



Surveillance of contrast-media-induced hypersensitivity reactions using signals from an electronic medical recording system

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ABSTRACT

Background: Contrast-media (CM) hypersensitivity is a well-known adverse drug reaction. Surveillance of adverse drug reactions usually depends on spontaneous reports. However, the rate of spontaneous reports is low. Recent progress in information technology enables the electronic search on signals of adverse drug reactions from electronic medical recording (EMR) systems.

Objectives: To analyze the incidence and clinical characteristics of CM hypersensitivity using an EMR-based surveillance system.

Methods: The surveillance system used signals from standardized terms within the international classification of nursing practice terms that can indicate symptoms of CM hypersensitivity and from the order codes for procedures that used contrast media, antihistamine, and epinephrine. The search strategy was validated by allergists comparing the electronic search strategy versus manually reviewing medical charts over one month. The main study covered for one year period.

Results: Detection rate of the electronic search method was 0.9% (7/759), while that of the manual search method was 0.8% (6/759). EMR-based electronic search method was highly efficient: reduced the charts that needed to be reviewed by 96% (28/759). The sensitivity of electronic screening was 66.7%, specificity was 99.6%, and the negative predictive value was 99.7%. CM hypersensitivity reactions were noted in 266 among 12,483 cases (2.1%). Urticaria was the most frequent symptom (74.4%). CT was the most frequent procedure (3.6%) that induced CM hypersensitivity.

Conclusion: A surveillance system using EMR may be a useful tool in the study of drug hypersensitivity epidemiology and may be used in an adverse drug reaction alarm system and as a clinical, decision making support system.

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Introduction

Contrast media (CM) hypersensitivity is a well-known adverse drug reaction. Two kinds of CM hypersensitivity occur, based on the time interval from contrast exposure.^{1,2} Immediate reactions, which occur within 1 hour after exposure, are non-immunological

or IgE-mediated reactions.^{3–6} Symptoms of such reactions are cutaneous (itching and urticaria), respiratory (bronchospasm and dyspnea), and cardiovascular (dizziness and anaphylactic shock). The incidence is 3.8 to 12.7% (severe reactions: 0.1–0.4%) for hyper-osmolar ionic contrast and 0.7 to 3.1% (severe reactions: 0.02–0.04%) for low-osmolar ionic contrast.^{7–10} Fatal immediate reactions are very rare (approximately 1–3 per 100,000) regardless of contrast type.¹¹ Delayed reactions, which occur from 1 hour to 7 days after exposure, are T cell-mediated reactions.^{12–15} Symptoms of delayed reactions are usually cutaneous: itching, maculopapular exanthema, Stevens-Johnson syndrome, and toxic epidermal necrolysis.¹⁶ Delayed reactions have been reported to occur with a frequency of 0.5 to 23% for low-osmolar nonionic contrast.¹⁷

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The incidence of adverse drug reactions may have large variation depending on the surveillance system used.¹⁸ Patient safety is important, and adverse drug reaction is the most frequent type of safety issue affecting patients.¹⁸ Therefore, a surveillance system for monitoring adverse drug reactions is essential within the quality control system of a hospital. A spontaneous reporting system is commonly used for such surveillance; however, the low rate of spontaneous reporting is a problem.¹⁸ The incidence of CM hypersensitivity reaction was 0.27% in a study from Korea, an incidence that was very low compared with those reported previously.¹⁹ That prospective Korean study depended on spontaneous reporting by doctors and nurses; thus, a limitation in that study was the low rate of spontaneous reporting. This type of reporting approach can underestimate the frequency of adverse events; thus, there is a need for a more accurate process.^{18,20}

A manual chart review surveillance is usually considered as the gold standard in retrospective studies of adverse drug reactions. However, recent progress in information technology enables computer-based surveying of trigger words and signals associated with adverse drug reactions. Electronic medical record (EMR) systems [for example, the standardized nomenclature of medicine-clinical terminology (SNOMED-CT) and the international classification of nursing practice (ICNP)] have standard vocabularies for use in computerized record keeping. The authors assume that, in an EMR system, one can easily search and retrieve standard vocabulary items that contain information on symptoms, procedures, and treatments, and that contain trigger words or signals associated with adverse drug reactions.

