Risk of Hypersensitivity Reactions to Iopromide in Children and Elderly
An Analysis of 132,850 Patients From 4 Observational Studies and Pharmacovigilance Covering >288 Million Administrations

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Purpose: The aim of this study was to analyze the risk of hypersensitivity reactions (HSRs) to iopromide in children and elderly patients in comparison to adults.

Materials and Methods: Four observational studies were pooled and analyzed (analysis I). In addition, spontaneous reports from 1985 to 2020 from the pharmacovigilance database were evaluated (analysis II). All patients received iopromide for angiographic procedures or contrast-enhanced computed tomography in various indications. In analysis I, a nested case-control analysis, including a multivariable logistic regression model, based on pooled observational study data, was performed. Cases were defined as patients with a typical and unequivocal HSR; controls were patients without any recorded reaction. In analysis II, all spontaneous reports on HSRs after iopromide administration recorded in the pharmacovigilance database were descriptively analyzed. Exposure estimates on the size of the exposed age groups were derived from sales data and data from market research. The primary target variable was the risk of HSR to iopromide in children (<18 years) and elderly patients (≥65 years) compared with adults (18 to <65 years).

Results: In analysis I, a total of 132,850 patients were included (2978 children, 43,209 elderly, and 86,663 adults). Hypersensitivity reactions were significantly less frequent in children (0.47%) and elderly (0.38%) compared with adults (0.74%). The adjusted odds ratio (vs adults) for children was 0.58 (95% confidence interval, 0.34–0.98; P < 0.043), and that for the elderly was 0.51 (95% confidence interval, 0.43–0.61; P < 0.001), indicating a lower risk for both subpopulations as compared with adults. In analysis II, of the overall >288 million iopromide administrations, 5.87, 114.18, and 167.97 million administrations were administered to children, elderly, and adults, respectively. The reporting rate for HSRs in children (0.0143%) and elderly (0.0071%) was significantly lower as compared with adults (0.0143%; P < 0.0001).

Conclusions: Hypersensitivity reactions to iopromide were significantly less frequent in children and elderly compared with adults.

Key Words: iopromide, hypersensitivity reactions, children, elderly

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MATERIALS AND METHODS

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This study consists of 2 analyses based on 2 different databases: analysis I is based on 4 company-sponsored observational studies, analysis II on the company’s pharmacovigilance (PV) database.

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Four observational company-sponsored studies on iopromide comprising a total of 152,233 patients were pooled and analyzed: (1)

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Analysis I: Observational Studies
Four observational company-sponsored studies on iopromide comprising a total of 152,233 patients were pooled and analyzed: (1)
HSR as defined by the ACR Committee on Drugs and Contrast Media after administration of any dose of iopromide for any indication.

DICMAs with iopromide 300 or 370 mg I/mL.

Analysis II: Pharmacovigilance

Bayer's PV captures spontaneous cases as well as data from other sources. The estimated exposure covered >288 million injections from January 1995 to December 2020 (Table 2). Exposure estimates were derived from sales data and data from market research. Also, the age distribution was calculated on the basis of market data from the Decision Resources Group (Clarivate).25

Study Population

Analysis I

Analysis I includes routine patients of all ages who underwent contrast-enhanced CT scans or angiographic procedures for various indications with iopromide 300 or 370 mg I/mL.

Analysis II

Analysis II includes patients of all ages from all over the world, after administration of any dose of iopromide for any indication.

Definition of Cases and Controls

Analysis I

Cases were defined as patients with a typical and unequivocal HSR as defined by the ACR Committee on Drugs and Contrast Media 2018, Version 10.3.56 Irrespective of the investigators’ assessment, all cases were categorized as drug related, that is, always the most conservative approach for drug relationship was chosen.

Controls were defined as subjects in whom 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.

Analysis II

The PV database includes cases from patients for which HSRs according to ACR26 have been reported by any health care professional.

Objectives

The primary objective was the risk of HSRs to iopromide in children (<18 years) and elderly patients (≥65 years) compared with adults (18 to <65 years). The secondary objective was to describe the profile of HSRs in the 3 age groups.

