

Safety and Efficacy in Selecting a Contrast Agent for MRI

A question-and-answer session with Jeffrey H. Maki, MD, PhD, Professor of Radiology and Section Chief of Abdominal Imaging, Department of Radiology, University of Colorado, on the use of macrocyclic gadolinium-based contrast agents (GBCAs) in MR imaging.

This article discusses the use of macrocyclic gadolinium-based contrast agents (GBCAs) in magnetic resonance imaging.

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This supplement and the ensuing post test are designed to be completed within 60 minutes. The goal is to provide an overview of key considerations when evaluating the efficacy of a contrast agent and to provide a review of key studies related to the evaluation and use of specific contrast agents.

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Applied Radiology (AR): Dr. Maki, please briefly describe some of the challenges you face when selecting an MR imaging contrast agent.

Dr. Maki: As with any pharmaceutical agent we administer to our patients, the challenges can be distilled down to safety, patient tolerance, efficacy, and cost.

Safety is always my foremost concern. I want to ensure my patients are subjected to the lowest possible risk of adverse events. This includes relatively immediate events such as severe contrast reactions, longer-term but definitely related disorders such as nephrogenic systemic fibrosis (NSF), and what I term “not yet understood” but fundamentally concerning associations, such as our growing awareness that gadolinium is not only retained in different body tissues, but also that, as it is excreted from patients, it is finding its way into the earth’s water – a process termed “anthropogenic,” meaning related to the influence of humans on nature.

Going hand-in-hand with safety is patient tolerance, by which I mean the more short-term and less-severe side effects that cause no lasting harm, such as nausea, flushing, headache, and others. These are, of course, undesirable, particularly from the patient’s perspective, but they go with the territory when administering any contrast agent.

By efficacy I mean, “How well does the contrast agent do what it is intended to do?” On a fundamental level, this means shortening T1 (or, in some applications, shortening T2 or T2*), and on a clinical level, this means providing evidence that it allows us to make a diagnosis, or to make a diagnosis earlier or more accurately, than could be done with another test or another contrast agent.

Finally, and particularly in today’s cost-conscious medical environment, expense plays an important role. When choosing between otherwise equal MR contrast agents, price can be a differentiator.

AR: Which contrast agents have you used in the past? Tell us about your experience with and knowledge of macrocyclic GBCAs. What attributes (eg, physiochemical properties, stability, efficacy, and safety) figured most prominently in your selection process?

Dr. Maki: I have used multiple GBCAs over the years. Most of my earliest work was with Magnevist, which was the first MR contrast agent to market back in 1988, and with Omniscan. I performed a lot of double-dose MR angiography (MRA) examinations before the relationship between gadolinium contrast and NSF was known, and these contrast agents were used at my hospitals based primarily on the perceived lack of side effects and contractual considerations. All of the gadolinium agents were seemingly magic back in the 1990s, as we produced ever-improving contrast-enhanced MRA (CE-MRA) images. Compared to iodinated contrast agents, the general perception at the time was that gadolinium contrast was near absolutely safe under almost any circumstances.

As my research with MRA progressed, I became more focused on the efficacy component of gadolinium contrast than the safety component, which at that time was considered quite similar for the four US-approved agents (Magnevist, Omniscan, OptiMARK, and ProHance). By this I’m mainly referring to T1 relaxivity, with the recognition that higher-relaxivity contrast agents (such as MultiHance, which was approved in the US in 2004) cause more T1 shortening at a given dose, which translates to greater T1 signal intensity or signal-to-noise ratio (SNR). This was extremely important to us for CE-MRA, particularly when using older MR machines and coil systems, as increased SNR allows for increased speed and/or spatial resolution. The benefits of MultiHance for MRA have been shown in numerous studies, but the benefits are known to extend beyond MRA; additional studies in neuro, breast, and liver MR show combinations of superiority at equal dose and noninferiority at half dose.¹⁻⁵

With the recognition of a link between gadolinium contrast and NSF in 2006, the MR community began to more carefully scrutinize various gadolinium formulations and dosages. Suddenly, new terms previously relegated to chemists and pharmacologists, such as “thermodynamic and kinetic stability constants,” “transmetalation,” “excess chelates,” and “macrocyclic vs linear ligand structure,” became common nomenclature and hot topics of discussion.