To investigate that assumption, the authors analyzed the incidence and clinical characteristics of CM hypersensitivity using trigger words and signals from an EMR system in a fully digital-record-keeping hospital and examined the efficiency of the EMR search strategy.

Methods

Study site

Seoul National University Bundang Hospital (SNUBH) is a teaching hospital with 905 beds and an average of 3,211 outpatients visiting each day. Approximately 400 physicians and 700 nurses work in the hospital. It is the first fully digital hospital in Korea. SNUBH has a fully computerized EMR system in which medical terms are mapped to a standardized vocabulary, mainly SNOMED-CT and ICNP since May 2003. SNOMED-CT is a comprehensive biomedical terminology recently developed in native-descriptive, logic-based formalism and is likely to become widely used in medical information systems.²¹ At SNUBH, chief complaints were mapped to SNOMED-CT using 6,745 concepts and 11,455 synonyms. A total of 12,187 diagnoses have been mapped to SNOMED-CT and to International Classification of Diseases, 10th Revision. In addition, 9,609 procedures have been mapped to SNOMED-CT. Nursing charts are mapped to ICNP, a unified nursing language system comprising compositional terminology for nursing practice that facilitates the development of, and cross-mapping among, local terms and existing terminologies.²² ICNP's elements include nursing phenomena, actions, and outcomes. The ICNP system at SNUBH is an "extended ICNP," because it has an "attribute" element that can be used to provide more detailed descriptions of other elements. A total of 6,100 nursing items have been mapped to ICNP.

Search strategy

Within a 1-year period (2004.8–2005.8), we searched EMRs of in-hospital patients using standardized ICNP electronic terms that could represent the symptoms of CM hypersensitivity reactions and using codes for orders of procedures that used CM, antihista-

mine, and epinephrine. The computerized search strategy was "1 AND {2 OR 3}" with the numerals representing:

1. Codes for procedures that used CM in in-hospital patients of SNUBH.
2. Codes for prescriptions (antihistamine or epinephrine); to a maximum of 7 days after the procedure to cover delayed reactions.
3. ICNP codes for hypersensitivity reactions in the EMR and based on the following trigger words: *itching, pruritus, skin rash, urticaria, hives, angioedema, edema, laryngeal edema, bronchospasm, dyspnea, respiratory difficulty, hypotension, dizziness, anaphylaxis, anaphylactoid, and shock*.

Electronically screened medical charts were reviewed by board-certified specialists in internal medicine working at the division of allergy and clinical immunology, the department of internal medicine, in our hospital. They were trained to detect only very clear cases with some example charts, and they were supervised with a board-certified allergist. If they found cases in which whether the cases were CM-induced hypersensitivity was uncertain, they discussed with the board-certified allergist. During the chart review, we excluded the cases with any premedication (eg, antihistamines, steroid), so no case with premedication was recruited in this study. Immediate reactions were those occurring within 1 hour of exposure, and delayed reactions were those occurring from 1 hour to 7 days after exposure. The Ring and Messmer classification was used to grade the severity of immediate hypersensitivity reactions: grade I, cutaneous symptoms; grade II, mild systemic reactions; grade III, life-threatening systemic reactions; grade IV, cardiac or respiratory arrest.^{23–25} We defined grades III and IV as severe reactions. Delayed hypersensitivity reactions were graded in 3 grades: mild, no treatment was required; moderate, symptoms readily responded to treatment and no hospitalization was required; severe, hospitalization required or life-threatening reactions occurred.^{23,25}

In a preliminary chart review, we found that too many patients complained of nonspecific gastrointestinal symptoms or nausea or vomiting as symptoms of their co-morbid disease. To enhance screening efficacy, we excluded ICNP terms related to gastrointestinal symptoms in the electronic screening.

