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Contrast-Enhanced Neuroimaging with Dotarem® (Gadoterate Meglumine)



The Benefits of a Macrocyclic, Ionic Contrast Agent | An Expert Forum Summary

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Introduction

At present, in the United States, six general-use, extracellular fluid (ECF) gadolinium (Gd)-based contrast agents (GBCAs) are approved for use for a number of magnetic resonance imaging (MRI) indications. From a safety perspective, most GBCAs were once considered essentially interchangeable, but we now know that GBCAs vary in their safety profile. As a result, selecting a GBCA has become an increasingly complex challenge, as well as an opportunity, for radiologists and referring physicians.

Applied Radiology assembled a group of six well-respected radiologists experienced in adult and pediatric MR neuroimaging to discuss and debate their views on selection of contrast agents for contrast-enhanced neuro-MRI. This article summarizes those discussions, with particular emphasis on differentiation among currently available GBCAs based on safety and stability, and on how clinicians can use this information to institute evidence-based best practices at their institutions.

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Contrast-Enhanced Neuroimaging with Dotarem® (Gadoterate Meglumine)

The Benefits of a Macrocyclic, Ionic Contrast Agent | An Expert Forum Summary

The properties of available ECF GBCAs are provided in Table 1.¹⁻⁸ GBCAs consist of a Gd ion chelated to a carrier molecule. In terms of structure and stability, GBCAs may be macrocyclic or linear, and ionic or nonionic. In macrocyclic agents, the Gd ion is encircled by a chelate “cage,” and such complexes have been shown to be more stable than GBCAs with linear chelates.^{7,10,11} In addition, for GBCAs, ionicity also contributes to tighter binding between the Gd and chelate; ie, ionic GBCAs are less likely to dissociate and release the Gd ion.¹²

These concepts align with the prevailing theory that the most stable Gd-chelate complex would be ionic and have a macrocyclic backbone. In fact, Dotarem® (gadoterate meglumine), the first macrocyclic and ionic GBCA, demonstrates the highest thermodynamic and kinetic stability constants.¹⁻⁸ (Table 1)

For neuroradiology applications, all the ECF GBCAs are indicated for MRI evaluation of the central nervous system (CNS) in adults and children over the age of 2 years. Dotarem, Gadavist® (gadobutrol), and MultiHance® (gadobenate

Table 1. ECF GBCAs Approved for Use in the United States¹⁻⁸

Contrast Agent	Type	Nonionic	Stability		(T _{1/2} @ pH 1.0, 25°C)	Overall Stability
			log K _{therm}	log K _{cond} (pH 7.4)		
Dotarem® (gadoterate meglumine)	Macrocyclic	Ionic	25.6	19.3	338 hr	High
Gadavist® (gadobutrol)	Macrocyclic	Nonionic	21.8	14.7	43 hr	High
ProHance® (gadoteridol)	Macrocyclic	Nonionic	23.8	17.1	3.9 hr	High
Clariscan™ (gadoterate meglumine)	Macrocyclic	Ionic	25.6	19.3	NA*	High
MultiHance® (gadobenate dimeglumine)	Linear	Ionic	22.6	18.4	< 5 sec	Medium
Omniscan™ (gadodiamide)	Linear	Nonionic	16.9	14.9	< 5 sec	Low

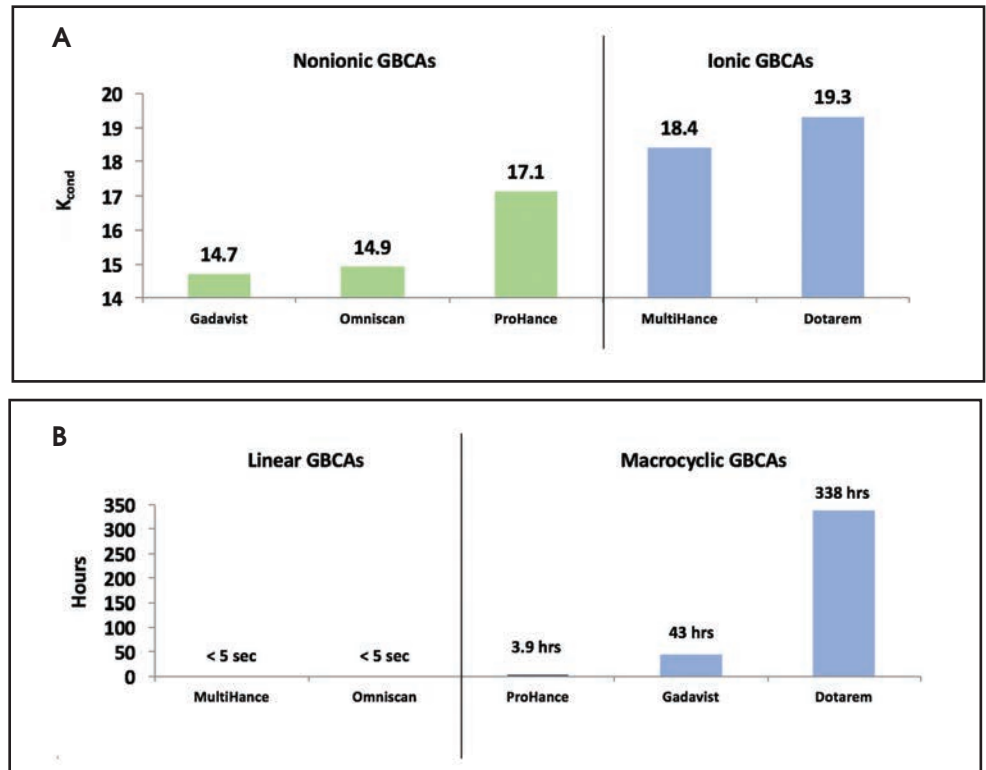
*Data shown related to gadoterate meglumine were not derived from a study using Clariscan, but the study drug has an active pharmaceutical ingredient equivalent to Clariscan.

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Donna R. Roberts, MD

“Contrast-enhanced imaging is indicated in children for a wide variety of situations, including evaluation of intracranial, spine, and head and neck pathologies.”



NOTE: Data shown are related to Dotarem; Clariscan was not used in this study, but has an equivalent active pharmaceutical ingredient.