While we still do not completely understand NSF, we appear to have effectively eradicated it worldwide through a modification of our contrast administration behavior. My best understanding of NSF is that it is a pathologic process caused by prolonged exposure to certain gadolinium formulations, which in certain biochemical environments (eg, those associated with renal failure) can lead to the release of the toxic, heavy-metal gadolinium ion (Gd³⁺) from its chemical ligand (the molecule that binds or “chelates” the free gadolinium, and the factor that differentiates the different gadolinium formulations). Once Gd³⁺ is free in the body, it can bind with an anion such as phosphate to form an insoluble precipitate that subsequently deposits in soft tissues of the body, thereby inciting a pathologic inflammatory response we term NSF.

I conceptualize the situation as a race between the body eliminating the contrast agent and the gadolinium ion dissociating from its ligand. The worse the patient’s renal function and the higher the administered dose, the more slowly the agent is cleared from the body. Where the agent-to-agent differences come into play is that different formulations have different kinetic and thermodynamic stabilities (all based on their ligand structure). I think of thermodynamic stability as a measure of how much free gadolinium ion will ultimately dissociate from the ligand, and the kinetic stability as a measure of how long it takes that gadolinium chelate to dissociate and reach the “equilibrium” described by the thermodynamic

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stability. While other factors are certainly involved, this strongly suggests the “safest” agent in terms of NSF risk is one with high thermodynamic stability, but perhaps even more importantly, one with high kinetic stability.

Magnevist, Omniscan, and OptiMARK all have thermodynamic stability constants at least three orders of magnitude lower than the other US-approved gadolinium formulations.⁶ Not surprisingly, these are the three agents most associated with NSF, and the three agents the American College of Radiology (ACR) classifies as “Group I.” These agents are contraindicated in cases where the patient is considered “at risk” — ie, dialysis patients; patients with chronic kidney disease with estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m²; and patients with acute renal injury. This is well documented in the *ACR Manual on Contrast Media*.⁷

Now, considering kinetic stability (or how quickly any dissociation that might occur will occur), all three macrocyclic agents — Dotarem, Gadavist, and ProHance — have higher kinetic stability than their linear counterparts Eovist, Magnevist, MultiHance, Omniscan, and OptiMARK. This is nicely demonstrated in work by Frenzel et al.⁸ Thus many, including myself, consider macrocyclic agents the safest to use in terms of potential NSF risk. Furthermore, kinetic stability likely plays a role in the recently reported and very hot topic of gadolinium retention in tissues such as the bone and the brain.

But back to NSF. The track records of the different agents are important to consider. Almost all reported cases of NSF have been with Omniscan, Magnevist, or OptiMARK. To the best of my knowledge, among all of the macrocyclic agents, there are at most a few cases of unconfounded (single agent) cases of NSF for each agent — most of which are disputed, with the exception of 3 cases after administration of Gadavist.⁹ Given the millions of doses patients have received, this is very reassuring. It is important (and somewhat intriguing) to note that there have been no unconfounded cases of NSF with MultiHance, the high-relaxivity linear agent.¹⁰⁻¹³ While MultiHance does have one of the highest thermodynamic stability constants, it is a linear agent, and its kinetic stability is similar to that of Magnevist, which has been associated with many cases of NSF. This suggests we still do not fully understand the pathogenesis of NSF. Perhaps the dual-elimination pathway of MultiHance (ie, primarily renal with a small hepatic excretory component) or its benzyloxymethyl side-ring adds some protective factor.¹⁴ Regardless, the results speak loudly to me, and I feel very safe using MultiHance.

