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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 (0.0114%) 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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Iopromide (Ultravist) is a low-osmolar nonionic x-ray contrast medium (LOCM). The active ingredient is iodine[1] that causes the x-ray attenuation in contrast-enhanced computed tomography (CT) and other radiographic procedures. Iopromide was first approved in February 1985, thus clinical experience for more than 36 years of use is available. As of June 30, 2021, more than 306 million have been administered to patients in more than 117 countries.[2] The overall safety has been documented in numerous studies.[3–8] Despite vast clinical experience with LOCMs, including iopromide,[9] few questions on the safety are not fully elucidated yet. This pertains to the exact nature of hypersensitivity reactions (HSRs), for which previously other terminology has been widely used, such as "anaphylactoid reactions," "immediate hypersensitivity reactions,"[10] "allergy-like reactions,"[11] "allergic-like reactions,"[12] or "nonallergic contrast material–induced hypersensitivity," "non–IgE-mediated allergy."[13] Although serious reactions to iodine-based contrast media are uncommon,[14] HSRs can be potentially severe or even lethal.[15] The pathomechanism of HSRs is still not fully understood. It is assumed that the majority of HSRs are caused by release of histamines from basophils and eosinophils. Hypersensitivity reactions are not considered as IgE-mediated. Antibodies to contrast media have not been unanimously identified yet; that explains why contrast media–naive patients could experience HSRs at the first time of exposure.[12] Thus, HSRs are still considered to be unpredictable, and further research is needed, in particular with respect to a deeper understanding of the pathophysiological mechanisms of these reactions.

The safety profile of nonionic LOCMs has been extensively investigated and recently reviewed by Suh et al.[16] Yet the topic of HSRs is still of high clinical interest and relevance in day-to-day practice.[12,17] Although the overall safety of iopromide has been shown in numerous studies, studies particularly on HSRs are limited.[3–6,15,18–20]

Most recently, Endrikat et al[15] used this study cohort to investigate the correlation of HSRs with the administration route, demonstrating a significantly lower risk after intra-arterial versus intravenous administration.

However, the question of an age dependency of HSRs has not been thoroughly investigated yet. The very first large-scale analysis of adverse events to low-osmolar iodine-based contrast media was reported by Katayama et al back in 1990.[21,22] A first signal of lower rates in children aged 0 to 9 years and elderly 60 years or older could be seen. Only very few reports have been published in the meantime.[3,6,19,20]

The purpose of the study was to describe the risk of HSRs to iopromide specifically in children (<18 years) and elderly patients (≥65 years), compared with adults (≥18 to <65 years).

MATERIALS AND METHODS

Databases

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.

Analysis I: Observational Studies

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

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TABLE 1. Essentials of Pooled Studies for Analysis I

Study Name	Countries	Study Duration	Children, n = 2978 (2.2%)	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 al[3]
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 al[5]
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 al[23]
Ultravist in CT	Germany, Iran, Romania, Saudi Arabia	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 al[24]

CT, computed tomography.

PMS I (n = 74,717)[3]; (2) IMAGE (n = 44,835)[5]; (3) TRUST (n = 17,513)[23]; and (4) Ultravist in CT (n = 15,168).[24] All 4 studies had recruited patients of all 3 age groups (Table 1).

Approvals from institutional review boards/ethics committees and patient informed consents were obtained from study centers in the respective countries. This study is a voluntary Post-Authorization Safety Study, and it has been registered at ClinicalTrials.gov (NCT04605471) and at ENCePP (EUPAS37597).

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.[25] 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.[26] 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 ACR[26] 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, quantiles, 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 of exploratory 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 years times 10^4. The 2 null hypotheses of equal reporting rates between

TABLE 2. Pharmacovigilance Database, 1995–2020, Analysis II

	Children (0 to <18 y)	Adults (≥18 to <65 y)	Elderly (≥65 y)	Total
Administrations	5,871,303 (2.0%)	167,970,157 (58.3%)	114,186,767 (39.6%)	288,028,227 (100%)
HSRs	672	23,953	8109	32,734
Reporting rates (%)	0.0114	0.0143	0.0071	—

HSRs, hypersensitivity reactions.

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 second 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 excluded. 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).

