

Retrospective Analysis of Acute Adverse Reactions of 4 Iodine Contrast Agents

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Abstract

Objective Incidence of acute adverse reactions (ADR) of 4 kinds of iodine contrast agents were retrospective analyzed in 10532 cases of CT enhanced scan and 6130 cases of arteriography in our hospital, and to investigate the safety of these 4 types agents in clinical application.

Materials and Methods The occurrence of ADR to Iohexol, Ioversol, Iopromide and Iodixanol (expressed as I₁, I₂, I₃ and I₄) were recorded in detail from August,2007. 36 months' data were analyzed by Fisher's 'Exact Test. The incidences of ADR were calculated, and medicine information and features of adverse reactions induced by these 4 types agents are analyzed.

Results: CT enhanced scan and arteriography was performed in 16662 cases, including body enhanced scan, CTA &CTU and arteriography. Acute adverse reactions occurred in 25 cases, and the incidence of ADR was 0.15%. Among them, 18 cases had mild ADR (0.10%), 7 cases had moderate ADR (0.04%) and 0 cases had severe acute adverse reaction. There was a difference in the incidence of acute adverse reaction between the 4 contrast agents used ($\chi^2=5.854$, $p=0.022$). I₄ had the highest incidence of ADR, it was 0.32%, and the lowest incidence of ADR occurred in I₂, it's 0.08%. The incidence of ADR with I₁ and I₃ was 0.14% and 0.18%, respectively. The incidence of ADR in intravenous administration was significantly higher than that in arterial administration $\chi^2=4.655$, $p=0.036$.

Conclusion In this study, the incidence of acute adverse reaction to Iodixanol was the highest, and Ioversol was the lowest. The incidence of ADR in arteriography was significantly lower than that in patients with intravenous administration enhanced CT.

Introduction

Medical imaging plays an important role in clinical diagnosis and medical research. CT imaging is widely used in clinic, while arteriography not only plays a role in clinical diagnosis, but also is an important means of treatment. Among them, the application of iodine contrast agent is an indispensable part of CT enhanced scanning technology and arteriography, and the adverse reactions caused by iodine contrast agent are one of the most concerned problems in the clinical application of radiology, especially the most common acute adverse reactions (ADR), even death in severe cases. Suh et al. published a meta-analysis in 2019 to analyze the incidence of adverse reactions in 1,360,488 subjects using seven different types of iodine contrast agents. According to the report in this paper, the incidence of acute adverse reactions and severe adverse reactions of 7 kinds of iodine contrast agents were 1.03% and 0.0141% respectively. The incidence of ADR from high to low respectively Iomeprol, Iohexol, Iopamidol, Ioversol, Iodixanol, Iopromide, Iobitridol [1]

Among them, iodixanol is a new type of non-ionic dimer iso-osmolar contrast agent, which is well tolerated and has a low incidence of adverse reactions according to some studies on Visipaque, the original agent of iodixanol [2][3]. Aidixian is the generics of iodixanol in China firstly produced by Jiangsu Hengrui Pharmaceutical Co. LTD. For its clinical application, there is still a lack of corresponding clinical data. In this study, we retrospectively analyzed the incidence of ADR of 4 types iodine contrast agents(Iohexol (I₁), Ioversol (I₂), Iopromide (I₃) and Iodixanol (I₄))in 16,662 persons of CT enhanced scan and angiography in our hospital during the past three years from May 2017 to April 2020.

Material And Methods

Ethic statement

All experimental protocols were approved by the Institutional Review Board (IRB) for clinical study of Beijing Aerospace General Hospital (Beijing, China). All methods were carried out in accordance with the Guide for International Ethical Guidelines for Biomedical Research Involving Human Subjects, CIOMS and for Ethical review of biomedical research

involving people in China. Informed consents of patients were exempted from IRB because this study only used retrospective chart review data and all personal data was eliminated and code as arbitrary number which were not personally-identifiable.

Study subjects

We recruited all the patients who had enhanced CT scan and arteriography at the department of Radiology in our hospital From May 1, 2017 to April 30, 2020. The informed consent was obtained before enhanced CT scans and arteriography. There were 8948 male patients, with an average age of 63.80 ± 12.64 years. There were 7714 female patients with an average age of 63.50 ± 12.50 years. 72% of the subjects were the first time with iodine-contrast agent (11997/16662), and 28% were administration for iodine-contrast agent before (4665/16662), including 10,532 cases of intravenous administration and 6,130 cases of arterial administration.

