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Comparison of the Safety of Seven Iodinated Contrast Media

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We aimed to determine the characteristic adverse events (AEs) of iodinated contrast media (IOCM) and to compare the safety profiles of different IOCM. This study used the database of AEs reports submitted by healthcare professionals from 15 Regional Pharmacovigilance Centers between June 24, 2009 and December 31, 2010 in Korea. All reports of IOCM, including iopromide, iohexol, iopamidol, iomeprol, ioversol, iobitridol and iodixanol, were analyzed. Safety profiles were compared between different IOCM at the system organ level using the proportional reporting ratio (PRR) and 95% confidence interval (95% CI). Among a total of 48,261 reports, 6,524 (13.5%) reports were related to the use of IOCM. Iopromide (45.5%), iohexol (16.9%), iopamidol (14.3%) and iomeprol (10.3%) were identified as frequently reported media. 'Platelet, bleeding & clotting disorders' (PRR, 29.6; 95%CI, 1.9-472.6) and 'urinary system disorders' (PRR, 22.3; 95% CI, 17.1-29.1) were more frequently reported for iodixanol than the other IOCM. In conclusion, the frequency of AEs by organ class was significantly different between individual media. These differences among different IOCM should be considered when selecting a medium among various IOCM and when monitoring patients during and after its use to ensure optimum usage and patient safety.

Key Words: Contrast Media; Adverse Drug Reaction Reporting Systems; Patient Safety

INTRODUCTION

Iodinated X-ray contrast media are the most commonly used drugs in diagnostic and interventional procedures. Procedures that employ contrast media have shown rapid growth. In the last two decades, the use of computed tomography (CT) increased by 800% and the use of cardiac catheterization increased by 390% (1, 2). With the increasing use of these procedures, the number of patients receiving iodinated contrast media has also continued to increase. Given such widespread use, it is important to be aware of associated adverse events (AEs) and have a good knowledge about the management of various contrast media.

Most AEs of iodinated contrast media, such as nausea, vomiting, urticaria and itching, are mild. However, severe AEs can occur, including hypotensive shock, respiratory arrest, cardiac arrest and convulsions. The incidence of these AEs has decreased considerably with the change of usage from high-osmolar contrast media (HOCM) to low-osmolar contrast media (LOCM); the incidence of AEs has been reported as 5% to 15% for HOCM and 0.2% to 0.7% for LOCM (3, 4). Although the overall incidence of AEs has decreased, severe AEs still continue to occur. Recently, many different kinds of iodinated contrast media have been used. However, it is not clear whether differences exist in AEs among various LOCM (including iso-osmolar contrast media) (5). Also, it is controversial whether iso-osmolar media are safer than LOCM on the topic of risk for contrast-induced nephropathy. Previous studies have evaluated various LOCM versus an iso-osmolar media iodixanol, but have shown conflicting results (6-8). Therefore, it is important to assess whe-

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ther the risks associated with these media are class-specific, osmolality based, or individual medium-specific. Different iodinated contrast media may have different biological characteristics. In fact, knowledge of different safety profiles of individual iodinated contrast media is essential.

Spontaneous reporting systems (SRSs) are database resources encompassing reports of suspected adverse drug reactions (ADRs). The availability of real-world data from SRSs provides a rich opportunity to detect post-marketing AEs that are novel in terms of their clinical nature, severity, or frequency since they include populations that are not well represented in clinical trials (9).

Therefore, the objectives of this study were to determine the characteristic AEs of iodinated contrast media and to compare the safety profiles of different iodinated contrast media using data from spontaneous post-marketing AE reports submitted by healthcare professionals of Korean Regional Pharmacovigilance Centers.

