

Prevalence of Acute Reactions to Iopromide: Postmarketing Surveillance Study of 74,717 Patients

A. F. KOPP, K. J. MORTELE, Y. D. CHO, P. PALKOWITSCH, M. A. BETTMANN & C. D. CLAUSSEN

Department of Diagnostic Radiology, Eberhard-Karls-University Tuebingen, Germany Division of Abdominal Imaging and Intervention, Department of Radiology, Brigham and Women's Hospital, Boston, Massachusetts, USA Kosin University Gospel Hospital, Busan, South Korea Bayer Schering Pharma AG, Berlin, Germany; WFU School of Medicine-Radiology, Winston-Salem, North Carolina, USA

Kopp AF, Morteles KJ, Cho YD, Palkowitsch P, Bettmann MA, Claussen CD. Prevalence of acute reactions to iopromide: postmarketing surveillance study of 74,717 patients. *Acta Radiol* 2008;49:902-911.

Background: Iodinated X-ray contrast media (CM) are recognized worldwide to be among the safest and most widely used injectable drugs. However, adverse drug reactions (ADRs) may still occur, ranging in severity from minor disturbances to severe and potentially fatal complications.

Purpose: To prospectively determine the incidence and characteristics of acute ADRs during clinical utilization of a single nonionic monomeric contrast agent, iopromide, in routine radiological practice in a large number of nonselected patients.

Material and Methods: 74,717 patients were enrolled in a prospective international postmarketing surveillance registry with iopromide (Ultravist; Bayer Schering Pharma AG, Berlin, Germany). A standardized questionnaire was used to collect the following patient information from 762 centers in 27 countries: baseline demographics, risk factors, premedication regimen, type of examination, route of injection, volume and selected concentration of iopromide, and overall tolerance to CM (utilizing specific criteria and descriptors).

Results: The overall rate of ADRs, including tolerance indicators (TI) (i.e., heat sensation and pain at the injection site), was 2%; when TIs were excluded, the rate was 1.5%. Fourteen serious adverse reactions were reported (rate 0.02%), of which none were fatal. There was a higher incidence of ADRs among women and for the age group ranging between 18 and 30 years. Patients with established risk factors, such as a history of previous CM reaction or allergic diathesis (7.4% and 4.1%, respectively), were at an increased risk for developing an ADR when compared to patients without risk factors (1.2%). The incidence of ADRs was not altered by the use of premedication.

Conclusion: The safety of iopromide in routine clinical practice was shown to be comparable to the published safety profiles of other nonionic iodinated contrast agents. Adverse drug reaction rates were affected by age, gender, and risk factors (especially previous CM reactions or allergies), but not by premedication.

Key words: Adverse drug reactions; computer tomography; contrast agents; radiography

Andreas F. Kopp, Department of Diagnostic Radiology, Eberhard-Karls-University Tuebingen, Hoppe-Seyler-Str. 3, Tuebingen, D-72076, Germany (tel. +49 7071 29 82087, fax. +49 7071 295845, e-mail. andreas.kopp@uni-tuebingen.de)

Accepted for publication May 29, 2008

Iodinated X-ray contrast media (CM) are recognized worldwide to be among the safest and most widely used injectable drugs. Because they are administered purely for diagnostic reasons, they are expected to have higher risk margins and improved safety profiles compared to therapeutic agents. However, despite their generally excellent safety record, ad-

verse drug reactions (ADRs) may still occur, ranging in severity from minor disturbances to, in very rare cases, fatal complications (1, 2).

Because of the relatively small numbers of patients used in phase-II and -III clinical trials, it is difficult to determine the occurrence and frequency of extremely rare ADRs. Postmarketing

surveillance (PMS) studies and observational trials, therefore, provide an opportunity to obtain further knowledge of a contrast agent's safety and tolerability in the "real world" setting (3). The framework of a PMS program was chosen for this study because this method provides an opportunity to collect prospective data from a very large, non-selected patient population. Over the past 25 years, several large-scale clinical and PMS studies (4–8) have been conducted worldwide, using various nonionic contrast agents, for the purpose of identifying and assessing the profiles and rates of ADRs for X-ray CM. Although differing in focus, design, and patient population, these investigations have certain methodological features in common which permit the comparison of individual results, such as large patient populations, the routine clinical use of CM, clear definition of ADRs, and well-defined data collection. An underlying assumption of all of these reports is that because contrast agents in a particular class (i.e., nonionic monomers) have very similar molecular structures, they will also have similar safety profiles, both in terms of the nature and the frequency of ADRs. There are obvious concerns with any such registries, but with the control of certain parameters, such as the definition of clear criteria for including patients according to the local package insert, recording of risk factors, and uniform assessment and reporting of ADRs, some of these limitations can be addressed.

This prospective observational surveillance study was conducted to provide reliable quantitative estimates of the risks associated with the administration of intravascular iopromide (Ultravist; Bayer Schering Pharma AG, Berlin, Germany) in large patient populations, particularly with respect to variances in ADRs among different patient populations, following the use of different diagnostic procedures, and for rarer ADRs. In addition, we investigated the safety of iopromide in patients thought to be at a greater risk for ADRs (i.e., patients with a previous CM reaction and/or with a history of allergies) and the relative efficacy of prophylactic measures.

