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Original article

Safety and diagnostic image quality of iopromide: results of a large non-interventional observational study of European and Asian patients (IMAGE)

Petra Palkowitsch[1], Philipp Lengsfeld[1], Kathrin Stauch[2], Christian Heinsohn[3], Soon Tae Kwon[4], Shui-xing Zhang[5] and Chang-hong Liang[5]

[1]Global Medical Affairs Diagnostic Imaging, Bayer HealthCare, Berlin, Germany; [2]Global Non-interventional Studies, Bayer HealthCare, Berlin, Germany; [3]Radiological Center, Göppingen, Germany; [4]Department of Radiology, Chungnam National University Hospital, Daejeon, Republic of Korea; [5]Department of Radiology, Guangdong General Hospital/Guangdong Academy of Medical Sciences, Guangzhou, China

Correspondence to: Petra Palkowitsch. Email: Petra.Palkowitsch@bayer.com

Abstract

Background: Iodine-based contrast agents such as iopromide play a central role in improving the diagnostic quality of imaging modalities using ionizing radiation.

Purpose: To investigate the safety and diagnostic image quality of iopromide in the routine clinical setting.

Material and Methods: This was an international, multicenter, prospective, single-arm, non-interventional study (NIS). The study was performed in out- and inpatients in 738 study centers in 21 countries in Europe and Asia. Iopromide was administered in a routine manner, in compliance with the local package insert. The use of premedication was at the discretion of the attending physician. Case report forms for 44,835 patients were analyzed (57.4% men). The median age of the patients was 55 years.

Results: For the vast majority of patients (94.8%), the contrast quality was rated as 'good' (55.8%) or 'excellent' (39.0%). For 1265 (2.8%) patients, there were reports of adverse drug reactions (ADRs) excluding tolerance indicators (TIs) (i.e. injection site warmth, feeling hot, or injection site pain of mild intensity). At least one ADR including TIs was reported in 2415 (5.4%) patients. There were 11 (0.02%) patients with serious ADRs, and no drug-related deaths. Events of injection site warmth and/or feeling hot were reported by 3.5%, nausea and/or vomiting by 0.96%, and urticaria, erythema, and/or rash by 0.54% of patients. Patients at risk for an acute idiosyncratic reaction (i.e. patients with a history of bronchial asthma, allergies, and/or contrast media reaction) had a higher incidence of ADRs compared with the overall study population. At-risk patients who did not receive premedication reported distinctly more ADRs compared with those who received premedication (12.0% versus 5.9%).

Conclusion: Iopromide was shown to be a well-tolerated contrast agent whose usage resulted in high image quality. No unknown ADRs were observed. Premedication with antiallergy drugs should be considered in at-risk patients.

Keywords: Contrast agent, iopromide, nonionic, adverse drug reactions, antiallergic premedication

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Iodine-based contrast agents play a central role in improving the diagnostic quality of computed tomography (CT) or urography and other imaging modalities that use ionizing radiation. Several epidemiologic surveillance studies have been conducted to document adverse drug reactions (ADRs) that can occur with the use of contrast agents in large patient populations (1–7). The ADR rates reported for ionic contrast agents range from 3.8–24.4% (1, 3, 5, 8, 9) and are much higher than those reported for non-ionic contrast agents (0.7–6.5%) (6, 7, 10). Nevertheless, ADRs such as urticaria, dyspnea, hypertension, and even fatal anaphylactic reactions sometimes occur (3, 5, 11). Allergy-like

(anaphylactoid) reactions to contrast agents are more likely to occur in patients with an allergic predisposition or a history of allergy-like (idiosyncratic) reactions to contrast agents (4, 6, 7, 12).

The occurrence and frequency of rare ADRs is difficult to determine because the overall frequency of ADRs is low and only a small number of patients are exposed to contrast agents in randomized controlled trials (RCTs). Non-interventional studies (NIS) are observational studies that do not alter the clinical routine and treatment of the patients included in the study; these studies were in the past typically called PMS (post-marketing surveillance) studies. The study itself consists of data collection and analysis. NIS, therefore, provide an opportunity to obtain further evidence to determine any harmful effects of a medical treatment (13). The benefits of observational studies to determine the safety and tolerability of contrast agents in the 'real-world' setting have been previously described (7).

