

Gadolinium-associated nephrogenic systemic fibrosis

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The authors explain why physicians should refrain from ordering MRIs for patients with renal dysfunction unless the test is essential to provide diagnostic information. A possibly class-wide toxicity from the contrast agent gadolinium has been reported.

Because of its paramagnetic properties, solutions of organic gadolinium complexes and gadolinium compounds are used as intravenous radiopaque contrast agents to enhance images in medical MRI. Gadolinium is the only US Food and Drug Administration (FDA)-approved MRI contrast agent. A silvery white, malleable, and ductile metal that is relatively stable in dry air, gadolinium is strongly paramagnetic at room temperature and exhibits ferromagnetic properties below room temperature.

Recently, instances of severe gadolinium-associated nephrogenic systemic fibrosis (NSF) have been reported. Many of these reports have included patients with cancer who have undergone surveillance contrast MRI studies. Using published studies and spontaneous reports to the FDA's MedWatch program, investigators at the pharmacovigilance program known as RADAR (Research on Adverse Drug events And Reports) have studied the frequency and clinical characteristics of gadolinium-associated NSF.

The clinical features include fibrosis of the skin and subcutaneous tissue including the underlying muscle, mainly involving the trunk and limbs, but at times also the diaphragm, lungs, and heart. This extremely painful condition makes it difficult for patients to move their joints, leading to an inability to rest and/or perform the normal activities of daily living. The clinical course of NSF is progressive and can be fatal.¹

Between 1988 and 2004, the FDA approved five gadolinium-containing contrast agents:

- Omniscan
- OptiMARK
- Magnevist
- ProHance
- MultiHance.

Although Omniscan is the only agent implicated in the Grobner study,² there are concerns that this signal represents a class effect.

Where reported

To date, the FDA's Adverse Event Reporting System (AERS) database includes 371 cases of NSF among cancer patients undergoing MRI with gadolinium to monitor their disease.

The cancers include bladder, renal, and liver cancers as well as multiple myeloma. Adverse outcomes range from disability to death, with hospitalization, the need for intervention,

Fast Facts

NEPHROGENIC SYSTEMIC FIBROSIS (NSF) was first observed in 1997 and described in 2000 by Shawn E. Cowper, MD. Termed nephrogenic fibrosing dermopathy, the name was later changed to NSF when the systemic nature of the disease became evident. It is theorized that the fibrosis seen in NSF may be related to aberrant circulating fibrocytes (distinct from fibroblasts in that these fibrocytes have CD34/procollagen dual-positive profile and are blood borne). The fibrocytes differentiate into terminal fibroblast-like cells in the presence of gadolinium in the setting of abnormal renal function. Additionally, thrombosis and/or endothelial damage might instigate a cascade of events resulting in NSF.

and life-threatening events in between.

In May 2006, the Danish Medicines Agency (DMA) reported that in a study involving 370 patients who received Omniscan, 13 developed NSF; 400 patients did not receive the contrast agent; none developed the illness. The only risk factor identified by the DMA was a history of renal failure. Additionally, Grobner found a strong link between gadolinium exposure and subsequent onset of NSF in patients with renal insufficiency, with or without acidosis ($n = 13$ patients with NSF; odds ratio of 32.5 for gadolinium exposure).²

Recommendations

Gadolinium appears to be linked to NSF in the setting of underlying renal failure. Long-term observation of all gadolinium contrast agents is needed to further evaluate this signal. In the interim, physicians should use gadolinium in patients with renal dysfunction only if it is essential to

provide diagnostic information. Creatinine levels should be obtained prior to each study, and where the creatinine level is 2.0 or above, clinicians should contemplate using different imaging modalities. Note that in patients older than age 50 years, serum creatinine is an unreliable indicator of renal function. In this age group, glomerular filtration rate (GFR) or creatinine clearance should be the test of choice for assessing renal function.

On May 23, 2007, the FDA requested that additional warnings about the risk of NSF be included with the full prescribing information for all five gadolinium-based contrast agents. This new labeling highlights and describes the risk for NSF following exposure to a gadolinium-based contrast agent in patients with acute or chronic severe renal insufficiency ($\text{GFR} < 30 \text{ mL}/\text{min}/1.73\text{m}^2$) and patients with acute renal insufficiency of any severity secondary to the hepatorenal syndrome or in the perioperative liver transplanta-

tion period.³ Clinicians should watch carefully for this toxicity and report the relevant clinical findings to the FDA's MedWatch program (www.fda.gov/medwatch/) or to Dr. Charles L. Bennett at the RADAR program (cbenne@northwestern.edu).

References

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