Gadolinium Use in Patients with Kidney Disease: A Cause for Concern

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ABSTRACT

Gadolinium is widely used as a magnetic resonance imaging contrast agent and is considered to have a good overall safety profile. Recently, both renal and extra-renal toxicities have been reported following exposure to gadolinium in patients with underlying kidney disease. Gadolinium-related contrast-induced nephropathy appears to be a risk in patients with advanced kidney disease and especially those with diabetic nephropathy. Even more concerning is the strong association of gadolinium with nephrogenic systemic fibrosis (NSF), a devastating fibrosing disorder of the skin and other systemic organs. Although cause and effect have not been proven for the NSF-gadolinium link, the impaired renal elimination of gadolinium in patients with kidney disease and the instability of gadolinium-chelate binding may expose tissues to toxic free Gd^{3+} and promote this fibrosing disorder. Caution should be exercised when utilizing gadolinium as a contrast agent in patients with advanced CKD or ESRD.

Significant concern over the administration of iodinated radiocontrast to patients with acute and chronic kidney disease exists among nephrologists and radiologists. Not uncommonly, radiologists ask their nephrology colleagues to dialyze end-stage renal disease (ESRD) patients after radiocontrast exposure to "remove the toxic dye." As recently pointed out (1), however, concerns over volume overload and nonrenal tissue toxicity associated with hyper-osmolar or low-osmolar radiocontrast in ESRD patients are generally unfounded. Potential loss of residual renal function in these patients when exposed to radiocontrast is also a concern, but is not a clearly established complication nor is it likely preventable by any means of prophylaxis, including hemodialysis (1,2).

What has become a matter of urgent concern for physicians caring for patients with kidney disease is the recently described association of exposure to magnetic resonance imaging (MRI) contrast agents (gadolinium) with the development of nephrogenic systemic fibrosis (NSF) (3,4). Many nephrologists are unfamiliar with the details of gadolinium as an MR contrast agent. This article will review the basic characteristics of the gadolinium preparations that are currently available for commercial use in the United States, the pharmacokinetics of gadolinium in healthy subjects as well as patients with advanced kidney disease and ESRD, the controversial issue of nephrotoxicity associated with these agents, and finally the newly identified potential association between gadolinium exposure and NSF in patients with kidney disease.

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Gadolinium Characteristics and Pharmacokinetics

Gadolinium (Gd) is a paramagnetic rare earth lanthanoid metallic element with an atomic number of 64 and a molecular weight of 157 Dalton (Da). It has ferromagnetic properties (strongly attracted by a magnet). This quality makes it extremely useful as an intravenous/intra-arterial contrast agent for MRI/MRA to enhance images of various body organs and tissues. As it is a metal, it must be in an ionic form to be soluble in water and allow it to serve as an injectable contrast agent that will distribute throughout the body. However, gadolinium in this free ionic form (Gd^{3+}) is highly toxic and has been shown to precipitate in tissues (liver, lymph nodes, bones), obstruct calcium-ion passage through muscle cells and nerve tissue cells (reducing neuromuscular transmission), and interfere with intracellular enzymes and cell membranes by the process of transmetallation, a phenomenon whereby Gd^{3+} replaces endogenous metals such as zinc and copper (5).

To prevent the deleterious effects of Gd^{3+}, and allow its use in humans, Gd^{3+} needs to be sequestered by nontoxic substances (5). This is achieved by binding Gd^{3+} to another agent, known generically as a "chelate." These chelates are large organic molecules that form a stable complex around the Gd^{3+}, do not readily dissociate in vivo, and thus serve to help make the ion