Statistics

Analysis I

All variables were analyzed descriptively: categorical variables by absolute and relative frequencies and continuous variables by the mean, standard deviation, minimum, median, quartiles, and maximum. Logistic regression was used to estimate odds ratios (ORs) for HSRs in children or elderly compared with adults. A set of possible confounders was prespecified similar to the previous publication of the same pooled database.15

Adjustment for possible confounders related to age was performed by backward selection using a P value <0.10 as important to keep for further adjustments. At the final step, all possible risk factors and confounders found to be important earlier were fitted simultaneously in a multivariable model, and those with P value <0.10 were retained. The results from the final model are presented. The analysis was exploratory in nature, without adjustment for multiplicity.

Analysis II

The reporting rate per 10,000 administrations was calculated by dividing the sum of all HSRs in one age group in the years 1995 to 2020 by the number of total administrations in this age group during these times years 10. The 2 null hypotheses of equal reporting rates between

| Study Name | Countries | Study Duration | Adults, n = 86,663 (65.2%) | Elderly, n = 43,209 (32.5%) | Cases, n = 818 | Controls, n = 132,032 | Total, n = 132,850 | Reference |
|------------|-----------|----------------|-----------------------------|---------------------------|--------------|---------------------|----------------|-----------|
| PMS I      | 27 countries in Europe, Africa, and Asia | 6/1999–11/2003 | 1607 (54.0%) | 39,432 (45.5%) | 21,541 (49.9%) | 351 (42.9%) | 62,229 (47.1%) | 62,580 (47.1%) | Kopp et al7 |
| IMAGE      | 21 countries in Europe and Asia | 2/2008–11/2009 | 1064 (35.7%) | 27,380 (31.6%) | 10,477 (24.2%) | 342 (41.8%) | 38,579 (29.2%) | 38,921 (29.3%) | Palkowitsch et al2 |
| TRUST      | China | 8/2010–11/2011 | 8 (0.3%) | 11,652 (13.4%) | 5626 (13.0%) | 16 (2.0%) | 17,270 (13.1) | 17,286 (13.0) | Chen et al23 |
| Ultravist  | Germany, Iran, Romania, in CT | 11/2006–12/2008 | 299 (10.0%) | 8199 (9.5%) | 5565 (12.9%) | 109 (13.3) | 13,954 (10.6) | 14,063 (10.6) | Palkowitsch et al24 |

Survival analysis was performed with a log-rank test, with the number of people at risk at the end of the follow-up as the denominator.

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children and adults and between elderly and adults were exploratively
tested using the Fisher exact test with a comparison-wise significance
level of 5%.

RESULTS

Disposition of Patients

Analysis I

All 4 observational studies comprised 152,233 patients. In a first
step, patients with no age recorded (n = 11,646) were excluded. In a sec-
ond step, 4937 patients were excluded from the full analysis set because
they lacked information on the injected contrast or were otherwise not
eligible for the primary analysis. In a final step, 2800 patients with no
data on parameters known to impact the incidence of HSRs were ex-
cluded. The completed case analysis set used for this study comprised
132,850 patients: 2978 children (2.24%), 86,663 adults (65.32%), and
43,209 elderly (32.52%) (Fig. 1, Table 1).

Analysis II

Of the >288 million administrations, 5.87 (2.04%), 167.97 (58.32%),
and 114.18 (39.46%) million administrations were estimated to have
been applied to children, adults, and elderly, respectively (Table 2).

Characteristics of Study Population

Analysis I

The baseline characteristics of the study population are shown
on Table 3. The majority of the patients (47.9%) were recruited in
Europe, about one quarter in China (27.7%) and one quarter in other
Asian countries (excluding China) (24.2%). Very few patients came
from Africa.

In all geographic regions, patients of all 3 age groups were re-
cruited. Although 43.2% of children were recruited in other Asian
countries (excluding China), 11.6% were from China. On the other
hand, elderly were more frequently enrolled in China (25.5%) compared
with other Asian countries (18.3%).

Iopromide concentration, sex, and race were comparably dis-
tributed within the 3 age groups. The incidence of concomitant dis-
ease was lowest in children (33.5%) and highest in elderly (52.3%).
For premedication, injection route, examination region, and indica-
tion, no remarkable difference could be stated. The iodine dose was
lowest in children. Two thirds of adults and elderly received 20 to
40 g of iodine (Table 3).

