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 Director of Body MR, Department of Radiology, University of Washington, on the use of macrocyclic gadolinium-based contrast agents in MR Imaging.

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

Dr. Maki: Some of the most important challenges center on 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, both immediate, in terms of severe contrast reactions, and long-term, when considering sequelae such as nephrogenic systemic fibrosis (NSF).

Going hand-in-hand with this 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, 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, physicochemical 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 approved back in 1988, and with Omniscan. I did a lot of double-dose magnetic resonance angiography (MRA) before the relationship between gadolinium contrast and NSF was known, and these contrast agents were used at my hospitals based primarily on perceived side effects and contractual considerations. All of the gadolinium agents were seemingly magic back in the 1990’s, as we produced ever-improving contrast-enhanced MRA (CE-MRA) images.

As part of my research with MRA, 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 approved US agents (Magnevist, Omniscan, OptiMark, 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 signal intensity or 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 spatial resolution. The benefits of MultiHance for MRA have been shown in many studies, but beyond MRA there are multiple additional studies in neuro, breast, and liver MR, showing combinations of superiority at equal dose and non-inferiority at half dose.

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

While I don’t believe we completely understand NSF yet, what is clear to me is that it is a disease 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, which is subsequently deposited (through transmetallation) in the soft tissues of the body, thereby inciting a pathologic inflammatory response. In my understanding, it is 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 dose, the longer the contrast agent stays in the body. Where the agent-to-agent differences come into play is that different formulations have different kinetic and thermodynamic stabilities. I think of thermodynamic stability as a measure of how much free gadolinium ion may ultimately dissociate, and the kinetic stability as a measure of how long it takes that gadolinium to dissociate and reach the “equilibrium” described by thermodynamic 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 Optimar all have thermodynamic stability constants at least three orders of magnitude lower than the other U.S.-approved gadolinium formulations. Not surprisingly, these are the three agents most associated with NSF, and the three agents the American College of Radiology classifies as “Group 1,” being 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; and patients with acute renal injury. This is well documented in the ACR Manual on Contrast Media. Now, considering kinetic stability, all three macrocyclic agents — Dotarem, Gadavist and ProHance — have higher kinetic stability than their linear counterparts Ablavar, Eovist, Magnevist, MultiHance, Omniscan and Optimar. Thus many, including myself, consider these agents the safest to use in terms of potential NSF risk.

The track records of the different agents are also important. To the best of my knowledge, among all of the macrocyclic agents, there are at most one or two cases of unconfounded (single agent) cases of NSF for each agent — most of which are disputed — and the true number may be zero. Given the millions of doses patients have received, this is very reassuring. It is important to note that there have been no unconfounded cases of NSF with MultiHance, the high-relaxivity linear agent. While it does have a high thermodynamic stability constant, its kinetic stability is similar to that of Magnevist, which has been associated with many cases of NSF. This tells me we don’t quite understand everything about the pathogenesis of NSF. Perhaps MultiHance’s dual-elimination pathway (primarily renal with small hepatic excretory component) or its benzoxylomethyl side-ring adds some protective factor; regardless, the results speak loudly to me, and I feel very safe when using this agent.

Another factor worth mentioning, and causing a buzz in the literature these days, are the accounts of T1-bright signal intensity in the dentate nucleus of the brain that correlates with cumulative doses of certain gadolinium agents — not surprisingly Magnevist and Omniscan. Pathologic analysis of autopsy specimens confirms the gadolinium deposition. While this is not known to cause any pathologic brain dysfunction, it does provide a brilliant way to look for gadolinium dissociation. Follow-up work has demonstrated that no such dentate nucleus hyperintensity is seen with the agents ProHance and Dotarem, corroborating the supposition that macrocyclic agents are much less likely to dissociate and deposit in the body. While to the best of my knowledge no such data yet exists regarding the other macrocyclic agent, Gadavist, and the linear agent, MultiHance, they may likely behave similarly to ProHance in not being deposited in the brain. Hopefully, these studies will be performed soon.