FIGURE 1. Conditional thermodynamic stability (A) and $T_{1/2}$ (B) values for GBCAs.⁸

dimeglumine; at half dose) are also indicated for evaluation of the CNS in term neonates and children 0-2 years old.^{1,2,5}

Relaxivity, defined as the ability of the GBCA to create enhancement, is comparable among all the available GBCAs (with the exception of MultiHance, which is a bit higher), and stable over the range of magnetic fields used in clinical practice (0.2-1.5T).¹⁻⁸ Another differential property is the formulation: all the ECF GBCAs have a concentration of 0.5 mmol/mL, with the exception of Gadavist, which is twice as concentrated as the others (ie, formulated at 1 mmol/mL), and thus requires half the volume to deliver the same amount of Gd as the other agents.²

GBCA Structure and the Implications for Stability

Measuring GBCA Stability

Stability of GBCAs can be assessed by measuring the conditional thermodynamic stability constant ($\log K_{cond}$, measured at physiologic pH 7.4) and the half-life ($T_{1/2}$).^{8,13} Figure 1A shows that the ionic contrast agents Dotarem and

MultiHance have higher conditional thermodynamic stability compared with nonionic agents. Note that these constants are measured on a logarithmic scale and, therefore, small differences represent large differences in stability. In addition, the half-life, or $T_{1/2}$, is substantially different among the GBCAs: the $T_{1/2}$ of the linear agents is <5 seconds, while the $T_{1/2}$ is 3.9 hours for ProHance® (gadoteridol), 43 hours for Gadavist, and up to 338 hours for Dotarem (the endpoint of the experiment).⁸ (Figure 1B) The same relationships were confirmed in a study performed in human plasma in the absence and presence of competitor ions:⁷ the presence of competitor ions in the plasma hastened the release of Gd, and the macrocyclic agents remained most resistant to transmetallation.

Nephrogenic Systemic Fibrosis (NSF)

It has been known for just over 10 years that the least stable GBCAs increase the risk for NSF among patients with severe renal dysfunction. NSF is a painful, potentially fatal disease in which severe fibrosis is seen in

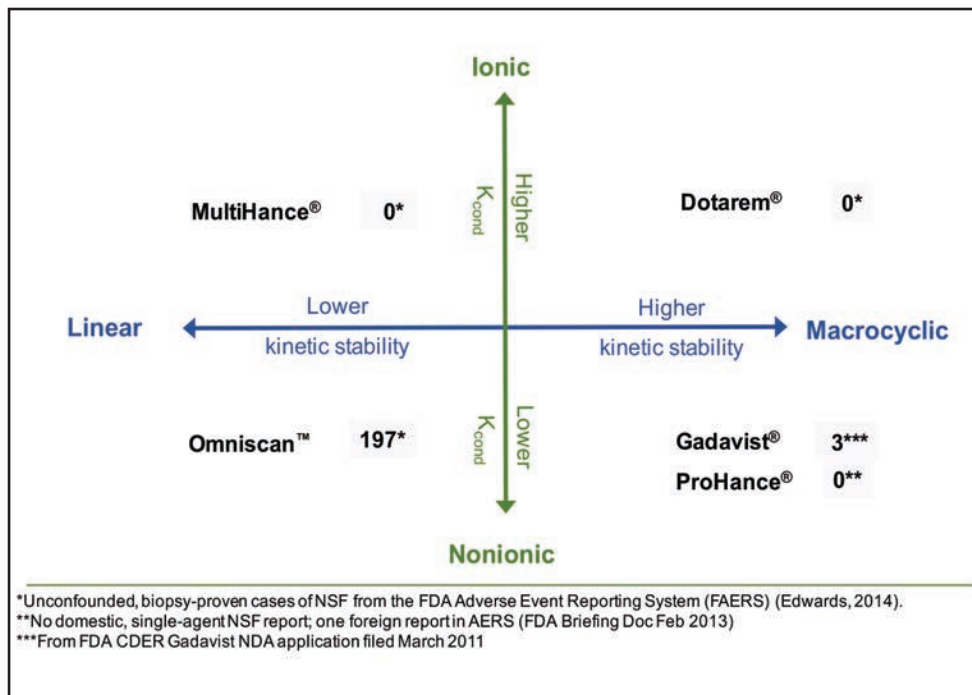


FIGURE 2. Graphic representation of the relationship between chelate structure and ionicity, and confirmed unconfounded NSF cases.¹⁸⁻²⁰

various organs, including the skin, muscle, and internal organs.¹⁴⁻¹⁷ In addition to end-stage renal disease, the main risk factors for developing NSF include administration of high and repeated doses of a low-stability GBCA.^{14,15} As NSF does not occur in the majority of patients with end-stage renal disease administered high/multiple doses of a low-stability GBCA, other unique and less well-understood physiologic or clinical factors are presumed to contribute to NSF incidence.

Based on the number of unconfounded (ie, single agent) cases of NSF seen following administration of each GBCA, we know the risk of NSF is: highest with linear, nonionic agents; intermediate with linear, ionic agents; and lowest with macrocyclic agents. (Figure 2) Although factors such as market share and usage patterns undoubtedly contribute to some skew in the data,¹⁸⁻²⁰ it is noteworthy that among the macrocyclics, no unconfounded cases of NSF have been associated with the highly stable macrocyclic and ionic GBCA Dotarem, despite extensive use in the “pre-NSF era” and after over 100 million doses have been administered worldwide. (Guerbet; data on file)

Since the association of GBCA use with NSF was reported, various government regulatory bodies and professional societies, including the U.S. Food and Drug Administration (FDA) and the American College of Radiology (ACR), have issued guidelines classifying the various GBCAs according to their inherent NSF risk, as well as recommendations for GBCA use in patients with various degrees of renal dysfunction.^{21,22} The recommendation by both groups is to avoid (contraindicated by the FDA) low-stability agents in patients with acute kidney injury or severe renal dysfunction (eGFR <30 mL/min/1.73 m²). (Table 2) These guidelines, together with the ensuing changes in clinical practice patterns around GBCA administration, have resulted in a dramatic decrease in the number of newly reported NSF cases.

Administration of GBCAs in Patients with Known Renal Dysfunction

Patients with end-stage renal disease are at greatest risk for NSF. However, evidence shows that the risk of NSF is reduced when Group II agents are used. For example, in the RESCUE Study, Deray et al compared the safety of contrast-enhanced MRI with Dotarem to

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Children’s Health System



Daniel J. Podberesky, MD

“I would say without a doubt, having Dotarem on the shelf has changed my personal level of anxiety in the patient with a low GFR. Again, the individual patient matters, the clinical indication, etc., but having that on the shelf has changed my threshold for saying that I don’t feel comfortable giving contrast in a particular patient.”

DOTAREM[®]

(gadoterate meglumine) Injection

**REAL-WORLD TESTED.
REAL-WORLD
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The Dotarem[®] safety profile has been tested and proven in both studies and 30 years of global clinical use.*



0.007%

Spontaneously Reported
Worldwide Adverse Events.
(>50 million doses)³⁻¹⁰

1 Dotarem[®]
The first macrocyclic
and ionic GBCA molecule.¹

Dotarem remains an industry standard for contrast imaging with a low incidence of immediate adverse events for patients of all ages.²⁻¹⁰

A low incidence of adverse events can help your patient focus on what matters most in their life.

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IMPORTANT SAFETY INFORMATION¹

WARNING: NEPHROGENIC SYSTEMIC FIBROSIS (NSF)

Gadolinium-based contrast agents (GBCAs) increase the risk for NSF among patients with impaired elimination of the drugs. Avoid use of GBCAs in these patients unless the diagnostic information is essential and not available with non-contrast MRI or other modalities. NSF may result in fatal or debilitating fibrosis affecting the skin, muscle and internal organs.

