What nephrologists need to know about gadolinium

Jeffrey G Penfield* and Robert F Reilly Jr

SUMMARY

Gadolinium chelates are commonly used to improve tissue contrast in MRI. Until recently the use of gadolinium was thought to be risk-free compared with alternative contrast agents. Recent studies, however, have raised serious concerns regarding the safety of gadolinium chelates. Although safe in patients with normal kidney function, administration of these agents in people with renal dysfunction can result in up to three clinical problems that the nephrologist should be familiar with. The first is nephrogenic systemic fibrosis (NSF), which was initially observed in 1997. Although manifesting primarily in skin, NSF can also cause systemic fibrosis, leading to disabling contractures and even death. Gadodiamide is the agent that has been most frequently associated with NSF, but other chelates might also pose a risk. The second clinical problem is that gadolinium chelates cause acute kidney injury, especially at high doses required for angiography. The third problem is that several laboratory artifacts are associated with gadolinium administration, with pseudohyopocalcemia being the most important. The risk of a patient experiencing all three of these complications increases as renal function declines. In light of these problems, nephrologists need to re-evaluate the risks and benefits of gadolinium administration in patients with chronic kidney disease stage 3 or greater, as well as in those with acute kidney injury.

KEYWORDS contrast-induced nephropathy, gadolinium, nephrogenic fibrosing dermopathy, nephrogenic systemic fibrosis, pseudohyopocalcemia

INTRODUCTION

MRI has become an essential part of current medical practice on the basis of the high quality of the images the method is able to produce. Vascular enhancement with a gadolinium-based contrast agent further improves the results of MRI. Clinical trials and extensive clinical experience have proven that gadolinium-based contrast agents are safe in patients with normal kidney function. As renal function deteriorates, however, the safety of these agents diminishes. Nephrogenic systemic fibrosis (NSF) is associated with gadolinium chelates and occurs exclusively in patients with decreased renal function. The nephrotoxicity of these agents also becomes more pronounced as renal function declines. Derangement of laboratory measurements as a result of administration of gadolinium chelates is observed in patients with normal renal function, but the effect is greater and its duration longer in patients with renal insufficiency. This Review discusses the adverse effects of gadolinium-based contrast agents in patients with decreased renal function.

CME

Learning objectives

Upon completion of this activity, participants should be able to:
1. Describe the metabolism and properties of gadolinium.
2. Identify the connection between gadolinium and renal disease and its mechanism.
3. Specify laboratory abnormalities associated with the use of gadolinium.
4. Describe the clinical presentation and treatment of nephrogenic systemic fibrosis.
5. List recommendations for the use of gadolinium.

REVIEW CRITERIA

We searched a variety of medical literature sources, including PubMed, MEDLINE, and nephrology and basic science journals, for information on gadolinium, mechanisms of gadolinium toxicity, nephrogenic fibrosing dermopathy, nephrogenic systemic fibrosis, and pseudohyopocalcemia and other laboratory artifacts. Three hundred and eleven references published between 1962 and June 2007 were selectively reviewed.

Correspondence

*Veterans Affairs North Texas Health Care System, 4500 S Lancaster Road, Dallas, TX 75216, USA jeffrey.penfield@va.gov

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Gadolinium is a rare earth element from the lanthanide series that is used as a contrast agent in MRI because of its powerful paramagnetic properties. Its seven unpaired electrons perturb proton relaxation in water, resulting in a shortened T1 relaxation time and increased magnetic resonance signal intensity. Gadolinium in its unbound state is highly toxic. It is a potent inhibitor of calcium channels and has considerable cardiovascular and neurologic toxicity. In mice, the median lethal dose (LD50; i.e. the amount required to kill 50% of the population) of GdCl₃ is just 100–200 mg/kg.¹ Free gadolinium is deposited in liver, bone and lymph nodes and, once there, is slowly released from the body at a rate of less than 1% per day.²

Gadolinium must be chelated for use in humans. Chelation improves the water solubility and reduces the toxicity of the agent. The LD50 in rodents increases 100-fold with chelation.³ Five different gadolinium chelates are approved in the US by the FDA for use as MRI agents (shown in Table 1). In the US, approximately 26.9 million MRI scans were performed in 2006 and in 45% of these cases a gadolinium chelate was administered.⁴ To date, more than 200 million patients worldwide have been exposed to gadolinium chelates.⁵

The only FDA-approved indication for gadolinium chelates is use as a contrast agent in MRI at a dose of 0.1 mmol/kg.⁶ These agents are also used for magnetic resonance angiography (MRA) and as contrast agents in arteriography and venography, but these are not FDA-approved indications. Dosages for these procedures are not standardized, but in a 1999 survey the nephrotoxicity of doses as high as 0.9 mmol/kg

