

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

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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 and safety of a contrast agent, and to provide a review of key studies related to the evaluation and use of specific contrast agents.

Original Release: 11/01/2016

Updated Release: 03/01/2019

Expiration date: 03/31/2022

Supported by an unrestricted educational grant from



## 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.<sup>1</sup> 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.<sup>2,5</sup> 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.<sup>3</sup> In this intraindividual study, 4 patients with "solitary" brain metastases demonstrated on contrast-enhanced

**Table 1. Currently-Available ECF GBCAs<sup>7,35-41</sup>**

<b>Contrast Agent</b>						
<b>Trade Name</b>	<b>ProHance®</b>	<b>Gadavist®</b>	<b>Dotarem®</b>	<b>MultiHance®</b>	<b>Magnevist®</b>	<b>Omniscan™</b>
Generic Name	Gadoteridol	Gadobutrol	Gadoterate meglumine	Gadobenate dimeglumine	Gadopentetate dimeglumine	Gadodiamide
Year FDA-approved	1992	2011	2013	2004	1988	1993
<b>Physicochemical Properties</b>						
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
<b>Indications and Dosage</b>						
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.<sup>3,6</sup> ProHance (gadoteridol) is the only agent approved for use at triple dose (0.3 mmol/kg) in the United States.<sup>7</sup>

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.<sup>8</sup> 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.<sup>9</sup>

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<sup>34</sup>**

### 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.<sup>10</sup> 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.<sup>11</sup> 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.<sup>12</sup>

#### **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.<sup>13</sup> In addition, in terms of NSF, ProHance (gadoteridol) is in the safest class of agents (Class II).<sup>11</sup> Importantly, ProHance (gadoteridol) has demonstrated efficacy and safety in children,<sup>5,14</sup> and has a pediatric indication.<sup>7</sup> 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.<sup>3,15</sup> 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.<sup>16</sup> 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).<sup>17</sup> 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).<sup>18</sup>

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,<sup>3</sup> but also for imaging of multiple sclerosis lesions.<sup>19</sup> 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.<sup>7</sup>

**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).<sup>20</sup> We also know gadolinium can be found in the skin of patients with NSF.<sup>21</sup>

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.<sup>22-26</sup> 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.<sup>27-29</sup> However, most recently, it was demonstrated that exposure to any agent can potentially result in gadolinium deposition.<sup>30</sup> Very recently, a study showed gadolinium deposition in the liver of pediatric patients, even with a macrocyclic agent, in this case Dotarem (gadoterate meglumine).<sup>31</sup> 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.<sup>32</sup> 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  $\geq 1$  GBCA exposure in almost 100,000 patients.<sup>33</sup>

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.<sup>34</sup> 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.