One important consideration voiced in the recent *ACR-ASNR Position Statement on the Use of Gadolinium Agents*⁷ is that GBAs often “provide crucial, life-saving medical information.” The often profound diagnostic benefits of administering gadolinium contrast must be evaluated relative to the risk of administering that contrast agent. In my opinion, the recent NSF era resulted in somewhat of an over-reaction among physicians who, in a substantial number of cases, withheld gadolinium contrast due to fear of causing NSF, when in fact the risk of not having contrast far outweighed what we now understand (with the correct agents) to be a truly negligible NSF risk. In my prior position as Director of Body MR, our safety committee addressed this by analyzing the available NSF rates and NSF-related literature, including several studies demonstrating the safety of ACR Group II agents (MultiHance, ProHance, Dotarem, Gadavist), even among dialysis patients.^{11,13,15,16} Based on these findings, we lowered our institutional GFR “threshold of concern” from 30 to 15 mL/min/1.73 m² (I realize that some institutions still become alarmed and may withhold gadolinium below 60 mL/min/1.73 m²), provided we use a “safer” ACR Group II agent (MultiHance, ProHance, Dotarem, Gadavist; the first two of which were used at this prior institution). In addition, we reached out to educate our clinical colleagues that Group II gadolinium agents can be safely used in many patients they formerly believed could not safely receive gadolinium. I believe this change has increased access to optimal MR imaging techniques, which in turn has positively impacted patient care.

Let me add a brief comment here regarding other safety concerns, such as mild-to-severe contrast reactions. This is always somewhat controversial, and we must consider that no randomized, controlled trial has shown any one gadolinium agent to have a greater or lesser incidence of contrast reactions of any severity compared to any other. Differences may exist, but the size of the study required to detect such differences effectively defies the possibility of being performed. Instead, one institution may have “success” with a certain agent and “problems” with another agent, while another institution may have the exact opposite experience; people love to share their experience with each other.

There are company representatives who may in some circumstances unscrupulously suggest that a competitor’s agent has more “adverse reactions” or is “less tolerated” (if you hear this, ask them to show you the paper). Realize also that there is a real phenomenon called the “Weber Effect:” when a new pharmaceutical agent is substituted for an existing agent, a transient increase in adverse reactions is often reported (typically peaking in Year 2).¹⁷ Davenport et al published a case study demonstrating this effect when they abruptly switched from Magnevist to MultiHance, noting a significant increase in allergic-like adverse events that returned to

baseline in Year 3.¹⁸ Thus, it is important for any institution that decides to try a new agent to give it a fair chance for a minimum of 6 months (and hopefully much longer), keeping careful record of reaction incidence and severity and then completing an internal evaluation.

AR: *You mentioned gadolinium retention in the brain being a hot topic of interest and potential concern. What is your take on how it relates to different contrast agents and whether the medical community should be concerned?*

Yes, this is indeed a hot topic, and one that is quite confusing, and both highly politically and socially charged. To summarize the issue, we know (and have known for a long time) that the Gd³⁺ ion escapes from its ligand in minute quantities and is retained in many body tissues (a different process than NSF, because it occurs in every subject, including those with normal renal function). We know this occurs for all gadolinium agents, although definite differences exist between agents in how much gadolinium is retained, and this is being actively investigated and hotly debated. Finally, although gadolinium agents have been on the market for almost 30 years and despite many a focused search, we have yet to find any evidence of harmful effects of this known gadolinium retention.

Our awareness of gadolinium retention stems from several recent papers noting a dose-related increase in T1 signal in the deep nuclei of the brain on noncontrast scans of people who had contrast in the past,¹⁹⁻²³ even among people with normal renal function. This focal T1 shortening suggests gadolinium retention, which has been confirmed by autopsy studies.²¹ The brain, it turns out, is an ideal tissue in which to see such effects, as retention is regional and there is a good background on which to base changes. This is not the case with other tissues, such as liver and bone, both of which are also known to be repositories for gadolinium, with bone being demonstrated to sequester much higher gadolinium concentrations than brain or other tissues.²⁴ One question that continually arises is: In what chemical form is the gadolinium retained — intact chelated contrast agent, Gd³⁺ bound to macromolecules via transmetallation (ie, exchanging places with a cation such as calcium or zinc), or Gd³⁺ bound to phosphate/carbonate to form an insoluble salt?

The chemists assure us free Gd³⁺ will not persist long in a biologic medium — free Gd³⁺ ion must rapidly bind to something, so that is an unlikely option. Next, Gd-phosphates do not cause T1 shortening, so while retention of such salts may occur, this would not result in the observed T1 shortening. This leaves Gd³⁺ remaining bound to its chelate and retained intact in tissue, or Gd³⁺ undergoing transmetallation to bind with tissue macromolecules. Of these, my understanding is that transmetallation is the favored current hypothesis.