MATERIALS AND METHODS

Data source

This study used the database of spontaneous reports of AEs from 15 Regional Pharmacovigilance Centers, including Yonsei University Sevrance Hospital, The Catholic University of Korea Seoul St. Mary's Hospital, Seoul National University Hospital, Asan Medical Center, Dongguk University Ilsan Hospital, Ajou University Hospital, Hallym University Sacred Heart Hospital, Chungbuk National University Hospital, Dankook University Hospital, Keimyung University Dongsan Medical Center, Kyongpook National University Hospital, Inje University Pusan Paik Hospital, Pusan National University Hospital, Chuncheon Sacred Heart Hospital, and Chonnam National University Hospital, in Korea. The ADR reporting system was developed in Korea in 1988 (10). Three Regional Pharmacovigilance Centers were established in 2006 to support the surveillance system and activate spontaneous reports. The initial 3 centers extended to 6 centers in 2007, 9 centers in 2008 and 15 centers in 2009. Since June 2009, the centers have been operating within the framework of the PharmacoVigilance Research Network (PVNet) of the Korea Food and Drug Administration (KFDA) and have been the main contributors to the Korean SRS in recent years. Using the standard operating protocol of PVNet, pharmacovigilance professionals (primarily physicians and pharmacists) collect information on cases of suspected ADR and review them for possible drug causality. Reports submitted by healthcare professionals of regional centers on standardized forms are stored in the national KFDA database (11).

We obtained all reports of ADRs submitted to the KFDA from the 15 Regional Pharmacovigilance Centers between June 24, 2009 and December 31, 2010. Each report contains information on patient demographics, suspected drugs and concomitant drugs, AEs, patient outcomes, results of causality assessment, and report centers. Verbatim drug names supplied in the KFDA data were coded to extract standardized generic names according to the Anatomical Therapeutic Chemical (ATC) classification. AEs were coded using the World Health Organization-Adverse Reaction Terminology (WHO-ART) coding dictionary (12). Results of causality assessment for each AE by the WHO criteria were recorded by the reporters in the database.

AEs of iodinated contrast media

All reports with low-osmolar and iso-osmolar iodinated contrast media (ATC code V08AB) listed as either a suspected or a concomitant medication were identified. Iodinated contrast media in the database were classified as low-osmolar and iso-osmolar. AEs were identified by the WHO-ART Preferred Terms. A report was defined as a serious report if at least one serious AE was present among all the AEs in the report. Serious AE is defined as either of the following: 1) serious outcome (death, life-threatening event, inpatient hospitalization or prolongation of existing hospitalization, persistent or significant disability/incapacity, congenital anomaly/birth defect, and others of medical significance) (13); or 2) the WHO-ART critical term (e.g. anaphylactic shock, angioedema, etc.) (12).

Statistical analysis

A report can contain more than one suspected drug, or more than one AE. We identified a drug-AE pair as a unique combination of a single drug and a single AE. For example, a report containing two AEs with one contrast medium counted as two medium-AE combinations. For the analysis, 2 levels of dataset were used: reports and medium-AE combinations. We analyzed the data at the level of reports; patient demographics (age, gender) and the presence of serious AEs were analyzed; and the number of total and serious reports for each contrast medium was counted. The frequency of AEs was analyzed at the level of contrast medium and AE combinations; the most commonly reported AEs were listed; the most commonly reported AEs were also listed for LOCM and iso-osmolar media, respectively; frequently reported medium and AE combinations were studied.

The safety profile was characterized and compared between LOCM and iso-osmolar media, and between each of the iodinated contrast media. For this analysis, AEs were grouped together as the primary System Organ Class (SOC) in the WHO-ART. The frequency of AEs at the SOC level was then calculated. The chi-square test was used to assess the differences in the frequency of AEs at the SOC level between low-osmolar and iso-osmolar media, and between individual media. A P value of 0.01 was used as the level of significance.

Proportional reporting ratio (PRR) was also calculated to com-

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Table 1. A two-by-two table for a contrast medium and group of adverse events of interest in spontaneously reported data. Proportional reporting ratio = [a/(a + b)]/[c/(c + d)]

	Specified group (SOC) of AEs	All other groups (SOCs) of AEs	Total
Each contrast medium	a	b	a + b
All other iodinated contrast media (reference group)	c	d	c + d
Total	a + c	b + d	a + b + c + d

AE, adverse event; SOC, system organ class.

