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Use of ProHance® (Gadoteridol) for MRI in Special Patient Populations: Geriatrics and Pediatrics

A question-and-answer session with Seferino Romo, RT(R)(MR), MR Technologist and MRI Clinical Educator at Memorial Hermann-Texas Medical Center, the primary teaching hospital for the UTHealth Medical School, on the selection of a gadolinium-based contrast agent (GBCA) for magnetic resonance imaging (MRI) in special patient populations, including elderly and pediatric patients

This is the third article in a 4-part series that discusses the use of macrocyclic GBCAs in MRI. The remaining part will appear in a forthcoming issue 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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In 1988, the first gadolinium-based contrast agent (GBCA) was approved by the FDA for contrast-enhanced magnetic resonance (MR) imaging. Since then, an additional 8 GBCAs have been approved, and these agents vary with respect to a number of important properties, including structure, concentration, and relaxivity (Table 1).[1-13] When selecting an imaging modality for the more vulnerable elderly or pediatric patient, contrast-enhanced MRI with a GBCA has often been considered preferable to contrast-enhanced computed tomography (CT) with an iodinated contrast agent, in the elderly because of the increased risk of contrast-induced nephropathy (CIN) in patients with poor renal function, and in children due to the increased lifetime risk of radiation exposure. Here, we discuss with Mr. Seferino Romo the selection and use of the macrocyclic agent ProHance (gadoteridol) for MR imaging in geriatric and pediatric patient populations.

Applied Radiology (AR): Welcome, Mr. Romo. Can you please describe for us the imaging facility at Memorial Hermann-Texas Medical Center?

Mr. Seferino Romo (SR): Memorial Hermann-Texas Medical Center is a Level I trauma center (pediatric and adult) located in Houston, TX. In our imaging center, we have two 1.5T magnets, and two 3T magnets (one devoted fully to research). We have 25 technologists and 12 nurses, and our service is open 24/7, every day of the year.

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?

SR: We service a very diverse and complicated population in our clinical service, everyone from young children to the elderly. Therefore, we like to provide our radiologists and referring physicians with options; having choices in contrast selection allows them to take advantage of the variety of available contrast agents, a boutique of contrast, if you will. The selection of a GBCA for a particular exam, therefore, can be based on a number of factors, including the clinical question, as well as the risks of contrast administration to that particular patient.

AR: What is the current agent of choice at Memorial Hermann-Texas Medical Center? Have you used any other agent(s) in the past? If so, why did you make the switch?

SR: Originally, in the beginning of the 1990s, we were an early adopter of Magnevist® (gadopentetate dimeglumine), and it was very exciting to see the benefits of contrast use for imaging of tumors in the brain. Rather than being technologists, we became anatomical architects for the surgeons. Adding contrast and using 1×1 resolution isotropic imaging with 3D reconstructions allowed us to essentially map the pathology. We then added Omniscan™ (gadodiamide) to our arsenal, along with the power injector, and the combination of accurately dosed contrast and saline, administered at precise milliliters per second, was magical. Such precisely timed injections also allowed us to introduce double and triple

Table 1. Currently Available ECF Gadolinium-based Contrast Agents and Their Properties[1-13]

Trade Name	Magnevist®	Omniscan™	OptiMARK™	MultiHance®	Dotarem®	Gadavist®	ProHance®
Chemical Name	Gadopentetate dimeglumine	Gadodiamide	Gadoversetamide	Gadobenate dimeglumine	Gadoterate meglumine	Gadobutrol	Gadoteridol
Company	Bayer	GE	Guerbet	Bracco	Guerbet	Bayer	Bracco
Classification	ECF	ECF	ECF	Dual ECF/liver	ECF	ECF	ECF
Protein Interaction	None	None	None	Weak	None	None	None
FDA-approved Indications	CNS, adults & pediatrics; Head & neck, and Body, adults & pediatrics	CNS, adults & pediatrics; Body, adults & pediatrics	CNS, adults; Liver, adults	CNS, adults & pediatrics; MRA, adults with known or suspected renal or aorto-iliofemoral occlusive vascular disease	CNS, adults & pediatrics	CNS, adults & pediatrics; Assess presence and extent of malignant breast disease	CNS, adults & pediatrics Head & neck, adults
Structure	Linear	Linear	Linear	Linear	Macrocyclic	Macrocyclic	Macrocyclic
Ionicity	Ionic	Nonionic	Nonionic	Ionic	Ionic	Nonionic	Nonionic
Concentration (M)	0.5	0.5	0.5	0.5	0.5	1.0	0.5
Approved Dose (mmol/kg)	0.1	0.1	0.1	0.1	0.1	Adults, 0.1 + 2nd dose of 0.2 up to 30 min after 1st dose if needed; Children, 0.1	0.1
r1 relaxivity ($L \cdot mmol^{-1} s^{-1}$) 1.5 T / 3.0 T	4.25 / 3.76	4.47 / 3.89	4.43 / 4.24	6.20 / 5.37	3.91 / 3.43	4.61 / 4.46	4.39 / 3.46

Bayer = Bayer Healthcare; GE = GE Healthcare; Bracco = Bracco Diagnostics; ACR=American College of Radiology; CNS=central nervous system; ECF=extracellular fluid; MRA=magnetic resonance angiography.

dosing for run-offs and other complex vascular studies that were now properly synchronized. The results were amazing for both neuro and vascular applications.

