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Stratified premedication strategy for the prevention of contrast media hypersensitivity in high-risk patients

Suh-Young Lee, MD [*,†]; Min Suk Yang, MD, PhD [*,‡]; Young-Hoon Choi, MD, PhD [§]; Chang Min Park, MD, PhD [§]; Heung-Woo Park, MD, PhD [||]; Sang Heon Cho, MD, PhD [*,||,¶]; Hye-Ryun Kang, MD, PhD [*,||,¶]

[*] Institute of Allergy and Clinical Immunology, Seoul National University Medical Research Center, Seoul, Korea
[†] Division of Pulmonary, Allergy and Critical Care Medicine, Department of Internal Medicine, Kangdong Sacred Heart Hospital, Seoul, Korea
[‡] Department of Internal Medicine, SMG-SNU Boramae Medical Center, Seoul, Korea
[§] Department of Radiology, Seoul National University College of Medicine, Seoul, Korea
[||] Department of Internal Medicine, Seoul National University Hospital, Seoul, Korea
[¶] Drug Safety Monitoring Center, Seoul National University Hospital, Seoul, Korea

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ABSTRACT

Background: Although the severity of hypersensitivity reactions to iodinated contrast media varies, it is well correlated with the severity of recurrent reactions; however, prophylaxis protocols are not severity-stratified.
Objective: To assess the outcomes of tailored prophylaxis according to the severity of hypersensitivity reactions to iodinated contrast media.
Methods: Our premedication protocols were stratified based on the severity of previous reactions: (1) 4 mg of chlorpheniramine for mild reactions, (2) adding 40 mg of methylprednisolone for moderate reactions, and (3) adding multiple doses of 40 mg of methylprednisolone for severe index reactions. Cases of reexposure in patients with a history of hypersensitivity reactions were routinely monitored and mandatorily recorded.
Results: Among a total of 850 patients who underwent enhanced computed tomography after severity-tailored prophylaxis, breakthrough reactions occurred in 17.1%, but most breakthrough reactions (89.0%) were mild and did not require medical treatment. Additional corticosteroid use did not reduce the breakthrough reaction rate in cases with a mild index reaction (16.8% vs 17.2%, $P = .70$). However, under-premedication with a single dose of corticosteroid revealed significantly higher rates of breakthrough reaction than did double doses of corticosteroid in cases with a severe index reaction (55.6% vs 17.4%, $P = .02$). Changing the iodinated contrast media resulted in an additional reduction of the breakthrough reaction rate overall (14.9% vs 32.1%, $P = .001$).
Conclusion: In a total severity-based stratified prophylaxis regimens and changing iodinated contrast media can be considered in patients with a history of previous hypersensitivity reaction to iodinated contrast media to reduce the risk of breakthrough reactions.

Introduction

Patients with a previous history of hypersensitivity reaction to iodinated contrast media (ICM) are at significantly increased risk for recurrent hypersensitivity reaction upon subsequent exposure to ICM. However, symptoms and severity of repeat hypersensitivity reactions are largely predictable because they are usually similar to those of the index reaction, and the risk of developing a severe breakthrough reaction (BTR) is very low in patients with a mild index reaction.[1,2]

Although it is still a precautionary principle to avoid causative agents once drug hypersensitivity occurs, enhanced computed tomography (CT) has become an essential part of modern medicine and is sometimes irreplaceable with other imaging modalities. To address this issue, diverse strategies have been considered, including premedicating patients,[3–6] changing the ICM,[7,8] and performing skin tests to determine ICM cross-reactive to the causative agent.[8]

However, owing to the paucity of large-scale studies to prove the efficacy of these strategies, global guidelines to prevent hypersensitivity to ICM have not been standardized. Several premedication regimens have revealed efficacy in preventing recurrent hypersensitivity reactions in observational studies[3,9–11]; nevertheless, an optimal premedication approach has not been

Reprints: Hye-Ryun Kang, MD, PhD, Department of Internal Medicine, Seoul National University College of Medicine, 101 Daehak-ro, Jongno-gu, Seoul, Korea; E-mail: helenmed@snu.ac.kr.
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determined because severe reactors were not included in most studies, and there was no distinct strategy for mild reactors, which comprised most cases. Therefore, we aimed to evaluate the potential benefit of severity-tailored prophylaxis in patients at risk of recurrent hypersensitivity reactions to ICM.

Methods

Study Participants and Injected Contrast Media

This study included all patients with a history of immediate ICM hypersensitivity who underwent enhanced CT between July 2012 and June 2014. Symptoms suggestive of ICM hypersensitivity were monitored and mandatorily recorded by trained nurses in real-time in the electronic medical record-based Contrast Safety Monitoring and Management System (CoSM^{2}oS) at Seoul National University Hospital. Data such as age, sex, injected ICM agent, and previous history of exposure and hypersensitivity reactions to ICM were also collected from the same system. Throughout the entire study period, 5 kinds of low-osmolar nonionic ICM (LOCM) were used for CT: iobitridol, iohexol, iomeprol, iopamidol, and iopromide.

