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Safety of Gadobutrol

Results From 42 Clinical Phase II to IV Studies and Postmarketing Surveillance After 29 Million Applications

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Objective: The aim of this study was to provide a systematic safety analysis of gadobutrol after more than 29 million applications in clinical routine.

Materials and Methods: Forty-two clinical development phase II to IV studies on gadobutrol or comparator and the postmarketing safety surveillance database for gadobutrol (1998–2015) were analyzed. Adverse events (AEs) and drug-related AEs were evaluated in the clinical development database and spontaneous adverse drug reactions (ADRs) in the postmarketing database. Subgroup analyses were run on patients with special medical history and on patients of different age groups.

Results: In the clinical development studies, 6809 and 2184 patients received gadobutrol or comparators, respectively. The incidence of drug-related AEs was 3.5% for both groups. With the exception of nausea (0.7% related cases in both groups), all other drug-related AEs were 0.3% or less in both groups. Hypersensitivity reactions were sporadic (<0.1%). Patients with history of allergies to contrast agents experienced slightly more drug-related AEs. No differences were seen between age groups.

The overall reporting rate of ADRs from postmarketing surveillance was 0.05%. The most frequent ADRs were anaphylactoid/hypersensitivity reactions, nausea, vomiting, and dyspnea.

For 3 single-agent reports of nephrogenic systemic fibrosis, using a conservative approach, association with gadobutrol could not be excluded.

Conclusions: Gadobutrol is well tolerated and has a favorable safety profile for patients of all age groups.

Key Words: gadobutrol, GBCA, contrast agent, MRI, safety

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Gadobutrol (Gadovist, Gadavist; Bayer Pharma AG, Leverkusen, Germany) is a gadolinium-based contrast agent (GBCA) for magnetic resonance imaging (MRI), approved for a broad range of indications in all age groups. In Europe and a number of other countries, gadobutrol is indicated for all body regions in adults and children including term newborns.[1] However, the range of approved indications and the age range depend on the country-specific label.

Gadobutrol is a second-generation extracellular, macrocyclic, nonionic GBCA[2,3] with particular physicochemical properties that enable the unique formulation of a 1 mol/L solution,[2,4] twice the gadolinium concentration of other currently licensed extracellular GBCAs. Thus, gadobutrol's 1 mol/L concentration halves the injection volume compared with 0.5 mol/L agents.[2] In addition, Gadobutrol features a 20% to 30% higher relaxivity at 1.5 T compared with other macrocyclic agents.[2,4,5] The macrocyclic structure of gadobutrol provides greater chelate stability and therefore a lower propensity of gadolinium release compared with linear GBCAs.[6,7] In this context, it is important to understand that for macrocyclic GBCAs, thermodynamic stability (ie, equilibrium between chelate and ligand + free gadolinium) is an inadequate and irrelevant parameter to assess the stability. The only relevant parameter is kinetic inertness (ie, the dissociation half-life to reach the equilibrium).[6,7] It can only be measured under extreme conditions such as pH 1, and the dissociation half-lives have been extrapolated from these measurements to pH 7.4.[7] As a result, at physiological pH, all macrocyclic GBCAs—also irrespective of their ionicity—show half-lives exceeding 1000 years,[7] which by far exceeds the elimination time even in patients with severe renal impairment of approximately 15 days. The stability of GBCAs is clinically important because the release of gadolinium ions has been associated with the development of nephrogenic systemic fibrosis (NSF) in patients with severe renal impairment.[8,9] In view of these characteristics, gadobutrol has been placed in the lowest risk category for development of NSF.[10–12]

The recommended standard dose of gadobutrol for intravenous injection is 0.1 mmol/kg body weight (bw), with doses up to 0.3 mmol/kg bw approved in Europe and some other countries for specific indications in adults. At these doses, the efficacy and safety of gadobutrol have been demonstrated in numerous clinical studies in adults and children, including term newborns.[2,13–17]

Gadobutrol was first introduced in Switzerland in February 1998. Through December 31, 2015, more than 29.6 million patients worldwide are estimated to have received gadobutrol. While monitoring safety continuously, passing the 29 million landmark was the trigger for this comprehensive summary of gadobutrol's safety data.

MATERIALS AND METHODS

Data Sources

This comprehensive retrospective safety analysis was based on 2 data sets: (1) an integrated safety analysis database of 42 clinical development phase II to IV studies and (2) the global postmarketing surveillance database for gadobutrol.

