

Differences in Adverse Reactions Among Iodinated Contrast Media: Analysis of the KAERS Database



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What is already known about this topic? Because the chemical properties of iodinated contrast media (ICM) are different, the incidence of adverse drug reactions (ADRs) might also depend on the ICM used. However, the difference in the frequency of ADRs according to the total usage cases is unknown.

What does this article add to our knowledge? On comparing the frequencies of ADRs after the use of 7 different ICM in relation to their total usage cases, we found that iomeprol resulted in the highest incidence of ADRs and serious ADRs.

How does this study impact current management guidelines? Our results indicated the differences in ADRs for total usage cases among 7 ICM. A better understanding of the differences in ADRs for each ICM is essential to select the optimum ICM for patient safety.

BACKGROUND: The various adverse drug reactions (ADRs) arise from different types of iodinated contrast media (ICM). **OBJECTIVE:** Thus, we investigated the occurrence rate and types of ADRs according to the total usage cases of the 7 most common ICM. **METHODS:** We retrospectively reviewed 74,242 causal ADRs caused by ICM from the Korea Adverse Event Reporting System database between January 2014 and December 2016. The 11,712,796 total usage cases that represent all administrations of ICM reported from individual medical institutions were received from the Health Insurance Review and Assessment Service. A proportionality test was used to examine the differences in the frequency ratio of causal ADRs to total usage cases. **RESULTS:** Immediate hypersensitivity (44,467 cases, 88.56%) occurred more frequently than delayed hypersensitivity (5,725 cases, 11.4%; $P < .001$). The overall occurrence rate of causal ADRs and serious ADRs considering total usage cases was 0.37%

and 0.02%, respectively ($P < .001$). The ICM most commonly resulting in ADRs were iomeprol (0.7%) and iopromide (0.59%). The serious ADRs were most common for iomeprol (0.05%). When ADRs were classified according to the system organ class, “skin and appendages disorders” (47,065 cases, 63.4%) occurred most common. Iodixanol resulted in the highest frequency of “urinary system disorders.” **CONCLUSIONS:** By comparison of the ADRs considering total usage cases, the incidence and classification of ADRs were different for each contrast medium. A prospective study is needed because the differences in these 7 major contrast media may assist in the selection of ICM tailored for each patient. © 2019 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2019;7:2205-11)

Key words: Contrast media; Adverse drug reaction; Hypersensitivity; System organ class; Computed tomography

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INTRODUCTION

Computed tomography (CT) often involves the use of intravenous contrast media to improve imaging resolution between tissues. Globally, more than 70 million diagnostic radiographic studies use radiocontrast media each year. Owing to the recent increases in the use of enhanced CT procedures, the frequency of use of low-osmolar nonionic contrast media has gradually increased.¹ Iodinated contrast media (ICM) can generally be classified into ionic (high-osmolar) and nonionic (low and iso-osmolar) agents; iohexol, iobitridol, iodixanol, iomeprol, iopamidol, iopromide, and ioversol are the most commonly used iodinated nonionic contrast media.

Although ICM are known to be relatively safe, the occurrence of mild and severe adverse drug reactions (ADRs) after the use of nonionic low-osmolar contrast media is reported to be 3.1% and 0.04%, respectively.²⁻⁴ Some studies reported that the incidence

Abbreviations used

ADR- Adverse drug reaction
 CT- Computed tomography
 HIRA- Health Insurance Review & Assessment Service
 ICM- Iodinated contrast media
 KAERS- Korea Adverse Event Reporting System
 SOC- System organ class
 WHO- World Health Organization
 WHO-ART- World Health Organization-Adverse Reaction Terminology

of immediate ADRs was reduced remarkably from the range 3.8% to 12.7% to the range 0.2% to 3.1% as the use of low-osmolar nonionic contrast media replaced the use of high-osmolar ionic contrast media^{4,5}; however, immediate ADRs to ICM have continued to occur.⁶⁻⁸

Various studies have reported the occurrence of ADRs after ICM use; however, it is not known whether the incidence of ADRs is affected by the type of ICM. Recently, a prospective study with a large population (8931 patients) reported that iomeprol and iopromide had a higher incidence of immediate ADRs among various nonionic low-osmolar ICM.⁸ Some studies have also indicated that iopromide resulted in a high frequency of total and immediate ADRs among commonly used ICM.^{9,10} However, these studies have limitations, such as not including the total national usage and the difficulty in identifying the real incidence of ADRs for each ICM.

