OPEN

Risk of Hypersensitivity Reactions to Iopromide After Intra-Arterial Versus Intravenous Administration

A Nested Case-Control Analysis of 133,331 Patients

Jan Endrikat, MD, PhD,† Alexander Michel, MD, PhD,‡ Ralf Kölbach, BSc,§ Philipp Lengsfeld, PhD,* and Kai Vogtländer, PhD||*

Objective: The aim of this study was to compare the risk of hypersensitivity reactions to iopromide after intra-arterial (IA) administration and intravenous (IV) administration.

Materials and Methods: Four observational studies were pooled. Almost half of the study population (48.1%) was from Europe, and one quarter each from China (27.6%) and other Asia countries (24.1%). All patients received iopromide either intra-arterially or intravenously for angiographic procedures (mostly cardioangiography) or contrast-enhanced computed tomography. A nested case-control analysis, including a multivariable logistic regression model, was performed. Cases were defined by patients with a typical and unequivocal hypersensitivity (assumed non–IgE-mediated) reaction; controls were patients without any recorded reaction. The primary target variable is the odds ratio of having a hypersensitivity reaction after IA versus IV administration.

Results: A total of 133,331 patients met the inclusion criteria, 105,460 and 27,871 patients received iopromide IV or IA, respectively. Hypersensitivity reactions were recorded for 822 patients, and 132,509 patients served as controls.

Major risk factors for hypersensitivity reactions were method of injection (IV vs IA), age (18 to <50 years vs ≥65 years), history of allergy or previous contrast media reaction (all $P < 0.001$), and asthma ($P = 0.005$).

A total of 766 patients (0.7%) and 56 patients (0.2%) were recorded with hypersensitivity reactions after IV or IA administration, respectively ($P < 0.0001$).

Adjusted odds ratio (IA vs IV) was 0.23 (95% confidence interval, 0.16–0.32) for all countries together: for China only, 0.22 (0.11–0.44); for all countries without China, 0.36 (0.25–0.53).

Most frequent reactions were erythema/urticaria/rash, pruritus, and cough/sneezing.

Conclusions: Hypersensitivity reactions to iopromide were significantly less frequently recorded after IA administrations. This could be related to the delayed and diluted arrival of iopromide to the lungs.

Key Words: iopromide, hypersensitivity reactions, intra-arterial administration

(*Invest Radiol* 2019;55: 38–44)

Iopromide (Ultravist) is a low osmolar nonionic contrast medium containing iodine,[1,2] which cause the x-ray attenuation in computed tomography (CT) examinations. Iopromide has been used for contrast-enhanced CT and other radiographic procedures since 1985. As of July 2018, approximately 260 million doses (≈16 million doses/year)[3] have been administered to patients in more than 100 countries. The overall safety has been proven in numerous studies.[4–9]

Although the overall safety profile of iopromide and other nonionic/low osmolar iodine-based contrast media (IBCM) are well understood,[10–13] there is a continuous discussion pertaining to the nature of hypersensitivity reactions. Hypersensitivity reactions, also called "immediate hypersensitivity reactions,"[14] "allergy-like reactions,"[15] "allergic-like reactions," "anaphylactoid reactions," "ideosynchratic,"[10] or "nonallergic contrast material–induced hypersensitivity, non–IgE-mediated allergy,"[16] are unpredictable and are potentially very severe or even lethal.

The majority of published studies investigated overall safety data on procedures with intravenous (IV) contrast administration. However, there is some evidence pointing to the fact that IV and intra-arterial (IA) administration might have different safety profiles. Such differences on the overall incidence of adverse drug reactions (ADRs) have been published by a few authors.[4,17,18] However, to the best of our knowledge, no study specifically focuses on clinically relevant hypersensitivity reactions after IV versus IA administration.

An initial hypothesis on the pathomechanism of these potential differences on hypersensitivity reactions was stated by Schild.[19] Histamines, released by specific cells in lung and heart tissue, are assumed to play a key role in this process. As IBCMs reach the lung earlier and at a higher concentration after IV compared with IA administration, the trigger on mast cells and basophils to release histamines and other vasoactive substances and consequently cause hypersensitivity reactions is assumed to be more pronounced.[19]

Because hypersensitivity reactions are rare,[20] a prospective approach is challenging, and randomization between IA and IV procedures is not feasible. However, a retrospective analysis based on a sufficiently large data pool bears the potential of answering this question. As the manufacturer of iopromide is in the possession of a large data set comprising patients who have been administered iopromide, the company deemed that it was clinically relevant to gather more evidence to support or reject this hypothesis.

The study design was a nested case-control design applied on a pool of 4 large observational studies.

The purpose of the study was to investigate the risk profile of hypersensitivity reactions to iopromide after IA administration compared with IV administration.

MATERIALS AND METHODS

Studies Analyzed

Four company-sponsored observational studies on iopromide were pooled and analyzed comprising a total of 152,233 patients (PMS I [n = 74,717],[4] IMAGE [n = 44,835],[6] TRUST [n = 17,513],[21,22] and Ultravist in CT [n = 15,168]).[23] Although PMS I and IMAGE included patients with IV and IA injection, TRUST only included IA patients and Ultravist in CT-only IV patients (Table 1).

