>Linear Nonionic</td>
<td>20 (4.5%)</td>
<td>0</td>
<td>6.1%-4.7%</td>
</tr>
<tr>
<td>Gadodiamide (Gd-DTPA-BMA)</td>
<td>Omniscan® (GE Healthcare, Chalfont St Giles, Buckinghamshire, JK)</td>
<td>FDA and EMEA (1993)</td>
<td>Linear Nonionic</td>
<td>283 (63.3%)</td>
<td>93 (79%)</td>
<td>25.6%-7.6%</td>
</tr>
<tr>
<td>Gadopentetate dimeglumine (Gd-DTPA)</td>
<td>Magnevist® (Bayer HealthCare Pharmaceuticals; Montville, NJ)</td>
<td>FDA and EMEA (1988)</td>
<td>Linear Ionic</td>
<td>125 (28%)</td>
<td>18 (15%)</td>
<td>53.9%-68.7%</td>
</tr>
<tr>
<td>Gabobenate dimeglumine (Gd-BOPTA)</td>
<td>MultiHance® (Bracco Diagnostics)</td>
<td>FDA and EMEA (2004)</td>
<td>Linear Ionic</td>
<td>10 (2.2%)</td>
<td>1 (also gadodiamide)</td>
<td>3.2%-9.9%</td>
</tr>
<tr>
<td>Gadoteridol (Gd-HP-DO3A)</td>
<td>ProHance® (Bracco Diagnostics; Princeton, NJ)</td>
<td>FDA and EMEA (1992)</td>
<td>Cyclic Nonionic</td>
<td>9 (2.0%)</td>
<td>0</td>
<td>11.1% -9.0%</td>
</tr>
<tr>
<td>Gadobutrol (Gd-BT-DO3A)</td>
<td>Gadovist® (Bayer Schering Pharma; Berlin, Germany)</td>
<td>EMEA (2001)</td>
<td>Cyclic Nonionic</td>
<td>0</td>
<td>0</td>
<td>N/A</td>
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<td>Gadoterate meglumine (Gd-DOTA)</td>
<td>Dotarem® (Guerbet; Paris, France)</td>
<td>EMEA (1989)</td>
<td>Cyclic Ionic</td>
<td>0</td>
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<td>0</td>
<td>0</td>
<td>N/A</td>
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<tr>
<td>Gadofosveset trisodium</td>
<td>Vasovist® (Bayer Schering Pharma)</td>
<td>EMEA (2005)</td>
<td>Linear Ionic</td>
<td>0</td>
<td>0</td>
<td>N/A</td>
</tr>
</tbody>
</table>
Clinical Presentation of NFD/NSF

- Thickening and hardening of skin overlying extremities and trunk
- Fibrosis of internal organs including fascia, subcutaneous tissue, skeletal muscle, diaphragm, pleura, pericardium, and myocardium
- Progression is rapid in a subset of pts, which could lead to death
Dermatologic Presentation of NFD/NSF


http://www.clinicalcorrelations.org
Joint Contractures in NFD/NSF

Definitive Dx of NDF/NSF by Bx

Thickened Dermis

Degenerated Collagen

Spindle Cell

Collagen

Mucin

CD34 stain

Procollagen-1 stain

Histology of NFD/NSF

- Thickened dermis
- Swollen collagen bundles with surrounding clefts
- Spindle cell proliferation
- Spindle cells stain positive for CD34 and procollagen-1, suggest they are fibrocytes
- Interstitial mucin deposition
- Absent inflammatory cells
From Discovery of NFD/NSF to its Association with Gadolinium

• NFD first seen in 1997, first described in literature in 2000 by Cowper et al. NFD was renamed to NSF in 2005.
• So far more than 400 cases are reported
• Disorder only seen in pts with decreased renal function
• No cases seen before 1997 suggesting NSF is a new dz probably d/t exposure of CRF pts to new medication, infectious agent, or toxin
• The first description of association b/w Gd and NSF in 2006 by Thomas Grobner from Austria
NSF at BIDMC

- Only one pt was found to have NSF after exposure to Gd at OSH.
- The patient is a dialysis patient awaiting renal transplant.
- He first developed symptoms attributable to NSF near a thrombosed left arm A/V graft in November, 2006.
- Unfortunately, he had another contrast enhanced MRI here at BIDMC in January, 2007.
- Skin bx performed at OSH confirmed the dx of NSF in March 2007.
- Symptoms have worsened since and now include hyperpigmentation of the skin of both upper extremities and flexion contractures at the bilateral elbows.
Risk of Developing NFD/NSF Following Gadolinium Exposure

• Over 400 cases of NSF have been reported, 90% of whom had previously received gadolinium-based contrast agents.

