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Safety of gadoterate meglumine in over 1600 children included in the prospective observational SECURE study

Chang De-Hua[1] and Pracros Jean-Pierre[2]; on behalf of the SECURE study group

Abstract

Background: To date, few data on the safety profile of gadoterate meglumine in pediatric patients are available.

Purpose: To assess the safety profile of gadoterate meglumine in routine practice, to detect any case of nephrogenic systemic fibrosis (NSF) suspicion and to collect efficacy data.

Material and Methods: The pediatric population of the observational SECURE study comprised 1631 patients scheduled for contrast-enhanced magnetic resonance imaging (MRI) with gadoterate meglumine (dose: 0.1 mmol/kg). Risk factors, MRI types and immediate adverse events (AEs) were systematically recorded. Patients with moderate to severe renal impairment were followed up for at least 3 months for detection of any NSF suspicion. Efficacy was assessed by the on-site radiologist in terms of image quality and ability to come to diagnosis.

Results: The population included 106 children (6.5%) aged <2 years, 815 (50.0%) aged 2 to <12 years and 710 (43.5%) aged 12 to <18 years, with a mean (± SD) age of 10.2 (± 4.9) years. Central nervous system exploration was the most frequent MRI type (80.4%) and main risk factors were any stage of renal insufficiency (9.8%) and allergies (5.2%). Only one AE (vomiting) that was deemed doubtfully related to gadoterate meglumine was observed. No suspicions of NSF were reported. Good to very good image quality was obtained for 98.4% of pediatric patients and diagnosis was established in 99.6% of cases.

Conclusion: This study confirmed the good safety profile of gadoterate meglumine in routine practice in a large pediatric population. The study is registered on https://clinicaltrials.gov/ with the identifier NCT01523873.

Keywords
Gadoterate meglumine, safety, pediatric, NSF, GBCA, MRI

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Introduction

Gadoterate meglumine is a gadolinium (Gd)-based contrast agent (GBCA) for magnetic resonance imaging (MRI), marketed in numerous countries worldwide since 1989. This contrast agent is indicated for intravenous use with MRI in cerebral and spinal diseases, diseases of vertebral column, and other whole-body pathologies. Gadoterate meglumine is the only Gd chelate to be macrocyclic and ionic (1), and, consequently, has the highest thermodynamic (log $K_{therm} = 25.6$; log $K_{cond} = 19.3$) and kinetic stability (2).

Safety and efficacy of gadoterate meglumine have been evaluated in 50 clinical studies that demonstrated its diagnostic efficacy along with a very good safety profile (3). The most frequent (≥0.2%) adverse drug reactions reported were nausea (0.6%), headache (0.4%), injection site pain (0.4%), and injection site coldness (0.2%).

[1]Department of Radiology, University Clinic of Cologne, Cologne, Germany
[2]Department of Pediatric Radiology, Women-Mother and Child Hospital, Hospices Civils de Lyon, Lyon, France

Corresponding author:
Chang De-Hua, Uniklinik Köln, Institut für Diagnostische und Interventionelle Radiologie, Kerpener Straße 62, 50937 Köln, Germany.
Email: de-hua.chang@uk-koeln.de

Nephrogenic systemic fibrosis (NSF) is an important late adverse reaction to GBCAs, which occurs in patients with impaired renal function. This rare and highly disabling disease is an idiopathic skin condition characterized by thickening and hardening of the skin of the extremities and sometimes the trunk, with an increase in the number of dermal fibroblast-like cells. In 2006, two European teams reported a causal relationship between GBCAs administration and NSF (4,5). The time to onset of the symptoms ranges between a few days and a few years following exposure to the GBCA, but the majority of published cases occurred within 2 months (6). Since 2006, numerous further publications have emphasized the evidence of GBCAs triggering NSF, almost exclusively linear GBCAs (7–11). Among the different hypothesis proposed to explain the pathophysiology of NSF, the most widely supported is that in a context of renal impairment where the retention of a GBCA in the body is increased, the risk of the release of toxic free Gd ions is enhanced (particularly in less stable Gd chelates). According to guidelines of health authorities and medical societies [European Medicines Agency (EMA) 2010, Food and Drug Administration (FDA) 2010 and American College of Radiology 2013], gadoterate meglumine as a macrocyclic GBCA was classified with a low risk of NSF.

