



Clinical features and risk factors of iodinated contrast media (ICM)-induced anaphylaxis

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ABSTRACT

Purpose: To evaluate the clinical features and risk factors of iodinated contrast media (ICM)-induced anaphylaxis. **Methods:** This retrospective study included all patients undergoing contrast-enhanced computed tomography (CT) with intravenous ICM administration (iopamidol, iohexol, iomeprol, iopromide, ioversol) at our hospital between April 2016 and September 2021. Medical records of patients who experienced anaphylaxis were reviewed, and the multivariable regression model using generalized estimating equations was employed to eliminate the effect of inpatient correlation.

Results: Of the 76,194 ICM administrations (44,099 men [58 %] and 32,095 women; age, median, 68 years) to 27,696 patients, anaphylaxis occurred in 45 cases in 45 different patients (0.06 % of administration and 0.16 % of patients), all with onset within 30 min after administration. Thirty-one (69 %) had no risk factors for ADRs, including 14 (31 %) who had previously used the same ICM that caused anaphylaxis. Thirty-one patients (69 %) had a history of ICM use without any ADRs. Four patients (8.9 %) received oral steroid premedication. The only factor associated with anaphylaxis was the type of ICM, with an odds ratio (OR) of 6.8 ($p < 0.001$) for iomeprol with iopamidol as a reference. No significant differences in OR of anaphylaxis were found for patients' age, sex, or premedication.

Conclusion: The overall incidence of anaphylaxis due to ICM was very low. More than half of the cases had no risk factors for ADRs and had no ADRs on past ICM administration, although the ICM type was associated with a higher OR.

1. Introduction

Adverse drug reactions (ADRs) caused by iodinated contrast media (ICM) have been categorized as either allergic-like or chemotoxic reactions, and classified into three general categories of severity (mild, moderate, or severe) [1–3]. Recent reports suggested that the overall incidence of ADRs and serious ADRs with nonionic ICM was about 1 % and 0.01 %, respectively [4–6]. ADRs caused by ICM may present with various clinical symptoms, but most of them are mild and self-limiting. These non-life-threatening ADRs may be of minor clinical importance. However, since moderate and severe ADRs can be life-threatening to the patient, it is quite important to accurately understand their clinical features.

Anaphylaxis is defined as “1. typical skin symptoms AND significant symptoms from at least 1 other organ system; or 2. exposure to a known or probable allergen for that patient, with respiratory and/or cardiovascular compromise.” This is a serious clinical condition that can be life-threatening [7]. It should be noted that anaphylaxis may be classified into not only severe ADRs but also moderate ADRs, according to the severity classification of ADRs caused by ICMs [8].

The pathogenesis of allergic-like reactions to ICM is unclear [9,10], but the risk factors for ADRs to ICM are, reportedly, a history of previous ADRs, asthma, and atopy [8], no external warming of ICM [11], and repeated examinations [12]. Although several studies described differences in the incidence of ADRs among ICMs used, a recent meta-analysis found that results varied by study design and that there was no

Abbreviations: ADR, adverse drug reaction; CI, confidence interval; GBCA, gadolinium-based contrast agents; ICM, iodinated contrast media.

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difference in the occurrence of overall ADRs or severe ADRs among ICMs used [13].

Although many studies have evaluated the risk factors for ADRs due to ICMs, there have been a few studies that have focused on the clinical features of anaphylaxis [14,15]. Information on the current status of the occurrence of life-threatening anaphylaxis and its clinical features would make for safer contrast examinations. The purpose of this study was to evaluate the clinical features of ICM-induced anaphylaxis.

2. Materials and methods

2.1. Study design, population, and clinical data

In accordance with the Declaration of Helsinki, this retrospective single-center study was approved by our Institutional Review Board (No. HS2021-229). The need for informed consent for patients was waived. Instead, information about the study was made public, and eligible patients who requested not to participate in the study were excluded. All personal data were removed and coded as arbitrary numbers for analysis.

This study retrospectively included all patients who underwent contrast-enhanced (CE) CT examinations with intravenous administration of ICM at our hospital between April 2016 and September 2021. Those for whom information on patient age, sex, type of examination, premedication, or ICM used was not available were excluded. Pediatric patients were excluded from this study due to the small number of cases.

All patients were interviewed prior to CE CT for their experience with ICM or gadolinium-based contrast agent (GBCA) use, history of ADRs if present, and possible risk factors related to ADRs (history of drug eruption, ADRs caused by past contrast agent use, bronchial asthma, and hay fever).