Because the chemical structures and properties of ICM are different, the incidence of immediate ADRs might also depend on the ICM used. The knowledge of the occurrence rate and the severity of ADRs related to each individual ICM is essential to ensure patient safety. Therefore, we retrospectively investigated the difference in the occurrence rate and the types of ADRs according to the total usage cases of the 7 most common ICM.

METHODS

Data source

We retrospectively reviewed all ADRs reported to the Korea Adverse Event Reporting System (KAERS) between January 2014 and December 2016. The KAERS database, which is effectively a spontaneous ADR reporting system, was established by the Korea Institute of Drug Safety and Risk Management in 2012 and comprises 27 regional pharmacovigilance centers.^{11,12} Each case includes information on the patient's age, sex, administration date of contrast media, type and symptom of ADRs, and patient's outcomes without individual identification. "Considering that multiple ADR symptoms may be observed in each patient, we analyzed the hypersensitivity and system organ class (SOC) classification on the basis of all the symptoms (74,242 symptoms) that occurred after ICM injections. ADRs and serious ADRs were analyzed according to the number of cases (43,623 cases); that is, the number of patients with ADR after administration of each ICM."

ADRs involving the following 7 nonionic ICM were considered (Table 1^{13,14}): iohexol, iopamidol, iopromide, iomeprol, iobitridol, ioversol, and iodixanol.

The total usage cases that represent all administrations of ICM regardless of ADR were used as the denominator and received from the Health Insurance Review & Assessment Service (HIRA) in Korea

for the same period of ADRs reported from KAERS. In Korea, 97.0% of the population is obliged to register in the Korea National Health Insurance Program. Therefore, the total usage cases of ICM for enhanced CT from HIRA data are representative, because almost all CT examinations are covered by health insurance. These data were provided by medical institutions, such as advanced general hospitals, general hospitals, hospitals, and clinics. Because KAERS data contained almost all the spontaneous ADRs reports from general hospitals, we considered the total usage cases of ICM in general hospitals and advanced general hospitals, including 27 regional pharmacovigilance centers; this accounted for more than 90% of the total usage cases in all medical institutions. This study was approved by the institutional review board of the appropriate ethics committee.

Assessment of ADRs

The ADRs of ICM were searched for by their Anatomical Therapeutic Chemical classification¹⁵ and were coded using the World Health Organization-Adverse Reaction Terminology (WHO-ART) coding dictionary.¹⁶ The SOCs were also codified using the WHO-ART. The results of the causality assessment for each ADR by the WHO criteria were recorded in the database by the reporters.

The serious ADRs included the following classifications: (1) death; (2) life-threatening event; (3) causing or prolongation of hospitalization; (4) causing persistent significant disability or incapacity; (5) resulting in a congenital anomaly or birth defect; and (6) others of medical significance. In addition, serious ADRs were represented by WHO-ART critical terms, such as anaphylactic shock and angioedema. The WHO causality assessment tool was used in the reported ADRs to confirm the relationship between the suspected drug and the adverse reactions. There were 6 categories for the evaluation of the causal relationship: (1) certain, (2) probable, (3) possible, (4) unlikely, (5) conditional or unclassified, or (6) unassessable/unclassifiable. From these, we selected only 3 categories as causal ADRs: certain, probable, and possible.

Hypersensitivity to ICM was classified into immediate and delayed types. The immediate hypersensitivity, occurring within 1 hour of ICM exposure, comprised angioedema, flushing, anaphylaxis, hypotension, urticaria, itching, and bronchospasm. The delayed hypersensitivity, occurring more than 1 hour after ICM administration, included erythema, maculopapular rash, drug reaction with eosinophilia and systemic symptoms, Stevens-Johnson syndrome, purpura, cytopenia, fixed eruption, and others (containing exanthema, eruption, rash, and dermatitis).

Statistical analysis

A multiple proportion comparison test was used to compare the differences in the rates of ADRs by sex, age, and year. A proportionality test was used to examine the differences in the frequency ratio of causal ADRs to total usage cases. All statistical analyses were computed in R 3.4.1, and all values of *P* less than .05 were considered statistically significant.

