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FULL PAPER

Clinical observation of the adverse drug reactions caused by non-ionic iodinated contrast media: results from 109,255 cases who underwent enhanced CT examination in Chongqing, China

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Objective: To analyse the pattern and factors that influence the incidence of adverse drug reactions (ADRs) induced by non-ionic iodinated contrast media and to evaluate their safety profiles.

Methods: Data from 109,255 cases who underwent enhanced CT examination from 1 January 2008 to 31 August 2013 were analysed. ADRs were classified according to the criteria issued by the American College of Radiology and the Chinese Society of Radiology.

Results: A total of 375 (0.34%) patients had ADRs, including 281 mild (0.26%); 80 moderate (0.07%); and 14 severe (0.01%) ADRs; no death was found. 302 (80.53%) of the ADRs occurred within 15 min after examination. Patients aged 40–49 years (204 cases, 0.43%; $p < 0.01$) or who underwent coronary CT angiography (93 cases, 0.61%; $p < 0.01$) were at a higher risk of

ADRs. Female patients (180 cases, 0.40%; $p < 0.01$) or outpatients had significantly higher incidence rates of ADRs. The symptoms and signs of most of the ADRs were resolved spontaneously within 24 h after appropriate treatment without sequelae.

Conclusion: The occurrence of ADRs is caused by the combined effects of multiple factors. The ADRs induced by non-ionic iodinated contrast media are mainly mild ones, while moderate or severe ADRs are relatively rare, suggesting that enhanced CT examination with non-ionic iodinated contrast media is highly safe, and severe adverse events will seldom occur under appropriate care.

Advances in knowledge: The study included 109,255 patients enrolled in various types of enhanced CT examinations, which could reflect ADR conditions and regulations in Chinese population accurately and reliably.

Non-ionic iodinated contrast media is currently the preferred option for enhanced CT examination. In recent years, the market sales of contrast media have been increasing by 20% annually in China, and the overall market sales had been >3 billion RMB in 2011. However, compared with the western countries, the market for contrast media in China is far from saturated; it has been estimated that the market sales of contrast media in China will be >6 billion RMB in 2015.¹

As the population using non-ionic iodinated contrast media is increasing rapidly, the safety profiles of this contrast media have been recognized as the most important

issue. Many studies have been performed to investigate the safety profiles of ionic and non-ionic iodinated contrast media.^{2–4} However, only very few studies involving Chinese patients have been performed, of which sample sizes are generally small and thus could not fully reflect the incidence and pattern of adverse drug reactions (ADRs) induced by contrast media in Chinese patients. In the present study, clinical data of patients who underwent enhanced CT examination in our department (Department of Radiology, Daping Hospital, Chongqing, China) from 1 January 2008 to 31 August 2013 were retrospectively analysed to evaluate the safety profiles of non-ionic iodinated contrast media, to explore the influencing factors involved in the

occurrence of ADRs and to access whether the ADRs had been appropriately treated. The findings of the present study will help radiologists, technicians and nurses to better understand and treat ADRs, and thus help in improving the safety of the patients undergoing CT examination.

METHODS AND MATERIALS

Clinical data

GE LightSpeed VCT® (GE Healthcare, Milwaukee, WI) and Philips Brilliance iCT Scanner (Royal Dutch Philips Electronics Ltd, Amsterdam, Netherlands) were used for CT scanning. Non-ionic iodinated contrast media were intravenously injected by a high-pressure injector (Ulrich Medical® Inc., Ulm, Germany). The dose of contrast media was 55–70 ml and the speed was 4.5–6 ml s⁻¹ for adult patients who underwent coronary CT angiography (CTA); 60–70 ml and 4–5 ml s⁻¹ for adult patients who underwent head and neck CTA; and 65–80 ml and 3–4 ml s⁻¹ for adult patients who underwent CTA of the body and other sites, respectively. From 1 January 2008 to 31 August 2013, a total of 109,255 patients underwent CT examination using non-ionic iodinated contrast media. Among these patients, there were 44,683 females (40.90%) and 64,572 males (59.10%); the mean age of the patients was 56.8 ± 15.3 years (ranging from 0 to 102 years); 17,471 (15.99%) of these patients were outpatients, while 89,155 (81.60%) were inpatients and 2629 (2.41%) were emergency patients. Coronary artery CTA, head and neck CTA and the enhanced CT examination of the body and other sites accounted for 14.22% (15,537 cases), 23.16% (25,306 cases) and 62.62% (68,412 cases), respectively. The contrast media used included Iopromide 370 (Bayer Healthcare, Leverkusen, Germany), Iodixanol 320 (GE Healthcare), Iohexolum 350 (GE Healthcare), Iopamidol 350 (Bracco, Milen, Italy), Ioversol 350 (Covidien, St Louis, MI), Ioversol 320 (Covidien) and Ioversol 300 (Covidien). The data of patients were collected from picture archiving and communication systems and recorded in self-designed case report forms (CRFs). The recorded data included patients' general characteristics, clinical presentations of ADRs, timing of ADRs, treatment methods, remission time and the outcomes of ADRs.