The aim of this NIS was to investigate the safety and diagnostic image quality of iopromide (Ultravist®; Bayer HealthCare, Berlin, Germany), an iodine-based, low-osmolar non-ionic contrast agent for X-ray and CT in a large patient population in the routine clinical setting. The study was part of the continuous safety monitoring of iopromide to take into account not only the rapidly changing technological and medicinal environment but also the increased worldwide use of this contrast agent. Since 1985, iopromide has been used in more than 150 million patients and is currently marketed in 100 countries globally. The current usage rate of iopromide amounts to over 10 million applications per year.

In addition to general safety, this study investigated the occurrence of ADRs in at-risk patients (i.e. patients with a history of bronchial asthma, allergies, or previous allergic reaction after contrast agent exposure), and the possible benefit of anti-allergic premedication in routine clinical practice.

Material and Methods

Study design and objective

This was an international, multicenter prospective, single-arm NIS, which was performed in accordance with the regulations for post-approval of the European Medicines Agency (EMA) (14) as well as the latest standards for conducting NIS established by the European Federation of Pharmaceutical Industries and Associations (EFPIA) (15). The official title IMAGE is an acronym for **I**opro**M**ide (Ultr**A**vist®) – to **G**ain further information on tolerability and safety in X-ray **E**xamination. The study was performed in out- and inpatients in cooperation with radiologists, urologists, and cardiologists in 21 countries in Europe and Asia. The purpose of this study was to gain further knowledge of the safety and diagnostic image quality of iopromide in routine clinical practice. The study was sponsored by Bayer HealthCare, Berlin, Germany. The study was registered at ClinicalTrials.gov (NCT00876083).

Patients

To avoid any influence on the usual diagnostic practice of the investigator, only patients with an indication for an X-ray or CT examination, and for whom the investigator had decided to use the contrast medium iopromide, were eligible for analysis. Patients did not meet the eligibility criteria when the iopromide application was not documented, the patient was retrospectively documented, or the patient withdrew consent.

A total of 44,835 patients from 738 study centers met the eligibility criteria and were included in the analysis. Enrollment started in February 2008 and ceased in September 2009.

Observational plan and variables

Iopromide was administered in a routine manner, specific to the investigator, on the day of the examination, once or more depending on the diagnostic indication and need, in compliance with the package insert. Premedication use was recorded on a checklist included on the case-report form (CRF) (corticosteroids, H_1/H_2 blockers and/or other); the use of premedication was at the discretion of the attending investigator, and was administered according to his/her usual practice. All investigators were clearly informed of the objectives, variables, and specific aspects of this NIS.

The following data were recorded for each patient using a two-page CRF (similar, but not identical to the CRF used in Kopp *et al.* (4)): demographics, concomitant diseases, pre- and concomitant medications, examination region, indication, contrast medium volume, type of application and examination, contrast quality, and adverse events (AEs). All paper CRFs were entered into a validated electronic database by a contract research organization according to a defined double-data-entry process. All returned CRFs were reviewed for completeness and plausibility using validated electronic edit checks, and any queries regarding the information in the CRF were directed to the investigators, where necessary. This included a follow-up of all hidden AEs as well as any queries that were generated. All queries were followed up until final resolution or until no further information could be obtained.

Investigators subjectively assessed the image quality according to the following five categories: excellent, good, adequate, non-diagnostic, and not specified.

All AEs that occurred within the patient observation time (30–60 min according to the local packaging information) were recorded in a separate questionnaire, in terms of symptoms, onset, duration, intensity, and causal relationship. The following AEs were anticipated based on their known potential occurrence in conjunction with the administration of contrast media, and could be ticked as a checkbox: warmth, heat sensation, taste disorder, nausea, vomiting, pain, itching, erythema, exanthema, urticaria, edema, sneezing, coughing, dyspnea, bronchospasm, and sudden change in blood pressure (increase or decrease). In addition, the investigator was given the opportunity to report any other observed AEs as free text. Injection site warmth, feeling hot, or injection site pain of mild intensity were defined *post hoc* as tolerance indicators (TIs). No laboratory tests