RESULTS

Characteristics of cases of ADRs

A total of 74,242 symptoms and 43,623 cases of causal ADRs were reported. There were 20,439 (46.9%) men, 22,676 (52.0%) women, and 508 (1.2%) patients for whom sex information was unavailable. The patients had a mean age of 53.9 ± 14.0 years and were most likely to be in the age group of 51 to 60 years (31.0%). The number of cases of ADRs for all

TABLE I. Comparison of properties of commonly used nonionic ICM*

ICM	Concentration (mg/mL)	Viscosity (cP at 37°C)	Osmolarity (mOsm/kgH ₂ O)
Nonionic monomer			
Iohexol (Omnipaque)	140-350	1.5-10.4	322-844
Iopamidol (Isovue)	200-370	2.0-8.6	413-796
Iopromide (Ultravist)	150-370	1.5-9.5	328-774
Iomeprol (Iomeron)	300-400	4.1-10.5	520-750
Iobitridol (Xenetix)	250-350	4.0-10.0	585-915
Ioversol (Optiray)	160-350	1.9-9.0	355-792
Nonionic dimer			
Iodixanol (Visipaque)	270-320	6.3-11.8	290

Nonionic monomer, low-osmolar; nonionic dimer, iso-osmolar; concentration, organic iodine (mg) content per milliliter.

*Adapted from Pannu et al¹³ and Solomon.¹⁴

TABLE II. Characteristics of reported ADRs cases

Characteristics	Case no. (N = 43,623)	%	P value
Sex			
Men	20,439	46.9	<.001
Women	22,676	52.0	
Unknown	508	1.2	
Age (y), mean ± SD	53.95 ± 14.0		
0-10	219	0.5	<.001
11-20	667	1.5	
21-30	1,777	4.1	
31-40	3,918	9.0	
41-50	8,464	19.4	
51-60	13,532	31.0	
61-70	9,093	20.8	
71-80	4,106	9.4	
81-90	555	1.3	
91-100	20	0.0	
Unknown	1,272	2.9	
Year			
2014	12,937	29.7	<.001
2015	14,027	32.1	
2016	16,659	38.2	

ICM was 12,937 (29.7%), 14,027 (32.1%), and 16,659 (38.2%) in 2014, 2015, and 2016, respectively. The reported ADRs increased steadily between 2014 and 2016 (Table II).

Prevalence of hypersensitivity by contrast media

The prevalence of immediate-type hypersensitivity (88.6%) was significantly higher than that for the delayed type (11.4%; Figure 1, A). For each ICM, immediate responses of hypersensitivity were greater than the delayed response hypersensitivity (Figure 1, B). The symptoms predominantly associated with immediate hypersensitivity reactions were urticaria (47.3%) and itching (43.9%), which mostly involved the skin (Figure 1, C). The delayed hypersensitivity reactions mainly involved maculopapular rashes (88.0%; Figure 1, D).

Frequency of causal ADRs to the total usage cases

Of the 11,712,796 total usage cases of ICM, iohexol (3,816,072 [32.6%]) resulted in the highest number of usage,

followed by iopamidol (2,333,794 [19.9%]) and ioversol (1,592,523 [13.6%]), whereas the iodixanol resulted in the lowest number of usage (679,667 [5.8%]). The overall number of ADRs for the total usage cases was 43,623 (0.37%), and the overall number of serious ADRs was 2,409 (0.02%). In the comparison of the various ICM, the occurrence rate of causal ADRs for the total usage cases was as follows: 0.70% for iomeprol, 0.59% for iopromide, 0.55% for iobitridol, 0.30% for iopamidol, 0.27% for iodixanol, 0.24% for iohexol, and 0.23% for ioversol ($P < .001$). The prevalence of serious ADRs was highest in iomeprol (0.05%), iopromide (0.03%), and iodixanol (0.03%; $P < .001$). Among the serious ADRs, iopromide was found to be the most common cause of prolongation of hospitalization (136 [0.01%]) and resulted in 10 (0.001%) of the 14 deaths ($P < .001$). The other 4 deaths were caused by ioversol. Iomeprol resulted in the highest number of life-threatening ADRs (127 [0.012%]) and other ADRs of medical significance (340 [0.033%]; $P < .001$). Furthermore, iodixanol was found to have the highest ratio of serious ADRs to ADRs (0.12), and iobitridol was found to have the lowest (0.04; $P < .001$; Table III; Figure 2).

