

Current Status of Gadolinium Toxicity in Patients with Kidney Disease

Mark A. Perazella

Department of Medicine, Section of Nephrology, Yale University School of Medicine, New Haven, Connecticut

Gadolinium-based contrast (GBC) agents have recently been the subject of intense interest for physicians across numerous specialties. These agents are widely used as contrast for magnetic resonance imaging and have been generally considered safe. Early on, phase III trials and small studies in low-risk patients suggested a benign renal profile; however, more recent studies raised the possibility of nephrotoxicity, although it is not clear whether it approaches the incidence of nephropathy associated with iodinated radiocontrast. In 2006, reports of a rare systemic fibrosing condition called nephrogenic systemic fibrosis (NSF) were recently linked to exposure of patients with advanced kidney disease to GBC agents. Analysis of the data suggests that certain GBC agents are more likely to be associated with NSF. Also, not all patients with kidney disease are at risk for developing NSF, only those with advanced acute or chronic kidney disease. Avoidance of GBC exposure is the best approach for high-risk patients. When GBC is required to obtain optimal images, use of low dosages of more stable macrocyclic agents is safer and preferred. This article reviews the current status of GBC agents as nephrotoxins and causes of NSF and provides opinions on how to use these agents in patients with underlying kidney disease.

Clin J Am Soc Nephrol 4: 461–469, 2009. doi: 10.2215/CJN.06011108

Magnetic resonance imaging (MRI) scans are significantly enhanced by use of gadolinium-based contrast (GBC) agents. They also have the advantage of avoiding iodinated radiocontrast agents, which have significant overall toxicity. Thus, imaging with GBC agents has been considered a relatively safe alternative to computed tomography scan in situations in which a radiocontrast agent is thought to be required for enhanced image attainment; however, two complications of GBC agents have come to light.

First, concern for GBC-associated nephrotoxicity has been raised as a potential problem in patients with underlying kidney disease. Second and potentially more concerning is the recognition that GBC exposure in patients with advanced kidney disease may trigger the development of nephrogenic systemic fibrosis (NSF) (1–12). This review focuses on the current status of these clinically important complications of GBC agents.

GBC Agents

General Properties

Gadolinium is a lanthanide metal with paramagnetic properties, which makes it an excellent intravenous and/or intra-arterial contrast agent to improve imaging of various tissues. Because it is a metal, it must be in an ionic form to be soluble in water and allow it to be injected as a contrast agent; however,

gadolinium in this free ionic form (Gd^{3+}) is highly toxic in humans.

The toxic effects of Gd^{3+} are circumvented by sequestration of the metal by a “chelate” (13). Chelates are large organic molecules that form a stable complex with Gd^{3+} and make the ion biochemically inert and nontoxic (13,14). The GBC agents are classified into four main categories on the basis of their biochemical structure (linear *versus* macrocyclic) and their charge (ionic *versus* nonionic; Figure 1). Macrocyclic chelates bind Gd^{3+} more tightly than linear chelates, tend to be more stable both *in vitro* and *in vivo*, and possess lower dissociation rates (15). The various properties of the chelates have implications for possible toxicity and the risk for liberation of free Gd^{3+} from its chelate, a process known as transmetallation (Figure 2). The characteristics of the commonly used Food and Administration Drug (FDA) approved GBC agents and iodinated radiocontrast agents are noted in Table 1.

Pharmacokinetics

After injection, GBC agents are rapidly distributed into the extracellular space, quickly equilibrating between the plasma and interstitial compartments. They have limited protein binding and do not undergo biotransformation. These agents have small volumes of distribution, approximately 0.3 L/kg body wt. They are eliminated unchanged by the kidneys *via* glomerular filtration. GBC agents maintain a mean terminal half-life ($T_{1/2}$) of approximately 1.3 to 1.6 h. More than 95% of an injected dose is eliminated within 24 h, with <3% being eliminated in the feces (13,14,16). The mean terminal $T_{1/2}$ is prolonged in moderate (5.6 h) and severe (9.2 h; up to 30 h with GFR <5 ml/min) kidney disease as compared with healthy individuals (1.3 to 1.6 h).

Published online ahead of print. Publication date available at www.cjasn.org.

Correspondence: Dr. Mark A. Perazella, Department of Medicine, Section of Nephrology, Department of Medicine, Yale University School of Medicine, New Haven, CT 06520-8029. Phone: 203-785-4184; Fax: 203-785-7068; E-mail: mark.perazella@yale.edu

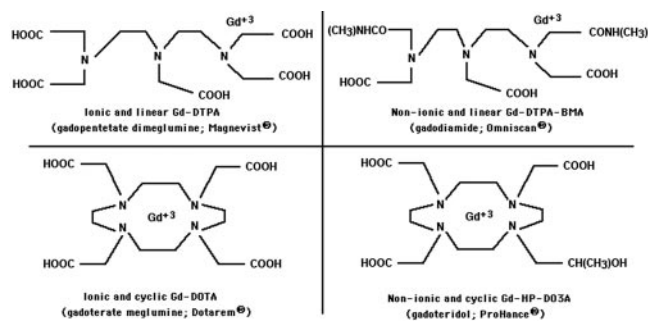


Figure 1. Structures of various GBC agents. The agents vary on the basis of linear *versus* macrocyclic structure and ionic *versus* nonionic charge.

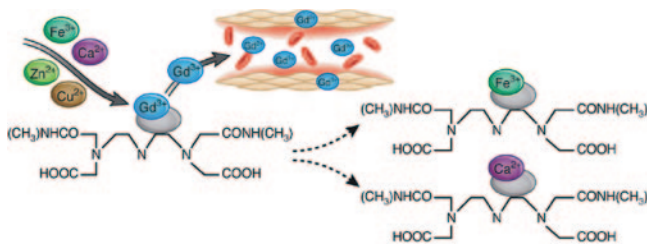


Figure 2. The process of transmetallation. A nonionic linear chelate binds Gd^{3+} less tightly than other chelates, allowing endogenous cations such as copper (Cu^{2+}), iron (Fe^{3+}), zinc (Zn^{2+}), and calcium (Ca^{2+}) to compete with Gd^{3+} for chelate binding. This allows free Gd^{3+} to be released into the circulation, where it may bind other anions such as phosphate.