<table>
<thead>
<tr>
<th>Chelate (abbreviation)</th>
<th>Trade name (manufacturer)</th>
<th>Approving body (year of approval)</th>
<th>Chemical structure</th>
<th>Charge dissociation half-life</th>
<th>Molecular weight (Da)</th>
<th>Half-life (h ±SD)</th>
<th>Proportion excreted within 24 h (% ±SD)</th>
<th>NSF cases reported to FDA May 2007</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gadopentetate dimeglumine (Gd-DTPA)</td>
<td>Magnevist® (Bayer HealthCare Pharmaceuticals; Montville, NJ)</td>
<td>FDA and EMEA (1988)</td>
<td>Linear Ionic</td>
<td>10min</td>
<td>939.0</td>
<td>1.60±0.13</td>
<td>91±13</td>
<td>21</td>
</tr>
<tr>
<td>Gadoteridol (Gd-HP-DO3A)</td>
<td>ProHance® (Bracco Diagnostics; Princeton, NJ)</td>
<td>FDA and EMEA (1992)</td>
<td>Cyclic Nonionic</td>
<td>3h</td>
<td>558.7</td>
<td>1.57±0.08</td>
<td>94.4±4.8</td>
<td>1 (patient also received Omniscan®)</td>
</tr>
<tr>
<td>Gadodiamide (Gd-DTPA-BMA)</td>
<td>Omniscan® (GE Healthcare, Chalfont St Giles, Buckinghamshire, UK)</td>
<td>FDA and EMEA (1993)</td>
<td>Linear Nonionic</td>
<td>30s</td>
<td>573.6</td>
<td>1.30±0.27</td>
<td>95.4±5.5</td>
<td>85</td>
</tr>
<tr>
<td>Gadobenate dimeglumine (Gd-BOPTA)</td>
<td>MultiHance® (Bracco Diagnostics)</td>
<td>FDA and EMEA (2004)</td>
<td>Linear Ionic</td>
<td>NA</td>
<td>1,058.2</td>
<td>1.17±0.26</td>
<td>2.02±0.60</td>
<td>NA</td>
</tr>
<tr>
<td>Gadoversetamide (Gd-DTPA-BMEA)</td>
<td>OptMARK® (Mallinckrodt; Hazelwood, MO)</td>
<td>FDA (1999)</td>
<td>Linear Nonionic</td>
<td>NA</td>
<td>661.8</td>
<td>1.73±0.32</td>
<td>95.5±17.4</td>
<td>6</td>
</tr>
<tr>
<td>Gadobutrol (Gd-BT-DO3A)</td>
<td>Gadovist® (Bayer Schering Pharma; Berlin, Germany)</td>
<td>EMEA (2001)</td>
<td>Cyclic Nonionic</td>
<td>NA</td>
<td>604.0</td>
<td>1.50</td>
<td>NA</td>
<td>None</td>
</tr>
<tr>
<td>Gadoterate meglumine (Gd-DOTA)</td>
<td>Dotarem® (Guerbet; Paris, France)</td>
<td>EMEA (1989)</td>
<td>Cyclic Ionic</td>
<td>NA</td>
<td>559.0</td>
<td>1.50</td>
<td>90</td>
<td>None</td>
</tr>
<tr>
<td>Gadoxetic acid disodium salt (Gd-EOB-DTPA)</td>
<td>Primovist® (Bayer Schering Pharma)</td>
<td>EMEA (2004)</td>
<td>Linear Ionic</td>
<td>NA</td>
<td>682.0</td>
<td>0.95</td>
<td>&gt;99⁷</td>
<td>None</td>
</tr>
<tr>
<td>Gadofosveset trisodium</td>
<td>Vasovist® (Bayer Schering Pharma)</td>
<td>EMEA (2005)</td>
<td>Linear Ionic</td>
<td>NA</td>
<td>958.0</td>
<td>2.0–3.0</td>
<td>NA</td>
<td>None</td>
</tr>
</tbody>
</table>

¹Being reviewed by the EMEA. ²Excreted in both urine and feces. Abbreviations: EMEA, European Agency for the Evaluation of Medical Products; NA, not available; NSF, nephrogenic systemic fibrosis.
was not considered to be important by the majority of practitioners.7

The pharmacokinetic properties of most gadolinium chelates are similar. The compounds are water soluble, excreted unchanged by glomerular filtration, do not undergo biotransformation, and are distributed in extracellular fluid. Notable exceptions to these rules include gadoxetic acid (Primovist®; Bayer Schering Pharma, Berlin, Germany), gadofosveset trisodium (Vasovist®; Bayer Schering Pharma) and gadobenate dimeglumine (MultiHance®; Bracco Diagnostics, Princeton, NJ). Gadoxetic acid is taken up by hepatocytes; up to 50% of the agent is excreted in feces and 50% in urine. The chelate is used for enhanced imaging of the liver.8 Between 80–96% of circulating gadofosveset trisodium is bound to plasma proteins, and the compound has been used as a blood pool agent.9 Only a small proportion of circulating gadobenate dimeglumine is protein bound; it is taken up by hepatocytes and has a fecal excretion rate of 4%.10 Other gadolinium chelates are not bound by proteins or eliminated in feces. Molecular weights of the compounds range from 558 to 1,058 daltons. The half-life of gadolinium chelates in patients with normal renal function is approximately 1.5 hours, and more than 90% of a dose is excreted in 24 hours (Table 1).

The differences in the effects of various gadolinium preparations are attributable to gadolinium’s capacity to dissociate from chelates. The LD$_{50}$s in rodents for various gadolinium chelates were found to vary up to 50-fold, but all were lethally toxic when the same amount of gadolinium was released from the chelate.11 Gadodiamide (Omniscan®, GE Healthcare, Chalfont St Giles, Buckinghamshire, UK) has the shortest dissociation constant—30 seconds compared with 10 minutes and with 3 hours for gadopentetate dimeglumine (Magnevist®; Bayer HealthCare Pharmaceuticals, Montville, NJ) and gadoteridol (ProHance®, Bracco Diagnostics), respectively. The longer dissociation constant of gadoteridol is probably a function of its cyclic structure; most other gadolinium chelates have a linear structure. Release of gadolinium from a cyclic chelate requires all four covalent bonds to be broken simultaneously. The more flexible structure of linear chelates more readily facilitates gadolinium release. This fact might account for the higher incidence of NSF associated with gadodiamide and gadopentetate dimeglumine. These two agents are the gadolinium preparations most frequently used in the US, which could account for a proportion of the increased incidence of NSF associated with these chelates. Market share alone does not, however, explain the disparity in the number of cases reported to be caused by these two agents.

The propensity of gadolinium chelates to undergo transmetalation might influence their toxicity. Transmetalation refers to the capacity of other cations in the body (e.g. zinc, copper and calcium) to displace gadolinium from its chelate.12 Copper has high affinity for the chelates, but is not present in the body at sufficient concentrations to displace large amounts of gadolinium. The concentration of calcium in serum is high, but the affinity of calcium for chelates is low. Zinc has moderate affinity and a sufficiently high serum concentration to displace gadolinium.11 In humans and experimental models, the extent of transmetalation can be evaluated in vivo as urinary zinc excretion. If gadolinium is displaced from its chelate by zinc, zinc binds the chelate and is subsequently excreted in urine. There are marked differences among the gadolinium chelates in the rates of short-term (within 3 hours) urinary zinc excretion after administration of 0.1 mmol/kg of chelate. Interestingly, these differences correspond to the kinetic stability of these agents. In a study in humans, urinary zinc excretion was highest with gadodiamide (27.4 μmol) and intermediate with gadopentetate dimeglumine (5.9 μmol), both of which are linear chelates.13

By contrast, in the same study, urinary zinc excretion was lowest with the cyclic chelate gadoteridol (1.2 μmol).