Material and Methods

Study design and objective

This was a prospective, noninterventional, nonrandomized, multicenter, open-label, observational project. The primary objective was to gain further knowledge on the tolerance of iopromide in X-ray examinations, in unselected patients, in routine clinical practice. The study was sponsored and

financially supported by Bayer Schering Pharma AG, Berlin, Germany.

Patients

A total of 74,717 nonselected patients underwent contrast-enhanced (CE) X-ray examination. Patient enrollment started in centers in Germany in 1999 and was expanded gradually to include 27 countries around the world (details of the countries involved are included in Table 1). The different centers participated at different times of the surveillance project. Patient enrollment ceased in November 2003.

Observational plan

Contrast agent was administered in accordance with the policies and procedures in force in the individual institutions and countries. The number of patients per center and the total number of centers were

Table 1. Participation by region.

Country/region	Number of patients
Europe	52,996
Germany	34,989
Bulgaria	292
Latvia	400
Croatia	496
Switzerland	1,440
Estonia	173
Finland	447
Lithuania	2,562
Italy	167
Poland	1,140
Romania	1,411
Serbia/Montenegro	865
Slovakia	1,336
Slovenia	4,851
Turkey	340
Spain	2,008
Ukraine	79
Africa	400
Egypt	300
South Africa	100
America	7,101
USA	7,101
Asia	14,555
Thailand	297
Turkey	340
Jordan/Syria	1,677
China Rep. (Taiwan)	200
Philippines	1,807
Saudi Arabia	239
Korea Rep.	9,995
Total patients	75,052

From a total of 75,052 patients, some patients were not eligible for analysis and had to be excluded. A total of 74,717 patients were included in 27 countries from June 1999 to November 2003.

not predetermined. The centers were recruited consecutively as the registry was extended to include other countries. The length of their participation was driven by the anticipated number of patients to be enrolled.

All investigators were informed of the objectives, variables, and specific aspects of this surveillance. A standardized questionnaire, which permitted the systematic and integrated analysis of the data, was used. Inclusion and exclusion criteria were according to the indications and contraindications specified in the local package insert. Iopromide was administered in a routine manner at the operator's discretion, according to diagnostic indication and need. The use of premedication was at the discretion of the attending physician.

Observational variables

The following variables were recorded in the case report form (CRF) for each patient: demographics (within the confines of local regulations, e.g., American Health Insurance Portability and Accountability Act), risk factors (allergic diathesis, prior CM reaction), comorbidity (those identified were: renal failure, cardiac failure, coronary artery disease, diabetes mellitus, autoimmune disease, dehydration, and compromised general condition; other comorbidities could be reported as free text), premedication regimen, type of examination, route of injection, volume and selected concentration of iopromide, and overall tolerance to CM.

Any acute ADRs that occurred within the observed time (by definition, 1 hour; this timeframe was chosen because it seemed to be feasible for routine clinical practice) were described in a separate questionnaire, detailing the symptoms, onset, duration, intensity, and causal relationship. The following anticipated ADRs were identified based on their known potential occurrence in conjunction with the administration of contrast media and were queried by check box: warmth/heat sensation, alteration in taste, nausea/vomiting, pain (location specified), itching, erythema/exanthema/urticaria, edema (location specified), sneezing/coughing, dyspnea/bronchospasm, and sudden decrease/increase in blood pressure. In addition, the investigator was given the opportunity to report any other observed ADRs as free text. Specific common symptoms were defined as tolerance indicators (TIs). These included heat sensation and/or pain (occurring 0–5 min after injection and localized at the injection site). No laboratory tests were required. The intensity of the reaction/symptom was classified as mild, moderate, or severe, and was up to the assessment of the

investigator. In addition, the ADR was to be designated serious if it met one of the following criteria: resulted in death; was life threatening; required inpatient hospitalization/prolongation of current hospitalization; resulted in persistent or significant disability/incapacity; or resulted in a congenital anomaly/birth defect.

Statistical analysis

All data obtained from the CRF for the patients who were included in the surveillance were analyzed using basic statistical methods, such as frequency tables and descriptive statistical parameters. Statistical analysis of ADRs was confined to the intravascular use of iopromide, unless stated otherwise. Not all parameters were available for all patients. The results are based on the number of patients for whom specific parameters were available. The chi-square test was conducted according to Pearson. *P* values were not calculated for all ADR rates because of the design of this observational registry.

Software used

Management and analysis of data were performed in Windows 2000 (Microsoft, Redmond, Wash., USA) and with Novell NetWare (version 4.11; Waltham, Mass., USA). Data analysis was performed with SAS (version 8.2; SAS Institute Inc., Cary, N.C., USA).

Ethical approval

The surveillance was conducted in accordance with local legal and ethical requirements. Investigational review board approval was obtained where it was required.

