

Varied incidence of immediate adverse reactions to low-osmolar non-ionic iodide radiocontrast media used in computed tomography

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Summary

Background Low-osmolar non-ionic radiocontrast media (RCMs) are commonly used throughout hospitals. However, the incidence of immediate adverse drug reactions (ADRs) to various low-osmolar non-ionic RCMs is not well studied. We compared the incidence of immediate ADRs among different low-osmolar non-ionic RCMs used in computed tomography (CT).

Methods Severance Hospital has collected data for adverse reactions occurring in-hospital using an internally developed system. Using this data, we reviewed 1969 immediate ADRs from 286 087 RCM-contrasted CT examinations of 142 099 patients and compared the immediate ADRs of iobitridol, iohexol, iopamidol, and iopromide. We analysed the incidence of immediate ADRs to different RCMs, as well as the effect of single or multiple CT examinations per day.

Results Iopromide showed the highest incidence of immediate ADRs (1.03%) and was followed by iopamidol (0.67%), iohexol (0.64%), and iobitridol (0.34%). In cases of anaphylaxis, iopromide also showed the highest incidence (0.041%), followed by iopamidol (0.023%), iohexol (0.018%), and iobitridol (0.012%). Risk of immediate ADR due to multiple CT examinations (1.19%) was significantly higher than the risk due to a single CT examination (0.63%). Risk of anaphylaxis was also higher for multiple CT examinations (0.052%) than for a single CT examination (0.020%).

Conclusions and Clinical Relevance The incidence of immediate ADRs varied according to the low-osmolar non-ionic RCM used. Iopromide-induced immediate ADRs were more frequent, while iobitridol was associated with fewer immediate ADRs than other RCMs. Multiple CT examinations per day resulted in a higher incidence of immediate ADRs and anaphylaxis than a single CT examination. Clinicians should consider these risk differences of immediate ADRs when prescribing contrasted CT examinations.

Keywords anaphylaxis, immediate adverse drug reaction, non-ionic radiocontrast media

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Introduction

Radiocontrast media (RCMs) are utilized in many different imaging studies in hospitals. More than 70 million diagnostic radiographic examinations using RCMs are performed worldwide each year [1]. Since the introduction of non-ionic radiocontrast media, immediate adverse drug reactions (ADRs) have decreased [2]. However, immediate ADRs to RCMs continue to occur, and the prevalence of immediate ADRs caused by non-ionic RCMs has been reported to be between 0.2% and 2.7% [2–5].

Although assorted low-osmolar non-ionic RCMs have been used, it is not known whether the incidence of

immediate ADRs varies according to RCM type. As the chemical structures of various low-osmolar iodide RCMs are quite different, the incidence of immediate ADRs for each RCM might also differ. However, previous studies have not found significant differences in the incidence of immediate ADRs among different RCM products [6–10].

Recently, Gomi et al. prospectively studied the incidence of immediate ADRs among five different low-osmolar non-ionic RCMs in a large population (8931 patients) [5]. In the study, iomeprol and iopromide were associated with higher incidence rates of immediate ADRs compared to iopamidol, iohexol, and ioversol

(1.8%). Furthermore, Seong *et al.* reported a significantly higher proportional reporting ratio for whole adverse reactions to iopromide compared to the other six low-osmolar or iso-osmolar iodide RCMs using Korean national pharmacovigilance data [11]. However, their study did not reveal the incidence of immediate ADRs, as whole prescription cases of each RCM were not evaluated. As such, it is not known whether the risk of immediate ADR varies among RCMs, and additional verification is needed. Our hospital has used iobitridol, iohexol, iopamidol, and iopromide in contrast studies performed via computed tomography (CT). Therefore, we retrospectively evaluated the incidence rates of immediate ADRs caused by four different low-osmolar non-ionic RCMs used in contrasted CT examinations at a single institute.