Similarly, in vitro studies have shown that linear chelates (i.e. gadodiamide, gadopentetate dimeglumine and gadobenate dimeglumine) are susceptible to transmetalation, but cyclic chelates (i.e. gadoteridol, gadobutrol [Gadovist®; Bayer Schering Pharma] and gadoterate meglumine [Dotarem®; Guerbet, Paris, France]) are resistant to this process.14

**NEPHROTOXICITY OF GADOLINIUM CHELATES**

MRI and/or MRA with gadolinium enhancement is often used instead of iodinated-contrast radiographic methods. MRI provides superior image quality to iodinated contrast methods, and methods that use iodinated contrast are...
associated with a risk of acute kidney injury (AKI); for many years, gadolinium chelates were thought to be risk-free. Gadolinium is used in X-ray angiography in place of iodinated contrast, particularly in patients with chronic kidney disease (CKD). Early investigations reported that gadolinium chelates were not associated with AKI in patients with CKD (Table 2). The limitations of these reports include small sample size, lack of control groups, poor uniformity of pretreatment regimens, variable gadolinium doses and routes of administration, and different definitions of contrast-induced nephropathy (CIN). Higher than recommended doses of gadolinium chelates (>0.2 mmol/kg) were used in several of the studies. In response to these early reports and the desire to avoid CIN, gadolinium chelates were frequently used for standard venography and arteriography, and higher doses than those approved by the FDA were administered.

Subsequent reports (Table 3) detected an increased risk of AKI associated with gadolinium chelates in patients with CKD. These studies included more patients, one study was prospective, and the doses used were, on average, higher than those used in earlier series. There is at least one biopsy-documented case report of gadolinium-induced AKI; histological examination of the sample showed acute tubular necrosis, similar to that associated with CIN caused by iodinated contrast. One case report describes a patient with CKD who received iodinated contrast for coronary angiography but suffered no nephrotoxic effects. Three years later he developed AKI after receiving just 0.14 mmol/kg of gadodiamide for an MRA, indicating that gadolinium could be more nephrotoxic than iodinated contrast even at doses less than 0.2 mmol/kg.

It is not known whether the cause of nephrotoxicity associated with gadolinium chelates is the chelate itself or free gadolinium. As both gadolinium chelates and iodinated contrast cause acute tubular necrosis, it is reasonable to recommend avoiding high doses of gadolinium and maintaining adequate hydration in patients with CKD. In a 2000 position paper, the Contrast Media Safety Committee of the European Society of Urogenital Radiology recommended, on the basis of nephrotoxicity data, that gadolinium chelates should not be used in place of iodinated contrast media for radiographic examinations in patients with CKD.

**Nephrogenic Systemic Fibrosis**

NSF was first observed in 1997 and the initial case series published in 2000. The condition was originally known as ‘nephrogenic fibrosing dermopathy’ because it manifested primarily in skin. Later cases revealed more-diffuse involvement including subcutaneous tissue, striated muscle, the diaphragm and pleurae, the pericardium, and the myocardium. The name of the disorder was changed to NSF in 2005.

Potential etiological agents for NSF remained elusive for many years, but the condition was known to occur exclusively in patients with decreased renal function. The association with gadolinium chelates was first described in January 2006 in an Austrian study by Grobner. Five of nine patients who received gadodiamide developed NSF within 2–4 weeks of exposure. These patients had metabolic acidosis whereas the four patients without NSF did not, but this association was not confirmed in later reports. In May 2006, the Danish Medicines Agency reported 25 cases of NSF that had occurred after gadodiamide exposure. Five of these cases had been reported previously by Grobner, and twenty were newly reported cases from Denmark. The FDA issued a black box warning in June 2006 that was updated in December 2006 and again in May 2007. The warning reiterated the association of gadolinium chelates with NSF.

Although there is good evidence that only three of the five FDA-approved gadolinium chelates are associated with NSF, the FDA warned that all gadolinium chelates had the potential to cause NSF. The FDA recommended that gadolinium chelates be used in patients with advanced kidney failure (i.e. those on dialysis or with an estimated glomerular filtration rate [GFR] <15 ml/min per 1.73 m²) only if absolutely necessary, and that it might be prudent to initiate hemodialysis promptly after gadolinium administration in these patients. This recommendation was formulated on the basis of studies by Okada and colleagues that showed gadolinium excretion rates of 78.2%, 95.6%, 98.7% and 99.5% in the first, second, third and fourth post-gadolinium dialysis sessions, respectively.

**Link Between Gadolinium and Nephrogenic Systemic Fibrosis**

Several groups have examined the potential link between gadolinium administration and NSF. Deo et al. studied a group of patients treated in a dialysis practice in Bridgeport, CT. Three cases of
Table 2 Summary of the results of studies that showed that gadolinium did not cause acute kidney injury.

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Sample size (mean age)</th>
<th>Agent(s) used</th>
<th>Dose used (mmol/kg)</th>
<th>Renal status</th>
<th>Renal outcome</th>
<th>Preventive treatment used</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rofsky et al. (1991)²⁰</td>
<td>Workup of renal mass</td>
<td>5 (69 years)</td>
<td>Magnevist®</td>
<td>0.1</td>
<td>Creatinine &gt;2.0 mg/dl (range 2.2–6.0 mg/dl)</td>
<td>No increase in creatinine concentration</td>
<td>NA</td>
</tr>
<tr>
<td>Bellin et al. (1992)¹⁵</td>
<td>Prospective study of consecutive patients; intravenous gadolinium (n=10) vs no contrast (n=10)</td>
<td>20</td>
<td>Dotarem®</td>
<td>0.1</td>
<td>GFR (Cockcroft–Gault) &lt;60 ml/min (mean 21.1±3.2 ml/min)</td>
<td>No &gt;25% increase in creatinine concentration; creatinine concentration increased &gt;10% in 5 controls and 3 gadolinium-exposed patients</td>
<td>None</td>
</tr>
<tr>
<td>Rieger et al. (2002)¹⁹</td>
<td>Retrospective study of iodinated contrast vs gadolinium</td>
<td>64</td>
<td>Magnevist® (n=21), Omniscan® (n=37) or ProHance® (n=6)</td>
<td>0.2–0.4</td>
<td>Creatinine &gt;1.5 mg/dl</td>
<td>CIN (defined as ≥0.5 mg/dl increase in creatinine concentration) occurred in 25% (9 of 31 patients) exposed to iodinated contrast and 0% exposed to gadolinium</td>
<td>NA</td>
</tr>
<tr>
<td>Sancak et al. (2002)²¹</td>
<td>Digital subtraction venography</td>
<td>14 (66.7 years)</td>
<td>Omniscan® or Magnevist®</td>
<td>≤0.4</td>
<td>Creatinine ≥1.5 mg/dl (mean 2.8±1.1 mg/dl)</td>
<td>CIN (defined as ≥0.5 mg/dl increase in creatinine concentration at 48 h) did not occur; creatinine concentration of 3 patients increased as a result of causes other than gadolinium exposure</td>
<td>Hydration</td>
</tr>
<tr>
<td>Townsend et al. (2000)²⁴</td>
<td>Arterial digital subtraction angiography</td>
<td>34 (53.1 years)</td>
<td>Magnevist®</td>
<td>0.4</td>
<td>Creatinine &gt;1.5 mg/dl</td>
<td>CIN (defined as ≥0.5 mg/dl increase in creatinine concentration) occurred in 3% (1 of 34 patients)</td>
<td>NA</td>
</tr>
<tr>
<td>Spinosa et al. (2000)²²</td>
<td>Retrospective study of iodinated contrast and CO₂ (n=15), gadolinium and CO₂ (n=20) and CO₂ alone (n=7)</td>
<td>42</td>
<td>Omniscan®</td>
<td>≤0.4</td>
<td>Creatinine &gt;1.5 mg/dl (mean 2.2±2.2 mg/dl, range 1.6–3.6 mg/dl)</td>
<td>CIN (defined as ≥0.5 mg/dl increase in creatinine concentration) occurred in 40% (6 of 15 patients) exposed to iodinated contrast and 5% (1 of 20 patients) exposed to gadolinium</td>
<td>300–500 ml normal saline before procedure</td>
</tr>
<tr>
<td>Sancak et al. (2002)²¹</td>
<td>Upper extremity or superior vena cava venography</td>
<td>16 (53 years)</td>
<td>Omniscan®</td>
<td>0.3</td>
<td>Mean creatinine 1.5 mg/dl (range 1.2–1.8 mg/dl)</td>
<td>Largest increase in creatinine concentration was 0.2 mg/dl</td>
<td>NA</td>
</tr>
<tr>
<td>Rieger et al. (2000)²¹</td>
<td>Prospective procedures (arterial and intravenous)</td>
<td>32</td>
<td>Magnevist®</td>
<td>0.34±0.06</td>
<td>Creatinine &gt;1.5 mg/dl (mean 3.6±1.4 mg/dl)</td>
<td>CIN (defined as &gt;0.5 mg/dl increase in creatinine concentration at 72 h) did not occur; creatinine concentration of 1 patient increased as a result of cholesterol emboli</td>
<td>Normal saline</td>
</tr>
</tbody>
</table>