Results

Patients

A total of 767 centers across 27 countries agreed to participate in this study, from which 74,717 patients, who had undergone routine radiographic examinations with iopromide, were included. Inclusion of patients in this study was dependent on the treating physician (radiologist, cardiologist, urologist, or other specialist). Most patients (almost 70%) in our observed population received iopromide for contrast-enhanced computed tomography (CECT) using a power injector. Overall, 87.6% (error) had IV (intravenous) administration.

The majority of patients were from Germany ($n = 34,989$), South Korea ($n = 9,995$), and the US ($n = 7,101$). These countries were analyzed separately

because of the large patient population involved. Demographic data are shown in Table 2. The mean age of patients in this study was 56.1 ± 16.66 years, with the majority of patients between 50 and 80 years of age (65.1%). Twenty-six percent of the patients included in the study had one or more risk factors or the presence of chronic disease. In this group of at-risk patients, women were overrepresented: 62% of the patients with allergic diathesis and 53.1% of the patients with a history of prior CM reaction were female.

Premedication was administered to 6,577 patients (8.8%); however, it was apparent that there were considerable differences in the premedication regimens across the various countries involved. For example, in the US, the majority of the patients (66.9%) were premedicated with H1-blockers only, while the use of corticosteroids (33.7%) was much

more frequent in Asia than in other regions. Premedication was given to a total of 23.6% of patients with a documented allergic diathesis and 43.3% of patients with a documented previous CM reaction. Altogether, 27% of these at-risk patients had received some type of premedication. Premedication was not confined to the patients with identifiable risk factors: 2.7% of patients without specific risk factors received premedication.

Type of examination/administration of contrast media

The most frequent examination was CECT followed by IV urography (Table 2). Iopromide was administered in concentrations of 150, 240, 300, and 370 mg/ml. The most common iodine concentration utilized was 300 mg/ml (76.1%), followed by 370 mg/ml (21.9%). A greater proportion of the

Table 2. Demographic summary, contrast administration, and type of examination

Patients										
Gender	Male 52.9%						Female 47.1%			
Age, years	<1	1–10	10–18	18–30	30–40	40–50	50–59	60–69	70–80	≥80
	0.4%	1.0%	1.2%	4.6%	8.8%	14.9%	20.7%	26.4%	18.0%	4.1%
	Risk factor/comorbidity, % patients									
	26%									
Risk factor/comorbidity	Distribution of risk factors/comorbidities									
Allergic diathesis	10.3%									
Prior CM reaction	2.1%									
Renal failure	4.2%									
Cardiac failure	6.1%									
Coronary disease	28.1%									
Diabetes mellitus	18.3%									
Autoimmune disease	0.6%									
Dehydration	1.1%									
Reduced general condition	9.8%									
Others	19.2%									
Premedication										
Total patients with premedication	8.8%									
H1-blocker	15%									
H2-blocker	6.2%									
Corticosteroids	12.1%									
H1- and H2-blocker	4.1%									
Combination therapy (H1, H2, and corticosteroids)	17.3%									
Other	45.3%									
Route of administration	Intravenous					Intraarterial			Others*	
	87.6%					11.2%			1.2%	
Dose of iodine	≤20 g			>20–40 g			>40–60 g		>60 g	
	19.5%			62.3%			15.9%		2.3%	
Type of examination	CECT	Urography		Angiocardioradiography			Angiography	Phlebography	Rest [†]	
	69.2%	14.8%		6.9%			5.3%	2%	1.8%	
Means of administration	Automatic injection			Manual injection			Infusion		Multiple entities	
	58.9%			25.6%			10.8%		4.6%	

* "Others" includes intrathecal and administration into other body cavities, or missing information.

† "Rest": percutaneous transluminal coronary angioplasty (PTCA), percutaneous transluminal angioplasty (PTA), and "not specified." CM: contrast media; CECT: contrast-enhanced computer tomography.

Table 3. Incidences of adverse drug reactions.

ADR rate										
Route of administration	Overall 2% Intravenous 2.1%						Excluding TIs 1.5% Intraarterial 1.1%			
	Mild 0.55%			Moderate 0.48%			Severe 0.17%		Serious 0.02%	
Gender	Male 1.3%						Female 1.7%			
	<1 year 0%	1–10 1%	10–18 0.8%	18–30 1.9%	30–40 1.8%	40–50 1.7%	50–60 1.3%	60–70 1.2%	70–80 1%	≥ 80 years 0.6%

ADR: adverse drug reaction; CM: contrast media; TI: tolerance indicator.

exams involved IV administration than intraarterial (87.6% versus 11.2%, respectively). About 65% of the intraarterial (IA) examinations were angiocardigraphies and percutaneous transluminal angioplasties. For 1.2% of the examinations, the route of administration was either missing or iopromide was administered by other routes (e.g., intrathecally). Administration was by automatic injector in 58.9% of exams, manual injection in 25.6%, infusion in 10.8%, and a combination in the remaining 4.6%. The mean volume of iopromide administered was 99.3 ml (mean IV 95.6 ml, IA 132.6 ml).

