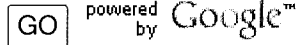


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Questions and Answers on Gadolinium-Based Contrast Agents

1. What information is new since the Questions and Answers from December 2006?

Since December 2006, FDA has continued to investigate reports of nephrogenic systemic fibrosis (NSF) in patients who received gadolinium-based contrast agents (GBCAs) to help define risk factors for NSF.

In addition, the FDA has requested the manufacturers of all five GBCAs (Magnevist, MultiHance, Omniscan, OptiMARK and ProHance) to add a new boxed warning and a new Warnings section to their labels to describe the risk of developing NSF.

2. What is gadolinium and what is its use in clinical medicine?

Gadolinium is a paramagnetic metal ion. Paramagnetic ions, such as gadolinium, move differently within a magnetic field. This trait makes gadolinium useful for magnetic resonance imaging (MRI).

GBCAs are manufactured by a chelating process, a procedure in which large organic molecules form a stable complex around the gadolinium. The chelate reduces the chances of toxicity that could result from exposure to gadolinium. This stable complex is eliminated predominantly via the kidneys.

GBCAs are approved by FDA for use with MRI as a contrast agent to provide an improved image of body organs and tissues.

GBCAs are also used for magnetic resonance angiography (MRA), an imaging procedure used to evaluate blood vessels. FDA has not approved GBCAs for use in MRA.

3. What is the difference between MRA and MRI?

MRA is a special type of MRI used to study blood vessels. MRA aids the detection of heart disorders, stroke, and vascular diseases.

4. Can an MRI and MRA be performed without gadolinium-based contrast?

Yes, MRI and MRA can be performed without contrast.

MRI with GBCAs provides additional diagnostic information as compared to MRI without contrast.

Although GBCAs are not FDA-approved for MRA, some radiologists believe that these agents help provide detailed images of blood vessels.

5. Are there any FDA approved MRA contrast agents?

No.

6. Are there other approved MRI contrast agents that do not contain gadolinium?

Yes. However, the two other approved MRI contrast agents, Feridex, I.V. (an iron-containing injectable solution) and Teslascan (a manganese-containing injectable solution) are FDA-approved only for the evaluation of lesions of the liver.

Imaging contrast agents, such as iodinated contrast agents are used in Computed Tomography, plain X-ray and X-ray angiography. However, these iodinated contrast agents require X-ray imaging rather than MRI. These agents also have serious risks such as anaphylaxis (a severe and life-threatening allergic reaction) and kidney damage.

7. What is the concern regarding gadolinium-based contrast agents?

At this time, only certain patients who receive GBCAs appear to be at an increased risk for developing a serious systemic fibrosing disease, NSF. The patients at risk are those with acute or chronic severe renal (kidney) insufficiency (glomerular filtration rate < 30 mL/min/1.73m²); or renal dysfunction due to the hepato-renal syndrome or in the perioperative liver transplantation period. In the hepato-renal syndrome or in the perioperative liver transplantation period, the risk applies to any severity of renal dysfunction.

A possible association between NSF and GBCAs was first reported in a May 29, 2006, press release from the Danish Medicines Agency (DMA) and the April 2006 report by Grobner et al in *Nephrology, Dialysis and Transplantation* (2006) Vol 21 (4):1104-1108 and following erratum (2006) 21(6): 1745.

Recent publications have provided additional important information implicating a role for GBCAs in the development of NSF among some patients. Researchers have found gadolinium in the tissue of patients with NSF (High et al, *J Am Acad Dermatol* 2007; 56 (1): 21-26). Also, a retrospective study with Omniscan in about 370 patients with severe renal insufficiency estimated the risk of NSF to be 4% (Marckmann et al, *J Am Soc Nephrol* 2006; 17: 2359-2362). A case-control study of the occurrence of nephrogenic fibrosing dermopathy (NFD) indicated that exposure to GBCA was independently associated with NFD (MMWR 2007; 56 (07):137-141).

Together, accumulating data indicate that GBCAs increase the risk for the development of NSF among patients with severe renal insufficiency or renal dysfunction due to the hepato-renal syndrome or in the perioperative liver transplantation period.

8. The information FDA released in December 2006 said that patients with moderate renal insufficiency are at risk for developing NSF. Why has this changed?

The December information was based upon reports of NSF among patients with purportedly moderate renal insufficiency. Since issuing the information in December 2006, FDA has received new information regarding these patients. Additional details have clarified that the patients actually were in acute renal failure at the time they received a GBCA. Considering this clarification, FDA has not received reports of NSF among patients with normal renal function or moderate renal insufficiency.

9. What is Nephrogenic Systemic Fibrosis (NSF)?

NSF was first described in the medical literature in 2000. The first case of NSF was identified in 1997. The cause of NSF is unknown but it has been reported only in patients who have severe kidney disease. NSF causes fibrosis of the skin and connective tissues throughout the body. Patients develop skin thickening that may prevent bending and extending joints, resulting in decreased mobility of joints. NSF usually starts in the lower extremities. Fibrosis can also develop in the diaphragm, muscles in the thigh and lower abdomen, and lung vessels. Over time, NSF becomes worse and can cause death.

10. What is the treatment for NSF?

There is no known treatment for NSF.

Improved renal function (spontaneous or via renal transplantation) appears to slow or arrest NSF and may even result in a gradual reversal of NSF. Other treatments are being tested.

