Contains the following two sections:
-- Adverse Reactions to Gadolinium-Based Contrast Media
-- Nephrogenic Systemic Fibrosis

Reprinted with permission of the American College of Radiology. A full text of the ACR Manual on Contrast Media, Version 6 is available at:

No other representation of this material is authorized without expressed, written permission from the American College of Radiology.
Gadolinium chelates have been approved for parenteral use since the late 1980s. Although these agents can be differentiated on the basis of stability, viscosity, and osmolality, they cannot be differentiated on the basis of efficacy. Gadolinium chelates are extremely well tolerated by the vast majority of patients in whom they are injected. Acute adverse reactions are encountered with a much lower frequency than is observed after administration of iodinated contrast media.

Adverse Reactions

The frequency of all acute adverse events after an injection of 0.1 or 0.2 mmol/kg of gadolinium chelate ranges from 0.07% to 2.4%. The vast majority of these reactions are mild, including coldness at the injection site, nausea with or without vomiting, headache, warmth or pain at the injection site, paresthesias, dizziness, and itching. Reactions resembling an “allergic” response are very unusual and vary in frequency from 0.004% to 0.7%. A rash, hives, or urticaria are the most frequent of this group, and very rarely there may be bronchospasm. Severe, life-threatening anaphylactoid or non-allergic anaphylactic reactions are exceedingly rare (0.001% to 0.01%). In an accumulated series of 687,000 doses there were only 5 severe reactions. In another survey based on 20 million administered doses there were 55 cases of severe reactions. Fatal reactions to gadolinium chelate agents occur but are extremely rare.

Gadolinium chelates administered to patients with acute renal failure or severe chronic kidney disease can result in a syndrome of nephrogenic systemic fibrosis (NSF) (See chapter on NSF).

Risk Factors

The frequency of acute adverse reactions to gadolinium contrast media is about 8 times higher in patients with a previous reaction to gadolinium-based contrast media. Second reactions to gadolinium-based media tend to be more severe than the first. Persons with asthma and various allergies are also at greater risk, with reports of adverse reaction rates as high as 3.7%. Although there is no cross-reactivity, patients who have had previous allergic-like reactions to iodinated contrast media are also in this category.

In the absence of any widely accepted policy for dealing with patients with prior contrast reactions (especially to gadolinium-based media) and the need for subsequent exposure to magnetic resonance (MR) agents, it does seem prudent to at least take precautions. It should be determined if gadolinium-based contrast medium is necessary, if a different brand could be used, and if 12 to 24 hours of premedication with corticosteroids and antihistamines could be initiated. This administration is particularly applicable in patients with prior moderate to severe reactions to gadolinium-based contrast media.

Nephrotoxicity

Gadolinium agents are considered to have no nephrotoxicity at approved dosages for MR imaging. MR with gadolinium has been used instead of contrast-enhanced CT in those at risk for developing worsening renal failure if exposed to iodinated contrast media. However in view of the risk of NSF in patients with severe renal dysfunction, this practice should only be considered after reviewing the recommendations for use of gadolinium-based contrast in this group of patients.
Gadolinium agents are radiodense and can be used for opacification in CT and angiographic examinations instead of iodinated radiographic contrast media. However, there is controversy about whether gadolinium contrast media are less nephrotoxic at equally attenuating doses. Caution should be used in extrapolating the lack of nephrotoxicity of intravenous gadolinium at MR dosages to its use for angiographic procedures, including direct injection into the renal arteries. No assessment of gadolinium versus iodinated contrast nephrotoxicity by randomized studies of equally attenuating doses is currently available. Initially, radiographic use of high-doses of gadolinium agents was proposed as an alternative to nephrotoxic iodinated contrast media in patients with renal insufficiency. However, because of the risk of NSF following gadolinium-based contrast material administration, especially in patients with acute renal failure or severe chronic kidney disease, and because of the unknown nephrotoxicity of high-doses of gadolinium agents, use of these contrast media for conventional angiography is no longer recommended.