## REFERENCES


- Hamm B, Kirchin M, Pirovano G, Spinazzi A. Clinical utility and safety of MultiHance in magnetic resonance imaging of liver cancer: results of multicenter studies in Europe and the USA. *J Comput Assist Tomogr.* 1999;23(Suppl 1):S53-S60.
- Kuhn MJ, Youssef HT, Swenson LC, Gleason TJ. Comparison of triple dose gadoteridol with standard dose gadopentetate dimeglumine in the evaluation of intracranial lesions. *J Magn Reson Imaging.* 1993;3(P):100.
- Kuhn MJ, Hammer GM, Swenson LC, Youssef HT, Gleason TJ. MRI evaluation of “solitary” brain metastases with triple-dose gadoteridol: comparison with contrast-enhanced CT and conventional-dose gadopentetate dimeglumine MRI studies in the same patients. *Comput Med Imaging Graph.* 1994;18:391-399.
- Youssef H, Kuhn M, Hammer G, Meis L, Burk T, Pencsek T. Phase III multicenter evaluation of high-dose gadoteridol in neurologic pathology: comparison of 0.1 mmol/kg gadopentetate dimeglumine and 0.3 mmol/kg gadoteridol in patients with lesions of the CNS. *Neuroradiology.* 1995;37:558-559.
- Kuhn MJ, Swenson LC, Youssef HT, Hammer GM, Gleason TJ, Binstadt DH. Safety and sensitivity of high dose gadoteridol in children. Proceedings from the Thirty-sixth annual meeting of the Society for Pediatric Radiology. 1993;95.
- Mayr NA, Yuh WTC, Muhonen MG, et al. Cost/benefit analysis of high-dose MR contrast studies in the evaluation of brain metastases (abstr). In: *American Society of Neuroradiology Book of Abstracts.* 1993;193-194.
- ProHance® (Gadoteridol) Injection, [prescribing information]. Princeton, NJ: Bracco Diagnostics Inc.; January 2019.
- Maravilla KR, Maldjian JA, Schmalfuss IM, Kuhn MJ, et al. Contrast enhancement of central nervous system lesions: multicenter intraindividual crossover comparative study of two MR contrast agents. *Radiology.* 2006;240:389-400.
- Kuhn MJ, Picozzi P, Maldjian JA, et al. Evaluation of intraaxial enhancing brain tumors on magnetic resonance imaging: intraindividual crossover comparison of gadobenate dimeglumine and gadopentetate dimeglumine for visualization and assessment, and implications for surgical intervention. *J Neurosurg.* 2007;106:557-566.
- Soulez G, Bloomgarden DC, Rofsky NM, et al. Prospective Cohort Study of Nephrogenic Systemic Fibrosis in Patients with Stage 3-5 Chronic Kidney Disease Undergoing MRI with Injected Gadobenate Dimeglumine or Gadoteridol. *Am J Roentgenol.* 2015;205:469-478.
- American College of Radiology (ACR) Committee on Drugs and Contrast Media. *ACR Manual on Contrast Media.* Version 10.3. 2017. Available at <https://www.acr.org/Clinical-Resources/Contrast-Manual>. Accessed October 22, 2018.
- Fornell D. 2017. Recent Developments and Issues in Contrast Media. Diagnostic and Interventional Cardiology. Available at: <https://www.dicardiology.com/article/recent-developments-and-issues-contrast-media>. Accessed October 15, 2018.
- Morgan DE, Spann JS, Lockhart ME, Winningham B, Bolus DN. Assessment of adverse reaction rates during gadoteridol-enhanced MR imaging in 28,078 patients. *Radiology.* 2011;259:109-116.
- Debatin JF, Nadel SN, Gray L, et al. Phase III clinical evaluation of gadoteridol injection: experience in pediatric neuro-oncologic MR imaging. *Pediatr Radiol.* 1992;22:93-98.



