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Safety profile of gadoxetate disodium in elderly patients (≥65 years)

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Abstract

Background: Safety data on routine clinical use of gadoxetate disodium in elderly patients is not reported yet.
Purpose: To assess the safety of liver specific gadoxetate disodium in contrast enhanced magnetic resonance imaging in elderly patients (≥65 years) in comparison to adults (18–64 years).
Material and Methods: Safety data on gadoxetate disodium were analyzed from 12 clinical phase II–III studies and from our pharmacovigilance database. A comparison between elderly (≥65 years) versus adults (18–64 years) was performed with respect to the frequency of drug-related adverse events (AEs) in clinical phase II–III studies and adverse drug reactions (ADRs) in the pharmacovigilance database.
Results: In clinical studies, 1989 patients were enrolled: 675 elderly and 1314 adults. Twenty-three elderly patients (3.4%) suffered at least one drug-related AE in contrast to 58 patients (4.4%) in the group of adults (odds ratio = 0.76; 95% confidence interval = 0.45–1.27). Since marketing authorization in 2004, more than 3.5 million patients have been exposed to gadoxetate disodium worldwide: 1.7 million (48.6%) in elderly and 1.8 million (51.4%) in adults. The number of patients with post-marketing ADRs (total n = 793) was 354 (0.021%) in the elderly group and 439 (0.024%) in the adult group. Thus, there were significantly fewer patients with ADRs reported in the group of elderly versus adults ($P = 0.028$). Hypersensitivity/immune system disorders, gastrointestinal disorders, and respiratory disorders were the most frequent ADRs in both groups, elderly and adults.
Conclusion: The incidence of drug-related AEs in clinical studies was similar and that of patients with ADRs in the post-marketing setting was lower in elderly (≥65 years) compared with younger adults aged 18–64 years. Overall, gadoxetate disodium shows a favorable safety profile in both age groups.

Keywords
Gadoxetate disodium, safety, elderly

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Introduction

Gadoxetate disodium (Primovist/Eovist®) is a gadolinium-based contrast agent (GBCA) for magnetic resonance imaging (MRI) of the liver. It is indicated for the detection, localization, and characterization of liver lesions. Gadoxetate disodium increased the frequency of correctly detected hepatic lesions versus spiral computed tomography (CT) by 10.4% (1). In particular, the highest rate of correctly detected lesions was for small hepatic lesions with a diameter < 1 cm. (1). Thus, gadoxetate disodium may improve diagnosis and assist surgical planning (2,3).

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Gadoxetate disodium belongs to the class of linear ionic GBCAs and features a high T1 relaxivity of 6.9 L $mmol^{-1}$ s^{-1} at 1.5 T (in plasma) (4). After intravenous application, gadoxetate disodium is first distributed in the extracellular space and then quickly and selectively taken up by the hepatocytes, thus providing both dynamic and hepatocyte-specific imaging (4). Hepatocyte/accumulation phase magnetic resonance imaging (MRI) can be done as soon as 10 min after the injection. In healthy participants, about 50% of the injected dose is excreted via the kidneys and 50% via the biliary system (5). Contrast enhancement of the liver parenchyma and liver-to-lesion contrast is highest at about 20 min after administration with a plateau lasting for at least to 45 min post injection (5).

Zech et al. have shown that the diagnostic performance of gadoxetate disodium enhanced MRI was better than that of contrast-enhanced CT and MRI with extracellular contrast agents as the initial imaging modality for detection of liver metastases in patients with colorectal cancer (6). No further imaging was needed in the gadoxetate disodium group, and comparison of efficacy parameters demonstrated diagnostic superiority in the gadoxetate disodium enhanced MRI group (6). The excellent safety profile of gadoxetate disodium has been demonstrated in several clinical studies and in post-marketing experience (1,7–9). As of 30 April 2016, more than 3.6 million patients have been exposed to gadoxetate disodium worldwide since approval in March 2004. No case of NSF has been reported so far (data on file, NSF Annual Surveillance Report).

While elderly patients generally experience more comorbidities and are more fragile, they are also more frequently examined for diseases by contrast-enhanced MRI. For another, second generation general purpose GBCA, gadobutrol, no greater incidence of adverse drug reactions (ADRs) in elderly patients (aged ≥ 65 years) compared with younger adults (18–64 years) was shown (10). Thus, the question about the safety profile of liver specific gadoxetate disodium in this special patient population came up.

