

## Contrast Agents: Safety Profile

Val M. Runge MD  
Scott and White Clinic and Hospital  
Texas A&M University Health Science Center  
Temple, Texas USA

### Introduction

Magnetic resonance contrast agents, in particular the gadolinium-based agents, are very safe and lack the nephrotoxicity (when injected intravenously) associated with iodinated contrast media. Minor adverse effects occur infrequently and include nausea, taste perversion, and hives. Whereas these agents cannot be differentiated on the basis of mild adverse effects, they do differ in regard to chelate stability, with clinical lab abnormalities known with the less stable agents. The issue of nephrogenic systemic fibrosis (NSF) and its relationship to the gadolinium chelates, and specifically their in vivo stability, is discussed in depth in the text that follows, together with recommendations for clinical practice.

### Gadolinium-based Agents

The vast majority of contrast-enhanced MR procedures are performed with agents based on chelates of the paramagnetic ion gadolinium (Gd 3+). Currently, nine gadolinium-based MR contrast agents are approved for use in one or more western countries. These include four agents approved in the United States, Europe and elsewhere, one approved in the United States and Canada only (OptiMARK), and four approved in Europe and elsewhere.

Details concerning the physicochemical properties of seven of these agents are given in Table 1. The first agent developed, gadopentetate dimeglumine (Magnevist), has a linear structure and is ionic in nature, with a net -2 charge of the gadopentetate chelate. The agent is formulated with two molecules of meglumine, each of which carries a charge of +1. The availability of Magnevist in Europe, the USA, and Japan (1988) was followed initially in Europe by gadoterate meglumine (Dotarem) which has a cyclic structure but is again ionic (with a net -1 charge of the gadoterate chelate), and subsequently in both Europe and the USA by gadoteridol (ProHance) and gadodiamide (Omniscan) which are non-ionic agents (no net charge) with cyclic and linear structures, respectively. Of these four agents, ProHance and Dotarem have the highest combined thermodynamic and kinetic stability, reflecting the greater energy and time required to remove the gadolinium ion from the ring structure in which it is held. Omniscan, on the other hand, has the lowest stability. The molecular structures of the more recently approved gadolinium chelates, gadobenate dimeglumine (MultiHance), gadobutrol (Gadovist) and gadoversetamide (OptiMARK), are not dissimilar from those of Magnevist, ProHance and Omniscan, respectively, and this is reflected in the corresponding stability constants. Of note is OptiMARK, a linear, non-ionic agent similar to Omniscan, which shares with that agent the lowest (weakest) of all thermodynamic and conditional stability constants.

One agent within this group with novel features is MultiHance, the fifth gadolinium agent to be developed. Compared with the gadopentetate chelate structure of Magnevist, the gadobenate chelate of MultiHance is characterized by the presence of a hydrophobic benzyloxymethyl substituent. This confers on MultiHance two unique properties: hepatobiliary (although only 2 to 4%) as well as renal excretion, and a markedly higher T1 relaxivity compared to other gadolinium agents, due to weak, transient interaction with serum albumin. These features are advantageous for imaging of the CNS and liver and for MRA.

A second unique agent among the currently available gadolinium agents is gadobutrol (Gadovist), the only agent to be prepared commercially as a 1.0 M formulation. Like an early non-commercial 1.0 M formulation of ProHance, another macrocyclic gadolinium chelate with a similar molecular structure (cyclic) to Gadovist, the 1.0 M Gadovist formulation is feasible due to low viscosity and osmolality.

Gadoxetic acid disodium (Primovist) received approval in Europe in late 2004. Primovist is indicated for detection and characterization of liver lesions. This agent allows dynamic as well as hepatocyte-specific imaging due to fast hepatocyte uptake of ~50% of the dose. It is excreted by the kidneys (~50%) as well as by the liver (~50%), both pathways compensating for each other in the case of hepatic or renal failure, respectively. Due to its recent approval, post-marketing safety information is limited. In clinical trials 76/1755 patients (4.3%) reported contrast injection related adverse events. In common with the other previously approved gadolinium chelates, the most frequently reported adverse events (related to contrast injection) include nausea, vasodilatation, taste perversion and injection site pain.