Inclusion criteria

All the patients were informed about the indications and about no contradictions for using iodinated contrast media before CT examination, according to the "Iodine contrast agents application guideline (2nd edn)".⁵ A self-designed examination and operation protocol was used to further evaluate and screen the patients, and all the patients signed informed consent before scanning. For some cases with high risk of ADR that needed examination, it was required to inform the patients, their families and the doctors in charge of the potential risks; dynamic observations were also performed during and after the CT examination.

Design of case report form for the adverse drug reactions induced by contrast media

The self-designed CRF included the following items: (1) data of examination, general characteristics of the patients (sex, age and body mass index), history of contrast media usage, allergic history, underlying diseases and high-risk factors; (2) scanning

regions; (3) type, dose and injection speed of contrast media; and (4) clinical presentations, the onset time, treatments, remission time and outcomes of ADRs. The CRFs were filled out by trained investigators and then archived.

Working mode and investigators involved in the examination and treatments

Since 2007, clinicians, technicians and nurses have been systematically trained to appropriately use contrast media and to treat the related conditions in our department; in addition, they were also asked to receive education on preventing and controlling contrast media-related ADRs once every year and to attend a simulating exercise of treating contrast media-related ADRs every month. The new staff were not allowed to participate in contrast media-related operations until they had already been trained and had adequate knowledge about contrast media-related ADRs, the awareness and competence of first aid for ADRs and the relevant first aid knowledge. Nurses were asked to perform the preparations before the examination, co-operate with the technicians during the examination and perform the observations after the examination; in addition, the nurses were also asked to inform the patients of potential normal physiology reactions (such as warm or hot sensation) and ADRs. During the examination, the technicians and nurses were asked to observe abnormal reactions of the patients and to inform the patients of the related information. The patients were not allowed to leave the CT room until 15 min after the examination was completed. The technicians and nurses were asked to treat the patients if ADRs occurred and to ask the radiologists for help immediately; for the cases of moderate or severe ADRs, or other special clinical presentations, the clinicians at the first aid department or the clinicians in charge of the patients were asked to come and treat the patients.

Classification criteria of contrast media-related adverse drug reactions

Contrast media-related ADRs were classified according to the criteria issued by the American College of Radiology (ACR)⁶ and the Chinese Society of Radiology (CSR).⁵ In brief, the ACR criteria were as follows:⁶ (1) mild ADR: nausea, vomiting, cough, headache, dizziness, trembling, shivering, sweating, taste changing, pale, flushing, red and swollen, urticaria, itching, nasal congestion, swelling (eyes and face) and anxiety; (2) moderate ADR: symptomatic bradycardia or tachycardia, hypertension, mild hypotension, dyspnoea, systemic or diffuse erythema, bronchospasm, wheezing and laryngeal oedema; and (3) severe ADR: laryngeal oedema (severe or rapidly progressive), non-responsive, seizure, severe hypotension, clinically significant arrhythmia and cardiopulmonary arrest. The CSR criteria were as follows:⁵ (1) mild ADR: cough, sneeze, transient chest tightness, conjunctivitis, rhinitis, nausea, systemic fever, urticaria, itching, angioneurotic oedema; (2) moderate ADR: severe vomiting, systemic urticaria, facial swelling, dyspnoea and vasovagal reactions; and (3) severe ADR: laryngeal oedema, seizure, trembling, convulsion, unconsciousness, shock, death and other unexpected adverse reactions.