Materials and methods

Severance Hospital is a tertiary care university hospital with 2496 licensed beds. Beginning in 2005, the hospital implemented a spontaneous reporting programme that allowed doctors, nurses, and paramedics to report adverse drug events (ADE). To address the problem of under-reporting in the spontaneous pharmacovigilance programme, the hospital's Allergy and Asthma Center examined the clinical data repository system (CDRS) regularly. The CDRS is an internally developed hospital information system that collects comprehensive data including orders, diagnostic codes, patient demographic information, laboratory results, medication profiles, nursing notes, and vital signs. Eventually, ADEs were also recorded using this system.

Using the spontaneous reporting programme and CDRS, 1969 immediate ADRs from 286 087 examinations of 142 099 patients who performed contrasted CT examinations between January 2006 and December 2010 were enrolled in this study, and their medical records were reviewed. Our hospital's ethical review board approved this study (4-2014-0725).

Immediate ADR was defined as an adverse reaction that occurred within 1 h after administration of an RCM. Immediate ADR included all allergic reactions and various non-specific reactions. Among the 1969 immediate ADRs, specific symptoms were recorded in 1910 ADRs. Based on these symptoms, anaphylaxis was diagnosed in specific cases. Diagnosis of anaphylaxis was assessed according to diagnostic criteria set forth in the 2011 World Allergy Organization Anaphylaxis Guidelines. Patients who had both skin-mucosal and respiratory symptoms, those who had both skin-mucosal involvement and persistent gastrointestinal symptoms, and those who had reduced blood pressure after contrast injections were regarded as experiencing anaphylaxis [12].

Possible risk factors for immediate ADR were also examined. Cases involving the following RCMs were considered (Table 1): iobitridol (Guerbet, Sulzbach, Germany), iohexol (GE healthcare, Amersham, UK), iopamidol (Bracco, Milan, Italy), and iopromide (Schering, Berlin, Germany). Cases were grouped according to the frequency of CT examinations per day (single CT, multiple CT). Single CT refers to one CT examination per day, while multiple CT refers to more than one CT examination per day. Patient age, gender, and body weight were also considered.

Statistical analysis

To elucidate differences in the incidences of immediate ADR and anaphylaxis according to the type of RCM and the type of CT, a chi-square analysis was performed. Additionally, to estimate the risk while excluding the effects of other variables, a logistic regression analysis was performed. Variables included age, gender, and body weight. Patients were divided into three groups according to age in order to determine differences in incidence according to age group (0–19 years, 20–50 years, > 51 years). *P* values of < 0.05 were considered to be statistically significant. All calculations were performed using SPSS version 20 (SPSS Inc., Chicago, IL).

Results

Demographic data and symptoms of immediate ADR

There were 1969 cases of immediate ADR (0.69%) among 286 087 cases in 142 099 patients who underwent contrasted CT examinations. The most frequent cases involved iopamidol (135 882), followed by iohexol (65 764), iopromide (51 685), and iobitridol (32 756; Table 2). There were 255 336 cases of single CT and 30 751 cases of multiple CT. Specific symptoms were reported in 1910 of 1969 immediate ADRs (97%). Rash (85.3%) and itching sensation (59.8%) were the most frequent symptoms, followed by nausea and vomiting (6.8%), dyspnoea (4.8%), dizziness (2.5%), general weakness (1.9%), chest discomfort (1.4%), oedema (1.2%), and hypotension (1.2%; Table 3). Among these immediate ADRs, 68 cases were classified as anaphylaxis (0.024%).