Clinical Development Phase II to IV Studies

The 42 interventional studies, conducted globally between 1993 and 2014, encompassed 13 phase II studies, 27 phase III studies (including 2 phase I/III studies in pediatric population 0–18 years), and 2 phase IV studies. Twenty-three clinical phase II to IV were single-arm gadobutrol studies, 13 had a parallel group design with either different gadobutrol doses or gadobutrol and a comparator contrast agent, and 6 were crossover studies with either different gadobutrol doses or gadobutrol and a comparator contrast agent. Comparators were either gadopentetate dimeglumine (Gd-DTPA, Magnevist), gadodiamide (Omniscan), gadoversetamide (OptiMark), gadoteridol (ProHance), or gadoterate meglumine (Gd-DOTA, Dotarem).

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Most studies were conducted for MRI of the central nervous system (CNS). Other studies were conducted for the indications of MR angiography (MRA) (the second most common) as well as MRI of the liver, kidney, breasts, and various other body regions.

All clinical studies were conducted in accordance with International Conference on Harmonization Good Clinical Practice, the principles of the Declaration of Helsinki, and all applicable national regulations valid at the time the studies were performed.

The global postmarketing surveillance database is run by the Bayer HealthCare Global Pharmacovigilance Department. This department receives reports on adverse drug reactions (ADRs) from worldwide sources, not only from health care professionals (physicians, pharmacists, nurses) but also from scientific publications, regulatory authorities, and patients or lay persons. During the period from the first marketing authorization in Switzerland on February 26, 1998, through December 31, 2015, nearly 30 million patients worldwide are estimated to have received gadobutrol.

Study Population

The study population of the 42 clinical phase II to IV studies consisted of patients of all ages (term newborns up to patients older than 90 years) with a clinical need for various diagnostic contrast-enhanced MRI. Special attention was paid to patients with specific risk factors, for example, renal impairment, reduced liver function, cardiovascular disorders, general history of allergies, and specific history of allergies to contrast agents. Two studies recruited children aged 0 to 18 years. All patients (or their legal representatives) gave written informed consent before the start of the study.

No selection criteria were applied for patients for whom ADRs were reported to the Pharmacovigilance Department.

Treatments

In the 42 clinical development phase II to IV studies, a total of 6809 patients received gadobutrol, and 2184 received one of the following comparators: Gd-DTPA (n = 1097), gadodiamide (n = 150), gadoversetamide (n = 227), gadoteridol (n = 555), and Gd-DOTA (n = 155). All contrast agents were administered by a single intravenous bolus injection followed by a saline chaser.

Gadobutrol was administered at a dose range from 0.01 mmol/kg to 0.51 mmol/kg bw. Most subjects (n = 4765) received the standard dose of 0.1 mmol/kg bw. Two hundred ninety-two subjects received a dose between 0.01 and less than 0.09 mmol/kg, and 47 patients received 0.31 to 0.51 mmol/kg bw, a dose above the approved dose. The dose for comparators was mainly 0.1 mmol/kg bw.

Study Procedures

In all clinical phase II–IV studies, demographic data and medical history (in particular history of renal, liver, cardiovascular diseases, and allergies) were recorded. Once contrast-enhanced MRI was performed, patients were asked about their well-being in an unsolicited way to gather information about adverse events (AEs). The follow-up period lasted from just the examination day up to 72 hours.

Target Variables

The key target variables of this analysis were the number of patients with and the characteristics of AEs, drug-related AEs, and serious AEs for the clinical phase II to IV studies and ADRs for the postmarketing surveillance part. All events were coded using MedDRA version 17.0. An AE was defined as any illness, sign or symptom, or unfavorable change in the clinical status that had appeared or worsened after study start, whether or not it was considered to be related to contrast agent administration. All AEs were evaluated for seriousness and potential relationship to contrast agent administration by experienced health care professionals in each institution. Drug-related AEs comprised the categories "possibly," "probably," and "definitely" related to contrast agent administration.

A serious AE was defined as any AE that (1) resulted in death, (2) was life-threatening, (3) required subject hospitalization or prolongation of existing hospitalization, (4) resulted in a persistent or significant disability/incapacity, (5) resulted in a congenital anomaly/birth defect, or (6) was considered an otherwise medically significant event.

