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Safety and Diagnostic Image Quality of Ultravist® in an Unselected Sub-Set of Chinese Patients: Data Analyses from a Previous Post Marketing Surveillance

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Abstract

Background: Iopromide (Ultravist®) has been shown to be a very safe CM agent in previous post-marketing surveillance studies on Western and Asian populations. Our study aimed to analyse data pertaining to the safety, tolerability and diagnostic image quality of Iopromide in an unselected sub-set of the Chinese population. Methods: we analysed data for Chinese ambulatory and in-patients who received Iopromide for an imaging procedure (in accordance with the local package insert and routine clinical practice), as part of an international post-marketing surveillance study. Use of premedication was at the discretion of the attending physician. Patient demographics, clinical history, type of examination, contrast quality and tolerability, including pre-specified adverse drug reactions, were recorded. All statistical analyses were descriptive. Results: case report forms for 20,000 Chinese patients (61.3% men) were analysed, of whom 153 patients (0.77%) had risk factors for idiosyncratic contrast media reactions (at-risk group). Use of premedication, most commonly corticosteroids, was recorded for 5658 patients (28.3%) and 86 at-risk patients (56.2% of the at-risk group), respectively. The mean (±standard deviation) dose of iodine administered was 29 ± 5.5 g. During the physician's evaluation of image parameters, contrast quality was considered to be "good" (64.7%) or "excellent" (29.3%) in the majority of patients. 571 patients (2.9%) experienced at least one adverse drug reaction [most frequently nausea (0.70%) and dysgeusia (0.62%)], which were typically transient and of mild intensity. Two serious adverse drug reactions were reported [edema (n = 1), decreased blood pressure and dyspnea (n = 1)]. The incidence of adverse drug reactions was increased in the at-risk group versus the overall patient popula-

tion, and tended to reduce with premedication (mainly corticosteroids). Conclusions: Iopromide was well tolerated and proved to be an efficient contrast agent in a large, non-selected sub-set of Chinese patients undergoing different types of diagnostic imaging procedures.

Keywords

Contrast Media, Iopromide, Adverse Drug Reaction, Chinese Sub-Population, Post-Marketing Surveillance

1. Introduction

Iodinated contrast media (CM) have been administered safely in millions of people worldwide [1], and constituted a crucial tool that is frequently used for imaging procedures carried out during diagnostic clinical practice. The first iodinated CM to be used for the purpose of diagnostic imaging was sodium iodide (1920), subsequent to which Sodium and Meglumine salts of tri-iodinated benzoic acid derivatives were developed in the 1950s. These CM were hyperosmolar (>1400 mOsm/kg), with an osmolality five to eight times that of blood [2]. Since then, low osmolality (600 - 850 mOsm/kg), non-ionic CM agents have been developed and Iopromide is one such example. The safety and tolerability of this agent has already been evaluated in previous post-marketing surveillance studies carried out on Western as well as Asian populations [3]. Currently, several different CM are available and while the use of iodinated CM has proved relatively safe [4] [5] [6] [7] [8], adverse drug reactions (ADRs) to these agents, although extremely rare, have been documented before. Risk factors such as a history of CM reactions, allergy and asthma increase the incidence of ADRs associated with their use [1] [9] [10].

Numerous iodinated CM are currently available in China, such as Iodixanol (Visipaque) and Iopromide (Ultravist®; Bayer Healthcare Pharmaceuticals), among others [11]. While their safety profiles have already been established as part of routine clinical trials that preceded their marketing and commercialization; extensive post marketing surveillance on a large number of patients is required in order to identify and determine the frequency of all extremely rare adverse drug reactions that may occur. To our knowledge, such a non-interventional study that seeks to quantify the rate of ADR and AE occurrence due to Iopromide use in an unselected Chinese population has not been conducted so far. The patient population analysed in this manuscript was recruited during the execution of a large, international, multi-centre, post marketing surveillance carried out in order to assess the safety and tolerability of Iopromide in various populations. The majority (44.6%) of patients who enrolled were from centres in China, and this study focuses on the detailed analysis of data from these Chinese patients in order to determine the safety and tolerability of Iopromide based on patient parameters such as pre-existing risk factors and use of pre-medication.