The CSR and ACR criteria have several differences. For instance, severe vomiting and facial swelling are classified as moderate

ADRs, whereas trembling and shivering accompanied with systemic symptoms are classified as severe ADRs in the CSR criteria. In the present study, we classified single severe vomiting, mild or localized facial swelling, mild trembling or shivering as mild ADR; substantial facial swelling and single systemic trembling or shivering as moderate ADR; and trembling or shivering accompanied with severe systemic symptoms as severe ADR when using the ACR classification criteria. Several symptoms including abdominal pain, transient blurred vision, numb limbs, urinary incontinence and transient blindness in the bilateral eyes were not included in either of these two criteria. In the present study, symptoms including single abdominal pain, transient blurred vision and numb limbs were classified as mild ADR, whereas these symptoms accompanying other symptoms were classified according to the ACR criteria; single urine incontinence was classified as moderate ADR; and urine incontinence accompanying conscious disturbance was classified as severe ADR; in addition, one case with blindness in the bilateral eyes that recovered in 24 h was classified as severe ADR.

Treatment strategy for adverse drug reactions

A specific rescue room with sufficient first aid facilities and monitoring devices (including monitoring instrument, defibrillator, ventilator, oxygen therapy devices, sputum suction devices, different airway tubes, pulse oximeters and endotracheal intubation packages) was established in the radiology department; sufficient rescue drugs were also prepared. Aggressive prevention, sufficient preparation and regular training were performed for the patients before examination. Once ADR occurs, all the radiologists, technicians and nurses could appropriately use the devices and drugs to treat the patients; in addition, they were also able to perform rapid evaluation, accurately determine and closely monitor [vital signs and pulse oxygen saturation (SPO₂)], timely treat, ask for help, record and follow up the patients. The basic principles for the treatment of ADRs were as follows: (1) for patients with mild ADRs, the injection of the contrast media should be stopped, no other special treatments are needed, and the patients could generally recover spontaneously; in addition, symptomatic treatment could also be performed by the radiologists, and the conditions should be monitored closely; (2) for patients with moderate ADRs, aggressive treatment should be performed; for the cases that need drug therapy, clinicians from the first-aid department should be asked for help, and the patients should be quickly transferred to the first-aid department or the inpatient department for further observation and treatment after the primary treatment; (3) for patients with severe ADRs, immediate treatment including symptomatic treatment should be performed, and the clinicians from the emergency, anaesthesia and other related departments should be asked to perform treatments in co-operation. When cardiorespiratory arrest occurs, heart, lung and brain resuscitations should be performed immediately, basic life support and advanced life support should be performed in the radiology department, parameters included blood pressure, impulse, respiratory, SPO₂ and electrocardiogram (ECG) should be closely monitored to ensure sufficient oxygenation and to maintain stable circulation; the patients should be transferred to the first-aid

department or intensive care unit for prolonged life support after disease had been stabilized.

Statistical analysis

The SPSS® v. 18.0 (SPSS Inc., Chicago, IL) software was used. χ^2 test was applied for the comparisons. $p < 0.05$ was considered statistically significant.

RESULTS

Incidence rate of adverse drug reactions

The overall incidence rate of ADRs was 0.34% ($n = 375$). The patients who developed ADRs included 195 males (52.00%) and 180 females (48.00%), with the mean age of 53.3 ± 14.7 years (ranging from 6 to 89 years). Among these ADRs, there were 281 mild (0.26%), 80 moderate (0.07%) and 14 severe (0.01%) ADRs; no death was observed. The mild, moderate and severe ADRs accounted for 74.93%, 21.33% and 3.74% of all the ADRs, respectively. For the patients in different age groups, the incidence rate of ADRs was the highest in the 40–49 and 50–59 years of age groups, while the ones in the 70–79 years of age group had the lowest incidence rate ($p < 0.01$) (Figure 1). The incidence rate of ADR was 0.61% (93 cases), 0.40% (100 cases) and 0.27% (182 cases) for the patients who underwent coronary artery CTA, head and neck CTA and examination of the body and other regions, and the difference was statistically significant ($p < 0.01$) (Figure 2). Among the different months, the incidence rate of ADRs was the highest in March (0.56%) (Figure 3). The incidence rate of ADRs was significantly higher in female patients (0.40%) than in male patients (0.30%, $p < 0.01$). We also found that the incidence rate of ADR in outpatients (0.77%, $n = 134$) was significantly higher than in emergency patients (0.19%, $n = 5$) and inpatients (0.26%, $n = 236$) ($p < 0.01$). Follow-up observation was performed for 360 of the 375 patients with ADRs (until the conditions remitted), and the follow-up time ranged from 0 to 48 h; no follow-up data were available for the other 15 patients.

