

Safety of Blood Pool Contrast Agent Administration in Children and Young Adults

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OBJECTIVE. The objective of our study was to determine the adverse reaction rate associated with the administration of blood pool contrast material in children and young adults.

MATERIALS AND METHODS. A review of the MRI and pharmacy databases identified all patients who received gadofosveset trisodium from October 1, 2011, to June 30, 2014. Patients were classified as having been anesthetized or not anesthetized for the MRI examinations. A review of the electronic medical records identified adverse reactions recorded within 24 hours of contrast administration. The adverse reactions were graded as mild, moderate, or severe. Risk ratios were calculated between the adverse reaction rate experienced by anesthetized patients and that experience by nonanesthetized patients.

RESULTS. During the study period, 626 patients (mean age, 11.7 years) received 711 doses of gadofosveset trisodium; 137 adverse reactions were recorded, which yields a 19.3% (137/711) adverse reaction rate. There were 115 adverse reactions experienced by 367 anesthetized patients (31.3%); 93.0% (107/115) were mild and 7.0% (8/115) were moderate. The remaining 22 adverse reactions were experienced by 344 (6.4%) nonanesthetized patients, and 90.9% (20/22) were mild. Three nonanesthetized patients had allergiclike reactions; of these allergiclike reactions, one was mild and two were severe for a severe allergiclike reaction rate of 0.28% (2/711). Severe allergiclike reactions were treated without any adverse outcomes. Anesthetized patients were 5.7 times more likely to experience an adverse event than nonanesthetized patients; most reactions in anesthetized patients were seen after the administration of anesthesia alone.

CONCLUSION. Most reactions after gadofosveset trisodium administration in children and young adults are mild; however, severe allergiclike reactions occur, so policies must be in place to treat patients with adverse reactions when using this contrast agent. These data may be useful to centers considering administering gadofosveset trisodium to pediatric patients.

Contrast agents used for MRI examinations include extracellular and blood pool agents. Most agents available for clinical use are extracellular agents. Extracellular agents initially distribute into the intravascular space, rapidly diffuse across capillary membranes into the extracellular space, equilibrate between these two compartments, and are then eliminated by the kidneys [1]; the plasma elimination half-time is approximately 70–90 minutes in patients with normal kidney function [1]. Most extracellular contrast agents have similar relaxivities and yield similar diagnostic information [1, 2]. These contrast agents have been used in pediatric patients for MRI examinations to assess the CNS, body, and cardiac and periph-

eral vascular anatomy and for myocardial perfusion imaging (myocardial late gadolinium enhancement) [3–15].

A blood pool contrast agent gadofosveset trisodium (Ablavar, Lantheus) was approved for use in the United States in 2008 for the assessment of aortoiliac disease in adults [16, 17]. Gadofosveset trisodium contains a gadolinium–diethylenetriamine pentaacetic acid core and is linked to a lipophilic diphenyl cyclohexyl group that is approximately 80% reversibly bound to serum albumin [2]. The albumin binding limits the distribution of bound gadofosveset trisodium to the intravascular space with a prolonged plasma elimination half-time of approximately 18 hours. The major route of gadofosveset trisodium elimination is via the kidneys (91%)

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with a small amount excreted in bile (9%) [1]. The albumin binding of gadofosveset trisodium slows down the tumbling of the molecule, thus increasing the relaxivity of the molecule by five times the relaxivity of standard extracellular contrast material at 1.5 T [2]. Gadofosveset trisodium has high thermodynamic stability in vitro relative to linear gadolinium-based contrast agents. The albumin binding of gadofosveset trisodium limits the amount of contrast material that is able to extravasate into the soft tissues. These properties may lessen the risk of nephrogenic systemic fibrosis with gadofosveset trisodium relative to other gadolinium-based contrast agents [16]. However, the increased plasma dwell time of gadofosveset trisodium may negate some of these effects. The increased plasma dwell time allows high-resolution imaging, so imaging with gadofosveset trisodium can be performed over a longer period of time than imaging with extracellular contrast agents. Additionally, beyond the first-pass distribution of contrast material into the intravascular compartment, contrast material is present in equilibrium in all vessels, thus allowing simultaneous arterial and venous imaging.