To convert mg/dl to μmol/l, multiply by 88.4. Abbreviations: CIN, contrast-induced nephropathy; GFR, glomerular filtration rate; NA, not available.
NSF were identified during an 18 month period that ended 1 July 2006; two of these patients had received gadodiamide and one had received gadopentetate dimeglumine. The incidence of NSF among all hemodialysis patients in this study was 4.3 cases per 1,000 patient years. The risk of developing NSF was 2.4% per gadolinium exposure. In another study, 33 cases of NSF were reported in the St Louis, MO, area. Nineteen confirmed cases were evaluated in more detail in a case-controlled study. Four patients had been exposed to gadolinium more than 1 year before diagnosis of NSF and one individual had no known exposure. The remainder had received gadolinium within a year of diagnosis. Two patients had AKI and the remainder were chronic dialysis patients. In multivariate analysis, the only statistically significant risk factor for NSF was gadolinium exposure within 12 months of diagnosis (odds ratio 8.97). The attack rate for peritoneal dialysis patients was 4.6 per 100 patients and was 0.61 per 100 for hemodialysis patients. The number of peritoneal dialysis patients in this study was small, but evidence from a study by Joffe et al. of poor clearance of gadolinium chelates during peritoneal dialysis supports this finding.

Khurana and co-workers reviewed the case records of six patients who had developed NSF between 19 days and 2 months after gadodiamide exposure. One patient had AKI, one patient had AKI superimposed on advanced CKD, another was on hemodialysis, and three had stage 5 CKD but were not yet on dialysis. This report emphasizes that NSF occurs in

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Sample size</th>
<th>Agent(s) used</th>
<th>Dose used (mmol/kg)</th>
<th>Renal status</th>
<th>Renal outcome</th>
<th>Preventive treatment used</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sam et al. (2003)&lt;sup&gt;28&lt;/sup&gt;</td>
<td>Retrospective, uncontrolled study of patients with CKD (January 1999 to January 2001)</td>
<td>195</td>
<td>Magnevist&lt;sup&gt;®&lt;/sup&gt; (&lt;i&gt;n&lt;/i&gt; = 195)</td>
<td>0.28</td>
<td>Creatinine clearance &lt;80 ml/min (Cockcroft–Gault); mean 38.2 ± 16 ml/min</td>
<td>CIN (defined as &gt;1.0 mg/dl increase in creatinine concentration at 48 h plus oligoanuria) occurred in 3.5% (7 of 195 patients); 1.9% (3 of 153) of magnetic resonance angiography group and 9.5% (4 of 42) of digital subtraction angiography group were affected</td>
<td>NA</td>
</tr>
<tr>
<td>Erley et al. (2004)&lt;sup&gt;27&lt;/sup&gt;</td>
<td>Prospective, randomized study</td>
<td>21</td>
<td>Gadovist&lt;sup&gt;®&lt;/sup&gt; (&lt;i&gt;n&lt;/i&gt; = 10) or iohexol (&lt;i&gt;n&lt;/i&gt; = 11)</td>
<td>0.57 ± 0.17</td>
<td>Creatinine &gt;1.5 mg/dl or GFR &lt;50 ml/min</td>
<td>CIN (defined as &gt;50% decrease in GFR) occurred in 50% (5 of 10 patients) exposed to gadolinium and 45% (5 of 11) exposed to iohexol</td>
<td>Intravenous hydration</td>
</tr>
<tr>
<td>Briguori (2006)&lt;sup&gt;25&lt;/sup&gt;</td>
<td>Retrospective study of consecutive patients who had undergone coronary procedures, compared with historical controls</td>
<td>25</td>
<td>Omniscan&lt;sup&gt;®&lt;/sup&gt; (&lt;i&gt;n&lt;/i&gt; = 8) or Gadovist&lt;sup&gt;®&lt;/sup&gt; (&lt;i&gt;n&lt;/i&gt; = 17); three parts agent mixed with one part iodinated contrast vs iodinated contrast alone</td>
<td>0.6 ± 0.3 (range 0.28–1.23)</td>
<td>Creatinine &gt;2 mg/dl or creatinine clearance &lt;40 ml/min</td>
<td>CIN (defined as ≥0.5 mg/dl increase in creatinine concentration within 48 h or need for dialysis within 5 days) occurred in 28% (7 of 25 patients) exposed to gadolinium plus iodinated contrast and 6.5% (2 of 32) exposed to iodinated contrast only</td>
<td>Normal saline plus N-acetylcysteine</td>
</tr>
<tr>
<td>Ergun et al. (2006)&lt;sup&gt;26&lt;/sup&gt;</td>
<td>Retrospective, uncontrolled study (February 1999 to March 2005); creatinine concentration measured before, and 1, 3, 7 and approximately 30 days after, exposure to gadolinium</td>
<td>91</td>
<td>Magnevist&lt;sup&gt;®&lt;/sup&gt;, Omniscan&lt;sup&gt;®&lt;/sup&gt; or Dotarem&lt;sup&gt;®&lt;/sup&gt;</td>
<td>0.2</td>
<td>Stage 3 and 4 CKD; mean estimated GFR 33 ml/min (range 15–58 ml/min)</td>
<td>CIN (defined as ≥0.5 mg/dl increase in creatinine concentration within 72 h) occurred in 12% (11 of 91 patients)</td>
<td>NA</td>
</tr>
</tbody>
</table>