Comparison of incidences of immediate ADRs and anaphylaxis

Incidences of immediate ADRs and anaphylaxis were compared via chi-square analysis. On comparison of immediate ADRs, iopromide (1.03%) had the highest incidence of immediate ADRs by a significant margin

Table 1. Properties of four different low-osmolar non-ionic iodide radiocontrast media (RCMs)

	Iobitridol	Iopamidol	Iohexol	Iopromide
Formula	$C_{20}H_{28}I_3N_3O_9$	$C_{17}H_{22}I_3N_3O_8$	$C_{19}H_{26}I_3N_3O_9$	$C_{18}H_{24}I_3N_3O_8$
Molecular mass (g/mol)	835.16	777.08	821.14	791.11
Osmolarity (mOsm/kgH ₂ O)	695	614	680	610

Table 2. Demographic data

	Cases	Patients	Body weight (kg, m ± σ)	Age (year, m ± σ)
Types of RCMs				
Iobitridol	32 756	26 053	53.54 ± 21.16	41.53 ± 25.08
Iohexol	65 764	36 833	63.43 ± 11.38	54.73 ± 16.31
Iopamidol	135 882	87 532	64.26 ± 11.39	54.34 ± 15.78
Iopromide	51 685	20 024	64.75 ± 10.97	56.95 ± 12.91
Types of CT				
Single CT	255 336	138 684	62.08 ± 14.36	51.52 ± 18.52
Multiple CT	30 751	11 546	64.00 ± 12.43	56.82 ± 15.37
Gender				
Male	156 312	71 908	66.67 ± 15.38	51.76 ± 19.39
Female	129 775	70 191	57.33 ± 11.35	51.42 ± 17.55
Age				
0–19	12 073	9283	35.56 ± 22.90	10.04 ± 5.85
20–50	77 910	46 907	64.66 ± 12.75	37.43 ± 8.30
> 50	196 104	85 909	63.67 ± 10.58	63.82 ± 8.91
Total	286 087	142 099	62.09 ± 14.34	51.60 ± 18.50

Table 3. Top ten symptoms of immediate ADRs

Symptom	n	%
Rash	1630	85.3
Itching sensation	1143	59.8
Nausea and vomiting	130	6.8
Dyspnoea	91	4.8
Dizziness	48	2.5
Chest discomfort	27	1.4
Oedema	23	1.2
Hypotension	22	1.2
General weakness	19	1.9
Heating sensation	18	0.9
Total	1910	100.0

($P < 0.001$). Conversely, iobitridol (0.34%) had the lowest incidence of immediate ADRs by a significant margin ($P < 0.001$). Iohexol (0.64%) did not differ from iopamidol (0.67%; $P = 0.227$; Fig. 1a). Multiple CT (1.19%) showed a significantly higher incidence than single CT (0.63%; $P < 0.001$; Fig. 1b).

The comparison of anaphylaxis cases indicated that iopromide (0.041%) also had the highest incidence of anaphylaxis by a significant margin ($P = 0.013$, 0.034, 0.044). Iopamidol (0.023%), iohexol (0.018%), and

iobitridol (0.012%) did not significantly differ from each other ($P = 0.443$; Fig. 1c). Multiple CT (0.052%) also had a significantly higher incidence of anaphylaxis than single CT (0.020%; $P = 0.002$; Fig. 1d).

Risk estimation associated with immediate ADRs and anaphylaxis

Risk factors associated with immediate ADRs were analysed via logistic regression (Table 4). As compared with iobitridol, the odds ratio for iopromide was the highest (OR: 2.718, CI: 2.167–3.409, followed by iopamidol (OR 1.592, CI: 1.281–1.978) and iohexol (OR 1.362, CI: 1.081–1.717). The OR for iopromide was significantly higher than for the other three RCMs, and all three RCMs had significantly higher ORs for immediate ADR than iobitridol. As compared with single CT, the OR for multiple CT (2.129, CI: 1.890–2.397) was significantly higher ($P < 0.001$). The OR for females (OR 1.505, CI: 1.355–1.672) was also significantly higher than for males ($P < 0.001$). When compared with patients < 20 years old, the OR for those 20–50 years old (OR: 1.548, CI: 1.012–2.369) was significantly higher; however, those older than 50 years did not significantly differ from the other two groups.

