New Guidelines

Use of Gadolinium Contrast Agents

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Disclosures

- Bracco Diagnostics
  - Honoraria for CME programs
- Bayer HealthCare Pharmaceuticals
  - Research Support
  - Consultant
  - Honoraria for CME programs
Recent reports strongly correlate development of NSF/NFD in patients with impaired renal function following exposure to gadolinium-chelate MRI contrast agents, but cause and effect relationship has not been established.
The U.S. Food and Drug Administration (FDA) has asked manufacturers to include a new boxed warning on the product labeling of all gadolinium-based contrast agents which are used to enhance the quality of magnetic resonance imaging (MRI).

May 23, 2007

The requested warning would state that patients with severe kidney insufficiency who receive gadolinium-based agents are at risk for developing a disabling, and a potentially fatal disease known as nephrogenic systemic fibrosis (NSF). In addition, it would state that patients just before or just after liver transplantation, or those with chronic liver disease, are also at risk for developing NSF if they are experiencing kidney insufficiency of any severity.

"FDA has been carefully monitoring potential safety signals related to these contrast agents after receiving reports about the risk of this potentially life-threatening disease," said Steven Galson, M.D., M.P.H., director of FDA's Center for Drug Evaluation and Research. "This latest action demonstrates FDA's ongoing vigilance about ensuring the safety of drug products once they enter the marketplace."

Patients with NSF develop thickening of the skin and connective tissues that inhibits their ability to move and may result in broken bones. Other organs are at risk of thickening as well. The cause of NSF is not known and there is no consistently effective treatment of this condition.

FDA first notified health care professionals and the public about the gadolinium-related risks for NSF in June 2006. Information on the risks was updated in December.

Gadolinium-based contrast agents are commonly used to improve the visibility of internal structures when patients undergo an MRI. Five gadolinium-based contrast agents have been approved for use in the United States: Magnevist (gadopentetate dimeglumine), Omniscan (gadodiamide), OptMARK (gadoversetamide), Multihance (gadobenate dimeglumine), and ProHance (gadoteridol).

Reports have identified the development of NSF following single and multiple administrations of the gadolinium-based contrast agents. The reports have not always identified a specific agent. Omniscan was the most commonly reported agent, when a specific agent was identified, followed by Magnevist and OptMARK.

NSF also has developed after the sequential administration of Omniscan and Multihance and Omniscan and ProHance. Because reports incompletely describe exposure to gadolinium-based contrast agents, it is not possible to know if the extent of risks for developing NSF is the same for all agents.

Patients should be screened for kidney problems prior to receiving one of these imaging agents. The recommended dose should not be exceeded and enough time should elapse to ensure that a dose has been eliminated from the body before the agent is used again.

There have been no reports of NSF among patients with normal kidney function or those with mild-to-moderate kidney insufficiency.

Bayer Schering Pharma, Berlin, Germany, manufactures Magnevist; GE Healthcare, Pittsburgh, Pennsylvania, U.K., is the maker of Omniscan; OptMARK is manufactured by Mallinckrodt, Inc., Hazelwood, Mo., and ProHance and Multihance are made by Bracco Diagnostics Inc., Princeton, N.J.

For more information see www.fda.gov/medwatch/safety/2007/121107.html
In pts with GFR<30 or acute renal insufficiency due to hepato-renal syndrome or in the perioperative liver transplantation period, avoid the use of GBCAs unless the diagnostic information is essential and not available with non-CE MRI

Screen all patients for renal dysfunction by obtaining a history and/or laboratory tests

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
Event date: date of known exposure or diagnosis
Gadolinium Lawyers

Gadolinium Lawyers & Gadolinium Side Effects

With the advancement of medical science comes great reward, but also great risk. Experts will argue over many situations regarding whether a particular advancement’s rewards outweigh its risks, but that’s often a question that cannot be answered until a certain amount of time has passed. One of these issues involves gadolinium.

Gadolinium is a chemical that has been used to help doctors reap greater benefits from MRIs, but it has also recently been linked to serious injuries. William Kerkher has gadolinium lawyers who have an understanding of the history and potential problems of this element, and if you’ve been injured as a result of this substance, you need to contact the gadolinium lawyers at our firm today for a free consultation.

Understanding How Gadolinium Lawyers Can Help You

If you have been injured as a result of the presence of gadolinium in your system, you face a daunting situation. You have a complicated medical recovery to manage, and if you rightfully pursue a claim, you face a potentially complicated legal situation for many reasons. The gadolinium lawyer are here to help you.

If you do decide to pursue a claim, questions will surround the situation, including:

- Determining the parties responsible
- Proving how this chemical caused your injuries
- Using expert testimony to help your case
- Minimizing the effect of expert testimony from the defense

These are just a few examples of the questions/issues that must be handled in order to successfully defend your rights.
Why has NSF disappeared?

