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This article is one in a series that discusses the use of macrocyclic GBCAs in MRI.

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This supplement to *Applied Radiology* confers 1.0 ARRT Category A Continuing Education credit, which will be awarded upon completion of an online post test. The entire text of this supplement and the post test are available at www.appliedradiology.org/aici.

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 and safety 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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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.

Matthew J. Kuhn, MD

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, several additional GBCAs have been approved, and now there are 6 ECF agents FDA-approved for use in the United States (Table 1), one of which has partial liver uptake and biliary excretion. This agent, MultiHance (gadobenate dimeglumine), has been shown to be useful in liver imaging.[1] Among other properties, the 6 ECF agents 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): Thank you! I currently practice at 4 major hospitals: UnityPoint Health-Methodist Hospital, UnityPoint Health-Proctor Hospital, UnityPoint Health-Pekin Hospital, and Galesburg Cottage Hospital. Among these 4 sites, we have over 10 scanners in total, most of which are GE and most of which are 1.5 or 3T, but we also have others, including a new 1.2T Hitachi open-MRI scanner.

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

MJK: I first used contrast at Massachusetts General Hospital 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) in patients with severely impaired renal function, 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.[2-5] 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.[3] In this intraindividual study, 4 patients with "solitary" brain metastases demonstrated on contrast-enhanced

Table 1. Currently-Available ECF GBCAs[7,35-41]

Contrast Agent						
Trade Name	**ProHance®**	**Gadavist®**	**Dotarem®**	**MultiHance®**	**Magnevist®**	**Omniscan™**
Generic Name	Gadoteridol	Gadobutrol	Gadoterate meglumine	Gadobenate dimeglumine	Gadopentetate dimeglumine	Gadodiamide
Year FDA-approved	1992	2011	2013	2004	1988	1993
Physicochemical Properties						
Chemical Structure	Macrocyclic	Macrocyclic	Macrocyclic	Linear	Linear	Linear
Ionicity	Nonionic	Nonionic	Ionic	Ionic	Ionic	Nonionic
Concentration (M)	0.5	1.0	0.5	0.5	0.5	0.5
Conditional Stability (pH7.4)	17.1	15.3	19.3	18.4	18.4	14.9
Kinetic Stability	High	High	High	Medium	Low	Low
Excess Chelate (mg/mL)	0.23	0.5	0	0	0.4	12
Indications and Dosage						
Approved Indications*	CNS (A,P); head & neck (A)	CNS (A,P,N); breast disease; supra-aortic /renal disease (A,P,N)	CNS (A,P, N)	CNS (A,P,N); MRA of renal or aorto-iliofemoral occlusive vascular disease (A)	CNS (A,P); head & neck (A,P); body (excluding heart) (A,P)	CNS (A,P); body (excluding heart) (A,P)
Approved dose (mmol/kg)*	0.1 + 2nd dose of 0.2 up to 30 min after 1st dose if needed (A); 0.1 (P)	0.1	0.1	0.1	0.1	0.1

*A=adult; P=pediatric; N=neonate.

CNS=central nervous system; ECF=extracellular fluid; GBCA=gadolinium-based contrast agent; MRA=magnetic resonance angiography.

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 2 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.[3,6] ProHance (gadoteridol) is the only agent approved for use at triple dose (0.3 mmol/kg) in the United States.[7]

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.[8] 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.[9]

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 favor the use of a macrocyclic agent in patients with low glomerular filtration rate (GFR), despite the fact that both agents are categorized as Class II (ie, low risk of NSF) by the ACR and FDA. In some 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

Table 2. 2018 NIH/ACR/RSNA Workshop on Gadolinium Chelates: Knowledge Gaps in Understanding Gadolinium Retention[34]

Animal/Basic Science Research Questions
What is the long-term biodistribution of intravenously administered GBCA?
What is the toxic potential of chronically retained amounts of gadolinium in tissues? What are the mechanisms of this toxicity?
What are the best approaches to identification and quantification of gadolinium species in tissues?
Are there measurable clinical manifestations (neurologic or nonneurologic)? Is there a toxic dose threshold for chronic gadolinium exposure?
Are there common molecular mechanisms and clinical manifestations between chronic gadolinium retention and NSF?
What is the long-term biodistribution of intravenously administered GBCA?