• The overall risk of NSF was estimated at 4.3 cases per 1000 dialysis pts per year.

• The risk of NSF is about 2.4% each time a pt with advanced kidney disease is exposed to gadolinium.
Risk Factors for Gadolinium-Induced NFD/NSF

- End-stage renal disease requiring dialysis, especially those with little or no residual renal function
- Chronic kidney disease stage 4 and 5 not on dialysis
- Acute renal insufficiency
- Renal dysfunction due to the hepato-renal syndrome or renal dysfunction in the perioperative liver transplantation period
- Metabolic acidosis
- Iron overload/intravenous iron
- Divalent ion disturbances
- Endothelial/vascular injury
- High erythropoietin doses
<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>GFR (ml per minute per 1.73 m²)</th>
<th>U.S. prevalence, number of affected patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Kidney damage with normal or elevated GFR</td>
<td>&gt;= 90</td>
<td>5.9 million (3.3)</td>
</tr>
<tr>
<td>2</td>
<td>Kidney damage with mildly decreased GFR</td>
<td>60 to 89</td>
<td>5.3 million (3.0)</td>
</tr>
<tr>
<td>3</td>
<td>Moderately decreased GFR</td>
<td>30 to 59</td>
<td>7.6 million (4.3)</td>
</tr>
<tr>
<td>4</td>
<td>Severely decreased GFR</td>
<td>15 to 29</td>
<td>400,000 (0.2)</td>
</tr>
<tr>
<td>5</td>
<td>Kidney failure</td>
<td>&lt; 15 (or dialysis)</td>
<td>300,000 (0.1)</td>
</tr>
</tbody>
</table>

http://www.aafp.org/afp/20040901/869.html
First Gadolinium contrast agent approved

1988

1997

First observation of NFD by Cowper et al.

First description of NFD in the literature by Cowper et al.

2000

NFD renamed to NSF

2005

2006

2007

2008

The first description of gadolinium-induced NFD/NSF, 4 more papers on the topic in the year

84 papers on gadolinium-induced NFD/NSF

Boxed warning

81 papers on gadolinium-induced NFD/NSF prior to mid-July this year
Proposed Pathogenesis of Gadolinium-Induced NFD/NSF

Removal of gadolinium-based contrast agent by dialysis

- Peritoneal dialysis (PD) is not an efficient means to remove gadolinium.

- Hemodialysis (HD) is an efficient means of gadolinium removal, with higher flux membranes enhancing clearance rates (78.2%, 95.6%, 98.7% and 99.5% removal rate in the 1\textsuperscript{st}, 2\textsuperscript{nd}, 3\textsuperscript{rd} and 4\textsuperscript{th} HD sessions).

Hemodialysis Has not Been Proven to Prevent NSF Following Gadolinium Exposure

- Standard three times weekly HD does not prevent post-Gd NSF.
- It would seem logical to initiate HD early ASAP, with extended length and daily initially. There is no evidence, however, that this strategy will prevent NSF.
Treatment of NFD/NSF

• **Therapies most likely to benefit:**
  - Recovery of renal function
  - Physical therapy and pain management

• **Treatments with anecdotal success:**
  - Extracorporeal photopheresis
  - Sodium thiosulfate
  - Pentoxifylline

• **Therapies with limited success:**
  - Glucocorticoids
  - Plasmapheresis
  - IVIG
  - Cyclophosphamide
  - Thalidomide
  - Other phototherapy
  - Intrallesional Interferon-α
  - Topical calcipotriene
Blackbox Warning on FDA-Approved Gadolinium Agents

**WARNING: NEPHROGENIC SYSTEMIC FIBROSIS**
Gadolinium-based contrast agents increase the risk for nephrogenic systemic fibrosis (NSF) in patients with:
- acute or chronic severe renal insufficiency (glomerular filtration rate <30mL/min/1.73m²), or
- acute renal insufficiency of any severity due to the hepato-renal syndrome or in the perioperative liver transplantation period.