2.2. Iodinated contrast media used

All CE CT examinations were performed using one of five low-osmolality ICM warmed to 37 °C: iopromide (Iopromide injection; Bayer Yakuhin, Osaka, Japan), iomeprol (Iomeron; Eisai, Tokyo, Japan), iopamidol (Iopamiron; Bayer Yakuhin), iohexol (Omnipaque; GE Healthcare Pharma, Tokyo, Japan), or ioversol (Optiray; Guerbet, Tokyo, Japan). We usually select ICM based on the purpose of the examination and the patient's body weight for a dose of 300–630 mg I/kg. ICMs were chosen to have the least amount remaining in the syringe after the appropriate dose was administered. For patients who experienced ADRs to ICM in the past and had a determined need for a subsequent contrast administration, the previously used ICMs were avoided, and another contrast agent was used. Steroid premedication was administered at the discretion of the referring physician when a patient had a history of ADR to GBCA or ICM (regardless of severity), possible risk factors for contrast-induced ADRs, or asthma, according to the European Society of Urogenital Radiology (ESUR) Guidelines on Contrast Agents v9.0 (methylprednisolone 32 mg administered orally as premedication 12 h and 2 h before ICM administration) [16].

Before July 2019, patients were encouraged to remain near the examination room if they had any symptoms after their CE CT examination. After July 2019, patients were instructed to wait in the waiting area in the radiology department for approximately 15 min after the CE CT examination. The patient was instructed to notify nearby hospital staff if they noticed any abnormalities after leaving the CT department, and to contact the CT department or emergency department if they noticed any abnormalities after leaving the hospital. Abnormalities, including AARs, were recognized by either a spontaneous complaint by the patient or his/her family, or by the medical staff.

2.3. Diagnosis of anaphylaxis and clinical record review

In our institution, when an ADR requires treatment, all medical

professionals involved in the CE CT examination must submit incident reports; this system is strictly enforced. Based on this information, we extracted data on the patients with ADRs from the patients' clinical records, which included the patients' age and sex, ICM used, patient province, experience with ICM or GBCA use, possible risk factors related to ADRs (history of drug eruption, ADRs caused by past contrast agent use, bronchial asthma, and hay fever), and steroid premedication. Experience with ICM was declared by the patient on the consent form for the use of ICM.

The definition of anaphylaxis followed that of the World Allergy Organization: 1. Typical skin symptoms (e.g., generalized hives, pruritus or flushing, swollen lips-tongue-uvula) and significant symptoms from at least one other organ system; or 2. Exposure to a known or probable allergen for that patient, with respiratory and/or cardiovascular compromise [7]. If the diagnosis of anaphylaxis was not specified in the clinical records, a radiologist (H.H., a board-certified radiologist with 21 years of experience) retrospectively reviewed clinical records to determine whether the reaction was anaphylaxis according to the grading system [7].

2.4. Statistical analysis

All analyses were performed using R version 4.1.2 (The R Foundation for Statistical Computing, Vienna, Austria, <https://www.R-project.org>), and a p -value < 0.05 indicated a significant difference. Descriptive statistics were described as medians (25th and 75th percentiles) for continuous variables, and frequencies and percentages were reported for categorical variables. We calculated odds ratios (ORs) considering inpatient correlations by multivariate analysis using generalized estimating equations to assess the effect of ICM and patient factors of sex, patient provenience, age range, or premedication on anaphylaxis. Because we did not obtain detailed clinical information on patients who did not develop anaphylaxis, experience with ICM, bronchial asthma, and other risk factors for ADR were excluded from the analysis. Analyses were performed using the geeM package in R, assuming an exchangeable correlation structure and calculating robust sandwich variance estimates to generate Wald statistics and 95 % confidence intervals (CIs) [17,18].

3. Results

3.1. Study population

We found a total of 76,194 ICM administrations with CE CT to 27,696 patients (Fig. 1 and Table 1; pediatric patients [<15 years of age; $n = 361$] were excluded). No patients were excluded from the study because of inadequate information on ICM.

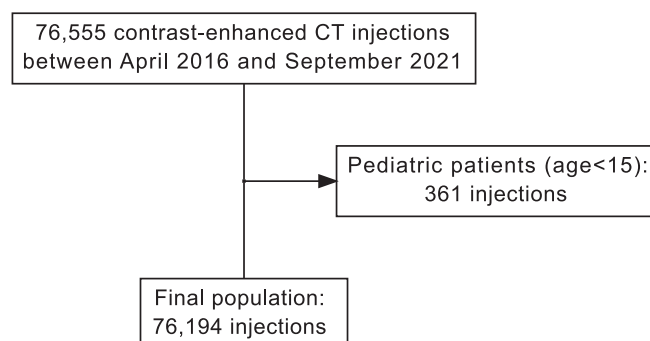


Fig. 1. Flowchart showing the study population.

Table 1

Study population and iodinated contrast media (ICM) used.

