

The Use of ProHance (Gadoteridol) in Patients with Renal Dysfunction

A question-and-answer session with Desiree Morgan, MD, Professor and Director of MRI, Body Imaging Section, and Rupan Sanyal, MD, Associate Professor, Body and Emergency Radiology Section, 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.

This is the second article in a 4-part series that discusses the use of macrocyclic GBCAs in MRI. The remaining 2 parts will appear in forthcoming issues of *Applied Radiology*.

CE credits available

This quarterly 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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Currently, there are 9 gadolinium-based contrast agents (GBCAs) approved by the FDA for magnetic resonance imaging (MRI), 7 of which are extracellular fluid agents: Dotarem (gadoterate meglumine; Guerbet), Gadavist (gadobutrol; Bayer Healthcare), ProHance (gadoteridol; Bracco Diagnostics), Magnevist (gadopentetate dimeglumine; Bayer Healthcare), MultiHance (gadobenate dimeglumine; Bracco Diagnostics), Omniscan (gadodiamide; GE Healthcare), and OptiMARK (gadoversetamide; Covidien). These agents vary in their physicochemical properties, potentially impacting their safety and efficacy.¹⁻⁹

In 2006, an association was made between nephrogenic system fibrosis (NSF), a potentially fatal, systemic disease, and administration of GBCAs.¹⁰ Factors that increase the risk for development of NSF include factors related to the patient (severe renal dysfunction), contrast administration parameters (high and/or repeated GBCA doses), and to the GBCA itself (lower-stability GBCAs).¹¹ 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 volumes and selecting a more stable agent. Here we discuss with Drs. Desiree Morgan and Rupan Sanyal considerations for contrast agent selection in patients at risk for developing NSF, with particular emphasis on those aspects 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)?

Drs. Morgan and Sanyal: The UAB Hospital is a large, 900-bed, tertiary-care, academic hospital that provides its patients with a complete range of primary and specialty care services. The UAB Department of Radiology has more than 80 highly-trained, subspecialized radiologists. Our department has eight 1.5- and 3.0-T MR imaging scanners, 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, safety) in choosing a GBCA? What considerations go into GBCA selection in patients with renal dysfunction?

Drs. Morgan and Sanyal: As you know, intravenous administration of GBCAs 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 present radiologists with a dilemma: NSF, a recently described rare but serious disease, can develop in a patient with severe renal dysfunction, and it has been associated with intravenous GBCA administration.¹⁰ In at-risk patients, radiologists have to weigh the benefit 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 hypothesized pathophysiology of NSF, and also to draw upon the past experience of various institutions. NSF is likely caused by soft tissue deposition of free gadolinium liberated from the GBCA chelate that cannot be adequately excreted by the kidneys.^{12,13} It is known that in patients with renal dysfunction, the rate of elimination of GBCAs is slowed: in moderately renally-impaired subjects

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(estimated glomerular filtration rate [eGFR] of 30–60 mL/min/1.73 m²), the GBCA half-life is increased from approximately 1–2 hours to 4–8 hours, while in those with severe renal impairment (eGFR of <30 mL/min/1.73 m²), the mean half-life increases to 18–34 hours.¹⁴ It has been postulated that this delayed excretion allows for prolonged persistence of free gadolinium in the body.¹⁵ The free gadolinium incites a toxic reaction in the soft tissues, resulting in fibrosis of skin, joints, eyes, and other internal organs.^{12,13}

Because NSF occurs due to release and subsequent soft tissue deposition of free gadolinium from GBCA chelates, chelates in which the gadolinium is more tightly bound are less likely to release the gadolinium and cause NSF. The stability of a GBCA chelate depends on its molecular structure. The currently available, extracellular fluid GBCAs include agents that are: linear and nonionic (Omniscan [gadodiamide] and OptiMARK [gadoversetamide]); linear and ionic (Magnevist [gadopentetate dimeglumine] and MultiHance [gadobenate dimeglumine]); and macrocyclic (Dotarem [gadoterate meglumine], Gadavist [gadobutrol], and ProHance [gadoteridol]). Of these, the linear nonionic chelates tend to have lowest in vitro and in vivo stability compared to the other two groups.^{9,16} Macrocyclic chelates, on the other hand, are nonlinear cyclical molecules in which the gadolinium is more tightly attached, decreasing the risk of disassociation and deposition.