- The risk for NSF appears highest among patients with:
 - Chronic, severe kidney disease (GFR < 30 mL/min/1.73m²), or
 - Acute kidney injury.
- Screen patients for acute kidney injury and other conditions that may reduce renal function. For patients at risk for chronically reduced renal function (e.g. age > 60 years, hypertension, diabetes), estimate the glomerular filtration rate (GFR) through laboratory testing.
- For patients at highest risk for NSF, do not exceed the recommended DOTAREM dose and allow a sufficient period of time for elimination of the drug from the body prior to any re-administration.



Indications and Usage

DOTAREM® (gadoterate meglumine) injection is a prescription gadolinium-based contrast agent indicated for intravenous use with magnetic resonance imaging (MRI) in brain (intracranial), spine and associated tissues in adult and pediatric patients (including term neonates) to detect and visualize areas with disruption of the blood brain barrier (BBB) and/or abnormal vascularity.

Contraindications

History of clinically important hypersensitivity reactions to DOTAREM.

Warnings and Precautions

- **Hypersensitivity Reactions:** Anaphylactic and anaphylactoid reactions have been reported with DOTAREM, involving cardiovascular, respiratory, and/or cutaneous manifestations. Some patients experienced circulatory collapse and died. In most cases, initial symptoms occurred within minutes of DOTAREM administration and resolved with prompt emergency treatment.
- Before DOTAREM administration, assess all patients for any history of a reaction to contrast media, bronchial asthma and/or allergic disorders. These patients may have an increased risk for a hypersensitivity reaction to DOTAREM.
- Administer DOTAREM only in situations where trained personnel and therapies are promptly available for the treatment of hypersensitivity reactions, including personnel trained in resuscitation.
- **Gadolinium Retention:** Gadolinium is retained for months or years in several organs. The highest concentrations have been identified in the bone, followed by brain, skin, kidney, liver and spleen. The duration of retention also varies by tissue, and is longest in bone. Linear GBCAs cause more retention than macrocyclic GBCAs.
- Consequences of gadolinium retention in the brain have not been established. Adverse events involving multiple organ systems have been reported in patients with normal renal function without an established causal link to gadolinium retention.
- **Acute Kidney Injury:** In patients with chronically reduced renal function, acute kidney injury requiring dialysis has occurred with the use of GBCAs. The risk of acute kidney injury may increase with increasing dose of the contrast agent; administer the lowest dose necessary for adequate imaging.
- **Extravasation and Injection Site Reactions:** Ensure catheter and venous patency before the injection of DOTAREM. Extravasation into tissues during DOTAREM administration may result in tissue irritation.

Adverse Reactions

- The most common adverse reactions associated with DOTAREM in clinical trials were nausea, headache, injection site pain, injection site coldness and rash.
- Serious adverse reactions in the Postmarketing experience have been reported with DOTAREM. These serious adverse reactions include but are not limited to: arrhythmia, cardiac arrest, respiratory arrest, pharyngeal edema, laryngospasm, bronchospasm, coma and convulsion.

Use in Specific Populations

- **Pregnancy:** GBCAs cross the human placenta and result in fetal exposure and gadolinium retention. Use only if imaging is essential during pregnancy and cannot be delayed.
- **Lactation:** There are no data on the presence of gadoterate in human milk, the effects on the breastfed infant, or the effects on milk production. However, published lactation data on other GBCAs indicate that 0.01 to 0.04% of the maternal gadolinium dose is present in breast milk.
- **Pediatric Use:** The safety and efficacy of DOTAREM at a single dose of 0.1 mmol/kg has been established in pediatric patients from birth (term neonates ≥ 37 weeks gestational age) to 17 years of age based on clinical data. The safety of DOTAREM has not been established in preterm neonates. No cases of NSF associated with DOTAREM or any other GBCA have been identified in pediatric patients age 6 years and younger.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088.

Please see the full Prescribing Information, including the patient Medication Guide, for additional important safety information.

*Dotarem was launched globally in 1989 and approved by the FDA for use in the US in 2013.

References:

1. Dotarem [package insert]. Princeton, NJ: Guerbet LLC; July 2019.
2. Internal data as of May 2019.
3. de Kerviler E et al. Adverse reactions to gadoterate meglumine: review of over 25 years of clinical use and more than 50 million doses. *Invest Radiol.* 2016 Sep;51(9):544-51.
4. Briand et al. Efficacy and safety of the macrocyclic complex Gd-DOTA in Children: Results of a Multi-Centre Study. *Proceedings of the 29th Congress of the European Society of Pediatric Radiology.* 1992; 128
5. Briand Y. Daily Paediatric Use of MRI Contrast Agents: Results of a Multi-Centre Survey. *Proceedings of the 29th Congress of the European Society of Pediatric Radiology.* 1992.
6. Ishiguchi T & Takahashi S. Safety of gadoterate meglumine (Gd-DOTA) as a contrast agent for magnetic resonance imaging: results of a post-marketing surveillance study in Japan. *Drugs R D.* 2010;10(3):133-45.
7. Emond S & Brunelle F. Gd-DOTA administration at MRI in children younger than 18 months of age: immediate adverse reactions. *Pediatr Radiol.* 2011 Nov;41(11):1401-6.
8. Maurer M et al. Tolerability and diagnostic value of gadoteric acid in the general population and in patients with risk factors: results in more than 84,000 patients. *Eur J Radiol.* 2012 May;81(5):885-90.
9. Soyer et al. Observational Study on the Safety Profile of Gadoterate Meglumine in 35,499 Patients: The SECURE Study. *J. Magn. Reson. Imag.* 2017; 45, 988-997
10. Radbruch A et al. Gadolinium retention in the dentate nucleus and globus pallidus is dependent on the class of contrast agent. *Radiology.* 2015 Jun;275(3):783-97.

Table 2. FDA and ACR Classification of Gadolinium-based Contrast Agents Relative to Nephrogenic Systemic Fibrosis Risk^{21,22}

Gadolinium-based Contrast Agent	FDA	ACR Group	NSF Risk per ACR
Dotarem® (gadoterate meglumine)	No contraindication	Group II	Associated with few, if any, unconfounded cases of NSF
Gadavist® (gadobutrol)	No contraindication	Group II	Associated with few, if any, unconfounded cases of NSF
ProHance® (gadoteridol)	No contraindication	Group II	Associated with few, if any, unconfounded cases of NSF
MultiHance® (gadobenate dimeglumine)	No contraindication	Group II	Associated with few, if any, unconfounded cases of NSF
Omniscan™ (gadodiamide)	Contraindicated in patients with AKI or eGFR <30 mL/min/1.73 m ²	Group I	Associated with the greatest number of NSF cases
Magnevist® (gadopentetate dimeglumine)	Contraindicated in patients with AKI or eGFR <30 mL/min/1.73 m ²	Group I	Associated with the greatest number of NSF cases

NOTE: Clariscan is not referenced in the ACR Contrast Media Manual, but it has an equivalent active pharmaceutical ingredient to Dotarem.

unenanced MRI in 114 patients with chronic kidney disease, and found no difference in the incidence of NSF in the two patient groups.²³ In the prospective ProFINEST Study, Amet et al assessed the incidence of NSF in long-term dialysis patients that either received or did not receive a GBCA.²⁴ Of the 571 included patients, almost all (88.9%) received Dotarem and, after a 4-month follow-up period, no cases of NSF were detected in these patients, supporting the use of a stable, macrocyclic agent when contrast-enhanced MRI is indicated, in even the most renal compromised.

