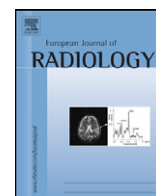




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Tolerability and diagnostic value of gadoteric acid in the general population and in patients with risk factors: Results in more than 84,000 patients

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ABSTRACT

Purpose: To review the tolerability and diagnostic effectiveness of gadoteric acid under daily practice conditions in the general population and at-risk patients.

Materials and methods: A total of 84,621 patients (45.4% men, 54.6% women, mean age 52.0 ± 16.9 years) were studied in 129 German centers. Patients underwent contrast-enhanced magnetic resonance imaging (MRI) using gadoteric acid (Gd-DOTA, Dotarem®, Guerbet, Roissy CdG, France) as IV contrast medium (mean volume, 16.4 ml). 22.9% of the patients had at least one risk factor (e.g., allergies, previous allergic reaction to a contrast medium, and renal impairment). 554 patients received pretreatment before contrast medium administration (0.7%). Adverse events were documented and image quality was assessed.

Results: A diagnosis was possible in 99.7% of all cases. Image quality was rated good or excellent in 97.1%. Adverse events (e.g., nausea, vomiting, and urticaria) were observed in 0.34% of the examinations and were mostly rated as minor. There were 8 patients with serious adverse events. The adverse event rate was significantly higher in patients with a history of allergies (0.62%; $p < 0.001$) and in patients with a previous allergic reaction to contrast medium (1.23%; $p < 0.001$). There was no elevated incidence of adverse events in patients with renal impairment.

Conclusion: Gadoteric acid is a well-tolerated MRI contrast medium in patients with and without risk factors that is associated with a low rate of adverse events and good or excellent image quality in most patients.

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1. Introduction

In the last two decades, magnetic resonance imaging (MRI) has evolved into a major imaging modality in the routine clinical setting. Paramagnetic MR contrast agents were first introduced for brain imaging in the late 1980s, and they have since markedly improved the sensitivity and specificity of MRI in the evaluation of cerebral lesions [1–3]. Soon afterwards, the use of MR contrast agents was expanded to other organs and the vascular system [4–6], and they have since become indispensable in daily clinical MRI examinations.

A number of different paramagnetic MR contrast agents are in clinical use, including gadoterate meglumine (Gd-DOTA, Dotarem®, Guerbet, Roissy CdG Cedex, France), which is approved for imaging of the central nervous system (CNS), of the abdomen, and for vascular indications. Gd-DOTA is a macrocyclic, highly

stable, hyperosmolar agent (1350 mosm/kg H₂O) with a molecular weight of 558.7 g mol^{-1} and a gadolinium concentration of 0.5 mol/L, characterized by r_1 and r_2 values (determined experimentally at 20 °C and a magnetic field strength of 1.0 T) of $3.4 \text{ mmol}^{-1} \text{ s}^{-1}$ and $4.8 \text{ mmol}^{-1} \text{ s}^{-1}$, respectively.

All paramagnetic contrast agents have undergone extensive safety and tolerability testing in patients at various stages of the development process and are generally considered to be very well tolerated. However, as with any medication, it is not possible to completely rule out the occurrence of contrast medium-related adverse events including occasional severe effects, especially in view of the fact that more than approximately 10 million contrast-enhanced MRI examinations are performed worldwide every year [7–9]. Moreover, the use of gadolinium-based MR contrast agents was recently associated with nephrogenic systemic fibrosis (NSF) in patients with terminal renal failure [10,11]. Against this background, the evaluation of the tolerability of MR contrast agents should be prolonged even after they have been approved for clinical use. Therefore, the aim of this large-scale postmarketing surveillance study was to investigate the tolerability, and diagnostic

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effectiveness of Gd-DOTA under daily practice conditions in the general population and at-risk patients.