were required. Investigators were asked to classify an AE as non-serious or serious. A classification as serious was to be detailed if it fulfilled one of the following criteria (checkboxes were to be chosen): hospitalization necessary or prolonged; persistent or significant disability/incapacity; congenital anomaly/birth defect; important medical event; and life-threatening or fatal outcome (in which the date and cause of death were to be documented). The investigator was asked to document the date of the AE, the onset of the AE post-injection in hours/min, and the duration (days, hours, minutes). The investigator was also asked to classify the intensity of an AE (mild, moderate, or severe) and to assess the causal relationship to iopromide administration (yes/no). A classification of a causal relationship to iopromide administration turned the respective AE into an ADR. Finally, the investigator was asked to document the actions taken (none, event treated with drugs, other measures [treatment or other measures to be detailed]), and the event outcome (recovered/resolved, recovering/resolving, recovered/resolved with sequelae, fatal, and unknown).

Statistical analysis

All data were analyzed using basic statistical methods, such as frequency tables and descriptive statistical parameters. The results are based on the number of patients for whom specific parameters were available.

Ethical approval

This NIS was conducted in accordance with local legal and ethical requirements. Investigational review board approval was obtained where necessary. In countries where a patient information and/or consent form was required by local law or regulations, a core information and informed consent form was provided. Informed consent was obtained from patients in most of the participating countries.

Results

Patients

A total of 44,835 out of 44,921 patients were eligible for analysis: 34,945 (77.9%) from Asia, 6627 (14.8%) from Eastern Europe, and 3263 (7.3%) from central Europe. The three countries with the largest patient contribution were China, Korea, and Germany. Table 1 displays the patients enrolled in every country. The population comprised 25,772 (57.4%) men and 18,862 (42.1%) women; 251 (0.6%) patients were of unknown gender. The median age was 55 years (interquartile range 44–66 years), with the majority of patients being over 40 years of age (82.1%).

At least one risk factor, or presence of a specific concomitant disease, was reported for 22,733 (50.7%) patients (Table 2). The most frequent specific concomitant diseases were arterial hypertension (15.4%), coronary heart disease (11.0%), and reduced general condition (10.4%). Risk factors specific for idiosyncratic contrast media reactions, such as bronchial asthma, contrast media reactions, and/or allergy, were reported for 1340 (3.0%) patients.

Table 1 Patients per country

Country	Sites (*n*)	Total patients (*n* = 44,835) Patients (*n*)	%
China	56	20,000	(44.6)
South Korea	8	3999	(8.9)
Germany	71	2687	(6.0)
Philippines	219	2424	(5.4)
Ukraine	17	2040	(4.6)
Vietnam	2	1980	(4.4)
Poland	107	1979	(4.4)
Singapore	6	1687	(3.8)
Pakistan	21	1514	(3.4)
Romania	10	1029	(2.3)
Malaysia	2	920	(2.1)
Russian Federation	28	779	(1.7)
Indonesia	52	720	(1.6)
Taiwan	2	643	(1.4)
Bosnia and Herzegovina	7	580	(1.3)
Italy	13	576	(1.3)
Moldova	3	358	(0.8)
Thailand	1	300	(0.7)
Hungary	3	220	(0.5)
Iran	7	201	(0.4)
Saudi Arabia	2	199	(0.4)

Overall, the use of premedication was reported for 8485 (18.9%) patients (Table 3). Corticosteroids were the most frequently used premedication (61.9% of all premedications). H_1-/H_2-blockers were used in $\leq$1.0% of patients. In the at-risk population, premedication was used by 410 of 1340 (30.6%) patients. Corticosteroids were also the most frequently used premedication (71.5% of all premedications) in this subgroup. More patients in the at-risk subgroup reported receiving multiple premedications compared with the overall population (14.4% vs. 3.1%).