Analyis 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 recruited. 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 distributed within the 3 age groups. The incidence of concomitant disease was lowest in children (33.5%) and highest in elderly (52.3%). For premedication, injection route, examination region, and indication, 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 countries, with 4 countries (China, United States, Italy, and Germany) accounting 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 evaluate various underlying conditions. The most commonly provided indication 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. Fourteen cases (1.7%) were in children and 164 (20%) in elderly. In the control 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 intravenous 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 factors 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,

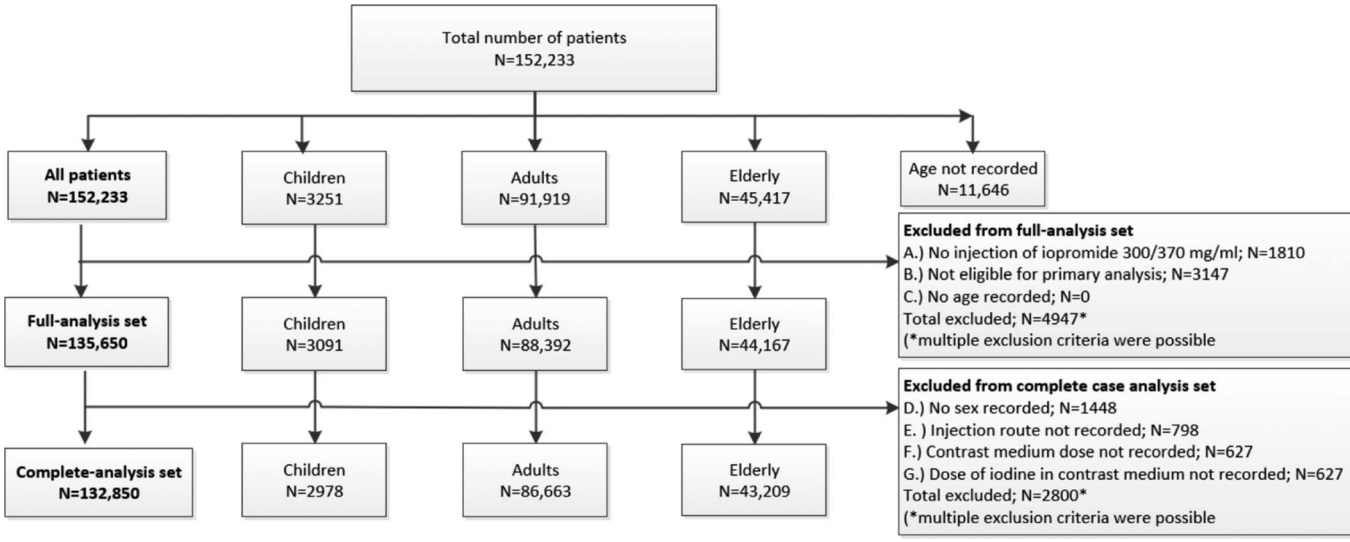

FIGURE 1. Disposition of patients.

TABLE 3. Baseline Characteristics of Study Population of Analysis I

	Children, n = 2978 (2.24%)	Adults, n = 86,663 (65.23%)	Elderly, n = 43,209 (32.52%)	Total, n = 132,850 (100%)
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	997 (33.5%)	38,801 (44.8%)	22,607 (52.3%)	62,405 (47.0%)
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%)

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TABLE 3. *(Continued)*

	Children, n = 2978 (2.24%)	Adults, n = 86,663 (65.23%)	Elderly, n = 43,209 (32.52%)	Total, n = 132,850 (100%)
Indication*				
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.

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 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)	640 (78.2)	86,023 (65.2)			
Children	14 (1.7)	2964 (2.2)	0.58	0.34–0.98	0.043
Elderly	164 (20.0)	43,045 (32.6)	0.51	0.43–0.61	<0.001
Sex (vs male)	411 (50.2)	74,575(56.5)			
Female	407 (49.8)	57,457 (43.5)	1.16	1.01–1.34	0.032
Injection route (vs intravenous injection)	762 (93.2)	104,257 (79.0)			
Intra-arterial	56 (6.8)	27,775 (21.0)	0.49	0.35–0.70	<0.001
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.