GBC Agents and Nephrotoxicity

Iodinated radiocontrast media–induced nephrotoxicity is well described and common in at-risk populations. Radiocontrast-induced nephrotoxicity is associated with significant morbidity, increased hospital length of stay, and increased in-hospital 1- and 5-yr mortality. Because GBC agents have characteristics very similar to those of iodinated radiocontrast

(Table 1), in particular hyperosmolality and renal clearance entirely dependent on glomerular filtration, nephrotoxicity was an obvious initial concern. However, GBC agents have significantly lower viscosity and are used at significantly lower volumes (four to 11 times less) than radiocontrast, making them potentially less nephrotoxic. For example, a typical body computed tomography scan uses 150 ml of radiocontrast, whereas a typical MRI study (0.1 to 0.3 mmol/kg) uses 14 to 42 ml of GBC. Thus, the possibility exists that GBC agents could be either similarly nephrotoxic or less nephrotoxic than radiocontrast. As a frame of reference, the nephrotoxicity of GBC agents is compared with that of iodinated radiocontrast agents.

Experimental Studies

GBC agent safety studies using multiple different animals were undertaken using a range of dosages (0.6 to 3.0 mmol/kg). Compared with human dosages, those used in animals ranged from large (0.6 to 1.0 mmol/kg) to massive (1.0 to 3.0 mmol/kg) (17). Minimal increases in blood urea nitrogen and serum creatinine were noted, whereas mild elevations in urinary tubular cell enzymes occurred in exposed animals. When nephrotoxicity developed, it occurred only with high dosages (>1.0 mmol/kg). Histopathology demonstrated vacuolization and necrosis of cortical tubular epithelial cells.

Human Studies

Early studies in healthy individuals as well as patients with mild/moderate levels of underlying kidney disease suggested a favorable renal safety profile (18,19). As a result, the GBC agents were considered relatively safe for use in patients with kidney disease. This led to the frequent use of GBC exposure as a “renal safe” alternative when other imaging techniques were too risky.

Absence of Significant Nephrotoxicity with GBC Agents

As noted in Table 2, several studies suggested that GBC agents lack significant nephrotoxicity (16,18,20–24). Only a few

Table 1. FDA-approved GBC agents and iodinated radiocontrast agents^a

Agent	Molecular Structure	Charge	Osmolality (mOsm/L)	Viscosity (mPa · S)	Stability Constant	Excess Chelate (mg/ml)
GBC formulation						
gadodiamide (Omniscan)	Linear	Nonionic	900	1.4	$10^{14.9}$	12.00
gadopentetate (Magnevist)	Linear	Ionic	1960	2.9	$10^{18.1}$	0.40
gadoversetamide (OptiMARK)	Linear	Nonionic	1110	2.0	$10^{15.0}$	28.40
gadobenate (MultiHance)	Linear	Ionic	1970	5.3	$10^{18.4}$	0.10
gadoteridol (ProHance)	Cyclic	Nonionic	630	1.3	$10^{17.1}$	0.23
Iodinated contrast						
diatrizoate	Monomer	Ionic	1980	6.0	N/A	N/A
iopamidol, iohexol	Monomer	Nonionic	600 to 1000	5.0 to 10.0	N/A	N/A
iodixanol	Dimer	Nonionic	280	11.0	N/A	N/A
iosmenol	Dimer	Nonionic	280	7.0	N/A	N/A

^aFDA, Food and Drug Administration; GBC, gadolinium-based contrast.

Table 2. Studies supporting renal safety of GBC agents^a

Reference	Study	Contrast Agent	Dosage (mmol/kg)	Renal Function ([Cr] in mg/dl)	Result
Niendorf <i>et al.</i> (18), 1993	Phase III trial, <i>n</i> = 1171 [Cr] at 24 h, subgroup with [Cr] at 5 d	Gadopentetate	0.10	[Cr] <1.3, [Cr] >1.3 to 1.4, [Cr] >1.4	No change in [Cr], Subgroup of patients: GFR 20 to 40: [Cr] ↑ 0.25 GFR <20: [Cr] ↑ 0.25
Arsenault <i>et al.</i> (20), 1996	Retrospective, <i>n</i> = 136, <i>n</i> = 90 with pre/post [Cr] at 3 d	Gadopentetate	0.10	[Cr] >2.0, mean [Cr] 2.5	No change in [Cr] baseline (2.5) to day 3 (2.3)
Prince <i>et al.</i> (21), 1996	Retrospective, <i>n</i> = 64, [Cr] 2 d pre and 2 d post, CIN ≥0.5 mg/dl	Gadopentetate, gadodiamide, gadoteridol	0.20 to 0.40	[Cr] >1.5, mean [Cr] 2.0 ± 1.4	CIN: RC- 11/64 (17%) Gado- 0/64 (0%)
Swan <i>et al.</i> (16), 1999	Prospective, double-blind random, 32 patients (2:1), CIN >0.5 mg/dl	Gabobenate dimeglumine	0.20	CrCl 10 to 30, CrCl 31 to 60, 24-h urine	No CIN
Hammer <i>et al.</i> (22), 1999	<i>n</i> = 31, 34 DSAs, mean age 53.1, CIN >0.5 mg/dl	Gadopentetate	0.40	[Cr] >1.5	CIN: 1/34 (3%)
Spinosa <i>et al.</i> (23), 2000	<i>n</i> = 40, LE angiograms, 42 procedures RC- 15, Gado- 20 CIN ≥0.5 mg/dl at 48 h	Gadodiamide	up to 0.40	[Cr] >1.5, mean [Cr] 2.2, range [Cr] 1.6 to 3.6	RC- 6/15 (40%) GBC- 1/20 (5%)
Spinosa <i>et al.</i> (24), 2001	Consecutive patients treated with Gado + CO ₂ , CIN > 0.5 mg/dl at 48 h	Gadodiamide	<0.30	[Cr] >1.5, mean [Cr] 2.7	CIN: 3/95 (3%)
Sancak <i>et al.</i> (25), 2001	<i>n</i> = 16, intravenous Gado for upper extremity or SVC	Gadodiamide	0.30	Mean [Cr] 1.5, range [Cr] 1.2 to 1.8	Largest increase in [Cr] 0.2 mg/dl
Rieger <i>et al.</i> (26), 2002	Prospective, <i>n</i> = 29, 32 procedures (IA and intravenous) CIN >0.5 mg/dl at 72 h	Gadopentetate	0.34 ± 0.06	[Cr] >1.5, mean [Cr] 3.6	AKI: 1/29 (atheroemboli)
Total	N/A	N/A	Average dosage ~0.26 (0.10 to 0.40)	Average mean [Cr] ~2.36; range 1.2 to 3.6	CIN: GBC: 0 to 5% RC: 17 to 40%