More recently, convincing evidences of gadolinium deposition in brain tissues following use of linear GBCAs have been highlighted (12), and, in July 2017, the EMA Pharmacovigilance Risk Assessment Committee has recommended the suspension of the marketing authorizations of linear GBCAs (gadodiamide, gadopentetic acid and gadoversetamide) in Europe and the limited use of gadoxetic acid and gadobenic acid for liver scans.

The use of GBCAs in high-risk populations, e.g., renal insufficient patients or pediatric patients, remains widely explored, even more since these unexpected safety issues. To date, safety profile and diagnostic efficacy of gadoterate meglumine in pediatric patients were essentially evaluated in four clinical studies ($n = 137$ children) and five post-marketing studies ($n = 2612$ children) (13). However, almost all of these studies were conducted in one single country, only one was European ($n = 305$ children) and one was international ($n = 38$ children), without assessment of NSF occurrence.

The SECURE study was a broad observational international study that aimed to assess the safety and efficacy of gadoterate meglumine for MRI examinations in routine practice. Soyer et al. recently published the results of the whole study population (14). The present article focuses on the pediatric subset and displays safety (frequency of immediate adverse events [AEs], NSF follow-up) and efficacy (image quality, ability to make a diagnosis) data in a large population of patients aged <18 years.

Material and Methods

The material and methods of the SECURE study were fully described by Soyer et al. (14). Briefly, this prospective, multicenter and observational study was conducted to assess the safety and efficacy of gadoterate meglumine for MRI examinations in routine practice. Pediatric patients (<18 years old) scheduled to undergo contrast-enhanced MRI with gadoterate meglumine were included in nine countries (Austria, China, France, Germany, India, Italy, Saudi Arabia, Spain, and the United Kingdom) between November 2008 and June 2013. Gadoterate meglumine (Dotarem®, Guerbet, Roissy CDG, France) was administered at the recommended dose of 0.1 mmol/kg of body weight (BW) (i.e., 0.2 mL/kg) by intravenous injection. Occurrence of AEs was assessed in all patients who received gadoterate meglumine. The nature, onset date, severity, outcome, and causal relationship to gadoterate meglumine of the AEs were assessed by the investigating radiologist during the MRI examination or the time of usual follow-up post-contrast agent administration (up to 1 h).

A specific follow-up of at least 3 months was planned for detection of any NSF suspicion in patients with moderate to severe renal impairment (estimated Glomerular Filtration Rate [eGFR] <60 mL/min/1.73 m^2). A specific form was completed by the physician who had prescribed the MRI examination and/or was in charge of the patient's follow-up. Date of follow-up, medical events since patient's inclusion, renal status and the answer (yes/no) to the question "is there any suspicion of NSF?" were collected. In case of positive answer, basis for suspicion was to be described according to a list of clinical diagnostic criteria and a biopsy could be decided by the medical team. Estimated creatinine clearance and eGFR were calculated with the Schwartz (15), and Modification of Diet in Renal Disease formulae, respectively.

Efficacy was evaluated by the on-site radiologist on contrast-enhanced images in terms of image quality, which was graded using a 5-point scale (very poor, poor, fair, good, and very good), and ability to make a diagnosis, which was assessed in a binary manner ("yes" or "no"). In case of inability to establish a diagnosis, the reason was recorded (technical problems, anxious patient or other).

Descriptive statistics were calculated for all variables.

