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# Gadobutrol for contrast-enhanced magnetic resonance imaging in elderly patients: review of the safety profile from clinical trial, post-marketing surveillance, and pharmacovigilance data

J. Endrikat [a,b,*], C. Schwenke [c], M.R. Prince [d]

[a] Department of Global Medical Affairs, Bayer HealthCare, Berlin, Germany
[b] Saarland University Hospital, Homburg, Saar, Germany
[c] SCO:SSiS Statistical Consulting, Berlin, Germany
[d] Department of Radiology, Weill Cornell Medical College, NY, USA

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AIM: To assess the safety of gadobutrol administration in elderly patients (≥65 years) by comparing the incidence of adverse drug reactions (ADRs) following gadobutrol-enhanced magnetic resonance imaging (MRI) procedures in elderly patients with that in adults aged 18–64 years.

MATERIALS AND METHODS: Safety data on gadobutrol administration from clinical trials, post-marketing surveillance (PMS) studies, and pharmacovigilance reports were collected in three databases. In each dataset, absolute and relative frequencies of ADRs between age groups were analysed, along with odds ratios and 95% confidence intervals. Logistic regression was used to identify significant influencing factors on ADRs in the PMS and pharmacovigilance data.

RESULTS: Rates of reported ADRs were lower in elderly patients versus adults aged <65 years due to a reduced incidence of non-serious ADRs; this was statistically significant for the clinical trials and pharmacovigilance populations, with a trend in the PMS database. Serious ADRs occurred infrequently in the clinical trials and PMS populations (too low for statistical comparison), and pharmacovigilance data demonstrated a low incidence (<0.005%) in both age groups.

CONCLUSIONS: This evaluation involving three large databases demonstrated no greater incidence of ADRs following gadobutrol-enhanced MRI in elderly patients (≥65 years) compared with younger adults, with gadobutrol having a favourable safety profile in both age groups.



* Guarantor and correspondent: J. Endrikat, Global Medical & Clinical Affairs Radiology, Radiology & Interventional, Bayer HealthCare Medical Care, Müllerstrasse 178, 13342 Berlin, Germany. Tel.: +49 30 468 194306; fax: +49 30 468 994306.
*E-mail address:* jan.endrikat@bayer.com (J. Endrikat).

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## Introduction

Gadolinium-based contrast agents (GBCAs) are used in magnetic resonance imaging (MRI) examinations to increase diagnostic confidence for the diagnosis of various conditions throughout the body. Gadobutrol, a macrocyclic GBCA with a 1 M concentration, has a proven favourable safety and efficacy profile and is approved for a wide range of MRI indications in all body regions in adults and children[e].[1–4] Gadobutrol is a second-generation (higher concentration and higher relaxivity compared with earlier agents), non-ionic GBCA, with favourable physicochemical properties that enable the formulation of a 1 M solution.[2] Gadobutrol's 1 M concentration allows smaller injection volumes to be used versus 0.5 M agents.[2]

Worldwide, there is a trend toward an aging population, due in part to increasing longevity, which may be related to improvements in primary disease prevention and healthcare provision.[5] Aging is frequently accompanied by chronic disease, comorbidity, frailty, and disability,[5] meaning that an aging population is predicted to undergo increasing numbers of diagnostic procedures, including MRI examinations. Due to this trend for greater numbers of comorbidities, elderly adults (aged >65 years) also tend to take a higher number of different drugs (polypharmacy) than younger adults.[5] Consideration of the health status of elderly patient is important with regard to administration of GBCAs, as these agents are excreted via the renal system (glomerular filtration) and elderly patients may have a decreased glomerular filtration rate.[6] An adverse reaction to a GBCA in a frail elderly patient might be expected to have a more severe outcome compared with a similar reaction in a healthier younger patient. Additionally, elderly patients with comorbidities may have an increased likelihood of adverse outcomes following medical procedures, due to the risks associated with polypharmacy and age-related changes in pharmacokinetic parameters and organ impairments.[5]

Adverse drug reactions (ADRs) are commonly used as a measure of the safety of pharmaceutical compounds, including contrast media. Results from randomised controlled trials provide reliable, unbiased evidence for the safety of contrast agents, while post-marketing surveillance (PMS) studies and pharmacovigilance reports add valuable data on "real-life" use of contrast agents in a large and varied population of patients, including the occurrence and frequency of rare ADRs. Previous analyses have reported on the safety of gadobutrol in a number of different patient populations,[1,3,7] but none have focused on the elderly population. The aim of this analysis was, therefore, to evaluate the incidence of ADRs following gadobutrol administration in elderly patients (aged ≥65 years) compared with that in adults aged <65 years (18–64 years), using three databases containing safety data from clinical trials, PMS studies, and pharmacovigilance reports, respectively. To the authors' knowledge, this is the first dedicated publication on the safety of an extracellular contrast agent in the elderly population.