The general consensus among radiologists is that if a patient is on hemodialysis (but not peritoneal dialysis, as there is no evidence that it is protective), the contrast-enhanced exam should be scheduled so the next dialysis session immediately follows the imaging exam.²²

The use of dialysis to minimize the risk of NSF has not been confirmed in any randomized, controlled trials, and it is generally agreed that initiating hemodialysis prior to or after GBCA administration in a patient not currently receiving hemodialysis is not warranted.

Neuroimaging in the Adult Population

Contrast-enhanced MRI in patients with malignant brain tumors provides information critical to diagnosis, treatment-related decisions, and treatment follow-up. (Figure 3) Historically, MRI contrast agents have been viewed as having a favorable safety profile, with low adverse reaction rates.^{25,26} (Figure 4) However, when using a GBCA for imaging adult patients with neurologic disease, several patient populations are at increased risk of

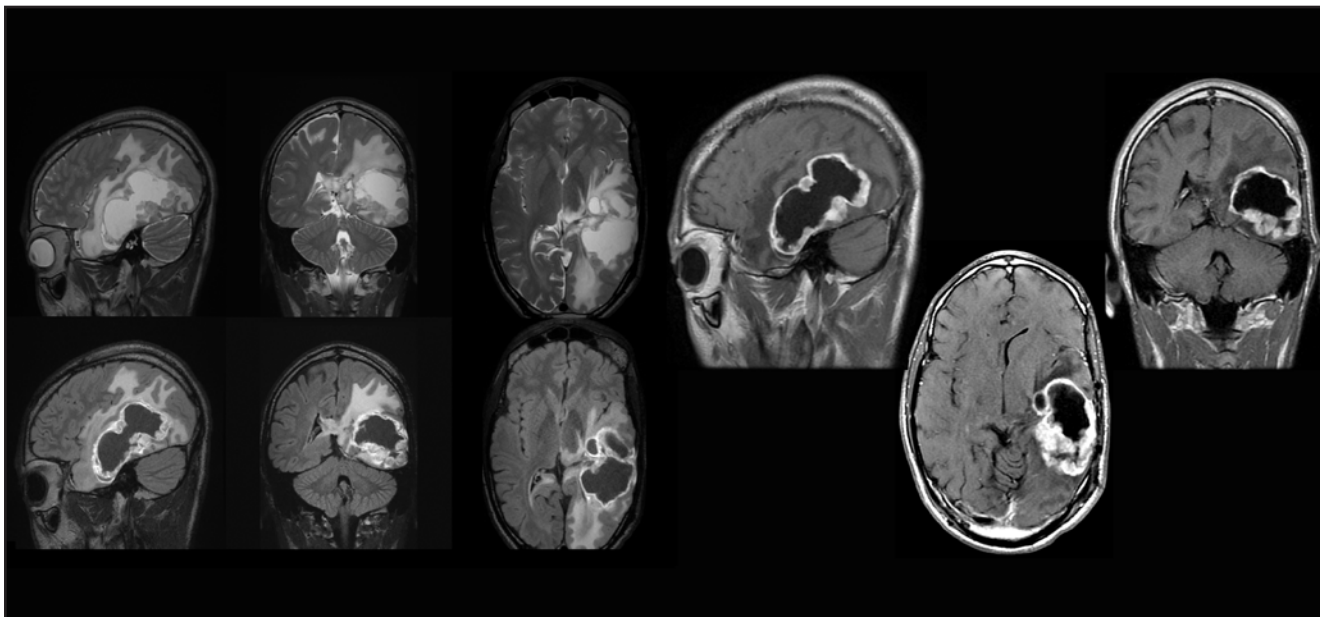


FIGURE 3. 67-year-old patient with new-onset seizures. Volumetric T2-weighted imaging, and postcontrast FLAIR and volumetric T1-weighted imaging after administration of 15 mL Dotarem reveal a heterogeneously enhancing mass with significant surrounding high signal and associated mass effect consistent with a diagnosis of glioblastoma. Images courtesy of Dr. L. Tanenbaum.

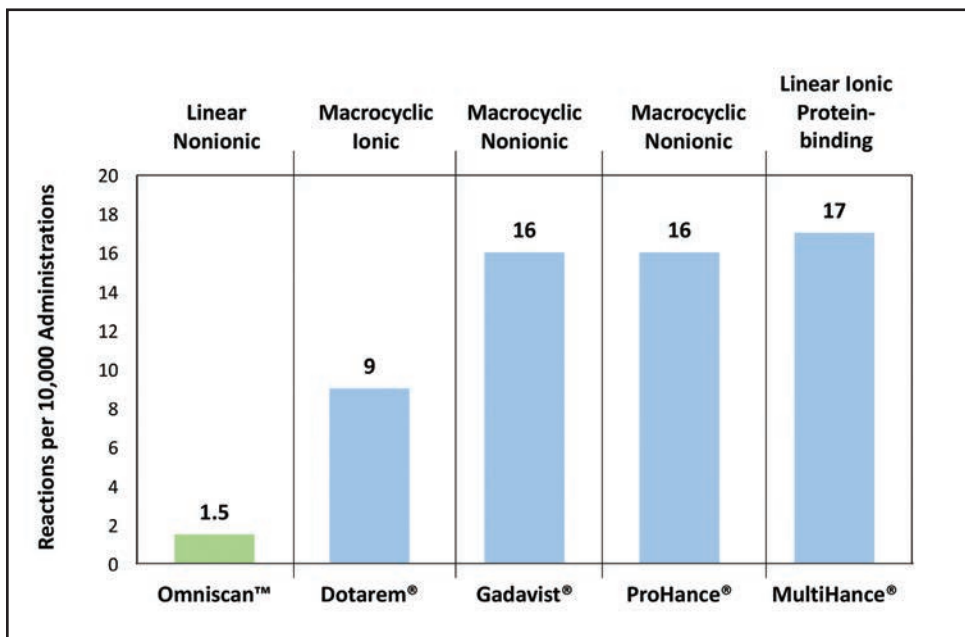


FIGURE 4. Rates of immediate allergic-like adverse events per 10,000 administrations, from a systematic review of 9 studies, including 716,978 GBCA administrations.²⁶

clinical sequelae, particularly when less stable GBCAs are used.