Gadofosveset trisodium (MS-325, Vasovist) was approved by the European Commission for all 25 European

Union member states in October 2005. Approval was granted for MR angiography in adult patients with suspected or known vascular disease of the abdomen and/or extremities. To date, this contrast agent has also been approved in Australia, Canada and Switzerland (in the latter country, approval was granted for contrast-enhanced MRA in general). As the first marketed blood pool agent, gadofosveset trisodium belongs to a new class of contrast agents that bind reversibly to human serum albumin. Compared with conventional extracellular magnetic resonance contrast agents, albumin binding provides higher relaxivity and extended intravascular enhancement, the latter enabling high-resolution steady-state imaging. Due to the tight albumin binding, an interaction with plasma protein bound active substances is possible (and thus this class of agents could have a markedly different safety profile). However, in vitro drug interaction studies to date have demonstrated no such adverse effect.

An indirect measure of the inherent stability of the gadolinium-based contrast agents is the amount of excess chelate in the formulation. For many agents, the excess chelate is considered necessary because of the possibility for transmetallation with trace amounts of zinc in the blood and a resulting release of free gadolinium ion. Accordingly, the least stable agents (Omniscan and OptiMARK, the two agents with the weakest thermodynamic stability constants) each have considerably larger amounts of excess chelate (12 mg/ml and 28.4 mg/ml, respectively) than the most stable agents, Dotarem and ProHance (zero and 0.23 mg/ml of excess chelate, respectively). In the case of Magnevist, the amount of excess chelate in the formulation (0.4 mg/ml) is two-fold higher than in the formulation first introduced into the USA, while in the case of MultiHance, there is no excess chelate in the approved formulation. The excess chelate in the formulation of Gadovist is 0.5 mg/ml, with that for Primovist being 1 mg/ml.

Of clinical concern is the spurious hypocalcemia known following Omniscan and OptiMARK administration. The propensity of Omniscan to interfere with the colorimetric assays for serum calcium was reported as early as 1995. The lower thermodynamic stability of Omniscan allows the colorimetric reagent to displace the gadolinium ion from the gadodiamide chelate with the result that the free DTPA-BMA ligand then binds the calcium in the serum sample rendering it unavailable for measurement. However, the interference was only recently included in USA drug labeling and in the American Association of Clinical Chemists references of known clinical laboratory interferences, and was thus largely unknown within the radiological community. Spurious hypocalcemia does not occur with ProHance, Dotarem, Magnevist, or MultiHance which all have higher stability constants.

When considering the stability of the gadolinium chelates, the major safety concern is the potential for the release of free gadolinium ion through transmetallation and its subsequent retention within the body. Of all agents, Omniscan is the most prone to release free gadolinium, performing especially poorly when compared to cyclic agents like ProHance, with this finding established clinically by the study of residual gadolinium in bone.

A frequent approach to comparing the clinical safety of gadolinium contrast agents is to compare the overall incidence of adverse events derived from clinical trials with the agents concerned. However, direct quantitative comparisons based on overall numbers of adverse events are generally misleading since clinical trials usually differ in terms of study design and end-point, phase of development and size, location of study and, importantly, the subjective opinions of different investigators. The findings of clinical trials on the same agent may also vary substantially for the same reason. Particularly noteworthy in this regard is the often dramatic differences between the USA and Europe in terms of the reported incidence of adverse events.

