Pediatr Radiol (2011) 41:1401–1406
DOI 10.1007/s00247-011-2167-3

ORIGINAL ARTICLE

Gd-DOTA administration at MRI in children younger than 18 months of age: immediate adverse reactions

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Received: 28 June 2010 / Revised: 7 April 2011 / Accepted: 14 May 2011 / Published online: 24 July 2011

Abstract
Background There is a paucity of evidence with regard to the safety of contrast medium administration at MRI in neonates and infants.
Purpose To assess immediate adverse reactions in children younger than 18 months of age during routine clinical utilization of gadoteric acid (Gd-DOTA) in a cohort of patients with nonselected indications.
Materials and methods One hundred and four neonates and infants were enrolled in a postmarketing survey with Gd-DOTA (Dotarem, Guerbet, Roissy, France) from a single pediatric hospital. A standardized questionnaire was used to collect the patient information.
Results All included children, ages 3 days to 18 months, received one injection of Gd-DOTA (volume 0.6–4 ml). No immediate adverse event was reported.
Conclusion This postmarketing study involving neonates and infants suggests a favorable safety profile of Gd-DOTA in routine practice.

Keywords Neonate · Infant · Gd-DOTA · Safety

Introduction

Although image contrast in unenhanced MRI is much more flexible than in other clinical imaging techniques, the diagnosis of many abnormalities requires the use of a contrast medium (CM) that can enhance the difference between normal and abnormal tissues by modifying their intrinsic relaxivities [1]. The performance of MRI examinations is improved by using paramagnetic CM, usually a gadolinium (Gd) compound. The need for paramagnetic MRI CM has become widely recognized, also in neonates and young children [2]. Although routinely used in clinical practice, these compounds can be associated with adverse side effects that can be particularly severe in patients with impaired kidney function [3]. Gd use is associated with the development of a serious, potentially fatal, adverse reaction: nephrogenic systemic fibrosis (NSF) in renally impaired patients [4–6]. Until now, very few pediatric cases of NSF have been reported [7]. Nevertheless, there is insufficient data to suggest that NSF is less likely to occur in children than in adults with similarly significant renal disease. Dotarem (gadoteric acid, Gd-DOTA), is a well-known macrocyclic Gd chelate and is the most stable of the commonly used paramagnetic contrast agent for MRI examination including magnetic resonance angiography (MRA) [8]. Gd-DOTA is marketed in more than 70 countries worldwide and is approved for three main indications: imaging of intracranial and spinal disorders, whole-body imaging in adults and children, and angiography in adults. The use of Gd-DOTA by the intravenous route at MRI, including its use in children, has been described [9–11].

As few safety data are available for children and because intravenous injection is considered technically difficult in this patient population, the purpose of this study was to gain further evidence that Gd-DOTA administration is safe in neonates and infants younger than 18 months of age.

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Materials and methods

Study design

This was an observational, non-randomized, single-center, open-label study. The aim of this postmarketing study was to gain further knowledge on the safety of Gd-DOTA at MRI in unselected children less than 18 months of age, in routine clinical practice.

In this noninterventional study, no ethics approval or parental consent was required from a regulatory point of view. Children were referred by their pediatricians on clinical indication only, and their participation in the study did not result in any change in clinical management.

Before the injection of the contrast agent, the procedure was explained to the parents. The information was given verbally and included the indications, possible side effects and adverse reactions (according to the package insert). The potential need for sedation was also explained.

Patients

Children younger than 18 months old, who were scheduled to undergo a routine MRI examination that per local protocol required intravenous administration of Gd, were eligible for this study. Children with contraindications to Gd, as defined by the regulatory licensing specifications, were not given Gd and were not included in the study. The following variables were recorded for each child: demographics (age, sex, weight), risk factors (prior contrast agent reaction and other known risk factors, i.e. renal failure, cardiac failure, coronary artery disease, autoimmune disease, dehydration and compromised general condition), premedication regimen, type of examination, route of injection, volume of Gd-DOTA, image quality, diagnostic contribution, therapeutic decision and overall tolerance to contrast agent.