15. Yuh WT, Fisher DJ, Engelken JD, et al. MR evaluation of CNS tumors: dose comparison study with gadopentetate dimeglumine and gadoteridol. *Radiology*. 1991;180:485-491.
16. Greco A, Parker JR, Ratcliffe CG, Kirchin MA, McNamara MT, Phase III, randomized, double-blind, cross-over comparison of gadoteridol and gadopentetate dimeglumine in magnetic resonance imaging of patients with intracranial lesions. *Australas Radiol*. 2001;45:457-463.
17. Maravilla KR, Smith MP, Vymazal J, et al. Are there differences between macrocyclic gadolinium contrast agents for brain tumor imaging? Results of a multicenter intraindividual crossover comparison of gadobutrol with gadoteridol (the TRUTH study). *Am J Neuroradiol*. 2015;36:14-23.
18. Bayer HealthCare Pharmaceuticals. Briefing Document for Gadobutrol Injection; NDA 201,277. Peripheral & Central Nervous System Drugs Advisory Committee. 21 January 2011. Available at: <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PeripheralandCentralNervousSystemDrugsAdvisoryCommittee/UCM240357.pdf>. Errata available at: <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PeripheralandCentralNervousSystemDrugsAdvisoryCommittee/UCM240356.pdf>. Accessed April 24, 2015.
19. Wolansky LJ, Finden SG, Chang R, et al. Gadoteridol in multiple sclerosis patients. A comparison of single and triple dose with immediate vs. delayed imaging. *Clin Imaging*. 1998;22:385-392.
20. White GW, Gibby WA, Tweedle MF. Comparison of Gd (DTPA-BMA) (Omniscan™) versus Gd (HP-DO3A) (ProHance®) relative to gadolinium retention in human bone tissue by inductively coupled plasma mass spectroscopy. *Invest Radiol*. 2006;41:272-278.
21. High WA, Ayers RA, Chandler J, Zito G, Cowper SE. Gadolinium is detectable within the tissue of patients with nephrogenic systemic fibrosis. *J Am Acad Dermatol*. 2007;56:21-26.
22. Kanda T, Ishii K, Kawaguchi H, Kitajima K, Takenaka D. High signal intensity in the dentate nucleus and globus pallidus on unenhanced T1-weighted MR images: relationship with increasing cumulative dose of a gadolinium-based contrast material. *Radiology*. 2014;270:834-841.
23. McDonald RJ, McDonald JS, Kalimes DF, et al. Intracranial Gadolinium Deposition after Contrast-enhanced MR Imaging. *Radiology*. 2015;275:772-782.
24. Errante Y, Cirimele V, Mallio CA, Di Lazzaro V, Zobel BB, Quattrocchi CC. Progressive increase of T1 signal intensity of the dentate nucleus on unenhanced magnetic resonance images is associated with cumulative doses of intravenously administered gadodiamide in patients with normal renal function, suggesting dechelation. *Invest Radiol*. 2014;49:685-690.
25. Quattrocchi CC, Mallio CA, Errante Y, Cirimele V, Carideo L, Ax A, Zobel BB. Gadodiamide and Dentate Nucleus T1 Hyperintensity in Patients with Meningioma Evaluated by Multiple Follow-Up Contrast-Enhanced Magnetic Resonance Examinations with No Systemic Interval Therapy. *Invest Radiol*. 2015;50:470-472.
26. Ramalho J, Castillo M, AIObaidy M, Nunes RH, Ramalho M, Dale BM, Semelka RC. High Signal Intensity in Globus Pallidus and Dentate Nucleus on Unenhanced T1-weighted MR