Type of examination and administration of contrast agent

The most frequent type of examination was CT (multislice 78.2%, single slice 9.7%), followed by angiocardiography

Table 2 Number and proportion of patients with specific concomitant diseases

Concomitant disease*	Total patients (*n* = 44,835) *n* (%)
Patients with any disease	22,733 (50.7)
Arterial hypertension	6919 (15.4)
Other	6473 (14.4)
Coronary heart disease	4952 (11.0)
Reduced general condition†	4645 (10.4)
Diabetes mellitus	2667 (5.9)
Cardiac arrhythmia	779 (1.7)
Allergy	772 (1.7)
Thyroid disorder	762 (1.7)
Bronchial asthma	544 (1.2)
Renal insufficiency	521 (1.2)
Autoimmune disorder	308 (0.7)
Heart failure	268 (0.6)
Contrast media reaction	89 (0.2)
Dehydration	45 (0.1)

*Multiple responses possible
†Defined as a reduced state of health with regard to a patient's general overall constitution

Table 3 Use of premedication: overall and in the subgroup of at-risk patients*

	Total patients (n = 44,835) n (%)	At-risk subgroup (n = 1340) n (%)
Premedication used		
Yes	8485 (18.9)	410 (30.6)
No	36,087 (80.5)	887 (66.2)
Not specified	263 (0.6)	43 (3.2)
Patients with any premedication	8485 (100)	410 (100)
H_1-blocker	69 (0.8)	8 (2.0)
H_2-blocker	84 (1.0)	2 (0.5)
Corticosteroids	5251 (61.9)	293 (71.5)
Other	2816 (33.2)	48 (11.7)
Multiple medications	265 (3.1)	59 (14.4)

*At-risk patients included those with bronchial asthma, contrast media reactions, and/or allergy

Table 4 Key safety summary

	Total patients (n = 44,835) n (%)
Patients with any AE	2551 (5.69)
Patients with any ADR	2415 (5.39)
At least one ADR, but without tolerance indicators only*	**1265 (2.82)**
Patients with any serious AE	16 (0.04)
Patients with any serious ADR	11 (0.02)
Patients died†	3 (0.01)

*Tolerance indicators are defined as any occurrence of injection site warmth, feeling hot, or injection site pain, but of mild intensity only
†All deaths occurred in Malaysia. Causes of death were pancreatic cancer, myocardial infarction in cardiogenic shock, and cerebrovascular accident secondary to thromboembolism. None of the deaths were considered by the investigator to be related to iopromide
ADR = adverse drug reaction; AE = adverse event

(4.4%), other examinations (4.3%), angiography (1.9%), phlebography (0.7%), digital subtraction angiography (DSA) (0.5%), and not specified (0.3%).

The most frequently used iodine concentrations were iopromide-300 (55.6%) and iopromide-370 (44.0%). Iopromide-150 and iopromide-240 were used infrequently (≤0.2%). The route of administration was intravenous in 41,703 (93.0%), intra-arterial in 2784 (6.2%), other in 238 (0.5%), and not specified in 110 (0.2%) of cases. The most frequent means of administration was automatic injection (79.1%), followed by manual injection (18.5%) and infusion (0.5%). The mean (standard deviation [SD]) dose of iodine administered was 30 (13.0) g with a median flow rate of 3.0 mL/s; 71.3% of patients received iodine doses between 20 g and 40 g.

Contrast quality

The contrast quality was rated as either 'good' or 'excellent' in the vast majority of patients (94.8%). Overall, contrast quality was rated as 'good' by 55.8% of investigators and 'excellent' by 39.0%. Approximately 5% of examinations were rated as 'adequate' or less. Only 15 out of 44,845 (<0.05%) scans were reported to be 'non-diagnostic'.

Adverse drug reactions

For 1265 (2.8%) patients, at least one ADR that was not considered to be a TI (i.e. injection site warmth, feeling hot, or injection site pain of mild intensity) was reported (Table 4). At least one ADR was reported by 2415 (5.4%) patients, while the total number of patients with at least one AE was 2551 (5.7%). For the majority of ADRs, the intensity of the event was considered as mild (91.3%) (Table 5). No action was taken for 89.6% of patients with an ADR. Drug treatment or other measures were reported for 9.7% of patients with an ADR. The outcome was reported as 'resolved' for the vast majority of patients (97.2%).

The incidence of ADRs (including TIs) was higher in women (1208 [6.4%]) compared with men (1194 [4.6%]). The ADR incidence was higher in those aged 18–39 years (7.9%) than other age groups (7.2% for those <18 years, 5.5% for 40–59 years, 4.2% for 60–79 years, and 3.2% for ≥80 years).