pare the safety profiles of different iodinated contrast media. The PRR is calculated in a similar way to a relative risk in a cohort study, whereby the proportion of specified group (SOC) of AEs is calculated for each medium and divided by the proportion of these AEs for the other iodinated contrast media in the database (reference group) (Table 1) (14, 15). A threshold of lower 95% confidence limit (95% LCI) of the PRRs greater than 1 was used to define the signal of disproportionate reporting between a medium and an event at the SOC level (16). Signals having a mean of the PRR and its 95% LCI of 15 or greater were categorized as high priority for further medical evaluation (17). A prioritizing signal was also defined as a medium-AE combination with the terms of 'rhabdomyolysis', 'agranulocytosis', 'Stevens–Johnson syndrome' or 'toxic epidermal necrolysis', which are more likely to be drug related than others (18). Detected signals were reviewed to identify previously unlabeled AEs. Due to the close attention to contrast induced nephropathy (19), an additional analysis was performed for renal AEs. In this analysis, AEs were classified into two groups: renal AEs and non-renal AEs. Renal AEs were defined as AEs that combined several preferred terms, including 'anuria', 'creatinine clearance decreased', 'nephropathy toxic', 'nephrosis', 'oliguria', 'renal failure acute', 'renal function abnormal', 'renal tubular disorder', 'renal tubular necrosis', 'azotaemia', 'renal failure chronic', and 'renal failure aggravation of chronic'. Two-by-two tables were created for each medium and compared with renal AEs and non-renal AEs for that media in each column. PRR and its 95% LCI were calculated in this table. All statistical analyses were performed using SAS software Version 9.2 (SAS Institute Inc., Cary, NC, USA).

Ethics statement

This study was approved by the institutional review board of the Seoul National University College of Medicine and the Seoul National University Hospital (IRB No. 1109-134-381). Informed consent was waived by the board.

RESULTS

A total of 48,261 reports and 153,557 medium-AE combinations from the database were used between the specified dates. Of these, 6,524 (13.5%) reports were of low-osmolar or iso-osmolar contrast media. The patients had a mean age of 53.2 yr (standard deviation, 12.8). There were 3,361 (51.5%) males, 3,127 (47.9%) females and 36 (0.6%) patients without gender information. Life-threatening events were reported in 12 cases; inpatient hospitalization or prolongation of existing hospitalization was found in 70 cases. The number of patients who experienced AEs of WHO-ART critical terms was 374 (5.7%) (Table 2).

Iopromide (45.5%) was the most commonly implicated iodinated contrast medium, followed by iohexol (16.9%), iopamidol (14.3%) and iomeprol (10.3%). The percentage of serious reports associated with each medium were as follows: for iopromide, 54.2%; iohexol, 11.3%; iopamidol, 8.5%; iomeprol, 10.7%; ioversol, 5.9%; iobitridol, 2.2%; and iodixanol, 7.6% (Table 3).

Of a total of 10,287 medium-AE combinations, the most often reported AEs were urticaria (35.0%), pruritus (26.6%), rhinitis (5.9%), rash (5.8%), and vomiting (2.9%). Among the 603 medium and serious AE combinations, the most frequently reported serious AEs were angioedema (23.6%), face oedema (10.8%), dyspnoea (8.3%), anaphylactic reaction (7.8%), and hypotension (5.8%). The 5 most commonly reported AEs in the low-osmolar media group were urticaria (35.7%), pruritus (26.9%), rhinitis (6.1%), rash (5.2%), and vomiting (2.9%). Those in the iso-osmolar media group were rash (22.9%), azotaemia (19.3%), pruritus (17.3%), urticaria (15.5%), and face oedema (3.0%). The most frequently reported medium-AE combinations were iopromide-urticaria (16.6%), iopromide-pruritus (11.0%), and iohexol-urticaria (6.2%). The most frequently reported medium-serious AE combinations were iopromide-angioedema (12.1%), iopromide-anaphylactic reaction (5.6%), and iopromide-face oedema (5.3%).

Table 4 presents a safety profile of the iodinated contrast media according to the SOC, by each medium. A statistically significant difference in the frequency of AEs at the SOC level was observed between the low-osmolar and iso-osmolar media groups: the percentage of AEs of 'skin and appendages disorders' was 69.8% and 60.1% ($P < 0.001$); the percentage of AEs of 'respiratory system disorders' was 9.1% and 3.6% ($P < 0.001$); the percentage of AEs of 'central & peripheral nervous system disorders' was 4.2% and 1.2% ($P = 0.006$); the percentage of AEs of 'vascular (extracardiac) disorders' was 1.9% and 0.6% ($P < 0.001$); and the percentage of AEs of 'urinary system disorders' was 1.1% and 24.4% ($P < 0.001$) in the low-osmolar and iso-osmolar media group, respectively. Differences in the AE profiles between individual media were also observed. For iopromide, the percentage of AEs of 'cardiovascular disorders, general' was significantly higher ($P = 0.001$); for iohexol, the percentage of AEs of 'body as a whole-general disorders' was significantly higher ($P = 0.006$); for iopamidol, the percentage of AEs of 'respiratory system disorders' and 'vision disorders' was signifi-