## Materials and methods

All available safety data on gadobutrol administration within clinical trials, and in clinical practice following marketing approval, were collected. Statistical analyses were performed on the collective data sets (three separate databases) to compare the incidence of ADRs (non-serious ADRs, and serious ADRs where numbers of events were high enough for meaningful comparison) between subjects of two age groups: elderly patients aged ≥65 years and adults aged 18–64 years. Categorical data were recorded as absolute and relative frequencies and two-sided $p$-values <0.05 were regarded as statistically significant. Statistical analysis was performed using SAS version 9.2 (SAS Institute, Cary, NC, USA) and NCSS 2007 (NCSS, Kaysville, UT, USA). For the calculation of the odds ratios (ORs) for the comparison of age groups, the value 0.5 was added to each cell of the 2×2 table to avoid zero counts in any cell (95% confidence intervals [CIs] were based on non-central hypergeometric distribution and the exact test, allowing at least one confidence limit to be estimated for assessment of whether the OR was different from 1).

ADRs were defined as any adverse reaction following a gadobutrol-enhanced MRI procedure, which may be at least possibly related to gadobutrol administration. A serious ADR was defined as any ADR resulting in death, disability, a life-threatening condition, hospitalisation, or an extension of hospitalisation.

### *Clinical trials data*

The clinical study database included all Bayer HealthCare-sponsored gadobutrol studies conducted between 1992 and 2013, involving combined data from participants in 38 prospective Phase 2 to 4 trials. All trials were conducted in accordance with the Declaration of Helsinki and approved by the relevant local institutional review board. ADR reporting and evaluation was standardised across all studies, and all ADRs were categorised by *Medical Dictionary for Regulatory Activities* system organ class (SOC) and rated for severity. ADRs were recorded during an observation period of 24 to 72 hours following gadobutrol administration. The data were analysed descriptively along with pure ORs and exact 95% CIs. No adjustment for cofactors was included.

### *PMS data*

Reported ADRs from six prospective PMS studies, conducted at 300 centres in 11 countries (Austria, Canada,

[e] Gadobutrol is approved for children and adolescents from 2–17 years of age in different markets, including countries of the European Union, Switzerland, Canada, China, Korea, Australia, Philippines, and Mexico, among others. In the USA, gadobutrol is approved for all age groups, including term neonates, for imaging of the central nervous system and assessment of malignant breast disease.

Germany, Greece, Hungary, the Netherlands, Poland, Slovenia, Spain, Sweden, and Turkey) were included.[7] All studies were approved by the relevant institutional review board, had similar methodologies with respect to ADR reporting, and all ADRs were assessed similarly to those from the clinical trials. The influence of the cofactors gender, dose per kilogram of bodyweight (b.w.), and presence of any allergies were considered. "Study" was included as a random factor to account for differences between the studies (e.g., study size and proportions of each age group). Logistic regression was used to identify significant influencing factors by backward selection. The final model contained only the significant factors, using all patients with complete data on these factors. Odds ratios were calculated for significant factors along with 95% Wald confidence intervals. Analyses were conducted for total ADR incidence rates only; the number of serious ADRs was insufficient for statistical analyses.

### *Pharmacovigilance reporting data*

All ADRs reported to the Bayer pharmacovigilance department following gadobutrol administration were included, up to the cut-off date of 26 February 2013. Pharmacovigilance reports commonly included basic patient information (age, sex, weight, height, or a local identification number) along with a brief description of the ADR. All ADRs were categorised similarly to those from the clinical trials database. Due to the nature of pharmacovigilance data reporting, while the number of patients for whom an ADR was reported is known, the total number of people who received gadobutrol as part of a contrast-enhanced MRI procedure during the reporting period (1999–2013) is unknown. To estimate the overall incidence rate of ADRs in all patients who received gadobutrol, utilisation data for the whole reporting period would be required; however, utilisation data are only available for the period of 2007 to 2011, allowing estimation of ADR rates for this period. Utilisation was estimated based on litre volume sold (according to Bayer internal reporting and assuming a 10 ml average dose) and data on clinical administrations to patients collected directly from radiology centres in Europe, the USA, and Asia (annual Imaging Market Guides 2007 to 2011 from Arlington Medical Resources [AMR], Exton, PA, USA), which included patient demographic information (age, sex) and reasons for performing contrast-enhanced MRI.[8] Using these utilisation data to approximate the total number of patients to whom gadobutrol was administered, the odds of experiencing at least one ADR or serious ADR in each age group were estimated.

Logistic regression was used for binary data and multinomial regression was used for categorical data. The cofactors of gender and global region were accounted for, as well as the interactions of these cofactors with age, using likelihood ratio statistics for Type 3 analyses. All ADRs by SOC, and the reported rates of serious ADRs and deaths, were compared between the age groups. For serious ADRs and deaths, ORs were provided with Wald 95% CIs.

## Results

### *Clinical trials data*

The clinical trials database included 5608 patients for whom age data were available; 3911 adults <65 years (aged 18–64 years) and 1697 elderly (aged ≥65 years). The age-categorised populations were similar with regard to the dose of gadobutrol received (mean 0.10 mmol/kg b.w. for each), but there were some differences in terms of gender and global region representation (Table 1).