Incidence of adverse drug reaction symptoms and remission of the conditions

Mild adverse drug reactions

281 patients (383 ADRs) developed mild ADRs (Table 1). The clinical presentations of the patients were classified into six

Figure 1. Incidence rate of adverse drug reactions (ADRs) in patients of different age groups ($p < 0.01$).

Figure 2. Incidence rate of adverse drug reactions (ADRs) in patients who underwent different examinations ($p < 0.01$). CTA, CT angiography.

categories. 239 cases were with single reactions, 42 were with ≥ 2 reactions. The presentations mainly included skin and mucosal symptoms. 263 (93.59%) of the cases remitted within 1 h, 15 (5.34%) cases remitted within 1–24 h, 1 (0.36%) case remitted after 24 h and data of 2 cases were not available.

Moderate adverse drug reactions

80 patients (170 ADRs) developed moderate ADRs (Table 2). The clinical presentations of the patients were classified into seven categories. 15 cases had single reactions, 65 had ≥ 2 reactions. The presentations mainly included severe respiratory, cardiovascular, neurological and systemic symptoms; other accompanied mild reactions were also found. 54 (67.50%) of the cases remitted within 1 h, 15 (18.75%) cases remitted within 1–24 h and data of 11 (13.75%) cases were not available.

Severe adverse drug reactions

14 patients developed severe ADRs (Table 3). The clinical presentations of the patients included severe cardiovascular, neurological and respiratory symptoms that were accompanied with other mild or moderate symptoms and substantial changes of the vital signs. Treating in first-aid department or inpatient department was required for all these patients. One of these patients was with transient blindness in the bilateral eyes, eight were with hypotension, three with conscious disturbance and two with urinary incontinence. Four of the cases remitted within 1 h, eight cases remitted within 1–24 h, one case remitted after 24 h and data of one case were not available.

Timing of adverse drug reaction onset

57 (15.2%) of the ADRs occurred during CT scanning (from the injection to the end of the CT examination), 302 (80.53%) occurred within 15 min after the examination, 1 (0.27%) occurred within 15–30 min, 1 (0.27%) occurred within 30–60 min, 11 (2.93%, including 5 cases received Iodixanol 320) occurred after 1 h and data of 3 cases were not available.

Allergic history, medication history and mental states of the patients

Routine screening was performed before the scanning according to the “Iodine contrast agents application guideline (2nd edn)”⁵ and found that only 15 patients with a history of mild iodine allergy underwent enhanced CT scanning owing to the disease conditions and 8 of them developed different degrees of ADRs. Seven patients had a history of skin symptoms and six of them

were found with single skin symptom after the examination. Two patients with palpitation, nausea and vomiting developed urticaria, shivering and chest distress after the examination, two patients with a history of throat tightening after the usage of contrast media before did not have an ADR this time, four patients who reported to be allergic to iodine (but the specific symptoms were not recorded) were not with ADRs this time.

18 patients who had received iodinated agents before but were not allergic to the agents were found with different degrees of ADRs after the use of contrast media this time. All 18 of these patients had different underlying diseases (including 9 patients with malignancies that received radiotherapy and chemotherapy, 6 patients with cardiac–cerebral vascular diseases, 1 patient with chronic insomnia, 1 with acute gastroenteritis and 1 with nerve deafness in the left ear). In addition, one patient was found with mild ADR after treating with Iopromide 370 before; after applying iso-osmotic contrast media Iodixanol 320 this time, ADRs still occurred. Another patient was found with skin symptoms after using iso-osmotic contrast media Iodixanol 320 the first time, but no skin symptom was found after using Iopromide 370 this time.

Among the 375 patients with ADR, 7 patients with no allergic history or iodine medication history were found with distinct anxiety, nervousness and fear before the examination; these 7 patients were also found with vasovagal symptoms, including transient palpitation and shortness of breath during the examination.

Treatments for contrast media-related adverse drug reactions

172 (45.87%) cases of ADR were not specifically treated but remitted spontaneously, while the other 203 (54.13%) cases required treatment. The treatment for these 203 cases of ADRs were as follows.

Hydration

All the patients (except the ones with contraindication for water drinking) who underwent enhanced CT examination were asked to drink 300–500 ml of water before and after the examination under the supervision of nurses. For the cases with mild ADRs,

Figure 3. Incidence rate of adverse drug reactions (ADRs) in different months (%).

