The use of gadolinium-based contrast agents in children

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At Cincinnati Children's Hospital, approximately one-third to one-half of MRI exams performed annually are contrast-enhanced, most often using gadolinium-based contrast agents (GBCAs). All but one of the U.S. Food and Drug Administration (FDA)-approved GBCAs may be administered to pediatric patients ages 2 years and older. The exception is gadoversetamide (Opti-Mark®), which is FDA-approved for use in children under 2 years, including term neonates as well as patients at least 18 years of age. The dosage for each contrast agent is shown in Figure 1. Fortunately the dosage instructions are the same for all agents except gadobutrol (Gadavist®). Gadobutrol has a higher concentration of gadolinium per unit volume and thus the dosage is different.

There are unique challenges and considerations when using GBCAs with pediatric patients. Children should not be regarded simply as little adults. While there is some concern for nephrogenic systemic fibrosis (NSF), The incidence seems to be lower than in adults. According to an article in *Pediatric Radiology* there have been 23 documented cases of NSF in children between January 1997 and October 2012.[1] It should be noted that of these 23 cases of NSF, only 17 were associated with a documented GBCA exposure.[1] Most patients who were diagnosed with NSF had significant renal dysfunction. There have been no cases of NSF associated with GBCA in children < 8 years of age.

Even though there have not been many cases of NSF in the pediatric population, we take the potential risk seriously. My practice is for children suspected to have abnormal renal

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Generic Name	Trade Name	Chain	Bond type	FDA approved age	Dosage (mmol/kg)	Gd conc (mmol/mL)
Gadopentetate dimeglumine	Magnevist	Linear	Ionic	> 2 years	0.1	0.5
Gadobutrol	Gadavist	Macrocyclic	Nonionic	> 2 years	0.1	1
Gadodiamide	Omniscan	Linear	Nonionic	> 2 years	0.1	0.5
Gadoversetamide	Optimark	Linear	Nonionic	> 18 years	0.1	0.5
Gadobenate dimeglumine	Multihance	Linear	Ionic	> 2 years	0.1	0.5
Gadoteridol	Prohance	Macrocyclic	Nonionic	> 2 years	0.1	0.5
Gadoterate meglumine	Dotarem	Macrocyclic	Ionic	> 2 years	0.1	0.5

FIGURE 1.

For children aged 2 – 18 years			
GBCA	GFR/eGFR < 60	GFR/eGFR 60 – 80	GFR/eGFR > 80
• Gadodiamide • Gadopentetate dimeglumine • Gadoversetamide	Not approved for use	Not approved for use	Should not be used
• Gadobenate dimeglumine	Not approved for use	Should not be used	Should not be used
• Gadoterate meglumine • Gadobutrol • Gadoteridol	May be used for compelling indications	May be used	May be used
For children aged 0 – 2 years (NOTE: No GBCA is approved by the FDA for use in children younger than 2 years of age)			
• Gadodiamide	Not approved for use	Not approved for use	Should not be used
• Gadoterate meglumine	May be used for compelling indications	May be used	May be used

References:
- Danish Health and Medicine Authority, Copenhagen. Guidelines for MRI scan examination – 2013

FIGURE 2.

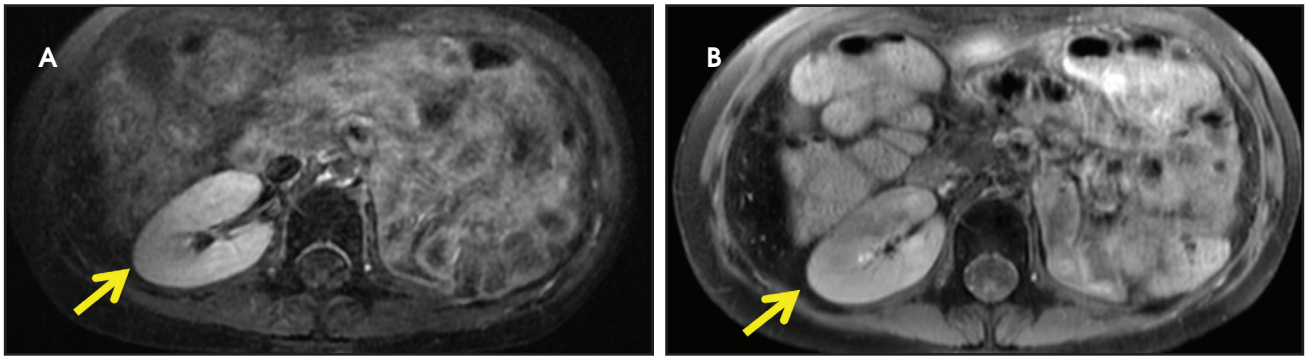

FIGURE 3. An 8-year-old girl status/post left nephrectomy for a Wilm's tumor was imaged at two distinct time points. Initially, the patient was imaged with gadopentetate dimeglumine (Magnevist). On her subsequent scan, imaging was performed using gadoterate meglumine. The images show that the enhancement of the right kidney is similar for both the gadopentetate dimeglumine study (A) and the gadoterate meglumine study (B).