Overall, 150 adults aged <65 years (3.8%) and 46 elderly patients (2.7%) reported an ADR (Table 1). The OR for a comparison between the age groups favoured the elderly population, with significantly fewer reported ADRs in these patients ($p = 0.0392$). Fewer ADRs in many individual SOC categories were also reported in the elderly population as compared with adults aged <65 years, although some individual ADRs were reported more often in elderly patients; for example, feeling hot (Table 1). No serious ADRs or deaths were reported in either population.

### *PMS data*

The PMS database included 14,064 patients for whom age data were available; 9664 adults aged <65 years and 4400 elderly. Differences between the age groups were noted in terms of gender (a higher proportion of adults aged <65 years were female) and dosing (higher doses [≥0.20 mmol/kg b.w.] were reported for a greater proportion of the elderly population). Elderly patients exhibited a lower incidence of history of allergy than adults aged <65 years (Table 2), but this difference did not reach statistical significance.

Overall, 64 non-serious ADRs were reported; 13 (0.3%) in the elderly and 51 (0.5%) in adults <65 years. Although the ADR incidence was numerically lower in the elderly population, the comparison with the adult population did not reach statistical significance (OR: 0.56; 95% CI: 0.30–1.03; $p = 0.0614$). In modelling analyses, the cofactors gender and dose were not found to be significant and were deselected in the logistic regression analysis using backward selection of significant factors. A history of allergy, however, had an effect on the ADR rate and further logistic regression analysis was performed to analyse the effect by incorporating the cofactor "history of allergy" into the logistic model when estimating the OR for the comparison between age groups. The OR without adjustment was 0.56 (95% CI: 0.30–1.03); when adjusting for history of allergy, an OR of 0.71 (95% CI: 0.33–1.53; $p = 0.3835$) was found; therefore, the OR after adjustment for history of allergy was closer to 1, suggesting a lesser effect of age on the incidence of ADRs when taking into account a history of allergy.

The incidence of nausea in the elderly (0.16%) versus adults <65 years (0.2%) was not statistically different (OR: 0.81; 95% CI: 0.34–1.93; $p = 0.6317$; Table 2). The rates of occurrence of all other types of ADR were too low for

**Table 1**
Characteristics and adverse drug reaction incidence in the clinical trials population (38 trials).

| | Elderly, ≥65 years *n* (%) | Adults, 18–64 years *n* (%) | Odds ratio for ADR incidence Elderly versus adults (95% CI) |
|---|---|---|---|
| Total population ($n = 5608$) | 1697 | 3911 | |
| Gender | | | |
| Female | 776 (45.73) | 2094 (53.54) | – |
| Male | 921 (54.27) | 1817 (46.46) | – |
| Global region | | | |
| Europe | 1159 (68.30) | 2093 (53.52) | – |
| Rest of World | 538 (31.70) | 1818 (46.48) | – |
| Median dose administered (mmol/kg b.w.; range 0.01–0.51) | 0.10 | 0.10 | – |
| Total experiencing any ADR | 46 (2.71) | 150 (3.84) | 0.70 (0.49–0.98); $p = 0.0392$ |
| ADRs by SOC preferred term[a] | | | |
| Gastrointestinal disorders | 14 (0.82) | 41 (1.05) | 0.80 (0.39–1.48) |
| Nausea | 12 (0.71) | 26 (0.66) | 1.09 (0.49–2.19) |
| Vomiting | 0 | 5 (0.13) | 0.21 (NA–2.52)[b] |
| General disorders/ injection site reactions | 17 (1.00) | 28 (0.72) | 1.42 (0.72–2.66) |
| Feeling hot | 8 (0.47) | 10 (0.26) | 1.87 (0.63–5.21) |
| Injection site pain | 2 (0.12) | 8 (0.20) | 0.68 (0.06–2.89) |
| Investigations | 2 (0.12) | 19 (0.49) | 0.29 (0.03–1.00) |
| Nervous system disorders | 10 (0.59) | 44 (1.13) | 0.54 (0.23–1.05) |
| Dizziness | 1 (0.06) | 8 (0.20) | 0.41 (NA–2.15) |
| Dysgeusia | 3 (0.18) | 17 (0.43) | 0.46 (0.08–1.41) |
| Headache | 5 (0.29) | 13 (0.33) | 0.94 (0.25–2.65) |
| Skin and subcutaneous tissue disorders | 7 (0.41) | 21 (0.54) | 0.80 (0.28–1.88) |
| Vascular disorders | 0 | 5 (0.13) | 0.21 (NA–2.52)[b] |

ADR, adverse drug reaction; b.w., body weight; CI, confidence interval; SOC, system organ class.
[a] Those SOCs for which at least five reports per age group were reported.
[b] The value 0.5 was added to each cell of the 2×2 table to avoid zero counts in any cell when estimating the odds ratio. Statistical comparison not made.