11. How many gadolinium-based contrast agents has FDA approved?

There are five FDA approved GBCAs (Magnevist, MultiHance, Omniscan, OptiMARK, and ProHance).

12. Has NSF been reported with all of the U.S.-approved gadolinium-based contrast agents?

NSF has been reported following administration of all five FDA approved gadolinium-based contrast agents (Magnevist, MultiHance, Omniscan, OptiMARK, and ProHance). However, some adverse event reports of NSF do not include complete information on patients' GBCA exposure history. Also, some reports indicate that some patients received more than one GBCA prior to NSF diagnosis. The lack of complete information of GBCA exposure, exposure to multiple GBCAs, along with similarities in structure and activity of all these contrast agents, make it impossible at present to definitively determine whether the extent of risks for developing NSF is shared by all GBCAs or vary for some of them. Therefore, FDA considers that NSF may occur following the administration of any of the approved GBCAs to certain patients.

13. Do the gadolinium-based contrast agents cause NSF?

Whether the GBCAs are the only agents or conditions that may be associated with NSF in patients with renal disease is unknown. The conclusions that can be drawn from the NSF reports are limited. However, the reports FDA has received, the published report of gadolinium deposits in the skin of patients with NSF/NFD, and other published reports suggest that GBCAs play a role in the development of NSF in patients with acute or chronic severe kidney insufficiency or kidney dysfunction due to the hepato-renal syndrome or in the perioperative liver transplantation period.

14. What actions is FDA taking regarding the new information about gadolinium-based contrast agent administration and the development of NSF/NFD in patients with severe kidney insufficiency or kidney dysfunction due to the hepato-renal syndrome or in the perioperative liver transplantation period?

FDA has requested that the manufacturers of the 5 GBCAs include a new Boxed Warning and new Warnings section in the labels that describe the risks of developing NSF. Additionally, FDA has requested that all manufacturers prospectively collect data on patients with varying degrees of renal insufficiency who are exposed to GBCA to more accurately estimate the magnitude of the risk for NSF for patients with kidney disease.

FDA will continue to evaluate new reports of NSF and may request additional studies and/or labeling changes.

15. What information was known about serious side effects prior to the approval of gadolinium-based contrast agents?

The five U.S. approved GBCAs were approved between 1988 and 2004. In the combined pre-marketing studies for these approved GBCAs, over 3000 patients were studied.

The most common serious side effect from GBCAs is an allergic reaction that is usually mild but is occasionally severe and even results in fatalities. Some patients develop skin conditions, such as rash, sweating, itching, hives, and facial swelling.

GBCAs can be very irritating to the veins into which they are injected, causing irritation of blood vessels and skin and the formation of blood clots.

Very few patients with severely compromised kidney function or those on dialysis have been studied in clinical trials. The labels for GBCAs caution that the risk of toxic reactions may be greater in patients with impaired kidney function because gadolinium is mostly excreted by the kidney.

16. What should patients do with this new information?

If you have severe renal insufficiency (severe kidney disease) and a physician has requested an MRI or MRA study with a contrast agent, ask if the use of the contrast agent is essential. In some situations, an acceptable study can be obtained without the use of contrast. If a GBCA is essential, you and your physician should consider that the dose of the contrast agent should not exceed that recommended in the product's label and that a repeat administration of the contrast agent should not be performed until enough time has passed to allow for the preceding contrast agent to be eliminated from your body.

If administration of a GBCA is essential and you are already receiving hemodialysis, your physician may recommend the performance of hemodialysis shortly following administration of a GBCA. This hemodialysis may help eliminate the GBCA from your body. Whether hemodialysis will help prevent NSF is unknown.

Contact your doctor right away after receiving a GBCA if you get any of these conditions that may indicate the development of NSF:

- **Skin and eyes**
 - Swelling, hardening and tightening of your skin
 - Reddened or darkened patches on the skin
 - Burning or itching of your skin
 - Yellow raised spots on the whites of your eyes

- **Bones and muscles**
 - Stiffness in your joints; problems moving or straightening arms, hands, legs, or feet
 - Pain deep in your hip bones or ribs
 - Muscle weakness

17. What should healthcare providers do in response to this new information?

Physicians should consider the risks and benefits of using GBCAs in patients with acute or chronic severe renal insufficiency (glomerular filtration rate <30 mL/min/1.73m²); renal dysfunction of any severity due to the hepato-renal syndrome or in the perioperative liver transplantation period. In these patients, GBCA should be avoided unless the diagnostic information is essential and not available with non-contrast enhanced MRI.

Additional risk factors that may increase the risk are repeated or higher than recommended doses of a GBCA and the degree of renal impairment at the time of exposure.

For patients already receiving hemodialysis, physicians may consider the prompt initiation of hemodialysis following the administration of a GBCA in order to enhance the contrast agent's elimination. However, the usefulness of hemodialysis in the prevention of NSF is unknown.

Physicians should also report all cases of NSF to the FDA's MedWatch at <http://www.fda.gov/medwatch/>.

18. What additional actions are likely to follow?


FDA may consider other risk management options. FDA will continue to evaluate any new reports of NSF and may request additional clinical studies and/or labeling alterations.

19. Where can I find more information about gadolinium-based agents and about NSF?

The new labels for the GBCAs will include more information about NSF. FDA is requesting that manufacturers make this new labeling change as soon as possible.

More information about NSF can be found at the following website:
<http://www.pathmax.com/dermweb/>.

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