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ORIGINAL ARTICLE

Safety of gadoterate meglumine in children younger than 2 years of age

Shannon G. Farmakis[1] · Anna K. Hardy[2] · Shamsheldeen Y. Mahmoud[2] · Scott A. Wilson-Flewelling[3] · Ting Y. Tao[1]

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Abstract

Background Few studies on the safety of gadolinium-based contrast agents have been performed in children with even fewer focusing on children younger than 2 years of age.

Objective To assess the safety of gadoterate meglumine (Dotarem) in patients younger than 2 years of age by evaluating adverse events following contrast administration.

Materials and methods Pediatric patients younger than 2 years of age undergoing magnetic resonance imaging (MRI) with and without contrast were prospectively enrolled and received a weight-based intravenous dose of gadoterate meglumine (0.1 mmol/kg). The occurrence of adverse events was assessed at the time of injection, 2 h after MRI, and by phone contact using a standard questionnaire 24 h after MRI. Adverse events were documented including the time of onset, duration of symptoms, intensity, causality and subsequent outcome. Descriptive statistics were used to characterize patient information.

Results One hundred fifty exams were completed in 150 patients (median age: 12.1 months, age range: 0.25–23 months; males: 56%). Almost all patients (97.3%) received sedation/anesthesia before and during MRI. Thirty-four adverse events were reported in 23 patients overall (15.3%; male: 73.9%; median age: 11 months, age range: 3–23 months). Within the initial 2 h after the injection, there was one report of transient flushing/warmth and one report of vomiting, the latter of which was related to drinking formula too soon after anesthesia. Twenty-two patients (14.7%), who had all received sedation/anesthesia, experienced minor adverse events within 24 h, most physiological. Fourteen patients (9.3%) reported emesis, eight (5.3%) reported transient flushing/warmth, seven (4.7%) reported nausea, one (0.7%) reported altered taste and one (0.7%) reported dizziness. No patient experienced anaphylaxis. Two patients (1.3%) reported allergic-like reactions, which consisted of wheezing or sneezing.

Conclusion No patient experienced adverse events directly related to gadoterate meglumine. Only two adverse events were reported to have occurred in the initial 2 h after the exam, while the rest were reported on the 24-h follow-up call. The higher reported rate of adverse events in this study may be related to concomitant sedation/anesthesia as well as to overreporting from parents on the 24-h follow-up questionnaire. The study confirms a good safety profile for gadoterate meglumine in this very sensitive population.

Keywords Adverse events · Children · Dotarem · Gadoterate meglumine · Infants · Magnetic resonance imaging · Safety

Introduction

Research emphasis on the safety of gadolinium-based contrast agents (GBCAs) for magnetic resonance imaging (MRI) remains high given concerns over gadolinium deposition in patients with normal renal function and previously over nephrogenic systemic fibrosis in patients with compromised renal function [1–10]. While these represent potential late-onset side effects of GBCA usage, there is still an emphasis on studying the potential immediate adverse reactions of these agents. Most of the studies evaluating the immediate safety of GBCAs have been performed in adults, with fewer dedicated

✉ Shannon G. Farmakis
sfarmakis@radiax.com

[1] Department of Radiology, SSM Health Cardinal Glennon Children's Hospital, St. Louis University School of Medicine, 3635 Vista Avenue at Grand Boulevard, St. Louis, MO 63110, USA

[2] Department of Radiology, St. Louis University School of Medicine, St. Louis, MO, USA

[3] St. Louis University School of Medicine, St. Louis, MO, USA

to the safety of the agents in children [11–13]. Even fewer studies have followed the patients beyond the window for immediate adverse reactions to see if there is a potential for delayed-onset adverse reactions.

Gadoterate meglumine (Dotarem; Guerbet LLC, Villepinte, France) is a contrast agent that was introduced in 1989 and has been in regular use in Europe and the rest of the world since then [12]. It was approved for use in the United States in 2013 [12]. It is thought that the high kinetic stability, which is provided by the macrocyclic structure, and the ionic nature of the drug, which results in a higher thermodynamic stability, allow for decreased free gadolinium deposition in the tissues [14, 15]. It is the only ionic macrocylic agent on the market, and it has no unconfounded reported cases of nephrogenic systemic fibrosis [10]. Its initial approval was for patients >2 years of age and eventually was broadened to include patients <2 years of age [16].