There have been reports on the imaging efficacy of gadofosveset trisodium in children for chest cardiovascular assessment, coronary artery evaluation, abdominal vasculature assessment, peripheral vascular assessment, and gastrointestinal bleeding evaluation [13, 18–22]. We have used gadofosveset trisodium for vascular assessment in the CNS, chest, abdomen, and extremities without significant perceived adverse reactions. Our purpose was to determine the adverse reaction rate associated with gadofosveset trisodium administration in our pediatric population.

Materials and Methods

Institutional review board approval was obtained for this HIPAA-compliant retrospective study. Informed consent was waived.

Study Patients

A retrospective review of the MRI and pharmacy databases was performed to identify all pediatric patients who had a clinically indicated imaging examination using gadofosveset trisodium from October 1, 2011, to June 30, 2014. Gadofosveset trisodium is the standard contrast agent used at our institution for chest, abdomen, and peripheral vascular assessments and for cardiac MRI examinations. The clinical indication for MRI with

gadofosveset trisodium does not include assessment for late gadolinium enhancement. Gadofosveset trisodium has also been used for CNS vascular assessment.

Each time a patient received gadofosveset trisodium during the study period, that dose administration was included in this study. Patients were not excluded if they received multiple doses of gadofosveset trisodium during the study period because adverse reactions can occur without or with prior contrast exposure. Patients were excluded if they received any other type of gadolinium-based contrast agent within 24 hours of gadofosveset trisodium administration.

Electronic Medical Record Review

The electronic medical records (EMRs) were reviewed to determine whether the MRI examinations were performed with the patient under general anesthesia and to determine the anesthetic regimen, the anatomic body part or parts imaged, and the gadofosveset trisodium dose. Additionally, the was reviewed for any recorded adverse reaction within 24 hours of contrast administration. There is an EMR field containing MRI-related documentation from our nursing staff and a specific note field that provides physician documentation related to the MRI examination. An MRI contact telephone number is also given to all nonanesthetized patients, and they are instructed to report any adverse event. Additionally, a follow-up telephone call is made to all anesthetized patients 1 day after the MRI examination. All documentation and notes from the day of and the day after the cardiovascular MRI examination were reviewed.

All reported reactions were retrospectively categorized as mild, moderate, or severe and as either allergiclike or physiologic according to the categories of acute reactions in the “ACR Manual on Contrast Media, Version 9,” which was published by the American College of Radiology (ACR) in 2013 [23]. According to the ACR Manual, mild allergiclike and physiologic reactions including reactions such as pruritus and nausea, respectively, are defined as self-limited without evidence of progression and as not requiring medical intervention. Moderate allergiclike reactions such as facial edema and moderate physiologic reactions such as protracted nausea and vomiting are defined by the ACR Manual as more pronounced and as requiring medical intervention. Severe allergiclike and physiologic reactions such as laryngeal edema with stridor and hypertensive emergency, respectively, are defined by the ACR Manual as life-threatening with the potential to cause permanent morbidity or mortality if not appropriately treated [23]. If an allergiclike reaction was recorded, the chart was reviewed to determine whether the pa-

tient had a prior allergiclike reaction to any gadolinium-based contrast agents.

For data analysis, patients were separated into two groups: those who underwent MRI with contrast material while anesthetized and those who were not anesthetized. We separated patients into these groups because we expected that there could be adverse reactions related solely to the anesthesia.