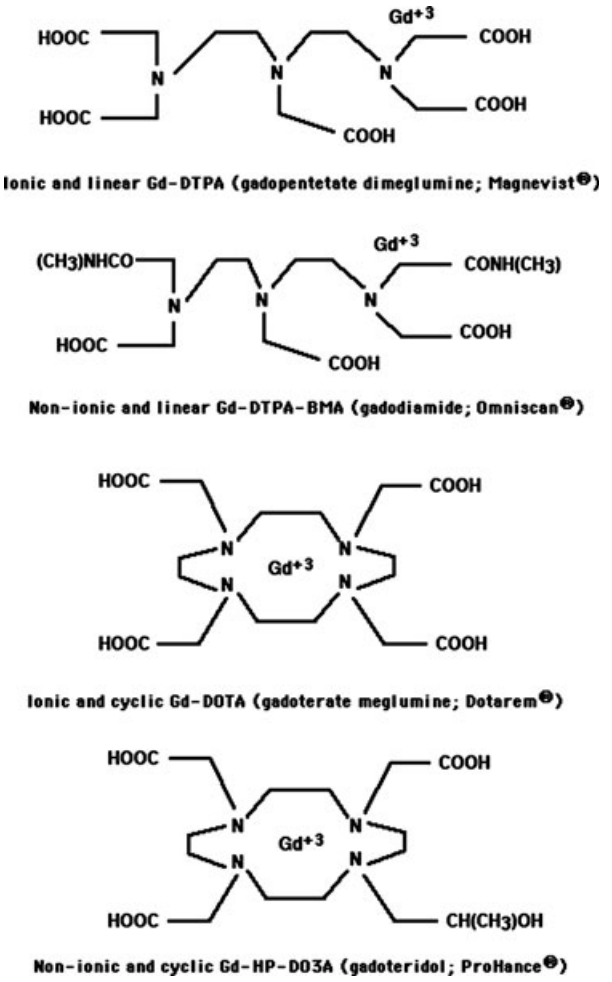

FIG. 1. Molecular structures of some gadolinium chelates commonly used in clinical practice. (With permission, ref (5))

biochemically inert (5,6). These "Gd-chelates" can be classified into four main categories (Fig. 1) based on their biochemical structure (linear versus macrocyclic) and their charge (ionic versus nonionic). Macrocyclic chelates hold Gd^{3+} more tightly than linear chelates, are more stable both in vitro and in vivo, and have lower dissociation rates (7). Despite differences in these physiochemical properties, the currently employed Gd-chelates appear to have similar diagnostic and safety profiles.

The commonly employed Gd-chelates that are Food and Administration Drug (FDA) approved are noted in Table 1. The usual dose of an MR contrast agent for nonvascular studies is 0.1 mmol/kg. When magnetic resonance imaging is needed for vascular structures (MRA), higher doses of 0.3–0.4 mmol/kg are usually required. Until recently, the Gd-chelates were FDA approved only for MRI studies, and typically only at the 0.1 mmol/kg dose. Gadoteridol is the only MR chelate approved at the higher 0.3 mmol/kg dose. Most MRA studies are therefore typically performed using Gd-chelates "off-label," and at dose ranges higher than at original FDA "approved" doses. A new gadolinium contrast formulation, gadofosveset trisodium (Vasovist®; Schering AG, Berlin, Germany) was recently approved by the FDA for use in MRA (8). It binds reversibly to human serum albumin in plasma, thus residing longer in the vasculature than conventional MR contrast agents and extending the time window available for examining the vessels. This property may explain the significantly lower recommended dose of 0.03 mmol/kg (8).

TABLE 1. FDA approved gadolinium contrast agents

Gadolinium formulation	Osmolality (mOsm/kg)	Charge	Molecular structure
Gadopentetate dimeglumine (Magnevist®)	1960	Ionic	Linear
Gadodiamide (Omniscan®)	650	Nonionic	Linear
Gadoteridol (Prohance®)	630	Nonionic	Cyclic
Gadobenate dimeglumine (MultiHance®)	1970	Ionic	Linear
Gadoversetamide (OptiMARK®)	1110	Nonionic	Linear

Most Gd-chelates possess a molecular weight of approximately 500 Da. They have a wide range of plasma osmolalities (630 mOsm/l up to 1970 mOsm/l), which are importantly influenced by charge; nonionic Gd-chelates, such as gadoteridol and gadodiamide have plasma osmolalities of 630 and 650 mOsm/l, respectively, while ionic agents such as gadopentetate dimeglumine and gadoversetamide are extremely hyperosmolar (1960 and 1110 mOsm/l, respectively) (5,6). Following intravenous administration, Gd-chelates are rapidly distributed into the extracellular space, quickly reaching equilibrium between the plasma and interstitial compartments (5,6). They are restricted to the extracellular space and have limited protein binding; however, some Gd-chelates (gadobenate dimeglumine, gadoversetamide) also enter cells such as the hepatocyte.