The primary objective of this study is to assess the safety of gadoterate meglumine in patients younger than 2 years of age for both immediate adverse events and adverse events that occur up to 24 h after GBCA administration.

Materials and methods

This was a prospective study approved by the Institutional Review Board and registered on https://clinicaltrials.gov (NCT02609919). As the study was initiated before U.S. Food and Drug Administration (FDA) approval of gadoterate meglumine in patients younger than 2 years of age, an Investigational New Drug Application was obtained from the FDA. Patients were enrolled between Feb. 2, 2016, and July 19, 2019.

A data safety monitoring board was convened annually to review collected data for safety. The data safety monitoring board was made up of radiologists and a statistician. At all reviews, the board determined the study had no safety concerns that should cause the study to terminate early.

Study patients

Eligible patients were those younger than the age of 2 years who had to undergo an MRI exam without and with contrast that had been protocoled to use gadoterate meglumine by an attending radiologist (either a pediatric radiologist or neuroradiologist) as part of a routine standard of care examination. MRI exams were performed with or without sedation/anesthesia. Written informed consent was obtained from the patients' parent(s) or caregiver.

Patients excluded were those with a glomerular filtration rate <30 mL/min/1.73 m^2, those with known renal failure or prior hypersensitivity reaction to GBCAs, those not accompanied by a parent, and those who were unable to complete the MRI exam before contrast administration. Patients who had more than one MRI during the study were also excluded from enrolling more than once.

All MRI exams were performed on either a 3-T GE Discovery 750 W or 1.5-T GE Signa HDXT 23.0 (GE Healthcare, Milwaukee, WI). MRI coil usage and sequences obtained varied depending on the protocol and body part being imaged. All protocols included at a minimum T1-weighted imaging and T2-weighted imaging, both with and without fat saturation, and T1-weighted fat-saturated post-contrast images.

The electronic medical record was reviewed for all patients to obtain age, gender, weight, risk factors (renal disease, autoimmune disease, other medical conditions), reason for exam, type of exam, dose of gadoterate meglumine, route of injection and tolerance to injection. In addition, when applicable, the types of medications used for sedation were recorded as well as the method of sedation: deep sedation, laryngeal mask airway or general endotracheal anesthesia.

Patients were given a weight-based dose of gadoterate meglumine of 0.2 mL/kg (0.1 mmol/kg) body weight. It was administered as an intravenous (IV) bolus injection at a flow rate of approximately 1–2 mL/s either by manual or power injection.

Adverse event monitoring

During the MRI exam, all patients had continuous monitoring of heart rate and peripheral oxygen saturation. Sedated patients were monitored similarly after the MRI exam until they reached an Aldrete score >6, which is based on scores of 0, 1 or 2 for activity, respiration circulation, consciousness and color [17]. After this, the monitoring devices were removed. The patients were then observed off the monitors until at least 2 h after the exam had elapsed.

Assessment for adverse events was performed at three time points. The first assessment was at the time of the contrast injection. The dose of gadoterate meglumine administered, the site of IV injection of the contrast agent and the presence of any adverse effects were documented by the MRI technologist. The second was made 2 h after the contrast injection and was documented by a registered nurse in the imaging department and included how the patient physically appeared (e.g., active, no acute distress), whether they had returned to baseline activities of daily living as reported by the parents, the appearance of the peripheral IV site, and whether there were any signs of systemic reaction. The third was conducted by phone 24 h after the MRI. The parents were called by the research coordinators or senior medical student the next day to identify any adverse events by a standard questionnaire (Table 1). Script modifications were routinely made for the parents when describing paresthesias as numbness or tingling and dyspnea as shortness of breath. Allergic reactions were categorized into allergic-like and physiological based on the

Table 1 Questionnaire given to parents on the 24-h follow-up phone call

Did your child experience any of the following after being discharged from the hospital from the MRI exam?	
Headache	Yes or No
Nausea	Yes or No
Dizziness	Yes or No
Altered or bad taste in mouth	Yes or No
Feeling hot or flushing	Yes or No
Injection site reactions	Yes or No
Vomiting	Yes or No
Rash (includes generalized, macular, popular, pruritic)	Yes or No
Erythema or redness	Yes or No
Hypersensitivity/anaphylactoid (i.e. urticarial, facial edema, eyelid edema, flushing, cough, sneezing, wheezing, chest pain, cyanosis)	Yes or No
Dyspnea[a]	Yes or No
Paresthesia[b]	Yes or No
Following your child's discharge from MRI, did he/she have any other clinic appointments or tests/exams in the hospital? If so, what were they?	Yes or No

[a] Shortness of breath was used in addition as a script modification when making calls

[b] Numbness or tingling was used in addition as a script modification when making calls

categories outlined in the American College of Radiology (ACR) Manual on Contrast Media Version 10.3 (Table 2) [18].