^aCIN, contrast-induced nephropathy; [Cr], serum creatinine concentration; CrCl, creatinine clearance; RC, iodinated radiocontrast; DSA, digital subtraction angiogram; IA, intra-arterial; LE, lower extremity; SVC, superior vena cava.

key studies are discussed in the text. In a phase III trial, 1171 patients were exposed to a 0.1-mmol/kg dose of high osmolar (1960 mOsm/L)/low viscosity (2.9 mPa · S) gadopentetate (18). Patients were grouped according to serum creatinine (<1.3, 1.3 to 1.4, or >1.4 mg/dl) and change in serum creatinine 24 h after GBC agent exposure was examined. No significant change in serum creatinine developed in the three groups. Two small subgroups of high-risk patients with more severe kidney disease (GFR 20 to 40 ml/min [*n* = 10] and GFR <20 ml/min [*n* =

5]) were also evaluated. These groups developed a mean increase in serum creatinine of 0.25 mg/dl at 5 d.

Arsenault *et al.* (20) reviewed 90 of 136 patients who had a mean serum creatinine of 2.5 mg/dl, were exposed to 0.1 mmol/kg gadopentetate, and had pre/post serum creatinine measurements. Day 3 serum creatinine was unchanged (2.5→2.3 mg/dl), suggesting absence of nephrotoxicity. In another study, a cohort of 64 patients with mild chronic kidney disease (CKD; baseline serum creatinine 2.0 ± 1.4 mg/dl) were

examined (21). All patients received both GBC and iodinated radiocontrast at separate times, thereby serving as their own control. The rate of contrast-induced nephrotoxicity, as defined by a rise in serum creatinine of 0.5 mg/dl, was compared between the two different exposures. The dosage of GBC agents administered during the study ranged from 0.2 to 0.4 mmol/kg. No patient who received GBC developed nephrotoxicity as compared with 17% of patients who received iodinated radiocontrast.

Patients with CKD (mean serum creatinine 2.2 mg/dl; range 1.6 to 3.6 mg/dl) were studied to compare nephrotoxicity of nonionic radiocontrast with CO₂ supplemented with either GBC (up to 0.4 mmol/kg gadodiamide) or nonionic radiocontrast (23). Forty patients underwent 42 lower extremity angiograms using one of the following contrast protocols: Radiocontrast, gadodiamide, and CO₂. Contrast-induced nephropathy (increase in serum creatinine >0.5 mg/dl at 48 h) developed in six (40%) of 15 iodinated radiocontrast studies but only one (5%) of 20 gadodiamide exposures.

Last, 29 patients who had stage 4 CKD (mean serum creatinine 3.6 mg/dl; range 1.6 to 7.0 mg/dl) and received 0.34 mmol/kg gadopentetate were prospectively studied (26). None of the patients developed GBC nephrotoxicity (increase in serum creatinine >0.5 mg/dl) during 3 d of observation. There was no change from baseline mean serum creatinine at 24 and 72 h. One patient developed acute kidney injury (AKI); however, this was attributed to renal atheroemboli.

It is notable that GBC-associated nephrotoxicity developed in 0 to 5% of patients, which was less than iodinated radiocontrast (17 and 40%). The mean baseline serum creatinine in the group was approximately 2.36 mg/dl (range 1.20 to 3.60 mg/dl), and the mean dosage of GBC agent was 0.26 mmol/kg (range 0.10 to 0.40 mmol/kg). Predominantly, intravenous injection of GBC agents was used.

Presence of Nephrotoxicity with GBC Agents

In contrast to the previous reports, a number of studies (27–31) suggested that GBC agents exhibit variable degrees of nephrotoxicity (Table 3). A retrospective study examined the effect of gadopentetate on kidney function in 260 patients, 195 of whom had underlying CKD (27). The average dosage of gadopentetate was 0.28 mmol/kg. Patients who had CKD and received intravenous and intra-arterial gadopentetate had mean baseline serum creatinine of 2.1 and 2.6 mg/dl, respectively. Contrast-induced AKI (increase in serum creatinine >1.0 mg/dl within 48 h) developed in 3.5% of the entire population: 1.9% (three of 153) with intravenous and 9.5% (four of 42) with intra-arterial administration. In the seven patients who developed nephrotoxicity, the average baseline serum creatinine was 2.5 mg/dl; four had diabetes, and five had hypertension. In patients who did not develop AKI, the average baseline serum creatinine was 2.2 mg/dl. Also, the GBC agent dosage was higher in patients with AKI (0.37 mmol/kg) than without AKI (0.27 mmol/kg).