Exclusion criteria :(1) patients with uncontrolled hyperthyroidism;(2) Patients with previous allergy to iodine agents;(3) patients with acute onset of allergic diseases;(4) Pregnant women.

The subjects underwent enhanced CT scanning or arteriography. The equipment parameters, examination types, and administration methods are described below. All subjects were given adequate hydration before and after the examination. They were visited once 0.5 hours before and 0.5 hours after the examination. If acute adverse reactions were found, they should be treated in time.

Equipment

We used Siemens SOMATOM Definition AS 64-Slice spiral CT scanner for the enhanced CT scan, and Siemens Artis Zee III Floor digital angiography for arteriography. We used Medrad Stellant VH600 CT dual head injection system for the injection of the contrast media.

The arteriography included whole cerebral arteriography, selective coronary angiography, selective peripheral arteriography and aorta angiography.

Types of Examination

The parameters for the types of examinations are as follows:

- 1) Enhanced visceral CT scan with automatic tube current, 120kV tube voltage and 5 mm slice thickness.
- 2) Coronary CTA with automatic tube current, 120kV tube voltage and 0.75 mm slice thickness.
- 3) CTA of the head and neck with automatic tube current, 120kV tube voltage and 0.6 mm slice thickness.
- 4) CT urography (CTU) with automatic tube current, 100kV tube voltage and 1 mm slice thickness.
- 5) Arteriography included whole cerebral angiography, selective coronary angiography, selective peripheral arteriography and aorta angiography. Injection parameters: injection pressure 2067kPa(300psi), rate 5ml/s.

Iodine-based contrast media

80 ml of iodine contrast media were injected into the median cubital vein at a flow rate of 3ml/s or 4 ml/s for enhanced visceral scan or CTA/CTU scan, respectively. The concentration of the contrast media are as follows:

- 1) Iohexol (I_1 , Yangtze River Pharmaceutical Group), 350 mgI/ml for enhanced visceral scan and CTA/CTU scan of patients below 85 kg,
- 2) Ioversol (I_2 , Jiangsu Hengrui Pharmaceutical Co. Ltd)320 mgI/ml for enhanced visceral scan, of patients below 85kg,350 mgI/ml for CTA/CTU scan of patients below 85 kg,

3) Iopromide (I₃, Ultravist 370, Bayer Pharmaceutical Co. Ltd) for CTA/CTU scan of patients over 85 kg.

4) Iodixanol (I₄, Jiangsu Hengrui Pharmaceutical Co. Ltd), 270 mg/ml for enhanced visceral scan and CTA/CTU scan of patients below 85 kg,

5) Iopromide, Iodixanol and Iohexol were randomly used for angiographic administration: whole cerebral arteriography, 5-10ml at a time; selective coronary artery, 4-8ml at a time; peripheral artery, 30-60ml at a time; aortic angiography, 40-60ml at a time

Definition of acute adverse reactions

According to the ESUR Contrast Media Safety Guidelines Version 10.0[4], acute adverse reaction defines to an adverse reaction which occurs within 1 hour of contrast agent injection. Acute reactions are either allergy-like, hypersensitivity reactions or chemotoxic responses. Allergy-like reactions may or may not be true IgE mediated allergy. (Table 1)

Table 1
the Classification of Acute Adverse Reactions according to ESUR10.0.

Hypersensitivity/ Allergy-like		Grade	Chemotoxic
		(Ring and messemer classification)	
Mild	Mild urticaria Mild itching Erythema	Grade1 Grade1 Grade1	Nausea/mild vomiting Warmth/chills anxiety Vasovagal reaction Which resolves spontaneously
Moderate	Marked urticaria Mild bronchospasm Facial/laryngeal edema	Grade1 Grade2 Grade2	Vasovagal reaction
Severe	Hypotensive shock Respiratory arrest Cardiac arrest	Grade3 Grade4 Grade4	Arrhythmia Convulsion

Statistical Analysis:

IBM SPSS23.0 software was used for row statistical analysis, and the normal distribution of quantitative data was expressed by $X \pm s$. Two independent sample T test was used for comparison between the two groups. Fisher Exact test was used to determine the incidence of adverse reactions among 4 different contrast agents. The difference in the number of cases between the groups was statistically significant with χ^2 difference or correlation.