Additionally, a subjective analysis of diagnostic image quality based on the investigators' evaluation has also been included in our analyses.

2. Methods

2.1. Study Design and Conduct

The rationale, design and conduct of the study from which data were collected and analyzed has previously been reported in detail [12]. Briefly, Data analysed in this manuscript were obtained during the conduct of a prospective, phase IV post-marketing surveillance study [IoproMide (UltrAvist®)—to Gain further information on tolerability and safety in X-ray Examination (IMAGE) study] (ClinicalTrials.gov identifier: NCT00876083) conducted in 21 countries in Europe and Asia and sponsored by Bayer HealthCare Pharmaceuticals, Berlin, Germany. Patients undergoing an X-ray or computed tomography (CT) examination, for which the investigator had elected to use Iopromide, were eligible. The 44,835 patients who comprised the overall patient population, a majority, *i.e.*, 20,000 (44.6%) were from China, with 56 centres in China participating in the study. Iopromide was administered in a routine manner, based on investigator discretion and procedure requirements and in accordance with recommendations in the local package insert.

2.2. Ethical Approval

This study was non-interventional and was conducted in a routine clinical setting in accordance with local and international legal and ethical requirements, which did not necessitate the provision of written informed consent from Chinese subjects.

2.3. Observational Plan

Investigators used case report forms (CRF) to capture demographic data, patient clinical history (including risk factors), drug administration, type of examination, contrast quality and tolerability, as previously described [12]. Briefly, CRFs recorded patient parameters such as demographics, concomitant diseases, pre-and concomitant medications, examination region, indication, contrast medium volume, type of application and examination, contrast quality, and adverse events. Paper CRFs were converted to electronic CRFs using a double data entry process and validated electronic edit checks were performed on all CRFs. In case any queries arose regarding the information recorder in the CRFs, they were redirected to the investigator wherever necessary. Investigators assessed image quality according to five qualitative categories: excellent, good, adequate, non-diagnostic and not specified.

2.4. Iopromide Administration

Patients requiring administration of iopromide for an imaging procedure were considered eligible for inclusion. The administration of Iopromide and any premedication was at the discretion of the investigator, providing it was in ac-

cordance with the local package insert. Two formulations of iopromide were compared in this study, Ultravist®-300 [1 mL contains 623 mg of iopromide (equivalent to 300 mg iodine)] and Ultravist®-370 [1 mL contains 769 mg of iopromide (equivalent to 370 mg iodine)].

2.5. Adverse Events and Adverse Drug Reactions

Investigator-observed adverse events (AEs) and pre-specified ADRs of interest that occurred within the observation period (30 - 60 min according to the local packaging information) were recorded in a separate questionnaire, and as free text, in terms of symptoms, onset, duration, intensity, and causal relationship (see [12] for further details). The intensity of each event was classified by investigators as mild, moderate, or severe (In line with the recommendations of the ACR Manual on Contrast media [20]). Mild symptoms included scattered urticaria, pruritus, rhinorrhea, nausea, brief retching, and/or vomiting, diaphoresis, coughing and dizziness. Moderate symptoms included persistent vomiting, diffused urticaria, headache, facial edema, laryngeal edema, mild bronchospasms or dyspnea, palpitations, tachycardia or bradycardia, hypertension and abdominal cramps. Severe symptoms included life-threatening arrhythmias (*i.e.*, ventricular tachycardia), hypotension, overt bronchospasm, laryngeal oedema, pulmonary oedema, seizures and syncope. In addition, events were designated as serious if they met one of the following criteria: resulted in death; were life-threatening; required inpatient hospitalization/prolongation of current hospitalization; resulted in persistent or significant disability/incapacity; or resulted in a congenital anomaly/birth defect. ADRs of special interest included injection site warmth and/or feeling hot, nausea and/or vomiting, urticaria, erythema, rash and/or papular rash, cough and/or sneezing, dyspnea and/or bronchospasm, and changes in blood pressure (increase and/or decrease). ADRs were compared between all patients and at-risk patients (those with history of bronchial asthma, allergies, and/or contrast media reaction). Injection site warmth, feeling hot or injection site pain of mild intensity were defined (post-hoc) as tolerance indicators. No laboratory tests were required.

