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Baseline characteristics, diagnostic efficacy, and peri-examinational safety of IV gadoteric acid MRI in 148,489 patients

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Abstract

Background: Magnetic resonance imaging (MRI) examinations with intravenous (IV) contrast are performed worldwide in routine daily practice. In order to detect and enumerate even rare adverse events (AE) and serious adverse events (SAE), and to relate them with patients' baseline characteristics and diagnostic effectiveness, high quantity sample size is necessary.

Purpose: To assess safety, diagnostic effectiveness, and baseline characteristics of patients undergoing IV gadoteric acid (Dotarem®) MRI in routine practice.

Material and Methods: Data from two observational post-marketing surveillance (PMS) databases compiled by 139 and 52 German centers in 2004–2011 and 2011–2013, respectively, were pooled, yielding data on a total of 148,489 patients examined over a 10-year period. Radiologists used a standardized questionnaire to report data including patient demographics, characteristics of MR examinations, and results in terms of diagnosis and patient safety.

Results: Overall, 712 AEs were reported in 467 (0.3%) patients, mainly nausea (n = 224, 0.2%), vomiting (n = 29, <0.1%), urticaria (n = 20, <0.1%), and feeling hot (n = 13, <0.1%). AEs were considered related to gadoteric acid in 362 (0.2%) patients. Higher frequencies of AEs were observed among patients with a previous reaction to a contrast agent (2.0%), liver dysfunction (0.7%), bronchial asthma (0.7%), and a history of allergies (0.6%). There were 49 SAEs in 18 (<0.1%) patients, including two children. No fatal SAE was reported. Examinations were diagnostic in 99.8% of all patients, and image quality was excellent or good in 97.7% of the patients.

Conclusion: Gadoteric acid is a safe peri-examinational and effective contrast agent for MRI in routine practice.

Keywords

Magnetic resonance imaging, gadoteric acid, post-marketing surveillance, safety, efficacy, adverse drug reactions

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Introduction

First clinically introduced in the late 1980s, paramagnetic gadolinium-based contrast agents (GBCAs) for magnetic resonance imaging (MRI) were soon used for visualization of brain lesions (1), liver lesions (2,3), and diseases of many other organs as well as visualization of the vascular system (4,5).

Today several intravenous (IV) GBCAs are used in daily practice, including gadoteric acid (gadoterate meglumine). Gadoteric acid has been approved for use in imaging of the brain and spine in both children (from neonates) and adults and, according to local

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regulatory labeling, for whole-body MRI including gastrointestinal, breast, renal, urogenital, cardiac, as well as bone and joint imaging and magnetic resonance angiography (MRA) (5). Gadoteric acid is a macrocyclic, highly stable agent (1350 mosm/kg H_2O) with a molecular weight of 558.7 g mol^{-1} and a gadolinium concentration of 0.5 mol/L, characterized by r1 relaxivities in plasma of 3.6 $mmol^{-1} s^{-1}$ at 1.5 T and 3.5 $mmol^{-1} s^{-1}$ at 3.0 T (6).

All contrast agents undergo extensive safety testing throughout the development process before the respective country authorities approve clinical use in patients (5). However, as with any medication, the possibility of contrast-agent-related adverse drug reactions—including severe adverse reactions—cannot be ruled out entirely, especially since millions of contrast-enhanced MRI examinations continue to be conducted worldwide every month (5,7–9).

It seems reasonable to gain additional insights into the peri-examinational safety profile and diagnostic efficacy in routine practice of MRI examinations performed with IV gadoteric acid administration, including safety evaluation by observing frequency and seriousness of adverse events (AEs) and diagnostic efficacy assessment through evaluation of image quality and of the ability to make a diagnosis based on the examination.

A thorough review of the literature regarding the safety profile of IV gadoteric acid in routine practice in Germany indicates that this is the first manuscript to present pooled data of two large multicenter post-marketing surveillance (PMS) databases (n = 104,033 in 139 centers from January 2004 to May 2011 and n = 44,456 in 52 centers from January 2011 to December 2013) of a decade of MRI with IV gadoteric acid. The two studies shared the same purpose and used a similar structure for data collection. The primary objective of this study was to assess the safety profile of IV gadoteric acid in MRI under daily practice conditions. The secondary objectives were to evaluate diagnostic effectiveness and patient demographics and baseline characteristics in this large pooled database.