All adverse events were documented including nausea, headache, injection site pain, injection site coldness, burning sensation, heart arrhythmia, nausea, vomiting, diarrhea, dizziness, paresthesias, seizures, tremors or muscle spasms, fever and allergic reactions (cardiac or respiratory arrest, laryngeal edema, angioedema or urticaria). While symptoms of headache, nausea, altered or bad taste in mouth, and paresthesias are difficult to assess in this age group as patients are unable to self-report, it was important to include them, as they are known potential adverse reactions from gadoterate meglumine [16]. Therefore, reporting of these symptoms relied on parent observations as something unusual or out of the ordinary for their child. If necessary, management and treatment of acute reactions to contrast media would follow the guidelines outlined in Table 2 of the ACR Manual on Contrast Media Version 10.3 [17].

If and when an adverse event was reported, the type of event, the time of onset relative to the administration of the GBCA, the duration of symptoms, the intensity of the reaction (mild, moderate, severe), the causality (not related, probably related, related, definitely related, unclassifiable) and the subsequent outcome (required treatment, favorable outcome, recovery with sequela, or death) were documented.

Parents were given an information sheet before their child's discharge indicating the possible adverse events that may occur related to gadoterate meglumine with instructions on what to do and whom to call, if necessary, should any of them occur.

Statistical analysis

Descriptive statistics were used to report the counts and percentages of patient characteristics. Descriptive statistics were done in Excel Version 1.5 (Microsoft 2016) and Calculator.net (Maple Tech International, LLC 2008–2019) [19, 20].

Results

A total of 170 patients were enrolled. Twenty were considered screening failures and were not included in the final analysis. These included reasons related to the parents being unable to stay the full 2 h after the MRI, gadoterate meglumine was not the contrast agent that was ultimately used, or the MRI was cancelled, most commonly because of the inability to get an IV catheter placed. A single patient was erroneously enrolled twice for two separate exams done on different days. This patient was counted as two separate exams and patients.

Of the 150 patients included in the study, 84 (56%) were male. The ages ranged from 0.25 to 23.0 months with a median age of 12.1 months (Table 3). Indications for the MRI exam included neurological (82.0%), body (10.0%), musculoskeletal (6.0%), body and musculoskeletal (0.7%), neurological and musculoskeletal (0.7%), and whole body (0.7%).

MRI exam types included brain, orbits and/or face (72.0%); chest, abdomen and/or pelvis (9.4%); spine (7.3%); extremity (7.3%); MR angiography/MR venography (1.3%); brain and spine (1.3%); or other (combination of brain and pelvis) (1.3%).

The mean (±standard deviation) volume of gadoterate meglumine given to patients was 1.85 (±0.5) mL (range: 0.6–3.4 mL).

A total of 23 patients reported 34 adverse events with an overall rate (both early and late onset) of 15.3% (male: 73.9%; median age: 11 months, age range: 3–23 months) (Table 4). All but one patient (95.7%) reporting adverse events underwent an MRI for a neurological indication with the single remaining patient getting a body MRI. No patient had an immediate reaction to the gadoterate meglumine injection. Two patients (1.3%) had a physiological reaction within the 2-h observation period. The first was reported by the parents on the 24-h follow-up call as facial redness for approximately 10–15 min after waking up from the MRI exam. This observation, however, was not supported by the nursing record during this time period, but it was included since the parents reported it. This patient had undergone sedation with propofol. The second patient had an episode of vomiting,