Patients were also asked to complete questionnaires to record AEs. Special attention was paid to ADRs among patients with risk factors for idiosyncratic CM reactions, specifically asthma, allergy and/or prior history of the occurrence of such reactions (at-risk group).

2.6. Statistical Analysis

Results are reported for all evaluable patients in the Chinese population, *i.e.* eligible patients with documented evidence of receiving iopromide. Qualitative descriptive statistical analyses were conducted.

3. Results

Patient demographics and clinical characteristics of the Chinese subpopulation included in this study are presented in **Table 1**. The majority of patients were

Table 1. Patient demographics and clinical characteristics.

Demographic Characteristics	All patients (N = 20,000)
Sex, n (%)	
Male	12,260 (61.3)
Female	7740 (38.7)
Not specified	2 (0.01)
Mean age, y (SD)*	54 (15.4)
Age category, n (%)	
<18 y	355 (1.8)
18 - 39 y	2837 (14.2)
40 - 59 y	9088 (45.4)
60 - 79 y	7005 (35.0)
≥80 y	676 (3.4)
Not specified	39 (0.20)
Patients with any concomitant disease, n (%)†	9042 (45.2)
Reduced general condition	3483 (17.4)
Hypertension	1581 (7.9)
Coronary heart disease	1417 (7.1)
Diabetes mellitus	541 (2.7)
Autoimmune disorder	214 (1.1)
Renal insufficiency	193 (1.0)
Cardiac arrhythmia	166 (0.83)
Thyroid disorder	93 (0.47)
Allergy	82 (0.41)
Asthma	69 (0.35)
Heart failure	36 (0.18)
Dehydration	7 (0.04)
History of contrast media reaction	3 (0.02)

*N = 19,961 patients; †Multiple responses possible (MedDRA preferred terms). SD: Standard deviation.

male (61.3%) and the mean age was 54 years. Approximately half the patient population (n = 9042, 45.2%) had at least one concomitant disease, most commonly a reduced general condition (17.4%), hypertension (7.9%) and coronary heart disease (7.1%). Risk factors for idiosyncratic CM reactions were reported for 153 patients (0.77% of the total; constituting the at-risk group). Premedication was recorded in 5658 patients overall (28.3%), including over half (n = 86, 56.2%) of the at-risk group (Figure 1). As premedication, corticosteroids were the most frequently prescribed drugs (84.4% and 89.5% of all patients and the at-risk group received premedication, respectively).

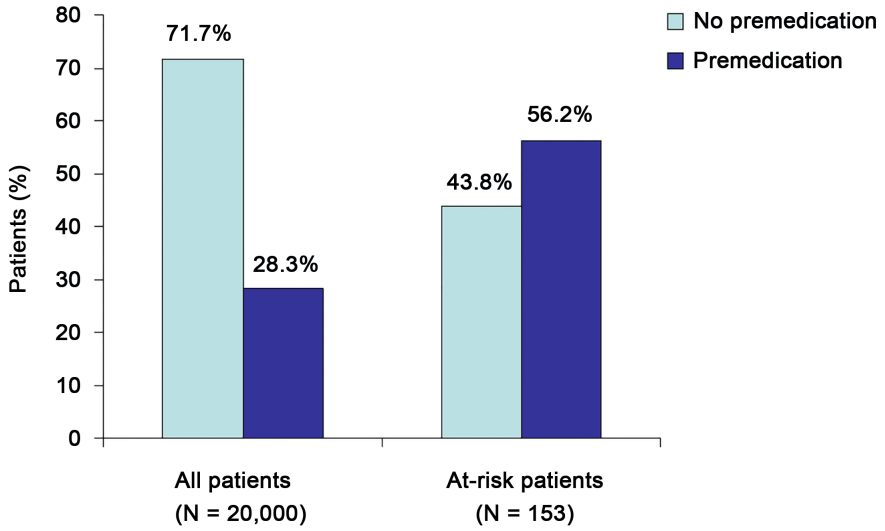

Figure 1. Use of premedication among all patients combined and only the at-risk subgroup. Caption: Graph showing the use of pre-medication in the at-risk versus group compared to the total population. A larger percentage of the at-risk patients were prescribed pre-medication.

