Use of ProHance® (Gadoteridol): A Safe, Effective, and Versatile Contrast Agent for MR Imaging

A question-and-answer session with Matthew J. Kuhn, MD, Clinical Professor at the University of Illinois College Of Medicine at Peoria, Illinois.

Gadolinium-based contrast agents (GBCAs) have been in use since the late 1980s. The first to be approved by the U.S. Food and Drug Administration (FDA), in 1988, was the linear agent Magnevist® (gadopentetate dimeglumine), and the second, in 1992, was the macrocyclic agent ProHance® (gadoteridol). Both Magnevist® (gadopentetate dimeglumine) and ProHance® (gadoteridol) are non–tissue-specific, extracellular fluid (ECF) agents that were initially approved for imaging the central nervous system (CNS). Since then, an additional 7 GBCAs have been approved, 4 of which are also ECF agents (Table 1). The remaining 3 include MultiHance® (gadobenate dimeglumine), a dual ECF–liver GBCA, Eovist® (gadoxetate disodium), a liver imaging agent, and Ablavar® (gadofosveset trisodium), a blood pool agent (no longer being manufactured). Among other properties, the 7 ECF agents (including MultiHance® [gadobenate dimeglumine]) vary in their chemical structure (macrocyclic or linear), concentration (0.5 or 1M), and stability, as well as their approved indications and doses (Table 1).

Here we discuss with Dr. Matthew J. Kuhn, an early pioneer of contrast-enhanced MRI, his personal experience with each of the currently available GBCAs, as well as his preference for ProHance® (gadoteridol) for MR neuro and cardiac imaging applications.

**Applied Radiology (AR): Welcome, Dr. Kuhn. Can you please describe your imaging facility?**

**Dr. Matthew J. Kuhn (MJK):** I currently practice at 4 hospitals: UnityPoint Health-Methodist Hospital (500 beds), UnityPoint Health-Proctor Hospital (289 beds), Pekin Hospital (107 beds), and Galesburg Cottage Hospital (173 beds). Among these 4 sites, we have 10 scanners in total, most of which are GE and most of which are 1.5 or 3T, but we also have others.

**AR: Can you tell us about your experience with the various GBCAs currently in use for contrast-enhanced MRI?**

**MJK:** I first used contrast in 1987, as co-principal investigator on a compassionate-use study of Magnevist® (gadopentetate dimeglumine) in patients with brain tumors. This was prior to its subsequent approval in 1988. We continued to use Magnevist® (gadopentetate dimeglumine) post-approval, and I have administered this agent to many patients over the years; however, since it is known to be associated with nephrogenic systemic fibrosis (NSF), we didn’t see any benefit in continuing its use.

In the early 1990s, I was involved in clinical research with ProHance® (gadoteridol), including Phase 3 studies in both adults and children.1,4 A major focus at that time was the potential use of the macrocyclic ProHance® (gadoteridol) for high-dose applications. In 1994, we published results of one of the first clinical trials evaluating high-dose ProHance® (gadoteridol) for detection of brain metastases.2 In this intraindividual study, 4 patients with “solitary” brain metastases demonstrated on contrast-enhanced computed tomography (CT) were administered both single dose (0.1 mmol/kg) Magnevist® (gadopentetate dimeglumine) and triple dose (0.3 mmol/kg) ProHance® (gadoteridol) in 2 separate MR exams to 6 days apart. Compared to the 4 lesions seen on CT, 18 metastases were detected on MR – 7 on unenhanced MR images, 9 with Magnevist® (gadopentetate dimeglumine), and all 18 with ProHance® (gadoteridol). This finding of additional lesions with ProHance® (gadoteridol) was significant because it changed the therapeutic planning in these patients from surgery to radiation. We also found the use of triple dose ProHance® (gadoteridol) allowed for reduced costs and shorter hospital stays.2,3 ProHance® (gadoteridol) is the only agent approved for use at triple dose (0.3 mmol/kg).5

MultiHance® (gadobenate dimeglumine) is a high-relaxivity agent that was approved for use in CNS MRI in the United States in 2004 (Table 1). In 2006, we published a large, multicenter, intraindividual crossover study comparing equivalent doses of MultiHance® (gadobenate dimeglumine) and Magnevist® (gadopentetate dimeglumine) for MRI of CNS lesions, and showed that the higher relaxivity of MultiHance® (gadobenate dimeglumine) provided significantly better enhancement and diagnostic information for MRI of the CNS.6 We performed a follow-up study focused on patient outcomes in which we found that the better enhancement and diagnostic information obtained with MultiHance® (gadobenate dimeglumine) potentially allowed for better surgical planning and follow-up, as well as improved disease management.8

So we have found that MultiHance® (gadobenate dimeglumine) is a great complement to ProHance® (gadoteridol) due to its higher relaxivity. I use only ProHance® (gadoteridol) and MultiHance® (gadobenate dimeglumine). However, MultiHance® (gadobenate dimeglumine) is linear, and some radiologists may want the extra security of a macrocyclic agent...
AR: Do you have personal experience with Omniscan™ (gadodiamide) or OptiMARK™ (gadoversetamide)?