In 2 separate reviews of the literature, the majority of unconfounded NSF cases (ie, those associated with administration of a single GBCA) were attributable to 3 specific linear agents: Omniscan (gadodiamide; 78–85%), followed by Magnevist (gadopentetate dimeglumine; 7–20%), and then OptiMARK (gadoversetamide; <2%).^{17,18} Interestingly, no unconfounded cases were found to result following administration of the protein-interacting, linear agent MultiHance (gadobenate dimeglumine), leading some to postulate that the portion of the agent responsible for protein interaction may also provide increased stability to this agent.¹⁹

A review of the literature for cases of NSF following administration of macrocyclics does not find any unconfounded cases of NSF following administration of ProHance (gadoteridol).^{17,18,20} Furthermore, Reilly evaluated the risk of NSF following administration of ProHance (gadoteridol) in 141 patients on long-term hemodialysis, and thus considered extremely high-risk for NSF.²¹ No cases of NSF were observed, and this was considered statistically significantly lower than the expected incidence of NSF in this population. There have been a small number of reports of unconfounded NSF cases occurring following administration of the macrocyclic agents Gadavist (gadobutrol) and Dotarem (gadoteridol meglumine);^{22–25} however, these have been difficult to confirm, and overall, the incidence of NSF with macrocyclic agents remains extremely low.^{11,15,19,21}

The American College of Radiology classification of GBCAs according to NSF risk is consistent with the observed incidence of unconfounded cases of NSF with each agent:¹¹ Group I agents (associated with the greatest number of unconfounded NSF cases) include the nonionic linear agents Omniscan (gadodiamide) and OptiMARK (gadoversetamide), and the ionic linear agent Magnevist (gadopentetate dimeglumine); the Group II agents (associated with few, if any, cases of NSF) include the ionic linear agent MultiHance (gadobenate dimeglumine), and the 3 macrocyclic agents ProHance (gadoteridol), Dotarem (gadoterate meglumine), and Gadavist (gadobutrol). Group III agents (Ab-lavar [gadofosveset trisodium] and Eovist [gadoxetate disodium]) were

introduced to the market so recently that there is considered insufficient data to further classify them. The Group I agents have been contraindicated by the FDA in patients with chronic, severe kidney disease (eGFR <30 mL/min/1.73 m²) or acute kidney injury;^{3,5,6} it is recommended that in such patients, alternative GBCAs should be used.

AR: *What is the current agent of choice at UAB? Have you used any other agent(s) in the past? If so, why did you make the switch?*

Drs. Morgan and Sanyal: Before the association between GBCAs and NSF was reported by Grobner,¹⁰ we were using Omniscan (gadodiamide) at our hospital and Magnevist (gadopentetate dimeglumine) at our large, multidisciplinary outpatient clinic. Shortly thereafter, in early 2007, we instituted a change in our MR contrast policy, taking a total macrocyclic approach, and switched completely over to ProHance (gadoteridol).

For the past several years, ProHance (gadoteridol) has been the main GBCA used at UAB for MRI scans. ProHance (gadoteridol) is a macrocyclic GBCA with a good safety profile in patients with renal dysfunction. We have found that ProHance (gadoteridol) is well-tolerated by our patients, whether they are hospitalized or undergoing MRI as outpatients. We monitor adverse reactions to GBCAs monthly in our practice. In 2011, when we reviewed our clinical experience utilizing ProHance (gadoteridol) in 28,078 patients,²⁶ the overall reaction rate (including simple nausea, as well as allergic-like reactions) was 0.666%, with the vast majority being mild. To date, we have now given more than 90,000 doses and the reaction rate is unchanged.