Commensurate with their essential exclusion from the intracellular compartment, they have small volumes of distribution (V_d), approximately 0.26–0.28 l/kg body weight (5,6). In healthy subjects with normal kidney function, plasma Gd-chelate concentrations are best fit by a two-compartment model (Fig. 2) with rapid equilibration between the plasma and interstitial compartments and a mean terminal half-life ($T_{1/2}$) of 2.0 hours. Gd-chelates do not undergo biotransformation and are eliminated unchanged by the kidneys via glomerular filtration without any contribution from tubular secretion (5,6). Renal clearance of Gd-chelates range from 1.1 to 1.6 ml/minute/kg in individuals with normal renal function (approximating the creatinine clearance). Over 95% of an injected dose is eliminated within 24 hours with $< 3\%$ being eliminated in the feces.

Studies in patients with underlying kidney disease demonstrate the importance of renal clearance in determining the pharmacokinetic profile of Gd-chelates (9). While the V_d for intravenous gadobenate dimeglumine (0.2 mmol/kg) was similar for patients with moderate [creatinine clearance (CrCl), 31–60 ml/minute; $n = 15$] and severe (CrCl, 15–30 ml/minute; $n = 17$) kidney disease, the mean terminal $T_{1/2}$ was longer in the moderate (5.6 hours) and severe (9.2 hours) groups than in healthy subjects (2.0 hours). Mean blood and renal clearance were both much lower in the moderate (56 ml/minute; 47 ml/minute) and severe (31 ml/minute;

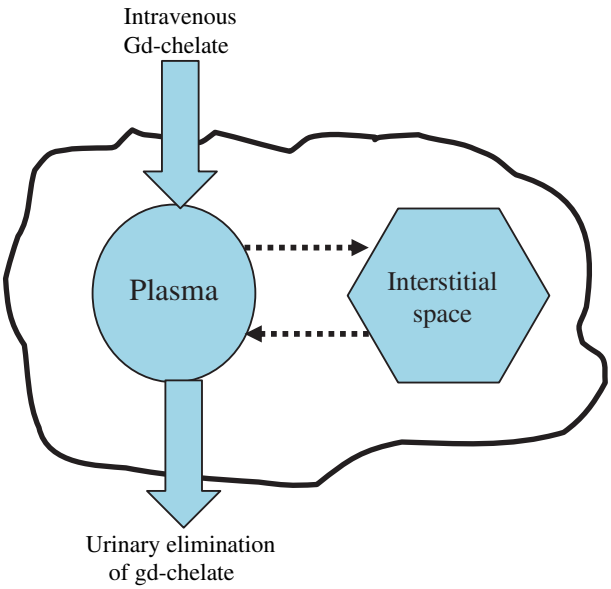

FIG. 1. Kinetics of extracellular gadolinium chelates. Following intravenous administration, Gd-chelates are rapidly equilibrated between the plasma and interstitial space. Elimination from the extracellular space occurs by the kidneys.

22 ml/minute) kidney disease groups than in normal subjects (183 ml/minute; 118 ml/minute). Moderate and severe kidney diseases were also associated with increased mean Gd-chelate recovery in feces (6% and 8%, respectively), suggesting increased fecal excretion in the setting of impaired kidney function. Other studies have reported comparable pharmacokinetics of Gd-chelates in patients with kidney disease (10,11).

In patients with more advanced (stage 5) chronic kidney disease (CKD), the pharmacokinetics of Gd-chelates is further impacted by the limited renal excretion. However, the relatively small molecular weight (500 Da), small V_d (0.28 l/kg), and negligible protein binding make the Gd-chelates ideal for removal with hemodialysis. In one study, the $T_{1/2}$ of Gd-chelates of nondialyzed patients with ESRD was quite prolonged at 34.3 hours but decreased significantly to 2.6 hours in those receiving hemodialysis (12). Peritoneal dialysis was not an effective method of Gd-chelate removal ($T_{1/2}$ of 52.7 hours) (12).