MJK: I did use the GBCA OptiMARK™ (gadoversetamide) early on, primarily for research, and I have used Omniscan™ (gadodiamide) only as a comparator, not for clinical use. Both of these agents are relatively unstable and considered higher risk for NSF (Table 1). In addition, we know that they are both formulated with excess chelate, and I don’t want my patients exposed to either unnecessary chelate or free gadolinium, both of which are more likely to be present with these agents. Biochemically, everything is in equilibrium – no agent has 100% gadolinium bound tight to the chelate – however, certainly, the unbound fraction is greater with Omniscan™ (gadodiamide) and OptiMARK™ (gadoversetamide) compared to other agents.

AR: What about the most recently approved agents, such as Gadavist® (gadobutrol) and Dotarem® (gadoterate meglumine)?

MJK: The newest agent on the market, Dotarem® (gadoterate meglumine), was actually the second agent approved in the world after Magnevist® (gadopentetate dimeglumine), but was only available in Europe for a very long time. I have no personal experience with this agent. Gadavist® (gadobutrol) is another relatively new agent and this agent has twice the concentration of gadolinium (1M) vs the other agents (0.5M). I have used it, but I have limited experience with this agent. We often use half dose in patients with renal dysfunction, and for most agents, this translates to half volume. When it comes to Gadavist® (gadobutrol), this would mean quarter volume, and we did have a tech give half volume Gadavist® (gadobutrol) to a patient, which is essentially overdosing a patient with Gadavist. So I find this difference in concentration adds an unnecessary layer of complexity.

AR: Can you describe in more detail the attributes that you think are most important in selecting a GBCA?

MJK: Absolutely. I like to consider 3 things: safety, efficacy, and versatility. You always want to use the safest agent for your patient – for reduction of adverse events (AEs), side effects, and NSF. In a large study of over 28,000 patients, AEs associated with administration of ProHance® (gadoteridol) have been demonstrated to be exceedingly low. In addition, in terms of NSF, ProHance® (gadoteridol) is in the safest class of agents (Class I). Importantly, ProHance® (gadoteridol) has demonstrated efficacy and safety in children, and the greater stability of a macrocyclic agent is potentially even more important, as they have longer lives ahead of them.

Second, you want the agent to be effective in order to get the best-quality images. Early Phase 2 and Phase 3 dosing studies comparing up to triple-dose ProHance® (gadoteridol) with single dose Magnevist® (gadopentetate dimeglumine) showed that at equivalent doses, the performance of these agents was comparable, while higher doses of ProHance® (gadoteridol) were safe and more effective at detecting and delineating CNS lesions. Since then, a number of double-blind, intraindividual, crossover studies comparing ProHance® (gadoteridol) with other GBCAs have been published. In a Phase 3 trial from 2001, Greco and colleagues showed that equivalent 0.1 mmol/kg doses of ProHance® (gadoteridol) and Magnevist® (gadopentetate dimeglumine) were equally effective for MRI of intracranial lesions in 92 patients. Most recently, equivalent single doses of ProHance® (gadoteridol) and the 1M agent Gadavist® (gadobutrol) were compared in a large, multicenter, crossover study in 229 patients with brain tumors (the TRUTH study). The authors found that the agents provided similar information for visualization and diagnosis of brain lesions and concluded that the 2-fold higher concentration of Gadavist® (gadobutrol) conferred no benefit for routine morphologic imaging. In addition, the clinical studies included as part of the Gadavist® (gadobutrol) clinical development program clearly state that the performance of 0.5M ProHance® (gadoteridol) is similar to that of 1.0M Gadavist® (gadobutrol).