2. Materials and methods

2.1. Patients and data collection

The surveillance study was conducted in 129 German centers between January 2004 and January 2010. Radiologists working in the participating centers reported data on routine MRI examinations performed with IV Gd-DOTA as contrast medium by completing a standardized questionnaire. Patient data included age, sex, height and weight, and different pre-existing risk factors (renal impairment, hepatic impairment, allergies, prior allergic reaction to Gd- or iodine-based contrast medium, asthma, coronary artery disease, heart insufficiency, hypertension, disorders of the central nervous system). In addition, the radiologist documented the type of MRI examination performed using the following classification: (1) neurological imaging (brain, head and neck, spine; multiple answers possible); (2) imaging of the body (liver, pancreas, kidneys, heart, lungs, breast, pelvis; multiple answers possible); and (3) musculoskeletal system (bones/joints, soft tissue). In addition, the radiologist was asked to provide information on the amount of contrast medium injected and the mode of injection (manual/automated) as well as on any premedication given. Diagnostic accuracy was given if the diagnosis was possible based on the examination. If the examination was considered nondiagnostic, the radiologist was asked to give the reason (e.g., technical problems and restless patient). Image quality was assessed using the grades “excellent” (i.e., superb and completely homogeneous signal enhancement of targeted structures, evaluation possible with high diagnostic confidence), “good” (i.e., adequate, almost completely homogeneous signal enhancement of target structures, evaluation possible with satisfactory diagnostic confidence), “moderate” (i.e., little, but still homogeneous enhancement of target structures, evaluation possible with reduced diagnostic confidence), “poor” (i.e., low and inhomogeneous enhancement of target structures), and “very poor” (i.e., no appreciable signal enhancement). The last questionnaire item pertained to the number and type of adverse events and a possible association with contrast medium administration. Each patient was monitored for adverse reactions during and for 30–60 min after the MR examination.

BMI – calculated as the weight in kilograms divided by the square of the height in meters – was classified according to the Centers of Disease Control (CDC) guidelines: underweight (BMI < 18.5), normal weight (BMI 18.5–24.9), overweight (BMI 25–29.9) and obesity (BMI ≥ 30).

Following the recommendations for observational studies issued by the German Federal Institute for Drugs and Medical Devices (BfArM) in 1998 [12] and in accordance with the definition of noninterventional trials (§2c of Directive 2001/20/EC [13]), the decision to perform an MRI examination was completely independent of a patient inclusion into the present study. Adverse events were classified in accordance with World Health Organization (WHO) Adverse Events Terminology, which was developed for coding clinical information in relation to drug therapy and to serve as a basis for rational coding of adverse reaction terms [14].

2.2. Statistical analysis

All data were recorded in an electronic data sheet using Visual Stats AWB (version 2002). Statistical analysis was done using SPSS for Windows. Whenever data were missing, the results were adjusted to 100% to allow comparison of percentages. The chi-

Table 1

Number and percentage of patients with different risk factors (multiple answers possible; basis: 84,621 patients).

Risk factor	n	%
History of allergies	9686	11.4
Hypertension	5546	6.6
Coronary heart disease	1920	2.3
CNS disorders	1627	1.9
Bronchial asthma	1132	1.3
Betablocker treatment	1101	1.3
Cardiac insufficiency	992	1.2
Renal failure	764	0.9
History of allergic reaction to contrast medium	649	0.8
Liver dysfunction	518	0.6
Other	1105	1.3
Total	19354	22.9

square test was used to test for statistical significance. A *p*-value less than 0.05 was considered statistically significant.

3. Results

3.1. Patient demographics and risk factors

A total of 84,621 patients were included in the study; 45.4% of the patients were men and 54.6% were women. The patients had a mean age of 52.0 years (range, 5–97; standard deviation, 16.9 years). Men had a mean weight of 83.6 kg and a mean height of 178.2 cm; women had a mean weight of 70.1 kg and a mean height of 166.4 cm. Weight distribution was as follows: 46.0% normal weight, 37.9% overweight, 14.3% obesity, and 1.8% underweight. Normal and underweight were more common in women (54.5% vs. 39.9%; *p* < 0.001), while overweight and obesity were more common in men (60.1% vs. 45.5%; *p* < 0.001).

A total of 19,354 of the 84,621 patients (22.9%) were at-risk patients, who had at least one risk factor (see Table 1). The most common risk factors were allergies (11.4%) and hypertension (6.6%). Risk factors were more common in women than in men (24.3% vs. 21.0%; *p* < 0.001). The higher rate in women is attributable to the higher prevalence of allergies (13.5% vs. 8.9%; *p* < 0.001). When allergies are disregarded, there are slightly more men with risk factors (13.9% vs. 13.3%; *p* = 0.019).

3.2. Pretreatment

Pretreatment was given in 554 of 84,621 patients (0.7%) before the MRI examination. The most common medications were sedatives (in 508 patients), followed by H1 – antihistaminics (*n* = 41), H2 – antihistaminics (*n* = 19), and cortisone (*n* = 14). Premedication was used more frequently in patients with a history of allergic reaction to a contrast medium (4.8%, 31 of 649 patients; *p* < 0.001). Among the patients with allergies, 1.1% received pretreatment (107 of 9686 patients).