Safety profiles of ICM by SOC

The most frequently involved SOC of the total ADRs was “skin and appendages disorders” (63.4%), followed by “gastrointestinal system disorders” (13.7%) and “respiratory system disorders” (8%; $P < .001$). There was a statistically significant difference in the prevalence of ADRs by SOC. The ICM that most commonly induced the incidence of ADRs of “skin and appendages disorders,” “gastrointestinal system disorders,” and “respiratory system disorders” were iodixanol (67.9%), iomeprol (20.9%), and iomeprol (13.7%), respectively ($P < .001$). Iodixanol resulted in the highest incidence of “urinary system disorders” (0.8%; $P < .001$). For iomeprol, the percentage of ADRs of “gastrointestinal system disorders,” “respiratory system disorders,” “central and peripheral nervous system disorders,” “vision disorders,” and “application site disorders” was higher than that induced by other ICM ($P < .001$); iodixanol induced the highest percentage of ADRs in the category of “skin and appendages disorders,” “body as a whole general disorders,” “cardiovascular disorders,” “heart rate and rhythm disorders,” and “urinary system disorders” ($P < .001$); for iopromide, the percentage of ADRs was the highest in the SOC of “vascular disorders” ($P < .001$; Table IV; Figure 3).

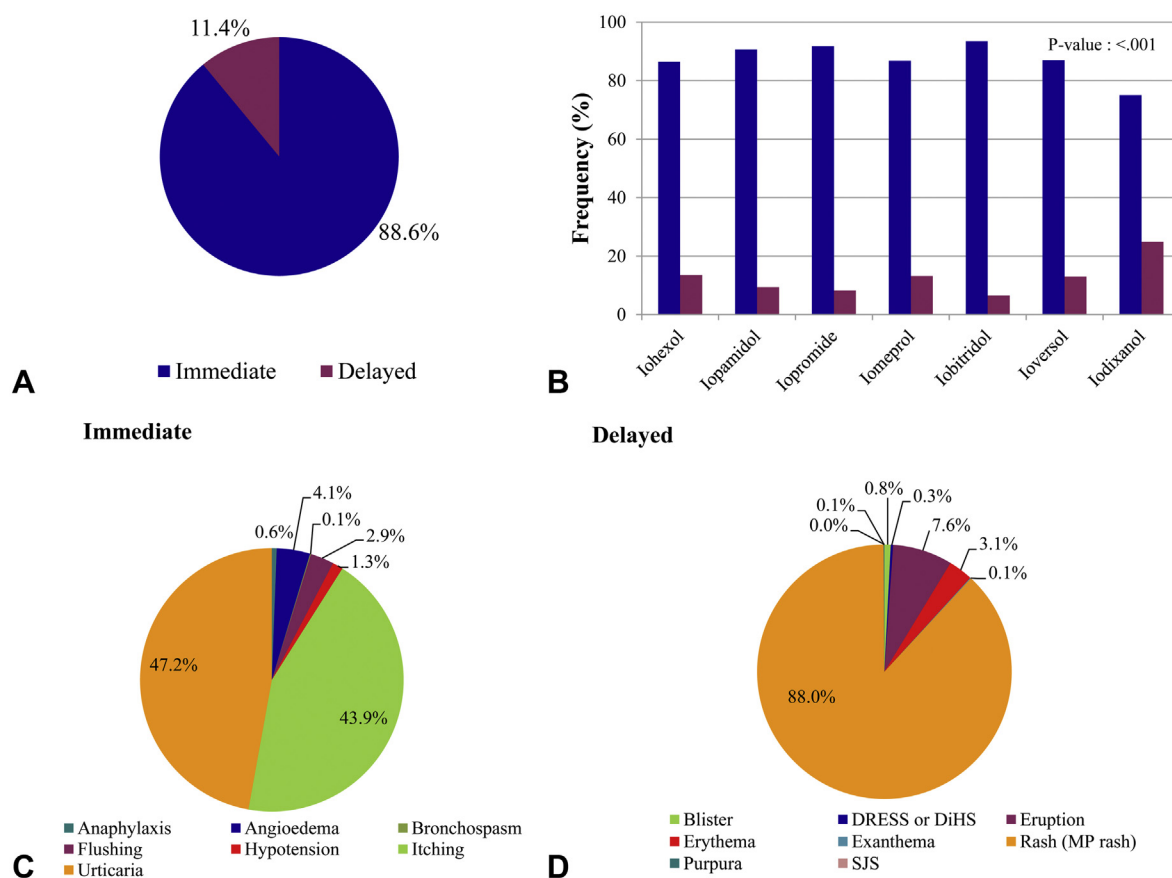


FIGURE 1. The frequency of hypersensitivity reactions for each ICM. **A**, In the total hypersensitivities, the incidence of immediate type was greater than that of delayed type. **B**, The incidence for each individual ICM. **C** and **D**, The classification of hypersensitivity reactions revealed “urticaria” and “rash (MP rash)” as the most common symptoms, respectively. *DiHS*, Drug-induced hypersensitivity syndrome; *DRESS*, drug reaction with eosinophilia and systemic symptoms; *MP*, maculopapular; *SJS*, Stevens-Johnson syndrome.