As mentioned above, in the literature, no unconfounded cases of NSF have been attributed to ProHance (gadoteridol).^{17,18} Our own experience at UAB also reflects the excellent safety profile of ProHance (gadoteridol): we have seen no cases of NSF on follow-up of 2,618 ProHance (gadoteridol) administrations in 2,106 patients with renal dysfunction (eGFR <60 mL/min/1.73 m²) who underwent contrast-enhanced MRI at UAB. In 508 of these administrations, the patients had an eGFR <45 mL/min/1.73 m², and in 25, the patients had an eGFR <30 mL/min/1.73 m². We can conclude from our experience that ProHance (gadoteridol) can be safely administered to patients with Grade 3 (eGFR 30–60 mL/min/1.73 m²) renal failure.

AR: *When selecting a contrast agent, the criteria that are typically deemed most important to radiologists include achieving diagnostic efficacy while maintaining patient safety. How does this particular agent, ProHance (gadoteridol), help you achieve both of these?*

Drs. Morgan and Sanyal: Safety and good diagnostic quality images are certainly the main concerns when choosing a GBCA. ProHance (gadoteridol) not only provides excellent diagnostic quality images, but it is also safe in patients with Grade 3 renal dysfunction who are at risk for NSF. A review of our own experience, as well as the published literature, does not yield a single case of NSF attributable to ProHance (gadoteridol). In addition, ProHance (gadoteridol) is the only available GBCA approved for triple dose administration, further supporting the safe use of this agent in patients, such as children and the elderly, in which additional safety precautions may be warranted.⁷ It is also worth noting that there does not appear to be any clinical advantage to using either of the newer macrocyclic agents approved by the FDA (Gadavist [gadobutrol] or Dotarem [gadoterate meglumine]): the relaxivity differences among them are minimal.⁸

and a recent, large, intraindividual study comparing ProHance (gadoteridol) and Gadavist (gadobutrol) for MR imaging of the CNS demonstrates no benefit for the higher concentration of Gadavist (gadobutrol).²⁷

AR: *Do you have experience with ProHance (gadoteridol) in elderly patients? Please explain some of the special considerations related to GBCA selection, as well your observations on the safety and efficacy of ProHance (gadoteridol), in this population.*

Drs. Morgan and Sanyal: Our hospital serves primarily the adult population, including a large number of elderly patients. Such patients often have multiple comorbidities and are, in general, at higher risk of renal dysfunction and associated complications. We have been very satisfied with the safety profile of ProHance (gadoteridol) in elderly patients, including those with Grade 3 renal dysfunction.

AR: *In the long run, do you expect to continue using your current contrast agent for MR imaging? If so, why?*

Drs. Morgan and Sanyal: Due to our satisfaction with patient acceptance, as well as the safety profile and quality of images obtained using ProHance (gadoteridol), it is currently, and will continue to be, the primary GBCA used at UAB.

Key Points

- In at-risk patients, radiologists have to weigh the benefit of GBCA administration during MRI with the risk of potentially life-threatening NSF.
- In patients with renal dysfunction, the rate of elimination of GBCAs is slowed, and it has been postulated that, in the case of the less stable GBCAs in particular, this delayed excretion allows for prolonged persistence of free gadolinium in the body that ultimately leads to NSF.
- Safety and good diagnostic quality images are the main concerns when choosing a GBCA; in our experience, ProHance (gadoteridol) not only provides excellent diagnostic quality images, but is also safe in patients with Grade 3 renal dysfunction who are at risk for NSF.
- The macrocyclic agents all have similar r1 relaxivities, and a comparison between ProHance (gadoteridol) and Gadavist (gadobutrol) for MRI of the CNS indicates no benefit to the higher concentration of Gadavist (gadobutrol).

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Case Study

MRI with Contrast in Renal Cyst with Enhancing Septa

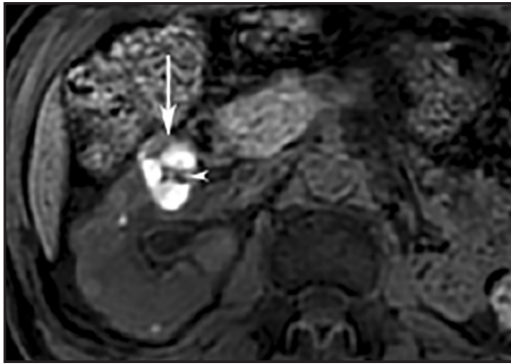


FIGURE 1. The fat-suppressed, axial, T1-weighted image shows a T1 hyperintense lesion in the anterior interpolar right kidney (arrow), consistent with a cystic lesion containing internal hemorrhage. Internal septa are noted (arrowhead).