Analysis II

Hypersensitivity reactions reports were received from 115 coun-
tries, with 4 countries (China, United States, Italy, and Germany) ac-
counting for approximately 50% of all reports. A total of 49.5% of
the patients who experienced HSRs were female, 37.7% were male,
and in 12.8% of the cases, sex was not reported (data not shown). Most
reactions were reported with iopromide 300, but concentration was not
always reported. Indications covered a wide range of procedures to eva-
uate various underlying conditions. The most commonly provided indi-
cation was “CT scan, not otherwise specified,” followed by abdominal
imaging, cardiac angiographic procedures, CT scans of the chest, and CT
of head and neck. Dosing varied widely, depending on the indication for
the procedure and the age/weight of the patient (data not shown).

Risk of HSRs and Covariates

Analysis I

The majority of cases, that is, 640/818 (78.2%), were in the group
of adults. Adults, however, comprised just 65.2% of the controls. Four-
teen cases (1.7%) were in children and 164 (20%) in elderly. In the con-
trol group, these patient groups comprised 2.2% and 32.6%, respectively.
Thus, the adjusted OR (vs adults) for children was 0.58 (95% confidence
interval [CI], 0.34–0.98; P < 0.043), and that for the elderly was 0.51
(95% CI, 0.43–0.61; P < 0.001), indicating approximately half the risk
compared with adults (Table 4).

A similar degree of risk reduction was seen for intra-arterial versus in-
travenous injection showing an OR of 0.49 (95% CI, 0.35–0.70; P < 0.001).
Furthermore, diabetes (OR, 1.57; 95% CI, 1.22–2.03; P < 0.001),
history of allergy (OR, 3.73; CI, 2.93–4.74; P < 0.001), asthma (OR,
2.14; CI, 1.26–3.63; P = 0.005), and previous contrast media reactions
(OR, 4.28; CI, 2.74–6.70; P < 0.001) were identified as major risk fac-
tors for HSRs (Table 4).