Postmarketing Surveillance

In the postmarketing surveillance database, all AE reports received by the company (drug-related or unrelated) and reports attributed to the product derived from the scientific literature are recorded. The global pharmacovigilance database also contains serious events occurring in clinical trials and from other studies. For regulatory and reporting purposes, a causal association is assumed for individual spontaneous reports of ADRs. However, these reports are assessed individually and in aggregate for causality by the Pharmacovigilance Department of Bayer HealthCare. During this process, the temporal relationship of the AE to drug administration, the known pharmacological properties of the product, confounding factors (eg, patient's medical history and concurrent conditions, concomitant medications), the epidemiology of the disease state and the reported event, possible reporting biases, and previous experience with the product and comparators are taken into account.[18]

Statistics

All patients who received at least 1 dose of gadobutrol or comparator were included in this safety analysis. Subjects who got multiple doses within less than 1 hour, the doses were summed up and counted once. Patients in crossover studies with different contrast agents were

TABLE 1. Demographic Data of Study Population of Clinical Studies Phase II–IV

No. Patients, n (%)	Gadobutrol 6809 (100)	Comparators* 2184 (100)
Sex		
Male	3444 (50.6)	1140 (52.2)
Female	3365 (49.4)	1044 (47.8)
Age, y		
Mean ± SD	55.6 ± 16.4	55.1 ± 14.8
Min, Max	7 d, 93 y	18 y, 89 y
<18	184 (2.7)	0
18 to 65	4383 (64.4)	1549 (70.9)
≥65	2242 (32.9)	635 (29.1)
Weight, kg		
Mean ± SD	69.4 ± 17.3	69.2 ± 16.6
Min, Max	2.8, 145.2	30.9, 145.0
Ethnic origin		
White	4161 (61.1)	1146 (52.5)
Black	109 (1.6)	42 (1.9)
Hispanic	370 (5.4)	44 (2.0)
Asian	1992 (29.3)	858 (39.3)
Other	177 (2.6)	94 (4.3)
Region		
Europe	3812 (56.0)	944 (43.2)
United States/Canada	562 (8.3)	194 (8.9)
South/Central America	446 (6.6)	184 (8.4)
Asia	1961 (28.8)	853 (39.1)
Australia	28 (0.4)	9 (0.4)

*Gadopentetate dimeglumine (n = 1097), gadodiamide (n = 150), gadoversatamide (n = 227), gadoteridol (n = 555), and gadoterate meglumine (n = 155).

SD indicates standard deviation; Min, minimum; Max, maximum.

TABLE 2. Incidence of AEs, Clinical Studies Phase II–IV

	Gadobutrol 6809 (100)		Comparators* 2184 (100)	
No. Patients, n (%)	**Total**	**Drug-Related**	**Total**	**Drug-Related**
AEs	663 (9.7)	241 (3.5)	216 (9.9)	77 (3.5)
SAEs	20 (0.3)	1 (<0.1)	4 (0.2)	0 (0.0)
Death	1 (<0.1)	0 (0.0)	1 (<0.1)	0 (0.0)
Most frequent AEs				
Headache	100 (1.5)	21 (0.3)	23 (1.1)	3 (0.1)
Nausea	75 (1.1)	48 (0.7)	30 (1.4)	15 (0.7)
Dizziness	34 (0.5)	9 (0.1)	13 (0.6)	4 (0.2)
Injection site reactions	30 (0.4)	18 (0.3)	12 (0.5)	5 (0.2)
Feeling hot	26 (0.4)	22 (0.3)	8 (0.4)	7 (0.3)
Vomiting	26 (0.4)	9 (0.1)	8 (0.4)	7 (0.3)
Dysgeusia	24 (0.4)	23 (0.3)	7 (0.3)	7 (0.3)
Rash	19 (0.3)	14 (0.2)	4 (0.2)	2 (0.1)
Erythema	11 (0.2)	4 (<0.1)	2 (0.1)	1 (<0.1)
Dyspnea	11 (0.2)	4 (<0.1)	1 (<0.1)	0 (0.0)
Pruritus	10 (0.1)	7 (0.1)	2 (0.1)	1 (<0.1)
Paresthesia	8 (0.1)	5 (<0.1)	5 (0.2)	2 (<0.1)
Hypersensitivity	2 (<0.1)	2 (<0.1)	0 (0.0)	0 (0.0)

*Gadopentetate dimeglumine (n = 1097), gadodiamide (n = 150), gadoversatamide (n = 227), gadoteridol (n = 555), and gadoterate meglumine (n = 155).