For these studies, institutional review board/ethics committee approvals and patient informed consents were obtained from participating

Received for publication May 28, 2019; and accepted for publication, after revision, July 14, 2019.

From the *Bayer AG, Radiology R&D, Berlin; †Department of Gynecology, Obstetrics and Reproductive Medicine, University Medical School of Saarland, Homburg/Saar, Germany; ‡Bayer Consumer Care AG, Division Pharmaceuticals, Epidemiology, Basel, Switzerland; §PAREXEL International GmbH, Berlin; and ||Bayer AG, Medical Affairs Statistics, Wuppertal, Germany.

Conflicts of interest and sources of funding: J.E., A.M., P.L., and K.V. are employees of Bayer; R.K. is a statistician for PAREXEL and paid for his service.

Correspondence to: Jan Endrikat, MD, PhD, Bayer AG, Müllerstraße 178, 13353 Berlin, Germany. E-mail: jan.endrikat@bayer.com.

ISSN: 0020-9996/20/5501–0038
DOI: 10.1097/RLI.0000000000000611

TABLE 1. Essentials of Pooled Studies

Study Name	Countries	Study Duration	Intravenous Injection (n = 105,460)	Intra-Arterial Injection (n = 27,871)	Cases (n = 822)	Controls (n = 132,509)	Total (n = 133,331)	Reference
PMS I	27 countries in Europe, Africa, and Asia	6/1999–11/2003	55,470 (52.6%)	7581 (27.2%)	353 (42.9%)	62,698 (47.3%)	63,051 (47.3%)	Kopp et al[4]
IMAGE	21 countries in Europe and Asia	2/2008–11/2009	35,903 (34.0%)	3016 (10.8%)	343 (41.7%)	38,576 (29.1%)	38,919 (29.2%)	Palkowitsch et al[6]
TRUST	China	8/2010–11/2011	—	17,274 (62.0%)	16 (1.9%)	17,258 (13.0%)	17,274 (13.0%)	Chen et al[21]
Ultravist in CT	Germany, Iran, Romania, Saudi Arabia	11/2006–12/2008	14,087 (13.4%)	—	110 (13.4%)	13,977 (10.5%)	14,087 (10.6%)	Palkowitsch et al[23]

countries. This voluntary Post-Authorization Safety Study was registered at ClinicalTrials.gov (NCT03622801) and at ENCePP (EUPAS25089).

For the purpose of study pooling, the data anonymization was increased to eliminate all potential links to patient charts. For example, the original site and patient identifiers were replaced by random numbers, and all free text was eliminated. For adverse events, only MedDRA-coded terms were stored.

Study Population

The population were composed of patients who received iopromide 300 or 370 mg I/mL (Ultravist 300/370; Bayer AG, Germany) either IA or IV for contrast-enhanced CT scans for various diagnostic reasons.

Definition of Cases and Controls

Cases were defined as patients with a typical and unequivocal hypersensitivity reaction, that is, shock, angioedema, asthma, bronchospasm, conjunctivitis, cough, dysphagia, dyspnea, edema mucosal, erythema/exanthema/rash, hoarseness, lacrimation, laryngeal/pharyngeal/face edema, laryngeal/pharyngeal spasm, nasal stuffiness, pruritus/itching, respiratory arrest, rhinitis, sneezing, stridor, swelling (eyes/face), throat irritation, tongue edema, urticaria/hives/blisters, and wheezing.[10] Terminology used was kept in accordance with the actual reporting of the participating physicians. All cases were considered as drug related, irrespective of the investigators' judgment, that is, the most conservative approach for drug relationship to hypersensitivity event was chosen. Controls were defined as subjects in which no adverse event was reported. Unspecific reactions (eg, headache, nausea) and possibly procedure-related reactions (eg, drop in blood pressure, bradycardia, tachycardia) were excluded from the cases and from the controls, to avoid misclassification and confounding by the procedure performed.

Adverse event data were coded by MedDRA version 21.0.

Target Variables

The primary target variable was the risk (odds ratio) of having a hypersensitivity reaction after IA versus IV administration of iopromide, adjusted for potential confounders.

Secondary target variables pertained to assessing the impact of pretreatment with antihistamines/corticosteroids and to evaluate the profile of reactions within each route of administrations.

Statistics

Statistical analyses were of exploratory and descriptive nature only. No confirmatory hypothesis tests were performed. *P* values from statistical tests were interpreted as a metric for uncertainty, thus no adjustment for multiplicity was necessary.

All variables were analyzed descriptively with appropriate statistical methods: categorical variables by frequency tables (absolute and relative frequencies) and continuous variables by sample statistics (ie, mean, standard deviation, minimum/median/maximum, lower and upper quartiles).

During the pooling of the 4 studies, categories of variables were harmonized. From the set of pooled studies, patients were selected based on the criteria described previously (received iopromide 300 or 370 mg I/mL in the injection route cohorts "intra-arterial" or "intravenous") and were classified either as cases or controls within those cohorts (nested case-control study).