Results

Characteristics of the study subjects with acute adverse reactions

1. Sample distribution:

8948 male patients with an average age of 63.80 ± 12.64 years;

There were 7714 female patients with an average age of 63.50 ± 12.50 years. 72% of the subjects were tested by iodine contrast for the first time (11997/16662), 28% had been tested by iodine contrast more than once (4665/16662). Among them, 10532 patients were tested for intravenous administration and 6130 patients were tested for arterial administration. In the sample, there were 9381 inpatients (56.3%), 6614 outpatients (39.7%), and 667 patients (4.0%) in physical examination and emergency.

2. Use of contrast agent:

7218 patients received I_1 , accounting for 43.3%; 5042 patients received I_2 , accounting for 30.3%; 2223 patients received I_3 , accounting for 13.3%; I_4 was used in 2179 patients, accounting for 13.1%. There was a significant difference between the number of patients receiving I_1 , I_3 and I_4 , $X^2 = 28.0150$, $P = 0.002$ (Table 2)

Table 2
Comparison of the use of four contrast media in the study population.

Contrast media	Inpatient		Outpatient		Emergency		Physical		Total	
	Cases	%	Cases	%	Cases	%	Cases	%	Cases	%
I_1	3677	39.2	3252 2916	49.2	208	44.8	81	39.9	7218	43.3
I_2	2562	27.3	2229	33.7	165	35.6	86	42.4	5042	30.3
I_3	1638	17.5	516	7.8	48	10.3	21	10.3	2223	13.3
I_4	1504	16.0	617	9.3	43	9.3	15	7.4	2179	13.1
II	9381	100.0	6614	100.0	464	100.0	203	100.0	16662	100.0

I_1 : Iohexol, I_2 : Ioversol, I_3 : Iopromide, I_4 : Iodixanol

3. Occurrence of acute adverse reactions:

Among the 16662 patients, 25 cases of acute adverse reactions occurred, with an incidence of 0.15%. Among them, 18 cases were mild, with an incidence of 0.10%. Moderate 7 cases, the incidence of 0.04%; There were 0 cases of severe. The incidence of acute adverse reactions was different among the four contrast agents used (Fisher's Exact Test $X^2 = 5.854$, $P = 0.022$). The incidence of I_4 was the highest, 0.32%. Seven of the 25 cases (28.0%) were from patients using I_4 , of which 4 were moderate. The incidence of I_2 was the lowest, 0.08%. The incidence of I_1 and I_3 was 0.14% and 0.18%, respectively. The incidence of I_4 was 0.32% (Table 3).

Table 3

Comparison of anaphylactoid reactions after the use of four iodine contrast media by the grade of severity.

Contrast media	Cases	Mild acute adverse reactions		Moderate acute adverse reaction		Total	
		Cases	%	Cases	%	Cases	%
I ₁	7218	8	0.11	1	0.01	9	0.12
I ₂	5042	2	0.04	1	0.02	3	0.06
I ₃	2223	2	0.09	1	0.04	3	0.13
I ₄	2179	2	0.10	4	0.18	6	0.28
Total	16662	14	0.09	7	0.04	21	0.13