Treatment

Treatment of moderate or severe acute adverse reactions to gadolinium-based contrast media is similar to that for moderate or severe acute reactions to iodinated contrast media (see Tables 3 through 6). In any facility where contrast media are injected, it is imperative that personnel trained in recognizing and handling reactions and the equipment and medications to do so be on site or immediately available. Most MR facilities take the position that patients requiring treatment should be taken out of the imaging room immediately and away from the magnet so that none of the resuscitative equipment becomes a magnetic hazard.

Extravasation

The incidence of extravasation in one series of 28,000 doses was 0.05%. Laboratory studies in animals have demonstrated that both gadopentetate dimeglumine and gadoteridol are much less toxic to the skin and subcutaneous tissues than are equal volumes of iodinated contrast media. The small volumes typically injected for MR studies limit the chances for a compartment syndrome. For these reasons the likelihood of a significant injury resulting from extravasated MR contrast media is extremely low. Non-ionic contrast media are less likely to cause symptomatic extravasation than hypertonic agents such as gadopentetate dimeglumine.

Serum Calcium Determinations

Some gadolinium-based MR contrast media interfere with total serum calcium values as determined with some calcium assay methods. It should be emphasized that these MR contrast media do not cause actual reductions in serum calcium, only that the contrast media interfere with the test, leading to falsely low serum calcium laboratory values. In one report by Brown and associates, calcium levels measured by only one of three different assays (the orthocresolphthalein assay) showed a temporary decrease for just two of four studied gadolinium-based contrast media, the length and severity of which closely mirrored the concentration of the measured gadolinium-based media in blood. This decrease was seen after injection of gadoversetamide and gadodiamide, but not with gadopentetate dimeglumine or gadoteridol.

Off-Label Usage

Radiologists commonly use contrast media for a clinical purpose not contained in the labeling and thus commonly use contrast media off-label. By definition, such usage is not approved by the Food and Drug Administration and the legal ramifications
are unclear. Physicians have some latitude in using gadolinium chelates off label as guided by clinical circumstances but must be prepared to justify such usage in individual cases. Examples include MR angiography, cardiac applications, and pediatric applications in patients younger than two years of age.

REFERENCES


NEPHROGENIC SYSTEMIC FIBROSIS (as of 10/06/2008)

Definition

Nephrogenic systemic fibrosis (NSF) is a fibrosing disease, primarily identified in the skin and subcutaneous tissues but also known to involve many other organs, such as the lungs, esophagus, heart, and skeletal muscles. Initial symptoms typically include skin thickening and/or pruritis. Symptoms and signs may develop and progress rapidly, with some affected patients developing contractures and joint immobility. Death may result in some patients, presumably as a result of visceral organ involvement.

Associations

When first described in 1997 the disease was noted to occur predominantly in patients with severe chronic kidney disease (CKD), particularly in patients on chronic dialysis. Initially, no other association was identified; however, in 2006 several groups noted a strong association between gadolinium-based contrast media (GBCM) administration and the disease. In fact, all patients in the two earliest reports [1,2] had been injected with one of the GBCM: gadodiamide. Subsequently, although the majority of affected patients still appear to have been exposed to gadodiamide (Omniscan – General Electric Healthcare), additional reports have implicated all of the other GBCM available in the United States: gadopentetate dimeglumine (Magnevist® – Bayer HealthCare Pharmaceuticals), gadoversetide (Optimark® – Covidien), gadobenate dimeglumine (MultiHance® – Bracco Diagnostics), and gadoteridol (ProHance® – Bracco Diagnostics), but at lower rates (although in many cases, affected patients had been injected with more than one type of GBCM prior to symptoms onset) [3-5].

In a 2007 survey by the American College of Radiology, 156 cases of NSF were reported by 27 responding institutions; 140 of these 156 patients were known to have received GBCM. In 78 patients, the specific GBCM was known. Forty-five of them received gadodiamide, 17 gadopentetate dimeglumine, 13 gadoversetamide, and three gadobenate dimeglumine. (ACR unpublished data.) NSF following gadoteridol administration has been reported elsewhere. Many of the cases in which agents other than gadodiamide and gadopentetate dimeglumine were utilized are confounded by the fact that affected patients were injected with other agents as well.