Table 2. Characteristics of contrast media adverse event reports

Characteristics	Total No. of reports	%	No. of reports with low or iso-osmolar iodinated CM	%
Gender				
Men	22,170	45.9	3,361	51.5
Women	25,656	53.2	3,127	47.9
Unknown	435	0.9	36	0.6
Age (yr, mean ± SD)	48.3 ± 20.7		53.2 ± 12.8	
0-9	2,874	6.0	17	0.3
10-19	2,561	5.3	59	0.9
20-29	3,720	7.7	209	3.2
30-39	5,067	10.5	578	8.9
40-49	7,327	15.2	1,415	21.7
50-59	9,512	19.7	2,204	33.8
60-69	8,246	17.1	1,344	20.6
70-79	5,868	12.2	579	8.9
80+	1,469	3.0	64	1.0
Unknown	1,617	3.4	55	0.8
Outcomes*				
Death	86	0.2	0	0.0
Life-threatening	88	0.2	12	0.2
Inpatient hospitalization or prolongation of existing hospitalizations	1,059	2.2	70	1.1
Persistent or significant disability/capacity	23	0.0	0	0.0
Congenital anomaly/birth defect	4	0.0	0	0.0
Other medically significant	944	2.0	98	1.5
WHO-ART critical term present	5,857	12.1	374	5.7
Total	48,261	100.0	6,524	100.0

*Each case may have 1 or more outcomes. CM, contrast media; SD, standard deviation; WHO-ART, World Health Organization-Adverse Reaction Terminology.

Table 3. Frequency of reports for each individual iodinated contrast medium

Class	Contrast media	No. of reports	% of the total reports* (n = 6,524)	No. of serious reports	% of the total serious reports (n = 459)
Low-osmolar	Iopromide	2,966	45.5	249	54.2
	Iohexol	1,101	16.9	52	11.3
	Iopamidol	935	14.3	39	8.5
	Iomeprol	670	10.3	49	10.7
	Ioversol	490	7.5	27	5.9
	Iobitridol	167	2.6	10	2.2
Iso-osmolar	Iodixanol	211	3.2	35	7.6

*More than one drug per report was possible.

cantly higher ($P < 0.001$, $P = 0.009$); for iomeprol, the percentage of AEs of 'skin and appendages disorders' was significantly higher ($P < 0.001$); for ioversol, the percentage of AEs of 'gastro-intestinal system disorders' and 'cardiovascular disorders, general' was significantly higher ($P = 0.002$, $P = 0.008$); for iobitridol, the percentage of AEs of 'gastro-intestinal system disorders' was significantly higher ($P < 0.001$); and for iodixanol, the percentage of AEs of 'urinary system disorders' was significantly higher ($P < 0.001$).

Of the 19 signals of disproportionate reporting, 2 were cate-

Table 4. Safety profiles of iodinated contrast media according to system organ class*

