In Renal Disease Patients, Think Twice Before MRI

Nephrogenic systemic fibrosis appears to increase with use of contrast agents, especially Omniscan.

BY AMY ROTHMAN SCHONFELD
Contributing Writer

CHICAGO — Radiologic professional associations and governmental regulatory agencies in the United States and Europe are in the midst of grappling with how best to deal with nephrogenic systemic fibrosis, a severe scleroderma-like syndrome that may arise in patients with poor kidney function after receiving gadolinium-based contrast agents administered during magnetic resonance imaging.

This problem necessitates practice changes, including restrictions on contrast magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA) in patients with moderate- to end-stage renal disease, attention to new, stricter screening recommendations, and foregoing sensitive studies that rely on high doses of contrast agents, according to Dr. Emanuel Kanal, who spoke at the American Society of Neuroradiology meeting.

"This has taken the world by storm," said Dr. Kanal, a neuroradiologist at the University of Pittsburgh, who has received hundreds of e-mails from concerned physicians. New developments are occurring almost daily. For instance, on June 22, the American College of Radiology Committees on Drugs and Contrast Media and MR Safety discussed recommendations for screening patients before contrast-enhanced MRI that go beyond verbal questioning.

Although final recommendations have not yet been issued, it is expected that plasma blood screening to assess glomerular filtration rates (GFRs) will be recommended before contrast-enhanced MRI for patients at risk.

Within the same week, on June 26:

► A European regulatory body representing 31 members of the European Union (the European Pharmacovigilance Working Party of the Committee for Medicinal Products for Human Use) added the gadolinium-based contrast agent Magnevist to the list of contraindicated drugs for patients with severe and end-stage renal disease.

► The Chairman of the Commission on Human Medicines in the United Kingdom, Sir Gordon Duff, released a "Dear Colleague" letter with similar content.

► The European Update issued a statement that "a review of the available data does *not* suggest that the risk of NSF in patients with advanced renal impairment is the same for all gadolinium-based contrast agents"—the first time any formal society or agency other than the American College of Radiology has arrived at that conclusion, Dr. Kanal said.

Nephrogenic systemic fibrosis (NSF) is a scleroderma/myxoderma-like condition that causes painful scarring, tightening, thickening, and discoloration of the skin. It also affects the lungs, myocardium, diaphragm, and striated muscle.

NSF can be debilitating and fulminant in about 5% of cases and can lead to immobility and death within weeks to months. There is no known cure, with occasional improvement noted following renal transplantation.

In 2006, Dr. Thomas Grobner, a nephrologist at the General Hospital of Wiener Neustadt, Austria, made the first association between gadolinium and NSF (Nephrol. Dial. Transplant. 2006 Oct. 11;E-pub ahead of print). Since then, more than 240 confirmed cases have been included in a registry maintained by Dr. Shawn Cowper, a dermatopathologist at Yale University, New Haven, Conn., who found that all affected patients had received gadolinium contrast agents within a few months before diagnosis.

Of the over 230 cases of NSF that have been reported to the Food and Drug Administration's MedWatch up until April 17 of this year, 160 were related to Omniscan and 73 to Magnevist, with 3 associated with isolated prior Optimark administration.

Patients with stage III kidney disease or worse shouldn't be routinely given standard doses of gadolinium-based agents.

DR. KANAL

Gadolinium concentrations in the biopsies of NSF patients were 35 to 150 times higher than those found in normal volunteers who received contrast material, Dr. Kanal said. Although the half-life of gadolinium is 70-90 minutes in those with normal renal function, gadolinium has been detected in tissue biopsy specimens of NSF patients as long as 11 months after administration.

Clinical data suggest several associations that impact clinical practice:

► The higher the dose of contrast, the greater the chance of developing NSF.

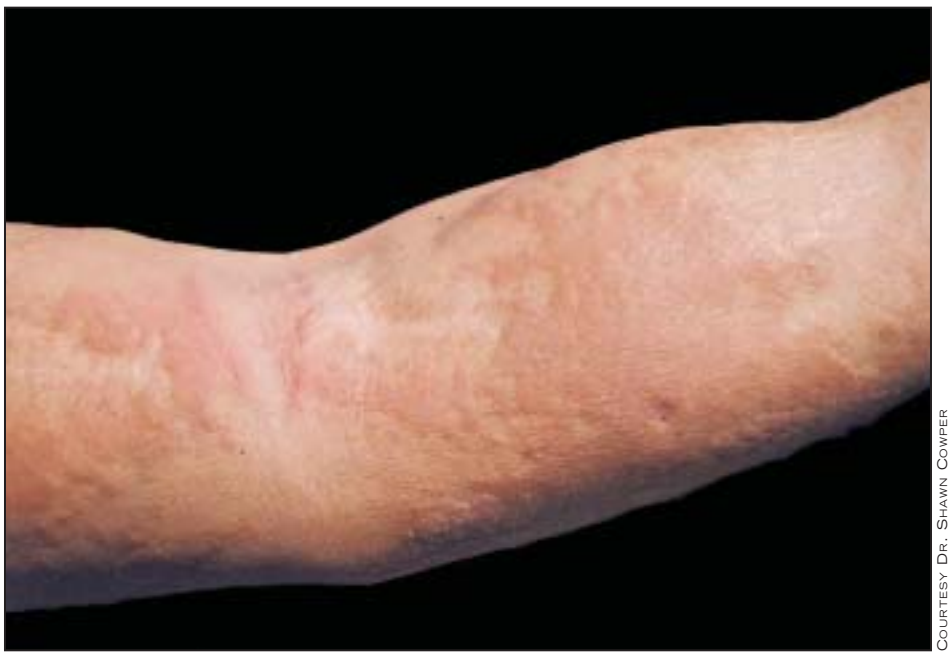
► The greater the severity of renal disease, the greater the chance of developing NSF.