The most direct approach to comparing the safety of different gadolinium contrast agents is through the use of controlled trials in which an agent is compared directly against another agent in the same study (i.e., by means of parallel-group or within-patient cross-over study designs). Thus, in various comparative studies of gadolinium chelates for MR imaging of the CNS, similar overall incidences of adverse events have been noted for Magnevist versus ProHance, Omniscan, Dotarem, OptiMARK and MultiHance; and for Omniscan versus Dotarem and MultiHance. There were no discernible differences in any of these studies noted between the different contrast agents in terms of the incidence or type of adverse events reported. Headache, nausea, taste perversion, and urticaria (hives) are typically the most frequent adverse events reported. It should be noted that anaphylaxis and death, although very rare, are known following gadolinium chelate administration.

Worth emphasizing in any discussion on the safety of MR contrast agents is the work of Lalli, who published a study in 1974 in which hypnotic suggestion was shown to be effective in reducing adverse reactions to urographic contrast agents to a significant degree. Specifically, the incidence of nausea and emesis in this study was reduced from 9.5% to 1.5% leading to the conclusion that “the most important factor in undesirable reactions to urographic contrast media is the fear inherent in the patient or engendered by the radiologist and his approach to the patient”. Although the safety profiles of MR contrast agents, and in particular the gadolinium chelates, are considerably better than those of the ionic urographic contrast agents, it is worth considering the impact that the physician and technologist can have in terms of either reducing or exacerbating the frequency with which adverse reactions are experienced and reported.

Nephrogenic systemic fibrosis (NSF) is an uncommon but serious acquired systemic disorder affecting patients

with renal insufficiency, and specifically patients on dialysis or approaching dialysis, first described in 1997. Originally coined nephrogenic sclerosing dermopathy (NSD) for the overt skin manifestations, its systemic sclerosing attributes, much like scleroderma, have led to a more descriptive and accurate name, nephrogenic systemic fibrosis. These systemic manifestations include involvement of the muscles, liver, and lungs, as well as difficulties with hypercoagulability and thrombotic events. The cutaneous lesions related to NSF are skin colored, sometimes erythematous, papules that arise symmetrically on the limbs and trunk which progress to brawny plaques with peau d'orange surface changes. Patients often report pruritus and sharp pain over the skin lesions. In some cases involving the extremities, the fibrosing effects are rapid in progression leading to limb contractures and decreased mobility. The disease can be fatal (< 5%), with no known cure. The severity of the renal insufficiency of patients affected with NSF varies from acute reversible renal insufficiency to patients with chronic renal failure on long-term dialysis. In the cases of patients with NSF who have had return to normal renal function through reversal of the acute dysfunction or by renal transplantation, the cutaneous manifestations have been shown to improve. At this date, skin biopsy is the definitive test for diagnosing NSF. Early publications from Austria, Denmark, and the United States raised concerns in regard to the possible relationship of NSF to the injection of a gadolinium chelate (specifically Omniscan) for contrast enhancement on MR. At this time, the vast majority of documented cases are associated with Omniscan injection. Cases have also been reported following injection of OptiMARK and Magnevist, although far fewer. Accounting for the number of doses used worldwide, the risk of developing NSF appears highest with Omniscan, intermediate with OptiMARK, and lowest (of these three) with Magnevist.

The clinical NSF case series published to date document in nearly all instances a chronological association between the exposure to a gadolinium chelate used for contrast enhancement on MR and the development of the disease. Caution is advised in interpretation of reports of this disease and its frequency and/or relationship to any single MR contrast agent, as the frequency would also be very much dependent upon the market share that such an agent has held over the past decade (and specifically the total number of administered doses).

Early in 2007, the use of Omniscan (and subsequently Magnevist) was banned in patients with an estimated GFR less than 30 ml/min/1.73 m<sup>2</sup> by European authorities. It should be noted that OptiMARK is not as of this date approved for use in Europe, and so was not addressed. Cautious use of the macrocyclic agents, with high thermodynamic and kinetic stability, is however still felt acceptable even in CKD4 and CKD5 (< 30 and < 15 ml/min/1.73 m<sup>2</sup>) patients.