Adverse drug reactions

Overview. A total of 2,388 single different manifestations of ADRs were reported in 1,470 patients (2.0%). Excluding TIs, the number of patients with at least one ADR was 1,069 (1.5%) (Table 3). A higher ADR rate was reported following IV administration compared with IA use (2.1% versus 1.1%, respectively; $P < 0.0001$). There was no apparent correlation between the incidence of ADRs and the amount of contrast medium received for either IV or IA administration. The incidences of different ADRs are shown in Table 4.

Maximum intensity and outcome. Serious ADRs (SADRs) were reported in 0.02% of the patients ($n=14$ patients). Eleven SADRs were considered to be anaphylactoid reactions and presented as skin reactions, edema, dyspnea, decrease in blood pressure, and/or other symptoms. Most of these cases required further medical treatment or hospitalization, or were considered potentially life threatening. One patient experienced atrial fibrillation, and two patients were reported to have lost consciousness. None of those 14 patients had documented allergic histories or prior CM reactions.

The maximum intensity of ADRs (excluding TIs) as rated by the investigators was mild in 38.0% (rate 0.55%), moderate in 32.2% (rate 0.48%), and severe in 15.5% (rate 0.17%) of patients; the maximum intensity was not specified for 17.3% of the ADRs (rate 0.25%). Eighty percent of these cases were considered to be TIs and taste disturbances, 15% anaphylactoid reactions (ranging from urticaria/erythema, nausea, coughing, and sneezing to a fall in blood pressure), and the remaining 5% were attributed to other symptoms such as pain, restlessness, and vertigo.

There were no permanent injuries or deaths reported in any of the patients. The most frequently reported ADR was heat sensation, followed by nausea/vomiting (Table 3). "Other" symptoms were documented in 0.18% of cases, the most common being vertigo; sensations/symptoms of the throat, tongue, or eye; tachycardia; muscle trembling; restlessness; and dizziness. No previously unidentified ADRs were reported.

Adverse drug reaction rates for specific symptoms also differed between IV and IA administration: "nausea/vomiting" 0.54% versus 0.35%, respectively; "itching and skin reactions" 0.59% versus 0.35%, respectively; and "blood pressure

Table 4. Incidences of adverse drug reactions.

Type of ADRs	
Heat sensation	1.14%
Nausea/vomiting	0.52%
Metallic taste	0.44%
Erythema/exanthema/urticaria	0.31%
Itching	0.25%
Sneezing/coughing	0.05%
Edema	0.06%
Dyspnea/bronchospasm	0.06%
Increase/decrease blood pressure	0.06%
Pain	0.18%
Other	0.18%

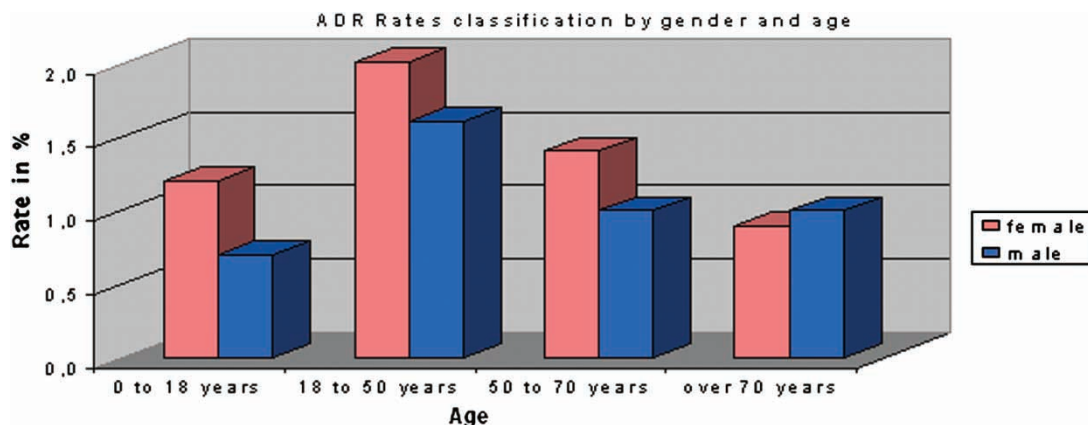


Fig. 1. Adverse drug reaction (ADR) rates in subgroups, categorized by age and gender.

changes" 0.06% versus 0.12%, respectively.

Adverse drug reaction rates as a function of age and gender. Among all patients ≤ 18 or > 70 years of age, the incidence of ADRs was less than 1% (Table 3). The highest rate of ADRs overall occurred in the subgroup aged 18–30 years (1.9%) ($P < 0.0001$). Females had a significantly higher rate of ADRs than males ($P < 0.0001$). This was true up to the 70 years of age, peaking in the 18–50 years age group, with an incidence of 1.9%. The distribution of ADR rates by gender and age is shown in Fig. 1.