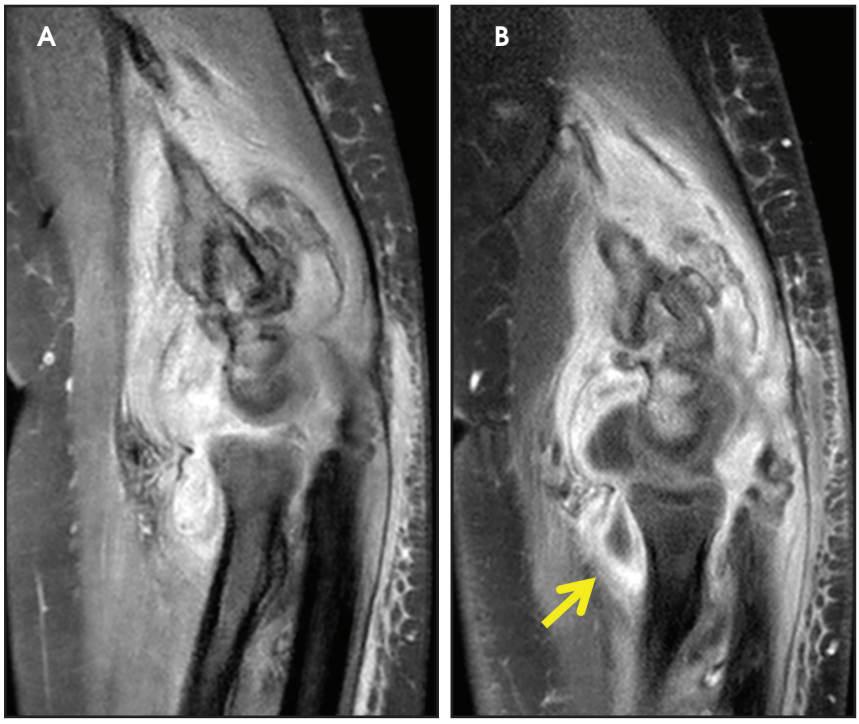

FIGURE 4. A 5-year-old girl with moderate renal insufficiency suffered a left supracondylar fracture and a subsequent septic joint. Sagittal proton density sequence of the elbow (A) and sagittal T1-weighted, postconstrast (gadoterate meglumine) image (B) shows a thickened and enhancing synovium (arrow) consistent with synovitis and septic arthritis. In addition, there is considerable enhancement in the subcutaneous tissues and edema related to the inflammation and infection.

function, to be screened with a serum creatinine prior to their scan. The normal creatinine value is not the 1.5 number used with adult patients; in children, the normal creatinine value varies with age, and the age-based lab standards must be used. I also pay attention to changes in renal function, so a change from a 0.4 to a 0.8, for example, is a significant change in a patient's renal function. Even though a 0.8 may be in the normal range for that patient, this change represents a two-fold worsening of their renal function. When needed, I use the Schwartz formula to calculate a GFR. This formula states that GFR = 0.413 * ((height in cm)/(serum creatinine)).[4]

Another concern related to renal function is in imaging neonates. Normal neonates have immature renal function with a GFR at birth of below 30 ml/min/1.73^2. While radiologists need to consider that GBCA administration may put neonates at risk for NSF, it is important to weigh the risks and benefits of using this medication. Radiologists should note that there are currently no documented cases of NSF in any patient under 8 years of age. In routine clinical practice, GBCA-enhanced MRI exams have been performed off label in children under age of 2 years. Until January 2015, there were no GBCA that were FDA-approved for children under 2 years old.

In addition to the risk of NSF, several recent studies have described a potential risk of free gadolinium deposition.[2,3] These studies suggest that free gadolinium deposits within the metaphyses of long bones as well as within the dentate nucleus and globus pallidus and patients who have received multiple doses of GBCA are more likely to have free gadolinium deposits.[2,3] The long-term effects of gadolinium deposition are unknown. However, similar to radiation exposure, children may be more vulnerable to free gadolinium deposition because gadolinium may be more likely to deposit or cause an effect on the developing bone or brain. In addition, the longer remaining life span of pediatric patients may make it more likely that patients who were exposed to gadolinium as children have a long term complication. In current theory, more stable GBCAs are thought to be safer in that they are more likely to be completely