MRI and imaging procedures

The Gd-DOTA-enhanced MRI examination was performed after an intravenous bolus of Gd-DOTA (ionic macrocyclic contrast agent) at 0.1 mmol/kg (0.2 ml/kg), using a manual injection technique. The injected volume of Gd-DOTA per child ranged from 0.6 ml in a newborn (male, 3 days, 3 kg) to 4 ml in the heaviest/oldest child (female, 18 months, 20 kg), with a median of 2 ml, followed by the same volume of normal saline flush.

Imaging was performed using a 1.5-Tesla GEMS Signa, with dedicated phased-array coils.

Children could potentially fall asleep during the examination but, if necessary, they were sedated just before imaging. Children with contraindications to chloral hydrate (severe renal failure, cardiac disorders, respiratory failure, severe hepatic insufficiency, active hydrocephalus) and children with intracranial hypertension and swallowing disorders were not included.

Children were laid in a supine position and immobilized with elastic bands during the imaging procedure. The infant's head was immobilized by molded foam, which was placed around the head during the imaging procedure. A pediatrician experienced in resuscitation was always available. A trained and competent neuroanesthesist was also available for advice.

Heart rate and peripheral oxygen saturation were monitored continuously during imaging.

Some abnormalities, such as vascular and/or lymphatic malformation and coccygeal fistulae, needed fat saturation.

According the age of the child and the area explored, the MRI protocol included the following sequences: fast spin-echo (FSE) T1-weighted imaging (TR=440–600 ms, TE=10–21 ms, section thickness=3/0.3 to 5/0.5 mm, matrix=512 × 224, NEX=4, FOV=18 × 18 or 24 × 18 cm). T2-weighted spin-echo sequences (TR/TE/NEX=3,800/22/1, matrix=256 × 256).

Primary outcome: safety assessment

Safety assessments included adverse events that occurred during the trial. Children were kept in the hospital under close surveillance for at least 2 h after the Gd-DOTA injection. Nature of event, time of onset, duration, intensity (mild, moderate, severe), causality (probable, doubtful, excluded) and outcome (favorable with or without treatment, recovery with sequela, death) of the event were recorded.

Parents were informed that due to the sedation protocol their child could sleep a long time after hospital discharge.

Parents were given an information sheet on the premedication drugs given, which included an emergency phone number. Parents were asked to call us if any adverse events were noticed during the first 24 h after hospital discharge.

Secondary outcome: image quality

Image quality was assessed with a five-point scale (excellent, good, average, poor, nil), diagnostic contribution with a five-point scale (definitely normal, probably normal, indecisive, definitely abnormal, probably abnormal), and consequence on the therapeutic decision defined according to four items (choice of initial treatment, continuation of treatment, change of treatment, no treatment).

All images obtained during the trial were read subjectively by one experienced reader (S.E.).

Statistical analysis

All data obtained for the children in the study were analyzed using standard statistical methods, such as frequency tables and descriptive statistical parameters. Data analysis was performed with SAS (version 8.2; SAS Institute, Cary, N.C., USA).

Results

Indications

As shown in Table 1, in the majority of children (50.8%), the contrast-enhanced MRI study was performed for etiological diagnosis (infection with meningeal enhancement, vascular and/or lymphatic malformations [hemangiomas, hemolymphangiomas, cystic lymphangiomas], coccygeal fistula, dysraphia, Sturge-Weber malformation with facial angioma, presence of tumoral lesion and characteristic of tumor), followed by 31.7% of children in which MRI studies were performed for diagnostic extension, i.e. metastasis (multiple localization), hemangioma (intra-orbital extension or bone extension), vascular and/or lymphatic malformation (vascular or cystic anomaly), infection (abscess), dermic fistula associated with dermic angioma (intradural extension). Also, in 11.1% in children, MRI was performed for postoperative control and in 6.3% of children for follow-up therapy.

All these types of indications were representative of the usual population examined in our department.

Sedation

Premedication was administered to 77 children (74.0%) and sometimes the youngest newborns needed only breast-feeding before examination. Premedicated patients received pentobarbital, sometimes followed by rectal chloral hydrate.

Demography and baseline characteristics

The 104 children enrolled ranged in age from 3 days to 18 months (mean age 8.1 months; median age 8.0 months), with a mean weight of 8.1 kg. A total of 58 children (55.8%) were male and 45 children (43.3%) were female (gender for one child was missing). No child reported risk factors or a history of prior contrast agent reactions.