DISCUSSION

This study is the first national survey to compare the frequencies of ADRs after the use of 7 different ICM (6 different low-osmolar contrast media and 1 iso-osmolar contrast medium) in relation to their total usage cases in Korea. Our results demonstrated that immediate hypersensitivity associated with ICM administration occurred more frequently than delayed hypersensitivity and that iomeprol resulted in the highest incidence of ADRs and serious ADRs. This study reported the differences in the ADR profiles of ICM by SOC, with “urinary system disorders” most frequently reported for iodixanol.

Some studies have reported that elderly patients were more prone to serious reactions to ICM.^{17,18} Analysis of data in the KAERS database showed that patients in the age group of 51 to 60 years were most likely to experience ADRs overall, followed by those aged 41 to 50 and 61 to 70 years, similar to the reports of Katayama et al.² Hence, older patients require more careful monitoring. Some studies have indicated that the risk of development of severe anaphylactic reactions was higher in women,^{19,20} but this was not found in our study. We also evaluated the number of ADRs per year and found a steady increase, most likely a result of the steadily increasing use of enhanced CT and angiography with ICM usage.

Hypersensitivity to ICM used in CT is estimated to occur in between 0.3% and 3% of patients.^{5,21,22} A previous study of a National Coordination Centre for the Pharmacovigilance Programme of India (NCC-PvPI) reported that acute and delayed hypersensitivity reactions occurred in 66.7% and 1.1% of patients with ADRs to ICM, respectively.²³ We also analyzed the immediate and/or delayed distribution of each ICM and found a higher incidence of immediate hypersensitivity (88.6%) than that of delayed hypersensitivity (11.4%) for all ICM. Of the immediate-type hypersensitivities, urticaria (47.2%) and itching (44.0%) were predominant; the incidence of anaphylaxis was 0.6%. In the delayed-type hypersensitivities, maculopapular rash (88.0%) was commonly represented among the skin reactions. This result was similar to that of other studies, which revealed that skin reactions occurred more frequently in delayed hypersensitivity and that maculopapular rash occurred in more than 50% of patients.²⁴

The ratios of ADRs and serious ADRs to the total usage cases were 0.37% and 0.02%, respectively, in our study, which were lower than those reported previously (3.13% and 0.04%, respectively).² This discrepancy in the results suggested that the total usage cases of ICM have increased more rapidly than the increase in ADRs. Another study reported a rate of 0.82% of total ADRs for patients receiving ICM in a hospital.²⁵

TABLE III. Frequency of ADRs in 11,712,796 cases (administrations)

ADR	iohexol	iopamidol	iopromide	ioimeprol	iobitridol	ioversol	iodixanol	Total	P value
Total usage	3,816,072 (32.6)	2,333,794 (19.9)	1,310,393 (11.2)	1,042,096 (8.9)	938,251 (8.0)	1,592,523 (13.6)	679,667 (5.8)	11,712,796	<.001
ADR (%)	9,041 (0.24)	8,853 (0.30)	7,734 (0.59)	7,334 (0.70)	5,128 (0.55)	3,725 (0.23)	1,808 (0.27)	43,623 (0.37)	<.001
Serious ADR (%)	454 (0.01)	444 (0.02)	418 (0.03)	479 (0.05)	208 (0.02)	181 (0.01)	225 (0.03)	2,409 (0.02)	<.001
Hospitalization (%)	64 (0.002)	130 (0.006)	136 (0.010)	31 (0.003)	64 (0.007)	37 (0.002)	53 (0.008)	515 (0.004)	<.001
Life-threatening (%)	72 (0.002)	72 (0.003)	32 (0.002)	127 (0.012)	49 (0.005)	39 (0.002)	36 (0.005)	427 (0.004)	<.001
Death (%)	0	0	10 (0.001)	0	0	4 (0.000)	0	14 (0.0001)	<.001
Congenital anomaly (%)	4 (0.000)	2 (0.000)	1 (0.000)	2 (0.000)	1 (0.000)	0	0	10 (0.000)	0.736
Other medical Significance (%)	322 (0.008)	270 (0.012)	272 (0.021)	340 (0.033)	97 (0.010)	112 (0.007)	144 (0.021)	1557 (0.013)	<.001
Serious ADR/ADR	0.05	0.05	0.05	0.06	0.04	0.05	0.12	0.06	<.001

Values are n (%).