Material and Methods

All available safety data on gadoxetate disodium administration from (i) clinical studies phase II–III and (ii) from the Bayer Pharmacovigilance database, i.e. from clinical practice following marketing approval, were analyzed. The key target variable of this analysis was the number of patients with related adverse events (AE) (clinical studies) or ADRs from the pharmacovigilance database in elderly patients (aged ≥ 65 years) versus younger adults (aged 18–64 years).

Clinical studies phase II–III

Our clinical study database included safety results of 1989 patients from 12 prospective phase II–III clinical development studies conducted and sponsored by Bayer AG. Four phase II studies enrolled 580 patients and eight phase III studies enrolled 1409 patients. All studies were performed between 1994 and 2015 in Europe, the USA, China, and Japan, and conducted in accordance with the Declaration of Helsinki. Approval by the relevant local institutional review boards was mandatory.

The study population of the clinical studies consisted of patients (aged ≥ 18 years) with a need for diagnostic liver imaging because of suspected or confirmed focal liver lesion(s), tumors, or metastases. The major inclusion criterion was suspicion or proof of focal liver lesion(s) by at least one diagnostic modality, e.g. contrast-enhanced CT, CT angiography, portography, unenhanced MRI or MRI enhanced with other, extracellular GBCAs. Contraindications to MRI were the major exclusion criterion. After giving written informed consent, patients received a single dose of gadoxetate disodium (0.025 mmol/kg bw; 0.1 mL/kg) followed by a saline flush.

Reporting and evaluation of AEs was standardized across all studies. All AEs were categorized by applying the Medical Dictionary for Regulatory Activities (MedDRA) system. AEs were recorded for all studies up to 20–28 h, in eight studies even up to 68–76 h post gadoxetate disodium injection.

A related AE was defined as any illness, sign or symptom, or unfavorable change in the clinical status that had appeared or worsened after study start and was considered as ''possibly,'' ''probably,'' or ''definitely'' plausibly related to gadoxetate disodium administration by experienced healthcare professionals in each institution.

All variables were analyzed by descriptive statistical methods. All AEs were re-coded to MedDRA version 18.1. AE incidence rates were calculated by dividing the number of patients where one specific related AE was reported by the number of patients exposed $\times 100$ in order to receive percentages. In addition, odds ratios (ORs) and exact 95% confidence intervals (CIs) were calculated for the difference between the two age groups. No adjustment for co-factors was performed.

Pharmacovigilance database

All worldwide ADR reports sent to the Bayer Pharmacovigilance Department from healthcare professionals (physicians, pharmacists, nurses) were included as well as from scientific publications, regulatory authorities, and patients or lay persons. Pharmacovigilance reports commonly include basic patient information

(age, sex, weight, height, or a local identification number) along with a brief description of the ADR. Thus, the number of ADRs is known precisely. The number of patients, however, who actually received gadoxetate disodium during the period 2004–2015 was not so easy to retrieve. We estimated this figure based on patient records from Arlington Medical Resources (AMR) (Exton, PA, USA) data. AMR data includes patient demographic information (age, sex) and reasons for performing contrast-enhanced MRI. AMR data comes from Europe (France, Germany, Italy, Spain, UK), China, Japan, Korea, and the USA and is therefore mirroring the world market (11).

We used the World Health Organization definition of ADRs from 1972: ''An ADR is a response to a drug which is noxious and unintended and which occurs at doses normally used in man'' (12). Here, ''response to a drug'' means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out. This relationship was assessed by experts from Bayer Pharmacovigilance Department.

The approximation of the total number of patients to whom gadoxetate disodium was administered in each age group was based on the utilization data. The proportions of patients with ADRs, with serious ADRs and deaths, were compared between the age groups. Incidence rates were compared between age groups using Fisher's exact test.

Results

Clinical studies phase II–III

In 12 clinical phase II–III studies, we enrolled a total of 1989 patients: 675 elderly patients and 1314 adults. No relevant differences were found between the two age groups with respect to the demographics (Table 1).