System organ class	Low-osmolar							Iso-osmolar	Total for the iodinated CM % (n = 10,287)
	Iopromide % (n = 4,613)	Iohexol % (n = 1,679)	Iopamidol % (n = 1,510)	Iomeprol % (n = 1,141)	Ioversol % (n = 773)	Iobitridol % (n = 235)	Total for the LOCM % (n = 9,951)	Iodixanol % (n = 336)	
Skin and appendages disorders	69.4	70.4	68.3	78.4‡	64.8‡	55.7‡	69.8†	60.1‡	69.4
Respiratory system disorders	8.8	6.7‡	13.7‡	6.2‡	10.6	11.5	9.1†	3.6‡	8.9
Gastro-intestinal system disorders	5.3	5.9	6.3	3.9‡	8.2‡	11.5‡	5.8	3.6	5.7
Body as a whole-general disorders	6.0‡	6.7‡	3.9‡	2.8‡	4.0	8.1	5.3	4.8	5.3
Central & peripheral nervous system disorders	4.3	5.1	2.6‡	3.3	5.7	5.5	4.2†	1.2‡	4.1
Vascular (extracardiac) disorders	2.2	1.2	1.8	2.5	1.0	1.3	1.9†	0.6	1.9
Urinary system disorders	1.0‡	0.8‡	1.5	0.8‡	2.2	0.4	1.1†	24.4‡	1.9
Cardiovascular disorders, general	1.5‡	0.5	0.3‡	1.1	2.1‡	0.9	1.1	0.6	1.1
Vision disorders	0.5	0.5	1.1‡	0.6	0.5	0.4	0.6	0.0	0.6
Others	1.0	2.1	0.5	0.4	0.9	4.7	1.1	1.2	1.1

*Adverse events classified according to the World Health Organization-Adverse Reaction Terminology (WHO-ART). †Significant differences (chi-square test, $P < 0.01$) among the total LOCM in the reports implicating this organ system versus iso-osmolar media. ‡Significant differences (chi-square test, $P < 0.01$) among iodinated contrast media in the reports implicating this organ system versus other reports. CM, contrast media; LOCM, low-osmolar contrast media.

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Table 5. Detected signals of iodinated contrast media by proportional reporting ratio

Contrast media	System organ class*	No. of medium-AE combination	PRR	(95% CI)
Iopromide	Cardiovascular disorders, general	68	1.8	(1.3, 2.6)
	Vascular (extracardiac) disorders	103	1.4	(1.1, 1.9)
	Body as a whole-general disorders	276	1.3	(1.1, 1.5)
Iohexol	Central & peripheral nervous system disorders	86	1.3	(1.0, 1.6)
	Body as a whole-general disorders	112	1.3	(1.1, 1.6)
	Application site disorders	5	5.1	(1.5, 17.7)
	Secondary terms-events	19	4.9	(2.6, 9.1)
Iopamidol	Vision disorders	16	2.1	(1.2, 3.7)
	Metabolic and nutritional disorders	4	11.6	(2.1, 63.4)
	Respiratory system disorders	207	1.7	(1.5, 2.0)
Iomeprol	Skin and appendages disorders	894	1.1	(1.1, 1.2)
Ioversol	Central & peripheral nervous system disorders	44	1.4	(1.1, 1.9)
	Gastro-intestinal system disorders	63	1.5	(1.2, 1.9)
	Cardiovascular disorders, general	16	2.0	(1.2, 3.4)
Iodixanol	Platelet, bleeding & clotting disorders†	1	29.6	(1.9, 472.6)
	Urinary system disorders†	82	22.3	(17.1, 29.1)
Iobitridol	Musculo-skeletal system disorders	1	8.6	(1.0, 73.0)
	Gastro-intestinal system disorders	27	2.1	(1.4, 3.0)
	Secondary terms-events	7	9.4	(4.2, 21.0)

*Adverse events classified according to the World Health Organization-Adverse Reaction Terminology (WHO-ART). †Signals categorized as high priority for further investigation.
AE, adverse event; CI, confidence interval; PRR, proportional reporting ratio.

Table 6. Adverse events included in the organ class as detected signals of iodinated contrast media