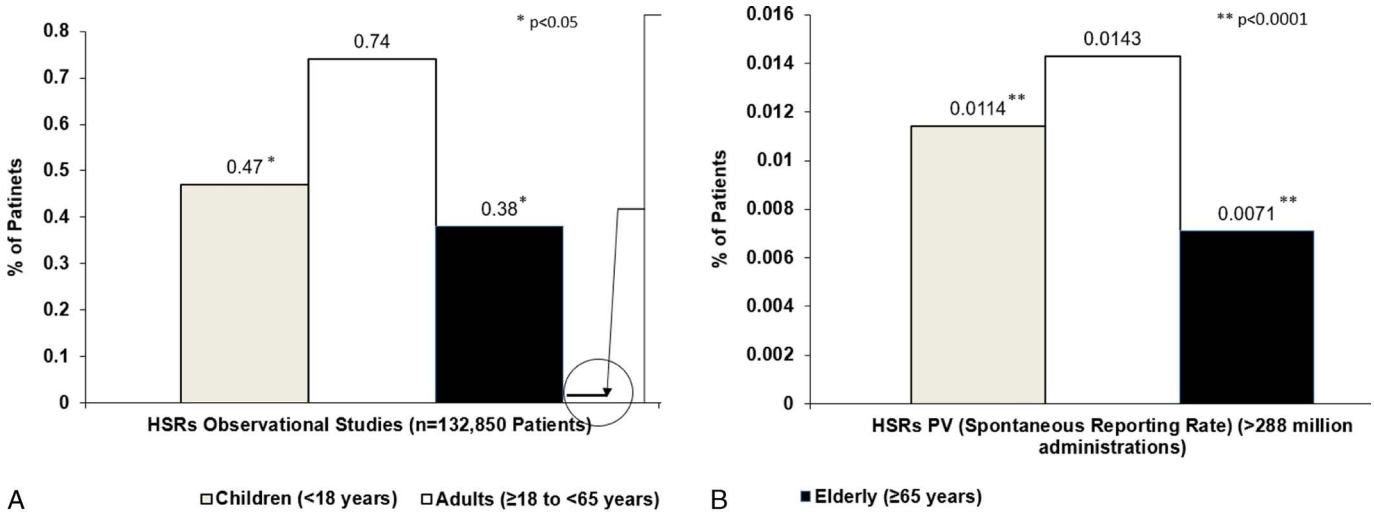

FIGURE 2. Hypersensitivity reactions in observational studies (analysis I) and pharmacovigilance database (analysis II).

clear protocol and well-defined data capture procedure. The HSR incidence is well in the range of similarly designed studies.[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.[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.[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 (≤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 (≥60 years). Unfortunately, HSRs were not specifically investigated by age group.[21]

Furthermore, Kopp et al[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.[31] Unfortunately, Kopp et al[3] also did not specifically analyze HSRs.