The most frequently reported ADRs (preferred term) were injection site warmth (1123 [2.5%] patients), feeling hot (468 [1.0%]), dysgeusia (distortion of the sense of taste; 397 [0.9%]), and nausea (325 [0.7%]) (Table 6).

Table 5 Intensity, action taken, and outcomes for adverse drug reactions (patient-based)

	Total patients (n = 44,835) n (%)
Total patients	
Without ADR	42,420 (94.61)
With ADR	2415 (5.39)
Seriousness of ADRs	
Not serious	2396 (5.34)
Not specified	8 (0.02)
Serious	11 (0.02)
Reasons for seriousness*	
Not specified	1 (0.00)
Hospitalization necessary or prolonged	3 (0.01)
Persistent or significant disability/incapacity	0 (0)
Congenital anomaly/birth defect	0 (0)
Important medical event	5 (0.01)
Life-threatening	2 (0.00)
Fatal	0 (0)
Multiple reasons	0 (0)
Intensity†	[% of 2415]
Not specified	2 (0.00) [0.08]
Mild	2207 (4.92) [91.34]
Moderate	184 (0.41) [7.62]
Severe	22 (0.05) [0.91]
Action taken	[% of 2415]
Not specified	16 (0.04) [0.66]
None	2165 (4.83) [89.65]
Any	234 (0.52) [9.69]
Event treated with drugs	216 (0.48) [8.94]
Other measures	24 (0.05) [0.99]
Outcome†	[% of 2415]
Not specified	3 (0.01) [0.12]
Recovered / resolved	2347 (5.23) [97.18]
Recovering / resolving	62 (0.14) [2.57]
Recovered / resolved with sequelae	2 (0.00) [0.08]
Not recovered / not resolved	0 (0)
Fatal	0 (0)
Unknown	1 (0.00) [0.01]

*Multiple responses possible for patients with more than one serious ADR and different reasons, but same reasons were counted only once
†Only worst score per patient was taken into account

Table 6 Adverse drug reaction frequencies

Adverse drug reaction*	Total patients (n = 44,835) n (%)	Events (n = 3157) n
Injection site warmth	1123 (2.50)	1132
Feeling hot	468 (1.04)	473
Dysgeusia	397 (0.89)	412
Nausea	325 (0.72)	326
Vomiting	133 (0.30)	134
Urticaria	120 (0.27)	120
Pruritus	102 (0.23)	104
Dizziness	57 (0.13)	57
Erythema	57 (0.13)	58
Rash	75 (0.17)	75

*Only adverse drug reactions events reported for more than 0.1% of patients are presented

Serious adverse events and serious adverse drug reactions

In total, 36 serious AEs were reported by 16 (0.04%) patients, of which 26 were considered drug-related (serious ADR) in 11 (0.02%) patients. Main reasons for seriousness were 'important medical event' (17 events), and 'hospitalization necessary or prolonged' (10 events). Of the 26 drug-related events, 22 resolved, two were resolving, one resolved with sequelae, and for one the outcome was unknown. The 26 serious ADRs included nausea, decreased blood pressure, edema (three events each), vomiting, dyspnea, pruritus, urticaria (two events each), fatigue, injection site warmth, dizziness, acute renal failure, acute pulmonary edema, bronchospasm, cough, throat tightness, and erythema (one event each), all of which occurred in $\leq$0.01% of patients. The drug-related ADRs were considered serious because they necessitated hospitalization (3 patients), were deemed to be important medical events (5 patients), or were life-threatening (2 patients); in one patient the serious drug-related ADR was not specified. Two out of the 11 patients with serious ADRs belonged to the at-risk group. Three life-threatening events were reported in two patients. Three deaths were reported (pancreatic cancer, myocardial infarction in cardiogenic shock, and cerebrovascular accident secondary to thromboembolism), none of which were considered to be related to iopromide.

Adverse drug reactions of special interest

Post-hoc analysis of the most frequently reported ADRs showed that events of injection site warmth and/or feeling hot were reported by 1568 (3.5%) patients (Table 7). Nausea and/or vomiting were reported by 431 (1.0%) patients, and urticaria, erythema, and/or rash by 243 (0.5%) patients. An extravasation injury was reported in one patient.