A retrospective study examined 91 patients with stages 3 and 4 CKD for contrast nephrotoxicity (increase in serum creatinine of 0.5 mg/dl within 24 to 72 h) (29). The patients received one

of three different GBC preparations (0.2 mmol/kg). Approximately 20% of patients had diabetes and 80% had hypertension. Eleven (12.1%) patients developed AKI, again suggesting that GBC agents can be nephrotoxic. Six of these patients had diabetes, and nine had stage 4 CKD.

Finally, a retrospective study of 163 patients who had CKD and underwent percutaneous renal angiogram for resistant hypertension or ischemic nephropathy compared the rates of contrast-induced AKI among GBC, a mixture of GBC/iodinated radiocontrast, and iodinated radiocontrast alone (31). The majority (81%) of patients had stage 4 CKD. Contrast-induced AKI was defined as an increase in serum creatinine of 0.5 mg/dl within 7 d of the procedure. The groups were well matched with respect to age, diabetes, and hypertension. The baseline estimated creatinine clearance was lower in the GBC agent groups (23.1 ml/min) as compared with the radiocontrast alone group (27.5 ml/min). The GBC group was exposed to a lower dosage of GBC (76 ml) as compared with radiocontrast alone group (102 ml). AKI developed in 5.3% of GBC agent-exposed patients compared with 10.5% in the GBC/radiocontrast group and 20.6% in the radiocontrast alone group ($P < 0.01$).

Table 3 summarizes all of the studies. It is notable that GBC-associated nephrotoxicity developed in 5.3 to 50% of patients, which was equal to or greater than the rate seen with iodinated radiocontrast (6.5 to 45%). The mean baseline serum creatinine in the GBC group was approximately 3.02 mg/dl (range 2.60 to 4.00 mg/dl), and the mean dosage of GBC agent was 0.41 mmol/kg (range 0.20 to 0.60 mmol/kg). In addition, the majority of studies used arterial injection of GBC.

GBC Nephrotoxicity: What Is the Bottom Line?

Data from the studies suffer from use of variable designs with small numbers, patients with varying levels of kidney function, wide ranges of GBC agent dosage, nonuniform measures of kidney function, and poor or no control groups. In general, the majority of studies suggested renal safety, but clearly GBC-induced nephrotoxicity can develop. On balance, it seems that GBC agents are less nephrotoxic than iodinated radiocontrast. This may be due to the lower viscosity of these

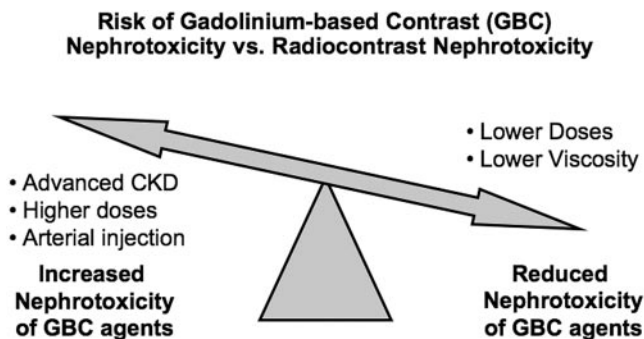


Figure 3. On the basis of the published literature, GBC is less nephrotoxic than iodinated radiocontrast; however, when GBC agents are used in high dosage with arterial injection in patients with advanced kidney disease, AKI can occur.

Table 3. Studies supporting nephrotoxicity of GBC agents^a

Reference	Study	Contrast Agent	Dosage (mmol/kg)	Renal Function ([Cr] in mg/dl)	Result
Sam <i>et al.</i> (27), 2003	<i>n</i> = 195 with CKD, no control group CIN >1.0 mg/d at 48 h with oligoanuria	Gadopentetate	0.28	CrCl <80 ml/min, CG 38.2 ± 16 ml/min, mean [Cr] 2.6	CIN: 7/195, MRA: 3/153 (1.9%), DSA: 4/42 (9.5%)
Erley <i>et al.</i> (28), 2004	Randomized prospective, <i>n</i> = 21, CIN >50%, decrease in GFR	Gadobutrol = 10 Iohexol = 11	0.57 ± 0.17	[Cr] >1.5 or CrCl <50 ml/min per 1.73 m ² , mean [Cr] 3.4	CIN: GBC: 5/10 (50%) RC: 5/11 (45%)
Briguori <i>et al.</i> (30), 2006	Retrospective, <i>n</i> = 25 (historical controls, <i>n</i> = 32), CIN ≥0.5 mg/dl within 48 h or dialysis within 5 d	Gadodiamide = 8 Gadobutrol = 17 3:1 mixture with RC	0.60 ± 0.30 0.28 to 1.23	[Cr] >2 mg/dl or CrCl <40 ml/min, mean [Cr] 2.3	CIN: GBC: 7/25 (28%); RC: 2/32 (6.5%)
Ergun <i>et al.</i> (29), 2006	Retrospective, <i>n</i> = 91, [Cr] measured pre-GBC, days 1, 3, and 7, and 1 mo, CIN ≥0.5 mg/dl within 72 h	Gadopentetate, gadodiamide, dotarem	0.20	Stages 3 and 4 CKD mean [Cr] 33 ml/min, range CrCl 15 to 58, mean [Cr] 4.0	CIN: 11/91 (12.1%); CKD Stage 4: 9/11 with CIN
Kane <i>et al.</i> (31), 2008	Retrospective, <i>n</i> = 163, [Cr] measured pre-GBC and within 7 d, CIN ≥0.5 mg/dl within 7 d	GBC agent, GBC + RC mixture, RC alone	GBC-76 ml, GBC + RC mixture-55 + 37 ml, RC-102 ml	Stages 3 to 5 CKD GBC [Cr] 2.77, GBC + RC [Cr] 2.63, RC [Cr] 2.48	CIN: GBC: 5.3% GBC + RC: 10.5%; RC: 20.6%
Total	N/A	N/A	Average dosage ~0.41 (0.20 to 0.60)	Average mean [Cr] ~3.02, range 2.60 to 4.00	CIN: GBC: 5.3 to 50.0%; RC: 6.5 to 45.0%

^aMRA, magnetic resonance angiography.

agents as well as the much lower volume of contrast required for imaging. That being said, there seem to be adequate data to suggest that GBC agents have enough of a nephrotoxic potential that caution should be exercised with their use in patients with stages 4 and 5 CKD. Higher dosages of GBC agents and intra-arterial injection also are likely risk factors for development of AKI in at-risk patients (Figure 3).