Material and Methods

The non-interventional PMS studies DOTAREM-2004-PMS and DGD-55-005 were conducted in accordance with Sec. 67, para. 6 of the German Drug Law (Arzneimittelgesetz, AMG) (10). MRI was performed with IV gadoteric acid (gadoterate meglumine, Dotarem®, Guerbet, Roissy CdG Cedex, France) in 139 centers during 2004–2011 (DOTAREM-2004-PMS) and in 52 centers in 2011–2013 (DGD-55-005).

Data acquisition and documentation

Radiologists in the participating centers reported data on patient and MRI performed with IV gadoteric acid as contrast agent by completing a standardized questionnaire with questions pertaining to three areas: (I) patient demographics and other baseline characteristics including details regarding the administration of gadoteric acid; (II) safety criteria; and (III) efficacy criteria.

(I) Patient demographics and other baseline characteristics data included:
- Patients' sex, age, height, weight, and body mass index (BMI);
- Risk factors (liver dysfunction, history of allergies, history of contrast agent reaction, bronchial asthma, beta-blocker treatment, coronary heart disease, heart failure, hypertension, central nervous system [CNS] disorders, and other risk factors);
- Possible premedication;
- Body area imaged by MRI (surrounding tissue, head/neck, brain, spine, liver, kidneys, pancreas, pelvis, lung, heart, breast, bones/joints, muscles, soft tissue, MRA, other body area);
- Gadoteric acid administration: packaging (bottle/prefilled syringe); mode of injection (manual/automatic); injected volume (mL), dose (mL/kg body weight), and number of injections.

(II) Safety was assessed by collection of AEs that occurred for up to 30–60 min (according to the usual follow-up practice of the center) after the end of the MRI examination in standardized, structured report form. The following safety criteria were reported:
- AEs;
- Serious adverse events (SAEs) and reasons for seriousness (life-threatening, death, hospitalization/prolongation of hospitalization, congenital anomaly or birth defect, persistent or significant disability/incapacity, medically important event);
- AEs requiring the administration of an AE-targeted medication;
- Outcome of the AE (recovered/resolved, permanent damage, not yet recovered, unknown, death);
- Causal relationship to gadoteric acid administration: related (causal relationship assessed as certain, highly probable, probable, possible, doubtful/unlikely), unassessable, or no causal relationship.

(III) Efficacy of gadoteric acid was assessed by:
- MR image quality (excellent, good, moderate, poor, very poor);
- Diagnostic value (diagnosis possible or not) and reason(s) why radiologists were not able to establish a diagnosis.

Analysis and statistical tests

Analysis was performed using SAS® Version 9.4 (SAS Institute, Cary, NC, USA). For quantitative parameters, the following summary statistics were calculated: number of patients, mean, SD, minimum, median, and maximum. For categorical data, frequencies were calculated. The numbers of observations in category as well as the percentage (%) relative to the respective group were displayed. Percentages were calculated on the total of non-missing recorded categories. AEs were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 20.0. For all AEs, the summaries were displayed at patient level and at event level. BMI was calculated by dividing body weight in kilograms by the square of the height in meters. The calculated values were categorized in accordance with the Centers for Disease Control and Prevention (CDC) classification system (Atlanta, GA, USA): patients with a BMI $<18.5\,kg/m^2$ were considered underweight; patients with a BMI in the range of 18.5–24.9 kg/m^2 as having a normal weight; patients with a BMI in the range of 25–29.9 kg/m^2 as overweight (pre-obesity); and patients with a BMI $\geq 30\,kg/m^2$ as obese (obesity class I = 30.0–34.9; class II = 35.0–39.9; class III ≥ 40) (11,12).

Results

Demographic and other baseline characteristics

The pooling of the two German PMS databases yielded a total of 148,489 patients aged 0.1–98 years undergoing MRI with gadoteric acid between January 2004 and December 2013 (n = 104,033 in 139 centers during 2004–2011 and n = 44,456 in 52 centers in 2011–2013). No relevant differences were observed between the two populations.

Patients, pre-existing risk factors, and premedications. The majority of patients (54.8%) were female (Table 1). Age was available for 146,107 (98.4%) of patients (with a mean ± SD of 52.2 ± 16.9 years). More than 50% of patients were in the 30–59 age class category. Patients aged ≥80 years accounted for 3.7% of the overall population. A total of 2459 (1.7%) children were included: 2147 (87.3%) were aged 12–17 years

Table 1. Demographic data and baseline characteristics including pre-existing risk factors.