Table 2 Classification of acute contrast reactions based on type and severity

Severity	Physiological	Allergic-like
Mild	Limited nausea/limited vomiting	Limited urticaria/pruritus
	Transient flushing/warmth/chills	Cutaneous edema
	Headache	Limited itchy/scratchy throat
	Dizziness	Nasal congestion/rhinorrhea/conjunctivitis
	Anxiety	Sneezing
	Altered taste	
	Mild hypertension	
	Vasovagal reaction that resolves spontaneously	
Moderate	Protracted nausea/vomiting	Diffuse urticaria/pruritus
	Hypertensive urgency	Diffuse erythema with stable vital signs
	Isolated chest pain	Facial edema without dyspnea
	Vasovagal reaction that requires treatment and responds to treatment	Throat tightness or hoarseness without dyspnea
		Wheezing/bronchospasm without or with mild hypoxia
Severe	Vasovagal reaction that is resistant to treatment	Diffuse edema/facial edema with dyspnea
	Arrhythmia	Diffuse erythema with hypotension
	Convulsions/seizures	Laryngeal edema with stridor and/or hypoxia
	Hypertensive emergency	Wheezing/bronchospasm with significant hypoxia
	Pulmonary edema*	Anaphylactic shock (hypotension and tachycardia)
		Pulmonary edema*

Adapted from the American College of Radiology Manual on Contrast Media Version 10.3 (with permission) [18]

*Pulmonary edema can be cardiogenic or non-cardiogenic. Non-cardiogenic pulmonary edema can be allergic-like (in tandem with other allergic-like reactions) or physiological (in the absence of other allergic-like reactions)

which occurred 45 min after completion of the MRI and was related to drinking formula too soon after waking up from anesthesia. Neither reaction was considered a direct result of gadoterate meglumine by the principal investigator. There were no serious adverse events.

On the 24-h follow-up call, 33 adverse events were reported in 22 patients (14.7%). The majority of these reactions were physiological (95.4%). Vomiting (n=13, 8.7%), transient flushing or warmth (n=8, 5.3%) and nausea (n=7, 4.7%) accounted for the majority. Seven of those with reports of vomiting had a history of gastroesophageal reflux. Other reported physiological reactions included dizziness (n=1, 0.7%) and altered taste (n=1, 0.7%), the latter of which was described by parents as the patient not having an appetite or spitting out food.

Two allergic-like reactions in 2 patients (1.3%) were reported on the 24-h follow-up call. A single moderate severity allergic-like reaction of wheezing (0.7%) was reported after the 2-h observation window in a patient with a history of tuberous sclerosis, seizures and cardiac rhabdomyoma who was getting an abdominal MRI. This patient had, however, also undergone sedation with rocuronium, sevoflurane and nitrous oxide and had received dexamethasone and sugammadex. No other reactions were reported in this patient and no treatment was required. One mild allergic-like reaction, sneezing, was reported in another patient who had undergone general anesthesia and sedation with vecuronium. The onset of the sneezing was after the 2-h observation period and occurred in addition to nausea, vomiting and transient warmth. Neither of these reactions was solely attributable to gadoterate meglumine.

No reports of headache or paresthesia were made, although, given the age group of the patients, this is not surprising as they would be unable to self-report those symptoms.

The large majority of patients (n=146, 97.3%) were sedated. All sedated patients received some form of pre-sedation drug, most commonly nasal versed. Deep sedation was obtained in one patient following nasal versed alone. Moderate sedation or general anesthesia (using a laryngeal mask airway or endotracheal tube) was performed using one or a combination of some of the following: propofol, vecuronium, rocuronium, cisatrocurium, sevoflurane, fentanyl and/or nitrous oxide. The majority of sedated patients received propofol either by itself (n=104, 71.2%) or in combination with other agents (n=13, 8.9%). During induction, six sedated patients (4.1% sedated) received glycopyrrolate. Some patients also received either sugammadex (n=6; 4.1% sedated) or neostigmine (n=6; 4.1% sedated) as anesthesia reversal agents. In addition, 12 patients (8.2% sedated) were given

Table 3 Patient demographics

Number of patients	150
Age	Median: 12.1 months (range: 0.25–23.0 months)
Male	84 (56%)
Female	66 (44%)
Weight	Mean: 9.3 kg (range: 0.6–17.0 kg)
Indications for MRI	
Neurological	82%
Body	10%
Musculoskeletal	6.0%
Body/musculoskeletal	0.7%
Neurological/musculoskeletal	0.7%
Whole-body	0.7%
Mean dose of gadoterate meglumine (range; standard deviation)	1.85 mL (0.6–3.4 mL; 0.5)
Patients receiving sedation or anesthesia	146 (97.3%)

dexamethasone, a steroid during the exam, and one of those patients also received albuterol. All of the patients who received dexamethasone underwent general anesthesia with an endotracheal tube or laryngeal mask airway. Of the patients who received dexamethasone, three reported adverse reactions. One reported vomiting, one reported wheezing and one reported sneezing, transient warmth, nausea and vomiting. The one patient who reported only vomiting had also received a dose of ondansetron before the reversal of anesthesia.