3.1. Radiological Examinations and Iopromide Administration

There were a total of 20,000 radiological examinations in which Iopromide was used as a CM agent in the Chinese population included in this study. Iopromide was administered via intravenous injection in 19,935 patients (99.7%) and via intra-arterial injection in the remainder (n = 65, 0.33%). The most frequent examination was multi-slice computerized tomography (99.5%). The most frequent means of administration was automatic injection (99.7%). The mean [± standard deviation (SD)] dose of iodine administered was 29 ± 5.5 g and the median flow rate was 3 mL/s. Ultravist®-300 was the most commonly used formulation of iopromide (Table 2).

3.2. Primary Outcome Measures: Treatment-Emergent Adverse Events and Adverse Drug Reactions

3.2.1. Treatment-Emergent Adverse Events

A total of 580 patients (2.9%) experienced at least one AE (Table 3), most commonly gastrointestinal disorders (n = 206, 1.0%), nervous system disorders (n = 152, 0.76%), general disorders and administration site conditions (n = 136, 0.68%), skin and subcutaneous tissue disorders (n = 107, 0.54%) and respiratory, thoracic and mediastinal disorders (n = 32, 0.16%). The most frequent AEs (annotated as per the MedDRA preferred term) were nausea, dysgeusia and feeling hot. The incidence of injection site pain and/or warmth was low, with a frequency of 0.01% and 0.02%, respectively.

3.2.2. Adverse Drug Reactions

ADR findings were similar to the overall AE profile, since only 14 of the 672 reported events were found to be unrelated to the administration of Iopromide. The overall incidence of ADRs was 2.9% (571 patients), the most frequent reac-

Table 2. Dosage and administration of Iopromide.

Dosage and Administration Parameters	All patients (N = 20,000)
Iopromide concentration, n (%)	
Ultravist®-300	12,979 (65.0)
Ultravist®-370	7018 (35.0)
Not recorded	3 (0.02)
Route of administration, n (%)	
Intravenous	19,935 (99.7)
Intra-arterial	65 (0.33)
Means of administration, n (%)	
Manual injection	50 (0.25)
Infusion	1 (0.01)
Automatic injection	19,949 (99.7)
Median flow rate, mL/s (range)	3.00 (0.1 - 20.0)
Mean iodine dose, g (SD)	29 (5.5)
Category of iodine dose (g), n (%)*	
≤20	684 (3.4)
20 - 40	18,861 (94.3)
40 - 60	445 (2.2)
>60	10 (0.05)

*Dose of iodine (g) was calculated as follows: For patients who received Ultravist®-300: [300 (mg iodine/mL)*applied volume (mL)]/1000. For patients who received Ultravist®-370: [370 (mg iodine/mL)*applied volume (mL)]/1000. SD: Standard deviation.

Table 3. Proportion of patients experiencing treatment-emergent adverse events, *by system organ class and preferred term, after iopromide administration.

Adverse Events (MedDRA preferred term)	Number of patients, n (%)
Patients with any adverse event	580 (2.9)
Gastrointestinal disorders	206 (1.0)
Nausea	144 (0.72)
Vomiting	75 (0.38)
Nervous system disorders	152 (0.76)
Dysgeusia	126 (0.63)
Dizziness	26 (0.13)
General disorders and administration site conditions	136 (0.68)
Feeling hot	119 (0.60)
Skin and subcutaneous tissue disorders	107 (0.54)
Rash	69 (0.35)
Pruritus	23 (0.12)
Respiratory, thoracic and mediastinal disorders	32 (0.16)

*Only those adverse events reported by more than 0.1% of patients are presented.

tions being nausea, dysgeusia and feeling hot. More patients receiving Ultravist®-300 experienced ADRs compared with those receiving Ultravist®-370 (3.4% and 1.9%, respectively). The majority of ADRs were of mild (n = 525) or moderate (n = 43) intensity and resolved without sequelae, and there were no clinically relevant sex or age-related trends (data not shown). Three ADRs were of severe intensity. Excluding tolerance indicators such as any occurrence of injection site warmth, feeling hot or injection site pain, (of mild intensity only), the overall incidence of ADRs was 2.4% (469 patients) and the corresponding value in the at-risk sub-group was 8.5% (13 patients; Figure 2). Two serious ADRs were reported following the administration of Ultravist®-300 [oedema (n = 1) and decreased blood pressure and dyspnea (n = 1)].