In a more recent study, 13 anuric hemodialysis patients were administered 0.1 mmol/kg of intravenous gadodiamide and underwent dialysis using a synthetic polymer membrane (1.5 m^2 surface area; PSE15NL; Terumo, Tokyo, Japan) within 1–4.5 hours postinfusion. Ten patients were dialyzed for 3 hours and three for 4 hours. The average Gd-chelate elimination from serum was 73.8% with one treatment, 92.4% with 2 treatments, and 98.9% after the third treatment. These data are consistent with Gd-chelate elimination rates with hemodialysis published by others who demonstrated average elimination rates of 98.7% with three treatments and 99.5% with a fourth treatment (13,14). The average $T_{1/2}$ with hemodialysis was 1.9 hours with a mean clearance of 64 ml/minute (13,14).

Gadolinium-Chelate Nephrotoxicity

Over the past 20 years of experience with the use of Gd-chelates for diagnostic imaging, these agents have come to be considered safe and well-tolerated. Adverse reactions to these agents include nausea, vomiting, headache, as well as pain and erythema at injection sites due to thrombophlebitis. Anaphylactoid and allergic reactions, consisting of sweating, rash, hives, itching and facial swelling are less common but nonetheless serious complications. The rate of minor reactions from gadolinium-based contrast media range from 1% to 4%, while serious reactions are extremely uncommon (1/100,000–1/500,000); both are relatively rare compared to what is typically reported for iodine containing contrast-media. While iodine containing contrast-media induced nephrotoxicity is well described and common, the issue of Gd-chelate induced nephrotoxicity is highly controversial, and perhaps overlooked.

As with any new medication or drug that may be used in humans, initial pharmaceutical trials are undertaken to examine potential adverse effects, including nephrotoxicity. Since Gd-chelates have characteristics similar to iodinated radiocontrast, including hyperosmolality and renal clearance entirely dependent upon glomerular filtration, nephrotoxicity was an obvious concern. Early studies in normal subjects as well as small groups of patients with mild to moderate levels of underlying kidney dysfunction suggested a favorable renal safety profile (15,16). Even up until recently, the Gd-chelates were considered relatively safe for use in patients with kidney disease. The importance of this issue deserves emphasis as many patients deemed at high risk for radiocontrast-induced nephropathy (RCIN) from an iodinated contrast study are exposed to a Gd-chelate as a "renal safe" alternative. Our critical review of the literature on this subject does not, unfortunately, allow a definitive answer to the question of Gd nephrotoxicity; however, we will try to shed as much light as possible on the subject by examining pertinent studies performed over the past decade (Table 2).

Three studies suggest that Gd-chelates lack nephrotoxicity. In 1996, a retrospective study (17) examined a cohort of 64 patients with mild CKD (baseline serum creatinine concentration = 2.0 ± 1.4 mg/dl) who received both Gd-chelates and iodinated contrast at separate times and compared the rate of RCIN (as defined by a rise in serum creatinine concentration of 0.5 mg/dl) following each exposure. The dose of Gd-chelates administered ranged from 0.2 to 0.4 mmol/kg. No patient receiving Gd-chelates developed RCIN as compared with 17% of patients receiving iodinated radiocontrast.

Swan et al. (9) prospectively evaluated 32 patients with moderate (CrCl, 31–60 ml/minute) and severe (CrCl, 10–30 ml/minute) kidney disease who received 0.2 mmol/kg of intravenous gadobenate dimeglumine (osmolality 1970 mOsm/l). They monitored 24-hour urine CrCl before and at days 1, 2, 3, 5, and 7 following gadobenate dimeglumine exposure. None of the patients received any contrast prophylaxis maneuvers such as

TABLE 2. Acute kidney injury associated with gadolinium-based contrast exposure

Study (ref)	Study type	Patient no.	RCP	Baseline kidney function	Gado amount (mmol/kg)	AKI from Gado (%)	AKI from Iod RC (%)
(14)	Retro	64	No	sCr = 2.0 mg/dl	0.2–0.4	0	17
(15)	Pros	32	No	CrCl, 10–30 ml/minute; CrCl, 31–60 ml/minute	0.2	0	N/A
(8)	Pros	29	IVF	sCr = 3.6 mg/dl	0.34	0	N/A
(16)	Retro	195	No	sCr = 2.1 mg/dl (IV) sCr = 2.6 mg/dl (IA) CrCl = 60.8 ml/minute (IV) CrCl = 39.6 ml/minute (IA)	0.28	3.5 IV = 1.9 IA = 9.5	N/A
(17)	Pros	21 Gado = 10 IoRC = 11	IVF	eGFR = 34 ml/minute eGFR = 29 ml/minute	0.34–0.9	50% (5/10)	45 (5/11)
(18)	Retro	91	No	Stages 3 and 4 CKD	0.2	Overall = 12.1 Stage 4 = 21	N/A
(19)	Pros*	25	IVF NAC	sCr = 2.3 mg/dl CrCl = 33 ml/minute	0.6 Gd + 0.4 ml/kg of Iod RC	28	6.5*