To convert mg/dl to μmol/l, multiply by 88.4. Abbreviations: CIN, contrast-induced nephropathy; CKD, chronic kidney disease; GFR, glomerular filtration rate; NA, not available.
patients with reduced renal function and is not confined to the dialysis population. In a study in Denmark, 13 people developed NSF between 2 and 75 days after exposure to gadodiamide.41 The odds ratio for exposure was 32.5 in these patients compared with patients with end-stage renal disease (ESRD) who had not been exposed. No association of NSF with acidosis was detected. The same authors reported no new cases of NSF at their institution since the use of gadodiamide was discontinued in March 2006.42 The total number of NSF cases related to gadodiamide that they have observed has now increased to 24. The extra cases are the result of delayed diagnosis of NSF that was caused by exposure to gadodiamide before its use was discontinued at their institution (P Marckmann, personal communication).

Broome et al.43 reported 12 patients who developed NSF after gadodiamide exposure. A total of 559 MRI exams were performed on 168 dialysis patients. The 12 patients who developed NSF (301 gadodiamide exposures) were compared with those who were not exposed to gadodiamide (258 MRI exams). Four of the twelve patients were liver transplant recipients with AKI secondary to hepatorenal syndrome. The odds ratio for exposure to gadodiamide was again high, at 22.3, and the prevalence of NSF among gadodiamide-exposed dialysis patients was 4%. Patients receiving gadodiamide doses of 0.1 mmol/kg and those receiving doses of 0.2 mmol/kg were compared. The odds ratio for developing NSF for those on the higher dose was 12.1, indicating that the risk of developing the condition is dose dependent. Daily dialysis, starting on the day of gadolinium administration, for 3 days did not prevent NSF in three patients.

In another series, thirteen patients developed NSF after being exposed to gadodiamine; all received gadodiamine, and one was exposed to both gadobenate dimeglumine and gadodiamine.44 These patients were compared with a group of 4,236 individuals who received gadolinium but did not develop NSF. Affected patients had higher serum creatinine concentrations and had undergone a greater number of contrast-enhanced magnetic resonance exams than those who did not develop NSF. Those with NSF were also affected by more proinflammatory events (defined as surgery, thromboembolic vascular events, or systemic infections), emphasizing the potential contribution of inflammation to the development of NSF. This series of patients also included two individuals with CKD stage 3 plus AKI. One was a liver transplant recipient, the other a renal transplant recipient. The authors emphasized that AKI in the setting of a proinflammatory event could have contributed to the development of NSF in these two patients.

Marckmann et al.45 reviewed 19 cases of gadodiamide-induced NSF to identify potential cofactors. The primary risk factor for NSF was an increasing cumulative dose of gadodiamide. The investigators also observed a statistically significant correlation between NSF and elevated serum calcium and phosphorus concentrations, and between NSF and higher doses of epoetin beta. There was no correlation of NSF with acidosis, use of angiotensin-converting-enzyme (ACE) inhibitors, or serum parathyroid levels.

At least 96 reported cases of NSF have been associated with gadolinium-containing contrast media. The type of gadolinium chelate used was reported for 63 cases; all but one patient received gadodiamide (this individual received gadopentetate dimeglumine) and one patient received both gadodiamide and gadobenate dimeglumine. There are no published case reports linking gadoversetamide (OptiMARK®; Mallinckrodt, Hazelwood, MO) with NSF, although six cases have been reported to MedWatch, the FDA safety information and adverse event reporting program. MedWatch reports are generated by volunteer clinicians and are not peer-reviewed. As of 17 January 2007, 85 cases of NSF associated with gadodiamide, 21 cases associated with gadopentetate dimeglumine, and 6 cases associated with gadoversetamide, had been reported to the FDA. NSF has also been reported to develop after sequential administration of gadodiamide and gadobenate dimeglumine, as well as after sequential administration of gadodiamide and gadoteridol.6 Only two patients who developed NSF without any known exposure to gadolinium are reported in the literature.38,46

TISSUE DEPOSITION OF GADOLINIUM

Gadolinium can be deposited in the bone tissue of normal individuals. Deposition in bone was examined in patients with normal kidney function undergoing hip replacement after gadolinium-enhanced MRI.47 Gadolinium was administered 3–8 days before surgery and levels in operative bone fragments were measured. The concentration of gadolinium was four times higher (1.77 ppm) in patients who received
Skin involvement in NSF is symmetrical, with extensive waxy thickening and hardening of the extremities and torso. Skin can become hyperpigmented and take on a ‘woody’ texture with plaques and subcutaneous nodules. Unlike scleromyxedema, NSF tends to spare the skin of the head and neck, and is not associated with paraproteinemia. A review of published cases by Mendoza et al. showed that skin of the lower extremities was affected in 97% of cases, and the distribution was from ankle to mid thigh. The upper extremities were involved in 77% of cases, most commonly from the wrist to mid upper arm. Truncal involvement was reported in 30% of cases, and there have been reports of yellow scleral plaques in the eye. Joint contractures are a common result of progressive skin, as well as muscle and fascia, fibrosis, and lead to severe immobility. Progression is rapid in a subset of patients, who can become bed or wheelchair bound as a result of contractures.