Validation of the electronic search strategy

To confirm the validity of the electronic search strategy, we compared the incidences, efficiency, sensitivity, specificity, positive predictive value, and negative predictive values from electronic screening and from a manual chart review over a single month (February 2005). We have performed various trials to have consistent data: the board-certified specialists in internal medicine (who finished the 4-year training course of the internal medicine and 1 year of internship) were recruited and reviewed some of the charts until they showed similar results. All of the data presented here for the validation of the electronic search strategy were evaluated by board-certified specialists, supervised with 1 board-certified allergist to have more consistent data for the validation. They reviewed both of electronically screened cases and all the cases of those who used CM during the periods.

The study protocol was approved by the institutional review board of Seoul National University Bundang Hospital.

Results

Validation and efficiency of the electronic search strategy

Seven hundred fifty-nine cases used CM in February 2005. By the electronic screening methods, 28 cases among 759 cases were initially selected as "candidate cases of CM hypersensitivity"; after

Table 1
Sensitivity and specificity of electronic search strategy

	Manual chart review (+)	Manual chart review (–)	Total
Electronic search (+)	4	3	7
Electronic search (–)	2	750	752
Total	6	753	759

Sensitivity = $4/6 \times 100 = 66.7\%$.Specificity = $750/753 \times 100 = 99.6\%$.Positive predictive value = $4/7 \times 100 = 57.1\%$.Negative predictive value = $750/752 \times 100 = 99.7\%$.

If we consider the manual chart review as gold standard, the sensitivity of electronic screening was 66.7%, specificity was 99.6%, and negative predictive value was 99.7%. Therefore, we assumed that our strategy for electronic screening was adequate for detecting contrast media hypersensitivity.

a subsequent manual chart review, 7 cases (0.9%) were finally confirmed as the cases of “CM hypersensitivity.”

By manual chart review only, 6 cases (0.8%) among 759 cases were confirmed CM hypersensitivity.

If we consider the manual chart review as a gold standard, the sensitivity of the electronic screening was 66.7%, specificity was 99.6%, positive predictive value was 57.1%, and negative predictive value was 99.7% (Table 1).

The results indicate that the electronic screening strategy was efficient. Moreover the electronic screening strategy found 1 more case. On the basis of the electronic screening results, we needed to review only 28 cases manually; the EMR surveillance reduced the number of charts that needed to be reviewed by 96%.

Incidence and clinical features of contrast-media hypersensitivity reactions overall features

Within the year of data studied, 12,483 cases used CM (computed tomography [CT], 49%; magnetic resonance imaging [MRI], 21%; angiography, 17%; and fluoroscopy, 13%). The male-to-female ratio was 1.2:1, and the male and female mean ages were 56.7 and 57.8 years, respectively.

Total hypersensitivity reactions were noted in 264 of the 12,483 cases (2.1%). CM hypersensitivity reactions were noted in 245 of the 9,862 cases (2.5%) with CT, angiography, and fluoroscopy; MRI dye hypersensitivity reactions were noted in 19 of the 2,621 cases (0.7%). In those 264, the male-to-female ratio was 1:1.5, and the male and female mean ages were 53.1 and 56.9 years, respectively. The incidence of severe reactions was 0.01%. Urticaria was the most

frequent symptom (73.9%), followed by itching (17.4%), exanthema (4.9%), flushing (1.9%), angioedema (0.4%), and anaphylaxis (0.4%) (Fig 1). Immediate reactions (within 1 hour) occurred in 21.6% of the reactive cases, whereas delayed reaction (after 1 hour to 7 days) occurred in 78.4% (Table 2).

Immediate reactions were as follows: urticaria (81.5%), itching (11.1%), rash (3.7%), angioedema (1.9%), and anaphylaxis (1.9%). Delayed reactions were urticaria (72.9%), itching (19.2%), rash (5.3%), and flushing (2.6%). Most of delayed reactions occurred within several hours after the exposure.