Shortly thereafter, we begin hearing talk of an incurable and potentially fatal disorder, nephrogenic systemic fibrosis (NSF), caused by GBCAs injected into some patients with low estimated glomerular filtration rates (eGFR). Apparently, in these patients, the poor kidney function resulted in a slower elimination of the GBCA. However, NSF occurred much more frequently following the administration of certain GBCAs, specifically the less stable linear agents Omniscan (gadodiamide), Magnevist (gadopentetate dimeglumine), and OptiMARK™ (gadoversetamide).[14,15] This association highlighted the importance of the property of GBCA stability; ie, the strength with which the chelate binds the gadolinium (Gd) ion and prevents the release of free, toxic Gd.

At that time, we realized that we needed re-education, retraining, on concepts like "ligand-chelate stability," "linear vs macrocyclic," etc. We turned to the industry, the contrast agent vendors, to help educate us about these important properties and the differences among the GBCAs. It turns out that by a variety of measurements, both in vitro and in vivo, the macrocyclic agents Dotarem® (gadoterate meglumine), Gadavist® (gadobutrol), and ProHance (gadoteridol) have the highest stability and are the most resistant to dechelation.[16-20] Human in vivo data, the most credible evidence, was provided by White and colleagues, who demonstrated that 4 times more Gd was deposited in the bone of hip replacement patients after administration of gadodiamide (Omniscan) vs gadoteridol (ProHance).[17]

At around the same time, the American College of Radiology (ACR) listed both of the agents we stocked, Magnevist (gadopentetate dimeglumine) and Omniscan (gadodiamide), as Group I agents (those with the greatest number of NSF cases),[14] and the FDA contraindicated these agents in patients with acute kidney injury or chronic, severe kidney disease (Table 2).[5-7] All of these safety guidelines led us to adopt the use of the more stable, Group II, macrocyclic agent ProHance (gadoteridol) for use in all patients with a low eGFR, and to implement a stricter screening program. Poor renal function is more common in elderly patients and can be nonsymptomatic, so we now screen patients prior to administering contrast and, if the eGFR is below 40 mL/min/1.73 m^2: the radiologist is contacted to review recent GFR data with attention to trending of the GFR over time; no Class I agents are permitted to be used and contrast dose may be reduced by the radiologist; patient and radiologist consent is required; and the study must be approved by nephrology.

So although we stock a number of different agents, since 2011, we primarily use MultiHance® (gadobenate dimeglumine) due to its higher relaxivity and dual elimination (renal and biliary), and then we use ProHance

Table 2. ACR and FDA Classification of GBCAs (5-7,14)

Trade Name	Generic Name	FDA Contraindication in AKI and Severe Chronic Kidney Disease	ACR Group/Definition	
Omniscan™	Gadodiamide	√	I	Agents associated with the greatest number of NSF cases
Magnevist®	Gadopentetate dimeglumine	√	I	
OptiMARK™	Gadoversetamide	√	I	
Gadavist®	Gadobutrol		II	Agents associated with few, if any, unconfounded cases of NSF
Dotarem®	Gadoterate meglumine		II	
ProHance®	Gadoteridol		II	
MultiHance®	Gadobenate dimeglumine		II	
Eovist®	Gadoxetate disodium		III	Agents that have only recently appeared on the market
Ablavar®	Gadofosveset trisodium		III	

ACR=American College of Radiology; FDA=Food and Drug Administration; AKI=acute kidney injury; GBCAs=gadolinium-based contrast agents; NSF=nephrogenic systemic fibrosis.

(gadoteridol) in patients with renal dysfunction for whom safety is a greater issue.

AR: Aside from those with low GFR, what other patients receive the macrocyclic agent ProHance (gadoteridol) at your institution?

SR: We have a number of radiologists that prefer to use ProHance (gadoteridol) for their pediatric patients. ProHance (gadoteridol) was the first macrocyclic approved for use in the United States in 1992. It has a long history of safety based on millions of administered doses.[21] A review of the literature shows that adverse event (AE) rates in children following administration of ProHance (gadoteridol) is very low,[21-24] with no correlation between AE rates and higher doses.[21] In fact, all of the other extracellular fluid (ECF) GBCAs are approved at 0.1 mmol/kg, while ProHance (gadoteridol) is also approved for up to triple dose (0.3 mmol/kg) (Table 1),[2] a testament to its excellent safety profile.

AR: Do you think you will continue to use ProHance (gadoteridol) at your institution?

SR: MultiHance (gadobenate dimeglumine) and ProHance (gadoteridol) are the workhorses at this site; we estimate about 4,335 doses of these agents were administered in 2015 alone. For patients in whom safety is the paramount consideration, ProHance (gadoteridol) will continue to be our GBCA of choice.

