Safety of Contrast Material Use in Children

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KEYWORDS

• Computed tomography • Magnetic resonance imaging • Contrast material • Pediatric imaging • Gadolinium • Nephrogenic systemic fibrosis

KEY POINTS

- Adverse reactions to intravenous contrast materials in children are rare and less common than in adults.
- To prevent contrast-induced nephrotoxicity in children, more emphasis should be given to estimation of the glomerular filtration rate (eGFR) than to measurement of serum creatinine.
- Nephrogenic systemic fibrosis (NSF) is extremely rare in the pediatric population, with approximately 23 reported cases (most with previously impaired renal function) and none in children younger than 8 years of age.
- Concerns about long-term effects of gadolinium deposition are particularly high in children, given the potential deleterious effects on the developing brain and their longer remaining life span.

INTRODUCTION

Intravenously injected iodinated and gadolinium-based contrast materials (GBCM) have been widely used for imaging pediatric patients with computed tomography (CT) and MR imaging. Most principles applicable to adults regarding contrast material administration and associated adverse events, described elsewhere in this issue, are generally similar in the pediatric population. The safety profiles of contrast material use in children match or exceed the low risk encountered when used in the adult population, particularly with respect to risk of acute adverse reactions and contrast-induced nephrotoxicity (CIN). However, since the establishment of the association between nephrogenic systemic fibrosis (NSF) and GBCM, particular concern is focused to pediatric patients and the currently unknown effects of gadolinium deposition in human tissues, especially in the brain. This article reviews the current knowledge regarding the safety of the most commonly used iodinated and gadolinium-based intravenously injected contrast materials in children.

TYPES OF CONTRAST MATERIALS

Intravenous Iodinated Contrast Materials

Nonionic iodinated contrast materials are the current standard of care for adults and children in the United States, and are considered safe. An important physical property of a contrast material, especially when used in children, is its osmolality. Several adverse effects seem to be related, at least partially, to this physical property. Neonates and small children are more susceptible to fluid shifts related to use of high-osmolality agents, and also have a lower tolerance for intravascular osmotic loads. Specifically, intravascular injection of hyperosmolar contrast material may result in

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fluid shift from the extravascular to intravascular compartment, and the resultant blood volume expansion may cause congestive cardiac failure and pulmonary edema. The risk is significantly higher in children with pre-existing cardiac dysfunction. The main advantage of nonionic agents is their lower osmolality compared with ionic agents. Ionic, high-osmolar agents are nowadays rarely used also because of their adverse safety profile regarding allergic-like reactions and CIN.

An additional important physical property of a contrast agent is its viscosity, defined as a measure of fluid resistance to stress. The higher the viscosity of a contrast agent, the higher is the pressure associated with its intravenous injection. This principle is relevant in pediatric patients where small-gauge catheters are frequently used. Both the contrast viscosity and the catheter gauge should be considered when determining the injection rate in children, to avoid vascular injury associated with rapid injections. A practical measure to decrease the viscosity of a contrast agent is to warm it to body temperature, thereby decreasing the risk of injecting higher volumes at faster flow rates. Contrast warming, however, seems to be more efficacious in higher viscosity agents.[1] Another method to lower the viscosity to facilitate high injection rates in children is dilution with saline, which may be especially useful in CT angiography procedures. An extra benefit is decreased beam hardening artifacts in the vessels. Manual injection of contrast should be preferred in small children and anytime access is considered tenuous, to minimize risk of extravasation or vascular injury.

Gadolinium-Based Contrast Materials

GBCM are considered safe. According to their molecular structure, GBCM are divided in two major groups: linear and macrocyclic agents. The latter are considered safer and less likely to be associated with development of NSF, because their molecular structure makes these agents more stable and therefore less prone to dissociate, potentially resulting in chronic deposition and toxicity. Similarly to iodinated contrast materials, there is wide variability in osmolality and viscosity of GBCM. However, these properties are not as important to consider when using GBCM because the administered volume is usually much smaller than with iodinated agents. Slower injection rates also result in lower risk of vascular injury or contrast extravasation.

The US Food and Drug Administration currently approves only one gadolinium-based contrast agent (gadobutrol) for use in pediatric patients younger than 2 years, including term neonates.[2] The safety and efficacy of other GBCM in children younger than age 2 years have not been established; all other agents are used as an off-label indication.

As of 2011, a survey showed that most pediatric radiology departments in the United States used linear contrast agents.[3] However, in the past few years, the increasing awareness of gadolinium deposition in normal bone and brain tissue has led to a gradual change toward use of macrocyclic agents. Food and Drug Administration approval in itself therefore seems to have little current influence on use patterns given the rapidly accumulating knowledge with respect to the safety profile of different gadolinium chelates.

ACUTE ADVERSE AND ALLERGIC-LIKE REACTIONS IN CHILDREN

Pediatric patients receiving intravenous contrast agents may experience several nonallergic-like reactions, which are caused by a variety of physiologic responses. These are more common than allergic-like reactions and include nausea, emesis, headache, and flushing. Even minor reactions are important in children, because they may cause the child to cry or move during the examination.[4] The pathomechanism of nonallergic-like reactions involves systemic vasodilation from transiently increased osmolality or brainstem stimulation. Clinical management usually requires only careful reassurance.

Allergic-like reactions to intravenous contrast agents, either iodinated or gadolinium-based, are mostly anaphylactoid in nature because no prior exposure is required and it occurs independently of the administered dose. The pathomechanism involves direct release of histamine and other mediators.

Fortunately, adverse reactions to contrast agents in children are even less common than in adults. A study including 12,494 iodinated contrast injections in patients up to 21 years of age noted a rate of 4.6 reactions per 1000 injections, or 0.46%. Of all 57 reactions observed, 47 were mild and none were severe.[5] The pediatric data on gadolinium-based contrast agents are even more reassuring: a study of 15,706 injections noted only eight reactions, of which none were severe and seven were mild, corresponding to a reaction rate of 0.05%.[1] Another study using gadobutrol, a macrocyclic gadolinium-based agent, in more than 1000 pediatric patients found a 0.5% rate of adverse reactions without any serious adverse events, and concluded that the safety profile of