Patient Screening Before Contrast Administration

All patients are screened for adequate kidney function before contrast administration according to our institutional gadolinium-based contrast screening policy and kidney disease risk assessment questionnaire. If the patient or patient's parent or guardian answers “Yes” to any of the questions in the questionnaire, a serum creatinine value is obtained. For patients younger than 1 year old, contrast material can be administered if the serum creatinine value falls within the normal range according to an isotope dilution mass spectrometry–traceable laboratory result. For patients ranging from 1 to 18 years old, an estimated glomerular filtration rate (GFR) calculation is performed using the bedside Schwartz formula. The Modification of Diet in Renal Disease (MDRD) formula is used to calculate estimated GFR for patients more than 18 years old. Gadolinium-based contrast agents are administered to patients 1 year old or older if the estimated GFR is 60 mL/min/1.73 m² or greater. For estimated GFRs ranging from 30 mL/min/1.73 m² to less than 60 mL/min/1.73 m², the ordering provider is contacted to discuss whether the benefits of a contrast-enhanced examination outweigh the risks before any gadolinium-based contrast agent is administered; a decision is then made to administer the contrast material or not. If the estimated GFR is less than 30 mL/min/1.73 m² or if there is acute kidney or liver failure, no gadolinium-based contrast material is administered.

Because a low incidence (0.4%) of a mildly prolonged corrected QT interval was reported in the Ablavar clinical trial [17], we used baseline ECG to assess all patients with congenital heart disease for a prolonged QTc interval (QTc interval > 480 ms). If there was a prolonged QTc interval, a pediatric electrophysiology consult was obtained before gadofosveset trisodium administration.

Statistics

The severe allergiclike adverse reaction rate in our study was compared with the anaphylaxis or anaphylactoid reaction rate reported in the Ablavar adult clinical trial [24] and reported in a conglomerate series of extracellular gadolinium-based contrast agents [23] and was compared with

the severe allergiclike reaction rate in a series of pediatric patients [25] using the Fisher exact test.

The risk ratio for overall adverse reaction rates between anesthetized and nonanesthetized patients was calculated using a generalized linear model [26]. An exact multinomial test was used to compare the mild, moderate, and severe adverse reaction rates within the groups of anesthetized and nonanesthetized patients. A one-sample binomial test was used to test mild, moderate, and severe adverse reaction proportions between the anesthetized and nonanesthetized patients for significant difference. Data were analyzed using statistics software (SAS, version 9.3, SAS Institute).

Results

During the study period, 626 patients received 711 doses of gadofosveset trisodium. Of the 711 doses of gadofosveset trisodium, 556 patients received 1 dose, 57 patients received two doses, 11 patients received three doses, and 2 patients received four doses of contrast material. The mean ($\pm$ SD) age of

patients at contrast administration was 11.7 ± 5.5 years (age range, 4 days–20.8 years) (Fig. 1). Of the 711 doses, 45.9% (326/711) were administered to females and 54.1% (385/711) were administered to males. The mean patient weight was 44.7 ± 24.5 kg (range, 2.4–144.0 kg).

Of the 711 MRI examinations, 367 (51.6%) were performed in anesthetized patients and 344 (48.4%) MRI examinations were performed in nonanesthetized patients. The anesthetic regimens used were dissimilar and included a variety of inhaled and IV anesthetic agents. The mean gadofosveset trisodium dose was 0.12 mL/kg (0.03 mmol/kg), which is the dose recommended by the manufacturer for assessment of aortoiliac disease in adults [17]. Most examinations (88.5%, 629/711) were performed for thoracic cardiovascular assessment, and a small number of studies were MR angiography studies of peripheral vascular anatomy or of the body, head, neck, or pelvis (Fig. 2). All contrast

material was injected via a power injector at rates between 1.5 and 3 mL/s, and contrast injection was followed by a normal saline flush (1 mL/kg of body weight [minimum, 5 mL; maximum, 20 mL]). All examinations were performed at 1.5 T.