As of May 2007, more than 200 cases of NSF had been reported. In terms of incidence of the disease, a recent paper reported this to be as high as 18% in CKD5 (dialysis) patients when given Omniscan. [16] In addition to the (primary) factor of renal function, the chance of developing NSF is thought to be related to chelate stability, dose, and cumulative (life time) dose.

The current leading hypothesis is that NSF is due to gadolinium chelate instability, and specifically dechelation in vivo. The instability of certain gadolinium chelates, and in particular Omniscan, is not a new topic, with references to this issue made throughout the development of these agents. Skin ulceration and degenerative lesions of the testicular germinal epithelium were described following repeated administration of high doses of both Omniscan and OptiMARK in rats during regulatory preclinical studies. It is important to note that the high stability of a gadolinium chelate in vivo forms the safety basis for this class of contrast media. The gadolinium ion itself is highly toxic (being a transition metal, and not a normal trace element in the body). Chelates that do not bind it tightly demonstrate poor LD50s and are not suitable for clinical use. Gadolinium is a well-known inorganic calcium channel blocker and its acute toxicity can be explained, at least in part, by this effect.

In a recent paper, which detailed development of an animal model of NSF, the occurrence of NSF-like lesions correlated with both Gd concentration in the skin and Gd chelate stability,[17] supporting the hypothesis that the Gd chelates elicit their toxic effects (in NSF) by direct loss of Gd<sup>3+</sup> (dechelation). Prolonged retention of Gd-containing contrast agents occurs in patients with severe renal impairment, leading in time to substantial dechelation and gadolinium deposition with the weaker chelates.

Given that NSF has been seen in patients not on dialysis (albeit with extremely poor renal function), the recommendation is made that at least for Omniscan, OptiMARK, and Magnevist (the three agents primarily implicated), injection in any patient should not be performed unless adequate renal function has been established by laboratory test (glomerular filtration rate (GFR) > 30 mL/min/1.73 m<sup>2</sup>), as per the FDA Public Health Advisory.

#### Manganese-based Agents

The only manganese-based MR contrast agent ever approved for clinical use was mangafodipir trisodium (Mn-DPDP, Teslascan). This liver-specific contrast agent provided improved detection, characterization and evaluation of liver lesions. Unlike the gadolinium agents, the mangafodipir (Mn-DPDP) chelate that composes Teslascan readily dissociates after injection to yield free manganese (Mn) ions. The instability of the chelate in vivo raised

concerns in the scientific literature about potential toxicity. Free manganese, in chronic exposure, accumulates in the brain and causes a Parkinsonism-like syndrome. Moreover, evidence suggests that significant neurological risk is associated with Mn intoxication in subjects with chronic liver failure whose ability to eliminate Mn is reduced. Free Mn ions released from Mn-DPDP have been reported to have a depressive action on heart function, possibly arising from their entry into myocardial cells through calcium channels. Teslascan has been effectively withdrawn from the USA market (as well as much of, if not all, the world), with the manufacturer supplying no new material and all available lots expired for a number of years.