No adverse reactions were reported in any of the four patients who underwent an MRI without sedation and received gadoterate meglumine. The single patient who was enrolled twice did not experience any adverse reactions.

Table 4 Reported adverse events

Number of adverse events (frequency)	34 in 23 patients (15.3%)
Gender	73.9% male; 26.1% female
Immediate	0
Within 2 h (% total patients)	2 (1.3%)
2–24 h after MRI (% total patients)	33 (14.7%)
Physiological reactions (% of adverse events)	32 (94.1%)
Vomiting (mild)	13
Transient flushing or warmth (mild)	8
Nausea (mild)	7
Dizziness (mild)	1
Altered taste (mild)	1
Allergic-like reactions (% of adverse events)	2 (5.9%)
Sneezing (mild)	1
Wheezing (moderate)	1

Discussion

The rate of adverse events for GBCAs is much lower than that of iodinated contrast agents and ranges from 0.07% to 2.4% [17, 21]. Most of these reactions are physiological with allergic-like reactions being even rarer at a reported frequency of 0.004–0.7% [17]. Children are believed to have even lower incidences of adverse events with iodinated contrast agents for CT compared to adults [22, 23]. However, there are fewer studies on adverse events following GBCAs in children, with even fewer in children younger than 2 years of age, and some of these studies are retrospective, which limits the ability to detect adverse events [17, 24]. In addition, most of these studies focused on the detection of immediate adverse events and did not follow patients for any extended period of time [12, 25–27]. While most severe symptoms and signs usually develop within the first 20 min after exposure to the contrast material, these symptoms may continue despite treatment or recur [21]. Delayed reactions are rare [17].

Our study was novel in that we monitored the patients for both immediate and delayed-onset adverse events and categorized them with regard to the time of onset. Only two other studies in pediatric patients receiving gadoterate meglumine performed any type of follow-up on patients. Emond and Brunelle [28] asked parents to self-report any adverse events within 24 h and Scala et al. [29] performed 24-h and 1-week follow-ups on patients. No parents self-reported any adverse events in the former study, while the latter study did not categorize all of the reported adverse events as immediate or delayed onset.

The overall frequency of adverse events in pediatric patients receiving gadoterate meglumine ranges from 0% to 28.9%. Chang and Pracros [25] performed the SECURE study, a prospective observational study in 1,631 pediatric

patients (0–18 years) with 106 of those patients younger than 2 years of age. These patients were only followed for 1 h post-injection, and only one adverse event was reported in a 2-year-old child, which was thought unlikely to be related to contrast agent [25]. Emond and Brunelle [28] performed a prospective observational study in 104 children younger than 18 months of age and reported no adverse events. Patients were monitored under close surveillance for at least 2 h following contrast administration. Scala et al. [29] performed a prospective study in 45 patients with a reported adverse event frequency of 28.9% in 13 patients in which only 1 adverse event (2.2%) was considered a result of gadoterate meglumine. This was a rash that occurred 8 h after receiving contrast and resolved within 5 days after receiving treatment. Patients in this study were initially observed between 2 and 4 h after contrast administration [29]. Briand et al. [30] studied 402 pediatric patients, including 26 patients younger than 2 years of age [26]. One 16-year-old developed a papule on the inside of the thigh thought to be related to gadoterate meglumine administration with a reported adverse event frequency of 0.25%. No adverse events were reported in patients 15 years of age or younger [30]. Neiss et al. [31] studied 305 patients younger than 18 years of age out of a total of 4,169 patients. Six of those patients were younger than 2 years of age. The overall rate of adverse events reported was 0.84% [31]. It is unknown how long patients were monitored following injection in both the Briand et al. [30] and Neiss et al. [31] studies. Maurer et al. [27] conducted a large post-marketing surveillance study on 84,621 patients, including 1,760 pediatric patients (ages 5 weeks–17 years), out of which 10 patients were younger than 2 years of age [26]. The patients were monitored for only 30–60 min following their MRI, and there was an overall adverse event frequency of 0.34% [27]. Ishiguchi and Takahashi [32] performed a post-marketing surveillance study on 3,444 patients receiving gadoterate meglumine. There were 41 pediatric patients in this cohort (age range: 1 month–14 years) with only 2 patients younger than 2 years of age. Outpatients were followed for 2 h onsite, and inpatients were followed for several days. No adverse events were reported in the pediatric patients, while the overall adverse event rate was 0.93% (32/3,444 patients) [32]. Forbes-Amrhein et al. [33] performed a retrospective study of multiple GBCAs in patients ages 0–17 years with a reported frequency of 0.2% adverse events in the subgroup of 12,012 administrations of gadoterate meglumine.