All adverse events were recorded in the EMR by a nurse. Severe adverse events were also documented in the EMR by a physician. Of the 711 contrast dose administrations, 80.9% (575/711) had no adverse reactions. There were 137 adverse reactions documented in 115 patients (mean age, 9.2 years; age range, 7.2 months–20.8 years), which yields an overall adverse reaction event rate of 19.3% (137/711). Of these 137 adverse reactions, 127 were graded as mild, 8 were graded as moderate, and 2 were graded as severe (Table 1).

There were 115 (31.3%, 115/367) adverse reactions recorded in 98 anesthetized patients (Table 1). The most common adverse reactions in this patient group were mild (93.0%, 107/115) in degree and included

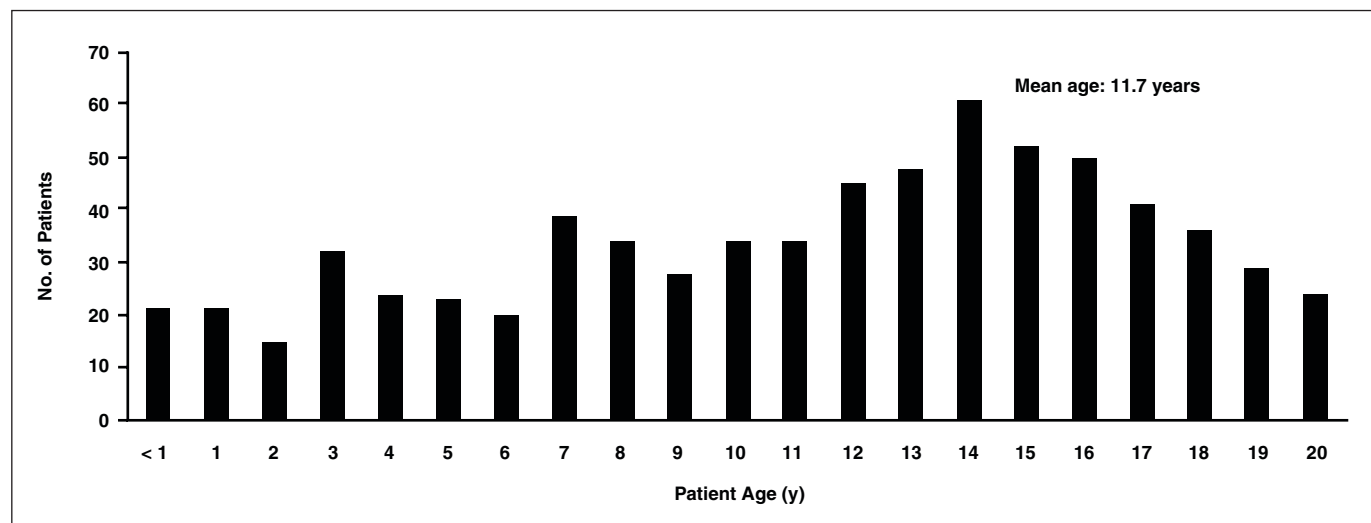


Fig. 1—Bar graph shows distribution of pediatric patients in study group by age at time each gadofosveset trisodium dose was administered.

TABLE 1: Classification of All Adverse Events

Patient Group	No. (%) of Adverse Events			<i>p</i>	Total
	Mild	Moderate	Severe		
Anesthetized patients	107 (93.0)	8 (7.0)	0 (0)	<0.0001 ^a	115 (100)
Nonanesthetized patients	20 (90.9)	0 (0)	2 (9.1)	<0.0001 ^a	22 (100)
Total no. (%) of adverse events	127 (92.7)	8 (5.9)	2 (1.5)		137 (100)
<i>p</i>	<0.0001 ^b	0.008 ^b	0.5 ^b		0.001 ^c

^aExact multinomial test.

^bBinomial test of proportions.

^cFisher exact test.