Adverse drug reaction rates as a function of risk factors/comorbidity. A total of 25,264 risk factors/comorbidity factors were documented in 19,402 patients. Excluding TIs, patients without documented risk factors had an ADR incidence of 1.2%, and among patients with one or more risk factors the ADR rate was 2.0% ($P = 0.23$). Regarding specific

risk factors, an ADR rate of 7.4% (a 6.2-fold increase compared to the population as a whole, $P < 0.0001$) was seen in the subgroup of patients with a history of a previous CM reaction, and a rate of 4.1% (3.4-fold increase) was observed in the group with an "allergic diathesis." The distribution of ADR intensity among patients with risk and/or comorbidity factors, as compared to those patients without, is shown in Fig. 2. The intensity of the ADRs did not differ between those patients with and without risk factors ($P = 0.06$). The intensity of ADRs among patients with an "allergic diathesis" or with a previous CM reaction was mild in 38% versus 58.3%, moderate in 48.9% versus 41.7%, and severe in 13% versus 0%, respectively.

Adverse drug reaction rates as a function of premedication. The classification of ADR rates according to premedication (excluding TIs) is shown in Table 5. There were no significant

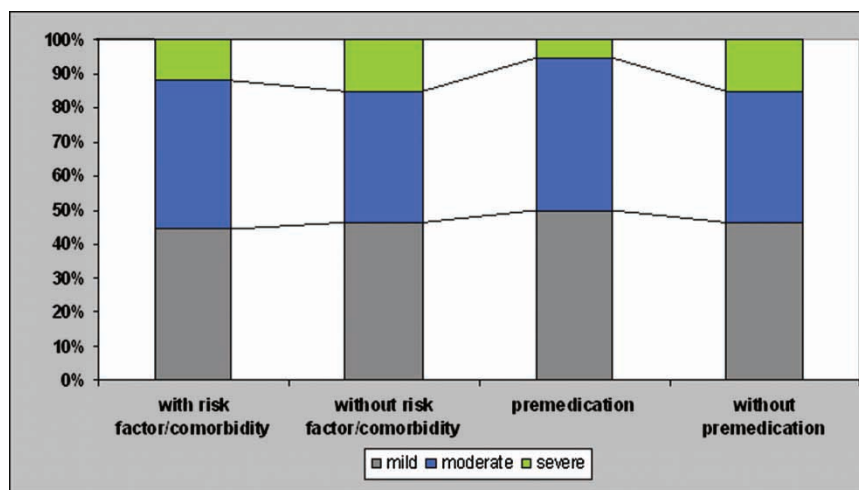


Fig. 2. Maximum intensity of adverse drug reactions in patients with/without risk factors and in patients with/without premedication.

Table 5. Adverse drug reaction rates.

	Premedication	No premedication
Patients with former CM reaction	6.7%	6.5%
Patients with allergic diathesis	3.1%	4.2%

CM: contrast media.

differences in the ADR rates between the subgroups ($P=0.34$). The distribution of ADR intensity among patients with and without premedication is shown in Fig. 2. The intensity of ADRs in the group of patients receiving pretreatment was similar to the group who did not receive pretreatment. However, there was a smaller proportion of severe ADRs in the group receiving premedication compared with those without pretreatment (5.6% versus 14.9%, respectively), but this was not statistically significant ($P=0.16$).

The rate of ADRs was also evaluated in the two subsets of patients thought to be at the greatest risk and most likely to benefit from premedication, i.e., those patients with an "allergic diathesis" and patients who had previously reported a prior reaction to CM injection. For these subgroups of patients, all TIs were excluded, as were those patients with premedication listed as "other" or "combinations with others" (i.e., not corticosteroids or H1/H2-blockers). These results are shown in Table 6. Among those with an "allergic diathesis," the incidence of ADRs was slightly, but not significantly, lower following premedication. Among those patients who had reported a prior reaction to CM, there was no difference in the rate of ADRs with and without premedication.

Adverse drug reaction rates as a function of region/country. There were notable international/regional

Table 6. Incidences of adverse drug reactions in patients with particular risk factors and with/without premedication.

Risk factor/comorbidity	With 2.0%	Without 1.2%
Allergic diathesis	4.1%	
Prior CM reaction	7.4%	
Premedication		
H1-blocker	1.6%	
H2-blocker	0.7%	
Corticosteroids	2.2%	
H1- and H2-blocker	1.1%	
Combination of H1/H2-blocker and corticosteroids	1.3%	
Any premedication versus no premedication	1.6% versus 1.4%	

CM: contrast media.

differences in the reported ADR rates (Table 7). The highest ADR rates of all were reported in the US and Asia (4.7% versus 3.6%, respectively). The rate of TIs was also slightly higher in the population of patients from the US compared with those from Asia (1.6% versus 1.0%, respectively). Furthermore, in the US, a high rate of metallic taste was reported (over 2%). For all other symptoms, a similar incidence of ADRs was reported across all regions/countries studied.