**Table 2**
Characteristics and adverse drug reaction incidence in the post-marketing surveillance population.

| | Elderly, ≥65 years *n* (%) | Adults, 18–64 years *n* (%) | Odds ratio for ADR incidence Elderly versus adults (95% CI) |
|---|---|---|---|
| Total population ($n = 14064$) | 4400 | 9664 | |
| Gender ($n = 13808$)[a] | | | |
| Female | 2176 (50.41) | 5206 (54.85) | – |
| Male | 2141 (49.59) | 4285 (45.15) | – |
| Administered dose (mmol/kg b.w.)[b] | | | |
| <0.10 | 628 (14.65) | 1697 (17.97) | – |
| 0.10 < 0.20 | 2230 (52.01) | 5224 (55.33) | – |
| 0.20 < 0.30 | 1091 (25.44) | 2126 (22.52) | – |
| ≥0.30 | 339 (7.91) | 394 (4.17) | – |
| History of allergy (any)[c] | | | |
| Yes | 344 (10.23) | 897 (13.89) | – |
| No | 3018 (89.77) | 5563 (86.12) | |
| Total experiencing any ADR | 13 (0.30) | 51 (0.53) | 0.56 (0.30; 1.03); $p = 0.0614$ |
| ADRs by MedDRA 8.0 term | | | |
| Agitation | 0 | 1 (0.01) | – |
| Anaphylactic reaction | 1 (0.02) | 0 | – |
| Cephalgia | 0 | 1 (0.01) | – |
| Chills | 0 | 1 (0.01) | – |
| Circulatory collapse | 0 | 1 (0.01) | – |
| Cough | 0 | 1 (0.01) | – |
| Dyspnoea | 1 (0.02) | 1 (0.01) | – |
| Erythema (facial) | 1 (0.02) | 0 | – |
| Feeling of warmth | 0 | 3 (0.03) | – |
| Flushing | 0 | 2 (0.02) | – |
| Itching | 0 | 1 (0.01) | – |
| Itchy throat | 0 | 2 (0.02) | – |
| Lip swelling | 0 | 1 (0.01) | – |
| Localized feeling of warmth | 0 | 0 | – |
| Malaise | 0 | 1 (0.01) | – |
| Mucosal swelling | 0 | 1 (0.01) | – |
| Nausea | 7 (0.16) | 19 (0.20) | 0.81 (0.34–1.93); $p = 0.6317$ |
| Nausea (aggravated) | 1 (0.02) | 0 | – |
| Oral dryness | 0 | 1 (0.01) | – |
| Paraesthesia (hand) | 0 | 1 (0.01) | – |
| Pruritus | 0 | 1 (0.01) | – |
| Redness (facial) | 0 | 0 | – |
| Sensation of heat | 0 | 1 (0.01) | – |
| Skin disorder | 0 | 2 (0.02) | – |
| Skin reaction | 0 | 1 (0.01) | – |
| Sore throat | 0 | 1 (0.01) | – |
| Stomach pain | 1 (0.02) | 0 | – |
| Swelling | 0 | 1 (0.01) | – |
| Swelling of the lips | 0 | 1 (0.01) | – |
| Urticaria | 0 | 2 (0.02) | – |
| Vasodilation | 0 | 2 (0.02) | – |
| Vasovagal reaction | 0 | 1 (0.01) | – |
| Vomiting | 1 (0.02) | 0 | – |

Statistical comparison not made.
ADR, adverse drug reaction; b.w., body weight; CI, confidence interval; MedDRA, Medical Dictionary for Regulatory Activities.
[a] Data missing in 256 patients (173 aged 18–64 years and 83 in those ≥65 years).
[b] Data missing in 335 patients (223 aged 18–64 years and 112 in those ≥65 years).
[c] Data missing in 4242 patients (3204 aged 18–64 years and 1038 in those ≥65 years).

statistical comparison, including serious ADR (one reported in each age group).[7]

### *Pharmacovigilance reporting data*

The pharmacovigilance database included 2031 patients for whom ADRs had been reported between 1999 and the cut-off date of 26 February 2013; 1701 adults aged <65 years and 330 elderly (Table 3). The global regions from which reports were received were similar between the elderly and younger adult populations. A greater proportion of reports were received regarding ADRs in female versus male adults <65 years (64% and 34%, respectively; Table 3), while the ratio of ADRs in male and female elderly patients was equal (49% for each). Most pharmacovigilance reports were spontaneous (>97% in both age groups), with a small

**Table 3**
Characteristics of the population for whom adverse drug reactions were recorded as part of pharmacovigilance reporting.

| | Elderly ≥65 Years *n* (%) | Adults 18–64 Years *n* (%) |
|---|---|---|
| Total population ($n = 2031$) | 330 | 1701 |
| Gender | | |
| Female | 162 (49.09) | 1091 (64.14) |
| Male | 162 (49.09) | 572 (33.63) |
| Missing data | 6 (1.82) | 38 (2.23) |
| Global region | | |
| Europe | 224 (67.88) | 1053 (61.90) |
| Rest of world | 106 (32.12) | 648 (38.10) |
| Origin of report | | |
| Spontaneous | 323 (97.88) | 1691 (99.41) |
| Study | 4 (1.21) | 8 (0.47) |
| Published report of study | 2 (0.61) | 0 |
| Literature | 1 (0.30) | 2 (0.12) |

number of entries from observational studies, study reports, and published literature (Table 3).

