Received:
8 July 2013

Revised:
24 October 2013

Accepted:
29 October 2013

doi: 10.1259/bjr.20130418

Cite this article as:

Kyung E-J, Ryu J-H, Kim E-Y. Evaluation of adverse reactions to contrast media in the hospital. *Br J Radiol* 2013;86:20130418.

FULL PAPER

Evaluation of adverse reactions to contrast media in the hospital

¹E-J KYUNG, PharmD, MS, ²J-H RYU, MS and ³E-Y KIM, PharmD, PhD

¹College of Pharmacy, Chungnam National University, Daejeon, Republic of Korea

²Department of Pharmacy, St Mary's Hospital, Daejeon, Republic of Korea

³College of Pharmacy, Chung-Ang University, Seoul, Republic of Korea

Address correspondence to: Professor Eun-Young Kim

E-mail: eykimjcb777@cau.ac.kr

Objective: To determine and analyse the characteristics of contrast media adverse reactions (CM-ARs) reported in a hospital.

Methods: A retrospective review of CM-ARs from the electronic spontaneous adverse drug reaction (ADR) report system between January 2011 and August 2012 was conducted. CM-ARs were evaluated in terms of causality, severity, preventability and affected organs. Also, agreement and correlation among the tools used to evaluate CM-ARs were analysed.

Results: The overall reaction rate was 1.5% ($n = 286$). In total, 269 CM-ARs were identified. For ADR causality, 96.7% ($n = 260$) and 98.5% ($n = 265$) were evaluated as "probable" ADR using the Naranjo probability scale and the World Health Organization-Uppsala Monitoring Centre causality categories, whereas 98.1% ($n = 264$) were evaluated as "certain" with Korean algorithm v. II. Of these, 91.4% ($n = 246$) were mild in severity and 96.7%

($n = 260$) were unpreventable. Most patients ($n = 233$, 86.7%) could be managed with observation and/or simple treatment. The most frequent reaction ($n = 383$, 79.5%) was dermatological. Spearman's correlation coefficient was 0.667 ($p < 0.01$), and the agreement was 98.1% between the Naranjo scale and the World Health Organization-Uppsala Monitoring Centre categories. No relationship was seen between CM-AR severity and gender or between in- and outpatients.

Conclusion: In our study, most CM-ARs were mild and managed with simple treatment. However, as the number of patients undergoing CT procedures continues to increase, it is essential to identify and observe patients at risk for CM-ARs to prevent severe ADRs.

Advances in knowledge: Continuous careful review of reporting and treatment protocols of CM-ARs is needed to prevent morbidity and mortality.

Contrast media (CM) are intravascular pharmaceuticals that are used in approximately 75 million procedures annually and are among the most common pharmacological agents injected into the human body.¹ As the number of patients undergoing CT or MRI increases,² more patients are affected by CM-related adverse events (AEs).

CM adverse reactions (CM-ARs) range from a mild inconvenience, such as itching associated with urticaria, to a potentially life-threatening emergency. Although low-osmolality non-ionic CMs have been used to reduce such side effects since the mid-1970s, ARs to them have also been reported.³⁻⁶

Most CM-ARs are mild events that usually require only observation and supportive measures,^{7,8} but sometimes severe and life-threatening ARs continue to occur unpredictably. Mortality was estimated at one death per 100 000 examinations on the basis of findings from 1991.⁹ Not only patient complications but also the cost of

treating CM-related ARs, in total, are considerable.¹⁰ Although CM-ARs cannot always be predicted, studies have shown that certain patients are at greater risk. To decrease and prevent CM-ARs, there are several guidelines to prevent AEs, and they are partially successful.¹¹⁻¹³ For example, the American College of Radiology (ACR), Reston, VA, recommends that patients with a known history of CM-ARs be pre-medicated with corticosteroids and antihistamines before receiving CM.¹³

Because patient safety should be the top priority, a spontaneous or automatic adverse drug reaction (ADR) reporting system would seem to be a useful tool. The introduction of regional pharmacovigilance centres in Republic of Korea and computerized surveillance systems have promoted the monitoring of ADRs; indeed, the number of ADRs reported is increasing rapidly. The purpose of this study was to determine and evaluate the CM-ARs reported from the spontaneous ADR reporting system of a single hospital in terms of type, severity, causality and preventability of CM-ARs.

METHODS AND MATERIALS

Data collection and study design

This study was conducted at a single secondary care hospital, St Mary's Hospital, in Daejeon, Republic of Korea, with 625 beds. The hospital introduced an electronic spontaneous ADR reporting system in January 2011. In this study, a retrospective review was conducted for all cases of CM-ARs accumulated from the ADR reporting system between 1 January 2011 and 31 August 2012. All doses administered in the outpatient, inpatient and emergency departments of the hospital were included.

Demographic data (*e.g.* age and gender) information regarding department (*e.g.* cardiology and pulmonary) disease status, medication history, major symptom, contrast agent administered, medical treatment initiated, prescription information, the need for hospitalization or transfer to the emergency room and outcome were obtained from the clinical history, electronic medical record (EMR) charts, physician notes and radiology reports.

Institutional review board approval was obtained prior to the initiation of the study. Informed consent was not required because of the retrospective nature of this investigation.