Even in low-risk patients, it is often beneficial to evaluate clinical situations when it might

be possible to avoid contrast use — eg, where the contrast may not actually contribute to the diagnosis or surveillance. MR contrast may be helpful for diagnosis and treatment planning,

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Lawrence N. Tanenbaum, MD, FACR

“Contrast-enhanced MRI in patients with malignant brain tumors provides information critical to diagnosis, treatment-related decisions, and treatment follow-up.”

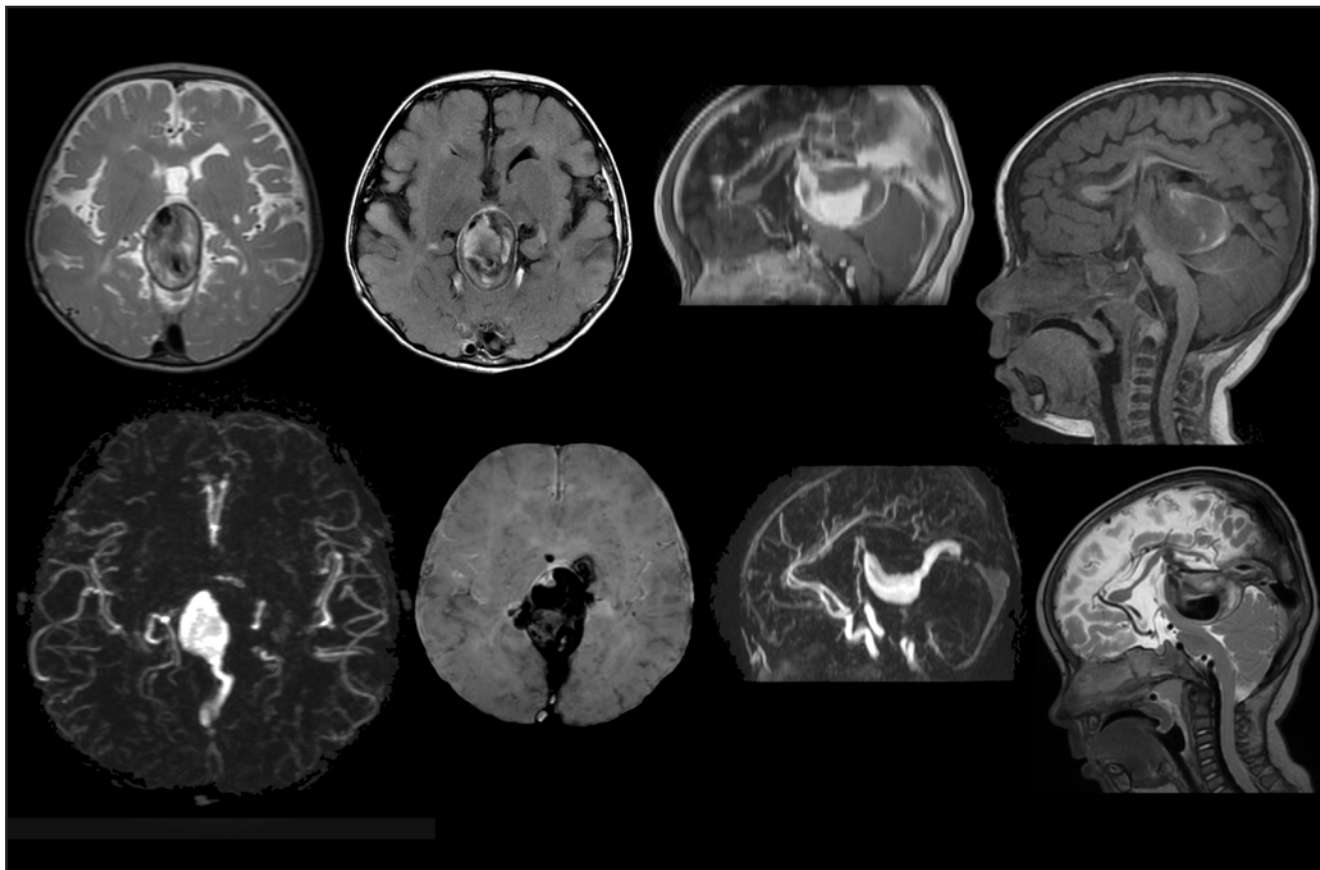


FIGURE 5. Postcontrast imaging from 6-month-old child with a vein of Galen malformation reveals the regions of most avid flow. Images courtesy of Dr. L.Tanenbaum.

Dr. Brown is Professor and Chair of the Department of Radiology at Saint Louis University



Jeffrey J. Brown, MD, FACR

"Dotarem is macrocyclic and ionic, so there is a chemical basis to support the fact that it's a very stable agent."

but consideration should be given to its value in assessing interval changes in lesion size. The ability to routinely surveil primary brain lesions without contrast is somewhat more controversial. However, if the primary brain lesion does not enhance, contrast may be less likely to contribute important information during surveillance. Imaging the blood-brain barrier with contrast is also of limited value in distinguishing between treatment-related findings and recurrent tumor. In such cases, alternative methods, such as arterial spin labeling, could be helpful in lesion interrogation and characterization.

Contrast-enhanced Neuroimaging: A Pediatric Perspective

Contrast-enhanced imaging is indicated in children for a wide variety of situations, including evaluation of intracranial, spine, and head and neck pathologies. (Figures 5, 6)

In fact, in many children, asymptomatic recurrence of brain tumors is detectable only with postcontrast imaging, justifying contrast-enhanced MRI for surveillance neuroimaging studies.^{27,28} However, when deciding whether to administer a GBCA, concerns for pediatric patients are somewhat different from those for adults. Surveillance imaging in children can potentially lead to a much larger cumulative burden of Gd exposure over the course of a lifetime. In addition, other challenges to contrast administration in children include the difficulty in administering small doses accurately (often <1 mL), and the desire to avoid initiating an IV or using sedation.

Finally, an important consideration when deciding whether to administer contrast in a child is the uncertain value of measuring eGFR in the very young. In the newborn, the GFR is only approximately 40 mL/min/1.73 m², and it doesn't reach adult levels of 100–125 mL/