The total number of ADRs (1999–2013) included in the analysis was 1834; 1533 in patients aged 18–64 years and 301 in elderly patients (age data not available in 197 patients). The distribution of ADR reports over time was not found to be significantly different between the age groups. A total of 600 patients reported 656 serious ADRs following gadobutrol administration; 474 (79%) of these patients were adults <65 years and 126 (21%) were elderly. Serious ADRs per patient by SOC are shown in Fig 1. Some variances between the age groups with respect to incidences involving each SOC were demonstrated; however, there was found to be, overall, no significant difference in the distribution of type of serious ADRs between the age groups ($p = 0.1497$). A record of death (at least possibly related to gadobutrol administration) was included for 16 of 1663 (1.0%) adults aged 18–64 years for whom an ADR was reported and data were available, and for seven of 324 (2.2%) elderly patients. Seven of the 16 deaths in adults aged <65 years and three of the seven deaths in elderly patients were associated with an acute anaphylactic reaction to contrast medium administration, which is a known adverse event previously reported in less than 0.5% of patients.[9,10] The trend for a higher percentage of mortality in elderly patients (2.2% versus 1.0% for adults) was not found to be significant (OR: 2.27; 95% CI: 0.93–5.57; $p = 0.0831$), but may be partially related to the higher morbidity expected in the elderly population (four of seven elderly patients suffered adverse events potentially related to underlying conditions or an unknown cause). Gender, region, and the respective interactions were not found to influence the incidence of deaths between the age groups significantly.

Utilisation data for gadobutrol during the period 2007 to 2011 (based on volume sold and AMR data) suggested a total of 13 million procedures were performed; 67.2% (8.74 million) in adults <65 years and 30.3% (3.94 million) in the elderly (the remaining 2.5% of procedures were performed in paediatric patients). The estimated distribution of body regions for which these examinations were performed are shown in Table 4. During this period, a total of 1145 ADRs were reported following an estimated 12.67 million administrations in patients aged ≥18 years; 958 (0.011%) in those aged 18–64 years and 187 (0.005%) in patients ≥65 years (Table 4). It might be anticipated that the rate of ADRs in each patient group would be proportional to the number of gadobutrol-enhanced examinations performed; however, the 30.3% of procedures performed in elderly patients accounted for only 16.3% of the 1145 ADRs reported, which is proportionally around half that which could have been expected (Fig 2; $p < 0.0001$). All ADRs reported during the period 2007–2011 for each age group are shown in Table 4, listed by SOC. There was a similar distribution of ADRs by SOC between the age groups ($p = 0.5660$). Serious ADRs were reported in 334 (0.0038%) adults <65 years and 87 (0.0022%) elderly patients. The comparison of the incidences of serious ADRs favouring elderly patients was

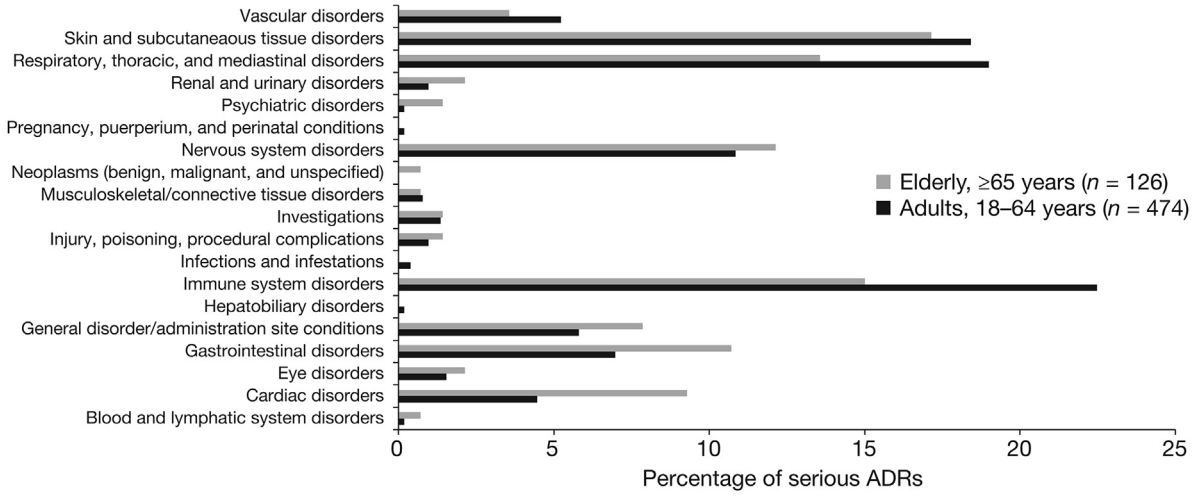


**Figure 1** Serious adverse drug reactions (ADRs) per subject, by system organ class, in the pharmacovigilance population (656 events in 600 patients, 1999–2013).