Contrast media adverse reaction evaluation

The identified CM-ARs were categorized in terms of causality, severity, preventability, type of CM-ARs and associated clinical manifestations. ADRs were analysed using several well-known ADR evaluation tools, such as the World Health Organization–Uppsala Monitoring Centre (WHO-UMC) causality categories, the Naranjo probability scale, the Korean algorithm v. II for ADR causality and the ACR manual on contrast media v. 8.0 (2012; <http://www.acr.org>), the LDS scale, the WHO Adverse Reaction Terminology, the National Coordinating Council for Medication Error Reporting and Prevention (NCC-MERP) scale for ADR severity and Shumock and Thornton's seven questions for ADR preventability.

Two pharmacists reviewed every record and evaluated each ADR case. Disagreements on the categorization of ADRs were resolved through consensus.

Causality evaluation

Because causality evaluations of CM-ARs are likely to be subjective, the WHO-UMC causality categories,¹⁴ the Naranjo probability scale¹⁵ and the Korean algorithm v. II¹⁶ tools were used to provide the most objective results. The causality assessment systems proposed by the WHO-UMC and the Naranjo probability scale are the generally accepted and the most widely used methods for assessing causality in clinical practice. The WHO-UMC causality system as a probabilistic method takes into account clinical pharmacological aspects and investigator experience, whereas previous knowledge of the ADR plays a less prominent role.^{14,17} The principal advantages of the Naranjo scale as an algorithmic method are that it is simple, less time-consuming and widely applicable.^{15,18} Both the above systems can be difficult to apply domestically because of differences in language, participant evaluation, case-reporting methods, medical information and awareness standards. Thus, each case was also evaluated using the Korean algorithm v. II to improve

objectivity.¹⁶ Although the Naranjo probability scale includes measurements for drug concentration, objective evidence of ADR, ADR to previous exposures, responses to placebo and the dose adjustment of drugs, the Korean algorithm v. II adds proportional dose-dependent responses, event abatement and clinical appearance on drug removal in descriptions of the clinical course. All these scales are structured, transparent, consistent and easy-to-apply assessment methods.

The WHO-UMC causality categories consist of six steps: certain, probable or likely, possible, unlikely, conditional or unclassified and unassessable or unclassifiable. The criteria consider nature of the event, its timing, the dose of the medicine being taken, the possible confounding factors and information to dechallenge or rechallenge with the suspected medicine. A causality assessment of certain, probable or possible assigned to an event identifies a reaction, whereas an AE deemed unlikely to be causally associated with the medicine is considered unrelated. The Naranjo probability scale is a simple 10-item questionnaire used to assess the likelihood of a drug causing an untoward event. This scale involves 10 yes, no or "unknown or non-applicable" questions. Specifically assigned numerical values are given to arrive at a total score, indicating the category of causality relationship (definite, probable, possible and doubtful) to which each drug-AE pair can be allocated. The "Korean algorithm" consists of eight questions addressing different issues related to alleged adverse drug reactions, which can be answered with yes, no, or "do not know". Pre-fixed numerical scores are attached to the answers, and these scores result in a cumulative value, which can be translated into a causality category, similar to the Naranjo scale.

Severity evaluation

CM-ARs severity was analysed using four tools: the NCC-MERP Index,¹⁹ the LDS scale,²⁰ the ACR manual on contrast media v. 8.0 "Categories of Reactions"¹³ and the WHO Adverse Reaction Terminology.²¹ Although the NCC-MERP Index is a tool for evaluating medication errors, but not ADR evaluation, ADRs can be included as a type of medication error. Also, this tool contains much more specific language describing the degree of severity than the LDS scale. All CM-ARs were classified by the NCC-MERP into nine categories (A–I) using yes or no questions. The LDS scale consists of 10 questions answered with yes, no or unknown and is scored as follows: a score of 1–4 indicates a mild reaction; 5–8, a moderate reaction; and >8, a severe adverse drug reaction. The ACR manual divides ADR severity into the following three categories: mild, moderate and severe. The WHO terminology categorizes ADRs as "serious" or "not serious" events, in accordance with the International Conference on Harmonization E2D guideline.²² In agreement with these criteria, serious reactions include those that are fatal, life-threatening, disabling or incapacitating, causing or prolonging hospitalization, causing congenital abnormalities or are medically important on the basis of a clinical or scientific judgment.

Preventability

The preventability of ADRs was assessed using Shumock and Thornton's criteria,²³ which consists of seven questions. If an ADR meets at least one of the criteria, it is considered to be preventable.

Type of contrast media adverse reactions

The CM-ARs were further classified by mechanism as Type A or B. Type A reactions are related to the pharmacological characteristics of a drug and are usually dose-dependent and predictable. Type B reactions are idiosyncratic, unpredictable, dose-independent or unrelated to a drug's pharmacological characteristics.²⁴

Clinical manifestations

Clinical manifestations associated with ADRs were classified further into 12 categories, according to the Micromedex® (Truven Health Analytics, Austin, TX) ADR classification.²⁵

Statistics

All analyses were performed using the IBM® SPSS® Statistics v. 19.0 (software package for statistical analysis; IBM Corporation, Armonk, NY). Spearman's χ^2 test was used to identify correlations between the two tools for causality and severity. A χ^2 test was performed to assess the correlation of severity of CM-ARs with gender and in-/outpatients. The kappa value was used to evaluate the level of agreement between the two reviewers. All values with differences were assessed by *p*-values. *p* < 0.05 was considered statistically significance.