Twenty-three elderly patients (3.4%) suffered at least one drug-related AE in contrast to 58 patients (4.4%) in the group of adults (OR = 0.76; 95% CI = 0.45–1.27). The most frequent related AEs were general disorders and administration site conditions (elderly = 0.89%; adults = 1.45%), nervous system disorders (elderly = 0.74%; adults = 1.52%), and gastrointestinal disorders (elderly = 0.74%; adults = 1.22%). In general, the incidence of patients with any related AE was lower in the group of elderly compared to the adults (Table 1). No contrast agent-related serious AEs or deaths were reported in the clinical studies.

Pharmacovigilance

From the product's first marketing authorization in Sweden on 25 March 2004 to the data cutoff point of 31 December 2015, more than 3.5 million patients have been exposed to gadoxetate disodium worldwide. Of these, a total of 793 patients reported ADRs: 354 (44.6%) elderly patients and 439 (55.4%) adults. About one-third of the elderly group were women, while the gender distribution in the adult group was more balanced. Most reports came from Japan and the USA (Table 2).

Fig. 1 shows the ADRs in the pharmacovigilance database by system organ classes (SOCs). The most frequent ADRs were hypersensitivity/immune system disorders (e.g. urticaria, rash, pruritus, erythema, decreased blood pressure, sneezing, eyelid edema, etc.). Hypersensitivity/immune system disorders were less frequent in the elderly than in adults (45.5% versus 65.6% of patients with reports in the groups of the elderly and adults, respectively, $P < 0.001$). Gastrointestinal disorders (34.2% versus 31.4%) and respiratory disorders (28.3% versus 24.8%) were second and third most frequent. Serious ADRs were significantly more frequent in the elderly (46.9%) versus adults (31.6%) ($P < 0.001$). All other ADRs added up to less than 20% of all ADRs.

There were 33 deaths among the elderly and 20 among the adults; however, 51 of these 53 events occurred in patients with cancer and were unrelated to gadoxetate disodium. In only two cases (both in elderly patients), a relationship to gadoxetate disodium could not be excluded. More ADRs in the elderly group were classified as serious (SAEs) (46.9%) compared to the adult group (31.7%, Fig. 1).

Of the 3.5 million procedures, 1.7 million (48.6%) were undertaken in the elderly and 1.8 million (51.4%) in adults. The majority of procedures (1.59 million) were for the detection of cancerous lesions (metastases or primary hepatocellular cancer) in the liver. Hypersensitivity/immune system disorders, gastrointestinal disorders, and respiratory disorders were the most frequent ADRs. The percentage of patients with any ADR since launch with respect to the utilization data was 354 ADRs (0.021%) in the elderly group and 439 (0.024%) in the adult group (Table 3).

Fig. 2 shows the comparison of performed procedures versus the rate of patients with reported ADRs since launch. While 48.6% of procedures were in the elderly, just 44.6% of patients with ADRs were reported in this age group. As a result, there were significantly less patients with ADRs reported in the elderly versus adults ($P = 0.0276$).

A comparison of overall rates of patients with related AEs and ADRs for the elderly versus adults in clinical studies and the pharmacovigilance database is shown in Fig. 3. While the rate of related AEs in the clinical studies does not differ between the two age

Table 1. Demographics and rates of patients with related AEs, cutoff > 0.1% – clinical phase II–III studies.

	Elderly ≥ 65 years (n (%))	Adults 18–64 years (n (%))	OR* for AE incidence in elderly vs. adults (95% CI)
Total population (n = 1989)	675 (33.9)	1314 (66.1)	
Gender			
Female	238 (35.3)	569 (43.3)	–
Male	437 (64.7)	745 (56.7)	–
Age (means ± SD)	70.5 ± 4.2	50.6 ± 10.4	
Weight (kg)			
< 60	208 (30.8)	300 (22.8)	
60–89	408 (60.4)	840 (63.9)	
≥90	59 (8.7)	174 (13.2)	
Global region			
Asia	237 (35.1)	361 (27.5)	–
USA/Canada	134 (19.9)	324 (24.7)	–
Europe	304 (45.0)	629 (47.9)	–
Patients with any related AE	23 (3.4)	58 (4.4)	0.76 (0.45–1.27)
Patients with related AEs by SOC,† PT			
Gastrointestinal disorders	5 (0.7)	16 (1.2)	0.61 (0.17–1.74)
Nausea	2 (0.3)	12 (0.9)	0.32 (0.03–1.46)
General disorders and administration site conditions	6 (0.9)	19 (1.4)	0.61 (0.20–1.60)
Feeling hot	2 (0.3)	11 (0.8)	0.35 (0.04–1.62)
Investigations	6 (0.9)	4 (0.3)	2.94 (0.69–14.19)
Nervous system disorders	5 (0.7)	20 (1.5)	0.48 (0.14–1.33)
Dysgeusia	2 (0.3)	4 (0.3)	0.97 (0.09–6.81)
Headache	1 (0.1)	7 (0.5)	0.28 (0.01–2.16)
Parosmia	1 (0.1)	4 (0.3)	0.49 (0.01–4.92)
Skin and subcutaneous tissue disorders	2 (0.3)	4 (0.3)	0.97 (0.09–6.81)
Serious AEs	0	0	