GBC and Nephrogenic Systemic Fibrosis

Nephrogenic Systemic Fibrosis: A New Disease

A previously unrecognized fibrosing disorder of the skin that was histologically similar to scleromyxedema was noted in nine renal transplant recipients who required long-term dialysis, five patients with ESRD, and one patient with AKI (7). After a publication describing the cases, the disease was initially called

a “scleromyxedema-like disorder of renal dialysis patients.” In a subsequent publication, the entity was descriptively coined “nephrogenic fibrosing dermatopathy” (7). The subsequent recognition that fibrosis also occurred in systemic organs led to a new name for the disease: “Nephrogenic systemic fibrosis” (NSF).

GBC Agents: The NSF Trigger?

After the initial report of cases, the NSF literature consisted predominantly of case reports/case series with the cause being ascribed to any of a number of potential agents or associations. In 2006, a major breakthrough occurred when Grobner (2) reported the development of NSF in five patients who had ESRD and were exposed to gadodiamide. Subsequently, Marckmann *et al.* (3) described 13 patients (ESRD and stage 5

CKD) who developed symptoms of NSF within 2 to 75 d after gadodiamide exposure. A number of publications have verified this association (4,5,32–35). Table 4 demonstrates the odds ratio for developing NSF in exposed *versus* unexposed patients with ESRD/CKD from five case-control studies (4,32,35–37).

Evidence to Incriminate GBC Agents in NSF

Further evidence of the importance of GBC agents as a trigger for NSF was provided by documentation of Gd^{3+} within the tissues of patients with NSF using scanning electron microscopy and energy dispersive x-ray spectroscopy (38,39). High *et al.* (40) also quantified the concentration of Gd^{3+} in tissues of the patients who had NSF and were previously examined. They found that the NSF tissues contained 35- to 150-fold higher amounts than the tissues of healthy individuals who were exposed to GBC. Others have confirmed these findings with even more sensitive techniques (41).

Are Certain GBC Agents More Likely to Cause NSF?

A complete review of the published literature on the association of GBC agents with NSF put the risk for NSF with certain GBC agents into perspective (42). A total of 190 cases of biopsy-proven NSF were identified using PubMed/MEDLINE. Gadodiamide was the culprit GBC agent in 157 cases; gadopentetate ($n = 8$) and gadoversetamide ($n = 3$) were the others noted. In the remaining cases, 18 were unspecified, four were confounded, and five were purported to have no GBC agent exposure.

A recently published retrospective study examined the relationship of GBC exposure and biopsy-proven NSF at four US academic medical centers (43). They collected data on type and cumulative dosage of GBC administered and calculated a benchmark incidence at the medical centers. Two centers used only gadodiamide; the other two centers used only gadopentetate. They found that predominantly patients with stage 5 CKD developed NSF after large cumulative GBC dosages. The benchmark incidence of NSF was one in 44,224 with gadopentetate and one in 2913 with gadodiamide. This calculates to an odds ratio of 13 for developing NSF with gadodiamide compared with gadopentetate.

In a recent publication that examined the FDA MedWatch reporting system data as of October 2007, numerous cases of NSF associated with exposure to GBC agents were reported (44). Gadodiamide was noted in 283 cases (246 alone) and gadopentetate in 125 (96 alone), the most common. It is interesting that gadoteridol, which has the third greatest market

share, had the least number of reported NSF cases, with only one case noted with exposure to gadoteridol alone.

An important retrospective study that shed light on the different risk potential of the various GBC agents was recently published (44). In that study, 141 patients with ESRD had 198 gadoteridol (macrocytic nonionic chelate) exposures during a 7-yr period (2000 through 2007). The majority of exposures were single ($n = 104$), but several were two or greater ($n = 37$). No cases of NSF were noted during this period, clearly less than the 2 to 18% prevalence described with gadodiamide exposure.

Recently, 42 rats with normal kidney function were exposed to various types of high-dosage GBC agents (gadodiamide, gadoversetamide, gadopentetate, gadobenate, gadobutrol, and gadoterate) or saline control daily for 28 d (45). Rats exposed to gadodiamide developed NSF-like skin lesions at 5 d, whereas the rest of the rats did not. Histopathology identical to NSF was noted only in the gadodiamide-exposed rats. Gadolinium tissue concentrations were highest in gadodiamide-exposed rats followed by gadoversetamide and gadopentetate. Although gadolinium was present in the other three groups, the gadolinium concentrations were approximately 30-fold lower in these rats.

Why Is Gadodiamide More Frequently Associated with NSF?

One theory to explain the gadodiamide association relates to its stability, defined as the ability of the chelate to bind to and sequester Gd^{3+} . Gadodiamide has the lowest stability constant and highest dissociation rate of the five GBC preparations available in the United States (Table 1). Because of this decreased stability, the Gd^{3+} ion of gadodiamide is more likely to dissociate from its chelate than other GBC agents. Reduced kidney function significantly increases the $T_{1/2}$ of GBC agents as they are slowly excreted by the kidneys. Thus, significant renal impairment is associated with increased time for transmetallation (Figure 2) and prolonged tissue exposure, which may promote deposition of toxic Gd^{3+} , leading to fibrosis. This process is less likely to occur with the more stable macrocyclic chelates.