#### Iron oxide-based agents

Unlike the gadolinium-based MR contrast agents with liver specific properties targeting hepatocytes, superparamagnetic iron oxide-based particulate agents are selectively taken up by Kupffer cells in the reticuloendothelial system (RES), primarily in the liver, and exert their effects on both T2- and T1-relaxation times. Iron oxide particles of different sizes can be prepared. Those that are >50 nm in size are referred to as superparamagnetic iron oxide (SPIO) agents while those that are <50 nm in size are the ultrasmall superparamagnetic iron oxides (USPIO) agents. To date, two iron oxide-based agents have been developed clinically and approved for MR imaging somewhere in the world: ferumoxides (Endorem, distributed in the USA as Feridex) with a particle size of 50 to 180 nm and ferucarbotran (SH U 555 A, Resovist,) with a particle size of about 60 nm. Endorem/Feridex consists of SPIO nanoparticles coated with dextran, while Resovist consists of SPIO nanoparticles coated with low molecular weight carboxydextran. The principal superparamagnetic effect of the SPIO particles is on T2\* relaxation and thus MR imaging is usually performed using T2\*-weighted sequences in which the tissue signal loss is due to the susceptibility effects of the iron oxide core. Enhancement on T1-weighted images can also be seen although this tends to be greater for the smaller SPIO and USPIO formulations. Both Feridex (Endorem) and Resovist are approved specifically for MR imaging of the liver, the difference being that Resovist is provided as a ready-to-use formulation and can be administered as a rapid bolus (and thus is used with both dynamic and delayed imaging) whereas Feridex needs to be administered as a slow infusion and is used solely in conjunction with delayed phase imaging.

In regard to the safety of these agents, the USA package insert for Feridex reports an overall incidence of adverse events of 9.4% (114/1535 subjects) with back and leg pain the most common event reported (3.6%). Pain severe enough to cause interruption or discontinuation of the infusion was reported to have occurred in 55/2240 (2.5%) patients. For Resovist the overall incidence of adverse events was 7.1% (75/1053 subjects) with vasodilatation and paraesthesia the most common event reported (< 2%). Unlike the first approved SPIO based contrast agent ferumoxides (Feridex/Endorem), which has been available in Europe, the USA and Japan for some time, Resovist is relatively newly approved (2001, first approved in Sweden) and is currently available in Europe and major Asian countries. Although considerably less post-marketing data is available on the safety of Resovist than on Feridex/Endorem, the safety profile appears more favorable for Resovist.

Acknowledgment: Parts of this article are reprinted with permission from Kirchin MA, Runge VM. Contrast Agents for Magnetic Resonance Imaging: Safety Update. *TMRI* 2003;14(5):426-35 and Khurana et al. NSF – A Review of Six Cases Temporally Related to Gadodiamide Injection (Omniscan). *Invest Radiol* 2007;42(2):139-145.

#### References

1. Runge VM. Safety of approved MR contrast media for intravenous injection. *J Magn Reson Imaging* **2000**;12:205-213
2. Runge VM. Safety of magnetic resonance contrast media. *Top Magn Reson Imaging* **2001**;12:309-314
3. Kirchin MA, Runge VM. Contrast agents for magnetic resonance imaging: safety update. *Top Magn Reson Imaging* **2003**;14:426-435
4. Rohrer M, Bauer H, Mintorovitch J, Requardt M, Weinmann HJ. Comparison of Magnetic Properties of MRI Contrast Media Solutions at different Magnetic Field Strengths. *Invest Radiol* **2005**;40:(in press)
5. Nelson KL, Gifford LM, Lauber-Huber C, Gross CA, Lasser TA. Clinical safety of gadopentetate dimeglumine. *Radiology* **1995**;196:439-443
6. Kirchin MA, Pirovano G, Venetianer C, Spinazzi A. Safety assessment of gadobenate dimeglumine (MultiHance): extended clinical experience from phase I studies to post-marketing surveillance. *J Magn Reson Imaging* **2001**;14:281-294
7. Knopp MV, Runge VM, Essig M, et al. Primary and secondary brain tumors at MR imaging: bicentric intraindividual crossover comparison of gadobenate dimeglumine and gadopentetate dimeglumine. *Radiology* **2004**;230:55-64