Adverse drug reaction rates as a function of the method of administration, total iodine dose, and concentration of iopromide. The different methods of contrast administration showed significant differences in the rates of reported ADRs, with the greatest number observed following the use of a power injector (power injector 1.6%, manual injection 1.3%, and infusion 0.9%; $P<0.0001$). The incidence of ADRs categorized by dose groups in patients who received CM was as follows: less than 20 g: 1.3%; >20 g: 1.5%. These results suggest a difference with no statistical significance ($P=0.5$). There was no significant difference in the incidence rates of ADRs and TIs between iopromide concentrations of 300 mg/ml and 370 mg/ml (1.5% and 0.5% versus 1.2% and 0.5%, respectively).

Discussion

We investigated the use of the nonionic monomeric X-ray contrast agent iopromide in 74,717 nonselected patients who underwent routine clinical imaging studies in individual medical departments across 27 countries. By collecting this large database for iopromide, we were able to compare its worldwide usage and risk-benefit profile with that of other contrast agents in use today.

We found that the overall rates of acute ADRs (reactions occurring in a timeframe of up to 1 hour after CM administration) (9) and ADRs excluding TIs following the administration of iopromide were similar to the findings reported for other nonionic iodinated contrast agents (2.0% and 1.5%, respectively) (4–8) in studies with a comparable methodology. The occurrence of SADR was extremely rare (0.02%) and comparable with the findings of a meta-analysis by Caro et al. (0.031%) (10). In addition, no serious unexpected ADRs were encountered in this study. Although the intensity of the ADRs was classified differently in other studies, similar rates were reported (Table 8). Patients who received higher concentrations of iopromide (370 mg I/ml) did not have a higher incidence of ADRs or TIs compared to

Table 7. Incidences of adverse drug reactions according to regions/countries.

Region	Asia	Europe	USA	Germany	South Korea
ADR incl. TIs	3.6%	1.8%	4.7%	1.2%	1.4%
TIs	1%	0.6%	1.6%	0.4%	0.05%
Taste perversions	0.04%	0.34%	2.04%	0.28%	0%

ADR: adverse drug reaction; TI: tolerance indicator.

those patients administered the lower concentration (300 mg I/ml). However, there were statistically significant differences in the rates of ADRs depending on the route and method of administration. Although the patients in our investigation, on average, received larger doses of IA CM compared with those administered IV CM, higher rates of ADRs were reported in the IV group. Similar findings have been reported in other studies (11–13), although in other studies the reverse has also been found to be true (14, 15). DAHLSTROM *et al.* reported a higher rate of ADRs in 1985 following IA iohexol compared with IV administration (4.3% versus 0.8%, respectively) (15); however, in this study, the population was composed of a large proportion of patients who had undergone cerebral angiographies, which may have influenced the findings. In our patient population, 65% of IA cases were coronary angiographies. Because coronary angiography is an invasive procedure, during which patients receive sedating medication, different ADRs may be recognized and reported.

In addition to the route of administration, the method of administration also appears to correlate

to the incidence of ADRs reported: more patients receiving iopromide via automatic administration reported ADRs than patients receiving manual injections. Although it has been suggested that extravasation leading to local reactions is more likely to occur with a power injector than with a manual injection, studies have not proven this (16). Furthermore, JACOBS *et al.* (17) have shown that no correlations exist between the injection and extravasation rate or the overall reaction rate.

Patients in the 18–50 years group experienced a higher rate of ADRs than patients in the 50 to over 80 years group; the highest rates were experienced by patients in the 18–30 years group. Again, similar results have been reported previously (4, 7). As suggested by PETERSEIN *et al.* (7), the higher rate of ADRs in the younger patient group might be attributable to a higher immunocompetence among younger adults, suggesting that an immune-mediated process is involved. This theory is also supported by the lack of any significant association of the ADR rate with the concentration of the CM and the total dose of iodine.

As with findings from previous studies (1, 5), female patients in this study reported a significantly higher rate of ADRs compared with male patients (1.7% versus 1.3%, respectively). In 1990, LASSER (18) noted that women of child-bearing age appear to be at an increased risk of anaphylactoid reactions. Furthermore, NARITA *et al.* (19) have suggested that the increasing prevalence of asthma and other allergic diseases in recent years may be associated with the presence of environmental estrogens, which would support the hypothesis

Table 8. Adverse drug reaction rates from various trials.