Findings for ADRs of special interest are summarised in Table 4. 119 patients (0.60%) reported injection site warmth/and or feeling hot, including one patient in the at-risk group (0.65%). Nausea and/or vomiting were reported in 200 patients from the overall population and in 4 at-risk patients (1.0% and 2.6%, respectively), and urticaria, erythema, rash and/or papular rash were reported in 94 and 4 patients, respectively (0.47% and 2.6%). Further analysis showed that at-risk patients who received premedication had a lower incidence of ADRs versus at-risk patients who received Iopromide alone (Table 5).

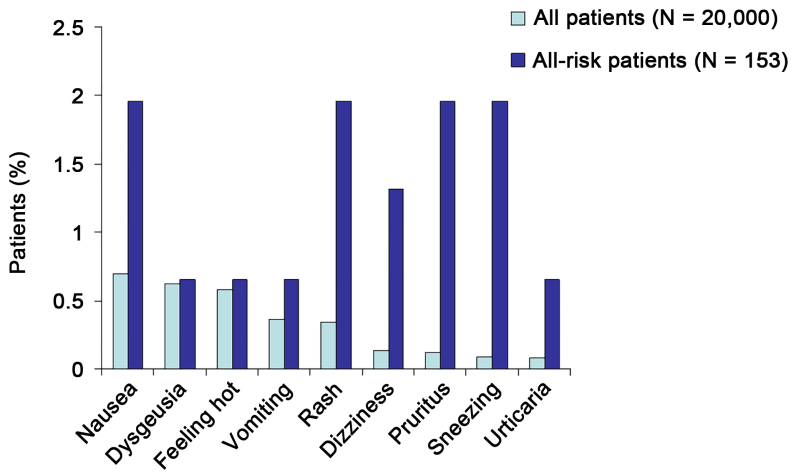

Figure 2. Proportion of patients experiencing adverse drug reactions after Iopromide administration: all patients combined and only the at-risk subgroup. Caption: graph showing the occurrence of adverse drug reactions in the at-risk group versus the total patient population. All ADRs occurred more frequently in the at-risk group of patients.

Table 4. Iopromide-related adverse drug reactions of special interest.

ADR of special interest	Patients, n (%) All patients (N = 20,000)	At-risk patients (N = 153)
Injection site warmth/and or feeling hot	119 (0.60)	1 (0.65)
Nausea and/or vomiting	200 (1.0)	4 (2.6)
Urticaria, erythema, rash and/or papular rash	94 (0.47)	4 (2.6)
Cough and/or sneezing	20 (0.10)	3 (2.0)
Dyspnea and /or bronchospasm	11 (0.06)	1 (0.65)
Blood pressure increase and/or decrease	6 (0.03)	0

Table 5. Incidence of adverse drug reactions after iopromide administration, (with and without premedication), in the at-risk subgroup.

ADR Description	At risk population, n (%) Premedication (N = 86)	No Premedication (N = 67)
Any adverse drug reaction	6 (7.0)	8 (11.9)
Nausea	3 (3.5)	0 (0)
Vomiting	1 (1.2)	0 (0)
Feeling hot	1 (1.2)	0 (0)
Dizziness	1 (1.2)	1 (1.5)
Dysgeusia	0 (0)	1 (1.5)
Dyspnea	1 (1.2)	0 (0)
Sneezing	0 (0)	3 (4.5)
Pruritus	0 (0)	3 (4.5)
Rash	1 (1.2)	2 (3.0)
Urticaria	0 (0)	1 (1.5)

3.3. Secondary Outcome Measures: Contrast Quality

Overall, contrast quality was considered by investigators to be "good" (64.7%) or "excellent" (29.3%) in the majority of patients. Contrast quality was comparable for the two Ultravist® formulations used, with 27.9% and 32.0% as "excellent" for Ultravist®-300 and Ultravist®-370 66.4% and 61.5% of investigators rating it as "good" respectively. Approximately 5% of examinations were reported as "adequate". Images were non-diagnostic for only one patient (of 20,000).