Results

Demographic characteristics

A total of 1631 children were included in the SECURE study, accounting for 4.6% of the overall study population (35,499 patients). Children were enrolled mainly in India (47.8%), Germany (19.8%), and France (19.1%) (Table 1). Among the 1631 children, 872 (53.5%) were boys and 759 (46.5%) were girls. Mean ± SD age was 10.2 ± 4.9 years [range: <1 month–17 years] with 106 children (6.5%) aged <2 years, 815 (50.0%) aged 2 to <12 years and 710 (43.5%) aged 12 to <18 years. BMI ranged from 10.1 to 69.3 kg/m^2, with a mean ± SD of 21.4 ± 7.7 kg/m^2. The safety population included 1629 children who had received gadoterate meglumine; two children were not exposed to the contrast agent.

Overall, 159 children (9.8%) presented with renal insufficiency at any stage, with a mean ± SD eGFR of 74.1 ± 7.6 mL/min/1.73 m^2 (Table 2). No children with severe, end-stage renal insufficiency, dialysis or kidney transplantation were included. Only three children (aged 0.5 months, 1 year, and 7 years) were considered with moderate renal insufficiency (eGFR of 28, 55, and 46 mL/min/1.73 m^2, respectively) and followed up for at least 3 months. The other most frequently reported

Table 1. Number of pediatric patients per country (all included patients; $N = 1631$).

	n (%) patients per age class			
Country	<2 years *n* = 106	2 to <12 years *n* = 815	12 to <18 years *n* = 710	Total *n* = 1631
Austria	0 (0.0%)	6 (0.7%)	6 (0.8%)	12 (0.7%)
China	7 (6.6%)	62 (7.6%)	82 (11.5%)	151 (9.3%)
France	28 (26.4%)	128 (15.7%)	156 (22.0%)	312 (19.1%)
Germany	11 (10.4%)	138 (16.9%)	174 (24.5%)	323 (19.8%)
India	56 (52.8%)	459 (56.3%)	264 (37.2%)	779 (47.8%)
Italy	0 (0.0%)	5 (0.6%)	7 (1.0%)	12 (0.7%)
Saudi Arabia	1 (0.9%)	7 (0.9%)	7 (1.0%)	15 (0.9%)
Spain	3 (2.8%)	10 (1.2%)	9 (1.3%)	22 (1.3%)
United Kingdom	0 (0.0%)	0 (0.0%)	5 (0.7%)	5 (0.3%)

Percentages are calculated on the total number *n* in each column.

Table 2. Pre-existing risk factors per pediatric population (Safety population; $N = 1629$).

	n (%) patients per age class			
Risk factor	<2 years *n* = 106	2 to <12 years *n* = 814	12 to <18 years *n* = 709	Total *n* = 1629
Any stage of renal insufficiency	15 (14.2%)	113 (13.9%)	31 (4.4%)	159 (9.8%)
If yes, eGFR (mL/min/1.73 m^2)				
N	15	112	31	158
Mean (SD)	69.60 (14.05)	73.99 (6.69)	76.56 (5.54)	74.08 (7.64)
Median	75.00	75.00	75.00	75.00
Q1-Q3	65.00–75.00	75.00–75.00	74.00–78.00	74.00–75.00
Min - Max	28.0–89.0	46.0–89.0	68.0–88.0	28.0–89.0
Allergies	1 (0.9%)	34 (4.2%)	50 (7.1%)	85 (5.2%)
Bronchial asthma	1 (0.9%)	6 (0.7%)	12 (1.7%)	19 (1.2%)
Liver disorders	0 (0.0%)	9 (1.1%)	8 (1.1%)	17 (1.0%)
Heart insufficiency	0 (0.0%)	3 (0.4%)	5 (0.7%)	8 (0.5%)
Other cardiovascular disease	1 (0.9%)	3 (0.4%)	7 (1.0%)	11 (0.7%)
Diabetes mellitus	0 (0.0%)	2 (0.2%)	3 (0.4%)	5 (0.3%)
Previous reaction to contrast agents	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.1%)

eGFR: estimated glomerular filtration rate; SD: Standard deviation.