AE indicates adverse event; SAE, serious adverse event.

analyzed by period. An analysis by age was performed, looking at 3 age brackets as follows: younger than 18 years, 18 to 65 years, and 65 years or older.

All variables were analyzed by descriptive statistical methods. Adverse event incidence rates were calculated by dividing the number of patients reporting 1 specific AE by the number of patients exposed times 100 to receive percentages. The same was done for the ADR reporting rates in the postmarketing surveillance part. All analyses were performed post hoc. The statistical evaluation was performed using the software package SAS release 9.2 for UNIX (SAS Institute Inc, Cary, NC).

RESULTS

Clinical Development Phase II to IV Studies

A total of 6809 and 2184 patients were included in the database for gadobutrol and comparators, respectively. The demographic data were very similar with the exception that patients younger than 18 years were only included in the gadobutrol group (Table 1).

The incidence of drug-related AEs was 3.5% in the gadobutrol and the comparator group. Serious AEs (including deaths) were similarly low (<0.1%) in both groups. For gadobutrol, the most frequent drug-related AEs were headache, nausea, dizziness, injection site reactions, feeling hot, and dysgeusia. With the exception of nausea, 0.7% drug-related cases in both groups, all other drug-related AEs were 0.3% or less. Hypersensitivity reactions were sporadic, that is, less than 0.1% (Table 2).

The most frequent indication for MRI was CNS imaging, followed by MRA and all other single body regions. Drug-related AEs were recorded in 4.2% and 4.6% for CNS and 3.7% and 4.9% for MRA in the gadobutrol and the comparator group, respectively. In 9 of 182 children (4.9%), drug-related AEs were reported (Table 3).

There were no remarkable differences in the incidence of drug-related AEs between patients with or without renal impairment, elevated liver enzymes, or cardiovascular diseases. Patients with history of allergies in general—or specifically allergies to contrast agents—experienced slightly more drug-related AEs. Within the small number of 25 patients with history of allergies to contrast agents, 3 (12%) showed a drug-related AE (Table 4).

The incidence of drug-related AEs by age group is shown in Figure 1. The rates of 4.9%, 4.0%, and 2.6% for the age groups younger than 18 years, 18 to 65 years, and 65 years or older, respectively, were not statistically significantly different.

Postmarketing Surveillance

Patient exposure to gadobutrol (per year) increased steadily from 416 patients in 1999, the year after market introduction, to more than 5.7 million in 2015. The ADR reporting rate in the postmarketing surveillance was highest in the years 2001 and 2002, reaching 0.09%. Lowest rates of 0.04% were seen in 2003, 2006, and 2013. The average from 1999 to 2014 was 0.05% (Fig. 2).

Through December 31, 2015, approximately 6000 AE reports have been received by the Pharmacovigilance Department, containing nearly 15,000 AEs. Most of these (approximately 75%) are nonserious. The reports were in males (31%), females (56%), and patients of unknown sex (13%) ranging in age from younger than 1 year to 94 years. There is no discernible difference in the nature and intensity of events by age group. The reports came from 61 countries, with the highest numbers of reports received from the United States (24%), Germany (16%), Canada (12%), France (7%), Great Britain (6%), and Italy (5%). The most frequently reported ADRs in the postmarketing surveillance database were anaphylactoid/hypersensitivity reactions featuring a reporting rate of 0.019%. As with most other GBCAs, fatal anaphylactoid reactions are exceedingly rare. Less frequent were nausea, vomiting, and dyspnea with rates of 0.005%, 0.004%, and 0.002%, respectively. All other single ADRs were

TABLE 3. Incidence of AEs by MRI Indication of Clinical Studies Phase II–IV

	Gadobutrol			Comparators		
Indication	**No. Patients (100%)**	**Total AEs, n (%)**	**Drug-Related AEs, n (%)**	**No. Patients (100%)**	**Total AEs, n (%)**	**Drug-Related AEs, n (%)**
CNS	2671	319 (11.9)	112 (4.2)	1316*	163 (12.4)	60 (4.6)
MRA	1548	135 (8.7)	57 (3.7)	81†	7 (8.6)	4 (4.9)
Body	2408	155 (6.4)	63 (2.6)	787†	46 (5.8)	13 (1.7)
Children	182	54 (29.7)	9 (4.9)	—	—	—

*Gadopentetate dimeglumine (n = 229), gadodiamide (n = 150), gadoversatamide (n = 227), gadoteridol (n = 555), and gadoterate meglumine (n = 155).