3.3. MRI examinations and contrast medium injection

The 84,621 contrast-enhanced examinations performed comprised 42,298 neurological examinations (50.0%), 10,324 examinations of internal organs (12.2%), 27,197 musculoskeletal examinations (32.1%), and 1906 MR angiographies (2.3%) (see Table 2). Information on the body region imaged was missing for 4185 patients (4.9%).

Table 2

Numbers of patients with MRI examinations and numbers of examinations according to body region (multiple answers possible).

Body region imaged	n	%
Neurological examinations	42,298	50.0
Neurocranium	30,911	36.5
Spine	8344	9.9
Head/neck	4750	5.6
Internal organs	10,324	12.2
Liver	4348	5.1
Pelvis	4027	4.8
Kidneys	3905	4.6
Pancreas	2987	3.5
Breast	971	1.1
Heart	269	0.3
Lungs	251	0.3
Musculoskeletal system	27,197	32.1
Bones/joints	25,738	30.4
Soft tissue	4724	5.6
MR angiographies	1906	2.3
Not specified	4185	4.9
Total	84,621	100

Table 3

Average total volumes of contrast medium injected by body weight class.

Weight (according to BMI)	Total volume (ml)	Total volume (ml/kg body weight)
Underweight	13.7	0.29
Normal weight	15.6	0.24
Overweight	16.9	0.21
Obesity	17.9	0.19

3.4. Contrast medium

The Gd-DOTA contrast medium was injected manually in the majority of cases (74.5%), whereas automated IV injection was performed in 25.5% of cases. The automated IV injection was more frequently used to perform MR angiographies ($p < 0.001$). Most patients (98.0%) received a single injection of Gd-DOTA. The average volume of contrast medium injected was 16.4 ml (range, 0.6–38 ml). The volume was between 10 and 20 ml in 90.0% of all examinations. The average volume injected per kg body weight was 0.22 ± 0.07 ml/kg, corresponding to a dose of 0.11 ± 0.04 mmol/kg body weight. Patients with a higher BMI received higher total amounts of contrast medium, while the volume per kg body weight decreased with increasing BMI (see Table 3).

3.5. Image quality and diagnostic accuracy

The MRI examinations were diagnostic in 99.7% of all cases. Image quality was rated as excellent in 40,171 examinations (47.9%), good in 41,258 examinations (49.2%), moderate in 2350 examinations (2.8%), poor in 105 examinations (0.1%), and very poor in 10 examinations (<0.1%) (see Table 4). The reasons given for poor or very poor image quality were motion artifacts ($n = 28$), tech-

Table 4

Image quality ratings of Gd-DOTA-enhanced MRI examinations (adjusted to 100%).

Image quality rating	n	Proportion in %
Excellent	40,171	47.9
Good	41,258	49.2
Moderate	2350	2.8
Poor	105	0.1
Very poor	10	<0.1
Total	81,429	100

Table 5

The 10 most common adverse events observed after contrast medium injection in a total of 84,621 patients.

Adverse event	n	%
Nausea	144	0.2
Vomiting	43	0.1
Pruritus	21	<0.1
Urticaria (wheals)	20	<0.1
Dizziness	14	<0.1
Feeling of warmth	14	<0.1
Retching	13	<0.1
Sweating increased	9	<0.1
Paresthesia	9	<0.1
Taste alteration	9	<0.1

nical problems ($n = 6$), metal artifacts ($n = 3$), respiratory artifacts ($n = 2$), and obesity ($n = 2$). There were no differences in the diagnostic quality of the MRI examination between men and women.

There was good or excellent image quality in 97.1% of all examinations. The proportion of examinations with good or excellent image quality decreased with increasing BMI, ranging from 98.3% in underweight, to 97.5% in normal weight, to 97.1% in overweight, to 95.7% in obesity. At-risk patients also had significantly poorer image quality: good or excellent image quality was achieved in 95.7% of at-risk patients vs. 97.5% of patients without known risk factors ($p < 0.001$). The proportion was 93.2% in patients with renal failure and 94.2% in patients with liver dysfunction.