Table 1. Incidence of the symptoms of mild adverse drug reactions

Symptoms	Case number	Incidence (%)
Cutaneous manifestations		69.20
Urticaria	198	51.70
Itching	48	12.53
Flushing	19	4.96
Gastrointestinal manifestations		14.10
Nausea and vomiting	51	13.32
Abdominal pain	3	0.78
Facial manifestations		7.83
Mild eyelid swelling, conjunctival congestion and tears	17	4.44
Transient blurred vision	2	0.52
Facial swelling in small area, sense of tension in face	6	1.57
Oral and lip swelling or numbness	5	1.31
Cardiovascular manifestations		2.61
Palpitation and flustering	7	1.83
Transient chest stuffiness	3	0.78
Respiratory manifestations		1.57
Coughing and sneezing	2	0.52
Sense of foreign body or pain in the larynx	4	1.04
Other manifestations		4.70
Mild trembling or shivering	5	1.31
Dizziness and headache	11	2.87
Acratia in the upper and lower extremities	2	0.52

oral hydration was performed first whereas for the patients with moderate ADRs, oral hydration and intravenous hydration were performed for 70 and 10 patients, respectively. Intravenous hydration was performed for all the 14 patients with severe ADRs, among which 0.9% normal saline (NS) or Ringer's solution was provided for 7 patients with hypotension.

Oxygen inhalation

Oxygen inhalation was performed for 70 patients. In detail, for the four cases with mild ADRs, nasal catheter oxygen inhalation ($3\text{--}5\text{ l min}^{-1}$) was performed. For the 52 cases with moderate ADRs, mask oxygen inhalation ($8\text{--}10\text{ l min}^{-1}$) was performed for 1 case with airway symptoms (dyspnoea), and the other cases also received nasal catheter oxygen inhalation (5 l min^{-1}). While for the cases with severe ADRs, nasal catheter oxygen inhalation ($5\text{--}8\text{ l min}^{-1}$) was performed for 13 cases and ventilator mask oxygen inhalation ($8\text{--}10\text{ l min}^{-1}$) was performed for another case.

H1 receptor blocker

Among the 375 cases of ADRs, intramuscular injection of Phenegan (Southwest Pharmaceutical Co., Ltd, Chongqing, China) was performed for 128 cases (34.13%), among which there were 90 cases with skin symptoms and 38 cases with non-skin symptoms.

The dose of intramuscular injection was 25–50 mg. 99 cases remitted within 1 h after the injection, 24 cases remitted within 24 h and 5 cases had unavailable data.

Corticosteroids

Among the 375 cases of ADRs, 58 (15.47%) received corticosteroids, among which there were 34 with skin symptoms accompanied with other symptoms and 24 with non-skin symptoms. 26 of the 58 cases received dexamethasone singly, 26 received dexamethasone and Phenegan, 4 received dexamethasone and epinephrine, while 2 received dexamethasone, Phenegan and epinephrine. All the drugs were intravenously injected for these 58 cases with a dose of 10–20 mg. Dexamethasone was provided for 11 cases with severe ADRs. For the 26 cases treated with dexamethasone singly, the symptoms of 22 cases remitted within 1 h and those of 2 cases remitted within 24 h, while data were unavailable for 2 cases.

Epinephrine

Epinephrine was applied for seven cases with severe ADRs. All these seven cases had hypotension, among which four also had dyspnoea and palpitation, and three had urinary incontinence or conscious disturbance. Intravenous injection of epinephrine

Table 2. Incidence of the symptoms of moderate adverse drug reactions

Symptoms	Case number	Incidence (%)
Respiratory manifestations		24.71
Sense of larynx obstruction, constricted throat	9	5.29
Hoarse voice	9	5.29
Dyspnoea, respiratory weakness	17	10.00
Coughing	5	2.94
Nasal stuffiness, sneezing, nose running	2	1.18
Cardiovascular manifestations		15.88
Chest congestion or short of breath	14	8.24
Palpitation, fluttering	11	6.47
Chest pain	1	0.59
Hypertension	1	0.59
Manifestations of the nervous system		12.94
Mental confusion	4	2.35
Dizziness, headache, fullness in the head	14	8.24
Blurred vision	3	1.76
Numbness of four limbs	1	0.59
Systemic manifestations		17.06
Systemic chillness, trembling or shivering	23	13.53
Profuse sweating, pale face	5	2.94
Waist pain	1	0.59
Cutaneous manifestations		16.47
Urticaria, itching, flushing	28	16.47
Facial manifestations		7.65
Facial swelling, eye swelling, numbness in oral lips, oral lip swelling	13	7.65
Gastrointestinal manifestations		5.29
Nausea and vomiting	5	2.94
Abdominal pain	4	2.35

(1:1000, 0.3–1 mg) was performed for all these seven patients under supervision of the clinicians from the first-aid or inpatient department. The symptoms of one patient and six patients remitted within 1 and 24 h, respectively.