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Case Study

MRI of 6-yr-old Boy for Discordant Ventriculoarterial Connection

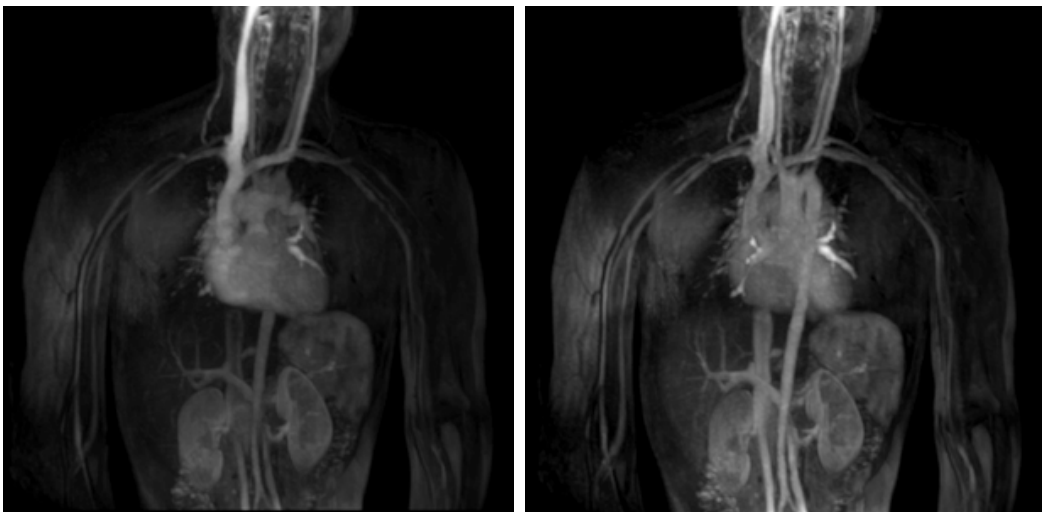

FIGURE 3. *Postcontrast images (left delayed time 26 sec; right delayed time 31 sec).*

Case Summary

A 6-year-old male with a history of dextrotransposition of the great arteries after an arterial switch operation presents for cardiac MRI to evaluate ventricular function, neoaortic root, neopulmonary root, and reimplanted coronary artery anatomy. Static T1-weighted spin echo, cine balanced TFE, balanced TFE 3D whole heart sequence, 4D Trak, phase contrast velocity mapping, and delayed myocardial enhancement sequences were performed using a 3 Tesla Philips Ingenia. The patient was administered 4 mL of ProHance (gadoteridol) at 2 mL/sec with a power injector.

Indication

Discordant ventriculoarterial connection

Imaging Findings (Figure 3)

There is moderate dilatation of neoaortic root. Neoaortic root measures 29 mm (Z score +3.9). There is no significant aortic valve regurgitation. There is mild narrowing of aortic root at sinotubular junction. The narrowest site of aortic root measures 15 mm. There is mild narrowing of neopulmonary root above the pulmonary valve. The narrowest site of main pulmonary artery measures 10 mm while distal main pulmonary artery measures 19 mm. No significant pulmonary valve insufficiency. There is mild stenosis of left pulmonary artery after LeCompte maneuver. Net fractional branch pulmonary artery blood flow distribution is 61% to RPA and 39% to LPA. The left pulmonary artery appears squashed in anterior-posterior view and it measures 9 mm in anterior-posterior dimension and 11 mm in superior-inferior dimension. RPA measures 13 mm (anterior-posterior dimension) x 15 mm (superior-inferior dimension). There is normal biventricular systolic function. Left ventricular ejection fraction is 61% and right ventricular ejection fraction is 55%. There is no evidence of ventricular myocardial fibrosis on late gadolinium enhancement study. There is no pericardial effusion. There is no kinking or ectasia of proximal coronary arteries. There is a left aortic arch with normal branching pattern. There is no coarctation of aorta. There is normal systemic and pulmonary venous connection. Liver is on the right and stomach is on the left. There is levocardia with apex of the heart pointing to the left.

Coronary Imaging: Spatial orientation of neoaortic and neopulmonary root is anterior-posterior. Right coronary artery arises from right facing sinus. Left coronary artery arises from left facing sinus and then divides into left anterior descending and left circumflex coronary arteries. There is no kinking or ectasia of proximal coronary arteries.

Regional Wall Motion Abnormality: There is no obvious ventricular regional wall motion abnormality.

Myocardial delayed enhancement: There is no evidence of myocardial scar or fibrosis.

Conclusions

(1) Dextrotransposition of great arteries after arterial switch operation
(2) Mild supravalvar pulmonary stenosis. No significant pulmonary valve insufficiency
(3) Moderate dilatation of neoaortic root (Neoaortic root measures 2.9 cm: Z score +3.9)
(4) Normal biventricular systolic function. LV ejection fraction was 61% and RV ejection fraction was 55%
(5) Mild stenosis of left pulmonary artery after LeCompte maneuver. Net fractional branch pulmonary artery blood flow distribution is 61% to RPA and 39% to LPA
(6) No evidence of myocardial scar or fibrosis;
(7) No kinking or ectasia of proximal coronary arteries
(8) No pericardial effusion.