In relation to the body regions imaged, the proportion of examinations with good or excellent image quality was 97.6% for neurological examinations, 95.8% for examinations of internal organs, 96.7% for musculoskeletal examinations, and 95.3% for MR angiographies.

3.6. Adverse events

A total of 421 adverse event symptoms were seen in 285 patients of a total of 84,621 patients examined, corresponding to an adverse event rate of 0.34%. Sixty-five different adverse events were observed. The 10 most common symptoms in the study patients were from the following groups in the WHO Adverse Reaction Terminology (see Table 5): Skin and Appendages Disorders (69/285; e.g., urticaria 20/285, pruritus 21/285, and increased sweating 9/285), Central & Peripheral Nervous System Disorders (31/285; e.g., dizziness 14/285 and paraesthesia 9/285), Gastrointestinal System Disorders (201/285; e.g., nausea 144/285, vomiting 43/285, and retching 13/285), Special Senses (10/285; e.g., taste alteration 9/285), and General Disorders (38/285; e.g., feeling of warmth 14/285).

Larger injection volumes were not associated with a higher risk of adverse events ($p = 0.286$). The risk was increased in patients with allergies and in patients with a history of allergic reaction to contrast medium (see Table 6). The risk of developing adverse reactions or serious adverse events was not increased in patients with renal failure, liver dysfunction, or betablocker intake (see Table 6).

Serious adverse events occurred in 8 patients (<0.01%, see Table 7). Three of the patients had life-threatening adverse events,

Table 6

Adverse events in at-risk patients.

Risk factors (number of patients with this risk factor)	No. of patients with adverse events	%
Allergies ($n = 9686$)	60	0.62 ($p < 0.001$)
History of allergic reaction to contrast medium ($n = 649$)	8	1.23 ($p < 0.001$)
Liver dysfunction ($n = 518$)	4	0.77 ($p = 0.086$)
Renal failure ($n = 764$)	3	0.39 ($p = 0.789$)

Table 7
Eight patients with serious adverse events.

Patient	Age, sex	Medical history	Adverse event	Causal relationship	Outcome
1	65 years, man	- Cervicobrachialgia - Cervical myelopathy - Alcohol and drug abuse - Symptomatic psychotic syndrome - Peripheral arterial occlusive disease - Dilatation of anterior interventricular ramus - Stenosis of LAD - Stent - Femoral–femoral left arterial bypass - Hypercholesterolemia - Gastric operation - Left bypass thrombosis	- Anaphylactic shock - Eructation - Pallor - Convulsions - Ventricular fibrillation - Sweating - Nausea	Probable	Recovered
2	55 years, man	Abdominal pain	- Urticaria	Possible	Recovered
3	28 years, woman	Penicillin allergy	- Circulatory failure - Vomiting - Vertigo - Nausea - Sweating - Dyspnea - Circulatory collapse - Shock - Vomiting - Sweating increased - Hypotension - Dyspnea	Possible	Recovered
4	40 years, man	No	- Shock	Doubtful	Recovered
5	46 years, woman	Spondylodiscitis	- Vomiting - Sweating increased - Hypotension - Dyspnea	Doubtful	Recovered
6	36 years, man	Allergy	- Dyspnea	Doubtful	Recovered
7	51 years, man	- Bronchial asthma - Bypass surgery - Chest injury - Coronary heart disease	- Heart arrest - Proarrhythmic effect	Possible	Recovered
8	49 years, man	Phobia	- Fainting - Vasovagal reaction - Nausea	Possible	Recovered

and in one case, inpatient treatment became necessary. These 8 patients had a total of 27 adverse events, among them 16 listed adverse events (anaphylactic shock, circulatory collapse, dyspnea (2×), fainting, heart arrest, hypotension, nausea (3×), shock, sweating, sweating increased, urticaria, vomiting (2×)) and 11 unlisted adverse events (circulatory failure, convulsions, eructation, ventricular fibrillation, pallor, perspiration, proarrhythmic effect, pulse decreased, vasovagal reaction, vertigo). A causal relationship with Gd-DOTA was considered probable in 1 patient, possible in 4 patients, and doubtful in 3 patients. All patients recovered (see Table 7).

4. Discussion

This surveillance study is the largest study so far that has been conducted on the tolerability of Gd-DOTA in routine clinical use since this MR contrast agent was approved. The 0.34% rate of adverse events reported in a total of 84,621 patients examined with Gd-DOTA is small and is even below the rates found in earlier surveillance studies [9,15]. Serious adverse events were reported in 8 patients, meaning that there is one serious adverse event in more than 10,000 applications.