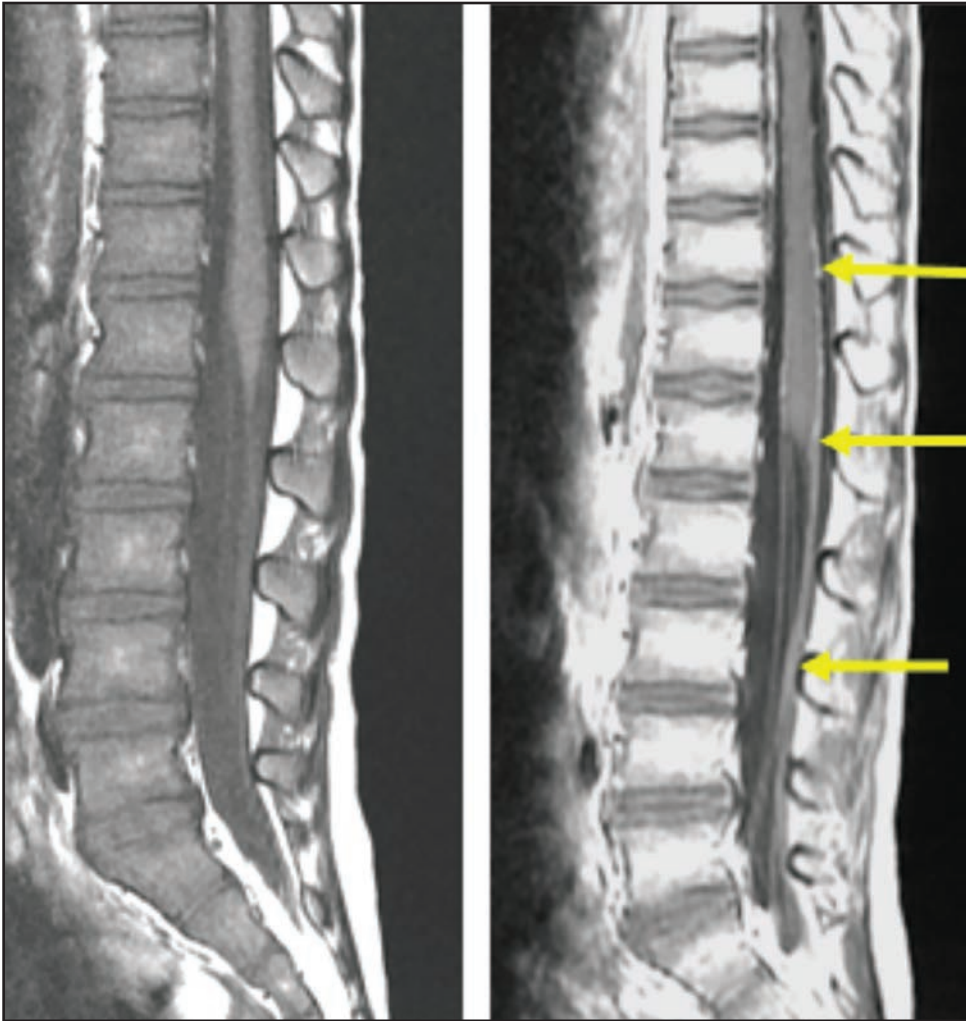


FIGURE 6. Contrast-enhanced MR image of the spine of a 24-month-old child with leptomeningeal drop-metastases from medulloblastoma (2.2 mL Dotarem [gadoterate meglumine]). Image courtesy of Prof. G. Sebag.

min/1.73 m² until the child is about 2 years of age.²⁹ As a result, eGFR thresholds typically used as guidelines for GBCA use in adults are not appropriate for pediatric patients. Rather, assuming the child is not known to have renal dysfunction, patient age is a better indicator of renal function than eGFR and often, waiting even 1 week before administering contrast can allow for substantial maturation in renal function. Although there are very few, if any, documented cases of NSF in children <2 years of age, their immature renal function potentially does, in theory, represent an NSF risk.³⁰ Therefore, it is important, particularly in children, (1) to administer a GBCA only when clinically

necessary, (2) to document the number of doses administered to a patient, (3) to consider temporal spacing between exams to permit full clearance, and (4) when indicated, to use a high-stability agent.

Recent practice-pattern surveys confirm a trend among pediatric radiologists to switch from linear agents to macrocyclics.³¹ Specifically, in a survey of over 5,000 physicians in various pediatric specialties conducted between January 2016 and March 2016, (overall response rate 690/5,390 [13%]), 80% of responding pediatric hospitals were found to use a macrocyclic GBCA. Of those pediatric radiology departments that switched in the

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"We keep several agents on formulary. We have a main agent, Dotarem, and we feel good about it, particularly in children. We keep a second agent for the rare patient who has a serious adverse 'allergic or allergic-like reaction' to a macrocyclic – we figure if they're going to get an agent next time, we're better off giving them a linear agent. And then we have other agents for niche uses. But 95% of what we're using now is Dotarem, because that was acceptable to everybody."

Dr. Johnson is Medical Director and Director of Neuroimaging at the Center for Diagnostic Imaging



Blake A. Johnson, MD, FACR

"We are primarily an outpatient imaging center provider with a dedicated business team responsible for purchasing decisions. When I first learned about differences in stability among contrast agents, we were using a nonionic linear agent. I decided it was imperative to switch to a macrocyclic agent, which is why we now use Dotarem."

last year (15/26 [58%]), most (8/15 [53%]) switched to Dotarem, and the most common reasons for switching included brain gadolinium deposition concerns (11/15 [73%]), improved safety profile (7/15 [47%]), and improved stability (5/15 [33%]). Previously, GBCAs were used off-label in children <2 years of age; however, Dotarem, Gadavist, and MultiHance are all currently FDA-approved for use in neonates and young children.^{1,2,5}

Administrative Considerations

When selecting a contrast agent, it is prudent practice that physicians with knowledge and experience be part of the decision-making team.

Upon switching agents, care must be taken to ensure a smooth transition, since increases in reports of adverse reactions shortly after a transition can occur due to staff on the "look-out" for new reactions (Weber effect), a phenomenon that has been recognized to occur after a GBCA switch.^{32,33} Educating nurses and technologists regarding the history of (ie, number of administrations worldwide) and safety profile of the newer agent can often ensure and boost comfort. An updated and current department-wide contrast agent policy that provides clear guidelines on which agent to use in which patients, when to screen for renal function, when to pretreat, etc., is essential.

Conclusions

In summary, the currently available ECF GBCAs have varying structures that impact their stability, and thus their propensity to release Gd from the chelate in vivo. Therefore, when a risk-benefit analysis supports the use of contrast with MRI, stability is a very important consideration when selecting from among the currently available GBCAs.

References

1. Dotarem® (gadoterate meglumine) [prescribing information]. Princeton, NJ: Guerbet LLC; October, 2019.
2. Gadavist® (gadobutrol) injection [prescribing information]. Wayne, NJ; Bayer HealthCare Pharmaceuticals; April 2016.
3. ProHance® (Gadoteridol) Injection, [prescribing information]. Princeton, NJ: Bracco Diagnostics Inc.; November 2013.