	Total (n = 148,489)
Sex	
Male (n (%))	66,251 (45.2)
Female (n (%))	80,476 (54.8)
Missing	1762
Age (years)	
N	146,107
Mean (SD)	52.2 (16.9)
Median (range)	53.0 (0.1–98.0)
Missing	2382
Age by class (years) (n (%))	
<2	11 (<0.1)
2–5	25 (<0.1)
6–11	276 (0.2)
12–17	2147 (1.5)
18–29	14,043 (9.6)
30–39	17,512 (12.0)
40–49	28,971 (19.8)
50–59	29,755 (20.4)
60–69	27,614 (18.9)
70–79	20,338 (13.9)
≥80	5415 (3.7)
Missing (n)	2382
Weight (kg)	
N	147,480
Mean (SD)	76.7 (15.6)
Median (range)	75.0 (3.0–195.0)
Missing	1009
Height (cm)	
N	145,203
Mean (SD)	171.7 (9.5)
Median (range)	170.0 (54.0–215.0)
Missing	3286
BMI (kg/m^2)	
N	145,093
Mean (SD)	25.9 (4.5)
Median (range)	25.4 (7.3–136.4)
Missing	3396
BMI by class (n (%))	
Underweight (BMI <18.5)	2722 (1.9)
Normal (BMI ≥18.5 and <25)	64,701 (44.6)
Overweight (BMI ≥25 and <30)	54,757 (37.7)
Obese (BMI ≥30)	22,913 (15.8)
Missing	3396
Pre-existing risk factors (n (%))	
History of allergies	19,644 (13.2)
Hypertension	8821 (5.9)
Coronary heart disease	3084 (2.1)
CNS disorders	2455 (1.7)
Beta-blocker treatment	1964 (1.3)
Other risk factors	1963 (1.3)
Bronchial asthma	1910 (1.3)
Heart failure	1544 (1.0)
History of contrast agent reaction	922 (0.6)
Liver dysfunction	684 (0.5)
Other risk factors	1963 (1.3)

(continued)

Table 1. Continued.

	Total (n = 148,489)
Premedication*	
At least one premedication (n (%))	
Yes	990 (0.7)
No	147,211 (99.3)
Missing (n)	288
If yes (n (%))	
Sedatives	910 (91.9)
H1	74 (7.5)
H2	42 (4.2)
Cortisone	22 (2.2)

*A patient could have more than one premedication.
BMI, body mass index; CNS, central nervous system.

and 11 (0.4%) children were aged <2 years. Mean ± SD BMI was 25.9 ± 4.5 kg/m^2. The majority of patients (53.5%) had a BMI greater than normal, including 37.7% overweight and 15.8% obese patients. Normal BMI was observed in 44.6% of patients.

The most common risk factors were history of allergies, reported in 13.2% of patients, followed by hypertension (5.9%), coronary heart disease (2.1%), and CNS disorders (1.7%). Beta-blocker treatment, bronchial asthma, heart failure, history of contrast agent reaction, liver dysfunction, and other risk factors were reported in <1.5% of patients. At least one premedication was administered in 990 (0.7%) patients: sedatives in 91.9% of the cases; antihistamines in 11.7%; and cortisone in 2.2% (a patient could have more than one premedication).

MRI examination and gadoteric acid administration. The most frequent body area examined (Table 2) was the CNS (49.2%) including examinations of the brain (37.4%), spine (9.9%), head and neck (3.8%), and surrounding tissues (0.6%). Bones/joints were imaged in 29.3% of patients and internal organs in 13.0%. MRA accounted for 3.0% of the examinations. A patient might have undergone MRI of more than one body area.

Parameters of gadoteric acid administration are displayed in Table 3. The volume injected was in the range of 0.6–50.0 mL with a mean ± SD of 15.9 ± 3.8 mL. The majority of patients (>89%) received 11–20 mL of gadoteric acid. The corresponding mean ± SD dose injected was 0.210 ± 0.06 mL/kg.

A dose in the range of 0.1–0.2 mL/kg was administered to 49.0% of patients and a dose of 0.2–0.25 mL/kg was given to 34.6% of patients. Less than 2% of patients received a dose of ≤ 0.1 mL/kg and 14.7% of patients received >0.25 mL/kg. The injection was most often single (97.6% of patients) and manual (73.5%).

Table 2. Anatomical area imaged.