Gado, gadolinium chelate; IoRc, iodinated radiocontrast; AKI, acute kidney injury; RCP, radiocontrast prophylaxis; sCr, serum creatinine concentration; IVF, intravenous fluids; NAC, *N*-acetylcysteine; IV, intravenous; IA, intra-arterial; N/A, not applicable; CrCl, creatinine clearance; eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease; ref, reference; retro, retrospective; pros, prospective.

*Matched historical control group

intravenous fluid or acetylcysteine. There was no significant change in CrCl at any time point in the study.

Another prospective study examined 29 patients with a mean serum creatinine concentration of 3.6 mg/dl (range: 1.6–7.0) who received 0.34 mmol/kg (range: 0.23–0.44) of gadopenetate dimeglumine (1960 mOsm/l) together with intravenous saline as "contrast prophylaxis"; none of the patients developed RCIN (increase in serum creatinine concentration > 0.5 mg/dl) over 3 days of observation (18). One patient developed acute kidney injury from renal atheroemboli.

In contrast to the prior reports, four other studies suggest that Gd-chelates exhibit variable degrees of nephrotoxicity. Sam et al. (19) published an uncontrolled retrospective study in 2003 that looked at the effect of both intra-arterial ($n = 42$) and intravenous ($n = 153$) Gd-chelate administration on kidney function in patients with underlying CKD. The average dose of high osmolality (1960 mOsm/l) gadopenetate dimeglumine was 0.28 mmol/kg and no contrast prophylaxis was provided. Patients who received intravenous and intra-arterial Gd-chelate had mean baseline serum creatinine concentrations of 2.1 mg/dl (estimated CrCl = 61 ml/minute) and 2.6 mg/dl (estimated CrCl = 40 ml/minute), respectively. They noted that RCIN (increase in serum creatinine concentration > 1.0 mg/dl within 48 hours) developed in 3.5% (7/195) of the entire population: 1.9% (3/153) with intravenous and 9.5% (4/42) with intra-arterial administration. In the seven patients who developed RCIN, the average baseline serum creatinine concentration was 2.5 mg/dl (estimated CrCl = 33 ml/minute); four had diabetes and five hypertension suggesting that these may be risk factors for Gd-chelate related RCIN. Although this study was uncontrolled, the authors felt that the high rate of acute kidney injury seen in this population was evidence for Gd-chelate nephrotoxicity.

In a prospective study, 21 CKD patients (serum creatinine concentration > 1.5 mg/dl; eGFR < 50 ml/minute/m^2) were randomized to either high dose Gd-chelates ($n = 10$, gadobutrol, 1603 mOsm/l, 0.34 to 0.90 mmol/kg) or iohexol ($n = 11$, 820 mOsm/l iodinated contrast) for digital subtraction angiography (20). Patients receiving Gd-chelate had a baseline eGFR of 34 ml/minute and 60% had diabetes while the iohexol group had an eGFR of 29 ml/minute with 36% of the patients having diabetes; both groups received intravenous fluids prior to contrast. RCIN, defined as a 50% decrease in eGFR within 48 hours, developed in 45% of iohexol patients and 50% of gadobutrol patients; none required dialysis.

In a retrospective study, 91 patients with CKD stage 3 ($n = 50$) and 4 ($n = 41$) were examined for RCIN, defined by an increase in serum creatinine concentration of 0.5 mg/dl within 24–72 hours of Gd-chelate exposure (21). The patients received one of three different Gd-chelate preparations (two with high-osmolality, one with low-osmolality) at 0.2 mmol/kg and did not receive contrast prophylaxis. Approximately 20% of patients had diabetes and 80% hypertension. Overall, eleven patients (12.1%) developed RCIN, again suggesting that Gd-chelates can be nephrotoxic; six of these patients had diabetes and nine had stage 4 CKD. The type of Gd-chelate (i.e., high versus low osmolality) administered to the patients who developed RCIN was not noted. No patient required hemodialysis.