*Odds ratio and exact 95% confidence intervals were computed for all SOCs and PTs with at least five patients in total.
†Those SOCs or PTs for which at least five patients with reports in total were reported.
AE, adverse event (drug-related); CI, confidence interval; PT, preferred term; SD, standard deviation; SOC, system organ class.

Table 2. Characteristics of the population for whom ADRs were recorded as part of pharmacovigilance reporting.

	Elderly ≥ 65 years (n (%))	Adults 18–64 years (n (%))
Total population (n = 793)	354 (44.6)	439 (55.4)
Gender		
Female	123 (34.8)	226 (51.5)
Male	228 (64.4)	202 (46.0)
Missing data	4 (1.1)	11 (2.5)
Global region		
Japan	160 (45.2)	145 (33.0)
USA	49 (13.8)	100 (22.8)
Germany	61 (17.2)	56 (12.8)
Rest of world	84 (23.7)	138 (31.44)

groups ($P = 0.34$, Fisher's exact test), the difference in the rate of patients with ADRs in the pharmacovigilance database is statistically significant in favor of the elderly group ($P = 0.03$, Fisher's exact test).

Discussion

While the general safety profile of gadoxetate disodium has been reported in several previous publications (1,7–9), this is the first safety analysis specifically in the population of elderly patients (≥65 years). Elderly people are nowadays a rapidly growing proportion of the patient population in the majority of Western countries, and aging seldom comes alone, often being accompanied by chronic diseases and co-morbidity (13). Therefore, it is important to specifically address the

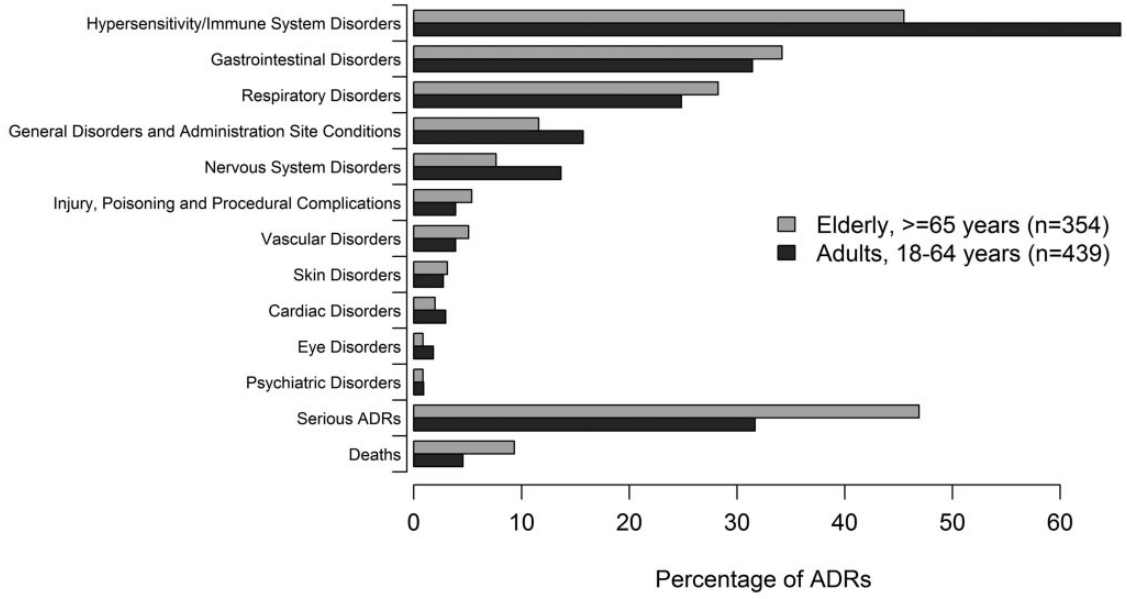

Fig. 1. ADRs by system organ class, in the pharmacovigilance population (793 patients with events, March 2004–December 2015, more than one ADR per patient possible)

Table 3. Gadoxetate disodium-enhanced MRI procedures between 2004 and 2015*, utilization data by body region,† and incidence of patients with ADRs since launch (pharmacovigilance population).