Anatomical area	Total (n = 148,489)
CNS	73,032 (49.2)
Brain	55,537 (37.4)
Spine	14,735 (9.9)
Head/Neck	5608 (3.8)
Surrounding tissue	907 (0.6)
Musculoskeletal system	45,712 (30.8)
Bones/joints	43,479 (29.3)
Soft tissue	6112 (4.1)
Muscles	1492 (1.0)
Internal organs	19,331 (13.0)
Liver	8322 (5.6)
Pelvis	7608 (5.1)
Kidneys	7583 (5.1)
Pancreas	5978 (4.0)
Breast	1718 (1.2)
Heart	796 (0.5)
Lung	382 (0.3)
MRA	4524 (3.0)
Other MRI examination	3259 (2.2)

Values are presented as n (%).
Patients may have no data available for the area imaged or may have undergone imaging of several areas.
CNS, central nervous system; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging.

When the mean dose of gadoteric acid was analyzed according to BMI class, it was observed that the greater the BMI, the lower the injected dose. Underweight patients received a mean dose of 0.27 mL/kg, patients of normal weight 0.23 mL/kg, overweight patients 0.20 mL/kg, and obese patients 0.18 mL/kg.

When considering the area imaged, the highest mean dose (0.27 mL/kg) was injected for MRA, while the lowest mean dose (0.20 mL/kg) was administered for imaging of the musculoskeletal system.

Safety

Overall, 467 patients (0.3%) experienced 712 AEs. Among them, 289 (61.9%) presented with one AE, 136 (29.1%) with two AEs, and 42 (9.0%) with three or more AEs. Outcomes were reported for 363 patients (78% of the patients with AEs); the majority of patients (98.1%) recovered. Two patients experienced four AEs whose outcomes were reported as "not yet resolved" within the usual follow-up period of 30–60 min. Targeted medication was required for 217 AEs in 117 (26.4%) patients. Assessment of the causal relationship was available for 79% of the patients with AEs. AEs were considered related to gadoteric acid in 362 of the 467 patients (77.5%, 0.2% of the total study population). The relationship was assessed as probable to certain in most cases (67.0% of available data), possible in

Table 3. Parameters of gadoteric acid administration.

	Total (n = 148,489)
Total volume injected (mL)	
N	146,564
Mean (SD)	15.9 (3.8)
Median (range)	15.0 (0.6–50.0)
Missing (n)	1925
Total volume injected by class (mL) (n (%))	
≤10	11,587 (7.9)
11–15	85,827 (58.6)
16–20	44,646 (30.5)
≥21	4504 (3.1)
Missing (n)	1925
Injected dose (mL/kg)	
N	147,216
Mean (SD)	0.210 (0.06)
Median (range)	0.2 (0.0–1.4)
Missing (n)	1273
Injected dose by class (mL/kg) (n (%))	
≤0.1	2520 (1.7)
>0.1 and ≤0.2	72,156 (49.0)
>0.2 and ≤0.22	25,503 (17.3)
>0.22 and ≤0.25	25,454 (17.3)
> 0.25	21,583 (14.7)
Missing	1273
Mode of injection (n (%))	
Manual	105,613 (73.5)
Automatic	38,103 (26.5)
Missing (n)	4773
Number of injections (n (%))	
1	120,558 (97.6)
2	2916 (2.4)
Missing (n)	25,015
Type of packaging (n (%))	
Prefilled syringe	58,931 (40.3)
Vial	87,214 (59.7)
Missing	2344
Injected dose (mL/kg) according to BMI and to area imaged	
BMI by class	
Underweight (BMI <18.5)	0.269 (0.10)
Normal (BMI ≥18.5 and <25)	0.227 (0.06)
Overweight (BMI ≥25 and <30)	0.201 (0.05)
Obese (BMI ≥30)	0.177 (0.05)
Missing	0.213 (0.05)
Area imaged	
CNS	0.208 (0.06)
Musculoskeletal system	0.204 (0.04)
Internal organs	0.222 (0.07)
MRA	0.265 (0.13)
Other MRI examination	0.205 (0.04)

BMI, body mass index; CNS, central nervous system; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging.

23.0%, and doubtful/unlikely in 8.1% of patients with AEs.

AEs are presented according to primary system organ class (SOC) and preferred terms in Table 4.

Table 4. All AEs by primary system organ class (SOC) and preferred term (PT).