There is an increased risk of thrombosis manifesting as deep venous thrombosis, a pulmonary embolus, thrombosed arteriovenous access, or an atrial thrombus, in patients with NSF. Elevated levels of antiphospholipid and anticardiolipin antibodies, deficiencies of protein C, protein S and antithrombin III, and presence of factor V Leiden, have all been observed in such patients. Patients with liver disease and those who have undergone liver transplantation seem to be at increased risk of developing NSF. Originally thought to be confined to skin, it is now known that the fibrosis can be systemic and involve fascia, subcutaneous tissue, and other organs, including lungs, heart, muscle, kidneys, dura mater, and testes. In one case of NSF, progressive fibrosis of the diaphragm eventually led to death from respiratory failure. Examination of skin biopsy samples from patients with NSF reveals haphazardly-arranged thickened dermal collagen bundles interspersed with increased numbers of plump fibroblasts and mucin deposition. The skin of some patients harbors osteoclast-like giant cells with focal areas of calcification and ossification. The histology resembles that of a healing wound. Fibrocytes positive for CD34 and procollagen-1 are found in affected tissue. These fibrocytes originate in bone marrow and are drawn to the dermis by an unknown stimulus (possibly gadolinium deposition). After migrating to the dermis, the fibrocytes differentiate into cells...
that resemble normal fibroblasts and could be responsible for the excessive fibrosis.64,70,71

TREATMENT OF NEPHROGENIC SYSTEMIC FIBROSION
Treatment of NSF is often unsuccessful. Most therapies have only been tested informally and the results published as case reports. NSF can improve with recovery of renal function after, for example, successful kidney transplantation or resolution of AKI. Published reports of treatments are often of limited value as they do not comment on the course of renal dysfunction. Disease regression must be interpreted in light of GFR; improvement of NSF in the setting of a rising GFR might result from reversal of the renal lesion and not from therapy for NSF per se. Ultraviolet A1 treatment was reported to be successful in one patient, but reversal of AKI might have been the true cause of improvement.72 Plasmapheresis was reportedly effective in another patient, but, again, improvement of renal function could have been the actual cause of recovery.57 Extracorporeal photopheresis was beneficial in three patients whose kidney function did not improve.57 Sodium thiosulfate was reported to improve symptoms in a patient with ESRD on chronic hemodialysis.73 The mobility of one peritoneal dialysis patient partially improved after the first, but not subsequent, courses of intravenous immunoglobulin.74 Physical therapy is recommended to prevent and treat joint contractures.

GADOLINIUM CLEARANCE AND RENAL DISEASE
The half-life and clearance of gadolinium chelates have been examined in patients with CKD or ESRD who are on hemodialysis or peritoneal dialysis.36,39,73–82 Swan et al.81 measured concentrations of gadolinium in serum, urine and stool after a single dose of gadobenate dimeglumine (0.2 mmol/kg) in patients with varying degrees of renal function. In people with a normal GFR, the half-life of gadolinium was 1.96 hours. It increased to 6.11 ± 2.95 hours in those with a GFR of 31–60 ml/min per 1.73 m² and to 9.48 ± 3.08 hours in those with a GFR of 10–30 ml/min per 1.73 m². Other studies of the half-life of gadobenate dimeglumine and gadoversetamide in patients with CKD yielded similar results.79,80 In nine patients with stage 5 CKD (GFR 2–10 ml/min per 1.73 m²) who received a single dose of gadodiamide (0.1 mmol/kg), Joffe and co-workers found that the half-life of gadolinium was prolonged to 34.3 ± 22.9 hours.39

There have been several studies of gadolinium pharmacokinetics in hemodialysis patients; data from peritoneal dialysis patients are limited. Published reports have several limitations. For example, conclusions are often drawn on the basis of decay curves of serum gadolinium concentration. During formulation of these curves, it is assumed that gadolinium is removed from serum solely by dialysis. This might not be the case; sequestration of gadolinium in interstitial or intracellular compartments would be erroneously interpreted as dialytic removal. Joffe et al.39 noted that the half-life of gadolinium (gadodiamide; 0.1 mmol/kg) during hemodialysis was 2.6 ± 0.4 hours when a low-flux biocompatible dialyzer was used for 4 hours three times per week. The authors reported that one hemodialysis session removed 65% of gadolinium; however, gadolinium levels in dialysate were not measured. Saitoh and colleagues78 reported a gadolinium half-life of 1.93 hours during hemodialysis in 13 patients dialyzed with a 1.5 m² synthetic-polymer dialyzer at low dialysate flow rates (200 ml/min). Gadodiamide was the administered chelate (0.1 mmol/kg), and dialysis was carried out on days 1, 3, and 5 after exposure to gadolinium. The estimated proportion of gadolinium removed after each of these three dialysis sessions was 73.8%, 92.4%, and 98.9%, respectively; however, dialysate was only collected during the first hemodialysis session. Okada and co-workers36 studied 70 hemodialysis patients who received a 0.1 mmol/kg dose of gadopentetate dimeglumine, and estimated the proportions of gadolinium removed after four 4-hour dialysis sessions to be 72.8%, 95.6%, 98.7%, and 99.5%. Dialysate samples were not collected—percentage gadolinium removal was estimated on the basis of serum concentration decay curves. The first dialysis session occurred at variable intervals after gadolinium administration (same day in 16 patients, next day in 34 patients, 2 days later in 14 patients, and 3 days later in 6 patients). The type of dialyzer used in the study was not reported.

Data from the largest series of peritoneal dialysis patients who had received a gadolinium chelate were reported by Joffe et al.39 Nine patients underwent continuous ambulatory peritoneal dialysis with four exchanges per day. Dialysate was collected and gadolinium half-life was estimated to be 52.7 ± 6.2 hours. Only 69% of gadolinium had been removed after 22 days of peritoneal dialysis. In a case report of another peritoneal dialysis patient, who had received gadoversetamide (0.1 mmol/kg),
the gadolinium half-life was reported to be 9 hours. The patient, however, was producing 3 liters of residual urine per day. The rate of removal of gadolinium by peritoneal clearance was low in both studies, at 3.8 ± 0.6 ml/min and 5.13 ml/min, respectively.

We will not review in vitro studies in detail in this article, but some useful insights can be gained from them. First-order kinetic modeling showed that 12.2–14.7 hours of dialysis were required to remove 97% of an injected gadolinium dose. Gadolinium clearance during dialysis is more efficient when membranes with a large pore size are used, and nonionic gadolinium chelates are more easily removed via positively-charged dialysis membranes thanionic gadolinium chelates (see Table 1 for charge status of gadolinium chelates).