Adverse drug reactions of special interest in at-risk patients

A *post-hoc* analysis of 1340 at-risk patients (history of bronchial asthma, allergies, and/or contrast media reaction) showed that events of injection site warmth and/or feeling hot were reported by 84 (6.3%) patients (Table 7). Nausea and/or vomiting was reported by 27 (2.0%) patients, and urticaria, erythema, and/or rash by 19 (1.4%) patients. In general, the severity of AEs in at-risk patients was similar to that in the overall population.

Table 7 Adverse drug reactions of special interest: overall and in at-risk patients

	Total patients (n = 44,835) n (%)	At-risk subgroup (n = 1340) n (%)
Any adverse event reaction	2415 (5.39)	134 (10.00)
Injection site warmth and/or feeling hot	1568 (3.50)	84 (6.27)
At least one adverse event reaction, but without tolerance indicators only*	1265 (2.82)	88 (6.57)
Tolerance indicators only*	1150 (2.56)	46 (3.43)
Nausea and/or vomiting	431 (0.96)	27 (2.01)
Urticaria, erythema, rash and/or rash papular	243 (0.54)	19 (1.42)
Cough and/or sneezing	52 (0.12)	7 (0.52)
Dyspnea and/or bronchospasm	29 (0.06)	5 (0.37)
Increased and/or decreased blood pressure	23 (0.05)	2 (0.15)

*Tolerance indicators are defined as any occurrence of injection site warmth, feeling hot or injection site pain, but of mild intensity only

Adverse drug reactions in at-risk patients as a function of premedication use

Analysis of ADRs in the at-risk patient subgroup, according to the use of premedication, showed that those who did not receive premedication reported more ADRs compared with those who received premedication (12.0% and 5.9%, respectively). In particular, this difference was seen for injection site warmth, dysgeusia, and feeling hot (Table 8).

Discussion

The aim of this observational study was to investigate the safety and diagnostic image quality of iopromide in the clinical setting of a large patient population in Europe and Asia. In total, data of 44,835 patients from 738 centers was collected and analyzed. The contrast quality of iopromide can be considered as very good, since the contrast quality was judged as 'good' or 'excellent' for 94.8% of patients. Regarding safety, a total of 1265 (2.8%) patients experienced ADRs excluding TIs (i.e. injection site warmth, feeling hot, or injection site pain of mild intensity). There were only 16 (0.04%) patients with serious AEs, and 11 (0.02%) patients with serious ADRs. Three (0.01%) patients died during the observation period; these deaths were not related to the application of iopromide. As the primary objective of this NIS study was safety, the following discussion will focus on this topic.

This NIS study confirms the well-established profile of one of the key members of the class of iodine-based contrast agents, the so-called low-osmolar non-ionic monomers that provide good or excellent image quality with a low rate of ADRs. It has been observed that the total ADR rate is usually lower in NIS than in randomized controlled trials (RCTs). This effect can be seen here as well. Goldstein

Table 8 Adverse drug reactions in at-risk patients with and without premedication use

	Total at-risk subgroup (n = 1340)*	
	Without premedication (n = 887) n (%)	With premedication (n = 410) n (%)
Patients with any adverse drug reaction	106 (11.95)	24 (5.85)
Injection site warmth	57 (6.43)	5 (1.22)
Dysgeusia	24 (2.71)	2 (0.49)
Feeling hot	20 (2.25)	5 (1.22)
Nausea	15 (1.69)	6 (1.46)
Pruritus	8 (0.90)	4 (0.98)
Urticaria	8 (0.90)	2 (0.49)
Vomiting	6 (0.68)	1 (0.24)
Erythema	6 (0.68)	0 (0)
Sneezing	4 (0.45)	0 (0)
Rash	4 (0.45)	1 (0.24)
Dyspnea	3 (0.34)	2 (0.49)
Injection site pain	2 (0.23)	3 (0.73)
Decreased blood pressure	2 (0.23)	0 (0)
Dizziness	2 (0.23)	2 (0.49)
Fatigue	1 (0.11)	0 (0)
Headache	1 (0.11)	0 (0)
Cough	1 (0.11)	1 (0.24)
Rhinorrhea	1 (0.11)	0 (0)
Edema	1 (0.11)	0 (0)
Pyrexia	1 (0.11)	0 (0)
Throat irritation	1 (0.11)	0 (0)
Vertigo	0 (0)	1 (0.24)
Skin mass	0 (0)	1 (0.24)