For the analysis of the primary objective, unconditional, logistic regression models were computed to identify relevant covariates and potential confounders. These primary models included fixed effects for injection route, age, sex, and the respective covariate. A covariate was considered as important when its effect, represented by a descriptive *P* value, was below 0.1. Subsequently, the covariates identified in the primary regression models were brought together in a secondary logistic regression model to identify the individual effect on the occurrence of

hypersensitivity reactions. The logistic regression model included the fixed effects for injection route, age, sex, and all identified covariates from the primary models. All reported odds ratios, confidence intervals, and *P* values were resulting from this adjusted model.

Secondary objectives were addressed by means of frequency and summary tables.

RESULTS

Disposition of Patients

A total of 152,233 patients were pooled from 4 studies. After checking exclusion criteria, 133,331 patients comprised the full analysis set (FAS). There were 105,460 and 27,871 patients with IV and IA injection, respectively (Fig. 1).

Almost half of the study population (48.1%) was from Europe, and one quarter each from China (27.6%) and other Asian countries (24.1%). Although the majority of patients in the IV arm were from Europe (54.2%), the majority of patients in the IA arm were from Asia (including China; 74.9%; Table 2).

Table 3 shows the baseline characteristics of cases (n = 822) and controls (132,509). Remarkable differences between the groups were recorded for geographic region (China, Asia), age, examination region (abdomen, heart, thorax, pelvis, kidneys), indication (tumor), and type of examination (CT, angiocardiography). No difference was seen for premedication, neither for corticosteroids nor for H1/H2 blocker (Table 3).

Significant Covariates for Hypersensitivity Reactions

The most striking effect was seen with respect to injection route: 93.2% of cases were seen after IV administration and 6.8% of the cases after IA, whereas 79% and 21% of controls were in the IV and IA group, respectively (odds ratio, 0.23 [95% confidence interval, 0.16–0.32]; $P < 0.001$). In addition, age 18 to younger than 50 years (vs ≥65 years; odds ratio, 2.16 [1.78–2.62]; $P < 0.001$), allergy (odds ratio, 3.61 [2.84–4.59]; $P < 0.001$), asthma (odds ratio, 2.14 [1.26–3.62]; $P = 0.005$), and contrast media reaction in the past (odds ratio, 4.31 [2.75–6.75]; $P < 0.001$) were identified as major risk factors for hypersensitivity reactions (Table 4).

Hypersensitivity Reactions

Hypersensitivity reactions were significantly more frequently recorded after IV than after IA administration, 0.7% versus 0.2%, respectively ($P < 0.0001$). The most frequent hypersensitivity reactions were skin reactions (erythema, urticaria, rash), reported in 508/133,331 patients (0.4%), followed by pruritus (n = 294; 0.2%), cough/sneezing (n = 151; 0.1%), and dyspnea/bronchospasm (n = 105; <0.1%). Clinically relevant severe adverse reactions such as anaphylactic shock, laryngeal edema, and respiratory arrest were recorded once each (Table 5, Fig. 2).

TABLE 2. Geographic Region

Region	Intravenous Injection (n = 105,460)	Intra-arterial Injection (n = 27,871)	Total (n = 133,331)
Europe	57,195 (54.2%)	6879 (24.7%)	64,074 (48.1%)
China	19,436 (18.4%)	17,339 (62.2%)	36,775 (27.6%)
Asia (excluding China)	28,541 (27.1%)	3550 (12.7%)	32,091 (24.1%)
Africa	288 (0.3%)	103 (0.4%)	391 (0.3%)

Impact of China

The TRUST study[21] was carried out only in China and investigated exclusively patients with IA injection contributing 17,274 (62.0%) of 27,871 of patients with IA injection (Table 1). In total, 36,775 (27.6%) of 133,331 patients were recruited in China (Table 2), with 151 (18.4%) of 822 cases recorded in China while only 16 (1.9%) of 822 of those cases were recorded in the TRUST study (Table 1).

A subanalysis for patients from China versus rest of the world showed the following: the Chinese odds ratio for IA administration was 0.22, very close to the whole cohort. Excluding Chinese patients, that is, 27.6% of the total population and 62.2% of the IA population, still resulted in an odds ratio of 0.36 ($P < 0.001$).

For allergy, the odds ratio for China only was nearly three times higher (9.51) compared with the world without China (3.39) or with the whole cohort (3.61). Neither contrast media reactions in the past nor asthma were documented for cases in China (Table 4).

DISCUSSION

This study analyzed the risk of hypersensitivity reactions after both IA and IV administration of iopromide and revealed substantial evidence for a lower risk after IA administration.

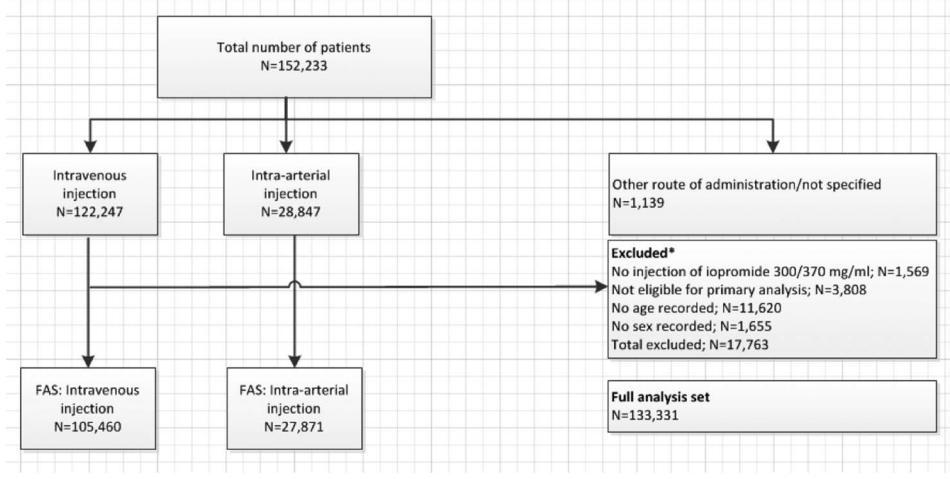


FIGURE 1. Disposition of patients. FAS indicates full analysis set.