- First GBCA approved: 1988
- First NSF cases dx’d: 1997
- Gd “trigger” proposed: 2000
- FDA PHA: 2007
- EMEA: 2009
- FDA Advisory: 2010
- ACR
- EMEA & FDA
- ACR Version 7.0
- New FDA policies

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FDA Drug Safety Communication: New warnings for using gadolinium-based contrast agents in patients with kidney dysfunction

Safety Announcement
Additional Information for Patients
Additional Information for Healthcare Professionals
Data Summary
Approved Gadolinium Based Contrast Agents

[09-09-2010] The U.S. Food and Drug Administration (FDA) is requiring changes in the drug label for gadolinium-based contrast agents (GBCAs) to minimize the risk of nephrogenic systemic fibrosis (NSF), a rare, but serious, condition associated with the use of GBCAs in certain patients with kidney dysfunction. GBCAs are intravenous drugs used in diagnostic imaging procedures to enhance the quality of magnetic resonance imaging (MRI) or magnetic resonance angiography (MRA). (See Approved Gadolinium-Based Contrast Agents below).

These label changes are intended to help ensure these drugs are used appropriately, and that patients at risk for NSF who receive GBCAs are actively monitored for the development of NSF. Symptoms of NSF include scaling, hardening and thickening of the skin; red or dark patches on the skin; and stiffness. NSF can also cause fibrosis of internal organs which may lead to death. There is no effective treatment for NSF.

NSF has not been reported in patients with normal kidney function. Patients at greatest risk for developing NSF after receiving GBCAs are those with impaired elimination of the drug, including patients with acute kidney injury (AKI) or chronic, severe kidney disease (with a glomerular filtration rate or GFR < 30 mL/min/1.73m²). Higher than recommended doses or repeat doses of GBCAs also appear to increase the risk for NSF.

The revised labeling will enhance the safe use of GBCAs, by recommending that healthcare professionals:

- **Not use three of the GBCA drugs—Magnevist, Omniscan, and OptiMark— in patients with AKI or with chronic, severe kidney disease.** These three GBCA drugs are contraindicated in these patients.
- **Screen patients** prior to administration of a GBCA to identify those with AKI or chronic, severe, kidney disease. These patients appear to be at highest risk for NSF.
- **Use the clinical history to screen patients** for features of AKI or risk factors for chronically reduced kidney function. Features of AKI consist of rapid (over hours to days) and usually reversible decrease in kidney function, commonly in the setting of surgery, severe infection, injury, or drug-induced kidney toxicity. Serum creatinine levels and estimated GFR may not reliably assess kidney function in the setting of AKI.
- **For patients at risk for chronically reduced kidney function** (such as patients over age 60 years, patients with high blood pressure, or patients with diabetes), estimate the kidney function (GFR) through laboratory testing.
- **Avoid use of GBCAs in patients suspected or known to have impaired drug elimination** unless the need for the diagnostic information is essential and not available with non-contrast MRI or other alternative imaging modalities.
- **Monitor for signs and symptoms of NSF after a GBCA is administered** to a patient suspected or known to have impaired elimination of the drug.
- **Do not repeat administration of any GBCA during a single imaging session.**
FDA recommends:

• Screening with clinical history to identify patients with AKI or chronic, severe kidney disease

• For patients at risk for chronically reduced kidney function, estimate the kidney function (GFR) through laboratory testing.

FDA recommends:

- To not use three of the GBCAs (Magnevist, Omniscan, Optimark) in patients with AKI or with chronic, severe kidney disease
  - \(<\text{eGFR} 30 \text{ ml/min/1.73m}^2\>
  - These three GBCAs are contraindicated in these patients


Data suggest that NSF may follow the administration of any GBCA and the agency will continue to monitor post-marketing safety data to better characterize the risk of developing NSF following exposure to each GBCA.
NEPHROGENIC SYSTEMIC FIBROSIS

(Revision performed with input from and approval of the ACR Subcommittee on MR Safety)
ACR Manual on Contrast Media v7

- **Group I: Agents associated with the greatest number of NSF cases:**
  - Gadodiamide (Omniscan®)
  - Gadopentetate dimeglumine (Magnevist®)
  - Gadoversetamide (OptiMARK®)

- **Group II: Agents associated with few, if any, unconfounded cases of NSF:**
  - Gadobenate dimeglumine (MultiHance®)
  - Gadoteridol (ProHance®)
  - Gadoteric acid (Dotarem®)
  - Gadobutrol (Gadavist®)

- **Group III: Agents which have only recently appeared on the market in the US:**
  - Gadofosveset (Ablavar®)
  - Gadoxetic acid (Eovist®)
<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Brand Name</th>
<th>EMEA Risk</th>
<th>FDA Contraindicated</th>
<th>ACR Category</th>
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<td>+</td>
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<td>gadoversetamide</td>
<td>OptiMARK</td>
<td>High</td>
<td>+</td>
<td>Group I</td>
</tr>
<tr>
<td>gadopentetate dimeglumine</td>
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<td>Dotarem</td>
<td>Low</td>
<td>NA</td>
<td>Group II</td>
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</table>
Clinical Practice Has Been Changed

- Fewer patients with dialysis and advanced CKD are referred for Gd-enhanced MRI/MRA
- Screening (verbal and eGFR) for CKD is SOC
- Use of GBCAs
  - Decreased use of IV contrast agents
    - alternative imaging tests (e.g. non-contrast MRI/MRA, DWI)
  - Decreased use of linear non-ionic GBCA(s)
    - Increased use of macrocyclic GBCA(s) and one of the linear ionic agents
  - Decreased volume of GBCA(s)
    - "High dose" (>FDA approved dose) MRI/MRA much less common
    - "Low dose" (< FDA approved dose) MRI more common
- Documentation of dose and specific GBCA
  - Patients with compromised renal function less likely to get repeat doses of GBCA at short time intervals