†Gadopentetate dimeglumine.

AE indicates adverse event; MRI, magnetic resonance imaging; CNS, central nervous system; magnetic resonance angiography.

TABLE 4. Incidence of Drug-Related AEs by Medical History, Clinical Studies Phase II–IV

	Gadobutrol		Comparators	
	No. Patients (100%)	Drug-Related AEs, n (%)	No. Patients, (100%)	Drug-Related AEs, n (%)
Renal impairment, eGFR,* mL/min				
<30	44	3 (6.8)	—	—
30 to <60	659	18 (2.7)	175	6 (3.4)
60 to <90	1940	68 (3.5)	567	21 (3.7)
≥90	2249	113 (5.0)	749	39 (5.2)
Liver function† (ALT or AST)				
3.0 ULN < max ALT/AST	90	3 (3.3)	32	0 (0.0)
1.8 ULN < max ALT/AST ≤ 3.0 ULN	159	7 (4.4)	—	—
Max ALT/AST ≤ 1.8 ULN	3815	160 (4.2)	1396	64 (4.6)
Cardiovascular disorder				
No	3578	142 (4.0)	1374	45 (3.3)
Yes	3231	99 (3.1)	810	32 (4.0)
History of allergies‡				
No	6048	199 (3.3)	1909	64 (3.4)
Yes	761	42 (5.5)	275	13 (4.7)
History of allergies to contrast agents				
No	6784	238 (3.5)	2170	77 (3.5)
Yes	25	3 (12.0)	14	0 (0.0)

*Estimated glomerular filtration rate level immediately before injection; patients with eGFR ˃60 mL/min were considered to have a normal renal function.

†Baseline maximum values of alanine aminotransferase or aspartate aminotransferase; patients whose liver enzymes were <1.8 upper limit of normal range were considered to have a normal liver function.

‡All allergies, including allergic reactions to contrast agents.

AE indicates adverse event; eGFR, estimated glomerular filtration rate; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal range.

0.001% or less (Table 5). Dosing was not a factor in the reports; where the information was provided, most patients appeared to be dosed appropriately.

As of December 2015, a total of 12 reports of NSF or NSF-like symptoms in patients who reportedly were administered gadobutrol have been received. Four of these are "single-agent reports"; that is, in which patients reportedly received only gadobutrol, 3 of the 4 single-agent reports were derived from literature.[19,20] The other 8 reports are confounded by the administration of other GBCAs ("multiple-agent reports"). In assessing these reports, Bayer utilizes the criteria developed by Girardi et al[21] and applies the criteria very conservatively. Not having direct access to the patient, the patient's past contrast use, or even to the biopsy report in most cases, thus often having to rely on minimal information, Bayer gives the report the highest possible score based on the information available. Using this conservative "worst-case scenario" approach, 3 of the 4 single-agent reports meet the criteria for being diagnostic of or consistent with NSF,[21] and a possible association with gadobutrol cannot be excluded. The fourth single-agent report contained information that was insufficient for evaluation. All 3 patients were multimorbid. The largest single dose administered to any patient with reported NSF was 0.49 mmol/kg bw. Onset of NSF-like symptoms in these 3 reports occurred in 2006, 2008, and 2009. Onset latency ranged from 14 days to 18 months.

DISCUSSION

This publication is a systematic analysis of safety data on gadobutrol reported in 42 prospective clinical phase II to IV studies performed all over the world complemented by reports from 17 years of postmarketing surveillance. The rate and quality of AEs, drug-related AEs, and ADRs was consistent with those of other GBCAs.[14,22–24] The findings did not give rise to any specific safety concerns regarding gadobutrol.

Clinical Development Phase II to IV Studies

The incidence of drug-related AEs was 3.5% in the gadobutrol and the comparator group. However, the comparator group, consisting of 5 agents, was not as homogeneous as it appears. The incidence rates for drug-related AEs of the comparators varied between 1.9% and 7.4%. We did not present these data because the single comparator groups were markedly smaller and the number of patients varied between n = 150 and n = 1097. Unfortunately, a direct comparison with the pertinent literature is difficult as there is no published overall safety