**Table 4**
Utilisation data on gadobutrol-enhanced MRI procedures between 2007 and 2011,[a] by body region,[b] and incidence of adverse drug reactions during this time period in the estimated pharmacovigilance population.

| | Elderly ≥65 years, *n* (%) | Adults 18–64 years, *n* (%) |
|---|---|---|
| **Total population (*n* = 12.67 million)**[c] | 3.94 million (30.3) | 8.74 million (67.2) |
| **Body region**[b] | | |
| Central nervous system | 1.52 million (38.7) | 3.63 million (41.6) |
| Blood vessels (angiography) | 1.47 million (37.3) | 2.01 million (23.0) |
| Extremities | 0.19 million (4.7) | 1.01 million (11.6) |
| Abdomen | 0.13 million (3.3) | 0.40 million (4.5) |
| Liver | 0.12 million (3.2) | 0.29 million (3.4) |
| Head/face/neck | 0.12 million (3.1) | 0.32 million (3.6) |
| Pelvis | 0.12 million (3.0) | 0.34 million (3.9) |
| Breast | 0.07 million (1.7) | 0.35 million (4.1) |
| Chest | 0.04 million (1.1) | 0.14 million (1.6) |
| Prostate | 0.06 million (1.6) | 0.04 million (0.5) |
| Kidney | 0.06 million (1.4) | 0.10 million (1.1) |
| Heart | 0.02 million (0.5) | 0.05 million (0.5) |
| Other | 0.02 million (0.5) | 0.05 million (0.5) |
| **Total ADRs** | 187 (0.005) | 958 (0.011) |
| **ADRs by SOC preferred term relative to the utilisation data** | | |
| Blood and lymphatic system disorder | 1 (<0.0001) | 0 |
| Cardiac disorder | 7 (0.0002) | 23 (0.0003) |
| Ear and labyrinth disorder | 0 | 6 (0.0001) |
| Eye disorder | 4 (0.0001) | 29 (0.0003) |
| Gastrointestinal disorder | 53 (0.0013) | 276 (0.0032) |
| General disorder/ administration site conditions | 14 (0.0004) | 65 (0.0007) |
| Hepatobiliary disorder | 0 | 1 (<0.0001) |
| Immune system disorder | 17 (0.0004) | 104 (0.0012) |
| Infections and infestations | 3 (0.0001) | 8 (0.0001) |
| Injury, poisoning, procedural, complication | 1 (<0.0001) | 9 (0.0001) |
| Investigations | 2 (0.0001) | 7 (0.0001) |
| Musculoskeletal/connective tissue disorder | 2 (0.0001) | 6 (0.0001) |
| Nervous system disorder | 14 (0.0004) | 55 (0.0006) |
| Pregnancy, puerperium, and perinatal conditions | 0 | 1 (<0.0001) |
| Psychiatric disorders | 1 (<0.0001) | 2 (<0.0001) |
| Renal and urinary disorders | 2 (0.0001) | 2 (<0.0001) |
| Respiratory, thoracic and mediastinal disorders | 20 (0.0005) | 112 (0.0013) |
| Skin and subcutaneous tissue disorders | 53 (0.0013) | 296 (0.0034) |
| Vascular disorders | 3 (0.0001) | 22 (0.0003) |
| **Serious ADRs** | 87 (0.0022) | 334 (0.0038) |
| **Deaths** | 4 (0.0001) | 13 (0.0001) |

ADR, adverse drug reaction; SOC, system organ class.
[a] Using litre volume sold according to Bayer internal sales reporting.
[b] Percentage distribution according to Arlington Medical Resources (AMR) for Gadovist® during 2007–2011. 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.
[c] Adults ≥18 years of age; a further 0.33 million administrations occurred in paediatric patients.

found to be significant (OR: 0.58; 95% CI: 0.48–0.71; $p < 0.0001$). Deaths at least possibly related to gadobutrol administration occurred in 13 of 1006 (1.3%) adults aged <65 years for whom an ADR was reported and data were

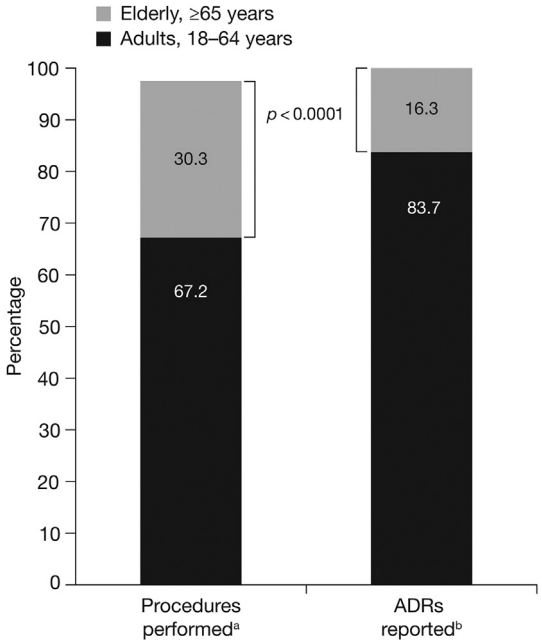


**Figure 2** Proportions of contrast-enhanced procedures performed and adverse drug reactions (ADRs) reported during the period 2007–2011, based on utilisation data. (a) Percentage of an estimated 12.67 million procedures, using utilisation data from litre volume sold according to Bayer internal sales. (b) Percentage of 1145 reported ADRs.