Percentages are calculated on number of available data for each risk factor (no more than 4 missing data per risk factor and age group with a maximum of 7 missing data out of 1629 patients per risk factor).

Table 3. Conditions of gadoterate meglumine administration per age class (Safety population; $N = 1629$).

	n (%) patients per age class			
	<2 years *n* = 106	2 to <12 years *n* = 814	12 to <18 years *n* = 709	Total *n* = 1629
Dose (mL/kg)				
Mean (SD)	0.34 (0.37)	0.24 (0.12)	0.21 (0.07)	0.24 (0.14)
Median	0.20	0.21	0.20	0.20
Min–Max	0.1–2.1	0.1–1.7	0.0–0.9	0.0–2.1
Dose (mL/kg) in class				
<0.18 mL/kg	18 (17.1%)	160 (20.0%)	150 (21.4%)	328 (20.4%)
0.18 to 0.22 mL/kg	47 (44.8%)	335 (41.8%)	348 (49.6%)	730 (45.4%)
>0.22 to 0.66 mL/kg	30 (28.6%)	300 (37.4%)	203 (28.9%)	533 (33.1%)
>0.66 mL/kg	10 (9.5%)	7 (0.9%)	1 (0.1%)	18 (1.1%)
Missing	1	12	7	20

SD: Standard deviation.
Percentages are calculated on number of available data for classes of doses.

pre-existing risk factors of the pediatric population were allergies (5.2%), bronchial asthma (1.2%), and liver disorders (1.0%) (Table 2). Only one child had previously experienced a reaction to contrast agents (the type of contrast agent was not specified).

MRI examination and conditions of gadoterate meglumine administration

Central nervous system exploration was the most frequent type of MRI (80.4%). Musculoskeletal system exploration was done for 11.1% of children, whole body (e.g., imaging of the liver, kidney...) for 6.7%, and other MRI types for 4.6%. MR angiography was performed in 0.8% of children, all aged ≥2 years.

Gadoterate meglumine was administered at a mean ± SD dose of 0.24 ± 0.14 mL/kg BW (i.e., 0.12 ± 0.07 mmol/kg), with a range from <0.1 to 2.1 mL/kg (Table 3). Children aged <2 years, from 2 to <12 years and from 12 to <18 years received a mean dose of 0.34, 0.24, and 0.21 mL/kg, respectively, median dose remaining consistent throughout age classes. The contrast agent was manually injected in 83.8% of cases.

Considering the dose of 0.2 mL/kg as the standard dose and 0.6 mL/kg as a triple dose, with a 10% non-significant variation as a reference, most pediatric patients (78.5%) received a dose consistent with the recommendations. A total of 328 children (20.4%) were administered less than the standard dose (<0.18 mL/kg) and 18 (1.1%) more than the triple dose (>0.66 mL/kg). Doses higher than the triple dose were more frequent in the youngest children, aged <2 years (9.5%), than in the two other age classes (0.9% and 0.1% for children from 2 to <12 years and 12 to <18 years, respectively).

A total of 121 children (7.6%) received premedication before MRI examination, mainly general anesthesia or sedatives. Premedication was performed according to local practice and was more often reported in Europe than in Asia. For the youngest cohort of children <2 years old ($n = 106$), premedication was reported for 55% of children in Europe and none of the children in China and India.

Safety—AEs and nephrogenic systemic fibrosis

Only one post-injection AE was reported in the pediatric population. This AE, vomiting of mild intensity, occurred in a 2-year old child with a brain tumor the same day as the MR examination and was assessed as doubtfully related to gadoterate meglumine. No concomitant drug was administered to the child and outcome of this AE was unknown.

No NSF suspicion was documented during the follow-up of the three children with at least moderate renal insufficiency (follow-up duration ranging from 3 months to more than 2 years).