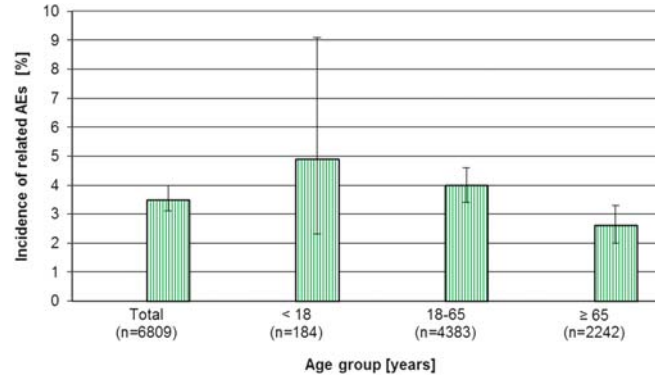

FIGURE 1. Incidence of drug-related AEs by age group, clinical studies phase II to IV (percent and 95% confidence intervals*). *Exact 95% confidence intervals were computed by Clopper-Pearson method.

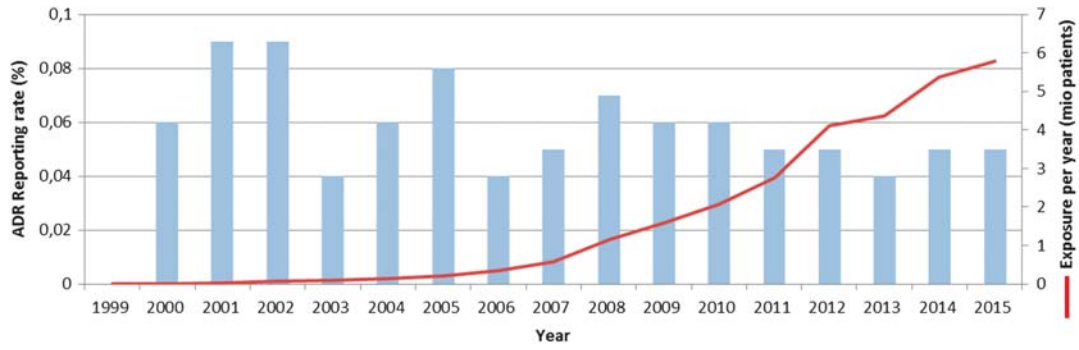

FIGURE 2. ADR reporting rate and patient exposure by year, 1999 to December 31, 2015.

evaluation of phase II to IV studies for other GBCAs. However, some data from phase III and IV studies are available. A recent phase III study by Gutierrez et al[25] compared gadobutrol with gadoteridol and recorded rates for treatment-related AEs of 10.0% and 9.7%, respectively. When focusing on phase IV studies, data for gadobutrol, gadoterate meglumine, and gadobenate dimeglumine are available. Forsting et al[13] reported on 14,299 patients on gadobutrol a rate of drug-related AEs of 0.55%, Ishiguchi and Takahashi[26] on 3444 patients on gadoterate a rate of drug-related AEs of 0.93%, and Fakhran et al[27] on 132,252 administrations of gadobenate a rate of drug-related AEs of 0.18%.

The most frequent drug-related AEs were headache, nausea, and dizziness. This is in line with other publications, although for other GBCAs, some different AEs were also in the group of most frequent reactions, for example, hives and dyspnea,[27] vomiting and hives,[22] vomiting and urticaria,[26] and vomiting and feeling hot.[13]

No increase in the incidence of drug-related AEs was seen in special risk populations, such as patients with renal impairment, elevated liver enzymes, or cardiovascular diseases. In addition, Maurer et al[28] did not report a higher risk for developing drug-related AEs in patients with renal failure, liver dysfunction, or on β-blocker in their study of 84,621 patients on gadoteric acid.[28] In contrast, patients with liver and kidney disorders showed a significantly higher ($P < 0.0001$) risk of experiencing drug-related AEs in the gadoterate study by Ishiguchi and Takahashi.[26] In a large multinational and multiethnical study on 37,788 patients who got contrast-enhanced cardiovascular MR, Bruder et al[29] investigated the safety of different GBCAs in this specific risk population. The rate of drug-related AEs varied from 0.05% (gadodiamide) to 0.42% (gadobenate). Gadobutrol featured a rate of drug-related AEs of 0.1%. They conclude that GBCA use in cardiovascular MR is to be regarded as safe.

Interestingly, patients with history of allergies—or specifically allergies to contrast agents—experienced slightly more drug-related AEs although the numbers were small. This result confirms the findings by Maurer et al who also found a higher drug-related AE risk in patients with allergies and patients with a history of allergic reactions to contrast agents.