TABLE 3. Baseline Characteristics of Study Population

	Cases n = 822	Controls n = 132,509
Geographic region		
Europe	344 (41.8%)	63,730 (48.1%)
China	151 (18.4%)	36,624 (27.6%)
Asia (without China)	327 (39.8%)	31,764 (24.0%)
Africa	0	391 (0.3%)
Concentration		
Iopromide 300	553 (67.3%)	84,447 (63.7%)
Iopromide 370	269 (32.7%)	48,062 (36.3%)
Sex		
Female	408 (49.6%)	57,666 (43.5%)
Male	414 (50.4%)	74,843 (56.5%)
Age, y		
Mean (SD)	50.9 (15.72)	56.0 (15.97)
Min–max	5–97	0–105
Race		
Asian	302 (36.7%)	49,320 (37.2%)
White	48 (5.8%)	6121 (4.6%)
Other	8 (1.0%)	156 (0.1%)
Black	0	23 (<0.1%)
Not specified	464 (56.4%)	76,889 (58.0%)
Concomitant disease		
Patients with any disease	374 (45.5%)	52,075 (39.3%)
Hypertension arterial	74 (9.0%)	16,633 (12.6%)
Coronary heart disease	49 (6.0%)	11,243 (8.5%)
Diabetes mellitus	68 (8.3%)	10,355 (7.8%)
Reduced general condition	45 (5.5%)	6917 (5.2%)
Specific contrast media risk factor	114 (13.9%)	4803 (3.6%)
Allergy	82 (10.0%)	3484 (2.6%)
Asthma	15 (1.8%)	802 (0.6%)
Contrast media reaction	22 (2.7%)	699 (0.5%)
Other	154 (18.7%)	19,247 (14.5%)
None specified	448 (54.5%)	80,434 (60.7%)
Premedication		
H1/H2 blocker or corticosteroids	87 (10.6%)	13,807 (10.4%)
Corticosteroids	62 (7.5%)	10,488 (7.9%)
H1/H2 blocker	25 (3.0%)	3319 (2.5%)
Other/not specified	38 (4.6%)	6023 (4.5%)
Examination region		
Abdomen	228 (27.7%)	25,033 (18.9%)
Cardiac/cardiac vessels	46 (5.6%)	22,776 (17.2%)
Thorax	108 (13.1%)	12,962 (9.8%)
Pelvis	91 (11.1%)	7631 (5.8%)
Head/brain	45 (5.5%)	6052 (4.6%)
Kidney/renal vessels	51 (6.2%)	4090 (3.1%)
Neck	20 (2.4%)	2551 (1.9%)
Blood vessels	13 (1.6%)	1733 (1.3%)
Limbs	1 (0.1%)	386 (0.3%)
Joints	0	43 (<0.1%)
Other/not specified	16 (1.9%)	922 (0.7%)
Indication		
Tumor/suspicion of tumor	216 (26.3%)	24,857 (18.8%)
Pain	60 (7.3%)	6969 (5.3%)
Posttherapy control	47 (5.7%)	6927 (5.2%)
Staging	36 (4.4%)	5127 (3.9%)
Inflammatory diseases	36 (4.4%)	3965 (3.0%)
Infarct/suspicion of infarct	25 (3.0%)	3361 (2.5%)
Hemorrhage	5 (0.6%)	832 (0.6%)
Trauma	1 (0.1%)	567 (0.4%)
Other/not specified	113 (13.7%)	23,500 (17.7%)
Iodine dose, g		
≤20	133 (16.2%)	22,668 (17.1%)
>20–40	561 (68.2%)	86,581 (65.3%)
>40–60	108 (13.1%)	16,548 (12.5%)
>60	16 (1.9%)	6135 (4.6%)
Not specified	4 (0.5%)	577 (0.4%)
Type of examination		
CT	673 (81.9%)	91,433 (69.0%)
Angiocardiography	20 (2.4%)	12,715 (9.6%)
Urography	60 (7.3%)	10,134 (7.6%)
Angiography	5 (0.6%)	1794 (1.4%)
Phlebography	0	296 (0.2%)
DSA	0	221 (0.2%)
Other/not specified	64 (7.8%)	15,916 (12.0%)

Continued next page

Study Design

As the risk for hypersensitivity reactions following low osmolar nonionic contrast medium administration is known to be low,[7,24] 4 large company-sponsored phase IV studies were pooled in a common database. A total of 17,763 patients had to be excluded from the FAS as key parameters were not sufficiently recorded, however, a cohort of 133,331 patients is still considered to be clinically meaningful. The sample size imbalance between the IV and IA group reflects the situation in daily clinical routine. The IA group of 27,871 patients is still considered sufficiently large.

