Nephrogenic Systemic Fibrosis and Gadolinium: A Perfect Storm

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In this issue of the *AJR*, Shellock and Spinazzi [1] review our current knowledge about the nephrogenic systemic fibrosis (NSF) syndrome. The apparent linkage of NSF to exposure to gadolinium-based contrast agents (GBCAs) [2–13] has dramatically affected clinical MRI practice. The associated U.S. Food and Drug Administration (FDA) "boxed warning" [14] advises practitioners of the risks of administering GBCAs to patients with renal failure. What factors [15] led to this unfortunate situation?

Increasing Approved and Nonapproved Applications with Increasing Doses of GBCAs

Nearly 30% of the 31 million annual MR examinations performed in the United States currently include enhancement with GBCAs. Many of these applications are for well-accepted indications not yet approved by the FDA. Such studies are typically performed with increased GBCA dosages, including contrast-enhanced MR angiography and delayed contrast-enhanced myocardial viability examinations.

Perceived Safety of GBCAs in Patients with Renal Dysfunction

Unlike the known risk of contrast-induced nephropathy with iodinated contrast agents, early investigations did not find evidence for renal function deterioration after the administration of GBCAs [16]. Radiologists believed that GBCAs were safe to deliver at any creatinine or estimated glomerular filtration rate (GFR) level. Confidence in the apparent safety of GBCAs in patients with renal dysfunction led to bold off-label applications [17], including the use of gadoterate meglumine (Dotarem, Guerbet), the European GBCA, as an angiographic contrast agent to evaluate malfunctioning hemodialysis fistulas [18]. That study reported no significant worsening of renal function in 15 patients who were not immediately treated with hemodialysis, with 2- and 6-month "monitoring" [18]. Because of this apparent safety, most radiology practices did not require serum creatinine measurements before the administration of GBCAs. This absence of data increased the difficulty in retrospective analysis of the relationship of NSF cases to preexisting renal dysfunction.

Ease of GBCA Application Due to Technologists Administering GBCAs

From 1988 to the mid or late 1990s, most radiology practices required venipuncture and contrast agent administration to be performed by a physician. Policy changes allowed trained technologists to perform venipuncture and contrast agent injection under indirect physician supervision. This freed up physician attention from the physical process of GBCA administration. It became easier to add enhanced protocols to more MR examinations, further increasing GBCA utilization. Radiologists became more isolated from the patient and less aware of potential administrative changes in the specific GBCA brand used in their practice.

Low Acceptability of ProHance (10% Market Share) Because of Perceived Increased Patient Nausea and Vomiting

The FDA approval of gadopentetate dimeglumine (Magnevist, Bayer Schering Pharma, Montville, NJ) for brain and spine image enhancement in 1988 led to its rapid integration into medical practice. Magnevist was well tolerated despite relatively high osmolality and viscosity, and according to all the available information, Magnevist appeared to be safe for general use [19]. A postmarket study of Magnevist involving 15,496 patients

found only 2.4% experienced headache, nausea, or other minor reactions [20].

In 1992, when gadoteridol (ProHance, Bracco Diagnostics, Princeton, NJ) challenged Magnevist as a new FDA-approved MR contrast agent with much lower osmolality and viscosity, there was much enthusiasm in the MR community. It was hoped that competition would reduce the GBCA unit dose price. By all predictions, based on its physical and chemical properties, preapproval safety results, and potential vendor contract linkage to established radiographic contrast agents, ProHance would rapidly establish a substantial market share. It is unfortunate that the initial deliveries of ProHance, including starter samples, were marred by unpredicted clusters of nausea and vomiting. This early clustering of adverse events of unknown origin led to a voluntary (i.e., not mandated by the FDA) withdrawal of a single lot of ProHance in April 1993 [21]. Even given little statistical supporting data [22] and even with data showing similar safety profiles [23, 24], many radiologists with good experiences with Magnevist rapidly lost interest in the perceived nausea risk of ProHance, especially given little or no cost advantage.

Competition with Reduced Pricing for GBCAs

How would users choose among the GBCAs available? This has been a prominent question for market analysis research. Multiple group and teleconference meetings of radiologists and administrators disclosed a key finding: Given adequate safety profiles and equivalent contrast enhancement efficacy, the key market driver is price. The unit dose cost rapidly dropped from the initial price of $135 for a 20-mL vial of Magnevist in 1988 to current prices of $30 for a 15-mL vial. Vendors offered competitive contrast agent contracts with substantial reductions in pricing for large agreements including iodinated and gadolinium-containing agents. Radiologists became more isolated from the choice of contrast agents as vendors presented contracts directly to administrators. This became clear when the link of NSF to GBCAs was initially described because it was noted that the specific contrast agent administered was typically not recorded. Regardless of the actual agent administered, radiologists' MR report templates may state "Post-contrast-enhanced MR images were acquired after the IV administration of Magnevist." On occasion, even authors of peer-review manuscript submissions have confused gadolinium-DTPA (Magnevist) with gadolinium-DTPA-BMA (gadodiamide [Omniscan, GE Healthcare, Chalfont St. Giles, UK]).

