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Diagnostic efficacy and safety of gadoteric acid MR mammography in 1537 patients

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ABSTRACT

Objectives: To perform a large-scale multicenter post-marketing surveillance study for analyzing diagnostic effectiveness and safety of intravenous (IV) gadoteric acid (Dotarem®) in magnetic resonance (MR) mammography under daily practice conditions.
Materials and methods: Patients underwent high-resolution MR mammography with gadoteric acid in 15 German centers. Radiologists used a standardized questionnaire to report data including patient demographics and medical history, characteristics of MR examination and results in terms of diagnosis and safety for the patient.
Results: A total of 1537 patients were examined. In 99.2% of all patients, a diagnosis was established. In 91.6% of all patients, image quality was excellent or good. Histopathological examinations were performed for 232 of 1537 patients (15.1%) with invasive ductal carcinoma being the most frequent diagnosis (109 patients, 47.0%). Based on histopathology as the standard of reference, IV gadoteric acid-enhanced MR mammography confirmed diagnoses of invasive ductal carcinoma in 93.5% of the patients. Adverse drug reactions occurred in 5 of 1537 patients (0.3%) and were classified as serious in one case (tachycardia, dysphagia, urticaria, rash). All patients with adverse drug reactions fully recovered after the examination.
Conclusion: This noninterventional surveillance study shows IV gadoteric acid to be a safe and effective contrast agent for use in MR mammography.

1. Introduction

Magnetic resonance imaging (MRI) has become a major imaging modality in the last decades. Since its development around 40 years ago (especially by Paul C. Lauterbur, with major contributions by Sir Peter Mansfield), MRI hardware and software have rapidly progressed. Paramagnetic gadolinium-based MR contrast agents were introduced in the late 1980s, first for visualization of brain lesions [1], followed by liver lesions [2,3] and disease of other organs as well as visualization of the vascular system [4].

The use of contrast agents has become indispensable in routine MR imaging. Several intravenous (IV) gadolinium-based contrast agents (GBCAs) are in clinical use, including gadoteric acid. Gadoteric acid has been approved for use in imaging of the brain and spine, for whole-body MRI including gastrointestinal, renal, urogenital, cardiac, as well as bone and joint imaging and breast examinations in both children (0–17 years in most countries, except USA; refer to respective local regulatory labeling) and adults. Gadoteric acid is a macrocyclic, highly stable, hyperosmolar 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 and r2 relaxivities (determined experimentally at 20 °C and a magnetic field strength of 1.0 T) of 3.4 $mmol^{-1}$ s^{-1} and 4.8 $mmol^{-1}$ s^{-1}, respectively [5].

All contrast agents undergo extensive safety testing throughout the development process before the respective country authorities approve its clinical use in patients. 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 are conducted worldwide every month [6–8].

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A thorough review of the literature indicates that this manuscript is to our knowledge the first to present a multicenter post-marketing surveillance study to generate and analyze data on diagnostic effectiveness and safety of IV gadoteric acid in MR mammography under daily practice conditions.

2. Materials and methods

This noninterventional surveillance study was conducted in accordance with Section 67, para. 6 of the German Drug Law (Arzneimittelgesetz, AMG) [9].

Patients underwent high-resolution MR mammography with gadoteric acid (or gadoterate meglumine, Dotarem®, Guerbet, Roissy CdG Cedex, France) in 15 centers.

2.1. Data acquisition and documentation

Radiologists in the participating centers reported data on patient and MR mammography performed with IV gadoteric acid as contrast agent by completing a standardized questionnaire. Data included patients' age, sex, height, weight, menopausal status and examination date, indication, risk factors and BRCA mutation, examination method, pharmaceutical form and dosage as well as image quality, diagnosis, histopathology and safety. History of allergies (e.g., hay fever, hives and asthma) or previous allergic reactions to contrast media were recorded as well as conditions such as serious cardiovascular disease, renal insufficiency and central nervous system disorders. Possible adverse drug reactions were recorded in an additional "Adverse drug reactions and suspected cases report".