RESULTS

During the period from 1 January 2011 to 31 August 2012, there were 32 711 CM administrations in the hospital. In total, 286 CM-ARs, representing 0.82% of CM administrations, were reported. The total number of ADR reports collected in the hospital data during the time window was 1335, of which 21.4% (*n* = 286) involved CMs. The remaining ADRs were historical ADRs (*n* = 699) and current ADRs (*n* = 351). Among CM-ARs, 17 cases were excluded because 2 cases were system tests and the others were not available for data access to analyse and evaluate causality and severity. Consequently, 269 CM-ARs were analysed. Indications reported for CM administration were CT (224), angio-CT (20), MRI (19), four-vessel angiography (4) and intravenous pyelography (2).

Study group and characteristics

Of the total 269 cases, 114 (42.4%) were males and 155 (57.6%) females (Table 1). The mean age $\pm$ standard deviation of the patients was 51.1 $\pm$ 16.7 (range, 7–84) years; 4 CM paediatric reports were received within the time period. There was a slight predominance of patients aged between 50 and 59 years (*n* = 79, 29.4%) and elderly patients (≥ 65 years; 20.4%). Of the CM-ARs, 55 (20.4%) occurred in an inpatient setting and 214 (79.6%) in an outpatient setting. Most CM-ARs were reported by radiologists (81.8%) or by nurses (12.6%). Pre-disposing risk factors were seen in 15 patients: a history of previous CM-AR was reported in 8 patients and 6 patients took beta-blockers before the procedure. The remaining patient had asthma.

Evaluation of contrast media adverse reactions

Causality of contrast media adverse reactions

Causality assessment using the WHO-UCM causality categories, the Naranjo probability scale and the Korean algorithm (v. II) showed differing trends in CM-ARs. The most frequent category according to the WHO-UCM categories was the “probably/likely”

Table 1. Demographic characteristics of patients with contrast media adverse reactions (CM-AR)

Characteristics	Number of CM-ARs (<i>n</i> = 269)	Percentage
Sex		
Male	114	42.4
Female	155	57.6
Age (years)		
<10	4	1.5
10–64	210	78.1
≥ 65	55	20.4
Patient		
Inpatient	55	20.4
Outpatient	214	79.6
Reporter		
Doctor	9	3.3
Nurse	34	12.6
Radiologist	220	81.8
Others	5	1.9

The mean age $\pm$ standard deviation of the patients was 51.1 $\pm$ 16.7 years.

category (98.5%), according to the Naranjo probability scale was the “possible” category (96.7%) and according to the Korean algorithm (v. II) was the “certain” category (98.1%; Table 2).

In more detail, according to the WHO-UCM causality categories, only two cases (0.7%) were in the “possible” or “certain ADR” category. Causality scores on the Naranjo scale of “probable ADR” (score of 5–8 on a scale of 13) occurred in 260 cases (96.7%), whereas 7 cases (2.6%) were “definite ADR” (Score ≥ 9), but “probable ADR” (Scores 1–4) occurred in only 2 cases (0.7%). The Korean algorithm (v. II) scores showed “certain ADR” (Score ≥ 14 , maximum, 21) in 264 cases (98.1%) and “probable ADR” (Scores 6–13) in 5 cases (1.9%).

Severity of contrast media adverse reactions

According to ACR manual, 240 cases (89.2%) were in the “mild” reaction category, 22 in the “moderate,” and 7 cases in the “serious” category (Table 2). With the LDS severity scale, a “mild reaction” (Scores 1–4, maximum, 16) was scored in 245 cases (91.4%), a “moderate reaction” (Scores 5–8) in 19 cases (7.1%) and a “severe reaction” (score > 8) in only 4 cases (1.5%). With the NCC-MERP Index, category E, which includes ADRs requiring intervention but only transiently harmful, had 257 cases (95.5%). 12 cases (4.5%) were category D, including ADRs requiring monitoring to confirm that no harm resulted. No statistically significant relationship was found between CM-AR severity and gender (*p* = 0.95), age (when considering 10-year intervals, *p* = 0.30) or in-/outpatient status (*p* = 0.58).

Preventability and type of adverse drug reaction

On analysing ADR preventability, 260 cases (96.7%) were deemed unpreventable and 9 cases (3.3%) were preventable

Table 2. The evaluation of contrast media adverse reactions (CM-ARs)

Characteristics	Number of CM-ARs (<i>n</i> = 269)	Percentage
Causality		
WHO-UCM		
Possible	2	0.7
Probable/likely	265	98.5
Certain	2	0.7
Naranjo scale		
Possible	2	0.7
Probable	260	96.7
Definite	7	2.6
Korean algorithm		
Possible	0	0.0
Probable	5	1.9
Certain	264	98.1
Severity		
ACR category		
Mild	240	89.2
Moderate	22	8.2
Serious	7	2.6
LDS scale		
Mild	246	91.4
Moderate	19	7.1
Serious	4	1.5
WHO severity		
Serious	5	1.9
Non-serious	264	98.1
NCC-MERP		
E	257	95.5
D	12	4.5
Preventability		
Preventable	9	3.3
Unpreventable	260	96.7
Type of ADR		
Type A	2	0.7
Type B	267	99.3

ACR, American College of Radiology; ADR, adverse drug reaction; NCC-MERP, National Coordinating Council for Medication Error Reporting and Prevention; WHO-UCM, World Health Organization–Uppsala Monitoring Centre.