In terms of which gadolinium agents are most associated with gadolinium retention, the data are complex, incomplete, and not yet fully understood. Initial reports by Kanda et al¹⁹ with Magnevist, and McDonald et al²¹ with Omniscan, demonstrated that these agents have a dose-related association with T1 “staining” (hyperintensity) in deep nuclei of the brain, whereas a follow-up study by Kanda looking at both Magnevist and ProHance demonstrated T1 staining only with Magnevist.²⁰ Thus, the belief emerged that macrocyclic agents, as a rule, have less gadolinium retention than the linear agents Magnevist and Omniscan (OptiMARK, which has a relatively low market share, has not to my knowledge been studied).

A study by Ramalho et al²² looked for T1 staining in cohorts that received multiple doses of Omniscan and MultiHance, again demonstrating significant T1 shortening for Omniscan, but only a nonstatistically significant “trend” toward T1 shortening for MultiHance. In contrast, Weberling et al. looked at patients who had received multiple doses of MultiHance and compared dentate and pons signal intensity over time with literature values for Magnevist and ProHance, demonstrating T1 shortening similar to Magnevist and much greater than for ProHance.²⁵ Add to this histologic work by Murata et al²⁴ that demonstrated brain and bone tissue retention for the macrocyclic agents Gadavist and ProHance in similar quantities to the linear agents MultiHance and Eovist, and the picture becomes much less clear.

What is clear, however, is the marketing/political/social landscape. Earlier in 2017, the Pharmacovigilance and Risk Assessment Committee (PRAC), an advisory committee to the European Medicines Agency (EMA), recommended suspending all four linear agents (Magnevist, MultiHance, Omniscan, and OptiMARK) in the EU, an opinion that was ultimately upheld by the EMA. This was based on their review concluding that linear agents have been implicated more in gadolinium retention in the brain, despite “no evidence that gadolinium deposition in the brain has caused any harm to patients.”²⁶ It should be noted they are correct in that multiple histopathologic brain studies and large observational trials^{27,28} have failed to demonstrate any tissue or clinical abnormality attributable to gadolinium retention in the brain.

Both the U.S. Food and Drug Administration (FDA) and ACR have been more restrained in their response. In May 2017, the FDA issued a warning that all gadolinium agents can be retained in body tissues, although to a greater degree with linear agents than with macrocyclic agents. However, due to no known negative health

impacts, they concluded that “restricting GBCA use is not warranted at this time.” The joint ACR-ASNR Position Statement⁷ essentially concurs, noting that there is no suggestion of neurotoxicity even among the agents with the highest retention, and that it is important to consider other factors in contrast selection such as “diagnostic efficacy, relaxivity, rate of adverse reactions, dosing/concentration, and propensity to deposit in more sensitive organs such as the brain.” The FDA and ACR recommend vigilance and more research. To add to the confusion, we have all heard of patient groups attributing various maladies to gadolinium administration. Thus, this becomes a socially charged issue, and we as radiology professionals will likely need to spend more time explaining these issues to our patients and offering reassurance.

To summarize, there is no known toxicity related to gadolinium retention by any of the agents. I agree it is prudent to avoid unknown risk, and if linear agents can be replaced with agents that deposit less gadolinium in the body tissues (and concurrently have less risk of NSF), there is at least the potential for benefit. Thus, from my perspective, it may be time to say goodbye to Magnevist, Omniscan, and OptiMARK. But I also agree with the FDA and ACR that to deny proven efficacy in favor of apprehension over some yet-to-be discovered syndrome related to very minute gadolinium retention (among the millions of doses administered worldwide) seems premature.