In addition, the participation of more the 27 countries from in Europe, Asia, and Africa allows for a generalization of the results on different populations and on different imaging settings.

Cases and Controls

Cases and controls differed in several baseline characteristics, in particular with respect to geographic region (China, Asia), examination region, indication, and examination type (Table 3). This reflects that most of the cases are patients with IV administration and examination of noncardiovascular regions. While for China, where 62.0% of patients with IA administration were recruited (Table 2), a subanalysis was carried out (see below); the other parameters are not considered to have a clinically meaningful impact on the risk for hypersensitivity reactions. Risk factors are mainly history of allergies and prior reaction to IBCM.[4,5,25]

Hypersensitivity Reactions

The overall incidence of hypersensitivity reactions was 822/133,331 (0.62%) (Table 5). This is well in the range reported by other studies, for example, Zhang et al (0.16%–0.21%),[26] Sodagari et al (0.48%),[24] and Kim et al (0.02%–0.05%).[27] A similar range is also seen in pediatric patients, as Dillman et al[7] reported a rate of 0.18% of acute allergy-like reactions in this population. Also, the higher risk for

TABLE 4. Risk of Hypersensitivity Reactions and Odds Ratios of Significant Covariates

	Cases n = 822	Controls n = 132,509	Odds Ratio (World) (95% CI)	*P*	Odds Ratio (China Only) (95% CI)	*P*	Odds Ratio (World Without China) (95% CI)	*P*
Injection route (vs IV)								
IV	766 (93.2%)	104,694 (79.0%)						
IA	56 (6.8%)	27,815 (21.0%)	0.23 (0.16–0.32)	<0.001	0.22 (0.11–0.44)	<0.001	0.36 (0.25–0.53)	<0.001
Age (vs ≥65 y)								
≥65 y	164 (20.0%)	43,209 (32.6%)						
50–<65 y	307 (37.3%)	49,345 (37.2%)	1.67 (1.38–2.02)	<0.001	1.57 (0.99–2.49)	0.057	1.69 (1.37–2.09)	<0.001
18–<50 y	337 (41.0%)	36,989 (27.9%)	2.16 (1.78–2.62)	<0.001	2.09 (1.32–3.31)	0.002	2.19 (1.77–2.71)	<0.001
<18 y	14 (1.7%)	2966 (2.2%)	1.14 (0.65–2.00)	0.646	1.72 (0.39–7.60)	0.474	1.13 (0.61–2.06)	0.702
Sex (vs male)								
Male	414 (50.4%)	74,843 (56.5%)						
Female	408 (49.6%)	57,666 (43.5%)	1.16 (1.01–1.34)	0.034	1.15 (0.83–1.59)	0.408	1.18 (1.01–1.37)	0.038
Arterial hypertension (vs no)								
No	748 (91.0%)	115,876 (87.4%)						
Yes	74 (9.0%)	16,633 (12.6%)	1.10 (0.85–1.43)	0.466	0.38 (0.18–0.81)	0.011	1.53 (1.17–2.02)	0.002
Diabetes mellitus (vs no)								
No	754 (91.7%)	122,154 (92.2%)						
Yes	68 (8.3%)	10,355 (7.8%)	1.54 (1.19–2.00)	0.001	1.02 (0.43–2.43)	0.958	1.56 (1.18–2.06)	0.002
Allergy (vs no)								
No	740 (90.0%)	129,025 (97.4%)						
Yes	82 (10.0%)	3484 (2.6%)	3.61 (2.84–4.59)	<0.001	9.51 (4.64–19.49)	<0.001	3.39 (2.62–4.38)	<0.001
Asthma (vs no)								
No	807 (98.2%)	131,707 (99.4%)						
Yes	15 (1.8%)	802 (0.6%)	2.14 (1.26–3.62)	0.005	NA		2.22 (1.31–3.78)	0.003
Contrast media reaction								
No	800 (97.3%)	131,810 (99.5%)						
Yes	22 (2.7%)	699 (0.5%)	4.31 (2.75–6.75)	<0.001	NA		4.80 (3.06–7.54)	<0.001
Concomitant disease: other (vs no)								
No	668 (81.3%)	113,262 (85.5%)						
Yes	154 (18.7%)	19,247 (14.5%)	1.42 (1.19–1.70)	<0.001	0.79 (0.49–1.26)	0.320	1.55 (1.28–1.89)	<0.001
Geographic region (vs Europe)								
Europe	344 (41.8%)	63,730 (48.1%)						
Asia (excluding China)	327 (39.8%)	31,764 (24.0%)	1.80 (1.54–2.11)	<0.001	NAP		1.78 (1.52–2.08)	<0.001
China	151 (18.4%)	36,624 (27.6%)	1.01 (0.82–1.25)	0.892	NAP		NAP	
Africa	0	391 (0.3%)	NA		NAP		NA	
Dose of iodine in CM (vs ≤20 g)								
≤20 g	133 (16.2%)	22,668 (17.1%)						
>20–40 g	561 (68.2%)	86,581 (65.3%)	1.24 (1.01–1.51)	0.036	1.78 (0.62–5.06)	0.283	1.22 (0.99–1.50)	0.058
>40–60 g	108 (13.1%)	16,548 (12.5%)	1.28 (0.98–1.66)	0.068	3.66 (1.12–11.90)	0.031	1.22 (0.93–1.60)	0.146
>60 g	16 (1.9%)	6135 (4.6%)	1.30 (0.73–2.30)	0.369	0.49 (0.05–4.62)	0.536	1.76 (0.98–3.18)	0.060
Iopromide concentration (vs iopromide 300)								
Iopromide 300	553 (67.3%)	84,447 (63.7%)						
Iopromide 370	269 (32.7%)	48,062 (36.3%)	1.31 (1.12–1.54)	0.001	0.71 (0.49–1.04)	0.079	1.45 (1.22–1.73)	<0.001

