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

A Nested Case-Control Analysis of 133,331 Patients

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**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 cardio-angiography) 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 (IV 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

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**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], IMAGE [n = 44,835], TRUST [n = 17,513], and Ultravist in CT [n = 15,168]). All trials analyzed 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 institutions.
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, bronchoospasm, conjunctivitis, cough, dysphagia, dyspnea, edema mucosal, erythema/exanthema/rash, hoarseness, 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. 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 (n = 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).

Impact of China

The TRUST study21 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.

* Multiple reasons per patient were possible

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

As the risk for hypersensitivity reactions following low osmolar nonionic contrast medium administration is known to be low,7,24 a large company-sponsored phase IV studies were pooled in a common data-base. 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 situ-ation in daily clinical routine. The IA group of 27,871 patients is still considered sufficiently large.

In addition, the participation of more than 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 reported a rate of 0.18% of acute allergy-like reactions in this population. Also, the higher risk for
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 4. Risk of Hypersensitivity Reactions and Odds Ratios of Significant Covariates

| Injection route (vs IV) | 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) | $P$ |
|------------------------|--------------|----------------------|-----------------------------|-----|---------------------------------|-----|------------------------------------------|-----|
| IV                     | 766 (93.2%)  | 104,694 (79.0%)      | 0.23 (0.16–0.32)            | <0.001 | 0.22 (0.11–0.44)              | <0.001 | 0.36 (0.25–0.53)                         | <0.001 |
| IA                     | 56 (6.8%)    | 27,815 (21.0%)       |                            |       |                                 |       |                                          |       |
| 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%)       |                            |       |                                 |       |                                          |       |
| 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                     | 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 |
| Asthma (vs no)         |              |                      |                            |       |                                 |       |                                          |       |
| 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   | NAP                                      |       |
| Africa                 | 0           | 391 (0.3%)           | NA                         |       | 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.
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 al30 demonstrated the opposite, that is, higher ADR rates after IA injections. Kopp et al (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 for 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 al14 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

![Image](https://www.investigativeradiology.com)

**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.

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in observational studies is usually less stringent compared with prospective clinical trials, thus some underreporting may have occurred.14 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.

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