Specific HSRs

Overall, HSRs were significantly more frequently recorded in
adults (0.74%) compared with children (0.47%) and elderly (0.38%)
( P < 0.05) (Table 5, Fig. 2). The most frequent HSRs were pruritus
(0.22%), urticaria/rash/erythema (0.38%), and cough/sneezing (0.11%).
It is always the adult group that showed the highest incidences (Table 5,
| TABLE 3. Baseline Characteristics of Study Population of Analysis I |
|---------------------------------------------------------------|
|                                                                 |
| **Geographic region**                                         |
| Europe                                                       | 1340 (45.0%) | 37,991 (43.8%) | 24,249 (56.1%) | 63,580 (47.9%) |
| Asia (excluding China)                                       | 1286 (43.2%) | 22,907 (26.4%) | 7903 (18.3%)  | 32,096 (24.2%) |
| China                                                        | 345 (11.6%)  | 25,431 (29.3%) | 11,011 (25.5%)| 36,787 (27.7%) |
| Africa                                                       | 7 (0.2%)     | 334 (0.4%)     | 46 (0.1%)     | 387 (0.3%)     |
| **Concentration**                                            |
| Iopromide 300                                                | 2209 (74.2%) | 54,085 (62.4%) | 28,275 (65.4%)| 84,569 (63.7%) |
| Iopromide 370                                                | 769 (25.8%)  | 32,578 (37.6%) | 14,934 (34.6%)| 48,281 (36.3%) |
| **Sex**                                                      |
| Male                                                         | 1629 (54.7%) | 49,186 (56.8%) | 24,171 (55.9%)| 74,986 (56.4%) |
| Female                                                       | 1349 (45.3%) | 37,477 (43.2%) | 19,038 (44.1%)| 57,864 (43.6%) |
| **Race**                                                     |
| Asian                                                        | 838 (28.1%)  | 34,673 (40.0%) | 14,110 (32.7%)| 49,621 (37.4%) |
| White                                                        | 210 (7.1%)   | 4083 (4.7%)    | 1889 (4.4%)   | 6182 (4.7%)    |
| Black                                                        | 1 (<0.1%)    | 14 (<0.1%)     | 9 (<0.1%)     | 24 (<0.1%)     |
| Other                                                        | 3 (0.1%)     | 117 (0.1%)     | 44 (0.1%)     | 164 (0.1%)     |
| Not specified                                                | 1926 (64.7%) | 47,776 (55.1%) | 27,157 (62.9%)| 76,859 (57.9%) |
| **Concomitant disease**                                      |
| Hypertension arterial                                        | 23 (0.8%)    | 9879 (11.4%)   | 6817 (15.8%)  | 16,719 (12.6%) |
| Coronary heart disease                                       | 25 (0.8%)    | 5996 (6.9%)    | 5222 (12.1%)  | 11,243 (8.5%)  |
| Diabetes mellitus                                            | 5 (0.2%)     | 5574 (6.4%)    | 4805 (11.1%)  | 10,384 (7.8%)  |
| Reduced general condition                                    | 215 (7.2%)   | 3980 (4.6%)    | 2737 (6.3%)   | 6932 (5.2%)    |
| Specific contrast media risk factor                          | 98 (3.3%)    | 3347 (3.9%)    | 1462 (3.4%)   | 4907 (3.7%)    |
| Allergy                                                      | 71 (2.4%)    | 2467 (2.8%)    | 1021 (2.4%)   | 3559 (2.7%)    |
| Asthma                                                       | 15 (0.5%)    | 489 (0.6%)     | 316 (0.7%)    | 820 (0.6%)     |
| Contrast media reaction                                      | 16 (0.5%)    | 515 (0.6%)     | 186 (0.4%)    | 717 (0.5%)     |
| Other                                                        | 315 (10.6%)  | 11,715 (13.5%) | 7304 (16.9%)  | 19,334 (14.6%) |
| None specified                                               | 686 (23.0%)  | 17,004 (19.6%) | 7135 (16.5%)  | 24,825 (18.7%) |
| **Premedication**                                            |
| Corticosteroids                                              | 138 (4.6%)   | 7297 (8.4%)    | 3067 (7.1%)   | 10,502 (7.9%)  |
| H1/H2 blocker                                               | 64 (2.1%)    | 2284 (2.6%)    | 934 (2.2%)    | 3282 (2.5%)    |
| H1/H2 blocker or corticosteroids                             | 0            | 22 (<0.1%)     | 12 (<0.1%)    | 34 (<0.1%)     |
| Other                                                        | 103 (3.5%)   | 3756 (4.3%)    | 1936 (4.5%)   | 5795 (4.4%)    |
| None specified                                               | 6 (0.2%)     | 185 (0.2%)     | 61 (0.1%)     | 252 (0.2%)     |
| **Injection route**                                          |
| Intravenous                                                  | 2852 (95.8%) | 68,275 (78.8%) | 33,892 (78.4%)| 105,019 (79.1%)|
| Intra-arterial                                               | 126 (4.2%)   | 18,388 (21.2%) | 9317 (21.6%)  | 27,831 (20.9%) |
| **Examination region**                                      |
| Abdomen                                                      | 445 (14.9%)  | 16,943 (19.6%) | 7884 (18.2%)  | 25,272 (19.0%) |
| Cardiac/cardiac vessels                                      | 76 (2.6%)    | 15,539 (17.9%) | 7213 (16.7%)  | 22,828 (17.2%) |
| Thorax                                                       | 365 (12.3%)  | 8207 (9.5%)    | 4478 (10.4%)  | 13,050 (9.8%)  |
| Pelvis                                                       | 203 (6.8%)   | 5284 (6.1%)    | 2245 (5.2%)   | 7732 (5.8%)    |
| Head/brain                                                   | 425 (14.3%)  | 4118 (4.8%)    | 1555 (3.6%)   | 6098 (4.6%)    |
| Kidney/renal vessels                                         | 161 (5.4%)   | 2908 (3.4%)    | 1069 (2.5%)   | 4138 (3.1%)    |
| Neck                                                         | 109 (3.7%)   | 1893 (2.2%)    | 564 (1.3%)    | 2566 (1.9%)    |
| Blood vessels                                                | 53 (1.8%)    | 1053 (1.2%)    | 637 (1.5%)    | 1743 (1.3%)    |
| Limbs                                                        | 10 (0.3%)    | 227 (0.3%)     | 149 (0.3%)    | 386 (0.3%)     |
| Joints                                                       | 3 (0.1%)     | 29 (<0.1%)     | 11 (<0.1%)    | 43 (<0.1%)     |
| Other                                                        | 55 (1.8%)    | 662 (0.8%)     | 218 (0.5%)    | 935 (0.7%)     |
| Not specified                                                | 2 (<0.1%)    | 3 (<0.1%)      | 3 (<0.1%)     | 8 (<0.1%)      |
| Missing                                                      | 1607 (54.0%) | 39,465 (45.5%) | 21,556 (49.9%)| 62,628 (47.1%) |