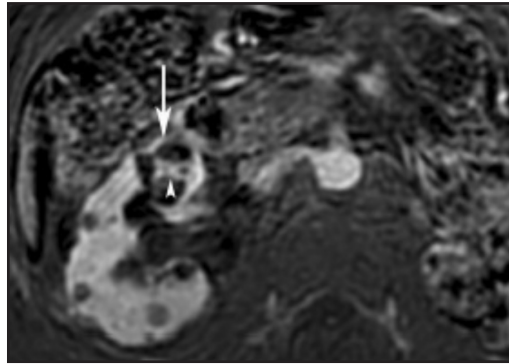


FIGURE 2. The contrast-enhanced subtraction image shows clear enhancement with the thick septa (arrowhead). Demonstration of enhancement within the septa is very concerning for malignancy (Bosniak III).

Case Summary

A 74-year-old man with a history of left nephrectomy presented for characterization of a right renal cystic lesion seen on ultrasound. The patient had poor renal function with an eGFR of 22 mL/min/1.73 m², but he was not on dialysis. After providing written and informed consent, the patient underwent a multiplanar, multisequence, contrast-enhanced abdominal MRI scan on a 3T Philips Achieva scanner. The patient was administered 10 mL of intravenous ProHance (gadoteridol).

Imaging Findings

The fat-suppressed, axial, T1-weighted image (Figure 1) shows a T1 hyperintense lesion in the anterior interpolar right kidney (arrow), consistent with a cystic lesion containing internal hemorrhage. Internal septa are noted (arrowhead). The contrast-enhanced subtraction image (Figure 2) shows clear enhancement within the thick septa (arrowhead). Demonstration of enhancement within the septa is very suggestive of malignancy (Bosniak III).

Diagnosis

Renal cyst with enhancing septa, concerning for malignancy (Bosniak III).

Discussion

This case represents a dilemma not infrequently encountered by radiologists. The patient had a solitary kidney with very poor renal function (eGFR of 22 mL/min/1.73 m²). Ultrasound had identified a complex cyst in the right kidney with internal septa that raised the possibility of malignancy. Preservation of the remaining renal function was very important for this patient. If possible, the urologist wanted to avoid a partial nephrectomy, as benign renal cysts can have septa. Demonstration of septal enhancement has a

much higher likelihood of malignancy than simply the presence of septa; thus, the urologist referred the patient for contrast-enhanced MRI to assess for septal enhancement.

After discussions with the referring team and the patient, it was determined that the risks of imaging with a GBCA (ie, the risk of causing NSF) were outweighed by the potential benefits of imaging (ie, avoiding partial nephrectomy for a benign pathology), particularly with ProHance (gadoteridol). Although severe renal dysfunction is a relative contraindication to GBCA administration at our institution, the only absolute contraindication is a prior history of NSF. We decided to perform the MRI examination with ProHance (gadoteridol). This macrocyclic chelate is more stable than many other agents, and in a patient with renal dysfunction, it is less likely to dissociate and deposit free gadolinium in the tissues. In this case, written informed consent was obtained and documented in compliance with our institutional policy of obtaining consent before GBCA administration in patients with an eGFR <30 mL/min/1.73 m².

The demonstration of septal contrast enhancement on MRI confirmed that this renal cyst did indeed have a high probability of being malignant; administering ProHance (gadoteridol) during the MRI had a major impact on patient management. The patient, moreover, did not develop NSF after three years of clinical follow up.

Conclusion

In the literature, no definite case of NSF has been attributed to ProHance (gadoteridol). Our experience suggests that it is safe in Grade 3 renal failure (eGFR 30-60 mL/min/1.73 m²). In patients with more advanced renal failure, a nuanced approach is required, and administration can be considered when the potential benefits outweigh the potential risks.