*Includes 43 patients for whom the premedication question was not ticked ('not specified')

et al. (16) reported in their pooled data analysis of 1367 patients from RCTs a study drug-related AE rate of 21% for iopromide versus 23% for comparator drugs. This tendency towards under-reporting has also been described for NIS vs. RCT by Papanikolaou *et al.* (17). The effect is most likely related to the fact that in a rigorous controlled setting more signs and symptoms are reported by patients being actively questioned and examined by the treating physician, who is also actively looking for minor reactions (e.g. at the injection site) that are more likely to go unnoticed in an observational setting. However, NIS can contribute valuable information for the risk assessment of drugs in addition to other sources such as RCT and spontaneous reporting systems (13, 18).

The incidence and distribution of ADRs according to age and gender, i.e. a higher rate of ADRs in women and younger and middle-aged patients, has been described in other studies, not only for iopromide (4) but also for other contrast agents (1, 3). Both effects are not fully understood, and should be further explored in future investigations.

A *post-hoc* analysis of the most frequently reported ADRs showed that events of injection site warmth and/or feeling hot were reported by 3.5% of patients, nausea and/or vomiting by 1.0%, and urticaria, erythema, and/or rash by 0.5%. At-risk patients (i.e. those with a history of bronchial asthma, allergies, and/or contrast media reaction) had a higher incidence of ADRs compared with the overall study population (10.0% vs. 5.4%). This was particularly noticeable for the combined rates of injection site warmth and/or feeling hot (6.3% vs. 3.5%), nausea and/or vomiting (2.0% vs. 1.0%), and urticaria, erythema, and/or rash (1.4% vs. 0.5%). This is a key consideration for safety guidelines in imaging centers, in that patients with specific risk factors for contrast media reactions should receive special attention by the treating physician. Indeed, the key for the safe utility of contrast agents is preparedness, in terms of the ability to deal with severe or potentially life-threatening reactions. Current guidelines give extensive recommendations on prophylactic as well as emergency measures (18, 19).

TIs such as injection site warmth, feeling hot, or injection site pain are symptoms that are not usually classified as anaphylactoid reactions. They are regarded as physiological reactions that occur when a highly concentrated osmolar solution is administered intravascularly. It therefore seems unlikely that the rate of non-allergy-like reactions would be higher in at-risk patients than in the overall population; the higher rate found in the at-risk patients in this study is therefore suggestive of a psychological effect. The influence of psychological effects especially when reporting mild ADRs has been described previously (20, 21). Indeed, for patients who have experienced a previous idiosyncratic reaction, it is probable that fear and agitation will be more prevalent and that their expectation of such an event occurring will also be higher. In these cases, patients are more likely to report, by paying more attention to the injection, other symptoms such as injection site warmth and/or feeling hot. These patients are also more likely to have increased rates of ADRs relating to allergy-like symptoms (e.g. nausea and/or vomiting and skin symptoms), as was observed in this study.

In this study there was a distinct difference in the reported number of ADRs of mild intensity, mainly injection site warmth and pain, compared with a previous observational study of iopromide (4) and single-country PMS studies of other products (6, 22). It is well-known that reporting of contrast media reactions depends on the physician (or technician) and the patient–physician interaction, as well as on the level of scrutiny by the physician. It thus seems likely that the increased number of mild ADRs observed in this study reflects a difference in the conduct of the two studies. In the previous observational study (4), for example, some of these factors were described as 'tolerance indicators'.