LABORATORY ABNORMALITIES ASSOCIATED WITH GADOLINIUM

Gadolinium chelates interfere with a wide variety of assays. The most widely reported laboratory artifact associated with gadolinium is pseudohypocalcemia. Gadolinium can also reduce ACE levels, alter serum iron concentration (reduce or elevate, depending on the assay), increase total iron-binding capacity, and lower serum zinc levels.

Pseudohypocalcemia was first reported to be associated with gadolinium in 1995. It is most common for gadolinium to affect colorimetric assays that employ orthocresolphthalein (OCP), the agent most frequently used to measure calcium concentration. Pseudohypocalcemia does not occur when assays that employ atomic emission spectroscopy or ion-selective electrodes are used. Artifactual reduction of calcium concentration is thought to result either from binding of gadolinium to OCP, which prevents OCP from binding calcium, or from binding of calcium to the excess chelate that is included in some (but not all) gadolinium chelate preparations. Gadodiamide has 0.025 mmol/ml of excess chelate and gadopentetate dimeglumine 0.001 mmol/ml; gadoterate meglumine contains no excess chelate. The purpose of including excess chelate in gadolinium preparations is to maintain gadolinium binding during storage.

In a study by Prince et al. of 896 patients whose serum calcium level was measured within 24 hours of gadodiamide administration, 165 developed pseudohypocalcemia. Calcium concentration declined by more than 0.5 mmol/l (2 mg/dl) in 42 patients, and in 25 patients was less than 1.5 mmol/l (6 mg/dl). Oral or intravenous calcium was administered to 18 patients for what was mistakenly interpreted as ‘true’ hypocalcemia, even though the patients had no clinical symptoms of the disorder. The pseudohypocalcemic effect persisted for up to 4.5 days in patients with CKD, and was more pronounced at high doses of gadodiamide. In patients with a normal GFR who had received low-dose gadodiamide, pseudohypocalcemia lasted 4–6 hours. In those whose GFR was reduced, the artifact persisted for more than 24 hours. Recommended minimum waiting times from administration of contrast medium to collection of plasma sample have been established for the Roche OCP assay (Hitachi 747 analyzer; Roche Diagnostics, Indianapolis, IN) on the basis of GFR (Table 4).

Kang et al. also examined the effect of several different gadolinium chelates on in vitro calcium concentrations. Gadodiamide and gadoversetamide both reduced calcium levels, whereas gadoteridol and gadopentetate dimeglumine did not. Interestingly, both the gadolinium chelates that cause pseudohypocalcemia in vitro are packaged with higher concentrations of excess chelate—331 mg/ml for gadoversetamide and 12 mg/ml for gadodiamide versus 0.2 mg/ml for gadoteridol and 0.4 mg/ml for gadopentetate dimeglumine. This fact indicates that pseudohypocalcemia might be the result of calcium binding to excess infused chelate, rather than of dissociation of gadolinium from chelate in vivo.

### Table 4

Recommended minimum waiting time from administration of contrast medium to collection of plasma sample for the measurement of calcium.

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<th>Estimated glomerular filtration rate (ml/min per 1.73m²)</th>
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The reduction in ACE levels observed after gadolinium administration is thought to result from binding of zinc by the chelate; measurement of ACE is zinc dependent. Iron concentration is increased by gadolinium when the Vitros® 950 (Ortho-Clinical Diagnostics, Raritan, NJ) and Synchron LX® 20 (Beckman Coulter, Brea, CA) assays are used. Likewise total iron-binding capacity is increased by gadolinium when either the Modular P or Dimension RxL (Roche Diagnostics, Indianapolis, IN, and Dade Behring, Deerfield, IL, respectively) methods are used to quantify this parameter. The formazan dye employed in the zinc assay probably binds gadolinium, resulting in a falsely low concentration of zinc being detected.

RECOMMENDATIONS FOR USE OF GADOLINIUM

The FDA, Danish Medicines Agency (DMA), United Kingdom Medicines and Healthcare products Regulatory Agency (MHRA), and American College of Radiology (ACR), among other organizations, have published recommendations regarding gadolinium use. Selected recommendations by these agencies have been chosen to frame our discussion of some of the more-controversial issues. The MHRA has submitted a public assessment report to the European Medicines Agency, but this statement does not represent the view of all member states. The DMA report is an independent Danish publication. The ACR recommendations were derived from a ‘blue ribbon’ panel and represent consensus of ACR members; they have not, however, been adopted as policy by the ACR.

The FDA is the only agency to suggest that all gadolinium chelates are potentially linked to NSF. The other three organizations mentioned above specifically implicate gadodiamide as being associated with the highest risk for NSF. This assertion is based on the fact that most cases of NSF are associated with this gadolinium preparation. The DMA and MHRA view gadodiamide as being contraindicated in patients with a GFR of less than 30 ml/min per 1.73 m² whereas the ACR recommends avoiding gadodiamide in patients with any degree of renal dysfunction. Although the FDA does not state that any specific preparation is contraindicated, it does recommend that physicians carefully consider the need for any gadolinium chelate in patients with moderate kidney dysfunction to ESRD. The ACR and MHRA regard gadoversetamide and gadopentetate dimeglumine as being associated with an increased risk of NSF, but do not specifically recommend that these agents be avoided. As gadodiamide is the agent most often associated with NSF in reported cases, we agree with the ACR and Kuo et al. that use of this preparation be avoided in patients with any degree of renal dysfunction. It is also prudent to avoid using gadoversetamide and gadopentetate dimeglumine until more data regarding their risk become available. These agents are reported to cause NSF and, like gadodiamide, have a linear structure and short dissociation half-lives.

The MHRA report states that serum creatinine concentration should be measured before gadolinium administration. By contrast, the ACR recommends relying on information regarding kidney disease provided by the referring physician or by the patient via a questionnaire. Given that even patients with advanced CKD are often unaware of their disease, we agree with the MHRA that a serum creatinine concentration should be obtained by the referring physician if a gadolinium chelate is to be administered. If a patient has any history of kidney disease, determination of serum creatinine level should be required by the radiology department within 30 days before the imaging procedure, or sooner if there is a clinical concern about recent deterioration in GFR (e.g. a preceding iodinated contrast study). We recognize that NSF is a rare occurrence in patients with stage 3 or 4 CKD, but we feel that this recommendation is justified given the serious consequences of the disorder.