It must be emphasized that the frequency with which NSF has been associated with different GBCM may reflect a combination of differences in agent toxicity and market share. In addition, reported frequency may also have been affected if some agents were used at higher doses disproportionately more frequently than others.

At this time very few pediatric cases of NSF have been reported, and no cases have been reported in children under the age of 7 years. It is not safe, however, to assume that NSF is any less likely to occur in children than in adults. It is therefore prudent to follow the guidelines for adults, described in the remainder of this document on NSF, for all pediatric patients.

Interval between GBCM Administration and Symptom Onset

A number of studies have noted the time between injection of GBCM and the onset of symptoms to be within days to six months in the vast majority of patients [1,2,58].

Incidence

Based on current knowledge it is estimated that patients with severe CKD have a 1% to 7% chance of developing NSF after exposure to GBCM [1-3,5-8], although in one series, in which the diagnosis was made
only clinically rather than histologically in most patients, the incidence was reported to be even higher [9]. It is important to note that NSF has been encountered in patients who have severe acute as well as severe chronic renal dysfunction.

**Additional Risk Factors**

Many of the published series have suggested that patients are at highest risk when they are exposed to high doses or multiple doses of GBCM. Nonetheless, there are reported instances of NSF occurring in patients who have been exposed to standard (0.1 mmol/kg) single doses of GBCM [8,10], or who have no known GBCM exposure [11]. Conversely, some patients with severe CKD who have received many doses of GBCM have not developed NSF [8]. Some researchers have also observed that a disproportionate number of affected patients have had severe liver as well as renal dysfunction. Indeed, many of the reported cases have been liver transplant candidates or recent liver transplant recipients [7,8].

A number of other comorbidities have been postulated to explain why some patients with severe CKD who are exposed to GBCM develop NSF and some do not. These include increasing cumulative GBCM exposure [12], metabolic acidosis or medications that predispose patients to acidosis [1,4], increased iron, calcium, and/or phosphate levels [4,12,13], high-dose erythropoietin therapy [12], immunosuppression [5], vasculopathy [14], an acute pro-inflammatory event [7,15], and infection alone [16], all at the time of GBCM exposure. None of these potential risk factors has been demonstrated consistently to be present in all affected patients in all studies. Therefore, at the present time, none of these risk factors can be considered to have been established as a true comorbidity with a high degree of confidence.

**Postulated Mechanism**

The exact mechanism of NSF is unknown; however, the most widely held theory is that the gadolinium ion dissociates from its chelate in patients with severe CKD, due to the prolonged clearance of the GBCM in CKD patients as well as to other metabolic factors associated with CKD. This dissociation occurs by a process known as transmetallation, whereby other cations replace the gadolinium on the chelate. Suspected cations include protons (in acidic environments), calcium, and rare metals. The free gadolinium then binds with other anions (such as phosphate), and the resulting insoluble precipitate is deposited in the skin and subcutaneous tissues (as well as at other locations) via a process that is still poorly understood [3,17]. A fibrotic reaction ensues, involving the activation of circulating fibrocytes [17,18]. Though still speculative, this theory is worthy of further investigation. It is unlikely that all GBCM are equally prone to transmetallation in vivo. If gadolinium dissociation from its chelate is eventually proved to contribute to, or even be primarily responsible for, the induction of NSF in many patients, the various GBCM eventually may be shown to differ in their NSF safety profiles in at-risk patients.

**Recommendations for Identifying High-Risk Groups**

A number of precautions have been recommended by the Food and Drug Administration (FDA) and the American College of Radiology (ACR) Committee on MR Safety in patients who have severe renal failure (generally defined as patients who have estimated glomerular filtration rates of less than 30 ml/min/1.73m²) [19,20]. In order to identify these patients, it is recommended that all patients be questioned for a history of renal disease. According to the FDA (www.fda.gov/CDER/drug/advisory/gadolinium_agents.htm) this could be accomplished by obtaining a history and/or laboratory tests. The ACR Committee on MR Safety (www.acr.org/Secondary
 MainMenuCategories/quality_safety/MRSafety/recommendations_gadolinium-based.aspx) recommends obtaining an estimated GFR within six weeks of an anticipated GBCM-enhanced study in patients with renal disease (including a solitary kidney, renal transplant, or renal neoplasm), in anyone over 60 years of age, or in patients with hypertension, diabetes mellitus, or a history of severe liver disease (including prior liver transplantation), with strong consideration of contemporaneous assessment in this last group as well as in patients who present acutely, including hospital inpatients.