- Images: Evaluation of Two Linear Gadolinium-based Contrast Agents. *Radiology*. 2015;276:836-844.
27. Robert P, Lehericy S, Grand S, et al. T1-Weighted Hypersignal in the Deep Cerebellar Nuclei After Repeated Administrations of Gadolinium-Based Contrast Agents in Healthy Rats: Difference Between Linear and Macrocyclic Agents. *Invest Radiol*. 2015;50:473-480.
28. Radbruch A, Weberling LD, Kieselich PJ, et al. High-signal intensity in the dentate nucleus and globus pallidus on unenhanced T1-weighted images: evaluation of the macrocyclic gadolinium-based contrast agent gadobutrol. *Invest Radiol*. 2015;50:805-810.
29. Robert P, Violas X, Grand S, et al. Linear Gadolinium-Based Contrast Agents Are Associated With Brain Gadolinium Retention in Healthy Rats. *Invest Radiol*. 2016;51:73-82.
30. Murata N, Gonzalez-Cuyar LF, Murata K, et al. Macrocyclic and Other Non-Group 1 Gadolinium Contrast Agents Deposit Low Levels of Gadolinium in Brain and Bone Tissue: Preliminary Results From 9 Patients With Normal Renal Function. *Invest Radiol*. 2016;51:447-453.
31. Maximova N, Gregori M, Zennaro F, Sonzogni A, Simeone R, Zanoni D. Hepatic Gadolinium Deposition and Reversibility after Contrast Agent-enhanced MR Imaging of Pediatric Hematopoietic Stem Cell Transplant Recipients. *Radiology*. 2016. [Epub ahead of print]
32. US Food and Drug Administration (FDA). Gadolinium-based contrast agents for magnetic resonance imaging (MRI): Drug Safety Communication - FDA evaluating the risk of brain deposits with repeated use. July 27, 2015. <http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm456012.htm>. Accessed August 6, 2015.
33. Welk B, McArthur E, Morrow SA, MacDonald P, Hayward J, Leung A, Lum A. Association Between Gadolinium Contrast Exposure and the Risk of Parkinsonism. *JAMA*. 2016;316:96-98.
34. McDonald RJ, Levine D, Weinreb J, et al. Gadolinium Retention: A Research Roadmap from the 2018 NIH/ACR/RNA Workshop on Gadolinium Chelates. *Radiology*. 2018;181151.
35. Dotarem® (gadoteric acid) [product information]. Roissy CdG Cedex, France: Guerbet; April 2018.
36. Gadavist® (gadobutrol) injection [prescribing information]. Wayne, NJ; Bayer HealthCare Pharmaceuticals; April 2018.
37. Magnevist® (brand of gadopentetate dimeglumine) injection [prescribing information]. Wayne, NJ; Bayer HealthCare Pharmaceuticals; April 2018.
38. MultiHance® (gadobenate dimeglumine) injection [prescribing information]. Princeton, NJ; Bracco Diagnostics Inc.; January 2019.
39. Omniscan™ (gadodiamide) injection [prescribing information]. Princeton, NJ: GE Healthcare; August 2013.
40. Idée JM, Port M, Robic C, Medina C, Sabatou M, Corot C. Role of thermodynamic and kinetic parameters in gadolinium chelate stability. *J Magn Reson Imaging*. 2009;30:1249-1258.
41. Shen Y, Goerner FL, Snyder C, et al. T1 relaxivities of gadolinium-based magnetic resonance contrast agents in human whole blood at 1.5, 3, and 7 T. *Invest Radiol*. 2015;50:330-338.

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**Contrast Imaging**

**MR Imaging Update** July 2015 • Supplement to Vol. 44, No. 7

**Safety and Efficacy in Selecting a Contrast Agent for MRI**  
A question-and-answer session with Jeffrey H. Male, MD, PhD, Professor of Radiology, and Director of Body MRI, Department of Radiology, University of Washington, on the use of macrocyclic gadolinium-based contrast agents in MRI imaging.

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This is the first article in a 4-part series discussing the use of macrocyclic gadolinium-based contrast agents (GBCAs) in magnetic resonance imaging. The remaining 3 parts will appear in forthcoming issues of Applied Radiology.

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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.

Date of release: 07-01-2015  
Date of expiration: 06-30-2017

Supported by an unrestricted educational grant from



LIFE 100-1410

**Applied Radiology (AR): Dr. Male, please briefly describe some of the challenges you face when selecting an MR imaging contrast agent.**  
**Dr. Male:** 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 exposed to the lowest possible risk of adverse events. Not immediate, in terms of severe contrast reactions, and long-term, when considering exposure such as nephrogenic systemic fibrosis (NSF).

Going hand-in-hand with this is patient tolerance, by which I mean the most 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 do 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, that 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 (ie, physicochemical properties, stability, efficacy, and safety) figure most prominently in your selection process?**  
**Dr. Male:** I have used multiple GBCAs over the years. Most of my contrast work was with Magnevist, which was the first MR contrast agent approved back in 1986, and with Dotarem. I did a lot of double-blind magnetic resonance angiography (MRA) before the relationship between gadolinium contrast and NSF was known, and these contrast agents were used at my hospital based primarily on perceived side-effect and cost considerations. All of the gadolinium agents were essentially swept back in the 1990s, 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, Dotarem, ProHance). By then, I was mainly relying on 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 signal and spatial resolution. The benefits of MultiHance for MRA have been shown in many studies, but beyond MRA there are multiple additional studies in spine, breast, and liver MRI, showing combinations of superiority at equal dose and near superiority at half dose.