	Elderly ≥ 65 years (n (%))	Adults 18–64 years (n (%))
Total population (n = 3.5 million)	1.7 million (48.6)	1.8 million (51.4)
Indications for procedures†		
Cancer – liver	0.91 million (53.5)	0.68 million (38.2)
Mass/cyst – liver/gall bladder	0.23 million (13.5)	0.42 million (23.6)
Pancreatitis	0.19 million (11.4)	0.01 million (0.6)
Cirrhosis	0.08 million (4.6)	0.09 million (5.0)
Viral infection	0.06 million (3.4)	0.10 million (5.5)
Cancer – colon/rectal	0.06 million (3.7)	0.06 million (3.5)
Hemangioma	0.01 million (0.8)	0.06 million (3.5)
Other	0.16 million (9.2)	0.36 million (20.1)
Patients with ADRs by SOC preferred term relative to the utilization data		
Hypersensitivity/immune system disorders	161 (0.009)	288 (0.016)
Gastrointestinal disorders	121 (0.007)	138 (0.008)
Respiratory disorders	100 (0.006)	109 (0.006)
General disorders and administration site conditions	41 (0.002)	69 (0.004)
Nervous system disorders	27 (0.002)	60 (0.003)
Injury, poisoning and procedural complications	19 (0.001)	17 (<0.001)
Vascular disorders	18 (0.001)	17 (<0.001)
Skin disorders	11 (<0.001)	12 (<0.001)
Cardiac disorders	7 (<0.001)	13 (<0.001)
Eye disorders	3 (<0.001)	8 (<0.001)
Psychiatric disorders	3 (<0.001)	4 (<0.001)

(continued)

Table 3. Continued

	Elderly ≥ 65 years (n (%))	Adults 18–64 years (n (%))
Serious ADRs	166 (0.010)	139 (0.008)
Deaths	33 (0.002)	20 (0.001)
Total ADRs	354 (0.021)	439 (0.024)

*Using liter volume sold according to Bayer internal sales reporting and assuming a 10 mL average dose; as of December 2015.
†% distribution according to Arlington Medical Resources (AMR) for Primovist® during 2011–2015. AMR covers Europe, USA, and Asia. Percentage distribution was provided rounded to one decimal place for each body region and absolute numbers are estimated from these data.
ADR, adverse drug reaction; SOC, system organ class.

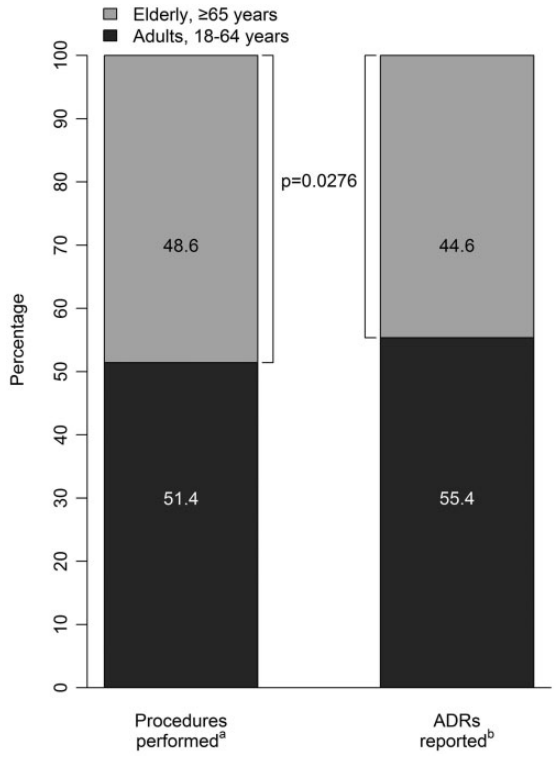

Fig. 2. Proportions of contrast-enhanced procedures performed and patients with at least one ADR reported during the period 2004–2015 based on utilization data. (a) Percentage of an estimated 3.5 million procedures; (b) percentage of 793 patients with at least one ADR reported.

wellbeing of this age group also in diagnostic procedures, like contrast-enhanced MRI. By analyzing two large databases—one including 12 clinical phase II–III studies and one including 3.5 million administrations in routine clinical use (pharmacovigilance database)—the favorable safety of gadoxetate disodium was demonstrated in elderly patients compared to younger adults aged 18–64 years.