**Recommendations for Imaging High-Risk Patients**

Once a high risk patient is identified, a number of additional recommendations can be made [19,20], including considering alternative studies, informing such patients about the potential risks of GBCM-enhanced magnetic resonance imaging (MRI) studies should such studies be deemed necessary despite the risks, using the lowest possible dose of GBCM required to obtain the needed clinical information, avoiding double or triple dose studies if at all possible, and avoiding those GBCM that have been most frequently associated with NSF.

**Specific Recommendations for High-Risk Groups**

*Patients with end-stage renal disease on chronic dialysis*

If a contrast-enhanced cross-sectional imaging study is required in this group of patients, it would be reasonable to consider administering iodinated contrast media and performing a CT rather than an MR when such a substitution is deemed possible. If a contrast-enhanced MR examination must be performed, the ACR Committee on MR Safety has recommended that GBCM-enhanced MRI exams could be performed shortly before dialysis, as prompt post-procedural dialysis may reduce the likelihood that NSF will develop, although this has not been proved definitively to date. For example, in one study, three patients who developed NSF received dialysis for three consecutive days beginning at 9, 17, and 18 hours after GBCM administration [21]. Because it may be difficult for a busy dialysis center to alter dialysis schedules at the request of imaging departments, it may be more feasible for the imaging studies to be timed to precede a scheduled dialysis session.

*Patients with CKD 4 or 5 (eGFR < 30 ml/min/1.73m²) not on chronic dialysis*

The correct course of action in this patient group is most problematic, as administration of iodinated contrast media for CT could worsen renal function and lead to the need for dialysis, while administration of GBCM for MRI could lead to NSF. Recent data suggests that the risk of NSF may be greatest of all in patients with an eGFR of < 15 ml/min/1.73m² and much less in patients with eGFRs that are higher. Accordingly, it is recommended that any contrast media administration be avoided if at all possible. If MRI contrast media administration is absolutely essential, judicious use of the lowest possible doses (needed to obtain a diagnostic study) of selected GBCM is probably safest. In this setting, the patient and his or her referring physician must be informed of the risks of GBCM administration and must give their consent to proceed. There is no proof that any GBCM is completely safe in this patient group; however, at the present time, should GBCM use be required in these patients, some have suggested avoiding gadodiamide and considering use of macrocyclic agents [22].

*Patients with CKD 3 (eGFR 30 to 59 ml/min/1.73m²)*

Assuming an accurate assessment of renal function can be made and that the patient is stable, this group can be considered to be at extremely low or no risk for developing
NSF (as long as a dose of GBCM of 0.1 mmol/kg or less is utilized).

Patients with CKD 1 or 2 (eGFR 60 to 119 ml/min/1.73m²)

Currently, there is no evidence that patients in these groups are at increased risk of developing NSF. Current consensus is that all GBCM can be administered safely to these patients.

Patients in acute renal failure

Administration of iodinated contrast media for CT is to be avoided in this group, as there may be otherwise recoverable renal function. GBCM should only be administered if absolutely necessary. The lowest dose necessary to achieve a diagnostic study should be administered. Again, current evidence suggests that gadodiamide should be avoided in these patients.

Other

The ACR Committee on MR Safety has also advised that GBCM generally should not be administered to patients who have fluid in spaces in which the GBCM may reside for long periods of time (such as the peritoneal cavity in patients with ascites or the amniotic cavity in pregnant women).

Caveat

It must be stressed that information on NSF and its relationship to GBCM administration is still very preliminary, and the summary included here represents only the most recent opinions of the ACR Committee on Drugs and Contrast Media (as of May 1, 2008). As additional information becomes available our understanding of causative events leading to NSF and recommendations for preventing it will likely change.

REFERENCES
