

## ADVERSE REACTIONS TO GADOLINIUM-BASED CONTRAST MEDIA

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 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 nonallergic 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 the 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 (GBCM) can be more severe than the first. Persons with asthma and various other allergies, including to other medications or foods 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 in a patient who previously had a reaction to GBCM. 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 who had prior moderate to severe reactions.

### *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 (IV) 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.

#### *The Safety of Gadolinium-Based Contrast Media (GBCM) in Patients With Sickle Cell Disease*

Early *in vitro* research dealing with the effects of MRI on red blood cells (erythrocytes) suggested that fully deoxygenated sickle erythrocytes align perpendicularly to a magnetic field. It was hypothesized that this alignment could further restrict sickle erythrocyte flow through small vessels and, thus conceivably could promote vaso-occlusive complications in sickle cell patients [1]. The further supposition that the IV administration of GBCM might potentiate sickle erythrocyte alignment, thereby additionally increasing the risk of vaso-occlusive complications, is

mentioned in the FDA package inserts (as of 2009) for two GBCM approved for use in the United States (gadoversetamide [OptiMARK, Mallinckrodt] and gadoteridol [Prohance, Bracco Diagnostics]).

To the best of our knowledge and noted in a review [2] of the literature, there has been no documented *in vivo* vaso-occlusive complication directly related to the IV administration of a GBCM in a sickle cell disease patient. Several small scientific studies [3-5] of sickle patients have employed MR imaging with GBCM without reported adverse effects. In addition, a review [2] of the literature fails to provide evidence for clinically significant hemolysis following the IV administration of GBCM in sickle cell disease patients.

Therefore, it is our opinion that any special risk to sickle cell patients from IV administered GBCM at currently approved dosages must be extremely low, and there is no reason to withhold these agents from patients with sickle cell disease. However, as in nonsickle cell disease patients, GBCM should be administered only when clinically indicated.

#### *Treatment of Acute Adverse Reactions*

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, 4, 5 and 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. Nonionic MR contrast media are less likely to cause symptomatic extravasation than hypertonic agents such as gadopentate 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 interferes with the test, leading to falsely low serum calcium laboratory values. In one report by Brown [6] 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. Specifically, 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. However, physicians have

some latitude in using gadolinium chelates off label as guided by clinical circumstances, as long as they can justify such usage in individual cases. Examples include MR angiography, cardiac applications, and pediatric applications in patients younger than two years of age. In addition, no gadolinium chelate is approved in the United States for use in a power injector.

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**Suggested Reading** (Articles that the Committee recommends for further reading on this topic are provided here.)

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