Lastly, in an oddly and yet ambitiously designed prospective study in 25 patients with CKD (mean serum creatinine concentration of 2.3 mg/dl) and a matched historical control ($n = 32$), the nephrotoxicity of Gd-chelates administered during cardiac catheterization was assessed (22). All patients received contrast prophylaxis with 0.45% saline and *N*-acetylcysteine. In the Gd-chelate group, they employed a contrast mixture that contained 0.6 mmol/kg of Gd-chelate (either low or high osmolality) and 0.4 ml/kg of iso-osmolar nonionic radiocontrast compared with the same iso-osmolar radiocontrast agent (without Gd-chelate) in the historical control group. The authors argue that

the two contrast protocols are equivalent based on the concept of "X-ray attenuating doses." In the GD-chelate/iso-osmolar contrast group, 28% of patients developed RCIN (increase in serum creatinine concentration of 0.5 mg/dl within 48 hours) as compared with 6.5% in the radiocontrast alone historical control group (22).

Taking all of the above information into account and trying to reach a firm conclusion is difficult. One is left to assimilate data from studies that use variable designs with small numbers, patients with varying levels of kidney function, wide ranges of Gd-chelate osmolality and dose, nonuniform measures of kidney function, erratic use of contrast prophylaxis, and poor controls when present at all. Better studies are sorely needed that at a bare minimum employ adequate numbers of high-risk patients (CKD 3 and 4, diabetic nephropathy) and the use of appropriate contrast prophylaxis (intravenous fluids, *N*-acetylcysteine). That being said, we believe that adequate data exist to suggest that Gd-chelates have enough of a nephrotoxic potential that caution should be exercised in their use in patients with CKD, and possibly even more so in patients with CKD and diabetes. Noncontrast studies (ultrasound, CO_2) may be preferred. If this is not possible, it would seem reasonable to consider some form(s) of contrast prophylaxis in higher-risk patients receiving Gd-chelates. Whether higher doses of Gd-chelates (>0.3–0.4 mmol/kg) or the use of higher osmolality Gd-chelate agents increase the nephrotoxic risk (as is noted when using iodinated radiocontrast agent) is uncertain since the nephrotoxic potential of Gd-chelates at different doses or osmolalities has not been systematically examined. Nevertheless, it still may be prudent to employ the lowest Gd-chelate dose possible to achieve adequate image quality in higher-risk patients. There is no evidence that these maneuvers would be efficacious, but the similarities of Gd-chelate "nephrotoxicity" to that of typical iodine related RCIN makes these suggestions tenable.

Gadolinium-Chelate and Nephrogenic Systemic Fibrosis

Most recently, Gd-chelates have come into the spotlight for both nephrologists and radiologists due to their potential association with NSF. NSF is a devastating disorder involving severe fibrosis, predominantly of the skin with subsequent extensive limitation in mobility and use of extremities. Systemic involvement of the liver, heart, lungs, diaphragm, and skeletal muscle has also been reported with potentially fatal consequences (23,24). The proximate cause of NSF is currently unknown (23).

An important insight into this disorder was recently published by Grobner (3). He observed the development of NSF in five ESRD patients following Gd-chelate exposure, a finding that was confirmed in another 13 ESRD patients (3,4,25). The NFD/NSF registry revealed that all of the 215 patients with available data diagnosed with this condition were exposed to a Gd-chelate at least once prior to the development of NSF (24). NSF has been reported in most European countries including Denmark ($n = 20$), United Kingdom ($n = 16$), Austria ($n = 5$), Belgium ($n = 3$), the Netherlands ($n = 2$), Norway ($n = 1$), Sweden ($n = 1$), and Switzerland ($n = 1$; personal communication, Henrik S. Thomsen, Department of Diagnostic Radiology, Copenhagen University, Copenhagen, Denmark), and an electronic survey by the European Society of Urogenital Radiology (ESUR) confirmed the association of Gd-chelate exposure with subsequent development of NSF (26). Further evidence of the importance of Gd-chelates as a trigger for NSF were provided by documentation of Gd^{3+} within the tissues of 5 patients with NSF using scanning electron microscopy and energy dispersive X-ray spectroscopy (27,28). The authors speculate that phagocytosis of Gd^{3+} retained in tissues by macrophages results in production of profibrotic cytokines that eventuate in dermal and/or systemic fibrosis.