Other medical significance, medically important situations such as drug dependence, abuse, and blood disorder.

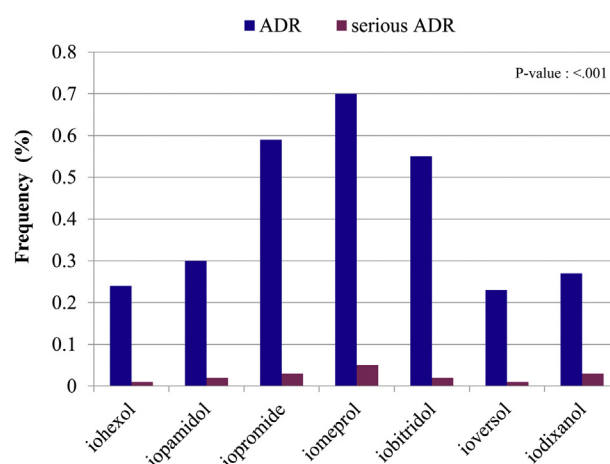


FIGURE 2. The comparison of ADRs for each individual ICM according to the total usage cases.

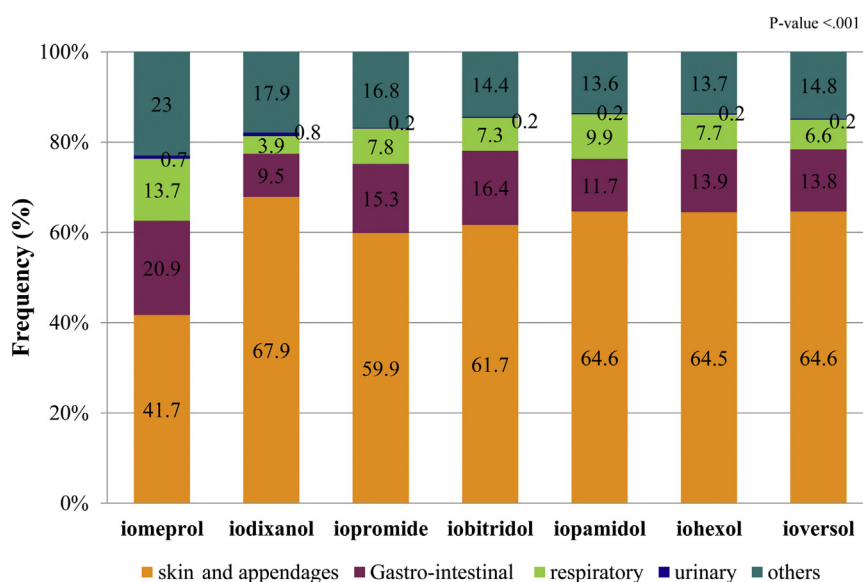
Potentially, inpatients with underlying diseases, especially cardiac diseases, have more comorbidities and a higher risk of the occurrence of ADRs.^{2,26}

The incidence of ADRs for individual ICM has been compared previously. Iomeprol resulted in a higher frequency of ADRs than did other ICM, including iohexol, iopamidol, iopromide, or ioversol.⁸ Furthermore, iopromide was most often associated with ADRs, followed by iohexol, when considering the proportional reporting ratio.⁹ Another study through the in-hospital reporting system in a single tertiary medical center also showed that iopromide-induced immediate ADRs were more frequent than those induced by the other 3 ICMs, which are iobitridol, iopamidol, and iohexol.¹⁰ Unlike previous studies, our study evaluated national total usage, and iohexol was the most commonly used, accounting for approximately one-third of all uses (32.58%), and then followed by iopamidol (19.92%). Iomeprol resulted in the highest incidence of ADRs (0.7%) and serious ADRs (0.05%) although it was the fifth most common ICM used. Of the 14 deaths, iopromide was responsible for 10 cases; therefore, we speculate that iopromide may have a hemodynamic effect, similar to a previous study that reported that iopromide resulted in a significant transient rise in heart rate and decrease in blood pressure under general anesthesia.²⁷ Further studies may be required to evaluate the effect of iopromide in patients with cardiac problem.