Competitive Contracting Giving Omniscan a Larger Market Share (35% Market Share)

When Omniscan was approved by the FDA in 1993 and again when gadoversetamide (OptiMARK, Mallinckrodt Imaging, Hazelwood, MO) was approved in 1999, there was little fanfare. Potential molecular advantages were unimpressive. Omniscan and OptiMARK have substantially lower thermodynamic stability by a factor of 1,000 or more compared with Magnevist or ProHance. This lower stability of Omniscan and OptiMARK was transparent to radiologists until it was noted that Omniscan contains 25–50 times the free-chelating agent as Magnevist or ProHance. The presence of this excessive free-chelating agent in Omniscan and OptiMARK led to apparent transient artifactual lowering of the serum calcium level when the orthocresol phthalein method of measuring serum calcium was used [25–27].

Delay in the Discovery of a Potential Linkage of GBCAs to NSF

Table 1 summarizes the NSF historical timeline. Three years passed from the first observations of NSF in 1997 to the first report in 2000 [28]. There was an additional 6-year delay before the publication of the first correlative reports matching NSF cases to recent GBCA administration in 2006 [2, 3]. Given the results reported by Reilly [29]—no cases of NSF with 198 ProHance administrations in 141 hemodialysis patients, one might speculate that linkage of NSF to GBCAs would have been delayed even more if the market fortunes of ProHance (10%) and Omniscan (35%) had been reversed. Anecdotally, the University of Southern California practices have administered more than 100,000 doses of Magnevist since 1988 with no cases of NSF noted by the nephrology, rheumatology, or dermatology services. It was common to receive referrals for body and vascular MRI based on an elevated creatinine level. A number of intraarterial Magnevist injections were also performed for use as an angiographic contrast agent [17]—still with no cases of NSF. Of course, it is difficult to prove a negative result especially when no prospective data are collected. Even so, given the striking clinical presentation [1, 8], NSF is a permanent condition not easily lost to interested physicians. By comparison, Omniscan users may be less fortunate, as the University of California at Los Angeles experience shows with 13

TABLE 1: MR Contrast Agent and Nephrogenic Systemic Fibrosis (NSF) Timeline

Year	Event
1988	FDA approval for gadopentetate dimeglumine (Magnevist, Bayer Schering Pharma, Montville, NJ); currently 50% market share
1991	ASRT proposes that administration of contrast media is within the scope of practice of radiologic technologists [35]
1992	FDA approval for gadoteridol (ProHance, Bracco Diagnostics, Princeton, NJ); 10% market share
1993	FDA approval for gadodiamide (Omniscan, GE Healthcare, Chalfont St., Giles, UK); 35% market share
1997	First case of NSF identified
1999	FDA approval for gadoversetamide (OptiMARK, Mallinckrodt Imaging, Hazelwood, MO); 5% market share
2000	First report of 15 patients with NSF [28]
2003	GE Healthcare purchases Nycomed/Amersham
2004	FDA approval for gadobenate dimeglumine (MultiHance, Bracco Diagnostics)
2005	GE Healthcare and Novation sign agreement for injectable contrast media
2006	Gadolinium "trigger" proposed for NSF [2, 3]
2007	FDA calls for "boxed warning" for gadolinium-based contrast agents
2008	First lawsuit alleging that "[T]he chemical make-up of Omniscan makes it more likely that gadolinium will become free within the bodies of recipients, thereby making it more likely that kidney patients will develop NSF" [36]

Note—FDA = U.S. Food and Drug Administration, ASRT = American Society of Radiologic Technologists.

cases of NSF identified over a 10-year period in a busy academic practice [30]. Perhaps the rareness of NSF with Magnevist in most clinical settings might lead to complacency; unlike the favorable results of Reilly with ProHance in hemodialysis patients, at the 2007 RSNA meeting, Abujudeh et al. [31] reported Magnevist-associated NSF in 24 patients with chronic kidney disease and on hemodialysis.

The Future of GBCAs and NSF

The extensive publicity surrounding GBCAs, NSF, and the FDA boxed warning has successfully reduced the incidence of GBCA-related NSF. Noncontrast examination protocols are being revisited. Lower-dose MR angiography and myocardial viability protocols are emerging. Omniscan and OptiMARK usage will likely diminish, and the use of ProHance and MultiHance may increase. Radiologists have become reluctant to administer GBCAs to patients with estimated GFRs < 30 mL/min/1.73 m^2. Special caution to avoid the use of GBCAs in patients with combined renal failure and liver dysfunction or with proinflammatory conditions [15] is recommended. When absolutely required, patients on dialysis receiving GBCAs should be followed carefully by nephrologists, likely with dialysis immediately after the MR examination and perhaps again at 12 or 24 hours [31–34]. Most assuredly, attorneys will protect the legal rights of the patients apparently injured by GBCAs. To date, the producers of GBCAs have been targeted. Certainly physicians may also be challenged for adverse outcomes of off-label applications [37]. Careful practice and good fortune will protect our future patients from the storm cloud of NSF.

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The reader's attention is directed to the article pertaining to this commentary, which appears on the preceding pages.