Demography and baseline characteristics data are shown in Table 2.

Safety

All children enrolled in this study received one injection of Gd-DOTA contrast agent (volume from 0.6 to 4 ml). No adverse event was reported in these children after Gd-DOTA injection.

Table 1 Indications for Gd-DOTA-enhanced MRI

Indication group	Children (percent of total)	List of findings in abnormal scans
Primary diagnosis	64 (50.8%)	- Infection with meningeal enhancement
		- Vascular and/or lymphatic malformations (hemangiomas, hemolymphangiomas, cystic lymphangiomas)
		- Coccygeal fistulae, dysraphia
		- Sturge-Weber malformation in facial angioma
		- Presence of tumoral lesions
Evaluation of the extension of a known condition	40 (31.7%)	- Metastasis, multiple localisation
		- Hemangioma (intra-orbital extension or bone extension)
		- Vascular and/or lymphatic malformation (vascular or cystic anomaly)
		- Infection (abscess)
		- Dermal fistula associated with dermal angioma (intradural extension)
Postoperative control	14 (11.1%)	- Tumor (recurrent, residual)
		- Dermal fistula
Follow-up	8 (6.3%)	- Infection
		- Tumor
		- Dysraphism

Table 2 Demography and baseline characteristics

Variable	Total (n=104)
Age (months): mean ± SD (min-max), median	8.1 ± 5.2 (0.1-18), 8.0
Weight (kg): mean ± SD (min-max), median	8.1 ± 3.0 (3–20), 8.0
Sex[1] (n, %)	
male	58 (55.8%)
female	45 (43.3%)
Children with reported previous reactions to contrast agent	0
Children with other known risk factors	0

[1] *The sex of one child was not indicated*

Image quality

Image quality was rated as "excellent/good" for Gd-DOTA-enhanced MRI in 102 (98.0%) children. Diagnostic contribution was assessed as optimal (definitely abnormal/normal diagnosis) in 101 children (97.1%). The examination with Gd-DOTA MRI confirmed the choice of initial treatment in 50 children (48.1%).

Discussion

MRI is increasingly used in the evaluation of various diseases such as neurological, musculoskeletal, abdominal, mediastinal and cardiovascular pathologies in children [8–17]. Intravenous administration of Gd as a contrast agent in MRI has been widely used worldwide, and Gd indications are commonplace and well accepted for tumor staging and diagnosis of infection, inflammation, necrosis, ischemia, thromboembolic conditions and for MRA and MR urography [18]. Its safety and tolerance have been well established in extensive clinical trials or postmarketing studies in adult and children at doses of 0.1 and 0.3 mmol/kg, with low incidence of minor side effects [19]. Adverse events in association with the use of Gd-DOTA are usually mild to moderate in intensity and transient in nature. Sensations of heat, cold and/or pain at the injection site are the most frequently observed reactions. Shortly after the product commercialization, one noncomparative postmarketing study was carried out on a pediatric cohort with various indications [20]. Our study, conducted in France, included 402 patients (81% of the children were 15 years old or younger and 6.5% were 2 years old or younger). Our results confirmed the advantages of Gd-DOTA injection in children as well as its favorable safety profile in terms of immediate adverse reactions. This is in line with a postmarketing surveillance study in more than 24,000 adult and children (2.7% of the children were 18 years old or younger and 0.008% were 2 years old or younger) [19]. The study, which included a significant proportion (20%) of patients with risk factors for adverse reaction to contrast agents, confirmed the diagnostic efficacy and safety of intravenous injections of Gd-DOTA in patients who underwent routine MRI examinations. Out of 24,000 patients, the overall incidence of reported adverse events was only 0.4%: one serious adverse event (anaphylactic shock) occurred in an adult patient and no adverse event in children younger than 2 years of age.

MRI protocols in children are usually similar to those in adults regarding the type of sequences (e.g., T1-weighted sequences after Gd injection with or without fat saturation). However, for high-quality MR images in children having various diseases, we should select optimal pulse sequence and optimize many imaging parameters, such as FOV, slice thickness and gap, number of acquisitions, etc. Some abnormalities, such as vascular and/or lymphatic malformation and coccygeal fistulae, need fat saturation to increase the enhancement. In a pediatric population, safety and patient tolerance are especially important considerations; thus, the use of a safer contrast agent might be considered of benefit.