It is assumed that the latest, strict standards for PMS studies, which were fully implemented in this study, raised the awareness of physicians to the importance of diligent reporting of ADRs. This probably resulted in a more extensive patient–physician interaction in the course of obtaining informed consent, and raised the awareness of patients to report ADRs. The use of a CRF that allowed the investigator to report a number of anticipated AEs by simply ticking a box may have also artificially lowered the threshold of reporting compared with other studies that asked the investigator to explicitly state an observed AE (no tick boxes). Interestingly, a recent single-country PMS study with another low-osmolar non-ionic monomer (iobitridol) observed the same effect but going in the opposite direction (22). The PMS study reported by Maurer *et al.*

(22) used a CRF without tick boxes and found an incidence of 'feeling of warmth' of 0.06%, markedly lower than the 1.3% reported in their first PMS on the same product (6). We conclude that differences in reporting of mild ADRs, especially feeling of warmth, are most likely not related to variations in the product or the patient population, but are very much influenced by the actual conduct of the study. A higher reporting rate can therefore be seen as a reflection of the stringent standards employed in the study conduct.

The results of the present study confirm the finding that the ADR incidence and the likelihood of reporting is dependent on several factors: patient history, underlying diseases, the patient's fear or agitation, quality of information received by the patient prior to the injection, and the uncertainty and increased awareness of medical staff. The latter phenomenon is often observed when well-established products are exchanged for new products that have not previously been used at a particular institution, which is a variation of the so-called Weber effect (23–26). However, ADR rates for events that are less susceptible to subjective factors are, in effect, very similar between the previously reported PMS that was conducted with iopromide in 74,717 patients between 1999 and 2003 (4) and the present study. The rate of ADRs of at least moderate intensity in these two studies was very similar (moderate intensity: 0.41% vs. 0.48%; severe intensity: 0.05% vs. 0.17%) and the rate of serious ADRs was identical (0.02%). The frequency of special ADRs was also similar. The results of the current study are also in agreement with previous observational trials on other iodine-based contrast agents of the same class (non-ionic, low-osmolar monomers) (1, 3, 6). Based on the observed incidences in this study, the following frequencies of ADRs can be extrapolated for iopromide: approximately four in 1000 patients may experience ADRs of moderate intensity; five in 10,000 may experience ADRs of severe intensity; two in 10,000 may experience a serious ADR; and one in 100,000 may experience a life-threatening ADR.

Regarding the topic of premedication, at-risk patients who did not receive such treatment reported distinctly more ADRs compared with those who received premedication (12.0% vs. 5.9%). In particular, this difference was found for injection site warmth, dysgeusia, and feeling hot. Thus, premedication seemed to result in a reduction of ADR rates in this study. The effect of premedication has been investigated in other studies with varying results. In the previous iopromide observational study by Kopp *et al.* (4), premedication did not lead to a reduced ADR rate. The uncertainty surrounding prophylactic measures for counteracting reactions to contrast media has also been reflected in a European Society of Urogenital Radiology survey (27). These contradicting findings can partly be attributed to the limitations of NIS that are neither randomized nor controlled. The way in which premedication is performed and the way certain risks are assessed and measured cannot be included in the study design and, therefore, cannot be investigated. This means that the findings can only be described and used to generate hypotheses that can be further investigated in the more rigorous setting of an RCT. The results of this study and the deep-drill analysis of its results do, however, suggest that premedication in at-risk patients be considered as an option, even if it is only to reassure the patient and physician.

The major strength of this study is that a large number of patients were enrolled in a multi-country, multi-indication study across a large number of centers, which limits bias caused by center/single-country and single-indication effects, and thus increases the representativeness of the results. The study was also performed according to strict new standards; for example, informed consent was obtained in the majority of patients. On the other hand, this NIS has the usual limitations inherent to the observational setting, i.e. no randomization/blinding and no reference standard, no uniform standard of assessment of risk factors and adverse events in the participating study centers and countries, as well as subjective assessment of the image quality.

In conclusion, iopromide was shown to be a well-tolerated contrast agent whose usage resulted in high image quality. No unknown ADRs were observed. The importance of psychological factors on the occurrence of ADRs and reporting behavior was reinforced. Premedication with antiallergic drugs should be considered in at-risk patients, since this may greatly reduce the occurrence of ADRs.

Conflict of interest: Petra Palkowitsch, Philipp Lengsfeld, and Karin Stauch are employees of Bayer HealthCare. Shuixing Zhang received a grant from the study sponsor for patient enrolment. All other authors report no conflicts of interest.

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