Out of 1989 patients (675 elderly and 1314 adults), 23 elderly patients (3.4%) and 58 adults (4.4%) suffered at least one drug-related AE. Therefore, a numeric but not significant advantage was found between the two age groups (OR = 0.76; 95% CI = 0.45–1.27). A similar study on gadobutrol, a non-targeted/extracellular GBCA, which analyzed 5608 patients from 38 clinical trials, reported a significantly lower incidence of related AEs in the elderly, 2.7% versus 3.8% in adults (10). Similar to this gadobutrol safety analysis, we did not see any serious drug-related AE or any death.

The results of the pharmacovigilance database confirmed the trend seen in the clinical studies towards lower rates of ADRs in the elderly population: in the elderly, we recorded 354 patients with ADRs in 1.7 million applications (0.021%) versus 439 patients with ADRs in 1.8 million applications (0.024%) in the adult group, which was statistically significant ($P = 0.0276$). This is in line with results from gadobutrol showing 0.005% and 0.011% of patients with ADRs in elderly and adults, respectively ($P < 0.0001$) (10).

The most frequent ADRs were hypersensitivity/immune system disorders, gastrointestinal disorders, and respiratory disorders. These results are in line with gadobutrol (10). The relatively high incidence of gastrointestinal disorders (>30%) might be due to the fact that only liver imaging patients were investigated while for gadobutrol MRIs from a large variety of body regions and diseases, mainly CNS or angiography, were taken.

The higher mortality in the elderly group is assumed to be related to the higher cancer morbidity expected in this population. For only two cases, a relationship to gadoxetate disodium administration could not be excluded.

Although the analysis of the two databases provided strong evidence for the consistent safety of gadoxetate disodium in both age groups, there are some limitations. First, the number of patients in the clinical studies was relatively small and the incidence of patients with drug-related AEs was low. Therefore, the different rates of patients with ADRs between the elderly and adults seen in the pharmacovigilance database could not be confirmed. Second, in pharmacovigilance databases as a tool for post-marketing reporting, however, under-reporting especially of mild delayed contrast media reactions (not so much for severe and acute

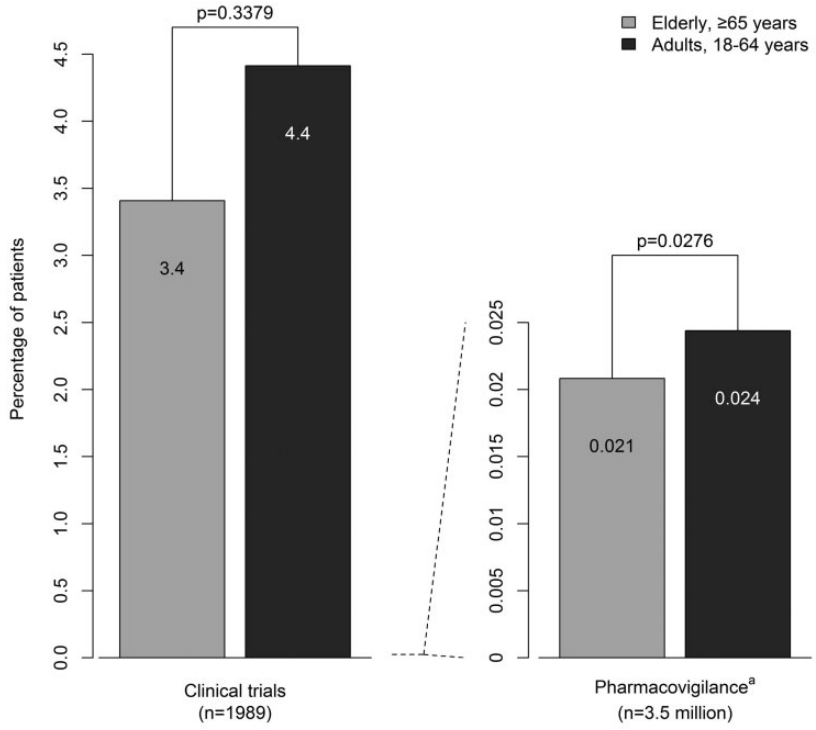

Fig. 3. Comparison of overall rates of patients with related AEs (clinical studies) and ADRs (pharmacovigilance database) in elderly vs. adults. (a) Pharmacovigilance rate of patients with ADRs is based upon utilization data for the number of administrations during the period 2004–2015, using liter volume sold according to Bayer internal sales reporting.

reactions) is well-known (14). The methodological differences in data capturing of the two databases must be respected when interpreting the findings.