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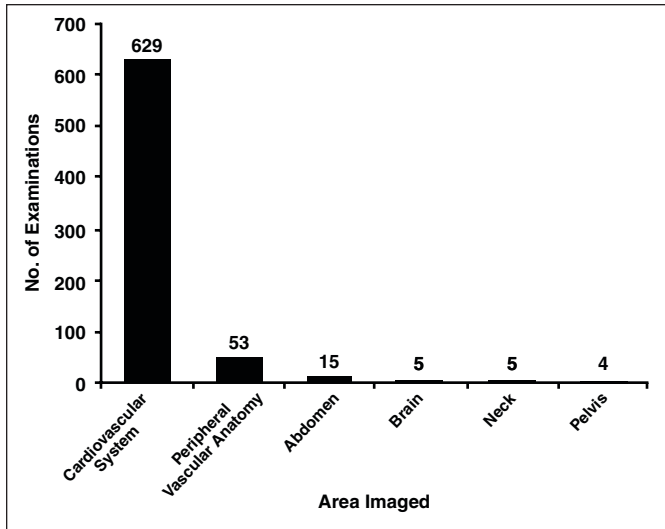


Fig. 2—Bar graph shows distribution of patients by anatomic regions imaged for each dose of gadofosveset trisodium.

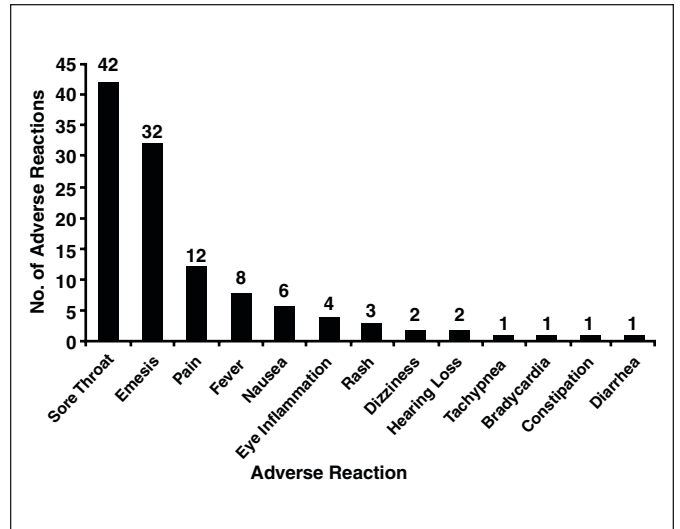


Fig. 3—Bar graph shows distribution of adverse reactions in patients who underwent MRI examinations while under general anesthesia. There were 115 adverse reactions recorded in 98 anesthetized patients.

sore throat (36.5%, 42/115), emesis (27.8%, 32/115), and pain (9.6%, 11/115) (Fig. 3). Eight reactions in this group (7.0%, 8/115) were moderate in degree and included nausea and repeated emesis in seven patients that required the administration of an antiemetic medication. Tachypnea was experienced by one patient with congenital heart disease, and overnight observation and oxygen administration were required but no other interventions were needed. Neither severe nor allergiclike adverse reactions were reported in the group of anesthetized patients.

There were 22 (6.4%, 22/344) adverse reactions recorded in 16 nonanesthetized patients (Table 1). Of the adverse reactions in this patient group, 90.9% (20/22) were mild and included dizziness (22.7%, 5/22) and anxiety (18.2%, 4/22) (Fig. 4). No moder-