The median time from Gd-chelate exposure and clinical evidence of NSF was 25 days (range: 2–75) (3,4) while the NFD/NSF registry notes Gd-chelate exposure 2–8 weeks before diagnosis of NSF (24). Metabolic acidosis was present in patients who developed NSF in one but not all of the studies (3,4).

In the two reports (total of 18 patients) where the specific MR contrast agent was identified, the Gd-chelate administered was gadodiamide. Care must be taken before gadodiamide is implicated as specifically responsible for NSF since this agent is one of the more commonly used Gd-chelates. In an FDA "Public Health Advisory," other Gd-chelates were associated with the development of NSF (gadopentetate: $n = 6$, and gadoversetamide: $n = 2$), although it is hard to ignore the observation that the overwhelming majority of cases in this report was associated with the use of gadodiamide: $n = 49$ (29).

There appears to be an association with the dose of Gd-chelate utilized to the development of NSF. Recall that a typical nonvascular MRI study uses 0.1 mmol/kg while an MRA requires 0.3 mmol/kg of Gd-chelate. In the five cases reported from Austria, the dose of Gd-chelate was not reported, but all of the patients had received an MRA and thus it is likely that this was in the 0.2–0.3 mmol/kg range (3). In the 13 cases reported from Denmark, the type of study was not reported but the average contrast volume was 18.5 mmol, which would be 0.26 mmol/kg for a 70 kg individual (4). Only one patient received less than a 10 mmol dose (0.14 mmol/kg if 70 kg). These data suggest that the risk of NSF is significantly correlated to the dose of Gd-chelate administered, and patients would therefore be at much higher risk if receiving an MRA as opposed to a typical nonvascular MRI study. While gadofosveset trisodium (Vasovist), the new MRA approved low dose Gd-chelate, can reduce or eliminate the risk of NSF is a question of great interest (8).

Why should Gd-chelates have the potential to trigger the development of NSF? Certainly, reduced renal function increases the $T_{1/2}$ of Gd-chelate considerably as it is slowly excreted by the kidneys (stages 4 and 5 CKD) and it requires three hemodialysis treatments to remove $>95\%$ of the administered dose. Thus, advanced CKD

is associated with prolonged tissue exposure, which may promote deposition of toxic Gd^{3+} leading to fibrosis. In addition, the association of high dose Gd-chelate with an increased risk of developing NSF also supports this hypothesis as higher doses further increase and prolong tissue exposure in the setting of impaired excretion.

Gadodiamide appears to be more commonly associated with NSF than other formulations of Gd-chelate. Gadodiamide is a nonionic, low osmolar contrast agent whose chelate binding to Gd^{3+} is linear and thus less stable. Because of this decreased stability, gadodiamide is more likely to dissociate from its stabilizing chelate moiety than other macrocyclic Gd-chelates. With this consideration in mind, excess chelate (12 mg/ml) is added to the commercial formulations of gadodiamide in an attempt to diminish freely circulating Gd^{3+} with its potential toxicity through transmetallation. (7,22). The increased $T_{1/2}$ of gadodiamide in CKD/ESRD further enhances the chance for transmetallation to occur, perhaps accounting for the apparent association of this type of Gd-chelate with NSF. Another possibility is that the excess chelates present in gadodiamide formulations may be the inciting culprit. The argument to implicate gadodiamide as a specific trigger for NSF is purely speculative and based on incomplete knowledge of the predominant type of gadolinium preparation used in the entire population in which NSF has been reported. Other Gd-chelates have been implicated in the development of NSF (29). Therefore, until more information becomes available, it should not be assumed that gadodiamide is more likely to cause NSF nor that the use of other Gd-chelates will decrease the risk of NSF.