(Table 2). Type B reactions, idiosyncratic or unrelated to pharmacology or dose, occurred in 267 cases (99.3%). Type A reactions, related to dose and pharmacological mechanism, occurred in 2 cases (0.7%).

Spearman's correlation coefficient (*R*) was 0.667 ($p < 0.01$), and the agreement between the Naranjo probability scale and the WHO-UMC causality categories was 98.1% (Table 3). However, the correlation between the Naranjo scale and the Korean algorithm showed only 3.7% agreement ($R = 0.312$, $p < 0.01$), whereas the agreement was only 1.9% ($R = 0.45$, $p < 0.01$) between the WHO-UMC categories and the Korean algorithm. Between the ACR manual and the LDS severity scale, the *R*-value was 0.646 ($p < 0.001$) and the agreement was 92.2%.

In evaluating CM-ARs in our study, all of the kappa values were >0.957 ($p < 0.001$) and statistically significant.

Clinical manifestations

The 269 reports included 587 different reactions (average: 2.18 per report and range: 1–5 symptoms). The total number may not be equal to the total number of CM-ARs because the drug-caused and clinical manifestations of ADRs could be >1 . The clinical manifestations associated with CM-ARs were variable. Types of reactions observed are set out in Table 4.

The overwhelming majority of CM-ARs were mild and had dermatological manifestations (81.4%), represented by urticaria ($n = 158$), localized skin reactions ($n = 152$) and pruritus ($n = 117$). These were followed by gastrointestinal manifestations (10.6%), including nausea and vomiting. Neurological, cardiovascular and respiratory symptoms associated with CM accounted for 4.4%, 2.6% and 1.5%, respectively, of all organ-specific side effects reported in the database.

Higher significant rates of CM-ARs than those reported in the total ADRs were found for dermatological, gastrointestinal, neurological and respiratory system complaints (χ^2 test, $p < 0.001$; Table 5). Because analysis of historical ADRs was not possible, owing to lack of data (e.g. disease, allergy, medical history and EMR data), total ADRs for analysis included only current ADRs and CM-ARs. No report of nephrotoxic CM reactions was present in the database.

Serious contrast media reactions and treatment

In this study, 4 patients who experienced serious adverse effects after the administration of CM were transferred to the emergency department and needed epinephrine, representing 1.4% of all CM-ARs (Table 6). All four cases involved iopromide (Ultravist® 350; Bayer Korea Ltd, Seoul, Republic of Korea). Two females were administered CM for a coronary artery CT and two males for an abdominal CT. One of the four serious cases had a predisposing factor of taking a beta-blocker 1 h before the CT procedure. No patients died, and all recovered. 23 (8.6%) patients required only observation, whereas 210 (78.1%) were managed with simple medication therapy of hydration and/or diphenhydramine (Table 6). The need for more aggressive treatment, including being transferred to an emergency department (62 cases, 23.0%) was not common. The other 35 patients with CM-ARs needed to be transferred to the emergency room and required medical treatment. Among these serious cases, six patients took beta-blockers (propranolol or bisoprol) for the examination 1 h before undergoing coronary angio-CT. Only eight patients who had an adverse effect to CM had a history of

Table 3. Agreement and correlation between the evaluation tools

Evaluation tools		Agreement (%)	Spearman's correlation coefficient (R)	p-value ^a
WHO-UCM	Korean algorithm v. II	1.9	0.451	<0.01
Naranjo	WHO-UCM	98.1	0.677	<0.01
Korean algorithm v. II	Naranjo	3.7	0.312	<0.01
LDS	ACR	92.2	0.646	<0.01

ACR, American College of Radiology; WHO-UCM, World Health Organization-Uppsala Monitoring Centre.

^aSpearman χ^2 test.

reactions to CM: five of them had CM-AR histories documented in the electronic system of the hospital and three of them had self-reported histories. All of these patients experienced symptomatic urticaria but were pre-medicated with diphenhydramine before undergoing CT.

Contrast media

All CM involved in our study were low-osmolality iodinate agents and gadolinium chelates. The top three drugs that induced the highest number of reports are iopromide, iodixanol and gadobutrol, and the overall reaction rates of CM are 1.11%, 0.7% and 0.27%, respectively. All CM were administered intravenously (Table 7).

The proportion of serious reports for CM was significantly lower compared with the overall rate obtained from total ADRs (χ^2 test, $p < 0.001$; Table 8).