Most of the reported adverse events in our study were of mild intensity and physiological in nature, consistent with the most commonly reported adverse events in prior studies. The majority of adverse events were gastrointestinal-related (nausea, vomiting) or related to transient flushing/warmth. One mild and one moderate allergic-like reaction were reported in patients who had also received anesthesia. The patient with the moderate allergic-like reaction, wheezing, received rocuronium and sevoflurane, which can rarely cause bronchospasm, and sugammadex, which can cause wheezing [34–41].

The frequency of immediate adverse events in our study of 1.3% is similar to those previously reported in pediatric patients receiving gadoterate meglumine when only looking at those reactions occurring in the first 2 h. However, our overall rate of adverse events of 15.3%, including both immediate and delayed onset, is higher than most previously reported in the literature [25–33].

Since most of our patients experiencing adverse events also received concomitant sedation or anesthesia, it is possible that many, if not all, of the reported symptoms were related to the administered anesthesia medications. In addition, all but one patient experiencing adverse events underwent an MRI for a neurological indication. While this may simply be a result of the fact that most patients in this study underwent an MRI for neurological indication, it raises the possibility, given the predominance of reporting of nausea and vomiting, that some of these symptoms may be the result of the patients' underlying disease processes, although this theory was not investigated in this study. Similarly, since more than half of the patients reporting vomiting had a history of gastroesophageal reflux, it is difficult to distinguish whether the vomiting was a result of that, anesthesia or the contrast agent. As a result, none of the adverse events in this study can be directly attributed to gadoterate meglumine exposure.

Furthermore, since all but two of the reported adverse events occurred after the initial observation period and were reported on the 24-h follow-up phone call, it is possible that there is recall bias due to parents' vigilance in looking for symptoms to report, or from the power of suggestion as parents heard the list of possible adverse events during the phone call, thus overreporting them. It is also possible that the overall incidence of adverse events to GBCAs may be underestimated since most studies do not follow patients for any significant length of time after completion of the MRI exam.

Interestingly, while the overall patient population was evenly divided between male and female, the majority of the patients who reported adverse events were male. This observation has not, to our knowledge, been made in prior studies in pediatric patients; however, this may be because we have a higher number of adverse events compared to most prior pediatric studies, likely as a result of our extended period of observation. de Kerviler et al. [12] in a review of 25 years of gadoterate meglumine use, which includes many of the studies summarized above, reported a higher incidence of adverse drug reactions in females (61.9%) although the majority of these patients were adults. Similarly, McDonald et al. [13], in their retrospective study on adverse events using various GBCAs, report a female predominance of both allergic-like and physiological reactions in addition to observing that allergic-like reactions occurred more frequently in inpatients and in patients undergoing an MRI for body indication. This

female predominance of adverse reactions has also previously been reported following administration of iodinated contrast material [42]. Further research in this area is warranted to see if there is, in fact, a pediatric male predominance to adverse events with GBCAs.

Our study does have some limitations. First, given the large number of patients who received sedation/anesthesia, it is difficult to determine whether adverse events are solely the result of gadoterate meglumine. However, this is an inherent limitation in studying pediatric patients, who often require sedation/anesthesia for MRI examinations, especially those younger than 2 years of age. Second, it is possible that the overall number of reported adverse events may have been reduced since six patients received dexamethasone, a steroid, during sedation. In addition to reducing nausea and vomiting, given its anti-inflammatory properties, it may have prevented or reduced any immediate adverse drug reactions in this group. Another limitation of the study is the potential variability in observations that was introduced as different individuals were performing the assessments at the three different time points. While one patient was enrolled twice, the addition of this patient a second time did not statistically alter the study results.