Gd-chelate exposure alone appears to be insufficient to cause NSF. Other cofactors may be required since most patients receiving Gd-chelates appear to be spared this abysmal complication. A number of cofactors (e.g., acidosis, intravenous iron dosing, severe hyperphosphatemia, intravenous erythropoietin) have been suggested, but are hardly confirmed. The vast majority of cases of NSF were in patients receiving hemodialysis, but 10% of the cases were in patients with advanced CKD (eGFR < 30 ml/minute) not receiving chronic renal replacement therapy. For the time being, it would seem reasonable to avoid administration of all Gd-chelates to patients with ESRD and those with CKD 4 or 5 not receiving dialysis. This recommendation is even stronger when considering an MRA in this population as the higher contrast dose required appears to significantly increase the risk of NSF. Alternative imaging modalities should be employed in these patients whenever possible, including studies using iodinated radiocontrast.

In patients with advanced CKD not on dialysis the decision as to whether to use Gd-chelates is more difficult. The risk of NSF is likely less, but the risk of nephrotoxicity from iodinated radiocontrast (well documented) and Gd-chelates (less certain) is higher. Since the latter is potentially reversible while NSF is not, using iodinated radiocontrast may be a better choice in this group of patients. If an MR study with contrast (especially MRA) were felt to be absolutely necessary in a patient with ESRD or CKD 4 or 5 not on dialysis, we would suggest the lowest possible dose of Gd-chelate and if feasible, consider using a Gd-chelate other than gadodiamide. Also, until further data are available on this topic, it would seem prudent to perform hemodialysis both immediately following, and again the day after, the MR study to accelerate Gd-chelate elimination, in patients already receiving hemodialysis. This maneuver should also be considered for patients receiving a high-dose of a Gd-chelate (MRA) in whom advanced CKD (e.g., stage 5) is present but who are not already receiving chronic dialysis at the time of the study. This is obviously an extremely inconvenient strategy, but this aggressive approach underscores the concern over, and uncertainty surrounding, the development of this frightening condition.

In conclusion, Gd-chelates should no longer be assumed to be the safe contrast agents we have typically considered them. Renal and extra-renal toxicity may occur, especially in those with advanced renal disease. They appear to have nephrotoxic potential when used in patients with advanced CKD and diabetic nephropathy. Of graver concern is the potential for developing NSF following Gd-chelate exposure, particularly gadodiamide. Patients with advanced CKD (eGFR < 20 ml/minute) and those with ESRD on dialysis are at highest risk. Although the Gd-chelate—NSF link is based purely on associative data at this point and cause and effect have not been proven, we feel that avoidance is the best prevention and strongly recommended if possible.

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Addendum

Since completion of this article, two relevant reports of the association of gadolinium to NSF have been published Broome and colleagues reported 12 cases of NSF within their institution from 2000–2006 (1). Eight of the twelve patients had ESRD and 4 had acute kidney injury secondary to the hepatorenal syndrome (with 2 of those 4 being on dialysis at the time of MR study). Each of the twelve patients had received gadodiamide, although that is the only Gd-chelate used at their institution. The gadodiamide was administered at "double dose " (0.2 mmol/kg) in each of the patients in whom NSF later developed. During the six-year time frame of the report, there were 559 MRI examinations (301 with gadolinium and 258 without) performed on 168 patients receiving dialysis. Since there were no cases of NSF in the patients receiving an MR study without gadolinium, the odds ratio for gadolinium causing NSF was 22.3. Of the 301 MR studies utilizing gadolinium, 207 were done at a dose of 0.2 mmol/kg while the remaining 94 received 0.1 mmol/kg. Since none of the cases of NSF were in patients receiving 0.1 mmol/l of gadolinium, the odds ratio developing NSFwith the higher dose of gadolinium was 12.1.

Khurana et al reported 6 cases of NSF (biopsy proven) identified at their institution over the past 4 years following exposure to gadodiamide, the only gadolinium formulation used during that time period (2). Five of the patients had advanced kidney dysfunction that eventually required renal replacement therapy (initiation ranged from 1 day before to 37 days after gadodiamide exposure). Onset of NSF symptoms was between 19 days and 2 months after exposure to gadodiamide. The dose of gadodiamide ranged from 0.11 to 0.36 mmol/kg;g, no other potential triggers were identified.

We believe these reports significantly strengthen the association of gadolinium, especially when administered in the higher dose ranges, to the development of NSF. Even though gadodiamide was the only Gd-chelate used at these institutions, we believe this report gives credence to the specific association of gadodiamide to NSF.

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