Likewise, Zhang et al[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

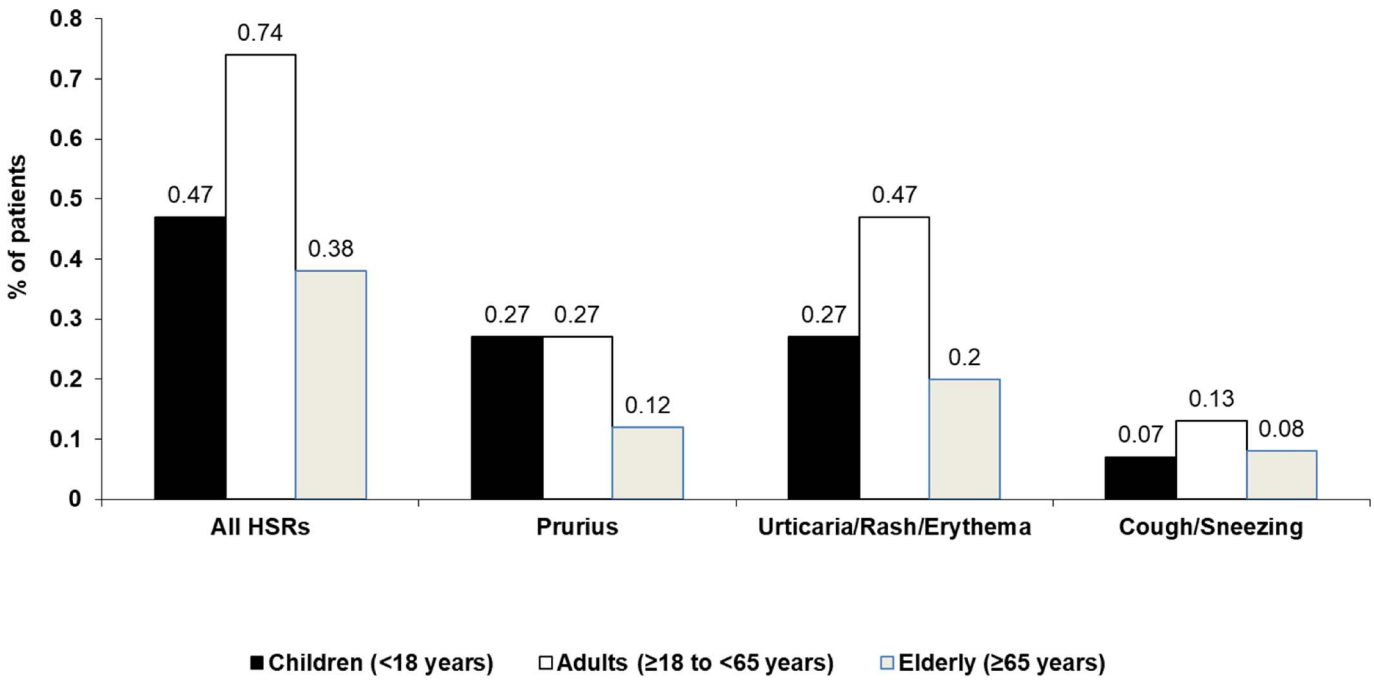

FIGURE 3. Occurrence of clinically most relevant hypersensitivity reactions in analysis I (cutoff ≥0.1% in at least 1 study group).

adults (20–60 years), 0.3% to 0.43%; and in elderly (>60 years), 0.11% to 0.27%, confirming our results. No details on HSRs were given.[32]

Finally, Callahan et al[33] focused on a pediatric population up to 21 years who got ioversol. Over a period of 7 years, they included 12,494 patients at a large urban children's hospital. The overall incidence of contrast media reactions was 0.46%. They conclude that ADRs in children are rare and mild but significantly increasing with advancing age. Although they did not find any severe reactions, no analysis focusing on HSRs was performed.[33]

A number of other publications also reported that the majority of ADRs happen in the adult age group, that is, less frequent in the pediatric[7,8,32,34,35] and older population.[7,8,24,32,34,36]

Ho et al[18] analyzed 29,962 patients in a tertiary Australian hospital who got intravenous iopromide and identified 47 cases of immediate HSRs (0.16%). There were 2 cases in the age group younger than 20 years; the peak incidence was between 50 and 59 years (16 cases) and declined after the age of 60. These results strongly confirm our results. Ho et al[18] finally claimed age younger than 55 years to be a statistically significant risk factor.

Dillman et al[6] investigated the incidence and severity of acute allergic-like reactions after administration of LOCMs specifically in 11,306 children. They recorded 20 cases, that is, 0.18% of all patients. This is in line with the range found in analysis I. Six children had a history of allergic-like reaction, 2 patients of them a history of reaction to iodinated contrast. Five children had a history of asthma.[6]

A small study published by Fjelldal et al[19] found 5 HSRs in 547 pediatric patients (0.9%) after iohexol administration, well comparable with our findings. In contrast, Kim et al[20] analyzed 286,087 contrast-enhanced CT examinations of 142,099 patients grouped in 3 age brackets (0–19, 20–50, and >50 years). They conclude that age had no significant effect on the incidence of HSRs (anaphylaxis).[20]

Many authors support the general notion that ADRs[3,8,21,33–35] and specifically HSRs[6,18,19] after iodine CM administration are lower in children than in adults. The lower incidence of ADRs in the elderly population was reported by Katayama et al,[21] Kopp et al,[3] and others,[8,24,34,36] but not focusing on HSRs. Just recently, Voltolini et al[37] reported findings from 9 Italian allergy centers. A total of 407 patients with HSRs were compared with 152 controls. Interestingly, male sex and age older than 65 years were associated with lower incidences of HSRs,[37] confirming what we report here.

To the best of our knowledge, this study is the first systematic analysis of HSRs in these 2 age groups, thus providing new and relevant information on safety of LOCMs.

Getting a better understanding of the age dependency of the HSR is of clinical importance. We hypothesize that the pathophysiological reason for the lower HSR incidence in children and elderly is that in children the immune system gradually matures during infancy and in elderly the immune system deteriorates with age.[38]

As excellently discussed in the 2021 ACR Guidelines,[12] there are some caveats when interpreting literature on the incidence of HSRs. First, discrimination between physiologic effects and HSRs is not always easy. Second, definitions of HSRs and degree of severity might not be always similar. Third, most publications are based on retrospective data analysis. Here, the question if HSRs have been thoroughly documented in the daily routine is an issue. Fourth, so far, no controlled prospective study on HSRs has been reported, possibly because the incidence of HSRs is extremely low and large patient numbers would be needed to yield statistically meaningful results.[12]

Although serious reactions to iodine-based contrast media are uncommon, children and elderly are more fragile and might require more attention during the follow-up than adults.[12] Both groups might be unable to adequately verbalize their adverse effects.[12] Elderly may even be used to certain signs of discomfort due to other concomitant disease and, therefore, might ignore important symptoms of HSRs.

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,[30] 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.[39] Seventh, we did not record the temperature of iopromide before injection, a topic also in current scientific focus.[40] 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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