Our study was conducted to evaluate the safety (immediate adverse reactions) of Gd-DOTA injection when administered intravenously in neonates and infants younger than 18 months of age using the standard dose of 0.1 mmol/kg.

No adverse events occurred in this study; the adverse events (cutaneous allergic reactions) usually found in adult patients were not seen in the children included in our study; also, some minor adverse events were not assessable due to premedicated children.

Shellock et al. [21] compared the safety and tolerability of Gd-BOPTA and gadopentetate dimeglumine (Gd-DTPA) in 174 children (mean age 8.6 years, range: 2 days to 17 years for Gd-BOPTA; mean age 4.7 years, range: 7 months to 17 years for Gd-DTPA) undergoing MRI for suspected central nervous system diseases.

In this trial, a total of 24 (14%) children experienced 34 adverse events after administration of study agent, including 11 (12.9%) children who were given Gd-BOPTA and 13 (14.6%) children who were given Gd-DTPA (P=0.75). For both the Gd-BOPTA and Gd-DTPA groups, fever was the most frequently reported adverse event (three children per group). Three children had adverse event considered to be serious, two in the Gd-BOPTA group (worsening of

vomiting, hypoxia), and one in the Gd-DTPA group (fever). None of the events was considered to be related to contrast agent administration, except the case of worsening of vomiting, which was considered to be possibly related to Gd-BOPTA administration.

Although in our study NSF was not prospectively evaluated due to a short safety follow-up, no case has subsequently been brought to our attention. Until now in the literature, all confirmed cases of NSF have been reported in patients with chronic kidney disease (CKD) with estimated glomerular filtration rates (eGFR) <60 ml/min per 1.73 m^2 [7]. Patients at risk also include children with known or suspected CKD, as well as newborns and infants with renal immaturity or congenital cardiopathy.

The pathophysiology of NSF remains unknown [5] and because NSF does not develop in all patients with renal impairment exposed to Gd-CM, additional cofactors might be involved in the pathophysiology of NSF [7]. Proinflammatory events, including thromboembolic events, surgical interventions, systemic infections and diseases associated with hypercoagulability, have been reported to increase the risk of developing NSF [22, 23]. Metabolic acidosis and high levels of erythropoietin have also been reported to be associated with NSF development [22]. Transmetallation has also been considered as a cofactor [24].

Anyway, it has been suggested that both the chemical stability of a particular chelate (cyclic compounds are more stable than linear ones in vitro) and the dose administered are risk factors for triggering NSF [7].

Otherwise, some risk factors contribute to a higher incidence of adverse reactions when contrast agents are used. As part of risk management, standard precautions are necessary (e.g., identification of allergic predispositions).

Our study showed that in the youngest newborns breast-feeding was sometimes enough for sedation. Immobilization with elastic bands may enable MRI in some neonates and small infants. Immobilization techniques and sedation guaranteed a sufficient time slot for high-quality investigations in children younger than 18 months of age, and allowed a practical and efficient use of our MR unit.

We believe that our data are of significant clinical and research utility for centers assessing children with central nervous system disorders by MRI.

Possible limitations of such studies are the small number of included patients and technical difficulties using MRI in children. Clinical trials in children are more challenging than those in adults. Recently, to facilitate the development and availability of medicines for children ages 0–17 years and to ensure that medicines for use in children are of high quality, ethically researched and authorized appropriately, a new pediatric regulation concerning clinical trial performance entered into force in the European Union on 26 January 2007.

Conclusion

Our results suggest that immediate adverse effects are negligible following intravenous administration of Gd-DOTA in neonates and infants younger than 18 months of age who are undergoing MRI on clinical indication, and when applying the regulatory-required screening for contra-indications to Gd. Although difficult to conduct, more extensive clinical studies are warranted to assess long-term safety.

Acknowledgments This study was partially supported by, and data analysis was performed by, the Guerbet group, Roissy, France. The authors have no conflicts of interest that are directly relevant to the contents of this study.