*Continued next page*
Fig. 3. The clinically most relevant severe adverse reactions, anaphylactic shock, laryngeal edema, and respiratory arrest, one of each, were recorded in the elderly cohort (Table 5).

Analysis II

The spontaneous reporting rates in the PV database were much lower than the rates in the observational studies. Overall, a total of 672, 23,953, and 8109 cases of HSRs were recorded for children, adults, and elderly, respectively. This yielded HSR reporting rates in children of 0.0114% and in elderly of 0.0071%. These rates were significantly lower as compared with adults (0.0143%) ($P < 0.0001$) (Table 2, Fig. 2).

In both analyses, adults showed the highest HSR reporting rate. 

DISCUSSION

This study analyzed the risk of HSRs to iopromide in children (<18 years) and elderly patients (≥65 years) compared with adults (≥18 to <65 years) and revealed substantial evidence for a lower risk of HSRs in children and elderly. 

The risk of HSRs was analyzed on the basis of 2 large data bases: a pooled data set of 4 large observational, prospective studies performed in 27 countries encompassing 132,850 patients and retrospective data from the company’s PV database, representing >288 million administrations, within the last 25 years. The PV database is the largest and probably the most representative iopromide data source. This approach with these 2 large patient cohorts was chosen to yield reasonably robust and representative results for all patients receiving iopromide for various indications. Both databases provide sufficient numbers of HSR cases for reliable statistical evaluations.6,27

A previous evaluation of the observational studies showed a number of parameters impacting the risk of HSRs: route of administration, sex, history of diabetes mellitus, allergy, asthma, and previous contrast media reaction.15 This set of confounders was prespecified, and the statistical model was adjusted accordingly to demonstrate the effect of age.

As expected, the number of patients in the 3 age groups was not evenly distributed. The majority of administrations were performed in adults (65 and 58% in analysis I and II, respectively) followed by elderly (32.5% in analysis I and II). Less than 2.3% of the study population were children (Table 1, Table 2). This is easily explainable by the different number of years summarized in the age brackets of the groups (children, 18 years; adults, 43 years) and the number of indications for contrast-enhanced imaging. Importantly, this age group distribution is fairly similar in both databases supporting the approach to commonly report on both data sets.