4. Clariscan™ (gadoterate meglumine) [prescribing information]. Marlborough, MA: GE Healthcare Inc.; November, 2019.
5. MultiHance® (gadobenate dimeglumine) injection [prescribing information]. Princeton, NJ: Bracco Diagnostics Inc.; July 2013.
6. Omniscan™ (gadodiamide) injection [prescribing information]. Princeton, NJ: GE Healthcare; August 2013.
7. Frenzel T, Lengsfeld P, Schirmer H, Hütter J, Weinmann HJ. Stability of gadolinium-based magnetic resonance imaging contrast agents in human serum at 37 degrees C. *Invest Radiol*. 2008; 43:817-828.
8. Port M, Idée JM, Medina C, Robic C, Sabatou M, Corot C. Efficiency, thermodynamic and kinetic stability of marketed gadolinium chelates and their possible clinical consequences: a critical review. *Biometals*. 2008; 21:469-490.
9. Rogosnitzky M, Branch S. Gadolinium-based contrast agent toxicity: a review of known and proposed mechanisms. *Biometals*. 2016; 29:365-376.
10. Puttagunta NR, Gibby WA, Smith GT. Human in vivo comparative study of zinc and copper transmetallation after administration of magnetic resonance imaging contrast agents. *Invest Radiol*. 1996;31: 739-742.
11. 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.
12. Morcos SK. Nephrogenic systemic fibrosis following the administration of extracellular gadolinium based contrast agents: is the stability of the contrast agent molecule an important factor in the pathogenesis of this condition? *Br J Radiol*. 2007;80: 73-76. Erratum in: *Br J Radiol*. 2007; 80:586.
13. 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.
14. Kanal E, Barkovich AJ, Bell C, et al; ACR Blue Ribbon Panel on MR Safety. ACR guidance document for safe MR practices: 2007. *AJR Am J Roentgenol*. 2007; 188:1447-1474.
15. Thomsen HS, Marckmann P, Logager VB. Nephrogenic systemic fibrosis (NSF): a late adverse reaction to some of the gadolinium based contrast agents. *Cancer Imaging*. 2007; 7:130-137.
16. Perazella MA. Nephrogenic systemic fibrosis, kidney disease, and gadolinium: is there a link? *Clin J Am Soc Nephrol*. 2007; 2:200-202.
17. Aime S, Caravan P. Biodistribution of gadolinium-based contrast agents, including gadolinium deposition. *J Magn Reson Imaging*. 2009;30: 1259-1267.
18. Edwards BJ, Laumann AE, Nardone B, et al. Advancing pharmacovigilance through academic-legal collaboration: The case of gadolinium-based contrast agents and nephrogenic systemic fibrosis—Research on Adverse Drug Events and Reports (RADAR) report. *Br J Radiol*. 2014; 87:20140307.
19. Food and Drug Administration (FDA). Advisory Committee Briefing Document, Dotarem® (gadoterate meglumine). Available at: <https://webcache.google->

us-ercontent.com/search?q=cache:pNy3Rdj4IJwJ:https://www.fda.gov/downloads/AdvisoryCommittees/UCM339378.pdf+&cd=1&hl=en&ct=clnk&gl=us. February, 2013.

20. Food and Drug Administration (FDA). Center for Drug Evaluation and Research (CDER). Summary Review. Gadovist. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/201277Orig1s-000SumR.pdf. March, 2011.

21. Food and Drug Administration (FDA). FDA Drug Safety Communication: New warnings for using gadolinium-based contrast agents in patients with kidney dysfunction. Available at: <https://www.fda.gov/Drugs/DrugSafety/ucm223966.htm>. December, 2010.

22. American College of Radiology (ACR) Committee on Drugs and Contrast Media. ACR Manual on Contrast Media, 2020. Available at: <https://www.acr.org/Clinical-Resources/Contrast-Manual>.

23. Deray G, Rouviere O, Bacigalupo L, et al Safety of meglumine gadoterate (Gd-DOTA)-enhanced MRI compared to unenhanced MRI in patients with chronic kidney disease (RESCUE study). *Eur Radiol*. 2013; 23:1250-1259.

24. Amet S, Launay-Vacher V, Clément O, et al Incidence of nephrogenic systemic fibrosis in patients undergoing dialysis after contrast-enhanced magnetic resonance imaging with gadolinium-based contrast agents: the Prospective Fibrose Néphrogénique Systémique study. *Invest Radiol*. 2014; 49:109-115.

25. Beckett KR, Moriarity AK, Langer JM. Safe Use of Contrast Media: What the Radiologist Needs to Know. *Radiographics*. 2015; 35:1738-1750.

26. Behzadi AH, Zhao Y, Farooq Z, Prince MR. Immediate Allergic Reactions to Gadolinium-based Contrast

Agents: A Systematic Review and Meta-Analysis. *Radiology*. 2018; 286:471-482.

27. Korones DN, Butterfield R, Meyers SP, Constine LS. The role of surveillance magnetic resonance imaging (MRI) scanning in detecting recurrent brain tumors in asymptomatic children. *J Neurooncol*. 2001; 53: 33-38.

28. Udaka YT, Yeh-Nayre LA, Amene CS, VandenBerg SR, Levy ML, Crawford JR. Recurrent pediatric central nervous system low-grade gliomas: the role of surveillance neuroimaging in asymptomatic children. *J Neurosurg Pediatr*. 2013; 11: 119-126.

29. Sulemanji M, Vakili K. Neonatal renal physiology. *Semin Pediatr Surg*. 2013; 22:195-198.

30. Thomsen HS, Morcos SK, Almén T, et al. Nephrogenic systemic fibrosis and gadolinium-based contrast media: updated ESUR Contrast Medium Safety Committee guidelines. *Eur Radiol*. 2013;23: 307-318.

31. Mithal LB, Patel PS, Mithal D, Palac HL, Rozenfeld MN. Use of gadolinium-based magnetic resonance imaging contrast agents and awareness of brain gadolinium deposition among pediatric providers in North America. *Pediatr Radiol*. 2017; 47:657-664.

32. Abujudeh HH, Kosaraju VK, Kaewlai R. Acute adverse reactions to gadopentetate dimeglumine and gadobenate dimeglumine: experience with 32,659 injections. *AJR Am J Roentgenol*. 2010; 194:4 30-434.

33. Davenport MS, Dillman JR, Cohan RH, et al. Effect of abrupt substitution of gadobenate dimeglumine for gadopentetate dimeglumine on rate of allergic-like reactions. *Radiology*. 2013; 266:773-782.

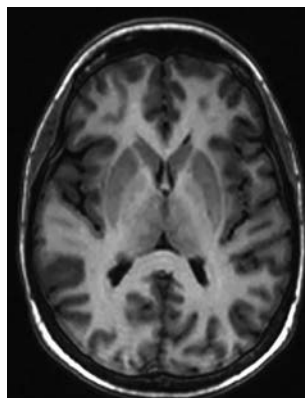
Case Studies

Patient: 46-year-old female with history of migraine and tension headaches.

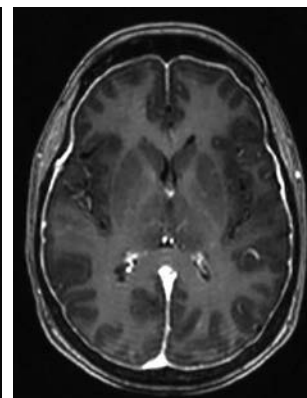
Procedure: Brain MRI; 11 mL Dotarem® administered. Patient dosage was weight-based.

Impression: MRI of the brain with contrast demonstrates diffuse leptomeningeal enhancement and thickening suggesting intracranial hypotension.