According to the type of contrast media

During the study period, 3 kinds of low-osmolar dye, an iso-osmolar dye, an ionic dye, and a dye for MRI, were used. The incidence of hypersensitivity reactions for those 3 kinds of low-osmolar dyes were 3.5% (204/5,756), 0% (0/644), and 5.2% (11/212), respectively. The hypersensitivity reaction incidence for the iso-osmolar dye was 3.4% (23/688), whereas that for the ionic dye was 0.54% (4/604). During the study period, the ionic dye was used only for fluoroscopy, especially for endoscopic retrograde cholangiopancreatography, and not for intravenous injection.

The incidence for MRI dye was 0.7% (19/2,621) (Table 2).

According to the types of procedures

According to the types of procedure, there was a difference in the amount of CM used. For CT or CT angiography, 100 to 150 mL of CM was used. For angiography such as arteriography or aortography, 10 to 40 mL of CM was used. For MRI, 15 to 30 mL of CM was used.

CT was the most frequent procedure (3.9%) that induced CM hypersensitivity, followed by angiography (1.1%), MRI (0.8%), and fluoroscopy (0.2%). One case of anaphylaxis occurred during CT angiography (Table 2).

Who showed hypersensitivity reactions?

In terms of allergic disorders, those who had previously exhibited CM hypersensitivity reactions were the most prevalent condition (12.1%), followed by drug allergy (5.7%), asthma (2.2%), urticaria (1.5%), allergic rhinitis (1.1), atopic dermatitis (1.1%), and food allergy (0.4%). Among other co-morbid conditions, cancer (47.2%) was the most prevalent condition, followed by subject age more than 60 years (44.9%), pulmonary diseases (15.1%), diabetes melli-

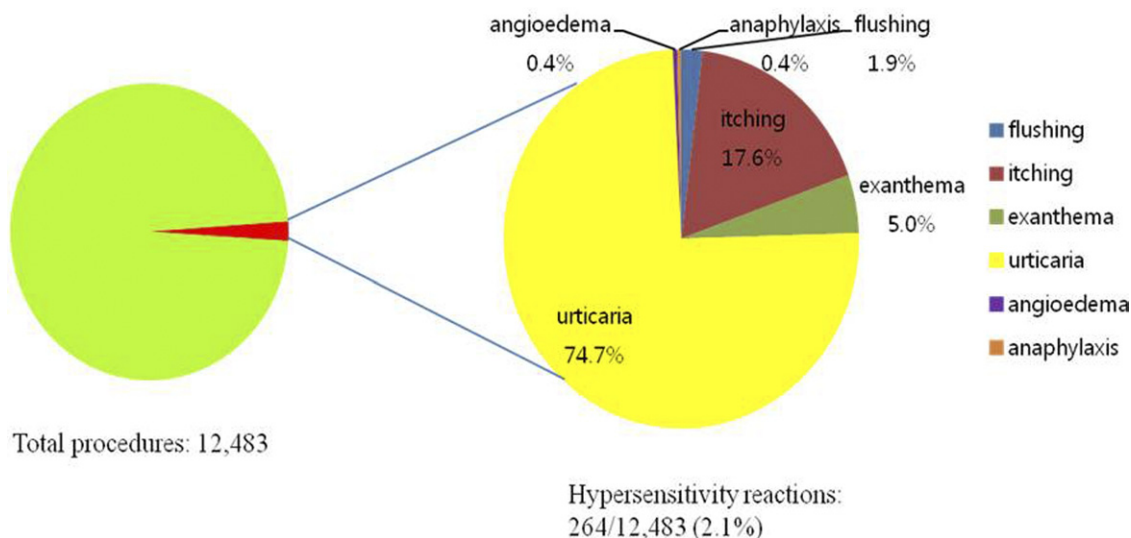
**Fig. 1.** Incidence and clinical manifestations of contrast media hypersensitivity.