| TABLE 3. (Continued) |
|-----------------------|
| **Indication**        | **Children, n = 2978 (2.24%)** | **Adults, n = 86,663 (65.23%)** | **Elderly, n = 43,209 (32.52%)** | **Total, n = 132,850 (100%)** |
| Tumor/suspicion of tumor | 476 (16.0%) | 16,508 (19.0%) | 8088 (18.7%) | 25,072 (18.9%) |
| Pain                  | 175 (5.9%) | 5212 (6.0%) | 1648 (3.8%) | 7035 (5.3%) |
| Posttherapy control   | 117 (3.9%) | 4509 (5.2%) | 2341 (5.4%) | 6967 (5.2%) |
| Staging               | 137 (4.6%) | 3194 (3.7%) | 1831 (4.2%) | 5162 (3.9%) |
| Inflammatory diseases | 214 (7.2%) | 2766 (3.2%) | 1011 (2.3%) | 3991 (3.0%) |
| Infarct/suspicion of infarct | 33 (1.1%) | 2202 (2.5%) | 1146 (2.7%) | 3381 (2.5%) |
| Hemorrhage            | 23 (0.8%) | 603 (0.7%) | 209 (0.5%) | 835 (0.6%) |
| Trauma                | 50 (1.7%) | 428 (0.5%) | 91 (0.2%) | 5 (0.4%) |
| Other                 | 291 (9.8%) | 15,917 (18.4%) | 7407 (17.1%) | 23,615 (17.8%) |
| Not specified         | 13 (0.4%) | 31 (<0.1%) | 0 (<0.1%) | 54 (<0.1%) |
| Missing               | 1616 (54.3%) | 39,692 (45.8%) | 21,713 (50.3%) | 63,021 (47.4%) |
| **Iodine dose**       |             |             |             |             |
| ≤20 g                 | 2035 (68.3%) | 14,825 (17.1%) | 5957 (13.8%) | 22,817 (17.2%) |
| >20–40 g              | 870 (29.2%) | 56,930 (65.7%) | 29,414 (68.1%) | 87,214 (65.6%) |
| >40–60 g              | 70 (2.4%) | 10,834 (12.5%) | 5759 (13.3%) | 16,663 (12.5%) |
| >60 g                 | 3 (0.1%) | 4074 (4.7%) | 2079 (4.8%) | 6156 (4.6%) |
| **Type of examination** |             |             |             |             |
| CT                    | 1297 (43.6%) | 35,293 (40.7%) | 20,898 (48.4%) | 57,488 (43.3%) |
| CT (multislice)       | 730 (24.5%) | 21,968 (25.3%) | 8574 (19.8%) | 31,272 (23.5%) |
| Angiocardiography      | 18 (0.6%) | 8577 (9.9%) | 3899 (9.0%) | 12,494 (9.4%) |
| Urography             | 487 (16.4%) | 6659 (7.7%) | 2951 (6.8%) | 10,097 (7.6%) |
| CT (single slice)     | 230 (7.7%) | 2115 (2.4%) | 670 (1.6%) | 3015 (2.3%) |
| Angiography           | 25 (0.8%) | 1099 (1.3%) | 672 (1.6%) | 1796 (1.4%) |
| Phlebography          | 10 (0.3%) | 212 (0.2%) | 74 (0.2%) | 296 (0.2%) |
| DSA                   | 9 (0.3%) | 150 (0.2%) | 62 (0.1%) | 221 (0.2%) |
| PTCA                  | 0          | 116 (0.1%) | 49 (0.1%) | 165 (0.1%) |
| PTA                   | 0          | 35 (<0.1%) | 43 (<0.1%) | 78 (<0.1%) |
| Other                 | 7 (0.2%) | 4464 (5.2%) | 2382 (5.5%) | 6853 (5.2%) |
| Not specified         | 165 (5.5%) | 5975 (6.9%) | 2935 (6.8%) | 9075 (6.8%) |

*Multiple reasons possible.

CT, computed tomography; DSA, digital subtraction angiography; PTA, percutaneous transluminal angioplasty; PTCA, percutaneous coronary angioplasty.
In both analyses, HSRs were significantly less frequent in children or elderly compared with adults. In analysis I, 0.47% of children and 0.38% of elderly experienced HSRs compared with 0.74% of adults. The adjusted ORs (vs adults) for children (0.58) and elderly (0.51) were significant ($P < 0.043$ and $P < 0.001$, respectively). A similar pattern was seen in analysis II: HSR reporting the rate for children as 0.0114%; for elderly, 0.0071%; and for adults, 0.0143% ($P < 0.0001$).

The HSR incidence is different between the 2 data sets. This is easily explainable by the nature of the 2 data sources. Analysis I included 4 thoroughly conducted prospective observational studies that followed a