Characteristics	N = 76,194 ¹
No. of patients	27,696
Age (years)	68 (58, 75)
Iodinated contrast media	
Iopamidol	22,923 (30 %)
Iohexol	18,793 (25 %)
Iomeprol	17,073 (22 %)
Iopromide	8,792 (12 %)
Ioversol	8,613 (11 %)
Sex	
Man	44,099 (58 %)
Woman	32,095 (42 %)
Patient provenience	
Outpatient	59,830 (79 %)
Inpatient	16,364 (21 %)
Premedication	
Without	73,166 (96 %)
With	3,028 (4.0 %)

¹ n (%); Median (IQR).

3.2. Anaphylaxis and clinical record review

Anaphylaxis occurred in 45 injections (0.06 %) in 45 different patients (0.16 %) due to ICM (Table 2). From the clinical records, it could be determined that all anaphylaxis due to ICM appeared within 30 min.

The risk factors for ADR and experience with ICM of anaphylaxis cases are shown in Table 3. Thirty-one patients (69 %) had no risk factors for ADRs, including four who received ICM for the first time and 14 (31 %) who developed anaphylaxis in spite of having previously used the same ICM without developing anaphylaxis. Twenty-seven patients with no risk factors for ADRs had a history of ICM use without ADRs. Only three patients (6.7 %) had a history of allergy-like reactions to ICM. Four patients (8.9 %) received oral steroid premedication before CE CT examinations: three because of a history of allergic-like reaction to ICM, and one because of bronchial asthma.

The incidence of anaphylaxis for each ICM was, in descending order: iomeprol (0.18 %), iopromide (0.06 %), iopamidol (0.03 %), iohexol (0.02 %), and ioversol (0.01 %). The multivariable regression analysis found that the use of iomeprol was more likely to result in anaphylaxis, compared with the other four ICMs (OR for iomeprol was 6.8 [95 % CI: 2.8–16.4] with iopamidol as a reference, $p < 0.001$). No significant differences in OR of anaphylaxis due to ICM were found for patients' age, sex, or premedication (Table 4).

4. Discussion

In this single-center retrospective study, anaphylaxis occurred in 45

Table 2

Characteristics of anaphylaxis cases.

Characteristics	n = 45 ¹
Age (years)	66 (48, 74)
Iodinated contrast media	
Iopamidol	6 (13 %)
Iohexol	3 (6.7 %)
Iomeprol	30 (67 %)
Iopromide	5 (11 %)
Ioversol	1 (2.2 %)
Sex	
Man	26 (58 %)
Woman	19 (42 %)
Patient provenience	
Outpatient	37 (82 %)
Inpatient	8 (18 %)
Premedication	4 (8.9 %)

¹ Median (IQR); n (%).**Table 3**

Risk factors for adverse reaction and experience with iodinated contrast media (ICM) of anaphylaxis cases.

Risk factors for adverse reaction	Experience with ICM				
	Overall (n = 45)	First time (n = 5)	Anaphylaxis with ICM use (n = 23)	Use of other ICM(s) (n = 6)	Past use of unknown ICM (n = 11) ¹
No	31	4	14	4	9
Drug rash caused by other than ICM	4	1	2	1	
Hay fever	4		3		1
Allergy-like reaction to ICM	3		2	1	
Adverse reaction to ICM (no data) ¹	1				1
Physiological reaction to ICM	1		1		
Hay fever and bronchial asthma	1		1		

ICM: iodinated contrast media.

¹ Information unavailable because examination(s) were performed at other hospitals.**Table 4**

Risk factors for anaphylaxis in contrast-enhanced CT by multivariable analysis.

Factors	No. of injections	Anaphylaxis ¹	Odds ratio ²	p-value
Iodinated contrast media				
Iopamidol	22,923	6 (0.03)	Reference	
Iohexol	18,793	3 (0.02)	0.6 (0.2, 2.4)	0.462
Iomeprol	17,073	30 (0.18)	6.8 (2.8, 16.4)	< 0.001
Iopromide	8,792	5 (0.06)	2.3 (0.7, 16.6)	0.117
Ioversol	8,613	1 (0.01)	0.4 (0.1, 3.7)	0.451
Sex				
Man	44,099	26 (0.06)	Reference	
Woman	32,095	19 (0.06)	1.0 (0.5, 1.8)	0.902
Patient provenience				
Outpatient	59,830	37 (0.06)	1.8 (0.6, 5.2)	0.266
Inpatient	16,364	8 (0.05)	Reference	
Age (years)				
15–40	4,552	5 (0.11)	2.1 (0.8, 5.4)	0.142
41–60	17,902	14 (0.08)	1.4 (0.7, 2.9)	0.304
61–80	45,380	22 (0.05)	Reference	
81≤	8,360	4 (0.05)	1.1 (0.4, 3.2)	0.854
Premedication				
Without	73,166	41 (0.06)	Reference	
With	3,028	4 (0.13)	2.7 (0.9, 7.7)	0.071