Table 1. Currently-Available ECF GBCAs<sup>6,31-38</sup>

<table>
<thead>
<tr>
<th>Trade Name</th>
<th>Year FDA-approved</th>
<th>Chemical Structure</th>
<th>Ionicity</th>
<th>Concentration (M)</th>
<th>Approved Indications*</th>
<th>Approved dose (mmol/kg)*</th>
<th>Conditional Stability (pH7.4)</th>
<th>Kinetic Stability</th>
<th>Excess Chelate (mg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Magnevist® Gadopentetate dimeglumine</td>
<td>1988</td>
<td>Linear</td>
<td>Ionic</td>
<td>0.5</td>
<td>CNS (A,P); head &amp; neck (A)</td>
<td>0.1</td>
<td>18.4</td>
<td>Low</td>
<td>0.4</td>
</tr>
<tr>
<td>ProHance® Gadoteridol</td>
<td>1992</td>
<td>Macro cyclic</td>
<td>Nonionic</td>
<td>0.5</td>
<td>CNS (A,P); head &amp; neck (A)</td>
<td>0.1 + 2nd dose of 0.2 up to 30 min after 1st dose if needed (A); 0.1 (P)</td>
<td>17.1</td>
<td>High</td>
<td>0.23</td>
</tr>
<tr>
<td>Omniscan™ Gadodiamide</td>
<td>1993</td>
<td>Linear</td>
<td>Nonionic</td>
<td>0.5</td>
<td>CNS (A,P); body (A,P)</td>
<td>0.1</td>
<td>14.9</td>
<td>Low</td>
<td>12</td>
</tr>
<tr>
<td>OptiMARK™ Gadoversetamide</td>
<td>1999</td>
<td>Linear</td>
<td>Nonionic</td>
<td>0.5</td>
<td>CNS (A); liver (A)</td>
<td>0.1</td>
<td>15.0</td>
<td>Low</td>
<td>28.4</td>
</tr>
<tr>
<td>MultiHance® Gadobenate dimeglumine</td>
<td>2004</td>
<td>Linear</td>
<td>Ionic</td>
<td>0.5</td>
<td>CNS (A,P); aorto-iliofemoral occlusive vascular disease</td>
<td>0.1</td>
<td>18.4</td>
<td>Medium</td>
<td>0</td>
</tr>
<tr>
<td>Gadavist® Gadobutrol</td>
<td>2011</td>
<td>Macro cyclic</td>
<td>Nonionic</td>
<td>1</td>
<td>CNS (A,P); breast disease; supra-aortic/renal disease (A,P)</td>
<td>0.1</td>
<td>15.3</td>
<td>High</td>
<td>0.5</td>
</tr>
<tr>
<td>Dotarem® Gadoterate meglumine</td>
<td>2013</td>
<td>Macro cyclic</td>
<td>Ionic</td>
<td>0.5</td>
<td>CNS (A,P)</td>
<td>0.1</td>
<td>19.3</td>
<td>High</td>
<td>0</td>
</tr>
</tbody>
</table>

*A=A=adult; P=pediatric
CNS=central nervous system; ECF=extracellular fluid; GBCAs=gadolinium-based contrast agents; MRA=magnetic resonance angiography.

In patients with low glomerular filtration rate (GFR). In some of our practices, in patients with a GFR <40, they will only use ProHance® (gadoteridol), while others are comfortable using MultiHance® (gadobenate dimeglumine) in these patients; it just depends on their policy. Note that there are no unconfounded NSF cases with either agent. In fact, very recently, we published a prospective, multicenter study to determine the incidence of NSF in patients with chronic kidney disease (CKD) exposed only to ProHance® (gadoteridol; n=171) or MultiHance® (gadobenate dimeglumine; n=363), and no cases of NSF were seen with either agent. These findings are consistent with the classification of these 2 agents as low-risk GBCAs.
Finally, an important quality in a GBCA is its versatility — the ability to use the agent in a variety of clinical settings. So, for example, the triple-dose approval of ProHance® (gadoteridol) has been a huge advantage in the past, and still remains so. We have a gamma knife center, and our surgeons insist on double and triple dose studies, and they are comfortable with using ProHance® (gadoteridol) at these higher doses in their patients. ProHance® (gadoteridol) is approved for triple dose and, since it has such an excellent safety profile and is macrocyclic, they feel comfortable doing that. No other GBCA has that triple-dose approval. There are many studies showing triple dose is better not only for metabolic disease, but also for imaging of multiple sclerosis lesions. For cardiac MR, we typically use a higher dose (30 mL), so it is also important to use a safe agent for this application. Finally, we use ProHance® (gadoteridol) in the setting of intraoperative MRI. This technique requires dynamic, real-time images to be acquired during the surgical procedure. This places greater demands on the contrast — it may be necessary to give multiple doses as the operation proceeds — and ProHance® (gadoteridol) is not just approved for high doses, but for repeat doses as well.

AR: Lately, there has been much discussion among radiologists and the public regarding gadolinium deposition in the brain. What is your thinking on this topic?

MJK: Well, we know from older studies that following GBCA administration, gadolinium can be found in the bones of patients. White and colleagues showed that gadolinium was retained in human bone following hip replacement surgery, and that approximately 4 times more gadolinium was left behind following administration of the less stable linear agent Omniscan® (gadodiamide) compared to the macrocyclic agent ProHance® (gadoteridol). We also know gadolinium can be found in the skin of patients with NSF.

Case Study

MRI of 75-year-old female with confusion, weakness, speech problems, and visual deficit

Case Summary
A 75-year-old woman presented with sudden onset confusion, weakness, expressive speech problems, and visual deficit following cardiac catheterization 3 weeks earlier. She also had a history of breast cancer with radiation therapy. An MRI of the head was performed on a 3T GE scanner. The patient received 14 mL of ProHance® (gadoteridol) administered intravenously without complication. Post-enhanced axial and coronal T1-weighted images are shown.

Imaging Findings
There is thick, curvilinear enhancement within the cortex of the left frontal lobe and right parietal-occipital lobes involving only the cerebral cortex. This produces a "gyriform" pattern of enhancement along the surface of the brain. There is minimal surrounding cytotoxic edema and mass effect.

Diagnosis
Subacute cerebral infarction

Conclusion
Blood brain barrier breakdown results in cortical contrast enhancement during the subacute phase of cerebral infarction. Contrast enhancement limited to the cerebral cortex produces a gyriform pattern of enhancement. In addition to subacute cerebral infarction (as seen above), the differential diagnosis includes encephalitis, cerebritis, the post-ictal state, hypertensive encephalopathy, and contrast material overdose.

Reference