NA indicates Not available odds ratio was not computed because no cases were observed in the corresponding category; NAP, not applicable.

hypersensitivity reactions for patients with history of allergy and previous IBCM reactions is well established.[28,29]

Hypersensitivity Reactions IV Versus IA

This study showed all hypersensitivity reactions to be significantly more frequent after IV than after IA administration, 0.7% versus 0.2% ($P < 0.0001$), respectively. This risk difference remained even after adjustment for potential confounders. Also, the specific symptoms, that is, erythema/urticarial/rash, pruritus, cough/sneezing, and dyspnea/bronchospasm, were more often seen after IV administration (Table 5, Fig. 2). To the best of our knowledge, this has not been shown before in a large cohort study.

TABLE 5. Occurrence of Hypersensitivity Reactions

	IV Injection (n = 105,460)	IA Injection (n = 27,871)	Total (n = 133,331)
All patients with any hypersensitivity reaction	766 (0.7%)	56 (0.2%)	822 (0.6%)
Erythema, urticaria, rash	481 (0.5%)	27 (<0.1%)	508 (0.4%)
Pruritus	277 (0.3%)	17 (<0.1%)	294 (0.2%)
Cough, sneezing	144 (0.1%)	7 (<0.1%)	151 (0.1%)
Dyspnea, bronchospasm	94 (<0.1%)	11 (<0.1%)	105 (<0.1%)
Face edema	4 (<0.1%)	0	4 (<0.1%)
Throat irritation	4 (<0.1%)	0	4 (<0.1%)
Dysphagia	3 (<0.1%)	0	3 (<0.1%)
Dysphonia	2 (<0.1%)	0	2 (<0.1%)
Eye swelling	2 (<0.1%)	0	2 (<0.1%)
Nasal congestion	2 (<0.1%)	0	2 (<0.1%)
Anaphylactic shock	0	1 (<0.1%)	1 (<0.1%)
Lacrimation	1 (<0.1%)	0	1 (<0.1%)
Laryngeal edema	1 (<0.1%)	0	1 (<0.1%)
Respiratory arrest	0	1 (<0.1%)	1 (<0.1%)
Rhinitis	1 (<0.1%)	0	1 (<0.1%)

An initial hint on a higher incidence of overall ADRs after IV iodine contrast media administration was given by Shenadi et al,[18] Bush et al,[17] and Kopp et al,[4] all reporting higher overall ADR rates after IV administration compared with IA Interestingly, Bettmann et al[30] demonstrated the opposite, that is, higher ADR rates after IA injections. Kopp et al[4] (who's dataset is part of this evaluation and trigger this study) found a statistically significant higher incidence of the overall ADR rate for IV administration (2.1%) versus IA (1.1%). Importantly, they excluded an impact of the IBCM dose, which is generally higher in IA examinations. Furthermore, by excluding tolerance indicators (ie, heat sensation and pain at the injection site), a faint hint of lower incidence of hypersensitivity reactions (eg, skin reactions and dyspnea/bronchospasm) after IA injection was given, though not on the whole spectrum of hypersensitivity reactions.[4]

An approach to explain the pathophysiology of hypersensitivity reactions and in particular the lower incidence of these reactions after IA administration has been provided by Schild.[19] He postulated that histamine plays a dominant role, as histamine can cause many symptoms similar to CM reactions by dilatation of smaller vessels, contraction of larger vessels, and increased vessel permeability. A further sign might be that IBCM injection increases histamine blood levels and, conversely, antihistamines can prevent hypersensitivity symptoms. Histamines are released by basophils and mast cells,[19,31] the latter are particularly abundant in lung and heart tissue. Iodine-based contrast media reach these 2 organs earlier and at higher concentrations after IV administration compared with IA since after IA administration, the IBCM is dispersed while passing through a capillary network before it reaches the right heart and pulmonary circulation. Other theories involve the complement system and the plasma contact system.[19] In general, the pathophysiologic mechanism of hypersensitivity reactions following IBCM administration is not fully elucidated.