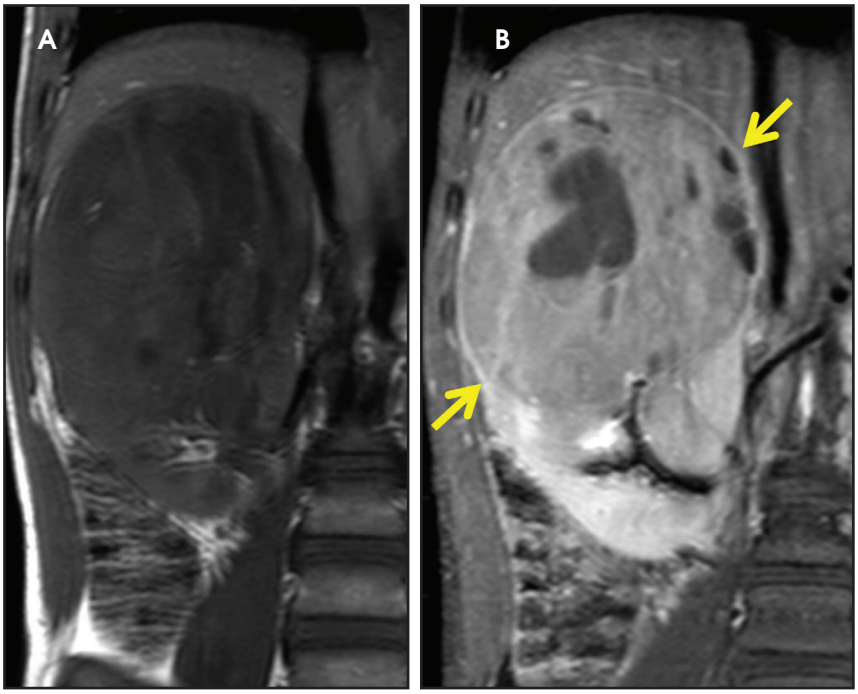

FIGURE 5. A 6-year-old boy with a Wilm's tumor and mild renal insufficiency. Precontrast, coronal, T1-weighted image of the right kidney without fat saturation (A) and coronal contrast-enhanced (gadoterate meglumine), T1-weighted image with fat saturation shows a large mass (arrows) within the upper pole of the kidney. The mass has a central area that is more necrotic, but the tumor itself has homogeneous enhancement that is slightly less than the residual normal kidney. This image can help guide renal-sparing resection.

cleared from the blood stream and thus less likely to deposit free gadolinium.

Evaluating a new contrast agent

Recently, our department decided to reevaluate our standard GBCA used for MRI. While our preexisting contrast agent had an excellent safety record over 20 years with very few adverse events, we were concerned about its chemical properties (linear chain) in comparison to some of the newer agents. We performed our due diligence by reading articles on the safety profiles of different agents, the relaxivity of different agents, and the dosing regimens. In addition we looked at national practice guidelines. The current American College of Radiology (ACR) guidelines for use of contrast agents in pediatric patients state that "The guidelines for IV use of GBCA are generally similar in both the pediatric and adult populations." They offer little guidance in helping practices choose a GBCA for their pediatric patients. The guidelines from the Danish Health and Medicines Authority are more straightforward with their recommendation. While not based on published research, they make a recommendation based on expert opinion and their clinical practice. Based on its safety profile, similar dosing regimen, and similar relaxivity to our preexisting contrast agent, my department chose gadoterate meglumine (Dotarem®, Guerbet) as our default contrast agent.

Gadoterate meglumine had been in use outside of the United States since 1989. In that time more than 20 million doses have been administered with no unconfounded cases of NSF. In Europe it has been used with patients with GFRs of less than 30. In theory, as the only macrorcyclic ionic GBCA, it is the most stable molecule and thus the safest.

Our radiology department was the first in North America to begin using gadoterate meglumine, in July 2013. The vast majority of contrast-enhanced scans are dosed according to the package insert: 0.2 mL/kg (0.1 mmol/kg) IV at 2 mL/sec with a maximum dose of 20 mL. As we began transitioning to gadoterate meglumine, our department initially limited its use to patients with borderline renal function (GFR 30-90 mL/min), patients under two years of age, patients with preexisting renal anomalies such as a solitary kidney, or patients whom recent laboratory tests were not available. In addition, because of our concern for potential gadolinium deposition, we decided that any patient who was likely to need multiple contrast-enhanced MRIs over time, such as cancer patients, should receive gadoterate meglumine. After several months of using two contrast agents, the department switched to using gadoterate meglumine exclusively.

Conclusion

There are several unique factors that the radiologist must consider when selecting a GBCA for imaging children. Properties such as the pharmaceutical's stability and dosing regimen help to determine its safety profile. Based on these factors, my department chose to use gadoterate meglumine as our standard GBCA. We have decided that we are more comfortable using a macrocyclic nonionic agent, particularly in patients with borderline renal function and in patients who will be receiving numerous doses over the course of their disease.

References

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