Which Patients Are at Highest Risk to Develop NSF after GBC Exposure?

The published literature clearly documents that patients with advanced kidney disease are at highest risk to develop NSF after GBC agent exposure. Nearly 80% of patients have ESRD and are on dialysis, whereas the rest have primarily stage 5 CKD and AKI. A small number of patients have been described

Table 4. Case-control studies with odds ratio for patients who had ESRD/CKD and were exposed to GBC agents

Reference	No. of NSF Cases	No. of Patients with ESRD and Exposure to GBC	Odds Ratio
Broome <i>et al.</i> (4)	12 (ESRD 8)	258	41.3
Collidge <i>et al.</i> (36)	14 (12 biopsy-proven)	1418	46.6
Deo <i>et al.</i> (32)	3	380	31.5
Othersen <i>et al.</i> (37)	4	588	20.6
Marckmann <i>et al.</i> (35)	13 (ESRD 8)	430	32.5

with stage 4 CKD (approximately five). It is important to note that no cases of stages 1 through 3 have been reported in the published literature. In fact, several studies that included patients who had stages 1 through 4 CKD and were exposed to GBC agents had not noted NSF as a complication. In the HALT-Polycystic Kidney Disease and Consortium for Radiologic Imaging Studies of PKD (CRISP), patients with autosomal dominant polycystic kidney disease and stages 1 through 3 CKD underwent 1111 GBC agent exposures with no cases of NSF developing (46). Patients who had stages 3 and 4 CKD ($n = 592$) and were exposed to GBC also did not develop NSF (37). Finally, patients who had stages 1 through 4 CKD ($n = 88$) and underwent 94 GBC agent exposures, including 38 patients with stage 4 CKD, did not develop NSF (47). On the basis of the literature, stage 4 CKD seems to be very low risk.

GBC and NSF: The Bottom Line

On the basis of the current published literature, a couple of conclusions can be drawn. First, patients who are at highest risk to develop NSF after GBC agent exposure are those with ESRD, stage 5 CKD, and AKI. Patients with stage 4 CKD maintain some risk, but it is likely much lower than the aforementioned groups. There seems to be little or no risk for patients with stages 1 through 3 CKD. Clearly, patients with normal kidney function have no risk.

The risk associated with the various GBC agents is likely different as well. Gadodiamide, the linear nonionic chelate-based formulation, maintains the highest risk on the basis of epidemiologic data and animal studies. Gadopentetate, the linear ionic chelate-based product probably has a medium risk, less than the linear nonionic chelates but more than the macrocyclic chelates. Gadoteridol, the only FDA-approved macrocyclic chelate, maintains less risk. Clearly, high dosages and large cumulative dosages of these agents will increase risk for NSF.

Current Status of GBC Agents in Kidney Disease

Because there is no effective therapy for NSF, avoidance of exposure by using alternative imaging modalities is the best option. This would entail identifying the high-risk groups. If an imaging test using a GBC agent is required, then a discussion with the health care providers and patient should ensue to discuss the risks and benefits. Once informed consent is obtained and documented, I recommend the following approach:

1. Use a macrocyclic chelate (gadoteridol in the United States), avoiding linear chelates.
2. Use the lowest dosage of GBC agent possible to achieve the image.
3. Avoid repeat exposures with GBC agents.
4. Consider performing hemodialysis after the exposure (and the next 2 d) in patients who are already maintained on hemodialysis, recognizing that there are no data that support prevention of NSF with this modality. The recommendation is based on the pharmacokinetics of GBC and the theoretical benefit of removing it with hemodialysis (>95%

plasma clearance). In contrast, peritoneal dialysis clears GBC poorly.

Conclusions

GBC agents can no longer be assumed to be as safe as they have traditionally been considered in patients with underlying kidney disease. Although less nephrotoxic than iodinated radiocontrast, GBC agents can cause AKI in high-risk patients who receive large dosages and/or intra-arterial injections. NSF can be a catastrophic complication of GBC agent exposure; avoidance in high-risk patients, when possible, is the best measure to prevent the disease. If GBC agent exposure is required, then using the smallest dosage of a macrocyclic chelate is the next best option. Hemodialysis should be considered after GBC agent exposure in patients who are already on this modality.

Acknowledgments

Parts of this work were presented at the annual meeting of the American Society of Nephrology; November 4–9, 2008; Philadelphia, PA.

Disclosures

None.

References

1. Perazella MA, Rodby RA: Gadolinium use in patients with kidney disease: A cause for concern. *Semin Dial* 20: 179–184, 2007
2. Grobner T: Gadolinium—a specific trigger for the development of nephrogenic fibrosing dermopathy and nephrogenic systemic fibrosis? *Nephrol Dial Transplant* 21: 1104–1108, 2006
3. Marckmann P, Skov L, Rossen, Dupont A, Damholt MB, Heaf JG, Thomsen HS: Nephrogenic systemic fibrosis: Suspected etiological role of gadodiamide used for contrast-enhanced magnetic resonance imaging. *J Am Soc Nephrol* 17: 2359–2362, 2006
4. Broome DR, Girguis MS, Baron PW, Cottrell AC, Kjellin I, Kirk GA: Gadodiamide-associated nephrogenic systemic fibrosis: Why radiologists should be concerned. *AJR Am J Roentgenol* 188: 586–592, 2007
5. Khurana A, Runge VM, Narayanan M, Greene JF Jr, Nickel AE: Nephrogenic systemic fibrosis: A review of 6 cases temporally related to gadodiamide injection (Omniscan). *Invest Radiol* 42: 139–145, 2007
6. Galan A, Cowper SE, Bucala R: Nephrogenic systemic fibrosis (nephrogenic fibrosing dermopathy). *Curr Opin Rheumatol* 18: 614–617, 2006
7. Cowper SE. Nephrogenic Fibrosing Dermopathy [NFD/NSF Website]. 2001–2007. Available at: <http://www.icnfd.org>. Accessed June 1, 2007
8. Thomsen HS, Morcos SK, Dawson P: Is there a causal relation between the administration of gadolinium based contrast media and the development of nephrogenic systemic fibrosis? *Clin Radiol* 61: 905–906, 2006
9. Thomsen HS: Nephrogenic systemic fibrosis: A serious late adverse reaction to gadodiamide. *Eur Radiol* 16: 2619–2621, 2006
10. Food and Drug Administration: Public Health Advisory: Gadolinium-Containing Contrast Agents for Magnetic Reso-