Other drugs

For the cases with moderate or severe ADRs, clinicians from the first-aid or inpatient department also applied some other drugs. For instance, 50% glucose solution (20–100 ml) was orally administered for three cases with suspicious hypotension, 20–100 mg of dopamine was intravenously dripped for five cases with hypotension, 2 ml of metaraminol was intravenously dripped for one case with hypotension, 0.5 mg of isoprenaline was intravenously dripped for one case with hypotension, 10 ml of 10% calcium gluconate was intravenously injected for two

cases with urticaria and 40 mg of omeprazole was intravenously dripped for one case with abdominal pain.

Monitoring of the patients

Patients with ADRs were closely observed; all the patients with moderate or severe ADRs were monitored in the radiology department. Blood pressure, impulse, respiratory, ECG and SPO₂ of the patients were monitored and recorded, and the patients were transferred by the clinicians from the inpatient department.

DISCUSSION

The present study included 109,255 patients who received intravenous injection of non-ionic iodinated contrast media for enhanced CT examination, and the overall incidence rate of ADRs was 0.34%, which was lower than the rates reported by

Table 3. Incidence of the symptoms of severe adverse drug reactions

Symptoms	Case number	Incidence (%)
Cardiovascular manifestations		39.13
Chest congestion or shortness of breath	2	4.35
Palpitation and fluttering	7	15.22
Hypotension (pale face, cold sweating, chills in whole body)	9	19.57
Manifestations of the nervous system		26.09
Dizziness	3	6.52
Conscious disturbance	4	8.70
Convulsed limbs or jerking of four limbs	2	4.35
Urine incontinence	2	4.35
Blindness of both eyes	1	2.17
Respiratory manifestations		13.04
Dyspnoea (lip and facial cyanosis)	5	10.87
Itching in larynx	1	2.17
Systemic manifestations		10.87
Systemic trembling or shivering	2	4.35
Myasthenia of limbs	3	6.52
Manifestations of cutaneous mucous membrane		6.52
Palpebral oedema	2	4.35
Flushing	1	2.17
Gastrointestinal manifestations		4.35
Nausea and vomiting	2	4.35

previous studies (3.13–0.60%).^{2–4,7–9} The reasons could be as follows: (1) strict screening was performed for all the patients before the examination and found only 15 cases who need contrast CT examination owing to their diseases were with the history of mild iodine allergic history; (2) a standard protocol was available in the radiology department to prevent and treat contrast media-related ADRs; (3) all healthcare was provided by specially trained nurses. When waiting for the examination, the nurses sufficiently informed the patients of the necessity, safety profiles and potential normal and systemic responses after the usage of contrast media, which effectively reduced the anxiety or fear of the patients; and (4) there could be some ethnic differences between Chinese patients and Western patients. The findings of the present study showed that the incidence rate of mild, moderate and severe ADRs was 74.93%, 21.33% and 3.74%, respectively. Most of the ADRs in the present study were mild or moderate, which was in accordance with previous findings. In addition, the incidence rate of severe ADRs was higher than the results reported by Wang et al,⁷ but the overall incidence was still very low (0.01%), which was in accordance with the results reported by Wang et al.⁷

Previous studies have shown that the incidence rate of ADRs is associated with the age of the patients. The findings of the present study showed that the patients aged 18–29 (0.42%),