The need for a gadolinium-based contrast study should be carefully considered in a patient with CKD stage 3 or greater and alternative imaging modalities should be considered. The lowest possible dose of gadolinium should be used because development of NSF might be dose related. The use of gadolinium in angiographic studies as an alternative to iodinated contrast should be carefully evaluated because the dose required is often high and recent studies indicate that gadolinium is nephrotoxic (see Table 3). Other recommendations that are consistent with those in published literature and prudent to adopt are that standard gadolinium doses should not be exceeded and repeat doses should not be given in less than 1 week, that gadodiamide should be avoided in patients with renal dysfunction who have had or are about to undergo liver transplantation, and that postponing the imaging study until renal function has recovered in patients with AKI should be considered.
Perhaps the most controversial issue is the need for post-gadolinium hemodialysis; there is a marked difference of opinion on this topic among recommending bodies. The FDA originally stated that it might be prudent to promptly initiate hemodialysis after administration of gadolinium chelates to patients with advanced kidney dysfunction (stage 5 CKD or ESRD). The most recent FDA update (23 May 2007) recommended consideration of prompt post-gadolinium dialysis only in patients who were already on hemodialysis (the term “prompt” is not defined in the recommendation). The FDA also stated that it is not known whether hemodialysis prevents NSF. The ACR advocates hemodialysis within 2 hours of gadolinium administration in patients already on hemodialysis. There is, as yet, no evidence to support this recommendation. The MHRA does not consider hemodialysis to be indicated in such instances, due to a lack of evidence regarding its efficacy. The risks associated with post-gadolinium hemodialysis are minimal for stable ESRD patients with functioning accesses; as such, the FDA recommendation is reasonable. The MHRA correctly asserts, however, that there is no evidence that hemodialysis will prevent NSF. Data reported by Broome and co-workers for three patients who developed NSF despite three consecutive daily hemodialysis sessions clearly show that NSF can still develop despite aggressive dialysis. Assumptions about gadolinium removal from the body that are made on the basis of plasma concentration decay curves might lead to overestimation of the efficiency of gadolinium clearance by hemodialysis.

The risk of developing NSF after gadolinium exposure in patients with stage 3–5 CKD is unknown, but seems to be less than the 2.5–4.0% postulated for the ESRD population. NSF has developed in two patients with stage 3 CKD; one patient was a renal allograft recipient, the other a liver transplant recipient, and GFR was declining in both at the time of multiple exposures to gadolinium. It is probable that the true GFR of both patients was lower than that estimated using the Modification of Diet in Renal Disease equation. The FDA’s original warning in June 2006 and subsequent update in December of that year stated that patients with a GFR of less than 60 ml/min per 1.73 m² were at risk of developing NSF after exposure to gadolinium. In the most recent update (23 May 2007), the GFR cutoff had been changed to less than 30 ml/min per 1.73 m². Five patients with stage 4 CKD have developed NSF after gadolinium administration. All had been exposed to gadolinium several times. One patient had undergone renal transplantation, two had undergone liver transplantation, and two had advanced stage 4 CKD (estimated GFR 17–18 ml/min per 1.73 m²).

Taken together, these findings indicate that subgroups of patients with CKD stage 3 or 4 might be at increased risk of developing NSF after gadolinium administration. These subgroups include those exposed to gadolinium more than once, liver graft recipients, and patients for whom the Modification of Diet in Renal Disease equation might overestimate true GFR (e.g. organ transplant recipients and those with AKI superimposed on CKD). The risk of developing NSF increases as GFR declines through CKD stages 3, 4 and 5 to ESRD, with a very low risk in CKD stage 3 and a 2.5% risk per exposure for patients with ESRD. We agree with the MHRA that the evidence to date does not justify the risks that are associated with acute access placement and hemodialysis after gadolinium exposure. Every effort should be made to postpone any gadolinium-enhanced imaging procedures in patients with AKI. At our institution, gadoteridol was in use before the association between NSF and gadolinium chelates was recognized. We will continue to use gadoteridol in preference to other FDA-approved gadolinium chelates because patients receiving gadoteridol have the lowest reported incidence of NSF.

Decisions regarding the benefit of hemodialysis for gadolinium clearance are also difficult when managing peritoneal dialysis patients. Peritoneal dialysis seems to be an inefficient means of removing gadolinium. It should be pointed out, however, that this opinion is based on data derived from patients maintained on older chronic ambulatory peritoneal dialysis regimens. Improved clearance might be possible with more-aggressive cycler-based regimens, and this possibility warrants further study. That said, data from the Morbidity and Mortality Weekly Report indicating that the incidence of NSF in gadolinium-exposed peritoneal dialysis patients is 7.5 times higher than that in hemodialysis patients is alarming. It seems prudent to avoid exposing peritoneal dialysis patients to gadolinium if possible, until the risk is further clarified. If gadolinium must be used, gadoteridol should be considered as the first choice of chelate. Initiating post-exposure hemodialysis should be considered, especially if the patient has a functioning access. Alternatively, the peritoneal dialysis prescription could be increased. It should be emphasized, however, that
these approaches might not prevent NSF and there are no data to support them.

CONCLUSIONS

Over time, the number of indications for, and doses of, gadolinium chelates have increased beyond those originally approved by the FDA. Although these increases have probably not compromised the safety of patients with normal renal function, for those with a reduced GFR the risk of developing NSF is now a concern. A strong association between NSF and gadolinium-based agents has emerged from retrospective analyses. Gadolinium has been detected in affected tissue, but there is as yet no definitive proof that gadolinium is the cause of NSF. Treating an animal model such as a 5/6 nephrectomized rat with gadolinium chelates might provide some insight into causal relationships. Until more data become available, it is advisable to avoid using gadolinium chelates (particularly gadodiamide) whenever possible in people with severe kidney disease to ESRD. As gadolinium chelates are nephrotoxic, their use should no longer be considered ‘safe’ in terms of CIN. If a gadolinium chelate is administered, the physician should be familiar with associated laboratory artifacts so that unnecessary treatment is not initiated on the basis of erroneous values.

KEY POINTS

- Originally thought to be safe contrast agents, gadolinium chelates have recently been shown to be associated with the development of nephrogenic systemic fibrosis (NSF) in patients with impaired renal function.
- NSF, previously known as nephrogenic fibrosing dermopathy, occurs only in patients with kidney dysfunction, is characterized by waxy thickening of the skin of the extremities and torso, and commonly leads to joint contractures and immobility.
- The proposed, but not yet proven, etiology of NSF is tissue deposition of free gadolinium that is liberated from chelates, secondary to prolonged gadolinium clearance time due to impaired renal function.
- Treatments for NSF have only been tested informally; the condition has been shown to improve in response to recovery of kidney function.
- Several authorities have issued recommendations for use of gadolinium chelates; most advise caution when considering use of these agents in patients with renal dysfunction.

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Competing interests
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