Risk factors associated with anaphylaxis were also analysed via logistic regression (Table 5). As compared with iobitridol, the OR for iopromide was the highest (OR: 6.238, CI: 1.322–29.443), followed by iopamidol (OR: 3.115, CI: 0.683–14.200) and iohexol (OR: 1.913, CI: 0.392–9.646). Only iopromide significantly differed from iobitridol ($P = 0.021$). As compared with single CT, the OR of multiple CT (OR: 3.256, CI: 1.810–5.858) was significantly higher ($P < 0.001$). Gender did not have a significant effect on the incidence of anaphylaxis ($P = 0.142$). Age groups did not significantly differ.

Discussion

This study was designed to identify the differences in the incidences of immediate ADRs between different low-osmolar non-ionic iodide RCMs, which have different chemical structures. Our results demonstrated that iopromide was associated with more immediate ADRs than the other three RCMs. In addition, iobitridol was associated with a relatively lower risk of adverse reactions than the others. Previous studies demonstrated no

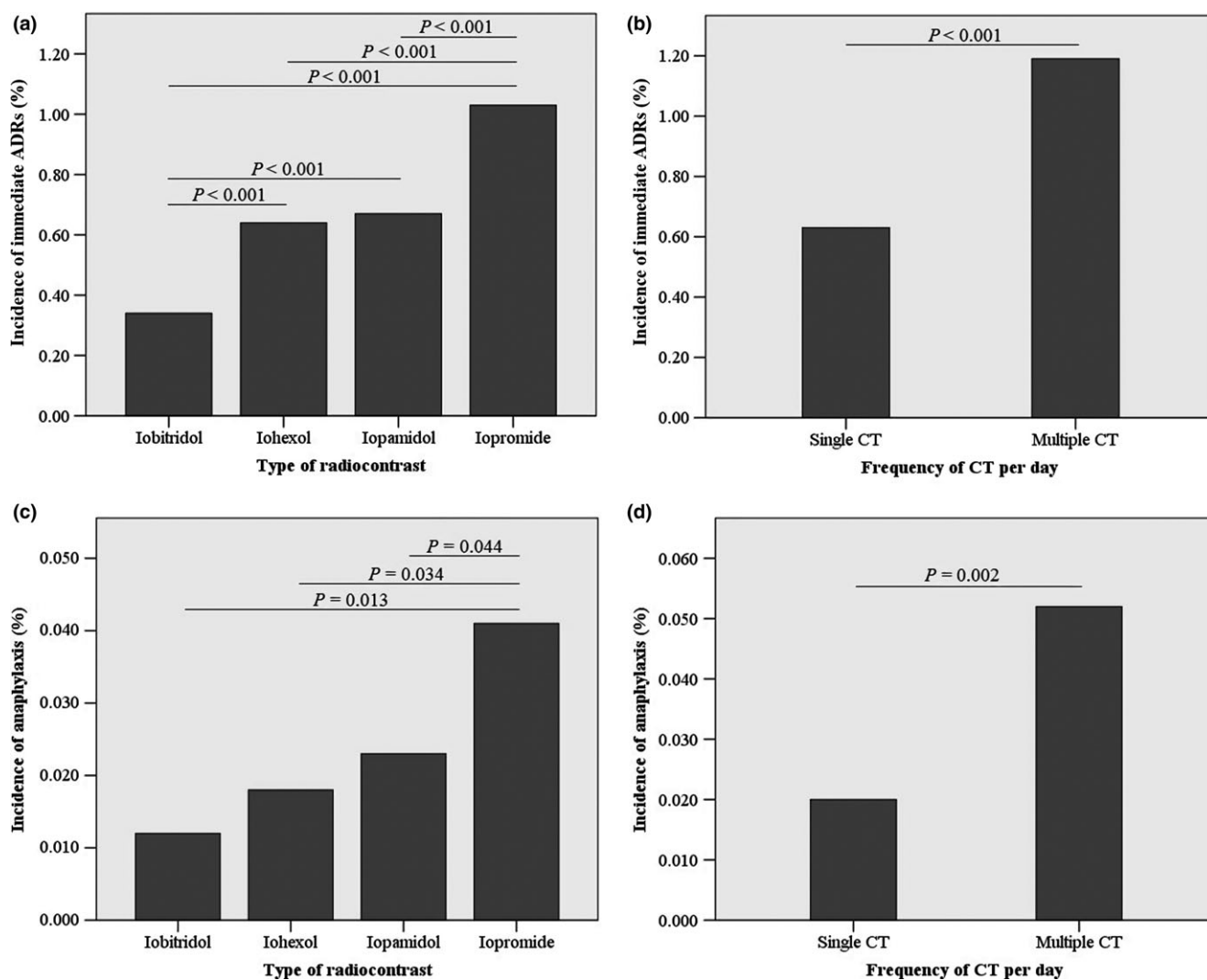


Fig. 1. Comparison of immediate ADR incidences according to the type of RCM (a) and frequency of CT examinations per day (b). Comparison of anaphylaxis incidences according to the type of RCM (c) and frequency of CT examinations per day (d). *P* values were calculated via chi-square analysis.

significant differences in the incidence of adverse reactions between RCMs [6–10]. However, these previous studies involved small sample sizes. Recently, Gomi, et al. conducted a prospective study in a large population, unlike previous studies. They reported that iopromide had a higher incidence of adverse reactions compared to other RCM products (including iopamidol, iohexol, and ioversol) [5]. Additionally, Seong et al. evaluated 6624 adverse reactions to low-osmolar RCMs. As they did not evaluate the total prescription number of the studied RCMs, they considered the proportional reporting ratio, rather than the incidence of adverse reactions. They reported a higher proportional reporting ratio for iopromide compared to the other RCMs [11].