available, and 4 of 192 (2.1%) elderly patients. The difference in incidence of death in favour of the adults aged <65 years was found not to be significant (OR: 1.63; 95% CI: 0.52–5.04; $p = 0.3346$). An estimated death rate, based on utilisation data for 2007–2011, would be 1.49 per million doses (13 in 8.74 million, 0.0001%) in adults <65 years and 1.02 per million doses (four in 3.94 million, 0.0001%) in elderly patients. These estimated death rates are within the range previously reported for GBCA use in the USA (0.15–2.7 deaths per million doses).[11]

*Summary*

Our data suggest that rates of reported ADRs were lower in elderly patients aged ≥65 years compared with adults aged <65 years, with statistical significance demonstrated for the clinical trials and pharmacovigilance populations and a trend for a lower incidence in elderly patients in the PMS database (Fig 3).

## Discussion

This analysis of the safety of gadobutrol in adults aged <65 years and in the elderly (≥65 years) included a large number of subjects and demonstrated a low rate of ADRs in both age groups, with similar results from each of the three data sources analysed. These data confirm the favourable safety profile of gadobutrol, as reported from a number of previous studies.[1–3,7] However, to the authors' knowledge, this is the first large study to specifically investigate the

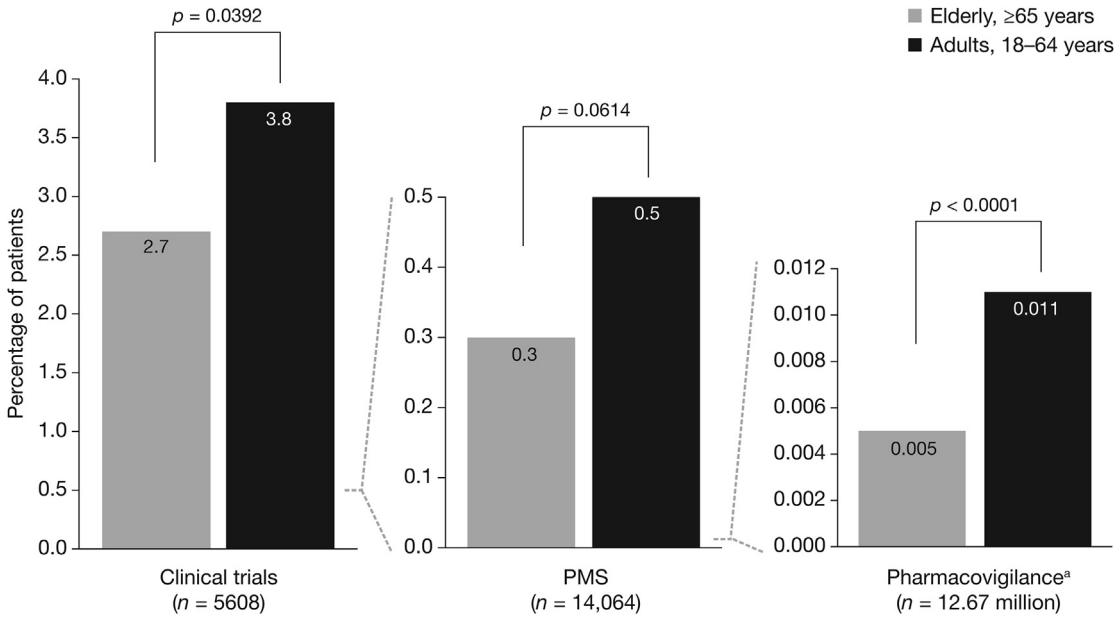


**Figure 3** Comparison of overall ADR rates for elderly versus adult patients from each database analysed. (a) Pharmacovigilance ADR rate based upon utilisation data for the number of administrations during the period 2007–2011, using litre volume sold according to Bayer internal sales reporting.

safety of GBCA administration in elderly patients, and a lower incidence of non-serious ADRs was demonstrated in these patients versus adults aged <65 years.