SOC PT	Total (n = 148,489)
At least one AE	467 (0.3)
Gastrointestinal disorders	263 (0.2)
Nausea	224 (0.2)
Vomiting	29 (<0.1)
Retching	7 (<0.1)
Hypoesthesia, oral	1 (<0.1)
Lip swelling	1 (<0.1)
Swollen tongue	1 (<0.1)
Skin and subcutaneous tissue disorders	55 (<0.1)
Urticaria	20 (<0.1)
Pruritus	12 (<0.1)
Rash	11 (<0.1)
Erythema	4 (<0.1)
Hyperhidrosis	2 (<0.1)
Skin reaction	2 (<0.1)
Swelling face	2 (<0.1)
Dermatitis, allergic	1 (<0.1)
Rash, papular	1 (<0.1)
Nervous system disorders	37 (<0.1)
Paresthesia	10 (<0.1)
Dysgeusia	9 (<0.1)
Dizziness	5 (<0.1)
Headache	2 (<0.1)
Presyncope	2 (<0.1)
Syncope	2 (<0.1)
Tremor	2 (<0.1)
Burning sensation	1 (<0.1)
Dizziness postural	1 (<0.1)
Loss of consciousness	1 (<0.1)
Neuralgia	1 (<0.1)
Seizure	1 (<0.1)
General disorders and administration site conditions	33 (<0.1)
Feeling hot	13 (<0.1)
Malaise	5 (<0.1)
Extravasation	4 (<0.1)
Injection site pain	3 (<0.1)
Injection site extravasation	2 (<0.1)
Edema	2 (<0.1)
Chest discomfort	1 (<0.1)
Chills	1 (<0.1)
Injection site erythema	1 (<0.1)
Injection site irritation	1 (<0.1)
Respiratory, thoracic, and mediastinal disorders	27 (<0.1)
Cough	11 (<0.1)
Sneezing	5 (<0.1)
Dyspnea	4 (<0.1)
Oropharyngeal pain	3 (<0.1)
Nasal congestion	2 (<0.1)
Throat irritation	1 (<0.1)
Throat tightness	1 (<0.1)
Cardiac disorders	15 (<0.1)
Cardiovascular disorder	5 (<0.1)

(continued)

Table 4. Continued.

SOC PT	Total (n = 148,489)
Tachycardia	5 (<0.1)
Angina pectoris	2 (<0.1)
Cardiac arrest	1 (<0.1)
Myocardial infarction	1 (<0.1)
Palpitations	1 (<0.1)
Vascular disorders	12 (<0.1)
Flushing	10 (<0.1)
Hemodynamic instability	1 (<0.1)
Pallor	1 (<0.1)
Ear and labyrinth disorders	10 (<0.1)
Vertigo	10 (<0.1)
Eye disorders	6 (<0.1)
Eyelid edema	4 (<0.1)
Eye irritation	1 (<0.1)
Visual impairment	1 (<0.1)
Immune system disorders	5 (<0.1)
Hypersensitivity	3 (<0.1)
Contrast media allergy	2 (<0.1)
Infections and infestations	3 (<0.1)
Rash, pustular	3 (<0.1)
Musculoskeletal and connective tissue disorders	1 (<0.1)
Pain in extremity	1 (<0.1)

Values are presented as n (%).
AEs were coded using MedDRA dictionary version 20.0.
AE, adverse event.

The most frequent AEs were nausea (224 patients, 0.2%), vomiting (29 patients, <0.1%), urticaria (20 patients, <0.1%), and feeling hot (13 patients, <0.1%).

A total of 18 patients (<0.1%) presented with 49 SAEs (Table 5). No SAE caused the death of a patient. Seriousness criteria were medically important in 11 (61.1%) patients, life-threatening in 3 (16.7%), hospitalization in 3 (16.7%), and hospitalization and life-threatening in 1 (5.6%). Among the 49 SAEs, 48 resolved; one (seizure) was reported with an unknown outcome.

Characteristics of patients with adverse events. Among the patients with AEs, there was a higher proportion with liver dysfunction, history of allergies, history of contrast agent reaction, or bronchial asthma than among patients without AEs (1.1% vs. 0.5%, 25.5% vs. 13.2%, 3.9% vs. 0.6% and 3.0% vs. 1.3%, respectively). Similarly, the proportion of patients with one of these four risk factors was higher among patients with SAEs or gadoteric acid-related AEs than among patients without SAEs or related AEs (Table 6).

Among the 18 patients who experienced SAEs, 7 (38.9%) had a history of allergy. There were no differences between patients experiencing AEs and patients without AEs in terms of body area imaged

Table 5. Serious adverse events.