Conclusion

No adverse events were directly attributed to gadoterate meglumine exposure. Only two adverse events were reported to have occurred in the 2-h observation period with the rest reported on the 24-h follow-up phone call, neither of which was directly attributable to gadoterate meglumine exposure. The higher reported rate of adverse events in this study may be related to concomitant sedation/anesthesia as well as to overreporting from parents on the 24-h follow-up questionnaire; however, since few studies follow patients beyond the time of injection, further studies looking at delayed-onset adverse events are warranted. The study confirms a good safety profile for gadoterate meglumine in this very sensitive population.

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Compliance with ethical standards

Conflicts of interest Dr. Farmakis has research grants from GE Healthcare and Guerbet, LLC, and is a consultant for GE Precision Healthcare, LLC.

References

1. Xia D, Davis RL, Crawford JA, Abraham JL (2010) Gadolinium released from MR contrast agents is deposited in brain tumors: in situ demonstration using scanning electron microscopy with energy dispersive X-ray spectroscopy. Acta Radiol 51:1126–1136
2. McDonald RJ, McDonald JS, Kallmes DF et al (2015) Intracranial gadolinium deposition after contrast-enhanced MR imaging. Radiology 275:772–782
3. Kanda T, Ishii K, Kawaguchi H et al (2014) High signal intensity in the dentate nucleus and globus pallidus on unenhanced T1-weighted MR images: relationship with increasing cumulative dose of a gadolinium-based contrast material. Radiology 270:834–841
4. Kanda T, Fukusato T, Matsuda M et al (2015) Gadolinium-based contrast agent accumulates in the brain even in subjects without severe renal dysfunction: evaluation of autopsy brain specimens with inductively coupled plasma mass spectroscopy. Radiology 276:228–232
5. Kanda T, Osawa M, Oba H et al (2015) High signal intensity in dentate nucleus on unenhanced T1-weighted MR images: association with linear versus macrocyclic gadolinium chelate administration. Radiology 275:803–809
6. White GW, Gibby WA, Tweedle MF (2006) 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. Investig Radiol 41:272–278
7. Maximova N, Gregori M, Zennaro F et al (2016) Hepatic gadolinium deposition and reversibility after contrast agent-enhanced MR imaging of pediatric hematopoietic stem cell transplant recipients. Radiology 281:418–426
8. Flood TF, Stence NV, Maloney JA, Mirsky DM (2017) Pediatric brain: repeated exposure to linear gadolinium-based contrast material is associated with increased signal intensity at unenhanced T1-weighted MR imaging. Radiology 282:222–228
9. Fraum TJ, Ludwig DR, Bashir MR, Fowler KJ (2017) Gadolinium-based contrast agents: a comprehensive risk assessment. J Magn Reson Imaging 46:338–353
10. Endrikat J, Dohanish S, Schleyer N et al (2018) 10 years of nephrogenic systemic fibrosis: a comprehensive analysis of nephrogenic systemic fibrosis reports received by a pharmaceutical company from 2006 to 2016. Investig Radiol 53:541–550
11. Behzadi AH, Zhao Y, Farooq Z, Prince MR (2018) Immediate allergic reactions to gadoliniums-based contrast agents: a systematic review and meta-analysis. Radiology 286:471–482
12. de Kerviler E, Maravilla K, Meder JF et al (2016) Adverse reactions to gadoterate meglumine: review of over 25 years of clinical use and more than 50 million doses. Investig Radiol 51:544–551
13. McDonald JS, Hunt CH, Kolbe AB et al (2019) Acute adverse events following gadolinium-based contrast agent administration: a single-center retrospective study of 281,945 injections. Radiology 292:620–627
14. Port M, Idée JM, Medina C et al (2008) Efficiency, thermodynamic and kinetic stability of marketed gadolinium chelates and their possible clinical consequences: a critical review. Biometals 21:469–490
15. Idée JM, Port M, Robic C et al (2009) Role of thermodynamic and kinetic parameters in gadolinium chelate stability. J Magn Reson Imaging 30:1249–1258
16. Guerbet LLC (2018) Dotarem (gadoterate meglumine) [package insert]. Princeton
17. Aldrete JA (1995) The post-anesthesia recover score revisited. J Clin Anesth 7:89–91
18. American College of Radiology (2018) ACR Manual on Contrast Media. Version 10.3. https://www.acr.org/ClinicalResources/Contrast-Manual. Accessed 25 Sept 2019
19. Microsoft (2016) Excel Version 1.5 [computer software]
20. Maple Tech International, LLC (2008–2019). Calculator.net [computer software]. https://www.calculator.net/standard-deviation-calculator.html. Accessed 25 Sept 2019