¹ Data in parentheses are percentages.² Data in parentheses are 95 % confidence intervals.

of 76,194 injections (0.06 %) and of 27,696 patients (0.16 %). More than half of the anaphylaxis cases had no risk factors for ADRs and had no ADRs on past ICM administration. There was a difference in the OR of anaphylaxis only among the five ICMs evaluated, and no significant differences in OR of anaphylaxis due to ICM were found for patients' age, sex, or premedication. While most ADRs due to ICM are mild and self-limiting and generally do not pose a major clinical problem, moderate and severe ADRs due to ICM can be life-threatening to patients and their clinical characteristics should be recognized.

The incidence of ICM-induced anaphylaxis in our study (0.06 %) was greater than the 0.014 % of severe ADR in the previous report [13]. This may be because both severe ADRs and moderate ADRs can be diagnosed as anaphylaxis [7,8]. In another previous report of anaphylaxis to ICM,

the incidence of anaphylaxis was 0.016 %, but it stated underreporting of adverse effects to the spontaneous reporting system as a limitation [14], which may explain the difference with our results.

Safe use of ICM requires recognizing risk factors for ADRs and avoidance or cautious use in patients with such risk factors, although our results suggested that even this may not prevent anaphylaxis. Our results showed that while a few patients who had allergic-like reactions to ICM in the past developed anaphylaxis, more than half of those who developed anaphylaxis did not have risk factors for ADRs, and that it is possible to have previously used ICM with mild or no ADRs and then experience anaphylaxis on the following examination. It has been known that repeated contrast use may increase the incidence of ADRs [12]. Radiologists, radiological technologists, and nurses responsible for CT examinations should be prepared for the occurrence of anaphylaxis in patients undergoing contrast examinations, regardless of the risk of ADRs or history of contrast media use.

The only factor, which was significantly associated with anaphylaxis, was the use of iomeprol as the type of ICM. A previous study reported a higher severity of ADRs with iomeprol [19], although the cause of this remains unknown. A meta-analysis study indicated that iomeprol showed the highest incidence of ADRs, but there was no significant difference in the OR of ADRs among nonionic ICMs [13]. There may be differences in the characteristics of the occurrence of ADRs and anaphylaxis, but the number of anaphylaxis cases in our study was small, and further studies with a large number of cases are needed.

There were no significant factors in the OR of anaphylaxis except among ICM used. Another study reported that ADRs may be more common in younger patients, but this was not the case in our study [20]. The OR of anaphylaxis was not significantly different in the premedication group. All patients in this study who received steroid premedication had one or more risk factors. The current study did not compare patients with risk factors who did not receive steroid premedication, so the effectiveness of steroid premedication could not be determined. Previous reports indicated that premedication can be expected to have a certain effect in suppressing ADRs [21–23], although our analysis of anaphylaxis did not confirm this effect.

ICM can cause various ADR symptoms, but anaphylaxis can lead to a bleak prognosis for the patient. The skin test has been known to be helpful in managing patients with severe ADR [24], and this may be done in patients with a history of ADR. It has also been recommended that patients with a history of severe ICM hypersensitivity avoid the same ICM [4,21,25]. Therefore, it may be helpful to consider the OR for anaphylaxis when choosing which ICM to use, whether for the first ICM or when changing ICM. There should be no need to choose an ICM with a higher OR.

There were several limitations to this study. First, this was a single-center retrospective study, which may limit the generalizability of the findings. Second, since anaphylaxis was infrequent in ICM, the power of statistical analysis may also be low. Third, the anaphylaxis risk analysis did not consider specific details of patient history, such as the number of adverse events experienced and previous administrations of contrast agents. Fourth, all anaphylaxis cases included in this analysis occurred within 30 min of ICM injection. It remains possible that there were unreported instances of delayed contrast-induced anaphylaxis. Fifth, patient backgrounds other than those analyzed in this study were not considered. Therefore, we could not evaluate the possibility that the occurrence of anaphylaxis may be influenced by medications for ongoing treatment other than steroids.

In conclusion, the overall incidence of anaphylaxis due to ICM was very low. It should be notified that more than half of anaphylaxis cases had no risk factors for ADRs and had no ADRs on past ICM administration, suggesting that recognizing risk factors for ADRs and avoiding ICMs or using them cautiously in patients with these risk factors are not sufficient precautions for their safety. ICM type was associated with a higher OR.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Yasuhiro Fukushima holds an endowed chair provided by Siemens Healthineers. The other authors have no conflict of interest to declare.

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