A particular strength of this research is the broad age range of the population. Data were captured from 7-day old newborns to elderly up to 93 years; however, only for gadobutrol but not for comparators. The incidence of drug-related AEs in children younger than 18 years was 4.9%, not statistically significantly different from the other age groups. Hahn et al[15] evaluated 138 children 2 to 17 years (2–6 years, n = 46; 7–11 years, n = 47; 12–17 years, n = 48) on gadobutrol and reported 8 children (5.8%) with drug-related AEs. Kunze et al[17] analyzed findings on newborns and toddlers younger than 2 years and found 1 (2.8%) of 44 case of drug-related AE. In an observational study also in children younger than 2 years, Bhargava et al[16] did not find any drug-related AE in 60 patients while Glutig et al[30] reported a rate of drug-related AEs of 0.5% in 1142 children younger than 18 years in another observational study. For gadobenate dimeglumine, no drug-related AEs were identified in a retrospective study of 200 children 4 days to 15 years of age.[31] The other end of the age range was evaluated by Endrikat et al who used 3 databases (clinical trials, postmarketing surveillance, and pharmacovigilance reports) to investigate the impact of age on safety in elderly patients. They conclude that gadobutrol has a favorable safety profile also in patients aged 65 years or older.[32]

Postmarketing Surveillance

While annual patient exposure to gadobutrol increased steadily from 416 patients in 1999 to more than 5.7 million in 2015, the postmarketing surveillance ADR reporting rate averaged approximately 0.05%. As the highest rates were documented in the early years in 2001–2002, a trend toward lower rates over time could be postulated. This is in line with the Weber effect, that is, increasing reporting rates toward the end of the second calendar year after market introduction followed by a decline.[33] The spikes in between might be caused by the sequential market introduction of gadobutrol over the whole world, for example, approval in 1998 in Switzerland, 1999 in Canada, 2000 in Germany, 2009 in China, 2011 in the United States, and 2015 in Japan. Thus, the initial increase and subsequent decrease is not as clear as described by Knopp et al,[34] who evaluated the safety of Gd-DTPA after 45 million applications. They reported an initial rate of 0.016%, declining to 0.002% after 14 years.[34] Likewise, Matsumura et al,[35] also looking into Gd-DTPA over 25 years, recorded a decline from 0.021% to 0.014%. Although Gd-DTPA was the first MR contrast on the market (1988), the average AE reporting rate is lower than the 0.05%, reported here for gadobutrol. Matsumura et al[35] recorded an AE rate of 0.0144%. This might be caused by an increasing vigilance and preparedness of health care professionals to report safety results to authorities. This hypothesis is supported by figures for gadobenate dimeglumine (Gd-BOPTA), introduced in 1998, approximately at the same time as gadobutrol (1999). Gd-BOPTA featured an overall ADR reporting rate of 0.05%,[36] nearly similar to gadobutrol. Gadobutrol's overall ADR spectrum was comparable with Gd-DTPA[35] and Gd-BOPTA.[34]

Finally, pharmacovigilance databases generally yield lower ADR rates compared with results from clinical development phase II to IV studies, as reporting is voluntary, and the motivation to report depends on a number of factors.

As of Dec 2015, pharmacovigilance has received 3 single-agent reports consistent with the clinicohistopathological definition of NSF. This classification was rigorously performed by Bayer scientists after the most stringent and conservative approach according to the criteria by Girardi[21]; that is, the assessment/classification represents a worst-case scenario. This needs to be considered when data and numbers regarding NSF reports from different sources are compared as the interpretation and the use of a categorical score when assessing non-categorical biological parameters leaves some room for interpretation and may introduce variance. Bayer continues to follow a policy of total

TABLE 5. ADRs From Postmarketing Surveillance (Exposure n = >29.6 million); Cutoff at 25 Events (≥0.0001%)