30–39 (0.40%), 40–49 (0.43%) and 50–59 (0.43%) years were with the highest incidence rate of ADRs, which was in accordance with the relatively high incidence rate in patients aged 18–50 years that was reported in previous studies,^{3,9,10} whereas the ones aged 70–79 (0.19%) years were with the lowest incidence rate of ADRs, which was not in accordance with the highest incidence rate in patients aged 20–29 years reported by Khachman et al.¹¹ The results of the present study showed no ADRs in the patients aged below 1 year, which was in accordance with the findings of Callahan et al.¹² The low incidence rate in this age group could be associated with the insufficient immune responses in infants, could not identify the mild and moderate ADRs and difficulties in communication; in addition, some infants were examined under monitored anaesthesia care or oral intake of 10% chloral hydrate, which caused mild and moderate ADRs not easily identified.¹³ Patients aged 18–59 years had a relatively high incidence rate of ADRs, which could be associated with the fact that the patient in these age groups had relative high pressure, hypochondriasis, tended to actively express themselves, and had relatively high immune activity¹⁴ and thus increased the reactivity of the body.⁴ Among the 14 cases with severe ADRs, 12 (86%) were aged more than 50 years, while 2 were aged more than 40 years, suggesting that the risk of developing severe ADRs was higher in patients with moderate or

advanced ages, which could also be associated with the relatively high prevalence of cardiopulmonary diseases and poorer basic conditions in these patients, which increased the risk of developing ADRs.¹⁵ The relatively low incidence of ADRs in the patients aged more than 60 years could be associated with the decreased immune activity in these patients.

Sex could also affect the development of ADRs to a certain degree. In the present study, the incidence rate of ADRs was significantly lower in the male patients (0.30%) than in the female patients (0.40%), which was not in accordance with the results reported by Katayama *et al*,² but in accordance with the results reported by several other studies.^{3,4,11,15,16} The authors speculated that the difference could be associated with the fact that the female patients were more likely to tell the care givers their slight discomforts than the male patients. Some other studies also reported that oestrogen could induce allergic responses,^{3,17} and the physical differences between the male and female patients could also be associated with this phenomenon.

The findings of the present study showed that 80% of the ADRs occurred within 15 min after the CT examination and 15% of the ADRs occurred during the examination. Therefore, during the time of the examination and within 15 min after the examination is critical for the observation of the development of ADRs. In our opinion, patients should not leave the CT room until 30 min after the examination. In a study performed by Katayama *et al*,² the injection of contrast media was the time with the highest incidence of ADRs (48.7%), which could be associated with the possibility that the investigators included some normal reactions during injection, including systemic fever, emotional lability and vascular pain into the ADRs. The present study also investigated the association between different seasons and the incidence of ADRs and found no pattern in the changes of ADR incidence in different months, which was also in accordance with previous findings.³ However, we found that the incidence of ADRs in March (0.56%) was significantly higher than in other months, which could be associated with the specific climate in Chongqing, China. In Chongqing, the temperature changes rapidly and frequently in the season changing from winter to spring, and the humidity is also very high (up to 90%), which makes March a month with high incidence of respiratory diseases; these factors could make it more difficult for patients to adapt to the difficulties in a short period of time and increase the risk of inducing ADRs after injection of contrast media. In addition, contact or inhalation of the allergens, including pollen in the air by people with a predisposition to allergies could also be associated with the phenomenon.^{18,19}

Some other phenomenon were also found in the present study. Although the phenomenon were not very common, we should also pay attention to it. For example, 15 patients with a known history of iodine allergy needed enhanced CT examination owing to their conditions, and ADRs with different degrees were found in 8 of them after examination under close monitoring, which was in accordance with previous findings that the contrast media-related ADR incidence was higher in patients with allergic histories.^{2-4,7} One patient was found with mild ADR after the previous use of hyperosmotic contrast media, and ADR still

occurred after using iso-osmotic contrast media this time; by contrast, skin symptoms were found for another patient after using iso-osmotic contrast media previously, but no skin symptom was found after using hyperosmotic contrast media this time. We also found different degrees of ADRs in 18 patients (all with different underlying diseases) who had a medication history of iodine but no allergic history. Therefore, additional attention should be paid to the patients with any allergic histories or underlying diseases during examination. In addition, using contrast media with different osmotic pressures may not be able to change the risk of developing ADRs. Further studies with larger sample sizes are needed to verify these findings.

Several studies reported that the incidence rate of ADRs was higher in outpatients than in patients treated in other departments.⁴ In the present study, we also compared the incidence rate of ADRs in inpatients, outpatients and emergency patients and found that the ADR incidence rate was significantly higher in outpatients (0.77%) than in inpatients (0.26%) and emergency patients (0.19%), which was in accordance with previous findings.³ This difference could be associated with the fact that most of the outpatients were not fully aware of their own diseases, the examinations were not comprehensive enough and the underlying risk factors were not clear; therefore, these patients were easier to neglect in the screening and thus were at higher risk of developing ADRs.