Severity of Immediate Hypersensitivity Reactions

Immediate hypersensitivity reaction was defined as a reaction that occurred within 1 hour of ICM administration. Patients' symptoms and signs were classified into 3 categories based on the American College of Radiology manual on contrast media: mild, moderate, or severe reactions.[2] Mild reactions included limited urticaria, pruritus, cutaneous edema, nasal congestion, rhinorrhea, and conjunctivitis. Moderate reactions included diffuse urticaria, erythema, facial edema without dyspnea, laryngeal edema, and mild wheezing without hypoxia. Severe reactions included signs and symptoms that are often life-threatening, such as diffuse erythema and edema with dyspnea, hypotension (defined as systolic blood pressure $<$90 mm Hg), laryngeal edema with hypoxia, wheezing with hypoxia, unresponsiveness, cardiopulmonary arrest, and clinically manifested arrhythmias.

Prophylaxis Strategy for High-Risk Cases on Reexposure to ICM

In CoSM^{2}oS, a premedication regimen determined by the severity of the index hypersensitivity reaction was recommended via an order communication system when physicians reordered enhanced CT for those who previously experienced a hypersensitivity reaction to ICM; regimens were as follows: (1) for patients with a mild index reaction, 4 mg of intravenous chlorpheniramine 30 minutes before ICM administration; (2) for patients with a moderate index reaction, 40 mg of intravenous methylprednisolone and 4 mg of intravenous chlorpheniramine 1 hour before ICM administration; and (3) for patients with a severe index reaction, 40 mg of intravenous methylprednisolone 4 hours and 1 hour before and 4 mg of intravenous chlorpheniramine 1 hour before ICM administration via the intravenous catheter inserted for ICM injection. For antihistamine premedication, 4 mg of intravenous chlorpheniramine was used instead of 50 mg of diphenhydramine because of the latter's unavailability in Korea.

For patients with near-fatal anaphylactic shock, life-threatening reactions, including hypotension that requires epinephrine injection in the previous exposure, a skin test to rule out potentially provoking ICM, and hospital admission for close monitoring were also recommended. Alternative ICM were determined if the agent was not related to previous hypersensitivity events and had a negative result on the skin test.

Physicians were allowed to modify a premedication regimen recommended by CosM^{2}oS. Patients were identified as underpremedicated if a lower dose or fewer kinds of premedication drugs were administered and were identified as overpremedicated if a higher dose or more kinds of premedication were administered compared with the CoSM^{2}oS recommendation.

Monitoring Strategy on Reexposure

After ICM reexposure, participants were monitored for an hour to determine the occurrence of immediate hypersensitivity reaction. BTR was defined as a repeat contrast reaction that occurred despite premedication. CT was considered successfully performed when patients had no symptoms or only mild reactions not requiring medical treatment.

Statistical Analysis

The incidence rate was calculated by dividing the number of cases of ICM hypersensitivity reactions by the number of cases undergoing contrast-enhanced CT during the study period. The differences between the groups with and without hypersensitivity reactions were assessed using the χ^2 test for categorical variables and the *t* test for continuous variables. The results after reexposure were analyzed as a whole and according to the severity of previous index reactions. Risk factors for BTR were determined by multiple logistic regression models. Analyses were adjusted for age, sex, previous ICM exposure history, and history of previous ICM hypersensitivity. A backward stepwise model was used, with the likelihood ratio criterion of a $P < .05$ to retain a variable; analyses were performed using the SPSS software package, version 22.0 (SPSS Inc, Chicago, Illinois).

Ethics Statement

This retrospective cohort study was conducted according to the ethical guidelines for epidemiologic research designed by the Korean Ministry of Health and Welfare and was approved by the institutional review board of Seoul National University Hospital. The need for informed consent was waived. The anonymous identifiers were obtained, and the participants' privacy was protected in a secure manner.

Results

During the study period, a total of 850 index cases with a history of prior immediate hypersensitivity reaction (762 mild, 65 moderate, and 23 severe cases) were premedicated at the time of reexposure to ICM in accordance with the CoSM^{2}oS recommendations. Their clinical characteristics are summarized in Table 1. Separately from these cases following the recommendations, there were 273 underpremedicated cases and 95 overpremedicated cases for which the severity-tailored prophylaxis recommendations were not applied.

Table 1
Clinical Characteristics of the 850 Patients With Previous Hypersensitivity Reactions[a]

Characteristic	Finding
Age, mean (SD), y	57.4 (0.3)
Female	459 (54.0)
Type of contrast media	
Iobitriol	251 (29.5)
Iohexol	255 (30.0)
Iomeprol	30 (3.5)
Iopamidol	73 (8.6)
Iopromide	241 (28.4)
Previous LOCM exposure	448 (52.7)
Total previous exposure time to contrast media, mean (SD)	4.9 (0.2)

Abbreviation: LOCM, low osmolar contrast media.
[a]Data are presented as number (percentage) of patients unless otherwise indicated.