ADR	No. Events	Reporting Rate, %
Anaphylactoid/hypersensitivity reactions*	5811	0.019
Nausea/retching	1626	0.005
Vomiting	1208	0.004
Dyspnea	542	0.002
Throat irritation	360	0.001
Cough	252	0.0007
Paresthesia	174	0.0006
Feeling hot	168	0.0006
Dizziness	167	0.0006
Malaise	158	0.0005
Chest pain	148	0.0005
Sweating	141	0.0005
Loss of consciousness	137	0.0005
Flushing	123	0.0004
Tachycardia/heart rate increased	116	0.0004
Headache	111	0.0004
Syncope	87	0.0003
Injection site reaction	86	0.0003
Hypoesthesia	85	0.0003
Feeling cold/chills	77	0.0003
Upper respiratory congestion/irritation	77	0.0003
Abdominal pain	67	0.0002
Convulsions/seizures	61	0.0002
Edema/localized edema	61	0.0002
Burning sensation	56	0.0002
Lacrimation increased	56	0.0002
Hypertension/blood pressure increased	51	0.0002
Rash pustular	51	0.0002
Difficulty swallowing	49	0.0002
Tremor	46	0.0002
Medication error	44	0.0001
Pallor	44	0.0001
Peripheral edema	44	0.0001
Lack of drug effect	42	0.0001
AE/ADR NOS	41	0.0001
Cardiac arrest	41	0.0001
Skin reaction	39	0.0001
Feeling abnormal	36	0.0001
Pain in extremity	36	0.0001
Taste disorders/dysgeusia	35	0.0001
Vertigo	33	0.0001
Cardiac disorder	32	0.0001
Asthenia	31	0.0001
Dysphonia/hoarseness	31	0.0001
Pain/discomfort	31	0.0001
Sensation of foreign body	31	0.0001
Respiratory arrest	30	0.0001
Pulmonary edema	29	0.0001
Cyanosis	28	0.0001
Bradycardia/heart rate decreased	27	0.0001
Increased salivation	27	0.0001
Dermatitis	26	0.0001
Hypoxia/oxygen saturation decreased	26	0.0001
Speech disorders	26	0.0001

Continued next page

TABLE 5. *(Continued)*

*Angioedema, anaphylactic/anaphylactoid reaction/shock, hypotension, bronchospasm, conjunctivitis, hypersensitivity reaction, erythema, rash, pruritus, laryngeal edema, sneezing, and urticaria.

ADR indicates adverse drug reaction; AE, adverse event; NOS, not otherwise specified.

transparency regarding NSF, with expedited case reporting to health authorities all over the world.

Finally, it is important to note that the European Medicines Agency[12] has defined 3 risk categories for GBCAs, which are also applied in the recommendations by the European Society of Urogenital Radiology.[11] Three macrocyclic agents, including gadobutrol, have been identified as GBCAs with the lowest risk potential for NSF. Nevertheless, even macrocyclics should be used with caution in patients with chronic kidney disease stage 4 or 5 (glomerular filtration rate <30 mL/min). There should be at least 7 days between 2 injections, and in pregnant women, contrast enhancement should only be considered in case essential information is expected. However, laboratory testing of renal function (estimated glomerular filtration rate) is not mandatory.[11] In the United States, the FDA has mandated a boxed warning on the product labeling of all GBCAs,[37] including gadobutrol, but gadobutrol is not one of the products that is contraindicated in the severely renally impaired population.

In October 2013, Kanda et al[38] reported about an increase in T1 signal intensity in the brain (globus pallidus and nucleus dentate) on unenhanced T1-weighted MRI scans and associated the signal increase with previous multipurpose linear GBCA administrations. Other groups reported meanwhile similar results, and 2 articles were able to measure gadolinium in tissue probes.[39,40] The signal increase in the brain is mainly seen with the linear GBCAs Omniscan,[41] Magnevist,[42–44] and MultiHance,[44,45] whereas no enhancement is seen with the macrocyclic GBCAs ProHance,[44] Dotarem,[43] and Gadovist.[42,46,47]

A safety review as presented with this study has mainly 2 limitations: (1) the comparator groups of the phase II to IV clinical studies are too small for a reasonable comparison, so that only pooling these agents allowed for a meaningful assessment; and (2) data on newborns and children are only available for gadobutrol because no head-to-head studies were carried out on safety in this vulnerable population.

There are many limitations to postmarketing reporting, including underreporting (more seen for mild and delayed contrast media reactions than for very severe acute contrast reactions) and differences in reporting behavior, which have been described previously.[48] For these reasons, data from postmarketing surveillance can only be represented by reporting rate and not by incidence.

CONCLUSIONS

Gadobutrol is a well-tolerated macrocyclic GBCA with higher relaxivity and higher concentration, which has a good safety profile as shown from results of 42 clinical phase II to IV studies and postmarketing surveillance over 17 years and more than 29 million applications.

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