Adverse events can never be fully excluded under routine conditions when a widely used contrast agent is administered despite comprehensive characterization of the safety profile of an agent before its approval. A radiologist using a contrast agent must always weigh the expected diagnostic benefit of a contrast-enhanced MRI examination and its significance for therapeutic decision-making against the residual risk of an adverse event.

The adverse event rate of 0.34% is in the range of that of other gadolinium-based contrast agents for MR imaging in large postmarketing surveillance studies. Herborn et al. reported a 1.2% adverse event rate in more than 38,000 patients undergoing MRI with Gd-BOPTA [8]. For Gd-DTPA, Niendorf et al. found an adverse event rate of 1.47% [16], while Nelson et al. reported a rate of 2.4% in a study including more than 15,000 patients [17]. Knopp et al. [7] analyzed over 45 million applications of Gd-DTPA-based contrast agents between 1988 and 2002, showing that reporting of adverse events changes over time (a phenomenon known as the Weber effect [18]) with an initial peak followed by a decline in reported adverse events. Cultural aspects also seem to play a role with higher rates of adverse events tending to be reported in the USA [7]. A placebo effect must also be considered [19].

While it is important to reliably determine the rate of adverse events in the general population, special attention must be paid to subgroups of patients with specific risks. In our study, patients with known allergies had significantly more adverse events (0.62%), which is consistent with reports on other gadolinium-based contrast agents. Herborn et al. [8] reported a 3.3% adverse event rate for Gd-BOPTA in allergic patients. Nelson et al. [17] saw adverse events in 3.7% of the patients with allergies who underwent MRI with Gd-DTPA. In our postmarketing surveillance study, patients with a history of allergic reaction to iodine-based or gadolinium-based contrast agents also had significantly more adverse events after Gd-DOTA administration (1.23%). In the study of Gd-BOPTA, such patients had an adverse event rate of 3.1%. In a detailed analysis of adverse effects of Gd-DTPA, Nelson et al. [17] observed adverse events in 6.1% of the patients with a history of allergic reaction to iodine-based contrast agents, but in as many as 21.3% of the patients with an earlier allergic reaction to a gadolinium-based contrast agent. These observations underline the importance of taking great caution when using Gd-based contrast agents in these patients despite the better overall safety profile of these agents compared with iodine-based agents [20–23].

Diagnostic image quality was accomplished in 99.7% of all MRI examinations in our study, which is nearly identical to the results reported by Herborn et al. [9]; the percentage of examinations with image quality rated as good or excellent was similarly high (97.1%). In contrast, Oudkerk et al. [24] achieved good or excellent image quality in 89.7% of MRI examinations with Gd-DOTA in a small patient population ($n = 518$).

Gadolinium-based contrast agents are generally considered to be safe and less nephrotoxic than iodine-based contrast agents [22]. Nevertheless, quite recently a discussion has come up about a possible association between cases of nephrogenic systemic fibrosis (NSF) and the use of gadolinium-based contrast agents [10,25,26]. Available data suggest that NSF mainly occurs in patients with severely impaired kidney function and mostly after use of Gd-based contrast agents with a linear chemical structure [11,27]. As the aim of our study was to document spontaneous adverse events during contrast medium administration and 30–60 min after the examination in a large patient population, our survey provides no data on delayed effects such as NSF. Nevertheless, there was no case of adverse effects typical of NSF spontaneously reported that occurred in association with Gd-DOTA administration in the patients included in this surveillance study.

As with other surveillance studies, our study also has limitations. The assessment of risk factors and adverse events in the participating study centers is likely to have induced some intraindividual bias.

Moreover, the responses concerning image quality and accuracy are affected to some extent by the investigators' subjective impressions. However, subjective effects can be assumed to have been minimized by the large number of participating centers, and our data can be assumed to be fairly representative. As a surveillance study by questionnaire allows collection of data from a very large population, it is also possible to identify very rare events. Adverse events which occurred later than 24 h after contrast-enhanced MRI examination might have been missed. Thus, it seems likely that some mild adverse events may have been underreported in our study.

5. Conclusions

In summary, in this large surveillance study with more than 84,000 examinations, including a significant proportion of patients with risk factors for adverse events, Gd-DOTA has shown to have an overall good tolerance and an excellent efficacy in clinical practice.

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