Impact of Premedication

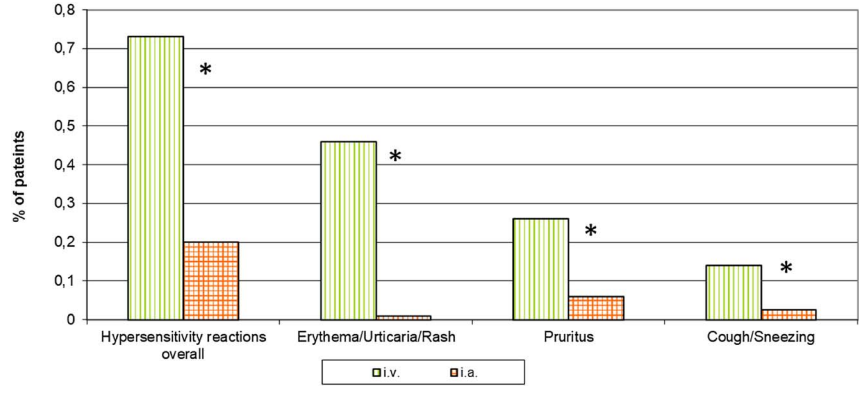
This study did not show any impact of premedication on the rate of hypersensitivity reactions, neither for corticosteroids nor for H1/H2 blocker (Table 3). This is in line with a recent report by Clement et al, who summarized the current knowledge by stating that several pretreatment protocols, mainly based on antihistaminic drugs and corticosteroids, do not prevent severe reactions and anaphylactic shock. Instead, Clement et al[14] propose skin testing with pure contrast agent. Also, Park et al evaluated premedication protocols involving administration of antihistamine and multidose corticosteroids. They suggested a combination of changing the culprit agent and antihistamine premedication for the best preventive outcome,[28] a strategy also suggested by Lee et al.[29]

Impact of China

As more than 62.0% of patients with IA injection came from China (Table 2), a subanalysis was carried out. Although the odds ratios for some covariates were affected by the Chinese dominance (administration route, arterial hypertension, allergy, contrast media reaction, dose, and concentration of iopromide), the results for the non-Chinese cohort were in the same range as for the whole population. A different reporting rate by the staff of the imaging suite or different sensitivities of Chinese patients cannot be excluded.

Limitations

Some limitations need to be addressed. First, as this was a pooled analysis of 4 similarly designed studies of different sizes in different countries, any impact of study-specific reporting standards could not be completely excluded. Second, a clear and scientifically proven explanation for some differences between the Chinese population versus non-Chinese patients could not be provided. Third, adverse event reporting



* p-value <0.001

FIGURE 2. Occurrence of clinically most relevant hypersensitivity reactions (cutoff ≥0.1% in at least one study group). Note that there was one case of laryngeal edema in the IV group and one case each of anaphylactic shock and respiratory arrest in the IA group. IV indicates intravenous; IA, intra-arterial.

in observational studies is usually less stringent compared with prospective clinical trials, thus some underreporting may have occurred.[32] Four, as IA administrations for coronary imaging are mainly done by cardiologists, an impact of different reporting habits of cardiologists and radiologists could not be excluded. However, case reporting standards, investigator trainings, and general study standards were kept similar over all studies. Fifth, cases were defined by patients with a typical and unequivocal hypersensitivity reaction. However, no laboratory tests (eg, IgE testing) were performed. Thus, a laboratory-confirmed distinction between "hypersensitivity" and "true allergic" reaction could not be provided. However, we think this does not invalidate the overall conclusion.

This study confirmed the long-standing presumption of a lower risk for hypersensitivity reactions after IA administration versus IV administration in a sufficiently large cohort.

CONCLUSIONS

Hypersensitivity reactions after iopromide administrations are rare but occur more often after IV injection than after IA injection. The pathomechanism has not been fully elucidated.

ACKNOWLEDGMENTS

The authors thank the team of the CRO "PAREXEL International GmbH," for the support of the biometrical evaluation. In addition, we thank Petra Palkowitsch for her scientific input in the research concept.