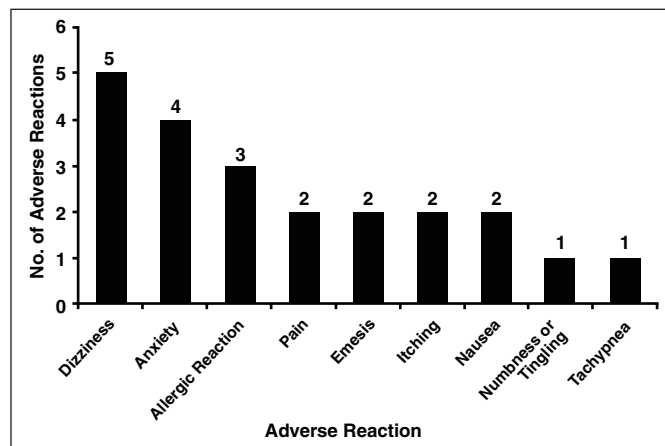
ate-degree adverse reactions were reported in this group. Allergiclike adverse reactions were seen in three patients, accounting for 13.6% (3/22) of the adverse reactions in the nonanesthetized group. The allergiclike reaction rate was 0.9% (3/344) in the nonanesthetized group and 0.42% (3/711) in the entire study population. No patient who had an allergiclike reaction had a prior recorded allergic reaction to a gadolinium-based contrast agent. The first patient had a mild allergiclike reaction consisting of prolonged sneezing. Two patients had severe allergiclike reactions, for an overall severe allergiclike reaction rate of 0.28% (2/711). One patient had erythema, diffuse urticaria, and hypoxia and was treated with IV diphenhydramine and epinephrine (EpiPen, Mylan). The second patient had face and lip angio-

edema, bronchospasm, and hypoxia and was treated with diphenhydramine IV and an albuterol nebulizer. The patient responded to the treatment immediately, and no epinephrine was administered. Both patients were discharged after a short hospital stay for observation. There were no adverse outcomes after treatment of the allergiclike reactions.

The severe allergiclike reaction rate for all dose administrations in our study was 0.28% (2/711) and does not significantly differ ($p = 0.376$; power, 14.3%) from the anaphylactoid or anaphylaxis rate for adults that is listed in the Ablavar package insert (2/1676 subjects, 0.12%) [24]. The severe allergiclike reaction rate of 0.28% is significantly greater ($p < 0.0001$) than the severe adverse reaction rate reported in a conglomerate series of 697,000 patients [23] and is significantly greater ($p < 0.01$) than the severe adverse reaction rate of 0.0075% in a series of pediatric patients reported by Dillman et al. [25].

The calculated risk ratio for the overall adverse reaction rates of anesthetized and nonanesthetized patients shows that anesthetized patients were 5.7 times more likely to experience an adverse reaction as nonanesthetized patients and that the frequency of adverse reactions in the anesthetized patients is significantly greater than that in the nonanesthetized patients ($p < 0.0001$). An exact multinomial test shows that there is highly significant evidence of a difference in the proportion of adverse reactions for each category (mild, moderate, severe) within each

Fig. 4—Bar graph shows distribution of adverse reactions in patients who underwent MRI examinations without general anesthesia. There were 22 adverse reactions recorded in 16 nonanesthetized patients.



group (anesthetized vs nonanesthetized; all p values, $p < 0.0001$). The proportion of anesthetized patients who experienced mild adverse reactions (106 patients, 28.9%) is significantly different from the proportion of nonanesthetized patients who experienced mild adverse reactions (20 patients, 5.8%) ($p < 0.0001$). The proportion of anesthetized patients who experienced moderate adverse reactions (8 patients, 2.2%) is also significantly ($p = 0.008$) different from the proportion of nonanesthetized patients (0 patients, 0%). However, there is no significant difference when comparing the proportion of anesthetized patients (0 patients, 0%) who experienced severe adverse reactions with the proportion of nonanesthetized patients (2 patients, 0.0058%) ($p = 0.5$) (Table 1).

Discussion

Reported adverse reaction rates to extracellular gadolinium-based contrast agents in large retrospective studies of adults are low and range from 0.04% to 0.48% [27–29]. The overall adverse reaction rate in our study population of 19.3% is significantly greater than these reported adverse reaction rates in adults. One likely cause for the difference in adverse reaction rates between these larger studies of adults and our study of pediatric patients is the retrospective nature of the studies. Minor adverse reactions that did not require treatment in those studies may not have been recorded. For example, Li et al. [28] explained that minor reactions were not recorded: “sensations of hot or cold, transient sensations of taste or mild pain at the injection site were excluded as adverse reactions.” In the study by Hunt et al. [27], only adverse reactions that occurred within 30 minutes of contrast medium administration were recorded.