Table 2
Clinical manifestations of hypersensitivity reaction according to the procedures

	CT	CT angiography	Arteriography	Fluoroscopy	MRI	Total
Symptoms						
Flushing	4 (2.0%)	0 (0.0%)	1 (4.5%)	0 (0.0%)	0 (0.0%)	5 (1.9%)
Itching	36 (18.0%)	3 (15.0%)	6 (27.3%)	0 (0.0%)	3 (15.8%)	48 (18.2%)
Exanthema	12 (6.0%)	0 (0.0%)	1 (4.5%)	1 (33.3%)	0 (0.0%)	14 (5.3%)
Urticaria	147 (73.5%)	16 (80.0%)	14 (63.6%)	2 (66.7%)	16 (84.2%)	195 (73.9%)
Angioedema	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
Anaphylaxis	0 (0.0%)	1 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
Onset time						
Immediate reactions	47 (23.5%)	5 (25.0%)	0 (0.0%)	1 (33.3%)	4 (21.1%)	57 (21.6%)
Delayed reactions	153 (76.5%)	15 (75.0%)	22 (100%)	2 (66.7%)	15 (78.9%)	207 (78.4%)
Total	200	20	22	3	19	264

tus (12.5%), hypertension (10.6%), cardiovascular diseases (8.3%), renal diseases (3.8%), and hepatic diseases (2.6%).

Discussion

Adverse drug reactions are difficult to detect because of the reluctance of clinicians to report them; therefore, medical record reviews have been an important source of information on adverse drug reactions.¹⁸ Based on our results, it is clear that an EMR system is a very useful tool in retrospective studies with chart review. The EMR system of SNUBH consisted of SNOMED-CT and ICNP.^{21,22} In that system, we were able to search and retrieve indexed clinical terminology by code number with the available search engines. Most previous studies using electronically stored information to search adverse drug events have used administrative data, diagnoses, laboratory results, and prescription codes. We are unaware of any prior studies that have evaluated adverse drug reactions using ICNP words that describe the patient's symptoms.^{18,19} In this study, the incidence of CM hypersensitivity was 2.1%, which is almost 10 times higher than that in a previous study of Korean data that was derived from a spontaneous reporting system used by doctors and nurses.¹⁹ Many search engines have been developed, some for free text. We hope that such free text search engines could be adopted in EMR systems; such adoption will provide a powerful tool for retrospective chart review, surveillance for adverse drug reactions, and similar activities.

In this study, most CM hypersensitivity reactions were cutaneous reactions such as urticaria. The anaphylaxis rate in the reactive cases was 0.4% and was 0.01% among all of the contrast-using procedures. Previous studies reported a severe reactions incidence of 0.22% for hyperosmolar ionic contrast and 0.04% for low-osmolar nonionic contrast.⁷ The incidence of severe adverse reactions was 0.04% for low-osmolar nonionic contrast among a general population who visited Seoul National University Hospital Healthcare System GangNam Center in Korea.²⁶ The incidences of those severe reactions are similar to that in this study (0.01%).

Gastrointestinal symptoms such as nausea, vomiting, and abdominal pain were initially included in the search as index clinical terminologies. However, so many patients complained of nonspecific gastrointestinal symptoms that those symptoms were not deemed useful to this study. Therefore, we excluded gastrointestinal symptoms and focused on other symptoms as index clinical terminologies. This exclusion may result in a hypersensitivity reaction incidence that is lower than the actual incidence, but we suggest that it enhances the sensitivity and specificity of the search strategy.

The incidence of CM hypersensitivity is related to the type of contrast medium used. Generally, ionic hyperosmolar contrast shows more incidence of hypersensitivity than low-osmolar contrast, and isotonic iso-osmolar contrast shows the least incidence of hypersensitivity.^{7,27} In this study, we found that 2 kinds of nonionic low-osmolar and an iso-osmolar contrast showed similar hyper-

sensitivity incidences; there was no hypersensitivity reaction with the one nonionic low-osmolar contrast. The incidence of hypersensitivity in an ionic contrast was low; however, ionic contrast is currently used only for fluoroscopy, especially for endoscopic retrograde cholangiopancreatography, and not for intravenous injection. Therefore, low hypersensitivity incidence using ionic contrast may result from its different access route.