REFERENCES

1. Krause W, Miklautz H, Kollenkirchen U, et al. Physicochemical parameters of x-ray contrast media. *Invest Radiol*. 1994;29:72–80.
2. Goldstein HA, Jacob G, Wiggins JR. New clinical trial experience with iopromide. *Invest Radiol*. 1994;29(suppl 2):S208–S210.
3. Bayer AG. Periodic benefit-risk evaluation report - periodic safety update report Ultravist® 150/240/300/370 BAY No. 86-4877 (Iopromide) No 241. 28 Aug 2018.
4. Kopp AF, Mortele KJ, Cho YD, et al. Prevalence of acute reactions to iopromide: postmarketing surveillance study of 74,717 patients. *Acta Radiol*. 2008;49:902–911.
5. Mortele KJ, Oliva MR, Ondategui S, et al. Universal use of nonionic iodinated contrast medium for CT: evaluation of safety in a large urban teaching hospital. *AJR Am J Roentgenol*. 2005;184:31–34.
6. Palkowitsch P, Lengsfeld P, Stauch K, et al. Safety and diagnostic image quality of iopromide: results of a large non-interventional observational study of European and Asian patients (IMAGE). *Acta Radiol*. 2012;53:179–186.
7. Dillman JR, Strouse PJ, Ellis JH, et al. Incidence and severity of acute allergic-like reactions to i.v. nonionic iodinated contrast material in children. *AJR Am J Roentgenol*. 2007;188:1643–1647.
8. An J, Jung H, Kwon OY, et al. Differences in adverse reactions among iodinated contrast media: analysis of the KAERS database. *J Allergy Clin Immunol Pract*. 2019.
9. Seong JM, Choi NK, Lee J, et al. Comparison of the safety of seven iodinated contrast media. *J Korean Med Sci*. 2013;28:1703–1710.
10. ACR Committee on Drugs and Contrast Media - ACR Manual on Contrast Media. 2018; Version 10.3. Available at: https://www.acr.org/-/media/ACR/Files/Clinical-Resources/Contrast_Media.pdf.
11. Suh YJ, Yoon SH, Hong H, et al. Acute adverse reactions to nonionic iodinated contrast media: a meta-analysis. *Invest Radiol*. 2019;54:589–599.
12. Jick SS, Hedderson M, Xu F, et al. Iodinated contrast agents and risk of hypothyroidism in young children in the United States. *Invest Radiol*. 2019;54:296–301.
13. Gorelik Y, Yaseen H, Heyman SN, et al. Negligible risk of acute renal failure among hospitalized patients after contrast-enhanced imaging with iodinated versus gadolinium-based agents. *Invest Radiol*. 2019;54:312–318.
14. Clement O, Dewachter P, Mouton-Faivre C, et al. Immediate hypersensitivity to contrast agents: the French 5-year CIRTACI Study. *EClinicalMedicine*. 2018;1:51–61.
15. ESUR Guidelines on Contrast Agents European Society of Urogenital Radiology 10.0. March 2018. Available at: http://wwwesurorg/guidelines/de/.
16. Trcka J, Schmidt C, Seitz CS, et al. Anaphylaxis to iodinated contrast material: nonallergic hypersensitivity or IgE-mediated allergy? *AJR Am J Roentgenol*. 2008;190:666–670.
17. Bush WH, Swanson DP. Acute reactions to intravascular contrast media: types, risk factors, recognition, and specific treatment. *AJR Am J Roentgenol*. 1991;157:1153–1161.
18. Shehadi WH, Toniolo G. Adverse reactions to contrast media: a report from the Committee on Safety of Contrast Media of the International Society of Radiology. *Radiology*. 1980;137:299–302.
19. Schild H. CM to See or not to see. Schering Diagnositics, Bayer. 1994. Last update 2018. ISBN 3-921817-56. 71, 79–84.
20. Gottumukkala RV, Glover M 4th, Yun BJ, et al. Allergic-like contrast reactions in the ED: incidence, management, and impact on patient disposition. *Am J Emerg Med*. 2018;36:825–828.
21. Chen JY, Liu Y, Zhou YL, et al. Safety and tolerability of iopromide in patients undergoing cardiac catheterization: real-world multicenter experience with 17,513 patients from the TRUST trial. *Int J Cardiovasc Imaging*. 2015;31:1281–1291.
22. He Y, Huang Y, Yang J, et al. Novel risk model for predicting acute adverse drug reactions following cardiac catheterization from TRUST study (the safety and tolerability of ultravist in patients undergoing cardiac catheterization). *J Thorac Dis*. 2019;11:1611–1620. Available at: https://academic.oup.com/eurheartj/article-abstract/39/suppl_1/ehy563.P4633/5081552.
23. Palkowitsch PK, Bostelmann S, Lengsfeld P. Safety and tolerability of iopromide intravascular use: a pooled analysis of three non-interventional studies in 132,012 patients. *Acta Radiol*. 2014;55:707–714.
24. Sodagari F, Mozaffary A, Wood CG 3rd, et al. Reactions to both nonionic iodinated and gadolinium-based contrast media: incidence and clinical characteristics. *AJR Am J Roentgenol*. 2018;210:715–719.
25. Pradubpongsa P, Dhana N, Jongjarearnprasert K, et al. Adverse reactions to iodinated contrast media: prevalence, risk factors and outcome-the results of a 3-year period. *Asian Pac J Allergy Immunol*. 2013;31:299–306.
26. Zhang B, Liu J, Dong Y, et al. Extrinsic warming of low-osmolality iodinated contrast media to 37 degrees C reduced the rate of allergic-like reaction. *Allergy Asthma Proc*. 2018;39:e55–e63.
27. Kim SR, Lee JH, Park KH, et al. Varied incidence of immediate adverse reactions to low-osmolar non-ionic iodide radiocontrast media used in computed tomography. *Clin Exp Allergy*. 2017;47:106–112.
28. Park SJ, Kang DY, Sohn KH, et al. Immediate mild reactions to CT with iodinated contrast media: strategy of contrast media readministration without corticosteroids. *Radiology*. 2018;288:710–716.
29. Lee SY, Yang MS, Choi YH, et al. Stratified premedication strategy for the prevention of contrast media hypersensitivity in high-risk patients. *Ann Allergy Asthma Immunol*. 2017;118:339–44e1.
30. Bettmann MA, Heeren T, Greenfield A, et al. Adverse events with radiographic contrast agents: results of the SCVIR Contrast Agent Registry. *Radiology*. 1997;203:611–620.
31. Gueant-Rodriguez RM, Romano A, Barbaud A, et al. Hypersensitivity reactions to iodinated contrast media. *Curr Pharm Des*. 2006;12:3359–3372.
32. Hazell L, Shakir SA. Under-reporting of adverse drug reactions: a systematic review. *Drug Saf*. 2006;29:385–396.