Image quality

Image quality was evaluated by the on-site radiologist in 1568 pediatric patients, and was rated "very good" for the majority of children (52.5%) and "good" for 45.9% of children (Table 4). A "fair" image quality was noted for 20 patients (1.3%), while "poor" or "very poor" image quality was noted for only 4 patients (0.3%) and 1 patient (0.1%), respectively. Consequently, the diagnosis could be achieved in a large majority of patients (1534 patients, 99.6%).

No differences in image quality were observed between the three age classes, with 98.1%, 98.3% and 98.7% of children presenting with "good" to "very good" image quality for the <2 years, 2 to <12 years, and 12 to <18 years classes, respectively.

Table 4. Image quality in pediatric patients per age class (Efficacy population; $N = 1568$).

	n (%) patients per age class			
Image quality	<2 years $n = 104$	2 to <12 years $n = 792$	12 to <18 years $n = 672$	Total $n = 1568$
Very poor	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (0.1%)
Poor	0 (0.0%)	1 (0.1%)	3 (0.4%)	4 (0.3%)
Fair	2 (1.9%)	12 (1.5%)	6 (0.9%)	20 (1.3%)
Good	54 (51.9%)	427 (54.1%)	236 (35.3%)	717 (45.9%)
Very good	48 (46.2%)	349 (44.2%)	424 (63.4%)	821 (52.5%)
Missing	0	2	3	5

Discussion

The pediatric population of this study comprised 1631 patients from Asia, Europe, and the Middle East, with a mean age of 10.2 ± 4.9 years and 6.5% of children aged under 2 years. Despite the fact that the FDA has not approved most of the GBCAs for the use in children under 2 years of age, it is widely accepted and administered in various indications to enhance and delineate pathologic changes in different anatomic regions of the pediatric patients. As of today, gadobutrol and gadoterate meglumine are the only macrocyclic GBCAs approved for use in children under 2 years. The indications of contrast-enhanced MRI in the current study are consistent with MRI indications generally reported in pediatric populations (16–19).

The risk factors reported were representative of a pediatric cohort in general and the prevalences of renal insufficiency, allergies and liver disorders in the present population were similar to those shown in previous pediatric studies (20–22). The prevalence of bronchial asthma (1.2%) was low compared with the values reported in the International Study of Asthma and Allergies in Childhood (ISAAC) study, ranging from 2% to 32% among countries (23). However, prevalence of asthma is prone to wide variations depending on environmental factors (climate, air pollution), age, and international differences in the diagnosis of childhood asthma and access to healthcare (24).

Although the median dose value for each age group was between 0.20 and 0.21 mL/kg, corresponding to the recommended dose of 0.2 mL/kg BW, a large range of doses of gadoterate meglumine was employed. There was a trend towards higher doses in children aged <2 years (0.34 mL/kg BW) compared with children aged from 2 to <12 years (0.24 mL/kg BW) and children aged from 12 to <18 years (0.21 mL/kg BW). Indeed, doses of gadoterate meglumine higher than the triple dose were more frequent in the children aged <2 years (9.5%) than in the other age classes. Consistent with our findings, a higher mean dose of gadobutrol was also administered to the group of the youngest children (<2 years) compared with the two other age classes (2 to <7 years and 7 to <18 years) in the GARDIAN study (25). The higher doses in the youngest children might be due to the difficulty of adequate volume adjustment to low weight, to the use of standard injection protocols insufficiently adjusted to the patient weight, and to the wish to ensure radiological success in one single MRI procedure in this delicate population.

GBCAs have been frequently used in neonates and infants. In a survey conducted by Meng and Grosse-Wortmann (26), 52 out of the 55 responders (cardiologists and radiologists) who performed scans in neonates aged less than 1 week, reported the use of GBCAs. According to a recent survey performed among the members of the Society for Pediatric Radiology (27), gadobutrol, gadoterate meglumine, and gadobenate dimeglumine were the most commonly used GBCAs (37.3%, 28.5%, and 26.0%, respectively) for neonates and infants younger than 1 year. Five post-marketing studies described the use of gadoterate meglumine in neonates and infants—the youngest patient being 3 days old (13).