### TABLE 4. Risk of Hypersensitivity Reactions and Adjusted Odds Ratios of Significant Covariates in Analysis I

|                          | Cases, n = 818 (%) | Controls, n = 132,032 (%) | Odds Ratio  | 95% CI        | $P$  |
|--------------------------|--------------------|----------------------------|-------------|---------------|------|
| Age group (vs adults)    |                    |                            |             |               |      |
| Children                 | 640 (78.2)         | 86,023 (65.2)              | 0.58        | 0.34–0.98     | 0.043|
| Elderly                  | 14 (1.7)           | 2964 (2.2)                 | 0.51        | 0.43–0.61     | <0.001|
| Sex (vs male)            | 411 (50.2)         | 74,575 (56.5)              | 1.16        | 1.01–1.34     | 0.032|
| Female                   | 407 (49.8)         | 57,457 (43.5)              |             |               |      |
| Injection route (vs intravenous injection) | 762 (93.2) | 104,257 (79.0) | 0.49 | 0.35–0.70 | <0.001 |
| Intra-arterial           | 56 (6.8)           | 27,775 (21.0)              |             |               |      |
| Diabetes mellitus (vs no) |                   |                            |             |               |      |
| Yes                      | 68 (8.3)           | 10,316 (7.8)               | 1.57        | 1.22–2.03     | <0.001|
| Allergy (vs no)          |                    |                            |             |               |      |
| Yes                      | 82 (10.0)          | 3477 (2.6)                 | 3.73        | 2.93–4.74     | <0.001|
| Asthma bronchial (vs no) |                    |                            |             |               |      |
| Yes                      | 15 (1.8)           | 805 (0.6)                  | 2.14        | 1.26–3.63     | 0.005|
| Contrast media reaction (vs no) |              |                            |             |               |      |
| Yes                      | 22 (2.7)           | 695 (0.5)                  | 4.28        | 2.74–6.70     | <0.001|
| Other (vs no)            |                    |                            |             |               |      |
| Yes                      | 152 (18.6)         | 19,182 (14.5)              | 1.37        | 1.14–1.64     | <0.001|

95% Confidence intervals (CIs) are constructed using asymptotic Wald confidence limits without correction.

$P$ value from Wald test.

In both analyses, HSRs were significantly less frequent in children or elderly compared with adults. In analysis I, 0.47% of children and 0.38% of elderly experienced HSRs compared with 0.74% of adults. The adjusted ORs (vs adults) for children (0.58) and elderly (0.51) were significant ($P < 0.043$ and $P < 0.001$, respectively). A similar pattern was seen in analysis II: HSR reporting the rate for children as 0.0114%; for elderly, 0.0071%; and for adults, 0.0143% ($P < 0.0001$).

The HSR incidence is different between the 2 data sets. This is easily explainable by the nature of the 2 data sources. Analysis I included 4 thoroughly conducted prospective observational studies that followed a

### TABLE 5. Occurrence of Hypersensitivity Reactions in Analysis I

|                          | Children, n = 2978 (%) | Adults, n = 86,663 (%) | Elderly, n = 43,209 (%) | Total, n = 132,850 (%) |
|--------------------------|------------------------|------------------------|-------------------------|------------------------|
| All patients with HSRs   | 14 (0.47%)             | 640 (0.74%)            | 164 (0.38%)             | 818 (0.62%)            |
| Pruritus                 | 8 (0.27)               | 232 (0.27)             | 53 (0.12)               | 293 (0.22)             |
| Cough, sneezing*         | 2 (0.07%)              | 113 (0.13%)            | 34 (0.08%)              | 149 (0.11%)            |
| Cough                    | 2 (0.07%)              | 62 (0.07%)             | 20 (0.05%)              | 84 (0.06%)             |
| Sneezing                 | 0                      | 55 (0.06%)             | 15 (0.03%)              | 70 (0.05%)             |
| Urticaria, rash, erythema* | 8 (0.27%)         | 411 (0.47%)            | 87 (0.20%)              | 506 (0.38%)            |
| Urticaria                | 3 (0.10%)              | 203 (0.23%)            | 39 (0.09%)              | 245 (0.18%)            |
| Rash                     | 1 (0.03%)              | 158 (0.18%)            | 31 (0.07%)              | 190 (0.14%)            |
| Erythema                 | 4 (0.13%)              | 80 (0.09%)             | 21 (0.05%)              | 105 (0.08%)            |
| Dyspnea                  | 2 (<0.1)               | 66 (<0.1)              | 28 (<0.1)               | 96 (<0.1)              |
| Bronchospasm             | 0                      | 7 (<0.1)               | 2 (<0.1)                | 9 (<0.1)               |
| Face edema               | 0                      | 4 (<0.1)               | 0                       | 4 (<0.1)               |
| Throat irritation         | 0                      | 4 (<0.1)               | 0                       | 4 (<0.1)               |
| Dysphagia                | 0                      | 2 (<0.1)               | 1 (<0.1)                | 3 (<0.1)               |
| Dysphonia                | 0                      | 1 (<0.1)               | 1 (<0.1)                | 2 (<0.1)               |
| Eye swelling              | 0                      | 0                      | 2 (<0.1)                | 2 (<0.1)               |
| Nasal congestion         | 0                      | 2 (<0.1)               | 0                       | 2 (<0.1)               |
| Anaphylactic shock       | 0                      | 0                      | 1 (<0.1)                | 1 (<0.1)               |
| Lacrimation increased    | 0                      | 1 (<0.1)               | 0                       | 1 (<0.1)               |
| Laryngeal edema          | 0                      | 0                      | 1 (<0.1)                | 1 (<0.1)               |
| Respiratory arrest       | 0                      | 0                      | 1 (<0.1)                | 1 (<0.1)               |
| Rhinitis                 | 0                      | 1 (<0.1)               | 0                       | 1 (<0.1)               |