DISCUSSION

In this study, there was a 0.82% adverse reaction rate, higher than that reported in previous studies.^{26–28} Our observed reaction rate to non-ionic iodinated contrast medium injections is comparable to those previously reported by Mortelet et al²⁶ in 29 508 patients, by Cochran et al²⁷ in 73 039 patients and by Wang et al²⁸ in 84 928 injections. Also, a 0.27% adverse reaction rate for gadolinium was observed in our study. This rate is >0.04% than that obtained by Hunt et al²⁹ in 158 439 gadolinium CM administrations. This difference may be owing to differences in the CM administered and the smaller number of CM administrations in

the study hospital than in other studies. However, most CM AEs in our study were mild in severity, like other studies,^{26–30} and managed with simple first aid. Although Mortelet et al²⁶ reported one death and Cochran et al²⁷ reported two deaths, there was no death in our study, as in a previous report.²⁸

Although our additional subgroup analyses revealed no statistically significant difference in AEs related to gender, age or in-/outpatient status, female cases were observed slightly more, as in previous studies,^{28–31} and three of the four patients with serious CM-AR reports were aged ≥ 65 years. In this study, the observation made was that outpatients reacted more frequently to CM than did inpatients or emergency department patients, as in the previous study.²⁸ Although the reason is unclear, a possible explanation could be that access to clinical information on outpatients is more difficult and less reliable and, perhaps, more outpatients with significant risk factors may have undergone contrast-enhanced CT.

The risk of ARs to CM increases owing to several pre-disposing factors, including history of previous CM-AR, asthma, allergy, beta-blockers and heart disease. There is a six-fold increase in reactions to ionic or non-ionic CM in patients who have previously experienced moderate or severe CM-ARs.²⁶ Pre-treatment with corticosteroids has been found to effectively decrease the incidence of serious adverse effects of CM.^{31–33} In the study, eight patients with CM-AR histories were pre-medicated (hydration and/or diphenhydramine) before undergoing CT. Additionally, the patients treated with beta-blockers are at increased risk of

Table 4. Clinical manifestations of contrast media adverse reactions (CM-ARs)

Clinical manifestation	CM-ARs	
	Number of CM-AR ($n = 587$) (%)	Symptom (n)
Dermatological	478 (81.4)	Urticaria (158), pruritus (117), erythema (21), localized skin reactions (152) and generalized skin reaction (30)
Gastrointestinal	52 (8.9)	Vomiting (51) and nausea (1)
Neurological	26 (4.4)	Dizziness (18), syncope (5) and facial paralysis (3)
Cardiovascular	15 (2.6)	Hypotension (9), hypertension (2) and anaphylactic shock (4)
Respiratory	9 (1.5)	Dyspnoea (9)
Other	7 (1.2)	Fever (10)

Total number may not be equal to total number of CM-ARs because the drug-causing and clinical manifestations of CM-ARs could be more than one.

Table 5. Contrast media adverse drug reaction (CM-ADR), according to organ or system

Organ or system	Total ADRs (<i>n</i> = 1114)	CM-ARs	
		Value (<i>n</i> = 587) (%)	<i>p</i> -value ^a
Dermatological	658	478 (72.6)	<0.001
Gastrointestinal	222	52 (23.4)	<0.001
Neurological	101	26 (25.7)	<0.001
Cardiovascular	38	15 (39.5)	NS
Respiratory	40	9 (22.5)	<0.001
Musculoskeletal	8	0 (0)	–
Immunological	7	0 (0)	–
Haematological	6	0 (0)	–
Hepatic	6	0 (0)	–
Renal	6	0 (0)	–
Psychiatric	1	0 (0)	–
Other	21	7 (33.3)	NS

ADR, adverse drug reaction; NS, not significant.

Total number may not be equal to total number of CM-ARs because the drug-causing and clinical manifestations of CM-ARs could be more than one. ^a χ^2 test.

Total ADRs = current ADRs (328) + CM-ARs (269).

CM-ARs.^{34,35} Four among the six patients who had taken beta-blockers for coronary artery CT examination in our study were transferred to the emergency room because of dyspnoea or hypotension and were treated with medication.

Although CM agents are used at *much* higher concentrations and total doses than other drugs, this study showed that the rate of serious CM-ARs was minor compared with other drug categories in the total ADR reports (Table 8). The low proportion of serious ADRs could be explained both by the protective role of preventative management (including a detailed questionnaire, education for patients, pre-medication and choice of the CM according to risk, including previous CM-ARs) before the examination and by the conduct of established protocols for the

Table 6. Management of contrast media adverse reactions (CM-ARs)

Treatment	No. patient (<i>n</i> = 269)	Percentage
Observation only	23	8.6
Simple management (hydration and/or diphenhydramine)	210	78.1
Additional medication	62	23.0
Transfer to emergency room	35	13.0
Received epinephrine	4	1.4

Table 7. Contrast media associated with contrast media adverse reactions (CM-ARs)

Contrast media		Total administrated CMs (<i>n</i> = 32 711)	No. CM-ARs (%)
Iopromide	Ultravist®	18 462	206 (1.11)
Iodixanol	Visipaque®	6253	44 (0.70)
Iohexol	Iobrix®	1041	0.00 (0)
Gadobutrol	Gadovist®	6955	19 (0.27)

Ultravist and Gadovist are manufactured by Bayer Korea Ltd (Seoul, Republic of Korea); Visipaque by Amersham Health (Oslo, Norway); and Iobrix by Taejoon Pharm Ltd (Seoul, Republic of Korea).

prompt treatment of serious ARs after CM administration by radiologists in the hospital. In fact, since NS 500 ml hydration and pre-medication with antihistamine were applied restrictively for some patients with a risk of CM-AR in 2012, the incidence of CM-AR decreased from 1.6% in 2011 to 1.3%.