Contrast media	Detected signals of AE at the SOC level	Included preferred term (No. of medium-AE combination)
Iopromide	Cardiovascular disorders, general	Circulatory failure (7), cyanosis (2), hypertension (6), hypotension (53)
Iopromide	Vascular (extracardiac) disorders	Flushing (102), vasodilatation (1)
Iopromide	Body as a whole-general disorders	Allergic reaction (10), allergy (38), anaphylactic reaction (34), anaphylactic shock (12), anaphylactoid reaction (6), asthenia (5), chest pain (50), drug hypersensitivity syndrome (1), fever (18), hyperpyrexia (1), oedema (6), oedema generalised (6), oedema mouth (6), oedema periorbital (22), oedema peripheral (1), rigors (23), syncope (15), temperature changed sensation (22)
Iohexol	Central & peripheral nervous system disorders	Anaesthesia mouth (1), dizziness (49), dysaesthesia (1), dysphonia (7), headache (11), hypoaesthesia (2), hypotonia (1), neuralgia (1), paraesthesia (5), stupor (5), torticollis (1), tremor (2)
Iohexol	Body as a whole-general disorders	Allergy (1), anaphylactic reaction (4), anaphylactoid reaction (2), asthenia (3), back pain (1), chest pain (35), drug hypersensitivity syndrome (2), fever (8), hypothermia (1), malaise (2), oedema (8), oedema generalised (4), oedema mouth (4), oedema periorbital (11), oedema peripheral (3), rigors (10), syncope (2), temperature changed sensation (11)
Iohexol	Application site disorders	Application site reaction (1), injection site reaction (4)
Iohexol	Secondary terms-events	Extravasation (19)
Iopamidol	Vision disorders	Conjunctivitis (10), eye abnormality (5), vision abnormal (1)
Iopamidol	Metabolic and nutritional disorders	Xerophthalmia (4)
Iopamidol	Respiratory system disorders	Coughing (13), dyspnoea (6), laryngitis (2), pharyngitis (2), rhinitis (178), sputum increased (1), throat tightness (5)
Iomeprol	Skin and appendages disorders	Angioedema (22), pruritus (388), rash (40), rash erythematous (5), sweating increased (3), urticaria (436)
Ioversol	Central & peripheral nervous system disorders	Dizziness (32), dysaesthesia (1), dysphonia (2), headache (1), hypertonia (1), paraesthesia (3), stupor (2), tremor (2)
Ioversol	Gastro-intestinal system disorders	Abdominal pain (1), diarrhoea (1), nausea (28), vomiting (33)
Ioversol	Cardiovascular disorders, general	Hypertension (2), hypotension (14)
Iodixanol	Platelet, bleeding & clotting disorders	Purpura (1)
Iodixanol	Urinary system disorders	Albuminuria (1), anuria (1), azotaemia (65), creatinine clearance decreased (1), dysuria (1), face oedema (10), haematuria (1), nephropathy toxic (1), renal function abnormal (1)
Iobitridol	Musculo-skeletal system disorders	Muscle weakness (1)
Iobitridol	Gastro-intestinal system disorders	Abdominal pain (1), diarrhoea (1), dysphagia (1), hiccup (1), nausea (13), vomiting (10)
Iobitridol	Secondary terms-events	Extravasation (7)

AE, adverse event; SOC, system organ class.

gorized as high priority for further investigation: 'Platelet, bleeding & clotting disorders' (PRR, 29.6) and 'urinary system disorders' (PRR, 22.3) were more frequently reported for iodixanol (Table 5). The AEs, in preferred terms, that are included in the SOC of signals are shown in Table 6. For the signal of iodixanol and 'platelet, bleeding & clotting disorders,' the number of medium-AE combinations was 1 as 'purpura.' The patient was male and 62 yr old; he used iodixanol (652 mg/mL) without other

concomitant medication and developed purpura with rash. For the signal of iodixanol and 'urinary system disorders', the number of medium-AE combinations was 82 including 65 'azotaemia'; three cases were either experienced inpatient hospitalization or prolongation of existing hospitalization due to AEs. There was only 1 case of Stevens–Johnson syndrome associated with iopromide (labeled AE). In the further analysis for comparison of renal AEs and non-renal AEs, iodixanol was more frequently reported than the other contrast media, with the PRR value of 37.3 (95% CI, 26.6-52.3).

DISCUSSION

This study shows the AE profiles of various iodinated contrast media: iopromide, iohexol, iopamidol, iomeprol, ioversol, iobitridol and iodixanol. Moreover, this study identified the differences in the AE profiles of iodinated contrast media by organ class between individual media. 'Platelet, bleeding & clotting disorders' and 'urinary system disorders' are more frequently reported for iodixanol.

Iodinated contrast media were the suspected drugs reported for comprising great proportions in the database of AEs from the Korean Regional Pharmacovigilance Centers. An increase in patient exposure as well as familiarity with AEs to contrast media by healthcare providers can be explained as a result of pharmacovigilance training by the centers. In Korea, known AEs should be reported along with previously unknown AEs. This was reflected in the results which showed that most centers most often reported known AEs of media (e.g. iopromide-urticaria).

