98. MR Contrast Agent Safety

Despite marketing strategies implying the contrary, no rigorous study has ever demonstrated a difference in the frequency of mild adverse reactions—which include nausea (1.5%) and urticaria (0.5%)—amongst the various gadolinium chelate contrast agents (and more specifically amongst the renally excreted extracellular agents). Severe anaphylactoid reactions with such agents are rare and even more rarely result in death. Treatment of anaphylactoid reactions to IV administration of a gadolinium chelate is similar to that for reactions induced by iodinated contrast media, initially consisting of cessation of agent injection and inhaled oxygen. Urticaria alone may only require use of diphenhydramine for treatment, whereas laryngeal edema and/or bronchospasm require administration of intramuscular epinephrine (1:1,000), supplemented for bronchospasm by an inhaled bronchodilator. The treatment of hypotension (alone, or with tachycardia) is fluid resuscitation. Hypotension with bradycardia (vagal reaction) may require in addition intravenous atropine. While MR provides a radiation-free alternative to CT in pregnant patients, gadolinium chelates do cross the placenta and persist in amniotic fluid. The effects of this are unknown, although no teratogenic consequences have been observed to date. Gadolinium chelates should only be administered in pregnancy if the desired information can be obtained by no other means and if such information is crucial to the fetus or patient imminently during pregnancy. If these pre-conditions are fulfilled, then macrocyclic agents should be administered at the smallest dose possible. Due to excretion in the breast milk, breast feeding should be avoided within 24 hours of gadolinium chelate administration. Unlike iodine-based contrast media, gadolinium chelates are not nephrotoxic. However, in patients with renal failure (GFR < 30 mL/min/1.73m²) such agents have been associated with nephrogenic systemic fibrosis (NSF), a potentially fatal disease first reported in 1997. NSF often manifests first in the legs with pain and swelling progressing to skin thickening and eventual contractures. Internal organ fibrosis may be seen later in the disease. The pathophysiology of NSF relates to in vivo dechelation with subsequent deposition of gadolinium ions in tissue inducing fibroblast proliferation. The vast majority of cases have occurred in renal failure patients who have received multiple, often high doses (such as those used in CE-MRA) of gadolinium chelates over time (with administration specifically of the less stable chelates)—the latter observation suggesting a cumulative dose dependence. Unlike with the rates of minor contrast reactions, the gadolinium chelates agents do differ in their association with NSF. The incidence of NSF depends on chelate stability and relates to the fundamental safety basis of the gadolinium chelates—that the gadolinium ion (a toxic transitional metal) must be tightly bound to the chelate providing
near complete renal clearance. The strength of this binding is related to chelate molecular structure. Specifically, macrocyclic agents are more stable than their linear counterparts, and among the latter, those bearing an ionic charge are more stable than those without. This correlates well with experience regarding the FDA-approved gadolinium chelates in the United States, where the majority of cases occurred. Omniscan—a non-ionic, linear agent—has been implicated in the majority of unconfounded (i.e. cases where only one agent has been administered) NSF cases in the US and worldwide. The rate of NSF with Omniscan given in patients with Stage 5 kidney disease (GFR < 15 mL/min/1.73m²) has been estimated to be as high as 18%. Optimark, another non-ionic, linear agent, is responsible for a smaller number of cases than Omniscan and Magnevist, the latter a more widely used, intermediate-stability ionic, linear chelate. When accounting for the lower market share of Optimark, however, the overall rate of NSF is higher for Optimark than for Magnevist. Soon after the association between NSF and gadolinium chelate administration became known, the European Union (EU) banned the use of Omniscan and Magnevist in patients with a GFR below 30 mL/min/1.73m². The manufacturer of Optimark subsequently voluntarily added a contraindication in patients at risk for NSF. The response of the FDA was initially muted, but with time changed to essentially reflect that of the EU.

In 2014, a second major concern was raised in regard to safety of the less stable gadolinium chelates, but this time in the entire group of patients receiving such agents (and specifically including patients with normal renal function). Omniscan, Optimark, Magnevist, MultiHance and Primovist/Eovist (all being linear gadolinium chelates) are now known to be associated with dentate nucleus hyperintensity, specifically high signal intensity within the dentate nucleus on T1-weighted scans seen pre-contrast after multiple prior contrast injections – due to dechelation and gadolinium deposition in association with macromolecules. This phenomenon has been shown not to occur with Dotarem, Gadavist/Gadovist and ProHance, the macrocyclic chelates. Dentate nucleus hyperintensity with the linear chelates reflects as well more general gadolinium deposition throughout the body (and specifically in the skin and bones), in these patients with normal renal function. In patients receiving a very high number of injections of the linear agents, hyperintensity is also observed in many other nuclei and structures within the brain. Preliminary reports to date have suggested clinical symptomatology in small subsets of patients. The European Commission ruled in November 2017 to suspend the whole-body marketing authorizations of the multi-purpose linear GBCAs (Omniscan, Optimark, Magnevist and MultiHance). The approval for the macrocyclic agents (Gadovist, ProHance and Dotarem) remains unchanged, with continued approval - at this time, for special indications - three linear GBCAs (Primovist and MultiHance specifically for delayed liver imaging only and...
Magnevist 2 mmol/L for intra-articular use. The chemical structures for the agents that remain on the European market, which is the world’s largest market, are shown in Figure 98.1. The action by the EU followed the March 10, 2017 recommendation of the Pharmacovigilance and Risk Assessment Committee (PRAC) of the European Medicines Agency (the equivalent of the FDA in Europe). Cited in the report was convincing evidence of gadolinium deposition in the brain months after injection of the linear agents. These recommendations were based on an extensive review of the safety of the gadolinium agents that began in March 2016. Like with NSF, the initial response of the FDA has been muted (with the US being the world’s second largest market for the gadolinium chelates), although it is anticipated that the FDA will with time rule in a similar fashion as the EU. In Japan, the world’s third largest market, the regulatory authorities have followed the lead set by the EU leaving only the macrocyclic agents in common clinical use.

Fig. 98.1