Diagnostic effectiveness was assessed on the basis of image quality (5-point scale from excellent to very poor), diagnosis and histopathological findings. Safety was assessed on the basis of frequency and severity of adverse drug reactions observed following injection of gadoteric acid.

2.2. Analysis and statistical tests

Analyses were performed using SPSS Statistics 20 (IBM Corporation, Armonk, New York). Descriptive data were analyzed in relative and absolute frequencies and are presented with mean and standard deviation if not otherwise indicated. For each parameter, percentages were calculated based on the overall population and based on the number of patients with available data for this specific question (adjusted results).

Body mass index (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 below 18.5 kg/m^2 were considered underweight, patients with a BMI between 18.5 and 24.9 kg/m^2 as having a normal weight, patients with a BMI between 25 and 29.9 kg/m^2 as overweight and patients with a BMI of 30 kg/m^2 and above as obese [10,11].

Adverse drug reactions were analyzed separately according to the Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC; McLean, VA 22102 USA) version 16. Seriousness, causal relationship and outcome of adverse drug reactions were analyzed and percentages calculated both based on the total number of patients and on the number of patients with adverse drug reactions.

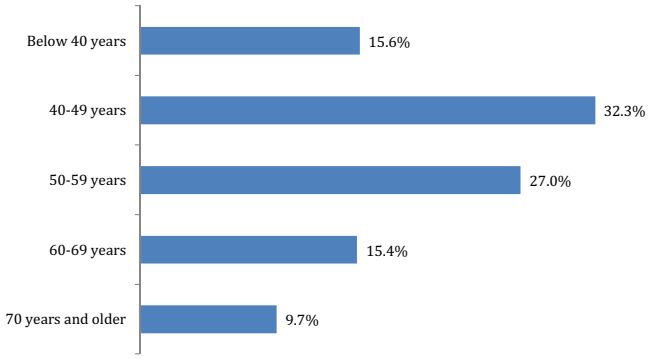

Fig. 1. Patient age distribution (n = 1537).

Table 1
Patient Body Mass Index (BMI; adjusted; n = 1528).

	Total	
	N	%
Underweight (BMI <18.5 kg/m^2)	39	2.6
Normal (BMI 18.5–24.9 kg/m^2)	840	55.0
Overweight (BMI 25–29.9 kg/m^2)	457	29.9
Obese (BMI 30 kg/m^2 and above)	192	12.6
Total	1528	100

3. Results

3.1. Patients

A total of 1537 patients underwent high-resolution MR mammography with gadoteric acid between January 9th, 2012 and October 28th, 2013 in 15 German centers.

The gender of 1494 of the 1537 patients was recorded on the questionnaire, thereof 1491 women (99.8%) and 3 men (0.2%). Patient age ranged from 16 to 88 years (mean (±SD) age 51.4 ± 12.3 years; Fig. 1).

Mean patient height was 166.9 ± 6.4 cm, mean weight 69.7 ± 13.5 kg. According to BMI (data available for 1528 patients), 55.0% of the patients had normal weight, 2.6% were underweight, 29.9% overweight and 12.6% of patients were categorized as obese (Table 1).

3.2. Menopausal status and menstrual phase at time of examination

At the time of examination, 54.8% of the women were postmenopausal, 33.6% premenopausal and 11.6% perimenopausal. Mean (±SD) age was 39.4 ± 6.8 years for premenopausal women, 47.2 ± 3.5 years for perimenopausal women and 59.6 ± 9.2 years for postmenopausal women.

Overall, 8% of women were on hormone replacement therapy at the time of examination. The percentage of women undergoing hormone replacement therapy was 9.4% in the premenopausal group of women, 6.7% in the perimenopausal group, and 6.5% in the postmenopausal group.

In the premenopausal group 80.4% of the examinations were conducted during the 2nd or 3rd week of the menstrual cycle and 19.6% during other stages. In the perimenopausal group 30.3% of the examinations were conducted in the 2nd or 3rd week of the menstrual cycle and 69.7% during other stages.