Patient no.	Seriousness criteria	Preferred term	Causal relationship
1	Life-threatening	Myocardial infarction/anaphylactic shock/eructation/pallor/seizure/heart rate decreased/ventricular fibrillation/hyperhidrosis/nausea	Possible
2	Medically important	Seizure	Missing
3	Medically important	Dyspnea	Possible
4	Medically important	Urticaria	Possible
5	Medically important	Cardiovascular disorder/vomiting/vertigo/nausea/hyperhidrosis	Possible
6	Life-threatening	Dyspnea/circulatory collapse/shock	Doubtful/unlikely
7	Hospitalization	Vomiting/hyperhidrosis/hypotension	Doubtful/unlikely
8	Medically important	Dyspnea	Doubtful/unlikely
9	Life-threatening	Cardiac arrest/arrhythmia	Possible
10	Medically important	Syncope/presyncope/nausea	Possible
11	Hospitalization and life threatening	Loss of consciousness/respiratory arrest	Possible
12	Medically important	Vomiting	Possible
13	Hospitalization	Swelling face/urticaria	Highly probable
14	Medically important	Urticaria	Probable
15	Medically important	Nasal congestion/eye pruritus/cough/sneezing	Highly probable
16	Medically important	Swelling face/oral pruritus/erythema	Doubtful/unlikely
17	Hospitalization	Contrast media allergy/renal failure	Probable
18	Medically important	Retching/nausea/paresthesia/feeling hot/cough	Highly probable

MedDRA dictionary version 20.0.

Table 6. Description of patients with adverse events (AEs), related AEs, and SAEs.

	Patients with AEs (n = 467)	Patients with related AEs (n = 362)	Patients with SAEs (n = 18)
Risk factor			
Liver dysfunction	5 (1.1)	2 (0.6)	0
History of allergies	119 (25.5)	94 (26.0)	7 (38.9)
History of a reaction to a contrast agent	18 (3.9)	15 (4.1)	2 (11.1)
Bronchial asthma	14 (3.0)	10 (2.8)	2 (11.1)
Beta-blocker treatment	3 (0.6)	2 (0.6)	0 (0.0)
Coronary heart disease	7 (1.5)	6 (1.7)	2 (11.1)
Heart failure	1 (0.2)	1 (0.3)	0 (0.0)
Hypertension	24 (5.1)	18 (5.0)	2 (11.1)
CNS disorders	4 (0.9)	3 (0.8)	1 (5.6)
Other risk factors	12 (2.6)	5 (1.4)	1 (5.6)
Body area imaged			
Central nervous system	208 (44.5)	152 (42.0)	6 (33.3)
Musculoskeletal system	161 (34.5)	130 (35.9)	10 (55.6)
Internal organ	64 (13.7)	49 (13.5)	2 (11.1)
Other MRI examination	11 (2.4)	10 (2.8)	0 (0.0)
Injected dose (mL/kg)			
$\leq$0.1	7 (1.5)	4 (1.1)	0
>0.1 and $\leq$0.2	224 (48.4)	179 (49.7)	10 (55.6)
>0.2 and $\leq$0.22	75 (16.2)	56 (15.6)	2 (11.1)
>0.22 and $\leq$0.25	88 (19.0)	67 (18.6)	5 (27.8)
>0.25	69 (14.9)	54 (15.0)	1 (5.6)
Missing	4	2	0
Age (years)			
<2	0	0	0
2–5	0	0	0
6–11	1 (0.2)	0	0
12–17	12 (2.6)	10 (2.8)	2 (11.1)
18–29	76 (16.7)	64 (17.9)	2 (11.1)
30–39	85 (18.6)	60 (16.8)	2 (11.1)
40–49	97 (21.3)	86 (24.1)	4 (22.2)
50–59	90 (19.7)	70 (19.6)	5 (27.8)
60–69	56 (12.3)	38 (10.6)	3 (16.7)
70–79	34 (7.5)	27 (7.6)	0
$\geq$80	5 (1.1)	2 (0.6)	0
Missing	11	5	0

Values are presented as n (%).
Related AE defined as AE with causal relationship stated as certain, highly probable, probable, possible, or doubtful/unlikely on the standardized questionnaire.

and in terms of injected dose of gadoteric acid. Thirteen children presented with at least one AE, including two with SAEs and 10 with related AEs. No AE was observed in children aged $\leq$5 years (Table 6). Among patients with AEs, 35.3% were aged 18–39 years. This age class represented 21.6% of patients without AEs. For patients aged 40–59 years, no differences were observed between the proportion of patients with and without AEs. Patients aged >59 years accounted for 20.9% of patients with AEs versus 36.5% of patients without AEs. AEs were more frequently observed in children aged 12–17 years than in all other age classes (0.6% vs. 0.3%, 0.4%, 0.2%, and 0.2% for 2–11, 18–59, 60–69, and >69 years age classes, respectively). The nature of AEs was similarly distributed among the different age classes.