- nance Imaging (MRI): Omniscan, OptiMARK, Magnevist, ProHance, and MultiHance, 2006. Available at: http://www.fda.gov/cder/drug/advisory/gadolinium_agents.htm. Accessed November 1, 2008
11. Food and Drug Administration: Public Health Advisory: Update on Magnetic Resonance Imaging (MRI) Contrast Agents Containing Gadolinium and Nephrogenic Fibrosing Dermopathy, 2006. Available at: http://www.fda.gov/cder/drug/advisory/gadolinium_agents_20061222.htm. Accessed November 1, 2008
 12. Perazella MA: Nephrogenic systemic fibrosis, gadolinium, and chronic kidney disease: Is there a link? *Clin J Am Soc Nephrol* 2: 200–202, 2007
 13. Bellin MF: MR contrast agents, the old and the new. *Eur J Radiol* 60: 314–323, 2006
 14. Lorusso V, Pascolo L, Ferneti C, Anelli PL, Uggeri F, Tiribelli C: Magnetic resonance contrast agents: From the bench to the patient. *Curr Pharm Des* 11: 4079–4098, 2005
 15. Runge VM: Safety of magnetic resonance contrast media. *Top Magn Reson Imaging* 12: 309–314, 2001
 16. Swan SK, Lambrecht LJ, Townsend R, Davies BE, McCloud S, Parker JR, Bense K, LaFrance ND: Safety and pharmacokinetic profile of gadobenate dimeglumine in subjects with renal impairment. *Invest Radiol* 34: 443–455, 1999
 17. Wible JH, Troup CM, Hynes MR, Galen KP, MacDonald JR, Barco SJ, Wojdyla JK, Periasamy MP, Adams MD: Toxicological assessment of gadoversetamide injection (OptiMARK), a new contrast-enhancement agent for use in magnetic resonance imaging. *Invest Radiol* 36: 401–412, 2001
 18. Niendorf HP, Alhassan A, Hausteiner J, Clauss W, Cornelius I: Safety and risk of gadolinium-DTPA: Extended clinical experience after more than 5,000,000 applications. *Adv MRI Contrast* 2: 12–19, 1993
 19. Bellin MF, Deray G, Assogba U, Auberton E, Ghany F, Dion-Voirin E, Jacobs C, Grellet J: Gd-DOTA: Evaluation of its renal tolerance in patients with chronic renal failure. *Magn Reson Imaging* 10: 115–118, 1992
 20. Arsenault TM, King BF, Marsh JW Jr, Goodman JA, Weaver AL, Wood CP, Ehman RL: Systemic gadolinium toxicity in patients with renal insufficiency and renal failure: Retrospective analysis of an initial experience. *Mayo Clin Proc* 71: 1150–1154, 1996
 21. Prince MR, Arnoldus C, Friscoli JK: Nephrotoxicity of high-dose gadolinium compared with iodinated contrast. *J Magn Reson Imaging* 6: 162–166, 1996
 22. Hammer FD, Goffette PP, Malaise J, Mathurin P: Gadolinium dimeglumine: An alternative contrast agent for digital subtraction angiography. *Eur Radiol* 9: 128–136, 1999
 23. Spinosa DJ, Angle JF, Hagspiel KD, Aassar OS, Harthun NL, Tribble CG, Matsumoto AH: Lower extremity arteriography with use of iodinated contrast material or gadodiamide to supplement CO₂ angiography in patients with renal insufficiency. *J Vasc Interv Radiol* 11: 35–43, 2000
 24. Spinosa DJ, Matsumoto AH, Angle JF, Hagspiel KD, Cage D, Bissonette EA, Koening KG, Ayers CR, McConnell K: Safety of CO₂- and gadodiamide-enhanced angiography for the evaluation and percutaneous treatment of renal artery stenosis in patients with chronic renal insufficiency. *AJR Am J Roentgenol* 176: 1305–1311, 2001
 25. Sancak T, Bilgic S, Sanldilek U: Gadodiamide as an alternative contrast agent in intravenous digital subtraction angiography and interventional procedures of the upper extremity veins. *Cardiovasc Intervent Radiol* 25: 49–52, 2002
 26. Reiger J, Sitter T, Toepfer M, Linsenmaier U, Pfeofer KJ, Schiffl H: Gadolinium as an alternative contrast agent for diagnostic and interventional angiographic procedures in patients with impaired renal function. *Nephrol Dial Transplant* 17: 824–828, 2002
 27. Sam AD, Morasch MD, Collins J, Song G, Chen R, Pereles FS: Safety of gadolinium contrast angiography in patients with chronic renal insufficiency. *J Vasc Surg* 38: 313–318, 2003
 28. Erley CM, Bader BD, Berger ED: Gadolinium-based contrast media compared with iodinated media for digital subtraction angiography in azotemic patients. *Nephrol Dial Transplant* 19: 2526–2531, 2004
 29. Ergun I, Keven K, Uruc I, Ekmekci Y, Canbakan B, Erden I, Karatan O: The safety of gadolinium in patients with stage 3 and 4 renal failure. *Nephrol Dial Transplant* 21: 697–700, 2006
 30. Briguori C, Colombo A, Airoidi F, Melzi G, Michev I, Carlino M, Montorfano M, Chieffo A, Bellanca R, Ricciardelli B: Gadolinium-based contrast agents and nephrotoxicity in patients undergoing coronary artery procedures. *Catheter Cardiovasc Interv* 67: 175–180, 2006
 31. Kane GC, Stanson AW, Kalnicka D, Rosenthal DW, Lee CU, Textor SC, Garovic VD: Comparison between gadolinium and iodine contrast for percutaneous intervention in atherosclerotic renal artery stenosis: Clinical outcomes. *Nephrol Dial Transplant* 23: 1233–1240, 2008
 32. Deo A, Fogel M, Cowper SE: Nephrogenic systemic fibrosis: A population study examining the relationship of disease development to gadolinium exposure. *Clin J Am Soc Nephrol* 2: 264–267, 2007
 33. Nephrogenic fibrosing dermopathy associated with exposure to gadolinium-containing contrast agents: St. Louis, Missouri, 2002–2006. *MMWR Morb Mortal Wkly Rep* 56: 137–141, 2007
 34. Sadowski EA, Bennett LK, Chan MR, Wentland AL, Garrett AL, Garrett RW, Djamali A: Nephrogenic systemic fibrosis: Risk factors and incidence estimation. *Radiology* 243: 148–157, 2007
 35. Marckmann P, Skov L, Rossen K, Heaf J, Thomsen HS: Case-control study of gadodiamide-related nephrogenic systemic fibrosis. *Nephrol Dial Transplant* 22: 3174–3178, 2007
 36. Collidge TA, Thomson PC, Mark PB, Traynor JP, Jardine AG, Morris ST, Simpson K, Roditi GH: Gadolinium-enhanced MR imaging and nephrogenic systemic fibrosis: Retrospective study of a renal replacement therapy cohort. *Radiology* 245: 168–175, 2007
 37. Othersen JB, Maize JC, Woolson RF, Budisavljevic MN: Nephrogenic systemic fibrosis after exposure to gadolinium in patients with renal failure. *Nephrol Dial Transplant* 22: 3179–3185, 2007
 38. High WA, Ayers RA, Chandler J, Zito G, Cowper SE: Gadolinium is detectable within the tissue of patients with nephrogenic systemic fibrosis. *J Am Acad Dermatol* 56: 21–26, 2007
 39. Boyd AC, Zic JA, Abraham JL: Gadolinium deposition in nephrogenic fibrosing dermopathy. *J Am Acad Dermatol* 56: 27–30, 2007
 40. High WA, Eng M, Ayers RA, Cowper SE: Gadolinium is