References

1. Burtea C, Laurent S, Vander Elst L et al (2008) Contrast agents: magnetic resonance. Handb Exp Pharmacol 185:135–165
2. Hanquinet S, Christophe C, Greef DD et al (1996) Clinical evaluation of gadodiamide injection in paediatric MR imaging. Pediatr Radiol 26:806–810
3. Sadowski EA, Bennett LK, Chan MR et al (2007) Nephrogenic systemic fibrosis: risk factors and incidence estimation. Radiology 243:148–157
4. Grobner T (2006) Gadolinium—a specific trigger for the development of nephrogenic fibrosing dermopathy and nephrogenic systemic fibrosis? Nephrol Dial Transplant 21:1104–1108
5. Altun E, Semelka RC, Cakit C (2009) Nephrogenic systemic fibrosis and management of high-risk patients. Acad Radiol 16:897–905
6. Janus N, Launay-Vacher V, Karie S et al (2010) Prevalence of nephrogenic systemic fibrosis in renal insufficiency patients: results of the finest study. Eur J Radiol 73:357–359
7. Mendichovszky IA, Marks SD, Simcock CM et al (2008) Gadolinium and nephrogenic systemic fibrosis: time to tighten practice. Pediatr Radiol 38:489–496
8. Morcos SK (2008) Extracellular gadolinium contrast agents: differences in stability. Eur J Radiol 66:175–179
9. Herve-Somma CM, Sebag GH, Prieur AM et al (1992) Juvenile rheumatoid arthritis of the knee: MR evaluation with Gd-DOTA. Radiology 182:93–98
10. Bonnerot V, Sebag G, de Montalembert M et al (1994) Gadolinium-DOTA enhanced MRI of painful osseous crises in children with sickle cell anemia. Pediatr Radiol 24:92–95
11. Ducou le Pointe H, Haddad S, Silberman B et al (1994) Legg-Perthes-Calve disease: staging by MRI using gadolinium. Pediatr Radiol 24:88–91
12. Hermans R (2006) Head and neck cancer: how imaging predicts treatment outcome. Cancer Imaging 6:S145–153
13. Hsu WC, Loevner LA, Karpati R et al (2005) Accuracy of magnetic resonance imaging in predicting absence of fixation of head and neck cancer to the prevertebral space. Head Neck 27:95–100
14. Bartels U, Shroff M, Sung L et al (2006) Role of spinal MRI in the follow-up of children treated for medulloblastoma. Cancer 107:1340–1347

15. Kobayashi S, Hayakawa K, Nakane T et al (2009) Visualization of intraneural edema using gadolinium-enhanced magnetic resonance imaging of carpal tunnel syndrome. J Orthop Sci 14:24–34
16. Drape JL, Thelen P, Gay-Depassier P et al (1993) Intraarticular diffusion of Gd-DOTA after intravenous injection in the knee: MR imaging evaluation. Radiology 188:227–234
17. Willinek WA, Schild HH (2008) Clinical advantages of 3.0 T MRI over 1.5 T. Eur J Radiol 65:2–14
18. Riccabona M, Simbrunner J, Ring E et al (2002) Feasibility of MR urography in neonates and infants with anomalies of the upper urinary tract. Eur Radiol 12:1442–1450
19. Herborn CU, Honold E, Wolf M et al (2007) Clinical safety and diagnostic value of the gadolinium chelate gadoterate meglumine (Gd-DOTA). Invest Radiol 42:58–62
20. Briand Y, Neiss AC, Vitry A (1992) Efficacy and safety of the macrocyclic complex Gd-DOTA in children: results of a multicentre study. In: 29th congress of the European Society of Pediatric Radiology, Budapest: R12.
21. Shellock FG, Parker JR, Pirovano G et al (2006) Safety characteristics of gadobenate dimeglumine: clinical experience from intra- and interindividual comparison studies with gadopentetate dimeglumine. J Magn Reson Imaging 24:1378–1385
22. Kuo PH, Kanal E, Abu-Alfa AK et al (2007) Gadolinium-based MR contrast agents and nephrogenic systemic fibrosis. Radiology 242:647–649
23. Grobner T (2008) Prischl FC (2008) Patient characteristics and risk factors for nephrogenic systemic fibrosis for gadolinium exposure. Semin Dial 21:135–139
24. Idee JM, Port M, Dencausse A et al (2009) Involvement of gadolinium chelates in the mechanism of nephrogenic systemic fibrosis: an update. Radiol Clin N Am 47:855–869