In conclusion, this comprehensive evaluation of data confirms the favorable safety profile of gadoxetate disodium in all age groups and in particular in the sub-population of elderly patients (≥65 years). The incidence of patients with drug-related AEs in clinical studies was numerically lower and that of patients with ADRs significantly lower in elderly patients compared with younger adults.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Carsten Schwenke is an independent statistician; all other authors are employees of Bayer.

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References

1. Hammerstingl R, Huppertz A, Breuer J, et al. Diagnostic efficacy of gadoxetic acid (Primovist)-enhanced MRI and spiral CT for a therapeutic strategy: comparison with intraoperative and histopathologic findings in focal liver lesions. Eur Radiol 2008;18:457–467.
2. Ahn SS, Kim MJ, Lim JS, et al. Added value of gadoxetic acid-enhanced hepatobiliary phase MR imaging in the diagnosis of hepatocellular carcinoma. Radiology 2010; 255:459–466.
3. Bottcher J, Hansch A, Pfeil A, et al. Detection and classification of different liver lesions: comparison of Gd-EOB-DTPA-enhanced MRI versus multiphasic spiral CT in a clinical single centre investigation. Eur J Radiol 2013;82: 1860–1869.
4. Ringe KI, Husarik DB, Sirlin CB, et al. Gadoxetate disodium-enhanced MRI of the liver: part 1, protocol optimization and lesion appearance in the noncirrhotic liver. Am J Roentgenol 2010;195:13–28.
5. Zizka J, Klzo L, Ferda J, et al. Dynamic and delayed contrast enhancement in upper abdominal MRI studies: comparison of gadoxetic acid and gadobutrol. Eur J Radiol 2007;62:186–191.
6. Zech CJ, Korpraphong P, Huppertz A, et al. Randomized multicentre trial of gadoxetic acid-enhanced MRI versus conventional MRI or CT in the staging of colorectal cancer liver metastases. Br J Surg 2014;101:613–621.
7. Halavaara J, Breuer J, Ayuso C, et al. Liver tumor characterization: comparison between liver-specific gadoxetic acid disodium-enhanced MRI and biphasic CT–a multicenter trial. J Comput Assist Tomogr 2006; 30:345–354.
8. Gschwend S, Ebert W, Schultze-Mosgau M, et al. Pharmacokinetics and imaging properties of Gd-EOB-

DTPA in patients with hepatic and renal impairment. Invest Radiol 2011;46:556–566.
9. Endrikat JS, Dohanish S, Balzer T, et al. Safety of gadoxetate disodium: Results from the clinical phase II-III development program and postmarketing surveillance. J Magn Reson Imaging 2015;42:634–643.
10. Endrikat J, Schwenke C, Prince MR. Gadobutrol for contrast-enhanced magnetic resonance imaging in elderly patients: review of the safety profile from clinical trial, post-marketing surveillance, and pharmacovigilance data. Clin Radiol 2015;70:743–751.
11. Arlington Medical Resources. The imaging market guide. http://www.amr-data.com/ Available at: http://www.amr-data.com/AMRDiagnostic-Imaging-Data (accessed Dec 20, 2016).
12. World Health Organization. Technical Report Series No. 498. Geneva: WHO. Available at: http://who-umc.org/graphics/24756.pdf (accessed 20 December 2016).
13. Nobili A, Garattini S, Mannucci PM. Multiple diseases and poloypharmacy in the elderly: challenges for the internist of the third millenium. J Comorbidity 2011;1:28–44.
14. Michel A, Abudulah A, Schumann W. Spontaneous reporting of adverse drug reactions: estimation of under-reporting for contrast media reactions in 14 countries. Pharmacoepidemiol Drug Saf 2001;10(S1):34.