21. Dillman JR, Trout AT, Davenport MS (2018) Allergic-like contrast media reaction management in children. Pediatr Radiol 48:1688–1694
22. Dillman JR, Strouse PJ, Ellis JH et al (2007) Incidence and severity of acute allergic-like reactions to i.v. nonionic iodinated contrast material in children. AJR Am J Roentgenol 188:1643–1647
23. Katayama H, Yamaguchi K, Kozuka T et al (1990) Adverse reactions to ionic and nonionic contrast media: a report from the Japanese committee on the safety of contrast media. Radiology 175:621–628
24. Dillman JR, Ellis JH, Cohan RH et al (2007) Frequency and severity of acute allergic-like reactions to gadolinium-containing I.V. contrast media in children and adults. AJR Am J Roentgenol 189:1533–1538
25. Chang DH, Pracros JP (2019) Safety of gadoterate meglumine in over 1600 children included in the prospective observational SECURE study. Acta Radiol 60:1450–1456
26. Balassy C, Roberts D, Miller SF (2015) Safety and efficacy of gadoteric acid in pediatric magnetic resonance imaging: overview of clinical trials and post-marketing studies. Pediatr Radiol 45:1831–1841
27. Maurer M, Heine O, Wolf M et al (2012) Tolerability and diagnostic value of gadoteric acid in the general population and in patients with risk factors: result in more than 84,000 patients. Eur J Radiol 81:885–890
28. Emond S, Brunelle F (2011) Gd-DOTA administration at MRI in children younger than 18 months of age: immediate adverse reactions. Pediatr Radiol 41:1401–1406
29. Scala M, Koob M, de Buttet S et al (2018) A pharmacokinetics, efficacy, and safety study of gadoterate meglumine in pediatric subjects aged younger than 2 years. Investig Radiol 53:70–79
30. Briand Y, Neiss AC, Vitry A (1992) 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, 128
31. Neiss AC, Le Mignon MM, Vitry A, Caille JM (1991) Efficacy and safety of DOTA-Gd from a European multicenter survey. Rev Im Med 3:383–387
32. Ishiguchi T, Takahashi S (2010) 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 10:133–145
33. Forbes-Amrhein MM, Dillman JR et al (2018) Frequency and severity of acute allergic-like reactions to intravenously administered gadolinium-based contrast media in children. Investig Radiol 53:313–318
34. Choi WJ, Choi SI, Mok JM et al (2010) Recurrent unilateral lung ventilation disorder in a patient that experienced rocuronium-induced anaphylactic bronchospasm during laparoscopic rectal surgery. Korean J Anesthesiol 59:275–278
35. Morimoto Y, Satake S, Kamitani A et al (2018) Rocuronium anaphylaxis in a 7-year-old boy during the induction of anesthesia. Immunol Med 41:85–88
36. Kim JM, Lee JH, Lee HJ, Koo BN (2013) Comparison of emergence time in children undergoing minor surgery according to anesthetic: desflurane and sevoflurance. Yonsei Med J 54:732–738
37. Bedirli N, Işik B, Bashiri M et al (2018) Clinically suspected anaphylaxis induced by sugammadex in a patient with weaver syndrome undergoing restrictive mammoplasty surgery. Clin Case Report 97:e9661
38. Çolak A, Yilmaz E, Kiray BK (2018) Sugammadex-induced hypersensitivity reaction in a pediatric patient. Turk J Anaesthesiol Reanim 46:66–68
39. Maruishi Pharmaceutical Company. Ultane (sevoflurane) [package insert]. U.S. Food and Drug Administration website. Revised April 2017. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/020478s030lbl.pdf. Accessed 16 Dec 2019
40. Merck & Co., Inc. (2015) Bridion (sugammadex) [package insert]. U.S. Food and Drug Administration https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/022225lbl.pdf. Accessed 16 Dec 2019
41. Teva Pharmaceutical Ind. Ltd. (2008) Rocuronium bromide [package insert]. U.S. Food and Drug Administration https://www.accessdata.fda.gov/drugsatfda_docs/label/2008/078717s000lbl.pdf. Accessed 16 Dec 2019
42. Kopp AF, Mortele KJ, Cho YD et al (2008) Prevalence of acute reactions to iopromide: postmarketing surveillance study of 74,717 patients. Acta Radiol 49:902–911