Risk differences according to type of RCM were reproduced in our study. We do not know the reasons for the differences between our results and the results

from previous research. However, the discrepancy in the results might be due to ethnicity, as our enrolled patients were all Korean. Previous studies that showed different incidences of immediate ADRs to RCMs used data from Korean and Japanese patients; however, the studies reporting no differences in the incidences were conducted in European countries or the USA.

The pathophysiology of adverse reactions to RCMs is poorly understood. Although an IgE-mediated mechanism [13] and the participation of T cells have been reported [1], the major factors that contribute to immediate ADRs involve the direct chemotoxic effects and the physicochemical properties of RCMs [14]. The RCMs in this study were similar in viscosity, hydrophilicity, ion content, and pH level. Generally, low-osmolar agents cause fewer adverse reactions [15]. However, in this study, iopromide, which has a relatively low

Table 4. Factor analysis of immediate ADR cases via logistic regression

	Total cases	Immediate ADRs	Immediate ADRs (%)	Odds Ratio (95% CI)	P-value
Types of RCMs					
Iobitridol	32 756	111	0.34		
Iohexol	65 764	418	0.64	1.362 (1.081–1.717)	0.009
Iopamidol	135 882	906	0.67	1.592 (1.281–1.978)	< 0.001
Iopromide	51 685	534	1.03	2.718 (2.167–3.409)	< 0.001
Types of CT					
Single CT	255 336	1602	0.63		
Multiple CT	30 751	367	1.19	2.129 (1.890–2.397)	< 0.001
Gender					
Male	156 312	956	0.61		
Female	129 775	1013	0.78	1.505 (1.355–1.672)	< 0.001
Age (year)					
0–19	12 073	27	0.22		
20–50	77 910	678	0.87	1.548 (1.012–2.369)	0.044
> 50	196 104	1264	0.64	1.100 (0.722–1.676)	0.656
Body weight				1.017 (1.013–1.022)	< 0.001