The type of procedure is also important in the development of CM hypersensitivity. Here, CT was the most common cause of CM hypersensitivity, followed by angiography. Other research has shown similar results. A significantly greater portion of patients reported hypersensitivity reactions after intravenous administration than after intra-arterial CM administration (98% vs 2%, respectively).²⁵ Kvedariene et al⁶ examined the causal procedures of 44 patients who consulted allergists because of CM hypersensitivity reactions: CT was the most common causal procedure (27 patients), followed by coronary angiography (6 patients), and urography (6 patients); their study did not discuss MRI or fluoroscopy.⁶ A difference in the amount of CM or the intravenous administration of CM may more easily cause hypersensitivity reactions; this hypothesis needs further investigation.

Interestingly, contrast for MRI showed 0.7% of the reactions. Most of the hypersensitivity reactions were cutaneous. Many doctors tend to consider that the use of MRI CM is safe; however, there are also reports of anaphylaxis caused by MRI CM.²⁸ Thus, physicians should be aware that hypersensitivity reactions can also be caused by MRI dye.

Previous reports have shown that CM hypersensitivity risk factors are previous reactions to CM, history of allergy or atopy, history of asthma or bronchospasm, cardiac disease, dehydration, renal disease, age (very young or old patients), hematological or metabolic disease, anxiety or depression, medications (β blockers, interleukin-2, aspirin, nonsteroidal anti-inflammatory drugs), and periods of pollinosis.^{26,27} This study also showed that the percentage of patients who experienced CM hypersensitivity reactions was high in those who had previously experienced CM hypersensitivity. The percentage of patients showing recurrence of CM hypersensitivity reactions can be very high (21–60%).²⁹ Katayama⁷ reported that the incidence of recurrent CM hypersensitivity is 11.2% for nonionic contrast and 44.0% for ionic contrast. Moreover, patients tend to get severe hypersensitivity reactions if they have had previous severe hypersensitivity reactions.²⁹ Obtaining medical history regarding previous CM hypersensitivity reactions is an important, preprocedure step in preventing CM hypersensitivity reactions. Premedication with a systemic steroid, antihistamine, and H₂ blocker can prevent severe CM hypersensitivity reactions.³⁰ Information on a medical history of allergy to other drugs or asthma could also be used to prevent such a reaction. Thus, physicians should be aware of the risk factors of CM hypersensitivity and should obtain patient information regarding those factors. During the study period, those who had previous history of CM hypersensitivity reactions were

not premedicated properly. After this study, we have developed an alert system within the EMR system to warn physicians about any history of CM hypersensitivity. We also provide the clinical guideline of premedications in electronic form and an automatic consultation (to an allergy specialist) system. In our study, the most frequent co-morbidity was cancer, followed by age (>60 years old), cardiovascular disease (hypertension, cardiac disease, and vascular disease), pulmonary disease, diabetes mellitus, renal disease, and liver disease. Those results, with the exception of cancer, are in accord with previous reports.^{26,27} The high frequency of cancer among CM-hypersensitive patients may be related to the frequent use of CT evaluation in cancer patients; that relationship requires further study.

This study was a retrospective chart review study and had some limitations. We could not evaluate how hospital discharge before 7 days affected the estimate of delayed reactions.

In conclusion, the incidence of CM hypersensitivity in SNUBH-admitted patients was 2.1%, with severe reactions in 0.01% of the cases. Most of the hypersensitivity reactions were delayed reactions. The EMR-based search strategy showed high efficiency: it reduced the work load related to performing chart reviews by 96%. Electronic medical record-based searches are useful when researching adverse drug reactions such as CM hypersensitivity.

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