The well-being of elderly people is of growing concern, due to an increase in the proportion of this age group worldwide, especially in Asian countries such as Japan (where the percentage of elderly people has quadrupled in 50 years, from 5.7% to 23.1%).[12] It is important to assess the safety of drugs in elderly patients, as this population can demonstrate greater comorbidity and frailty than younger adults.[5] Renal function may also be lower in elderly patients, which may have an influence on the elimination rate of drugs and contrast media. The lower rate of reported ADRs demonstrated for elderly patients who received gadobutrol may appear counterintuitive, given the greater likelihood of comorbidity in this population. An explanation for this finding may be that elderly patients have a less active immune system due to aging-related immunosenescence and immune remodelling,[13] and may be less likely to have an overt reaction to an allergic stimulus. Alternatively, it has been suggested that the elderly may be less likely to report ADRs (as they are for symptoms of illness in general) due to considering these a "normal" part of aging, as well as concerns over being dismissed or needing burdensome tests, or communication problems, including hearing and speech deficits.[14]

Each of the three databases analysed (clinical trials, PMS, and pharmacovigilance) yielded a similar result with regard to a lower rate of reported non-serious ADRs in elderly versus adults <65 years. This inter-database confirmation fosters confidence in the conclusion that gadobutrol demonstrates a favourable safety profile in elderly patients. It is notable that the overall rate of ADR reporting was higher in the clinical trials database compared with the other two spontaneous-reporting sources. Under-reporting of ADRs in post-marketing clinical use has been widely reported in the literature,[15–17] and this phenomenon may partially explain the difference in ADR incidence between the data sources.

A greater proportion of higher dosing of gadobutrol was noted for elderly versus adults aged <65 years in the PMS database; this may be related to a greater proportion of magnetic resonance angiography (MRA) procedures in these patients (as noted in the utilisation data, Table 4; 37.3% elderly versus 23.0% adults <65 years), for which higher dosing is indicated (standard dosing of gadobutrol for MRI of all body regions is 0.1 mmol/kg b.w., while standard dosing for MRA is 0.1–0.15 mmol/kg b.w. for one field of view and 0.2–0.3 mmol/kg b.w. for more than one field of view). As utilisation data for gadobutrol use were based on an average dose of 10 ml per MRI examination, a higher average dose of gadobutrol in elderly patients may have led to an overestimation of the number of examinations performed in these patients. This may, in part, account for the lower than expected ADR rate in elderly subjects within the pharmacovigilance database; however, if this assumption is made, it would follow that no increase in ADR incidence was associated with a higher dose. The PMS data also suggested an association between ADR incidence and patient history of allergy. These data support previous findings for GBCA, suggesting that the frequency of ADRs in patients with previous allergies is almost double that in subjects with no known allergies.[18]

In the pharmacovigilance database, a greater proportion of ADRs were reported in female versus male adults aged

<65 years, while for elderly patients the incidence of ADRs was similar between the genders. Female gender is a known risk factor for ADRs generally, due to differences in pharmacokinetics and pharmacodynamics between the sexes; specifically, females have a higher percentage of body fat (which can affect the volume of drug distribution), reduced renal clearance, and altered hormone and enzyme activities compared with males.[19] Females have also been noted to experience a higher incidence of drug-induced liver toxicity and allergic skin rashes versus males.[19] The equivalent rate of ADRs in both genders of elderly patients in this database may be partially explained by potentially smaller differences in hormone levels, renal function, and body composition between females and males with advancing age.[20,21] Other studies involving a number of different pharmacological agents have reported that female gender as a risk factor for ADRs persists for elderly patients,[22,23] while an American prospective cohort study found no influence of age or gender on ADR rates in multivariate analyses of ambulatory patients.[24] Therefore, further research may be required to fully elucidate the role of female gender on susceptibility for ADRs generally, and specifically, with regard to contrast media reactions rather than those to pharmacological agents.

Although the present study demonstrated strength in the consistent outcomes gained from a large number of patients in three separate data sources, it also had some limitations. The overall incidence of serious adverse reactions to contrast media is very low; therefore, the numbers of serious ADRs in the clinical trials and PMS populations were too low to allow statistical comparison between the age groups. Additionally, spontaneous reporting of ADRs following gadobutrol administration may have resulted in under-reporting of mild and moderate ADRs.

Reports of total ADRs following gadobutrol administration have been increasing in proportion with the growth in worldwide availability and the numbers of procedures performed; however, the future incidence of ADRs is predicted to remain stable or to decline below the current low rates due to a wider understanding of ADR risk factors and preventative measures, and a trend for reduced contrast media dosing.[25–27]

In conclusion, this comprehensive evaluation of data confirms the favourable safety profile of gadobutrol in general, and in particular, in elderly patients (≥65 years). The study utilised three separate data sources (clinical trials, PMS, and pharmacovigilance data) and demonstrated that non-serious ADRs were consistently less frequent in elderly patients compared with younger adults. A lower incidence of history of allergies may, in part, explain the reduced ADR rates in elderly compared with younger adult patients, and the likelihood of spontaneous reporting of mild ADRs may be lower in the elderly population. These data suggest that there is no greater incidence of ADRs following gadobutrol-enhanced MRI in elderly patients compared with younger adults, and that gadobutrol has a favourable safety profile in both age groups.

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