Finally, a comment regarding other safety concerns, such as mild to severe contrast reactions. This is a somewhat controversial topic; as such, we must consider that no randomized, controlled trial has shown any one gadolinium agent to have greater or lesser incidence of contrast reactions, of any severity, than any other. Differences may exist, but the size of the study required to detect such differences effectively defies the possibility of one 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. Add to this contrast company representatives who may in some circumstances unscrupulously suggest that a competitor’s agent has more “adverse reactions” or is “less tolerated” (if you ever hear this, ask them to show you the paper). I believe that it is important for any institution that decides to try a new agent to give it a fair chance for at least six months, keeping careful record of reaction incidence and severity and then completing an internal evaluation.

**AR: What is your facility’s current agent of choice?**

**Dr. Maki:** Across my institution, our primary agent for general MR imaging is ProHance. Prior to 2010, we primarily used Omniscan. The change was made in response to the NSF issue. The somewhat late date demonstrates the momentum that sometimes must be overcome to initiate change in a large medical center. We also use MultiHance in select cases — namely, CE-MRA and liver MRI.

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

**Dr. Maki:** Well, I do 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. But more important, as I previously alluded to, is that ProHance is a macrocyclic agent, and for all the reasons elaborated I believe it has the lowest potential to be retained in the patient’s body; therefore, it poses the lowest risk of harm. The facts that there are no dentate nucleus deposition and, at most, one questionable instance of NSF out of all the millions of doses administered worldwide since ProHance was approved in 1992 reassure me that the risks for NSF are extremely low should this agent be inadvertently administered to a patient with poor renal function. 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 al and Nandwana et al with MultiHance suggests this, and hopefully similar studies of macrocyclic agents will soon be available.

As I mentioned, while ProHance is our main agent, we use MultiHance for all CE-MRA and liver studies. This is because of its higher T1 relaxivity, which gives us a significant benefit. My work with contrast agents has explored the T1 and T2* relaxivities of different contrast agents in blood, where there are some surprises when talking about high blood concentrations that may be present in first pass CE-MRA. In particular, T1 shortening starts tapering off with concentration, and T2* relaxivity is quite high (meaning T2* is short), particularly at 3T.

The bottom line is that using the agent with the highest relaxivity allows for maintaining good blood enhancement for a longer duration...
by injecting the dose more slowly, which I believe decreases blurring artifacts. My group is actively working on this concept, and we hope to publish the results shortly.

**AR: The criteria for selecting a contrast agent typically deemed most important to radiologists include diagnostic efficacy and patient safety. How does this particular agent 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 any other agent, and we have not had any significant problems with it in the time we have been using it. Of note, ProHance is approved for pediatric use (in children > 2 yrs), and is the only agent of 9 GBCAs to be approved for cumulative dose up to 0.3 mmol/kg – which are both reassuring endorsements by the FDA.

ProHance’s T1 relaxivity is average for a “conventional” 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 also demonstrated no difference when considering Gadavist, which does have slightly higher relaxivity than the others. Thus, when comparing ProHance to any general agent other than MultiHance (and Ablavar and Eovist, although they have specific vascular and hepatic indications), 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 do use 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 does let us do things like peripheral MRA at single dose — where ordinarily I would use at least 1.5 doses of a conventional agent — and does let us decrease dose beyond what we could do with ProHance if we feel that is in the best interest of the patient’s safety.

**AR: In the long run, would you continue using your current contrast agents for MRIs?**

**Dr. Maki:** Yes, I would. I think the balance we have achieved using primarily a macrocyclic agent with what I believe is as good an all-around safety profile as is possible, and a special use, high-relaxivity agent is a great combination. For us to consider changing contrast agents, which is not as straight-forward as one may at first glance 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.

**REFERENCES**


Case Study

Diffusion weighted MRI with contrast in renal cell carcinoma

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.