When ADRs were analyzed by SOC, “skin and appendage disorders” was the most common ADR overall. However, iodixanol, which was the only nonionic iso-osmolar dimer, resulted in a significantly higher number of “urinary system disorders” than did other ICM. Until now, various studies have compared the incidence of contrast-induced nephropathy after iodixanol and low-osmolar contrast media. Some studies reported that iodixanol had lower rates of contrast-induced nephropathy than did low-osmolar contrast media.^{28,29} In other studies, iodixanol resulted in the highest frequency of “urinary system disorders”; the reason for this was that iodixanol was used more frequently by patients with underlying renal diseases, as recommended in some guidelines.⁹ One possible explanation is that iodixanol had the highest viscosity among the 7 ICM owing to its dimer structure.²⁹

TABLE IV. Symptoms and signs of ADRs according to organ system in 74,242 patients

Organ system	Iomeprol (n = 8,254)	Iodixanol (n = 3,086)	Iopromide (n = 13,227)	Iobitridol (n = 8,791)	Iopamidol (n = 14,589)	Iohexol (n = 15,098)	Ioversol (n = 6,198)	Total (n = 74,242)	P value
Skin and appendages	41.7	67.9	59.9	61.7	64.6	64.5	64.6	63.4	<.001
Gastrointestinal system	20.9	9.5	15.3	16.4	11.7	13.9	13.8	13.7	<.001
Respiratory system	13.7	3.9	7.8	7.3	9.9	7.7	6.6	8.0	<.001
Body as a whole—general	8.8	10.1	6.4	5.5	4.8	5.2	4.8	5.6	<.001
Central and peripheral nervous system	7.6	3.2	5.2	5.5	5.2	4.9	6.0	5.1	<.001
Vascular (extracardiac)	1.9	1.9	2.1	0.9	1.3	0.8	1.5	1.3	<.001
Cardiovascular	1.4	1.7	1.0	0.9	0.7	0.8	0.8	0.9	<.001
Vision	1.5	0.2	0.7	0.7	0.8	0.7	0.8	0.8	<.001
Heart rate and rhythm	0.5	0.7	0.3	0.3	0.3	0.3	0.3	0.3	0.003
Application site	0.8	0.1	0.2	0.2	0.2	0.3	0.2	0.3	<.001
Urinary system	0.7	0.8	0.2	0.2	0.2	0.2	0.2	0.3	<.001
Others	0.4	0.3	1.0	0.4	0.3	0.6	0.5	0.5	<.001

**FIGURE 3.** The difference in ADRs according to SOC.

There are several limitations to this study. First, ADRs and total usage cases were only analyzed in general hospitals and not in private clinics or small hospitals, because KAERS data mainly comprise spontaneous reports from general hospitals. In addition, the total usage cases of ICM from HIRA data did not include ADR cases outside insurance coverage (<1% in Korea). Second, data from KAERS and HIRA were supplied anonymously, and information about individual patient histories, and their effects on ADRs, such as comorbidity, concurrent medication, premedication before ICM injection, and presence of previous ADRs, was not available. Therefore, this study did not contain all the concomitant risk factors of ADR. Finally, assessment of the causal relationship between ADR and ICM was conducted without an allergy test. Although the true causality is difficult to prove, the assessment of the causal relationship was reliable because it was performed by medical experts such as physicians and nurses mainly, and allergists and/or professional pharmacists reviewed and reevaluated the cases of ADR reported

to the regional pharmacovigilance centers. Nevertheless, the main strength of the present study is that this is a representative result from a nationwide database of the Korean population.

In conclusion, our results indicated the differences in causal ADRs for total usage cases among 7 ICM from information in the KAERS database and through a comparison of hypersensitivity and ADRs according to SOC in Korea. This study promotes awareness of serious ADRs and safety related with various ICM for physicians and radiologists. A better understanding of the differences in ADRs for each ICM is essential to select the optimum ICM for patient safety. Therefore, a prospective study associated with ADRs of ICM that include each patient's medical history and comorbidities is needed to select more appropriate ICM for each patient.

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