I₁: Iohexol, I₂: Ioversol, I₃: Iopromide, I₄: Iodixanol

4. Samples of acute adverse reactions:

- 1) The 25 patients ranged in age from 58 to 76 years old, with a mean age of 3.7 ± 15.4 years. There was no significant difference in the average age of the patients without anaphylaxis (62.3 ± 13.4 years), $t = 0.529$, $P = 0.053$.
- 2) There were 15 male patients with an average age of 66.3 ± 5.8 years, and 10 female patients with an average age of 54.4 ± 19.3 years. There was no significant difference between male and female patients by sex and age ($T = 2.0324$, $P = 0.0563$).
- 3) Among the 25 patients, 14/11997 patients received iodine contrast agent for the first time, and the remaining 11/4665 patients had a previous history of iodine contrast agent examination. There was no significant statistical difference between the two patients, $X^2 = 3.18$, $P = 0.079$.
- 4) Among the 25 patients, 15 were inpatients, 6 were outpatients and 4 were emergency patients. Pulmonary CT enhanced scan showed mild acute adverse reactions in 3 cases and moderate acute adverse reactions in 2 cases. Contrast-enhanced abdominal CT scan showed mild anaphylaxis in 6 cases and moderate anaphylaxis in 2 cases. CTU3 cases, 1 mild anaphylaxis, 2 moderate acute adverse reactions. There were 6 cases of CTA, 5 cases of mild acute adverse reactions and 1 case of moderate acute adverse reactions. Arteriography showed mild acute adverse reactions in 4 cases. There were 21 cases of intravenous administration with an incidence of 0.19% (21/10532), and 4 cases of arterial administration with an incidence of 0.08% (4/6130), showing a significant difference between the two ($X^2 = 4.655$, $P = 0.036$) (Table 4).

Table 4
Comparison of anaphylactoid reactions after the use of four iodine contrast media by types of imaging.

Contrast media	Examine locations and the grade of severity of anaphylactoid reactions							
	Lung	Grade	Abdomen	Grade	CTA	Grade	CTU	Grade Arteriography grade
I ₁	1	moderate	4	mild	3c	mild	1	mild 1 mild
I ₂	1	moderate	2	mild	-	--	-	-- 1 mild
I ₃	-	-	-	-	2	mild	1	moderate 1 mild
I ₄	2	mild	2	moderate	1	moderate	1	moderate 1 mild
Total	4	-	8	-	6	-	3	- 4

There were significant differences between arterial and intravenous administration groups ($\chi^2 = 4.655, p = 0.036$). CTA, CT angiography. CTU, CT urography.

Discussion

1. The mechanism of ADR of iodine contrast agent.

Safety is a major concern in the use of iodine contrast agents, and all clinical strategies are used to avoid or reduce the ADR to iodine contrast agents which was initially thought to be an allergy-like reactions rather than a true immunoglobulin E (IgE) mediated hypersensitivity. These reactions are thought to result from the activation of complement, fibrinolytic system, and kinin system, as well as the release of histamine, prostaglandin, bradykinin, and other mediators [4]. However, studies have shown that because of the release of histamine and trypsin and the occurrence of positive skin tests, the IgE mediated allergic mechanism is also one of the evidences for the occurrence of acute adverse reactions of iodine contrast agents [5] [6]. Studies have shown that patients with IgE-mediated allergy-like reactions have a history of exposure to relevant allergens [7]. The data of this retrospective analysis showed that only 11 patients who had been exposed to iodine contrast agents should not be excluded from the IgE mediated acute adverse reactions of iodine contrast agents. There were no correlations between dose and severe allergies, and 1 ml dose for skin test may produce a fatal anaphylactic shock. Unless the pharmacopoeia states the need for skin testing prior to examination, Otherwise, our patients would not have skin test. However, studies have shown that the incidence of ADR in subjects with positive skin test is as high as 64.7%, and the incidence of anaphylactic shock is as high as 81.8%, indicating that positive skin test is an important early warning indicator of anaphylactic shock [7]. The cause of ADR to iodine contrast is not the iodine in the contrast itself, because iodine is necessary for the synthesis of thyroid hormones and is one of the elements that everyone needs to take. The mechanism of allergy-like reactions to iodine contrast has nothing to do with iodine itself. Fish and shellfish are rich in iodine. Some people who are allergic to shellfish can eat scaly fish, but some people who are allergic to scaly fish can eat shellfish, because what causes allergies is not iodine in seafood, but tropomyosin in shellfish or actin in scaly fish [8][9].

2. Relationship between categories of iodine contrast agents and adverse reactions

Studies have shown that the cause of ADR is related to high osmotic pressure and the high content of related ions in the blood [10]. In the development history of iodine contrast agents, there were three historical leaps, namely, the development of ionic contrast agents in the 1950s, the first and second generation of non-ionic monomer contrast agents in the early 1970s, and the development of non-ionic dimer contrast agents in the late 1970s. At present, there are four types of iodine contrast agents: ionic monomers, non-ionic monomers, ionic dimers and non-ionic dimers. These categories differ in three important

respects: iodine-particle ratio, osmotic pressure, and viscosity [1][12]. Large sample studies by Shehadi, Valls and Kopp showed that the total incidence of ADR and severe allergic reactions of high-osmolar agents were significantly higher than that of low-tonic iodine contrast agents [13][14][15]. Compared with ionic agents, non-ionic agents have the advantages of low-osmolarity, good stability, high temperature sterilization which were more stable and safe.