Clinical Research Questions
What is the long-term biodistribution of intravenously administered GBCA?
Define potentially altered dynamics in vulnerable populations
Standardize and validate gadolinium and GBCA tissue measurement methods and quality assurance procedures
What chemical forms of gadolinium are found in tissues and body fluids?
Are all GBCAs retained in human CNS tissue?
To what extent does gadolinium accumulate in tissues other than CNS?
Are there clinical or demographic factors that predispose patients to gadolinium retention?
How is gadolinium entering CSF?
Are there measurable human clinical manifestations (neurologic or nonneurologic) due to GBCA exposure, retention, or both?
What is the risk benefit of each GBCA in clinical use?
Are there measurable adverse outcomes from GBCA exposure in vulnerable populations (elderly, pediatric populations, specific disease population)? If so, what risk mitigation strategies are appropriate to minimize the risk in these populations?

ACR=American College of Radiology; CNS=central nervous system; CSF=cerebrospinal fluid; GBCA=gadolinium-based contrast agent; NIH=National Institutes of Health; NSF=nephrogenic systemic fibrosis; RSNA=Radiological Society of North America.

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.[10] These findings are consistent with the classification of these 2 agents as low-risk GBCAs.

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.[11] In addition, we know that they are both formulated with excess chelate, and I don't want my patients exposed to higher risk of gadolinium transmetallation with endogenous metals, which is more likely to occur with these agents. Note that in 2017, Guerbet announced that their linear agent OptiMARK (gadoversetamide) would be phased out and no longer available after 2019.[12]

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 CKD. 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 reducing the risk of adverse events (AEs), as well as NSF. In a large study of over 28,000 patients, AEs associated with administration of ProHance (gadoteridol) have been demonstrated to be exceedingly low.[13] In addition, in terms of NSF, ProHance (gadoteridol) is in the safest class of agents (Class II).[11] Importantly, ProHance (gadoteridol) has demonstrated efficacy and safety in children,[5,14] and has a pediatric indication.[7] In children, 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 certain CNS lesions.[3,15] 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.[16] 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).[17] 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 1M Gadavist (gadobutrol).[18]

Finally, an important quality in a GBCA is 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. At the local gamma knife center, our surgeons often 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, including the other 2 macrocyclic agents (Gadavist [gadobutrol] and Dotarem [gadoterate meglumine]). There are many studies showing triple dose is better not only for metastatic disease,[3] but also for imaging of multiple sclerosis lesions.[19] 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, ProHance (gadoteridol) is ideal 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.[7]

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).[20] We also know gadolinium can be found in the skin of patients with NSF.[21]

Recently, a number of groups have reported detecting T1 hyperintensity in the brain following repeated contrast-enhanced scans, and this signal has been attributed to residual gadolinium from prior GBCA administration.[22-26] The precise form and concentration of the gadolinium have yet to be elucidated, and no associated clinical sequelae have been demonstrated. At first, gadolinium deposition was thought to occur more frequently with linear than with macrocyclic agents.[27-29] However, most recently, it was demonstrated that exposure to any agent can potentially result in gadolinium deposition.[30] Very recently, a study showed gadolinium deposition in the liver of pediatric patients, even with a macrocyclic agent, in this case Dotarem (gadoterate meglumine).[31] Presently, the FDA has indicated that the use of GBCAs should be limited to clinical circumstances in which the additional information provided by the contrast is necessary, and that the necessity for repetitive GBCA MRIs should be reassessed; however, at this time, they are not recommending any changes to the labels of GBCA products.[32] Importantly, studies published recently support the lack of clinical consequences of gadolinium deposition in the brain: Welk et al showed no association between Parkinsonism symptoms and ≥1 GBCA exposure in almost 100,000 patients.[33]

In 2018, McDonald et al. published results from the 2018 NIH/ACR/RSNA Workshop on Gadolinium Chelates, the purpose of which was to provide a "research roadmap" that would highlight the information about gadolinium retention that is not known, and to identify and prioritize needed research.[34] Table 2 summarizes the knowledge gaps that were identified, pointing out that there is yet much to be learned and understood about this potentially important clinical topic.