- quantifiable within the tissue of patients with nephrogenic systemic fibrosis. *J Am Acad Dermatol* 56: 1–2, 2007
41. Schroeder JA, Weingart C, Coras B, Hausser I, Reinhold S, Mack M, Seybold V, Vogt T, Banas B, Hofstaedter F, Krämer BK: Ultrastructural evidence of dermal gadolinium deposits in a patient with nephrogenic systemic fibrosis and end-stage renal disease. *Clin J Am Soc Nephrol* 3: 968–975, 2008
 42. Broome DR: Nephrogenic systemic fibrosis associated with gadolinium based contrast agents: A summary of the medical literature reporting. *Eur J Radiol* 66: 230–234, 2008
 43. Wertman R, Altun E, Martin DR, Mitchell DG, Leyendecker JR, O'Malley RB, Parsons DJ, Fuller ER 3rd, Semelka RC: Risk of nephrogenic systemic fibrosis: Evaluation of gadolinium chelate contrast agents at four American universities. *Radiology* 248: 799–806, 2008
 44. Reilly RF: Risk for nephrogenic systemic fibrosis with gadoteridol (ProHance) in patients who are on long-term hemodialysis. *Clin J Am Soc Nephrol* 3: 747–751, 2008
 45. Sieber MA, Lengsfeld P, Frenzel T, Golfier S, Schmitt-Willich H, Siegmund F, Walter J, Weinmann HJ, Pietsch H: Preclinical investigation to compare different gadolinium-based contrast agents regarding their propensity to release gadolinium in vivo and to trigger nephrogenic systemic fibrosis-like lesions. *Eur Radiol* 18: 2164–2173, 2008
 46. Chapman A, Grantham JJ, Guay-Woodford LM, Braun W, Rahbari-Oskovi F, Kelleher C, Schrier RW, Perrone R, Steinman T, Miskalin D, Meyers C, Bost J, Miller P, Bae KT: Absence of NSF following gadolinium exposure in ADPKD individuals with stable CKD [Abstract]. *J Am Soc Nephrol* 18: 759A, 2007
 47. Rydahl C, Thomsen HS, Marckmann P: High prevalence of nephrogenic systemic fibrosis in chronic renal failure patients exposed to gadodiamide, a gadolinium-containing magnetic resonance contrast agent. *Invest Radiol* 43: 141–144, 2008

Correction

Erratum for Perazella: Current Status of Gadolinium Toxicity in Patients with Kidney Disease. *Clin J Am Soc Nephrol* 4: 461–469, 2009

There was an error in Table 4, and the acknowledgement was not included.

Table 4 was created and provided by Dr. Ali-Abu-Alfa (Section of Nephrology, Yale University). The author would like to thank him for his kindness in sharing the table. To permit the calculation of the odds ratios for cohorts with no NSF cases in unexposed ESRD patients, 0.5 was added to each cell in the contingency table (Haldane's estimator).

Table 4. Case-control studies with odds ratio for patients who had ESRD and were exposed to GBC agents

Author (ref)	No. of NSF Cases	No. of Exposed/Unexposed ESRD patients	Odds Ratio
Collidge <i>et al.</i> (36)	14	421/1405	44.7
Deo <i>et al.</i> (32)	3	87/380	31.5
Othersen <i>et al.</i> (37)	4	261/588	20.6
Markmann <i>et al.</i> (35)	13 (8 ESRD)	370/430	20.2