ESUR has reached a consensus that there is no significant difference in the incidence of ADR between low-osmolar and iso-osmolar contrast agents. In Suh's meta-analysis and Bertrand's multicentre double-blind study, there was no significant difference in the incidence of adverse reactions between low-osmolar and iso-osmolar contrast agents [1] [16]. However, in this study, the incidence of ADR of isot-osmolar contrast agents iodixanol was significantly higher than that of low-osmolar contrast agents ioversol, iohexol and iopromide. The high rate of ADR of iodixanol may not be related to its iso-osmolar properties, but to its high viscosity. Compared with other non-ionic monomer iodine contrast agents, iodixanol with iodine-particle ratios of 6:1 has higher viscosity. However, studies on the original drug of iodixanol, Visipaque, found that the incidence of adverse reactions of iodixanol was not significantly different from that of other low-osmolar contrast agents, so is the reason for the high adverse reactions of generics iodixanol (Aidixian) related to its produce? We need further studies with multi-center large samples of different batches of its products for more in-depth analysis.

3. Risk factors related to adverse reactions of iodine contrast agents

There are literature studies that reports that the history of allergy, asthma, allergic diseases, gender, age, dose, flow rate and route of administration of iodine contrast agents are statistically significant in the occurrence of adverse reactions of iodine contrast agents [17][18][19]. According to a prospective, observational study in coronary angiography, the history of iodine contrast agent by artery is immediate hypersensitivity is an important risk factor in arteriography, so for the patients who have undergone with iodinated agents may replace the other types of iodine contrast agent in arteriography for reducing the occurrence of ADR [20].

One of the main purpose of this study was to compare between iodixanol (Adixian) and several other iodine contrast agent differences in incidence of ADR. We apply the protocols with same doses and flow rates, results show that there were no significantly statistical difference of gender and age.

There was significant difference between the arterial administration group and the intravenous administration group ($P = 0.036$). At the same flow rate, high viscosity contrast agent may produce more adverse reactions. Kopp's study found that the incidence of ADR in patients by intravenous injection was significantly higher than that in patients by intravascular injection [15], which may be due to higher arterial pressure than venous pressure and less influence by the viscosity of contrast agent. In this study, the incidence of ADR of iodine contrast agent in arteriography was significantly lower than that of intravenous administration, which also indicated from another perspective that high viscosity contrast agents may produce more adverse reactions during intravenous administration.

4. Whether fasting, hydration, heating and corticosteroid prophylaxis can reduce the incidence of adverse reactions?

It is generally believed in the literature that premedication corticosteroid for at-risk patients cannot reduce the incidence of adverse reactions [21]. Fasting can reduce the incidence of nausea [22], and heating contrast agent in advance can make patients feel more comfortable, thus reducing the incidence of adverse reactions [19]. Hydration may have no obvious effect on reducing the occurrence of acute adverse reactions, but it can reduce the incidence of contrast-induced nephropathy [23] [24]. In our study, pre-heating with contrast agent, adequate hydration before and after the examination, and fasting for at least 4–6 hours before the examination was regularly used. Since this was a retrospective study, we did not set up the corresponding control group for the study analysis.

All patients in this study did not adopt pre-medication and they will be observed for at least 30–60 minutes by venous indwelling needle, because 90% of the adverse reactions happen during this period.

In conclusion, the overall incidence of ADR of the 4 types iodine contrast agents was low. In our study, the incidence of ADR of iodixanol(Aidixian) was the highest, and most of them were moderate acute adverse reactions, which may be related to the high viscosity of iodixanol. As a generic agent, we need to observe the acute and delayed adverse reactions of iodixanol, including CIN and other adverse reactions by a multicenter, prospective and observational study, and further analyze the risk factors of adverse reactions.

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