Iopromide was the most frequently reported medium, followed by iohexol. These findings need to be interpreted in light of the consumption data; iopromide (38.8%) and iohexol (18.4%) were the predominantly used iodinated contrast media according to the market share of each medium from the Intercontinental Marketing Services (IMS) KOREA data in 2009 (20). For iopromide and iodixanol, the proportions of each medium among serious reports were higher than those among all reports. This should be interpreted with caution, as difference in the proportion does not suggest difference in the incidence rate of serious AEs.

Frequently reported AEs included urticaria, pruritus, angioedema, hypotension, vomiting, and dyspnea; they appeared to fall under the umbrella of allergic reactions. This was an expected finding because allergic reactions have commonly occurred in patients receiving iodinated contrast media (21).

A significant difference in the AE profiles between low-osmolar and iso-osmolar media was observed. Although LOCM have very similar molecular structures, the individual media have different safety profiles. Gomi et al. (22) found that the proportion of patients experiencing AE varied by LOCM (iomeprol, 3.9%; iopamidol, 2.2%; iohexol, 2.0%; iopromide, 3.5%; ioversol, 1.8%; and all five combined, 2.7%) among the 8,931 patients who underwent contrast-enhanced CT. However, to our knowledge, this is the first study specifically designed to compare the frequency of AEs of iodinated contrast media by organ class between individual media, as well as between low-osmolar and iso-osmolar media.

The frequency of AEs of 'urinary system disorders' was significantly higher for iodixanol and the same was observed for renal AEs. We cannot exclude the possibility that iodixanol, a recommended medium by some guidelines (23), is more frequently used in patients with underlying renal diseases. However, there is still much controversy regarding the nephrotoxicity of iodixanol compared with that of LOCM (24). Nephrotoxicity of contrast media is the third leading cause of acute renal failure in hospitalized patients (25). This difference between iodixanol and the other iodinated contrast media should be considered when selecting a medium among various iodinated contrast media and when monitoring patients during and after its use.

In addition, PRR points to the relative frequency of 'platelet, bleeding & clotting disorders' for iodixanol, including purpura. Contrast media are known to cause some alterations in vascular endothelial function and in platelet function although these effects are not thought to be clinically relevant (26). These effects are related to purpura, however, it is not listed in product labeling. These findings may require continued monitoring.

A measure of disproportionality chosen for this analysis was PRR which cannot be calculated if denominator is zero. Only combination of ioversol and 'red blood cell disorders' were additionally generated signal with information component (IC) of Bayesian Confidence Propagation Neural Network analysis, even though IC can be calculated in all situation (16).

The strengths of this study include the following. First, all reported AEs are identified and reviewed by the healthcare professionals of Regional Pharmacovigilance Centers. The data are more valid than data reported by other reporting sources, e.g., consumers, manufacturers, etc. (27). Second, this study included diverse contrast media: six different LOCM and one iso-osmolar medium, allowing a comparative study of AE profiles; the present study provides better knowledge of the differences between each iodinated contrast medium. Third, since nephrotoxicity of contrast media have been gaining particular interest, the study performed further evaluation for renal AEs by grouping the related terms together.

However, our results should be interpreted in the context of several limitations. First, the lack of information on the denominator, number of patients exposed to each contrast medium, should be considered. It is difficult to assess the relative risk between different contrast media in this study because their incidence rates cannot be estimated. Second, data may have been

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affected by under-reporting. However, a comparison of the benefit-risk profiles of drugs using this data within the same therapeutic class is generally acceptable (28, 29). In these conditions, the under-reporting can be assumed to be more or less of the same magnitude for the compared drugs (29, 30). Therefore, under-reporting, regardless of its magnitude, does not affect the validity of the conclusions drawn from this study.

In conclusion, the results of this study suggest that the safety profiles of individual iodinated contrast media are significantly different. Particular attention should be paid to the comparative safety evaluation of these media. A better understanding of safety profiles is required to ensure optimum usage and patient safety. This study promotes awareness of diverse iodinated contrast media-related safety signals. Development of criteria for the most appropriate selection of contrast medium among various iodinated contrast media is needed.

DISCLOSURE

The authors have no conflicts of interest to disclose.

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