► Cumulative doses of contrast seem to increase the incidence of NSF.

These findings can have a significant impact on clinical practice. For instance, MRI studies that use double or triple doses of contrast, such as contrast dynamic bolus MRA, may no longer be an option for patients with severely impaired renal function. Alternatively, the radiologist may modify the study to minimize the administered dose of gadolinium-based contrast agent.

The spike in NSF cases in recent years is directly related to the more common use of high-dose contrast studies since the proliferation of especially non-neuroradiologic contrast bolus dynamic MR angiography in the mid-1990s, Dr. Kanal suggested.

"With iodinated contrast-related [contrast-induced nephropathy] concerns for CT and NSF-related concerns for gadolinium-based MR contrast agents in MRI, this is becoming a problem for neurologists and other referring physicians, as the number of imaging tests available for patients with severe renal disease that can sensitively evaluate problems is decreasing," he said.



COURTESY DR. SHAWN COWPER

The skin on the arm of a patient with contrast agent–induced nephrogenic systemic fibrosis shows scleroderma-like changes, including scarring (which is usually painful), tightening, thickening, and discoloration. Nephrogenic systemic fibrosis is fulminant in about 5% of cases and can prove to be fatal within weeks.

Patients with stage III kidney disease or worse should not routinely be administered standard doses of gadolinium-based MR contrast agents, he recommended. This can have serious implications for the 35 million U.S. adults over age 65 years who have stage III or IV renal disease, many of whom require access to diagnostic MR services, Dr. Kanal said.

Exacerbating the problem is poor patient awareness of renal disease. According to Dr. Kanal, 97% of women and 82% of men with stage III chronic kidney disease are unaware that they have it. Thus asking patients whether they have renal disease may no longer be a sufficient screening method.

It is anticipated that a subset of patients at risk for renal disease (over age 60 years, history of hypertension, diabetes, renal disease or severe hepatic disease) will be required to have their glomerular filtration rates assessed before receiving gadolinium-based MR contrast agents. Since the risk of NSF may increase with cumulative dosing, neurologists should carefully consider the potential risk of serial contrast-enhanced scans when following patients.

While the FDA has applied black box warnings to all five MR contrast agents available in the United States, "the available data 'screams' that [the risk of NSF] is not equal for all the five FDA-approved MR contrast agents, and appears to be higher or far higher for Omniscan," he said, estimating that roughly 3%-7% of patients with end-stage renal disease receiving high-dose Omniscan will develop NSF.

"In my opinion, the present data are sufficiently compelling to avoid Omniscan administration in patients with any significant level of renal disease," he added.

For gadolinium to be tolerated by humans, it must be chelated to a ligand molecule, he said. The likelihood of the ligand dissociating from the gadolinium ion (leaving the toxic free Gd+3) is far from equal among these five agents, being far greater in Omniscan and Optimark than in Magnevist, Multihance, or Prohance, judging from findings from in vitro and some in vivo studies. Because nonionic Omniscan and Optimark have a far lower conditional stability constant than do Magnevist, Multihance, and Prohance at normal body pH, it is possible that this may be related to the perceived greater incidence of NSF in patients who received Omniscan, Dr. Kanal said.

Elevated levels of calcium, phosphate, copper, iron, and zinc, which can compete with the gadolinium ion for coupling with the ligand molecule, may also exacerbate the risk of toxicity.

"You need a radiologist who knows what she or he is doing in this area to help design the study in a manner that will decrease dosing yet still be as diagnostic as possible. Trust your radiologist and then follow his feedback and guidance," he commented.

If a dialysis patient must have a contrast MRI, the American College of Radiology guidelines recommend that the patient be taken to hemodialysis immediately following the completion of the MR examination in which the gadolinium-based MR contrast agent had been administered. Radiologists should compile a database of all patients with stage III or more severe kidney disease who have had contrast-enhanced MRIs and follow them to ensure that they do not develop NSF, Dr. Kanal recommended.

"It used to be that patients with renal failure would specifically be sent to MR because the contrast agents were not directly nephrotoxic at the doses used, whereas giving iodine to patients with renal disease could cause iodine-induced nephropathy. Now we have something else to worry about for patients with renal disease: NSF," Dr. Kanal said. ■