Study	ADR rates					
	Overall ADR rate		Mild	Moderate	Severe	Serious
	incl. TIs	excl. TIs				
SCHROTT <i>et al.</i> (9)	2.1%		1.2%		0.9%	0.01%
PALMER <i>et al.</i> (7)		1.2%	1.1% at-risk patients 0.9% non-risk patients	0.1% at-risk patients 0.09% non-risk patients		0.03% at-risk patients 0% non-risk patients
KATAYAMA <i>et al.</i> (8)	3.13%					0.04%
CARO <i>et al.</i> (14)						0.031%
PETERSEIN <i>et al.</i> (10), iobitridol	2.3%	1.1%				
MORTELE <i>et al.</i> (11)	0.7 %		0.64 %	0.06 %	0.01 %	
Iopromide PMS study	2.0%	1.5%	0.55%	0.45%	0.17%	0.02%

ADR: adverse drug reaction; TI: tolerance indicator; PMS: postmarketing surveillance.

that CM reactions, allergy, and anaphylaxis are increased in the presence of high estrogen levels. A further analysis of the age distribution among women revealed that, for all age groups under 70, female patients were more likely to develop an ADR than their male counterparts. However, this is most likely a reflection of the higher prevalence of risk factors such as “allergic diathesis” among women in this study, and is not necessarily an indicator of increased risk. In our patient population, 62% of patients with a history of allergy were female. As expected, the incidence of ADRs was significantly higher among those patients with an “allergic diathesis,” and even higher among those patients with a reported prior CM reaction (3.4- and 6.2-fold increased risk, respectively). In both groups, however, the incidence remained relatively low, suggesting, as has been previously reported, that ADRs do not occur in a classic allergic fashion. Overall, the investigators classified 19,402 patients out of the total population as at-risk patients or patients with a relevant comorbidity. In these patient groups with risk factors, a higher rate of ADRs excluding TIs was reported compared with patients without risk factors (2.0% versus 1.2%, respectively). Most prior large studies have also shown an increased incidence of ADRs in these two groups, although the magnitude of the increase has varied (4, 8, 14). It is interesting to speculate whether the increased rate of ADRs reported in these two higher-risk groups is in any way causally related to the expected rather than the actual risk. A history of prior CM reaction (depending on the severity of the previous reaction) is not necessarily regarded as a contraindication to the use of CM. The low rate of ADRs reported for the group with a prior reaction to CM supports the theory that this is not a classical allergic or anaphylactic process.

Premedication, intended to prevent allergic-type reactions, was administered to 6,577 patients (8.8%) in the study population. The use of premedication was not necessarily correlated with the presence or absence of risk factors; 43.3% of the patients with previous CM reaction and 23.6% of patients with allergies received some kind of premedication. The premedication regimen varied widely by country and by region. These results reflect both the lack of a clear consensus regarding optimal premedication, and also the lack of consensus as to whether or not premedication is of value in preventing ADRs. The uncertainty surrounding prophylactic measures for counteracting reactions to CM has been further supported by reports in the medical literature (1) and in a survey by the European Society of

Urogenital Radiology (20). In general, most premedication regimens were developed during the time of ionic agents, which have been associated with a higher overall incidence of adverse reactions than nonionic agents (12.66% and 3.13%, respectively) (21). Although the *American College of Radiology Manual on Contrast Media* states that corticosteroids are an essential component of any premedication protocol (22), this recommendation is not universally followed. It is surprising, therefore, that, in this study, an increase, rather than a decrease, in the incidence of ADRs was found in the premedicated group. The likely explanation is that a higher percentage of those patients considered to be at the highest risk for an anaphylactoid reaction received premedication (27% of at-risk patients versus 8.8% of total population). It is important to note, however, that premedication did not alter the rate of ADRs in the two higher-risk groups, i.e., those patients with an “allergic diathesis” and those patients with a prior CM reaction. This is consistent with the findings from other studies that have suggested that the use of premedication in routine clinical practice does not alter the incidence of SADR (14). The lack of effectiveness of premedication indicates one of two possibilities: that either large groups of patients undergoing clinical care, such as reported here, do not receive any benefit, or that the application of the premedication was suboptimal. It is important to note, however, that the incidence of ADRs in this group is equivalent to that observed in previous studies, is relatively low, and is of a similar severity and distribution to the group as a whole; that is, the incidence and the severity of ADRs was not altered by the use of premedication.

The analysis of the ADR reporting rate by country disclosed a higher rate (3.16%, excluding TIs) in the US than in other regions. This might be attributed to the increased reporting of subjective symptoms that was substantially higher in the US. The overall rate of TIs in the US was 1.6% compared with 0.5% for the total population. In addition, the reported incidence of “metallic taste” was higher in the US than in other regions (over 2% versus less than 0.5%, respectively), although most reports came from a single US center. Despite the regional differences in reporting rates for ADRs, the profiles of the ADRs were comparable among regions. The minor differences in regional ADR rates may, therefore, be related to differences in reporting behavior, rather than to a higher or lower actual risk of ADRs among different populations. These differences in reporting behavior by country

have been described by MICHEL et al. (23) for spontaneous ADR reports and JOELSON et al. (24) for clinical trials.

As with any registry, there are limitations that need to be accounted for. The ADR rates, as already described, showed regional variations, which may introduce a potential bias. Furthermore, this was not a randomized study, nor was it known what percentage of patients in any given center who were eligible to be included was actually included. It is also possible that there were individual biases in recognizing and reporting particular ADRs. Nonetheless, the results from this large registry are consistent and can be validated by the findings from several other registries and trials. As this is the first large-scale report dealing with a single nonionic contrast agent, it is reassuring to note the consistent patterns of ADRs, the low incidence of serious ADRs, and the absence of unexpected adverse events.