With the recognition of a link between gadolinium contrast and NSF in 2006, the MR community began considering gadolinium formulations and designs carefully. Such new terms previously relegated to chemistry and pharmacology, such as "thermodynamic and kinetic stability constants," "transmetalation," "cyclic chelates," and "macrocyclic vs. linear ligand structures" became common nomenclature and hot topics of discussion.

While I don't believe we completely understood this issue, what is clear to me is that it is a disease caused by prolonged exposure to certain gadolinium formulations, which is a contrast biochemical phenomenon (ie, dose-associated with renal failure) not best to the release of the toxin, heavy metal gadolinium.



**APPLIED RADIOLOGY**

APPLICATIONS IN

**Contrast Imaging**

**MR Imaging Update** November 2015 • Supplement to Vol. 44, No. 11

**The Use of ProHance (Gadoteridol) in Patients with Renal Dysfunction**  
A question-and-answer session with Debra Morgan, MD, Professor and Director of MRI, Body Imaging Section, and Ragan Sanyal, MD, Associate Professor, Department of Radiology, University of Alabama at Birmingham, Birmingham, AL, on the selection of a gadolinium-based contrast agent (GBCA) for magnetic resonance imaging (MRI) in patients with renal dysfunction.

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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 and safety of a contrast agent and to provide a review of key studies related to the evaluation and use of specific contrast agents.

Release date: November 1, 2015  
Expiration date: June 30, 2017  
Expiration date: November 30, 2019

Supported by an unrestricted educational grant from



LIFE 100-1410

**Currently, there are 6 gadolinium-based contrast agents (GBCAs) approved by the FDA for magnetic resonance imaging (MRI). Tell which are extracellular fluid agents: Dotarem (gadoteric acid), Magnevist (gadoteric acid), ProHance (gadoteric acid), ProHance H2O (gadoteric acid), Dotarem (gadoteric acid), Dotarem (gadoteric acid), Dotarem (gadoteric acid), Dotarem (gadoteric acid), Dotarem (gadoteric acid), Dotarem (gadoteric acid), Dotarem (gadoteric acid), Dotarem (gadoteric acid).**

**Dr. Morgan and Sanyal:** The US FDA has approved 6 gadolinium-based contrast agents (GBCAs) for magnetic resonance imaging (MRI) in patients with renal dysfunction. These agents vary in their physicochemical properties, potentially impacting their safety and efficacy.<sup>1-6</sup>

In 2006, an association was made between nephrogenic systemic fibrosis (NSF), a potentially fatal, systemic disease, and administration of GBCAs.<sup>7</sup> Factors that increase the risk for development of NSF include factors related to the patient (ie, renal dysfunction), contrast administration parameters (highly and/or repeated GBCA doses), and to the GBCA itself (lower stability GBCAs).<sup>8</sup> For patients in whom the potential benefits of contrast-enhanced MRI outweigh the risks, it is appropriate to reduce the possibility of NSF by minimizing contrast volume and selecting a more stable agent. Here we discuss with Drs. Debra Morgan and Ragan Sanyal considerations for contrast agent selection in patients at risk for developing NSF, with particular emphasis on those agents most relevant to clinical practice in a large, busy, academic hospital.