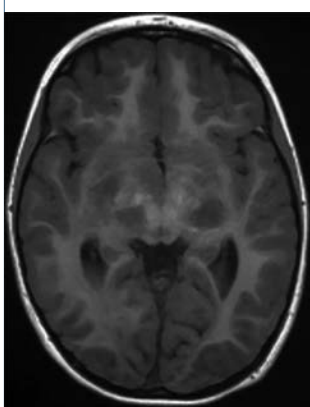
Case courtesy of: Peachtree Neurological Clinic, Atlanta, Georgia.



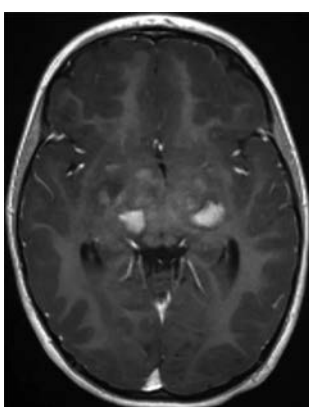
AXIAL NONCONTRAST



AXIAL CONTRAST



AXIAL T1 UNENHANCED



AXIAL T1 ENHANCED

Patient: 4-year-old with history of an optic pathway glioma and moderate renal insufficiency.

Procedure: Brain MRI; patient administered a weight-based dose of Dotarem®.

Impression: Axial T1-weighted images before and after the administration of Dotarem® show enhancement within the masses of the optic pathway.

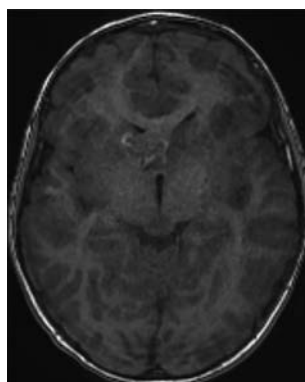
Case courtesy of: Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio.

Patient: 8-year-old with tuberous sclerosis and mild renal insufficiency.

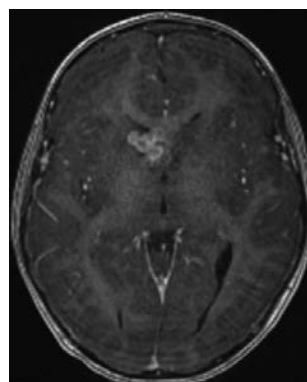
Procedure: Brain MRI; patient administered a weight-based dose of Dotarem®.

Impression: Axial T1-weighted images show enhancement of a right-sided subependymal giant cell astrocytoma at the level of the foramen of Monro.

Case courtesy of: Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio.



AXIAL T1 UNENHANCED



AXIAL T1 ENHANCED

Individual results may vary

For more information on Dotarem®, please see Full Prescribing Information, including Boxed Warning and Medication Guide.

WARNING: NEPHROGENIC SYSTEMIC FIBROSIS (NSF)

Gadolinium-based contrast agents (GBCAs) increase the risk for NSF among patients with impaired elimination of the drugs. Avoid use of GBCAs in these patients unless the diagnostic information is essential and not available with non-contrast MRI or other modalities. NSF may result in fatal or debilitating fibrosis affecting the skin, muscle and internal organs.

- The risk for NSF appears highest among patients with:
 - Chronic, severe kidney disease (GFR < 30 mL/min/1.73 m²), or
 - Acute kidney injury.
- Screen patients for acute kidney injury and other conditions that may reduce renal function. For patients at risk for chronically reduced renal function (e.g. age > 60 years, hypertension, diabetes), estimate the glomerular filtration rate (GFR) through laboratory testing.
- For patients at highest risk for NSF, do not exceed the recommended DOTAREM dose and allow a sufficient period of time for elimination of the drug from the body prior to any re-administration.

INDICATIONS AND USAGE

DOTAREM® (gadoterate meglumine) injection is a prescription gadolinium-based contrast agent indicated for intravenous use with magnetic resonance imaging (MRI) in brain (intracranial), spine and associated tissues in adult and pediatric patients (including term neonates) to detect and visualize areas with disruption of the blood brain barrier (BBB) and/or abnormal vascularity.

CONTRAINDICATIONS

History of clinically important hypersensitivity reactions to DOTAREM.

WARNINGS AND PRECAUTIONS

- Hypersensitivity Reactions: Anaphylactic and anaphylactoid reactions have been reported with DOTAREM, involving cardiovascular, respiratory, and/or cutaneous manifestations. Some patients experienced circulatory collapse and died. In most cases, initial symptoms occurred within minutes of DOTAREM administration and resolved with prompt emergency treatment.
- Before DOTAREM administration, assess all patients for any history of a reaction to contrast media, bronchial asthma and/or allergic disorders. These patients may have an increased risk for a hypersensitivity reaction to DOTAREM.
- Administer DOTAREM only in situations where trained personnel and therapies are promptly available for the treatment of hypersensitivity reactions, including personnel trained in resuscitation.
- Gadolinium Retention: Gadolinium is retained for months or years in several organs. The highest concentrations have been identified in the bone, followed by brain, skin, kidney, liver and spleen. The duration of retention also varies by tissue, and is longest in bone. Linear GBCAs cause more retention than macrocyclic GBCAs.
- Consequences of gadolinium retention in the brain have not been established. Adverse events involving multiple organ systems have been reported in patients with normal renal function without an established causal link to gadolinium retention.
- Acute Kidney Injury: In patients with chronically reduced renal function, acute kidney injury requiring dialysis has occurred with the use of GBCAs. The risk of acute kidney injury may increase with increasing dose of the contrast agent; administer the lowest dose necessary for adequate imaging.
- Extravasation and Injection Site Reactions: Ensure catheter and venous patency before the injection of DOTAREM. Extravasation into tissues during DOTAREM administration may result in tissue irritation.

ADVERSE REACTIONS

- The most common adverse reactions associated with DOTAREM in clinical trials were nausea, headache, injection site pain, injection site coldness and rash.
- Serious adverse reactions in the Postmarketing experience have been reported with DOTAREM. These serious adverse reactions include but are not limited to: arrhythmia, cardiac arrest, respiratory arrest, pharyngeal edema, laryngospasm, bronchospasm, coma and convulsion.

USE IN SPECIFIC POPULATIONS

- Pregnancy: GBCAs cross the human placenta and result in fetal exposure and gadolinium retention. Use only if imaging is essential during pregnancy and cannot be delayed.
- Lactation: There are no data on the presence of gadoterate in human milk, the effects on the breastfed infant, or the effects on milk production. However, published lactation data on other GBCAs indicate that 0.01 to 0.04% of the maternal gadolinium dose is present in breast milk.
- Pediatric Use: The safety and efficacy of DOTAREM at a single dose of 0.1 mmol/kg has been established in pediatric patients from birth (term neonates ≥ 37 weeks gestational age) to 17 years of age based on clinical data. The safety of DOTAREM has not been established in preterm neonates. No cases of NSF associated with DOTAREM or any other GBCA have been identified in pediatric patients age 6 years and younger.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088. Please see the full Prescribing Information, including the patient Medication Guide, for additional important safety information.