Several studies showed that anxiety was associated with moderate ADRs, and anxiety could increase the incidence rate of ADR in patients.^{7,20,21} In the present study, the 7 allergic history-free patients out of the 375 ADR patients were found with obvious anxiety, nervousness and fear before the examination, and vasovagal symptoms including palpitation or shortness of breath during the examination, which we believed could be largely associated with poor psychological factors. Therefore, technicians and nurses in the CT room should better communicate with patients, provide sufficient health education, comfort and encourage patients with anxiety, nervousness and fear, and help patients to complete the examination.²²

In the present study, we also found the incidence rate of ADRs was significantly higher in patients who underwent coronary artery CTA or head and neck CTA than in patients who underwent CT examination for the other parts of the body (incidence rate was 0.61%, 0.4% and 0.27%, respectively), which had never been reported before. Among the 93 patients who underwent coronary artery CTA, 7 received 25–50 mg of β -blockers to reduce the heart rate at 40–60 min before examination. As all these seven patients were with no contradictions for β -blockers and reported no discomfort after drug intake, we classified the symptoms after the injection of contrast media as ADRs instead of β -blocker-induced adverse effects. In addition, we also found that 54% ($n = 50$), 69% ($n = 69$) and 5% ($n = 9$) of the patients underwent coronary artery CTA, head and neck CTA and enhanced CT examination of the other body sites with different degrees of underlying diseases, including hypertension, diabetes, coronary heart diseases, cerebral ischaemia and cerebral infarction (Figure 2). These underlying diseases could

increase the risk of ADR in patients who underwent coronary artery or head and neck CTA.

Hydration is a major preventive and treatment method for contrast media-related ADR. In the present study, all patients were asked to drink 300–500 ml of water before the CT examination; in addition, intravenous hydration was also performed for the ones with moderate or severe ADRs, which could be effective to reduce the incidence and alleviate the symptoms of ADRs.^{7,21,23} For oxygen inhalation, mask oxygen inhalation or ventilator mask oxygen inhalation was effective.^{7,21,23} For cases with skin symptoms, H1 receptor blockers and glucocorticoids were provided for most, which effectively alleviated the symptoms.^{7,24} Epinephrine is the preferred drug for the treatment of anaphylactic shock; in the present study, epinephrine was applied for all the seven cases with hypotensive shock, which effectively controlled the disease; however, the application of epinephrine should strictly follow the indications to avoid the complications including myocardial damage.^{7,25}

All the patients included in the present study were routinely examined subjects. As the sample size was too big, only the 375 cases with ADRs were with detailed information, while the data of the other patients without ADRs were not so complete, and, thus, the incidence of iodinated contrast media-related ADR and the associations with the underlying diseases, injection dose, injection speed and type of contrast media could not be further analysed. For instance, clinical data showed that the injection speed was 4.5–6.0 ml s⁻¹ for coronary artery CTA, 4–5 ml s⁻¹ for head and neck CTA and 3–4 ml s⁻¹ for the examination of other body sites. The injection speed for coronary artery or head and neck CTA was higher than the examination of the other body sites, and the underlying diseases were more frequently found in patients who underwent coronary artery or head and

neck CTA; thus, although the results showed that the ADR incidence was significantly higher in patients who underwent coronary artery or head and neck CTA than in patients who underwent examination of other body sites, we could not determine whether this difference was associated with the underlying diseases or the injection speed.

In summary, the incidence rate of ADRs was very low, and most of the ADRs were mild, while moderate or severe ADRs were very rare; 95.47% of the ADR symptoms remitted within 24 h after appropriate prevention or treatment, and all the patients recovered well. The incidence rate of ADRs was significantly higher in coronary artery or head and neck CTA than in enhanced CT examination in other body sites, which should be noticed and prevented in clinical practices. 95% of ADRs occurred during the examination or within 15 min after the examination; thus, this time period should be considered as the high-risk duration and close monitoring should be applied. Contrast media-related ADR is not caused singly by the contrast media; instead, it could be the result of the combined effects of multiple factors. The psychological factors, physical conditions at different stages, age, sex, months and the source of the patients could also be associated with the ADR. However, more prospective randomized studies with large-scale clinical data are needed to further investigate the associations between ADRs and the underlying diseases, type of the contrast media, injection speed and dose of the contrast media.

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