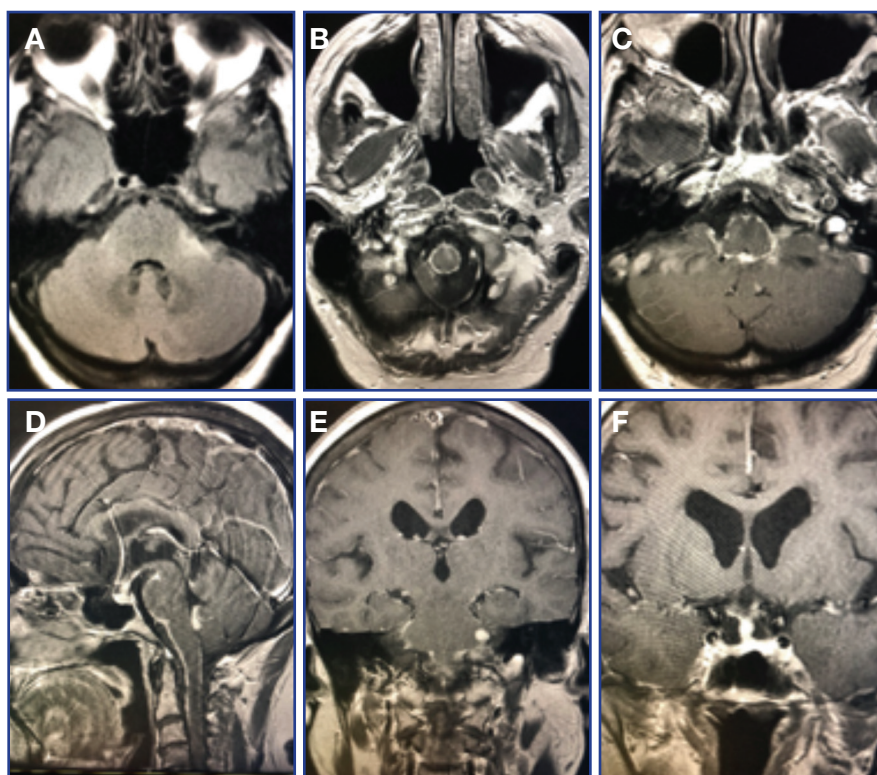
**Applied Radiology (AR): Welcome, Drs. Morgan and Sanyal. Can you please describe for us your imaging facility at the University of Alabama at Birmingham (UAB)?**  
**Dr. Morgan and Sanyal:** The UAB Hospital is a large, 800-bed, tertiary care, academic hospital that provides inpatient care with a complete range of primary and specialty care services. The UAB Department of Radiology has a complete range of imaging modalities and subspecialty services. Our department includes 1.5- and 3.0-T MRI imaging suites, and we perform approximately 30,000 MRI scans annually.

**AR: Briefly describe some of the challenges you are faced with when selecting a contrast agent for MR imaging. What attributes are most important (ie, physicochemical properties, stability, efficacy, and safety) in choosing a GBCA? What considerations go into GBCA selection in patients with renal dysfunction?**  
**Dr. Morgan and Sanyal:** As you know, numerous administrations of GBCA is an integral part of most MRI protocols. Intravenous GBCAs help radiologists better delineate anatomy and evaluate various pathologies, including tumors, inflammation, ischemia, patency of blood vessels, and others. With respect to the challenges we face at UAB, many of the patients referred for MRI have varying degrees of renal dysfunction. Although intravenous contrast agents have clear advantages in most clinical situations, patients with renal dysfunction have a higher risk of developing NSF. NSF is a potentially fatal disease, and developing a patient with severe renal dysfunction, and it has been associated with intravenous GBCA administration.<sup>9</sup> In at-risk patients, radiologists have to weigh the benefits of GBCA administration during MRI with the risk of potentially life-threatening NSF. Once a decision to administer a GBCA has been made, radiologists have to choose an appropriate agent, one that is least likely to cause NSF.

To choose an appropriate GBCA, it is important to understand the differences between the various types of GBCAs and the hypothetical pathophysiology of NSF, and also to draw upon the past experience of various institutions. NSF is likely caused by self and tissue deposition of free gadolinium (derived from the GBCA chelate) that cannot be adequately excreted by the kidneys.<sup>10-12</sup> It is known that in patients with renal dysfunction, the rate of elimination of GBCAs is altered, so radiologists usually require subjective

### 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, mid-brain, 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.

### REFERENCES

1. Hebel R, Dubaniewicz-Wybieralska M, Dubaniewicz A. Overview of neurosarcoidosis: recent advances. *J Neurol.* 2015;262:258-267.
2. Shah R, Roberson GH, Curé JK. Correlation of MR imaging findings and clinical manifestations in neurosarcoidosis. *AJNR Am J Neuroradiol.* 2009;30:953-961.