

## Conventional Contrast Agents (Gadolinium Chelates)

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### Introduction

Magnetic resonance contrast agents, in particular the gadolinium-based agents, are very safe and lack the nephrotoxicity (when injected intravenously in the approved dose range) associated with iodinated contrast media.[1-3] 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 seven general-purpose agents, and two specialty agents, with approval country to country differing predominantly due to historical marketing rationale.

Details concerning the physicochemical properties of seven of these agents are given in Table 1.[4] 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.[5] The availability of Magnevist in Europe, the USA, and Japan (1988) was followed initially in Europe by gadoterate meglumine (Dotarem) which has a macrocyclic 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 macrocyclic and linear structures, respectively. Of these four initial 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),[6] 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 Opti-MARK, a linear, non-ionic agent similar to Omniscan, which shares with that agent the lowest (weakest) of all thermodynamic and conditional stability constants.

There are two agents within this group that offer advantages, from an imaging perspective, over the other five. 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 (2 to 4% in patients with normal renal function, and up to 10% in renally impaired patients) as well as renal excretion, and a higher T1 relaxivity compared to other gadolinium agents, due to weak, transient interaction with serum albumin.[7] These features are advantageous for imaging of the CNS and liver and for MRA. The second unique agent amongst those currently available is gadobutrol (Gadovist), the only gadolinium chelate 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 (macrocyclic) to Gadovist, the 1.0 M Gadovist formulation is feasible due to low viscosity and osmolality. This offers advantages in MRA and perfusion studies. A second advantage is the higher relaxivity of this agent, independent of its formulation or concentration. This offers an advantage across all imaging applications, which is of particular significance given the

high stability of this macrocyclic agent. Approval of Gadovist in the US is anticipated in 2011, with this agent otherwise approved widely across the world.

Gadoxetic acid disodium (Primovist) received approval in Europe in late 2004. It was approved in the US in 2008 under the brand name Eovist. 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. This agent offers advantages due to its high hepatobiliary excretion, and the ability to obtain images in the hepatocyte uptake phase relatively soon following intravenous injection.

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. This agent became clinically available in the US in January 2010, marketed as Ablavar by Lantheus Medical Imaging. As the only clinically available blood pool gadolinium chelate, gadofosveset trisodium belongs to a 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.[8-11] 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 added to 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.[12] 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 relatively 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.[13] Spurious hypocalcemia does not occur with ProHance, Dotarem, Gadovist, 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 the macrocyclic agents, specifically Gadovist, ProHance, and Dotarem. A published study in 2004 by Gibby et al established in clinical patients higher gadolinium deposition in bone with Omniscan, although the chemical nature of the remaining gadolinium was not determined (only inferred to be free gadolinium).

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,[14] 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 dermatopathy (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 that can 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, together with clinical history, are employed for the diagnosis of NSF. There are very likely more than 10,000 cases world-wide of NSF, when all grades of the disease are included (personal communication, Henrik S. Thomsen, MD). In the US, there are approximately 500 cases in federal courts, with an additional 150 in state courts. 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 the current time, the vast majority of documented cases (> 80%) are associated with Omniscan injection. Cases have also been reported following injection of OptiMARK and Magnevist, albeit fewer (likely several hundred due to Magnevist administration, with this large number in part due to its widespread use). 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 safest agent, from both a theoretical basis and clinical data to date, would of course be a macrocyclic agent.

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). To clarify this further, in the United States, the market shares for the various agents (with sole renal excretion) have historically been Magnevist > Omniscan > ProHance > Optimark. However, the number of NSF cases by agent is Omniscan > Magnevist > Optimark > ProHance (with no biopsy proven cases involving solely ProHance administration).

Early in 2007, the use of Omniscan was banned in patients with an estimated GFR less than 30 mL/min/1.73 m<sup>2</sup> by European authorities. Cautious use of the macrocyclic agents, with high kinetic stability, is however still felt acceptable even in CKD4 and CKD5 (< 30 and < 15 mL/min/1.73 m<sup>2</sup>) patients. On 09-09-2010 the FDA issued “New warnings for using gadolinium-based contrast agents in patients with kidney dysfunction”, a response to the issue of NSF. An excerpt from this safety announcement (<http://www.fda.gov/Drugs/DrugSafety/ucm223966.htm>) is included below:

NSF has not been reported in patients with normal kidney function. Patients at greatest risk for developing NSF after receiving gadolinium-based contrast agents (GBCAs) are those with impaired elimination of the drug, including patients with acute kidney injury (AKI) or chronic, severe kidney disease (with a glomerular filtration rate or GFR < 30 mL/min/1.73m<sup>2</sup>). Higher than recommended doses or repeat doses of GBCAs also appear to increase the risk for NSF.

The revised labeling will enhance the safe use of GBCAs, by recommending that healthcare professionals:

- Not use three of the GBCA drugs--Magnevist, Omniscan, and Optimark-- in patients with AKI or with chronic, severe kidney disease. These three GBCA drugs are contraindicated in these patients.
- Screen patients prior to administration of a GBCA to identify those with AKI or chronic, severe, kidney disease. These patients appear to be at highest risk for NSF.
- Use the clinical history to screen patients for features of AKI or risk factors for chronically reduced kidney function.
  - Features of AKI consist of rapid (over hours to days) and usually reversible decrease in kidney function, commonly in the setting of surgery, severe infection, injury, or drug-induced kidney toxicity. Serum creatinine levels and estimated GFR may not reliably assess kidney function in the setting of AKI.
  - For patients at risk for chronically reduced kidney function (such as patients over age 60 years, patients with high blood pressure, or patients with diabetes), estimate the kidney function (GFR) through laboratory testing.
- Avoid use of GBCAs in patients suspected or known to have impaired drug elimination unless the need for the diagnostic information is essential and not available with non-contrasted MRI or other alternative imaging modalities.
- Monitor for signs and symptoms of NSF after a GBCA is administered to a patient suspected or known to have impaired elimination of the drug.
- Do not repeat administration of any GBCA during a single imaging session.

As of 2010, more than 500 cases of NSF had been reported in the US, with likely 10,000 world-wide. In terms of incidence of the disease, this has been reported 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.

In terms of etiology, it is generally accepted today 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 likely to substantial dechelation and gadolinium deposition with the weaker chelates. It should be noted that a review of preclinical safety data for Magnevist did not uncover any toxicological effects that could be construed as suggestive of NSF. [18] The situation is however different with Omniscan, for which concern was raised at the time of its development by the scientific community concerning animal toxicological results and the possible relationship to dechelation.

Given that NSF has been seen in patients not on dialysis (albeit with extremely poor renal function), the recommendation is made that 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, as per the FDA Public Health Advisory.

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**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	Macrocyclic, ionic	Macrocyclic, non-ionic	Linear, non- ionic	Linear, ionic	Macrocyclic, 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 ( $k(\text{obs}^{\prime})\text{s}^{-1}$ )	$1.2 \times 10^{-3}$		$6.3 \times 10^{-5}$	$> 2 \times 10^{-2}$			
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]	4.1	3.6	4.1	4.3	6.3	5.2	4.7
T1 relaxivity ( $\text{L}/\text{mmol} \cdot \text{s}^{-1}$ ) 3 T, plasma [4]	3.7	3.5	3.7	4.0	5.5	5.0	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