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Case Study

68-year-old female with weight loss, nausea, and vomiting, and a single episode of unresponsiveness

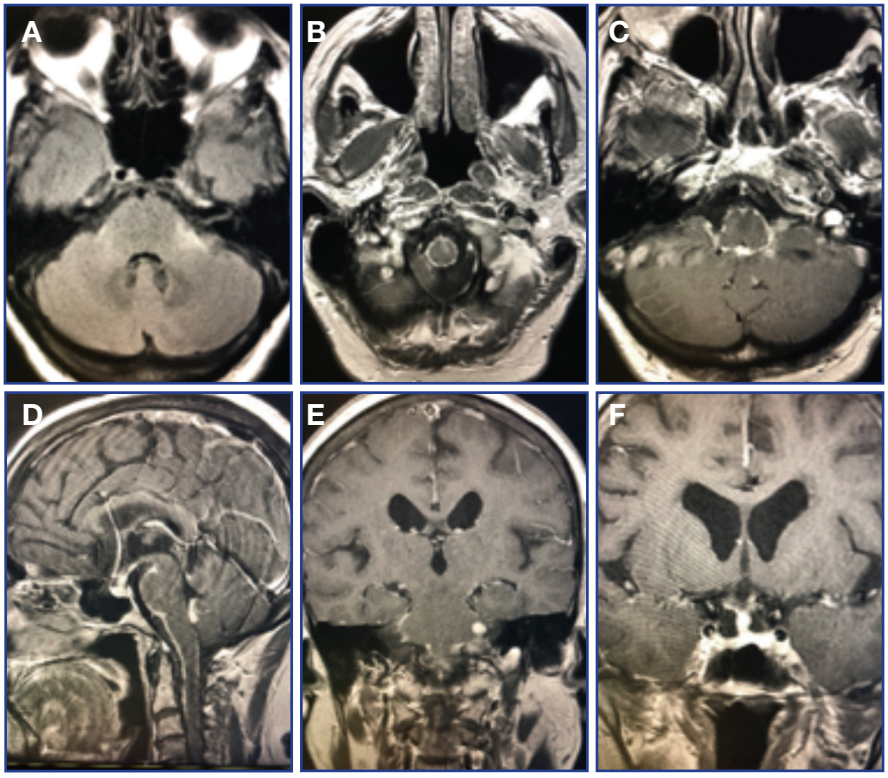

FIGURE 1. *Imaging findings: (A) Axial FLAIR; (B,C) axial T1-w with contrast; (D) sagittal T1-w with contrast; (E,F) coronal T1-w with contrast.*

Case Summary

A 68-year-old female presented with weight loss, nausea, and vomiting, and a single episode of unresponsiveness. Unenhanced images were obtained. Following the uncomplicated intravenous administration of 12 mL of ProHance (gadoteridol), axial, sagittal, coronal T1 images were obtained (Figure 1).

Imaging Findings

The axial FLAIR image shows subtle hyperintensity in the cerebellopontine angles, left greater than right. There are extensive areas of diffuse leptomeningeal enhancement and thickening involving the infundibulum, hypothalamus, midbrain, pons, medulla, cerebellar tonsils, and cervical spinal cord. In addition, there is focal nodular thickening in the left cerebellopontine angle and coating of cranial nerves seven and eight on the left.

Diagnosis

Neurosarcoidosis

Conclusion

Neurosarcoidosis is characterized by noncaseating granulomas in the dura, leptomeninges, subarachnoid and perivascular spaces and less commonly, in the brain parenchyma and spinal cord. Typical locations are demonstrated in this case, including suprasellar and cranial nerve involvement, cerebellopontine angle nodules and diffuse leptomeningeal thickening. Often there are only very subtle abnormalities on the unenhanced images. Judicious use of gadolinium-based contrast agents is key to diagnostic success.

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