AR: *What do you feel are the benefits of ProHance versus other GBCAs you have used?*

Dr. Maki: I like the fact that ProHance has the lowest osmolality and viscosity of all the agents. This means less potential for complications if the agent is extravasated, and it is easier to inject, especially by hand. More importantly, as I previously alluded to, ProHance is a macrocyclic agent, and for all the reasons just discussed, I believe it is among the agents with the lowest potential to be retained in the patient’s body. Therefore, it would seem to pose the lowest risk of harm. The fact that there has been no reported brain T1 hyperintensity and, at most, one questionable instance of NSF out of all the millions of doses administered worldwide since ProHance was approved in 1992, reassures me that, should this agent be inadvertently administered to a patient with poor renal function, the risks for NSF are extremely low.⁶

Furthermore, I believe ProHance to be among the safest agents to use in at-risk patients when the benefit of an enhanced MRI is deemed to outweigh any potential risk of NSF. Time will tell, but I believe that particularly when using a macrocyclic agent, our present guidelines may be too conservative and may ultimately be relaxed. Work by Martin et al¹³ and Nandwana et al¹¹ with MultiHance suggest this, and hopefully similar studies of macrocyclic agents will soon be available.

While ProHance was our agent of choice at my former institution, we did use MultiHance for all CE-MRA and liver studies due to its higher T1 relaxivity. In terms of safety, it really seems there is a “MultiHance Paradox.” By this I mean that although this is a linear agent, there are no proven unconfounded cases of NSF. So while MultiHance is linear, the data regarding its gadolinium retention is not yet fully clear, and it seems to behave somewhat differently, lying somewhere in between the other linear agents and the macrocyclic agents.

AR: *The criteria for selecting a contrast agent typically deemed most important to radiologists include diagnostic efficacy and patient safety. How did ProHance help you achieve high levels of both?*

Dr. Maki: To reiterate, ProHance is a macrocyclic agent with an essentially perfect record in terms of not causing NSF. Its side-effect profile is similar to other agents, and we did not have any significant problems in the time we were using it. Of note, ProHance is approved for pediatric use (in children >2 yrs), and is the only agent of the 9 approved GBCAs to be approved for use at a cumulative dose of up to 0.3 mmol/kg – both of which are reassuring endorsements by the FDA.

The T1 relaxivity of ProHance is average for a “conventional-relaxivity” contrast agent, and numerous studies, mainly in the central nervous system, have shown no diagnostic difference among Dotarem, Magnevist, Omniscan, or OptiMARK. A CNS study recently published by Maravilla et al.²⁹ also demonstrated no difference compared to Gadavist, which is formulated at twice the concentration and does have slightly higher relaxivity than the others. Thus, when comparing ProHance to any of the general-use agents other than MultiHance (and Eovist, although it is only approved for hepatic imaging), I believe ProHance stands with any of the others.

In cases where we do feel the extra relaxivity is particularly beneficial (eg, CE-MRA and liver MRI), we used MultiHance as our go-to agent. While perhaps the laboratory stability data is not as convincing for this linear agent, its track record of zero cases of NSF speaks volumes and, as I have said previously, suggests there is more to NSF than just stability constants. I look forward to advances that let us fully understand this issue someday soon. As an additional benefit of MultiHance, the high relaxivity lets us do things like peripheral MRA at a single dose — where ordinarily I feel it is necessary to use at least 1.5 doses of a conventional agent — and does let us decrease dose beyond what we could with ProHance, if we feel that is in the best interest of the patient’s safety.

In summary, I think the balance achieved using primarily a macrocyclic agent with what I believe is as good an all-around safety profile as possible, together with a special use, high-relaxivity agent, is a great combination. For us to consider changing contrast agents, which is not as straightforward as one may imagine, I would need to be convinced that this other agent either A) performed diagnostically better with the same safety profile, or B) was proven safer with an equivalent diagnostic efficacy.