Dermatological and gastrointestinal effects were most common according to the CM-AR reports received in our study, similar to previous reports.^{26–28,36} Unlike a previous study,³⁷ our results showed higher rates of not only CM respiratory but also CM dermatological, gastrointestinal and neurological events, compared with those reported in total ADRs. The reason seems to be because of the relatively smaller number of total ADR reports excluded from analysis and evaluation owing to lack of information. The incidence of CM-related nephropathy is estimated to be 2–7%.^{37,38} However, there was no nephrotoxic CM-AR report including elevated creatinine levels or other conditions indicating kidney AEs. This may be because kidney functionality and current medications with a risk of nephrotoxicity are now assessed routinely before CM administration to exclude high-risk patients.

Several scales were used to evaluate causality and severity of CM-ARs. The results with the Korean algorithm seemed to overestimate the situation *vs* the other scales. “Probable ADRs” were scored in most CM-AR cases from the WHO-UCM categories and the Naranjo scale, but by contrast, most ADRs were “certain ADRs” using the Korean algorithm (v. II). 96.6% agreement between the Naranjo and the WHO-UC, in the “probable ADR” category, was considerably higher than in previous studies.^{18,39} However, the agreement was very low between the WHO-UCM categories and the Korean algorithm and between the Naranjo scale and the Korean algorithm. The reasons for these results are likely because this study focused only on CM-ARs and the features of these evaluation scales. For example, the difficulty to apply domestically and the confusing questionnaire issues (including positive rechallenge and previous exposure) of the Naranjo scale lead problems to achieve a score ≥ 9 . This sub-analysis showed not only the differences and similarities but also the agreement and correlation between the evaluation systems compared with previous studies.^{18,39,40} To find any relationship among the evaluation systems, additional studies to analyse the differences in the scoring systems might be needed in the future.

Table 8. Drug categories involved in serious adverse drug reaction (ADR) reports

Drug categories ^a	Total reports	Serious reports	% Serious/total for each organ category	p-value ^b
Anti-infective for system (J)	89	12	13.5	<0.001
Antineoplastic agents (L)	4	1	25.0	NS
Antiparasitic products (P)	1	0	0	–
Blood forming organ (B)	7	0	0	–
Cardiovascular system (C)	5	0	0	–
Contrast media (V08)	279 ^c	4	1.4	<0.001
Digestive system (A)	19	3	15.8	<0.013
Genitourinary system (G)	2	0	0	–
Musculoskeletal system (M)	25	2	8.0	NS
Nervous system (N)	134	2	1.5	<0.065
Respiratory system (R)	25	1	4.0	NS
Systemic hormonal preparation (H) ^d	7	2	28.6	<0.002
Total	597	26	4.5	

NS, not significant.

Total ADRs = current ADRs (328) + CM-ARs (269).

^aAnatomical therapeutic chemical (ATC) second level; drug categories accounting for >269 reports are shown in detail.

^b χ^2 test.

^cContrast media 279 ADR reports = current ADR involved CM (10) + CM-ARs (269) reported from the ADR report system.

^dExcluding sex hormones and insulin.

This study has several limitations. Because we conducted a retrospective review of medical records to identify CM-ARs, obtaining information by interviewing the provider or the patient was not possible. It is possible that there was under-reporting of some minor reactions, most of which did not require treatment. Also, because the field regarding information on the patient's medical history was not sufficient for analysis, the contribution of risk factors to the occurrence of CM-ARs might be underestimated. Additionally, information about subsequent adverse effects or previous contrast-related adverse effects at other institutions was unavailable. This can produce bias in interpreting causality in ADRs or the incidence of an ADR. However, additional effort was made to ensure the validity of judgment by implementing pilot studies for the reviewers, assessing the validity of reviews and conducting a secondary review of all questionable alerts. These limitations, although not insignificant, only minimally affected the results of the study and are inherent in most retrospective studies. This study focused on CM-ARs from all ADRs including current, historical and CM ADRs, and the analysis was not applicable to finding any relationship or trend between ADRs and each agent.

Despite these limitations, to the best of our knowledge, few prior reports have addressed evaluation and analyses of CM-ARs using several diverse evaluation tools like those used in our study. Also, this study established CM-AR monitoring databases and suggested importance and improvement of the ADR monitoring system. Based on our study, continuous CM-AR monitoring and a prospective study, if available, are needed in the future.

CONCLUSIONS

We believe that several important conclusions can be drawn from our data: most CM-ARs were unpreventable and mild, resulting in dermatological symptoms. Although most of these CM-ARs can be managed in the hospital with simple medication and observation, some severe CM-ARs may require aggressive treatment and transfer to emergency care. Because patients suffer from CM-ARs, and these adverse effects are an overall social and economic burden,^{41,42} it is important for not only radiologists but also healthcare professionals, in general, to be aware of the potentially serious complications of radio-imaging procedures and pre-disposing risk factors. Also, careful review of reporting and treatment protocols is necessary to prevent morbidity and mortality, and the role of the spontaneous ADR reporting system as a pharmacovigilance measure is considered important.