No new safety concern was raised in this pediatric population. The single AE recorded was mild vomiting soon after the MRI examination in a 2-year-old child with brain tumor who received gadoterate meglumine at the recommended dose of 0.2 mL/kg. The symptom was self-limiting and most likely related to concomitant intracranial pressure due to the tumor. However, relationship to contrast agent cannot be excluded. Indeed, the most common AEs reported in 84,621 patients receiving gadoterate meglumine are vomiting (0.2%) and nausea (0.1%), followed by urticaria and pruritus (each <0.1%) (28).

Another adverse drug reaction of GBCAs is the development of NSF in patients with renal impairment (29). Previous studies had proven that the development of NSF depends on the dosage of GBCAs (8,30). Thus, the risk for developing NSF is 6.7 times higher after a single gadodiamide exposure compared with no gadodiamide exposure in chronic dialysis patients and this

risk becomes 44.5 times higher after multiple gadodiamide exposures (8). Based on the European Society of Urogenital Radiology (ESUR) Contrast Media Safety Committee guidelines (31), only GBCAs with highest risk of NSF (e.g., gadodiamide, gadopentetate dimeglumine, or gadoversetamide) represent a contraindication for patients with an eGFR below 30 ml/min/1.73 m^2, patients on dialysis, patients with acute renal insufficiency and neonates. These high-risk GBCAs should be used with caution in patients with an eGFR between 30 and 60 ml/min/1.73 m^2 and in children less than 1 year old. Gadoterate meglumine, as well as gadobutrol and gadoteridol, showed a low risk of NSF (31). No cases of NSF were reported in the children of the present study, including those with renal impairment. However, it must be considered that no children with end-stage renal insufficiency, dialysis, or kidney transplantation were included, reflecting the strict indications for MRI using gadoterate meglumine in the daily practice. Therefore, the incidence of NSF in this high-risk group cannot be assessed. To date, no unconfounded case of NSF with gadoterate meglumine have been reported in pediatric or adult patients. Regarding gadolinium deposition in brain with GBCAs (12), results have been recently published in the pediatric population, supporting a low risk with gadoterate meglumine following several administrations. Radbruch et al. demonstrated that no increase of the signal intensity (which has been shown to correlate with gadolinium deposition) were observed in the dentate nucleus of 41 pediatric patients after at least five serial injections of gadoterate meglumine (32).

Finally, this study confirmed the efficacy of gadoterate meglumine for MRI in the pediatric population. More than 98% of contrast-enhanced images were of "good" to "very good" quality for every age group, and the diagnosis could be achieved in more than 99% of children. These results are similar to those shown by Emond et al., where image quality with gadoterate meglumine was rated "excellent" or "good" in 102 of the 104 neonates and infants included in their study (33).

This observational study has several limitations. Most of the patients with severe renal impairment did not receive contrast-enhanced MRI examinations at all, thus a general recommendation for the use of gadoterate meglumine cannot be given in this risk group. The duration of the NSF follow-up was not sufficient to ensure the detection of all potential cases of NSF. Lastly, the evaluation of efficacy was dependent on the subjective perception of each on-site radiologist and was performed on the set of contrast-enhanced images only. The comparison with efficacy data of other studies is also restrained due to different assessment criteria.

In conclusion, this study has shown that the contrast agent gadoterate meglumine, when employed in routine MRI procedure, is safe for use in children under 18 years, owing to its low level of AEs displayed as well as the negative NSF detection. These findings align and reinforce those from previous clinical and post-marketing studies, extending the previous knowledge to different countries in Europe, Asia, and the Middle East.

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ORCID iD

Chang De-Hua https://orcid.org/0000-0001-8787-6782

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