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Case Study

Diffusion weighted MRI with contrast in renal cell carcinoma

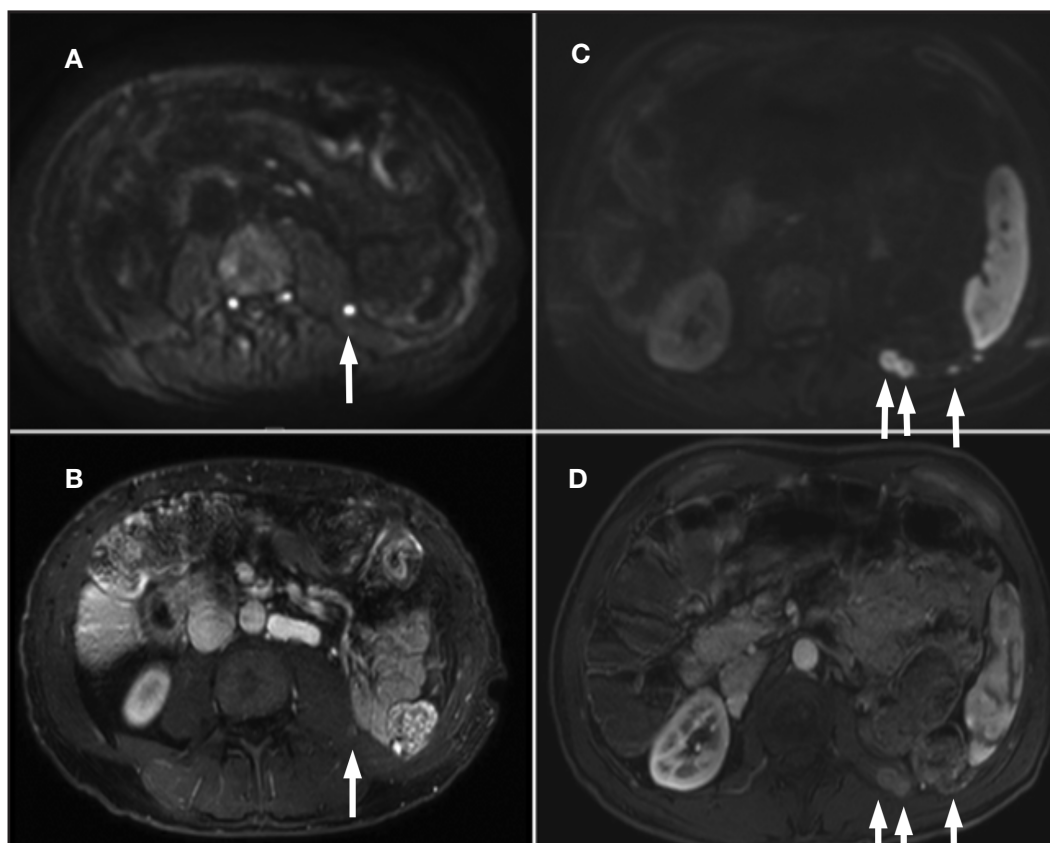


FIGURE 1. (A) Diffusion weighted MRI ($b=800$) showing a tiny focus of restricted diffusion in the left psoas muscle (arrow). Early phase, contrast-enhanced MRI using 0.1 mmol/kg ProHance (B) demonstrates a subtle focus of enhancement in the left psoas (arrow) corresponding to the region of restricted diffusion. This was called probable metastasis.

Follow-up diffusion MRI ($b=800$) 3 months later (C) demonstrates enlargement of previously seen psoas mass and multiple other retroperitoneal masses (arrows). Early phase, contrast-enhanced MRI (D) was performed using half dose (0.05 mmol/kg) ProHance due to mildly decreased GFR. This image demonstrates enhancement of the diffusion restricting lesions (arrows) consistent with enlarging metastasis.

The patient was a 52-year-old man with a history of Wilson's disease, for which he underwent an orthotopic liver transplant at age 40. He did well until a 3 cm left lower pole renal mass was discovered on surveillance CT 2 years ago. A needle biopsy was performed, demonstrating an xp11 translocation-type renal cell carcinoma, for which he underwent partial nephrectomy.

The patient was then followed with serial CT examinations, and one year later local recurrence was seen and a completion

nephrectomy was performed. In his first post-operative MR surveillance scan (Figure 1A and B), MRI detected a tiny psoas lesion that was suspicious for a local metastasis. A follow-up MRI 3 months later (Figure 1C and D) demonstrated multiple psoas/retroperitoneal masses with significant interval growth, confirming metastatic disease. Diffusion weighted MRI (DWI) was particularly helpful to find disease in this case, which was confirmed by the contrast-enhanced sequences.