In these patients, avoid use of gadolinium-based contrast agents unless the diagnostic information is essential and not available with non-contrast enhanced magnetic resonance imaging (MRI). NSF may result in fatal or debilitating systemic fibrosis affecting the skin, muscle and internal organs. Screen all patients for renal dysfunction by obtaining a history and/or laboratory tests. When administering a gadolinium-based contrast agent, do not exceed the recommended dose and allow a sufficient period of time for elimination of the agent from the body prior to any readministration (See WARNINGS).
Nephrogenic Systemic Fibrosis Attorneys
We Represent Victims Nationwide

Nephrogenic Systemic Fibrosis made its appearance in 1997, when the first case was diagnosed, and it was formally recognized in 2000.

At first it was seen as a skin disorder and was called Nephrogenic Fibrosing Dermopathy (NFD), but gradually wider symptoms were described and it is now considered a systemic disorder, as it affects internal organs as well as the skin.

NFS has been connected to the use of Gadolinium, a contrast agent used in preparation for MRIs (Magnetic Resonance Imaging) and MRA's (Magnetic Resonance Angiogram). Gadolinium is an ingredient in the injection, which is given before these procedures, with the purpose of creating visual contrast on the printed films, between normal and abnormal tissue. This enables the doctor to see your condition more clearly.

Since this is a recently discovered disease, there is little known about it and few studies have been done. The FDA approved Gadolinium in 1988, but since the number of NSF cases has been increasing, the FDA issued Advisories to medical professionals, warning them to use all possible caution when treating patients with chronic kidney disease.

If you have kidney disease and have had any MRIs or MRA's since 1988, and you notice any symptoms that suggest NSF, contact your doctor immediately. Then contact an NSF attorney as you may have a claim against the manufacturer of Gadolinium as well as other potential defendants.
Medico-Legal Implications

• So far, the target defendants are the manufacturers.

  1. Walker v. Tyco Healthcare Group, LP (filed in the U.S. District Court for the Northern District of Ohio)
  2. Snyder v. GE Healthcare, Inc (pending in the U.S. District Court for the Middle District of Tennessee)

• It does not appear as though physicians have been named in any gadolinium-based contrast agents-related lawsuits.
Current Recommendations and Guidelines

- Identify pts with a diagnosis of NSF or where there is strong clinical suspicion of NSF to prevent further Gd exposure.
- Identify pts who appear to have an increased risk for developing NSF following Gd exposure—ESRD pts on HD or PD, pts with CKD stages 4 or 5 not on dialysis, pts with AKI or pts with kidney or liver transplants with kidney disease.
- Once a pt with potential risk is identified, if possible, avoid administration of all types of gadolinium agents and employ an alternative form of imaging.
- If Gd administration is necessary, pts should be informed of the risks, benefits and alternatives, and this informed consent should be documented in the chart.
Recommendations and Guidelines—Cont’d

- If Gd administration is necessary, use the lowest dose required to provide the diagnostic information (avoid doses higher than 0.2 mmol/kg).
- Cyclic chelates might be preferable (gadoteridol is the only FDA-approved cyclic chelate).
- Avoid multiple exposures.
- For ESRD pts on HD, HD ASAP (within 3 hrs) after Gd. A second HD within 24 hours. Extending the dialysis time will enhance clearance.
- For ESRD pts on PD, avoid a dry abdomen, perform either frequent manual exchanges or increase the automated peritoneal dialysis for at least 48 hours. Utilize HD if possible.
- For stage 4 or 5 CKD pts not on HD or PD or pts with AKI, initiating HD for the sole purpose of removing Gd needs to be individualized.
References

Acknowledgements

• Dr. Gillian Lieberman
• Dr. Dan Siegel
• Dr. Neil Rofsky
• Dr. Robert Lenkinski
• Dr. Nicolas Bloch
• Maria Levantakis