REFERENCES

- Christiansen C. X-ray contrast media—an overview. *Toxicology* 2005; **209**: 185–7. doi: [10.1016/j.tox.2004.12.020](https://doi.org/10.1016/j.tox.2004.12.020)
- Maitino AJ, Levin DC, Parker L, Rao VM, Sunshine JH. Nationwide trends in rates of utilization of noninvasive diagnostic imaging among the Medicare population between 1993 and 1999. *Radiology* 2005; **227**: 113–7. doi: [10.1148/radiol.2272020617](https://doi.org/10.1148/radiol.2272020617)

3. Katayama H, Yamaguchi K, Kozuka T, Takashima T, Seez P, Matsuura K. Adverse reactions to ionic and nonionic contrast media. A report from the Japanese Committee on the Safety of Contrast Media. *Radiology* 1990; **175**: 621–8. doi: [10.1148/radiology.175.3.2343107](https://doi.org/10.1148/radiology.175.3.2343107)
4. Siegle RL. Rates of idiosyncratic reactions Ionic versus nonionic contrast media. *Invest Radiol* 1993; **28**: 95–8.
5. Lieberman PL, Siegle RL. Reactions to radio-contrast material. *Clin Rev Allergy Immunol* 1999; **17**: 469–96. doi: [10.1007/BF02737651](https://doi.org/10.1007/BF02737651)
6. Kim SS, Park CH, Park MJ, Choi SH, Kim YS, Park HW, et al. Adverse reactions to radio-contrast media in computed tomography (CT) in general population: incidence and clinical features. *Korean J Asthma Allergy Clin Immunol* 2007; **27**: 157–61.
7. Lieberman PL, Siegle RL. Reactions to radio-contrast material. *Clin Rev Allergy Immunol* 1999; **17**: 469–96. doi: [10.1007/BF02737651](https://doi.org/10.1007/BF02737651)
8. Dunnick NR, Cohan RH. Cost, corticosteroids and contrast media. *AJR* 1994; **162**: 527–9. doi: [10.2214/ajr.162.3.8109490](https://doi.org/10.2214/ajr.162.3.8109490)
9. Katayama H. Adverse reactions to contrast media: what are the risk factors? *Invest Radiol* 1990; **25**: 16–7.
10. Powe NR, Moore RD, Steinberg EP. Adverse reactions to contrast media: factors that determine the cost of treatment. *AJR Am J Roentgenol* 1993; **161**: 1089–95. doi: [10.2214/ajr.161.5.8273616](https://doi.org/10.2214/ajr.161.5.8273616)
11. Thomsen HS, Morcos SK. Contrast media and the kidney: European Society of Urogenital Radiology (ESUR) guidelines. *Br J Radiol* 2003; **76**: 513–8.
12. Stacul F, Molen AJ, Reimer P, Webb JA, Thomsen HS, Morcos SK, et al. Contrast induced nephropathy: updated ESUR Contrast Media Safety Committee guidelines. *Eur Radiol* 2011; **21**: 2527–41. doi: [10.1007/s00330-011-2225-0](https://doi.org/10.1007/s00330-011-2225-0)
13. American College of Radiology Committee. *ACR manual on contrast media*. 8th edn. Reston, VA: ACR; 2012.
14. World Health Organization–Uppsala Monitoring Centre (WHO-UMC). *Causality categories [internet]*. Uppsala, Sweden [cited 22 October 2012]. Available from: <http://who-umc.org>
15. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther* 1981; **30**: 239–45.
16. Hong KS, Park BJ, Sin SG, Yang JS, Lee SM, Kim YN. Development of a Korean algorithm for causality assessment of adverse drug reactions. *J Kor Soc Clin Pharmacol Ther* 2002; **10**: 129–42.
17. Motola D, Vargiu A, Leone R, Cocci A, Salvo F, Ros B, et al. Hepatic adverse drug reactions: a case/noncase study in Italy. *Eur J Clin Pharmacol* 2008; **63**: 73–9. doi: [10.1007/s00228-006-0222-z](https://doi.org/10.1007/s00228-006-0222-z)
18. Son MK, Lee YW, Jung HY, Yi SW, Lee KH, Kim SU, et al. Comparison of the Naranjo and WHO-Uppsala Monitoring Centre criteria for causality assessment of adverse drug reactions. *Kor J Med* 2008; **74**: 181–7.
19. Hartwig SC, Denger SD, Schneider PJ. Severity-indexed, incident report-based medication error-reporting program. *Am J Hosp Pharm* 1991; **48**: 2611–16.
20. Classen DC, Pestotnik SL, Evans RS, Lloyd JF, Burke JP. Adverse drug events in hospitalized patients. Excess length of stay, extra costs, and attributable mortality. *JAMA* 1997; **277**: 301–6.
21. Olsson S. The role of the WHO programme on international drug monitoring in co-ordinating world-wide drug safety efforts. *Drug Saf* 1998; **19**: 1–10.
22. International Conference on Harmonization. Post-approval safety data management: definitions and standards for expedited reporting [internet]. 2003 [cited 22 October 2012]. Available from: <http://www.emea.eu.int/pdfs/human/ich/394503en.pdf>.