Conversely, a higher frequency of AEs was observed among patients with a previous reaction to a contrast agent (2.0%), liver dysfunction (0.7%), bronchial asthma (0.7%), or history of allergies (0.6%) compared to a frequency of 0.3% in patients without these risk factors (Table 7). The highest frequencies of SAEs and gadoteric acid-related AEs were reported in patients with a previous contrast agent reaction (0.2% and 1.6%, respectively).

Table 7. AE/SAE rates in patients with and without specific risk factors.

Risk factor	Total (n = 148,489)	Patients with AEs (n = 467)	Patients with related AEs (n = 362)	Patients with SAEs (n = 18)
Liver dysfunction				
Yes	684	5 (0.7)	2 (0.3)	0 (0.0)
No	147,805	462 (0.3)	360 (0.2)	18 (<0.1)
History of allergies				
Yes	19,644	119 (0.6)	94 (0.5)	7 (<0.1)
No	128,845	348 (0.3)	268 (0.2)	11 (<0.1)
History of contrast agent reaction				
Yes	922	18 (2.0)	15 (1.6)	2 (0.2)
No	147,567	449 (0.3)	347 (0.2)	16 (<0.1)
Bronchial asthma				
Yes	1910	14 (0.7)	10 (0.5)	2 (0.1)
No	146,579	453 (0.3)	352 (0.2)	16 (<0.1)
Beta-blocker treatment				
Yes	1964	3 (0.2)	2 (0.1)	0 (0.0)
No	146,525	464 (0.3)	360 (0.2)	18 (<0.1)
Coronary heart disease				
Yes	3084	7 (0.2)	6 (0.2)	2 (<0.1)
No	145,405	460 (0.3)	356 (0.2)	16 (<0.1)
Heart failure				
Yes	1544	1 (<0.1)	1 (<0.1)	0 (0.0)
No	146,945	466 (0.3)	361 (0.2)	18 (<0.1)
Hypertension				
Yes	8821	24 (0.3)	18 (0.2)	2 (<0.1)
No	139,668	443 (0.3)	344 (0.2)	16 (<0.1)
CNS disorders				
Yes	2455	4 (0.2)	3 (0.1)	1 (<0.1)
No	146,034	463 (0.3)	359 (0.2)	17 (<0.1)
Other risk factors				
Yes	1963	12 (0.6)	5 (0.3)	1 (<0.1)
No	146,526	455 (0.3)	357 (0.2)	17 (<0.1)

Values are presented as n (%).
AE, adverse event; SAE, serious adverse event; CNS, central nervous system.

Efficacy

Efficacy was assessed in terms of image quality and diagnostic value. The results are presented in Table 8.

For the majority of patients (97.7%), images were of good (45.5%) or excellent quality (52.2%), while very poor quality was observed for <0.1%. A diagnosis was made in 99.8% of patients. In 312 (0.2%) patients, the radiologist was not able to establish a diagnosis. The main reason for non-diagnostic imaging was motion artifact.

Discussion

Overall, 712 AEs were reported in 467 (0.3%) patients. The most common AEs were nausea (n = 224, 0.2%), vomiting (n = 29, <0.1%), urticaria (n = 20, <0.1%), and feeling hot (n = 13, <0.1%). In terms of safety, the rate of 0.3% of AEs found here is the same as the one we found in the mammography-specific PMS (5) and similar to the 0.34% interim rate of AEs found in the first PMS (Dotarem-2004-PMS) in >84,000 patients (13), which is also part of the present study. The rate of AEs identified here is lower than that reported for various gadolinium-based contrast agents in other smaller PMS studies: 1.2% adverse drug reactions in a study on tolerance and clinical safety of gadobenate dimeglumine in >38,000 patients (8) and 2.4% in a study on clinical safety of gadopentetate dimeglumine in >15,000 patients (14). Considering six different GBCAs (two macrocyclic: gadoteric acid and gadobutrol, and four linear: gadobenate dimeglumine, gadoxetic acid, gadopentetate, and gadodiamide) in 84,367 patients (141,623 total doses), Jung et al. described an incidence of immediate hypersensitivity reactions of 0.079% and a recurrence rate of 30% in patients with previous reactions (15). In our pooled study, AEs resolved in 98.1% of

Table 8. Image quality and diagnostic value.