4. Discussion

To our knowledge, this is the first analysis of the safety and diagnostic image quality of the non-ionic, iodinated CM-Iopromide-in a routine clinical setting in a large group of Chinese patients. Indeed, we found that the safety profile of Iopromide was excellent in this population, with only very few patients experiencing ADRs that were typically transient and of mild intensity. The incidence of injection site pain and/or warmth was also low, indicating a good tolerability profile as well. Overall, our findings are consistent with earlier reports of favourable safety and tolerability profile of Iopromide in Western populations [3] [13] [14]. Our results are also in agreement with the results from a previous large-scale post-marketing surveillance study that included Asian patients and which concluded that the safety of Iopromide in routine clinical practice was comparable with the published safety profiles of other non-ionic, iodinated contrast agents [3]. In addition, a large-scale comparative study concluded that the use of non-ionic CM significantly reduced the incidence of ADRs when compared to ionic CM, including those categorised as severe and potentially life-threatening [4]. Moreover, in the present study, the contrast quality of Iopromide was considered to be "excellent" or "good" by investigators in the majority

of patients, and this was comparable for the two Ultravist® formulations investigated.

Allergy, asthma and a history of CM reactions are risk factors for idiosyncratic reactions to Iopromide, and 153 of the 20,000 Chinese patients (0.77%) were considered to be at risk of such reactions. The incidence of ADRs (excluding tolerance indicators) in this sub-group was higher compared with the total patient population, but such results were not entirely unexpected. Indeed, patients with asthma, previous reactions to CM, a history of allergy, pre-existing illness (diabetes mellitus, renal or cardiac impairment, myelomatosis and sickle-cell anemia), and children are generally at increased risk of developing ADRs [3] [4] [7] [8] [15] [16]. These differences may be attributed to a higher proportion of at-risk patients experiencing allergy-like gastrointestinal (nausea/vomiting), cutaneous (erythema, urticaria, rash) or respiratory (coughing, sneezing) reactions. Moreover, nausea and vomiting could also be anxiety-related [17]. Additionally, there may be a genetic component, given that Asian patients (mainly of Japanese heritage) are more likely to experience delayed skin reactions after administration of non-ionic iodinated CM [18] [19].

The American College of Radiology's Manual of Contrast media recommends that corticosteroids should comprise an essential component of the premedication protocol in at-risk patients [20]. Notably, in our study, the incidence of ADRs of special interest showed a favourable reduction with premedication (most frequently corticosteroids) in at-risk patients. This finding is in contrast to what was previously reported for Western and Asian populations in the post marketing surveillance study conducted by Kopp *et al*., where the use of pre-medication did not have a favourable impact on the incidence of ADRs in the at-risk population. In our analyses, the benefits of premedication were most pronounced in terms of a reduction in the incidence of sneezing, pruritus, urticaria and rash. However, "breakthrough" ADRs still occurred in some patients, and this finding is consistent with previous studies [21]. While a controversy remains regarding the use of premedication for patients at high risk of an ADR [1] [9], the present study appears to support the recommendation to use appropriate premedication in Chinese patients at risk of such reactions.

Study strengths include the population size and the fact that the study conduct mirrored routine clinical practice, with the inclusion of patients at risk of idiosyncratic CM reactions. However, the non-interventional design is a possible limitation; as such studies tend to detect a lower incidence of ADRs compared with randomized controlled trials. There could also be other sources of bias along with a lack of cardiac and renal monitoring that have not been accounted for during the analysis.

5. Conclusion

Iopromide, when given according to the prescribing information, is well tolerated among Chinese patients undergoing computed tomography and other diagnostic imaging procedures that require the use of contrast agents. Data from

this study supports its efficiency in 20,000 Chinese patients and confirms the very low risk of ADR occurrence associated with the use of Iopromide.

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Conflicts of Interest

Zhang Shuixing, Liang Changhong and Li Ziping received travel support from Bayer Healthcare Pharmaceuticals.

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