*Multiple HSRs per subject were possible.

HSRs, hypersensitivity reactions.
clear protocol and well-defined data capture procedure. The HSR incidence is well in the range of similarly designed studies.\textsuperscript{20,27–29} Pharmacovigilance is characterized by underreporting especially of less severe cases. In addition, reporting rates often go down with time of market presence of a drug.\textsuperscript{30} However, the trend in question in both analyses is consistent.

An initial glimpse of a potential impact of age on incidence of adverse drug reactions (ADRs) in general could be seen in an article by Katayama et al back in 1990.\textsuperscript{21} In this Japanese comparative study, they prospectively investigated 337,647 patients after administration of high-osmolar ionic and low-osmolar nonionic contrast media. In the LOCM group, ADR prevalence was 0.4% in babies (\(\leq 1\) year), 2.5% in children (1–9 years), 3.2% to 4.6% in the age group of 10 to 60 years, and 1.5% to 2.6% in elderly (\(\geq 60\) years). Unfortunately, HSRs were not specifically investigated by age group.\textsuperscript{21}

Furthermore, Kopp et al\textsuperscript{3} (a subset of our analysis I) studied the prevalence of acute reactions to iopromide in a postmarketing surveillance study in 74,717 patients. Here again, the ADR rate was lowest in children (0.0%–0.8%) compared with adults (18–60 years) with up to 1.9%. After the age of 60 years, the incidence declined from 1.2% to 0.6% for those aged 80 years or older. They concluded that patients with a history of previous CM reaction or allergic diathesis (7.4% and 4.1%, respectively), were at an increased risk for ADRs. This is a topic of ongoing investigation with special focus on prevention of recurrent events with corticosteroids.\textsuperscript{31} Unfortunately, Kopp et al\textsuperscript{3} also did not specifically analyze HSRs.

Likewise, Zhang et al\textsuperscript{32} investigated the incidence of ADRs by age in 137,473 patients after LOCM administration. A total of 428 cases of ADRs (0.31%) were recorded. The incidence in children was 0.23% to 0.32%; in
HSRs to Iopromide in Children and Elderly

Limitations

Some limitations need to be addressed. First, in analysis I, a total of 11,646 patients without documented age had to be excluded upfront. In analysis II, this was the case for 4937 reports. Second, cases reported in analysis I of the 4 observational studies are necessarily also included in the GPV database. However, these are just 818 cases in 32,734 cases. Third, although analysis I investigated a data pool of 4 very similar studies, slight differences in reporting standards could not be completely excluded. Fourth, in observational studies and even more in PV databases, underreporting cannot be ruled out, thus care is mandated when interpreting the absolute reporting figures. Fifth, an age-specific underreporting bias (eg, for very young children or very diseased elderly) seems unlikely but cannot be completely excluded based on the available data. Sixth, we did not analyze specifically HSRs that occurred after reexposure, a topic of current scientific discussion. Seventh, we did not record the temperature of iopromide before injection, a topic also in current scientific focus. Eighth, we did not run HSR subtyping with respect to severity of the event or the temporal relationship to the administration.

CONCLUSIONS

Hypersensitivity reactions to iopromide were significantly less frequent in children and elderly compared with adults.

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