	Total (n = 148,489)
Image quality	
Excellent	76,961 (52.2)
Good	67,193 (45.5)
Moderate	3239 (2.2)
Poor	167 (0.1)
Very poor	14 (<0.1)
Missing	915
Diagnosis	
Yes	132,441 (99.8)
No	312 (0.2)
Missing	15,736
If no, reason*	
Technical problem	39 (12.5)
Motion artifact	97 (31.1)
Other reason	62 (19.9)
Missing	120

Values are given as n (%).
*A patient may have more than one reason.

reported cases. Gadoteric acid-related AEs were observed in 362 of the 467 patients with AEs (77.5%). The relationship was most often assessed as probable, highly probable, or certain (67.0%). A possible and doubtful/unlikely relationship to gadoteric acid was noted in 23.0% and 8.1% of patients, respectively. A higher frequency of AEs was observed among patients with a previous reaction to a contrast agent (2.0%), liver dysfunction (0.7%), bronchial asthma (0.7%), or a history of allergies (0.6%). AEs were more frequently observed in children aged 12–17 years than in all other age classes (2–11, 18–59, 60–69, and >69 years). Thirteen children (0.5% of pediatric patients) presented with at least one AE. No AEs were observed in children aged ≤5 years. SAEs were observed in <0.1% of the overall population (n = 18/148,489; 0.012%), including two children. No SAE led to a patient's death.

GBCAs are considered rather safe with respect to immediate adverse reactions in the routine clinical setting. This also applies to pediatric MRI, with a reported well-established safety profile (16), and renally insufficient patients (17), and has been confirmed in a review of >50 million administered doses over a period of >25 years (18). Nevertheless, numerous publications have lately focused on gadolinium deposition within the central nervous system, especially in patients undergoing repeated IV GBCA MRI examinations (19–25). While the current topic of gadolinium and rare earths retention/deposition into brain and tissues is noteworthy and important (26–41), it is, however, not the genuine focus of this study. The mechanism of retention/deposition in the brain is different from AEs reported in this study, where the accumulation of gadolinium doses is almost not monitored (as only some of the patients received two injections and this information was unknown for most of the patients) and the retention of gadolinium—the lowest with gadoteric among the other agents—has not been related to any clinical event or symptom.

In 99.8% of patients examined, a diagnosis could be established, which is in line with published data. For instance, Herborn et al. reported >99% diagnostic examinations (7) and we found 99.2% diagnostic examinations in a previous PMS evaluation of MR mammography (5) and 99.7% in the interim analysis (Dotarem-2004-PMS) (13). Image quality was rated as "excellent" or "good" in 97.5%, 91.6%, and 97.1%, respectively. In an observational study (n = 35,499 patients) on the safety profile of gadoterate meglumine, Soyer et al. (42) reported good or very good image quality for 98.8% of cases. Lower rates of excellent or good image quality of 85.8% were reported by Oudkerk et al. (43) for central nervous system IV gadoteric acid MRI in a relatively small sample of patients (n = 518). In our pooled study, radiologists were not able to make a diagnosis in 312 (0.2%) patients, predominantly due to reported motion artifact (31.1%).

Due to the nature of observational studies, the two PMS databases analyzed in this study were compiled without a control group or randomization. Risks and adverse drug reactions were individually assessed by physicians, who may differ in their assessment. Hence, we cannot fully rule out interpersonal and intersite bias of participating study centers. Image quality and accuracy evaluation may likewise be affected by subjective differences among investigators. The questionnaire survey allowed compilation of a large amount of data and could therefore also identify rare events. In this large population with 148,489 MRI examinations, AEs and SAEs were identified, but both at relatively low rates: 0.3% (n = 467) experienced 712 AEs and <0.1% (n = 18) presented with 49 SAEs. In patients experiencing AEs, outcome was reported for 77.7% (n = 363) with a majority 98.1% recovering within the observational period, which still means that for 22.3% of the patients with AEs (n = 104), outcomes were not reported and, hence, missing. While we may conclude that AEs, and even more so SAEs, were very rare, it remains challenging to state a substantiated valid rate, especially for SAEs, because of its very low incidence. Safety assessments were performed according to the usual follow-up practice of the centers for a time period of up to 30–60 min. Therefore, later events might have been missed. To accomplish an overall 10-year observational time frame by pooling the two German PMS databases (with time frames of January

2004 to May 2011 for DOTAREM-2004-PMS and January 2011 to December 2013 for DGD-55-005), an overlap period from January to May 2011 was accepted: theoretically, there could be patients who were included in both studies. This could have happened in the rare case that a patient had another MRI examination in another center participating in both studies within this five-month overlap period.

In conclusion, the pooled results of the two observational PMS databases (n = 148,489) confirm that gadoteric acid (Dotarem®) is a safe periexaminational and diagnostically effective contrast agent in routine clinical practice.

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