In conclusion, the findings of our study suggest that the incidence, nature, and intensity of ADRs following the administration of iopromide are comparable to the safety profiles of other nonionic iodinated contrast agents reported in the medical literature to date. This broad database proves the safe use of iopromide in different patient groups across a variety of indications.

Declaration of interest: P. Palkowitsch is employee of Bayer Schering Pharma AG.

References

1. Bettmann MA. Frequently asked questions: iodinated contrast agents. *Radiographics* 2004;24 Suppl 1:S3–10.
2. Namasivayam S, Kalra MK, Torres WE, Small WC. Adverse reactions to intravenous iodinated contrast media: a primer for radiologists. *Emerg Radiol* 2006; 12:210–5.
3. Vogl TJ, Honold E, Wolf M, Mohajeri H, Hammerstingl R. Safety of iobitridol in the general population and at-risk patients. *Eur Radiol* 2006;16:1288–97.
4. Katayama H, Yamaguchi K, Kozuka T, Takashima T, Seez P, Matsuura K. Adverse reactions to ionic and nonionic contrast media. A report from the Japanese Committee on the Safety of Contrast Media. *Radiology* 1990;175:621–8.
5. Mortelet KJ, Oliva MR, Ondategui S, Ros PR, Silverman SG. Universal use of nonionic iodinated contrast medium for CT: evaluation of safety in a large urban teaching hospital. *Am J Roentgenol* 2005;184:31–4.
6. Palmer FJ. The RACR survey of intravenous contrast media reactions. Final report. *Australas Radiol* 1988;32: 426–8.

7. Petersein J, Peters CR, Wolf M, Hamm B. Results of the safety and efficacy of iobitridol in more than 61,000 patients. *Eur Radiol* 2003;13:2006–11.
8. Schrott KM, Behrends B, Clauss W, Kaufmann J, Lehnert J. Iohexol in excretory urography. Results of drug monitoring. *Fortschr Med* 1986;104:153–6.
9. Munechika H, Hiramatsu Y, Kudo S, Sugimura K, Hamada C, Yamaguchi K, et al. A prospective survey of delayed adverse reactions to iohexol in urography and computed tomography. *Eur Radiol* 2003;13:185–94.
10. Caro JJ, Trindade E, McGregor M. The risks of death and of severe nonfatal reactions with high- vs low-osmolality contrast media: a meta-analysis. *Am J Roentgenol* 1991;156:825–32.
11. Bush WH, Swanson DP. Acute reactions to intravascular contrast media: types, risk factors, recognition, and specific treatment. *Am J Roentgenol* 1991;157:1153–61.
12. Lasser EC, Berry CC, Talner LB, Santini LC, Lang EK, Gerber FH, et al. Pretreatment with corticosteroids to alleviate reactions to intravenous contrast material. *N Engl J Med* 1987;317:845–9.
13. Shehadi WH. Contrast media adverse reactions: occurrence, recurrence, and distribution patterns. *Radiology* 1982;143:11–7.
14. Bettmann MA, Heeren T, Greenfield A, Goudey C. Adverse events with radiographic contrast agents: results of the SCVIR Contrast Agent Registry. *Radiology* 1997;203:611–20.
15. Dahlstrom K, Shaw DD, Clauss W, Andrew E, Sveen K. Summary of U.S. and European intravascular experience with iohexol based on the clinical trial program. *Invest Radiol* 1985;20 Suppl 1:S117–21.
16. Miles SG, Rasmussen JF, Litwiller T, Osik A. Safe use of an intravenous power injector for CT: experience and protocol. *Radiology* 1990;176:69–70.
17. Jacobs JE, Birnbaum BA, Langlotz CP. Contrast media reactions and extravasation: relationship to intravenous injection rates. *Radiology* 1998;209:411–6.
18. Lasser EC. Contrast reactions. Eked data from contrast-reaction surveys. *Invest Radiol* 1990;25 Suppl 1:S14–5.
19. Narita S, Goldblum RM, Watson CS, Brooks EG, Estes DM, Curran EM, et al. Environmental estrogens induce mast cell degranulation and enhance IgE-mediated release of allergic mediators. *Environ Health Perspect* 2007;115:48–52.
20. Morcos SK, Thomsen HS, Webb JA. Prevention of generalized reactions to contrast media: a consensus report and guidelines. *Eur Radiol* 2001;11:1720–8.
21. Delaney A, Carter A, Fisher M. The prevention of anaphylactoid reactions to iodinated radiological contrast media: a systematic review. *BMC Med Imaging* 2006;6:2.
22. American College of Radiology. American College of Radiology manual on contrast media. 5th ed. Reston, Va: American College of Radiology; 2004.
23. 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):S34.
24. Joelson S, Joelson IB, Wallander MA. Geographical variation in adverse event reporting rates in clinical trials. *Pharmacoepidemiol Drug Saf* 1997;6 Suppl 3: S31–5.

Copyright of Acta Radiologica is the property of Taylor & Francis Ltd and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.