8. Tweedle MF, Wedeking P, Kumar K. Biodistribution of radiolabeled, formulated gadopentetate, gadoteridol, gadoterate, and gadodiamide in mice and rats. *Invest Radiol* **1995**;30:372-380
9. Puttagunta NR, Gibby WA, Puttagunta VL. Comparative transmetallation kinetics and thermodynamic stability of gadolinium-DTPA bis-glucosamide and other magnetic resonance imaging contrast media. *Invest Radiol* **1996**;31:619-624
10. Puttagunta NR, Gibby WA, Smith GT. Human in vivo comparative study of zinc and copper transmetallation after administration of magnetic resonance imaging contrast agents. *Invest Radiol* **1996**;31:739-742
11. Corot C, Idee JM, Hentsch AM, et al. Structure-activity relationship of macrocyclic and linear gadolinium chelates: investigation of transmetallation effect on the zinc-dependent metalloproteinase angiotensin-converting enzyme. *J Magn Reson Imaging* **1998**;8:695-702
12. Normann PT, Froyso A, Svaland M. Interference of gadodiamide injection (OMNISCAN) on the colorimetric determination of serum calcium. *Scand J Clin Lab Invest* **1995**;55:421-426
13. Prince MR, Erel HE, Lent RW, et al. Gadodiamide administration causes spurious hypocalcemia. *Radiology* **2003**;227:639-646
14. Lalli AF. Urographic contrast media reactions and anxiety. *Radiology* **1974**;112:267-271
15. Misselwitz B, Muhler A, Weinmann HJ. A toxicologic risk for using manganese complexes? A literature survey of existing data through several medical specialties. *Invest Radiol* **1995**;30:611-620
16. Rydahl C, Thomsen HS, Marckmann P. High prevalence of nephrogenic systemic fibrosis in chronic renal failure patients exposed to gadodiamide, a Gadolinium (Gd) containing magnetic resonance contrast agent. *Invest Radiol* **2008**;43(2):(in press)
17. Sieber M, Pietsch H, Walter J, et al. A Preclinical Study to Investigate the Development of Nephrogenic Systemic Fibrosis: a Possible Role for Gadolinium-based Contrast Media. *Invest Radiol* **2008**;43(1):(in press)

**Table 1.** Physicochemical characteristics of commercially-available, extracellular, predominantly renally excreted gadolinium-based MR contrast agents

Characteristic	Magnevist gadopentetate dimeglumine (0.5 mol/L)	Dotarem gadoterate meglumine (0.5 mol/L)	ProHance gadoteridol (0.5 mol/L)	Omniscan gadodiamide (0.5 mol/L)	MultiHance gadobenate dimeglumine (0.5 mol/L)	Gadovist gadobutrol (1.0 mol/L)	OptiMARK gadoversetamide (0.5 mol/L)
Molecular structure	Linear, ionic	Cyclic, ionic	Cyclic, non-ionic	Linear, non-ionic	Linear, ionic	Cyclic, non-ionic	Linear, non-ionic
Thermodynamic stability constant ( $\log K_{eq}$ )	22.1	25.8	23.8	16.9	22.6	21.8	16.6
Conditional stability constant at pH 7.4	18.1	18.8	17.1	14.9	18.4		15.0
Acid dissociation rate ( $k(\text{obs})\text{s}^{-1}$ )	$1.2 \times 10^{-3}$	$2.1 \times 10^{-5}$	$6.3 \times 10^{-5}$	$> 2 \times 10^{-2}$			
Osmolality (Osm/kg)	1.96	1.35	0.63	0.65	1.97	1.6	1.11
Viscosity ( $\text{mPa} \cdot \text{s}$ at 37°C)	2.9	2.0	1.3	1.4	5.3	4.96	2.0
T1 relaxivity ( $\text{L}/\text{mmol} \cdot \text{s}^{-1}$ ) 1.5 T, plasma	4.1	3.6	4.1	4.3	8.3	4.7	4.7
T1 relaxivity ( $\text{L}/\text{mmol} \cdot \text{s}^{-1}$ ) 3 T, plasma	3.7	3.5	3.7	4.0	6.2	3.6	4.5
Metal chelate (mg/ml)	469	278.3	279.3	287	334	605	330.9
Excess chelate (mg/ml)	0.4	0	0.23	12	0	0.5	28.4