The adverse reaction rate reported in a prospective adult clinical trial of gadopentetate dimeglumine was 19.9% (213/1068) [30], which is comparable to our reported adverse reaction rate of 19.3%. Because the gadopentetate dimeglumine clinical trial of adults recorded all adverse events prospectively, that study likely captured more adverse events than the retrospective studies.

Of the MRI examinations in our study, 51.6% were performed in anesthetized children. Reactions to the anesthetic agents alone have likely led to an increased rate of reported adverse reactions relative to contrast-related adverse reactions. In a study of 4998 ambulatory children who under-

went surgery performed with general anesthetic, Patel and Hannallah [31] reported a 34.6% (1728/4998) complication rate within 24 hours of discharge from the hospital. The complications seen in their study group included vomiting (8.9%, 447/4998), cough (6.5%, 324/4998), sleepiness (5.9%, 297/4998), sore throat (5.1%, 257/4998), fever (4.7%, 235/4998), and hoarseness or mild croup (3.4%, 168/4998). These types of adverse reactions are similar to the mild and moderate adverse reactions reported in our anesthetized patient group (Fig. 3). Because all of our patients did not receive the same anesthetic regimen, comparisons of adverse reactions related to specific anesthetic regimens could not be performed. Shellock et al. [32] compared 85 children (mean age, 8.6 years; age range, 2 days–17 years) who received gadobenate dimeglumine with 89 children (mean age, 4.7 years; age range, 7 months–17 years) who received gadopentetate dimeglumine for MRI studies of the CNS. They reported that 24 patients had 34 adverse reactions up to 24 hours after contrast administration, which yields an adverse reaction rate of 19.5% (34 reactions in 174 children) that is similar to our 19.3% overall adverse event rate. Fever was the most common mild adverse reaction seen in six patients in their study [32]. Three more serious reactions were reported in their study, including vomiting, fever, and hypoxia, and are similar to the types of physiologic reactions seen in our study. All adverse events in their study were attributed to the “patient’s underlying condition” except vomiting in one patient that the authors report could have been related to contrast administration. The number of patients undergoing examinations under anesthesia is not reported in their data, but given the age range of the patients (2 days–17 years), anesthesia was likely used in the younger children in their study.

Our risk ratio calculations for the overall rate of adverse events indicate that anesthetized patients were 5.7 times more likely to experience an adverse reaction as nonanesthetized patients and that there are significant differences ($p < 0.0001$) in each category of reaction (mild, moderate, severe) between the anesthetized and nonanesthetized patients. Although the adverse reactions seen in anesthetized patients in our study cannot absolutely be attributed to the anesthesia rather than to the gadofosveset trisodium, similar types of reactions are reported in children undergoing anesthesia [31]. Additionally, the

use of anesthetic greatly increased the incidence of nonallergiclike adverse reactions in our study, so it is likely that many of the adverse reactions in the anesthetized patient group were related to anesthesia.