23. Schumock GT, Thornton JP. Focusing on the preventability of adverse drug reactions. *Hosp Pharm* 1992; **27**: 538.
24. Rawlins MD. Clinical pharmacology. Adverse reactions to drugs. *Br Med J (Clin Res Ed)* 1981; **282**: 974–6.
25. Thomson Reuters. Micromedex healthcare series [internet]. 2011 [cited 26 October 2012]. Available from: <http://www.micromedex.com/>
26. Mortelet KJ, Oliva MR, Ondategui S, Ros PR, Silverman SG. Universal use of non-ionic iodinated contrast medium for CT: evaluation of safety in a large urban teaching hospital. *AJR Am J Roentgenol* 2005; **185**: 31–4. doi: [10.2214/ajr.184.1.01840031](https://doi.org/10.2214/ajr.184.1.01840031)
27. Cochran ST, Bomyea K, Sayre J. Trends in adverse events after IV administration of contrast media. *AJR Am J Roentgenol* 2001; **176**: 1385–8. doi: [10.2214/ajr.176.6.1761385](https://doi.org/10.2214/ajr.176.6.1761385)
28. Wang CL, Cohan RH, Ellis JH, Caoili EM, Wang G, Francis IR. Frequency, outcome, and appropriateness of treatment of nonionic iodinated contrast media reactions. *AJR Am J Roentgenol* 2008; **191**: 409–17. doi: [10.2214/AJR.07.3421](https://doi.org/10.2214/AJR.07.3421)
29. Hunt CH, Hartman RP, Hesley GK. Frequency and severity of adverse effects of iodinated and gadolinium contrast materials: retrospective review of 456,930 doses. *AJR Am J Roentgenol* 2009; **193**: 1124–7. doi: [10.2214/AJR.09.2520](https://doi.org/10.2214/AJR.09.2520)
30. Li A, Wong CS, Wong MK, Lee CM, Au Yeung MC. Acute adverse reactions to magnetic resonance contrast media—gadolinium chelates. *Br J Radiol* 2006; **79**: 368–72. doi: [10.1259/bjr/88469693](https://doi.org/10.1259/bjr/88469693)
31. Greenberger PA, Patterson R, Radin RC. Two pretreatment regimens for high-risk patients receiving radiographic contrast media. *J Allergy Clin Immunol* 1984; **74**: 540–3.
32. Morcos SK. Acute serious and fatal reactions to contrast media: our current understanding. *Br J Radiol* 2005; **78**: 686–93. doi: [10.1259/bjr/26301414](https://doi.org/10.1259/bjr/26301414)
33. Lasser EC. Pretreatment with corticosteroids to prevent reactions to i.v. contrast material: overview and implications. *AJR Am J Roentgenol* 1988; **150**: 257–9. doi: [10.2214/ajr.150.2.257](https://doi.org/10.2214/ajr.150.2.257)
34. Lang DM, Alpern MB, Visintainer PF, Smith ST. Increased risk for anaphylactoid reaction from contrast media in patients on β -adrenergic blockers with asthma. *Ann Intern Med* 1991; **15**: 270–6.
35. Lang DM, Alpern MB, Visintainer PF, Smith ST. Elevated risk of anaphylactoid reaction from radiographic contrast media is associated with both beta-blocker exposure and cardiovascular disorders. *Arch Intern Med* 1993; **153**: 2033–40.
36. Cutroneo P, Polimeni G, Cuecururto R, Calapai G, Caputi AP. Adverse reactions to contrast media: an analysis from spontaneous reporting data. *Pharmacol Res* 2007; **56**: 35–41. doi: [10.1016/j.phrs.2007.03.003](https://doi.org/10.1016/j.phrs.2007.03.003)
37. Barrett BJ. Contrast nephrotoxicity. *J Am Soc Nephrol* 1994; **5**: 125–37.
38. Barrett BJ, Carlisle EJ. Metaanalysis of the relative nephrotoxicity of high- and low-osmolality iodinated contrast media. *Radiology* 1993; **188**: 171–8. doi: [10.1148/radiology.188.1.8511292](https://doi.org/10.1148/radiology.188.1.8511292)
39. Kane-Gill SL, Kirisci L, Pathak DS. Are the Naranjo criteria reliable and valid for determination of adverse drug reaction in the intensive care unit? *Ann Pharmacother* 2005; **39**: 1823–7. doi: [10.1345/aph.1G177](https://doi.org/10.1345/aph.1G177)
40. Son YM, Lee JR, Roh JY. Causality assessment of cutaneous adverse drug reactions. *Ann Dermatol* 2011; **23**: 432–8. doi: [10.5021/ad.2011.23.4.432](https://doi.org/10.5021/ad.2011.23.4.432)
41. Bordet R, Gautier S, Le Louet H, Dupuis B, Caron J. Analysis of the direct cost of adverse drug reactions in hospitalised patients. *Eur J Clin Pharmacol* 2001; **56**: 935–4.
42. Powe NR, Moore RD, Steinberg EP. Adverse reactions to contrast media: factors that determine the cost of treatment. *AJR Am J Roentgenol* 1993; **161**: 1089–95. doi: [10.2214/ajr.161.5.8273616](https://doi.org/10.2214/ajr.161.5.8273616)