Table 5. Factor analysis of anaphylaxis cases via logistic regression

	Total cases	Anaphylaxis	Anaphylaxis (%)	Odds Ratio (95% CI)	P-value
Types of RCMs					
Iobitridol	32 756	4	0.012		
Iohexol	65 764	12	0.018	1.944 (0.392–9.646)	0.416
Iopamidol	135 882	31	0.023	3.115 (0.683–14.200)	0.142
Iopromide	51 685	21	0.041	6.238 (1.322–29.443)	0.021
Types of CT					
Single CT	255 336	52	0.020		
Multiple CT	30 751	16	0.052	3.256 (1.810–5.858)	< 0.001
Gender					
Male	156 312	34	0.022		
Female	129 775	34	0.026	1.533 (0.866–2.713)	0.142
Age (year)					
0–19	12 073	1	0.008		
20–50	77 910	25	0.032	0.987 (0.114–8.546)	0.990
> 50	196 104	42	0.021	0.670 (0.079–5.663)	0.713
Body weight				1.011 (0.987–1.035)	0.390

osmolality (containing 300 mg i/mL and an osmolality of 610 mOsmol/kgH₂O), was associated with higher incidence rates of immediate ADRs (Table 1). On the other hand, iobitridol has a relatively high osmolality (300 mg i/mL and an osmolality of 695 mOsmol/kg) and yet was associated with a lower incidence rate of immediate ADRs. These results suggest that this range of osmolality may be not critical for causing immediate ADRs. Differences in the incidence of adverse reactions between low-osmolar non-ionic RCMs might be associated with the formula and their chemical structure [16]. Our results may suggest that certain RCMs are more likely to cause an immediate ADR, and this specificity

should be considered before re-exposing RCM-allergic patients to specific RCMs.

Premedication with corticosteroid and antihistamine has been recommended to prevent recurrent immediate ADRs in patients with a history of ADRs to RCMs [17]. However, breakthrough events were also frequently reported even in patients who were premedicated [18–20]. Given these breakthrough events, patients who have a history of an immediate ADR may benefit from skin prick/intradermal tests to select a safe RCM [21]. However, these tests cannot predict all immediate ADRs. Considering the results of our study, it would be prudent to choose RCMs based on the risk burden of immediate ADRs.

The dose effect of RCMs was also analysed. A higher dose of RCM has been known to be a risk factor for immediate ADR [22]. This tendency was reproduced in this study. Multiple CT cases, which use more RCMs, showed higher incidence rates of immediate ADRs and anaphylaxis than single CT cases. This result may suggest the necessity of a sufficient intermission between CT examinations for the safety of the patient. However, considering the possibility of sensitization to RCMs from previous exposure, further studies may be required to determine an adequate intermission period between RCM-contrasted CT examinations.

The incidence of immediate ADRs appears to be the highest for 20- to 50-year-old patients. This result was similar to previous studies [11, 23]. However, older patients are often unable to withstand adverse reactions [23]. Therefore, older patients need to be observed carefully. In cases of gender, previous studies mentioned female sex as a risk factor for adverse reaction to RCMs [24, 25], and this study yielded similar results. However, the mechanisms explaining the observed gender difference are not well understood.

This study was based on a spontaneous and active pharmacovigilance system. A spontaneous reporting system is very useful for finding trends in adverse reactions, and it can collect data from various sources; however, it also has limitations, including under-reporting and an unknown denominator for calculating incidence [26]. An active surveillance

programme can supplement the limitations of a spontaneous reporting system [27], and we actively searched suspected immediate ADR cases using the CDRS. The electronic medical charts of suspected patients were also reviewed and enrolled in this study. In summary, the total incidence rate of immediate ADRs was 0.816%. As the incidence of adverse reactions is known to range between 0.2% and 2.7% [2–5], these results regarding immediate ADR incidence are considered both accurate and meaningful.

Conclusion

The incidence rates of immediate ADRs vary according to the type of low-osmolar non-ionic RCM. Iopromide was associated with a higher incidence of immediate ADRs than other RCMs, and iobitridol was associated with a lower incidence of immediate ADRs. Furthermore, the administration of multiple contrasted CT examinations per day was associated with a higher incidence of immediate ADRs. Consequently, clinicians should consider these risk differences of immediate ADR when prescribing contrasted CT examinations.

Conflict of interest

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