Allergiclike adverse reactions to gadolinium-based contrast agents constitute a small percentage (2.2% [28] to 3.1% [27] to 4.3% [29]) of all adverse reactions. In a conglomerate series of 697,000 doses of gadolinium-based contrast agents, there were five severe allergiclike reactions (0.0007%) [23]. Dillman et al. [25] reported a 0.04% (6/13,344 administrations) acute allergiclike reaction rate to a variety of gadolinium-based contrast agents (not including gadofosveset trisodium) in children, which is less than their reported allergiclike reaction rate of 0.07% (48/65,009 administrations) in adults. Two of the six allergiclike reactions in pediatric patients were reported as mild and one (0.0075%, 1/13,344) was reported as severe. In our study group, the severe adverse reactions were all allergiclike reactions, with an allergiclike reaction rate of 0.28%. This severe allergiclike reaction rate of 0.28% is significantly greater ($p < 0.0001$) than the 0.0007% severe adverse reaction rate reported in the conglomerate series of 697,000 patients [23] and is significantly greater ($p < 0.01$) than the severe adverse reaction rate of 0.0075% reported by Dillman et al. (Fig. 5). The severe adverse reaction rate in our study group is greater than the anaphylaxis rate in adults listed in the Ablavar package insert (0.12%, 2/1676 subjects) [24], but the difference is not statistically significant ($p = 0.376$) possibly because of the relatively small sample sizes in both studies. Prince et al. [13] reported a single severe allergiclike reaction to gadoteridol in 3371 injections of adult and pediatric patients, for a severe adverse reaction rate of 0.03%. The severe allergiclike reaction was observed in a 9-year-old boy undergoing an anesthetized MRI examination who had urticaria and wheezing with desaturation immediately after injection of gadoteridol. He was treated with epinephrine, albuterol, diphenhydramine, and dexamethasone and was discharged without complication [13].

The limitations to this study include the retrospective nature of data acquisition. It is likely that all severe adverse reactions would have been captured in our data review; however, because all patients were not specifically contacted for follow-up, mild or delayed adverse reactions may be underreported. Of

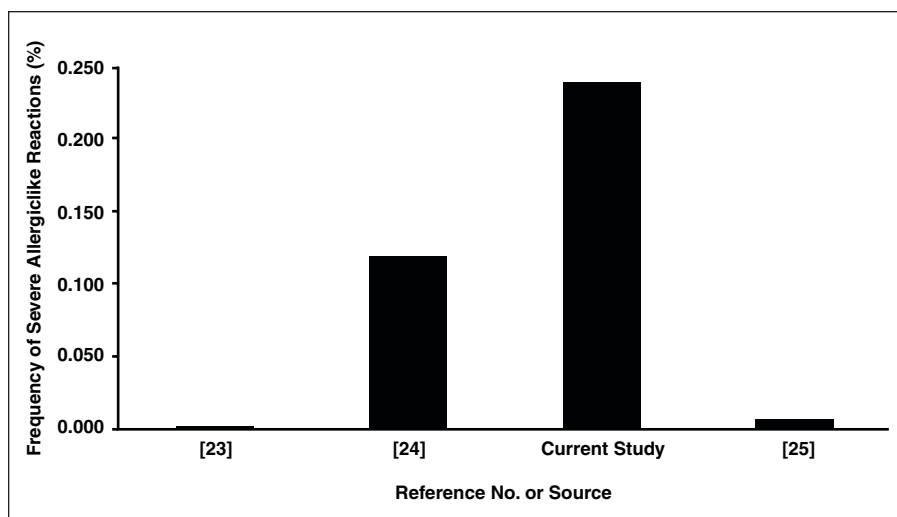


Fig. 5—Bar graph shows frequencies of severe allergiclike adverse reaction for this study and three other sources.

the patients in our study, 51.6% underwent MRI examinations while anesthetized. It is not possible to definitively separate anesthesia-related adverse reactions from contrast-related adverse reactions because some of the reactions including emesis, nausea, and dizziness were seen in anesthetized patients and in nonanesthetized patients. However, the risk ratio calculations show a significantly higher risk for anesthetized patients to have mild and moderate physiologic adverse reactions, which suggests that many of these reactions are related to anesthesia rather than to the contrast agent. Because the successful performance of MRI examinations in young children often requires anesthesia, having information about reactions seen in anesthetized children should be useful to other pediatric centers.

Conclusions

Most reactions seen after gadofosveset trisodium administration in children and young adults were mild and there were no adverse outcomes from any recorded reactions; however, because severe allergiclike reactions were observed, policies must be in place to treat patients with adverse reactions when using this contrast agent. These data may be useful to centers considering a program for administering gadofosveset trisodium to pediatric patients.

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