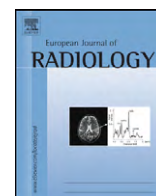




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Outcomes of premedication for non-ionic radio-contrast media hypersensitivity reactions in Korea

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ABSTRACT

Background: Radio-contrast media (CM)-related adverse reactions are important clinical problems that may cause fatal anaphylaxis. Accordingly, it has been common practice to premedicate patients who have had previous reactions to CM with corticosteroids, antihistamines, and H2 blockers to prevent hypersensitive reactions. However, the effectiveness of premedication has not been properly demonstrated, especially in cases related to non-ionic CM. In this study, we evaluated the effectiveness of premedication at preventing of non-ionic CM immediate-type hypersensitivity reactions.

Methods: A total of 30 patients who had been pretreated with corticosteroid and H1 antihistamines and/or H2 blockers in a 3-year period were enrolled. The results of premedication were evaluated in terms of clinical characteristics and the features of breakthrough reactions.

Results: Hypersensitivity reactions were not prevented in 5 of the 30 patients who had experienced prior CM reactions (overall recurrence rate after premedication 16.7%; 4/17 patients with mild previous reactions, and 1/13 patients with severe previous reactions). The recurrence rate after premedication was significantly higher in patients with mild previous reactions than in those with severe reactions (23.5% vs. 7.7%; $p < 0.001$). The breakthrough reactions were similar to the prior reactions in terms of severity and clinical manifestations.

Conclusion: Premedication with corticosteroid and H1 antihistamines and/or H2 blockers effectively prevent non-ionic CM-related adverse events in most patients who have had severe previous reactions to CM. However, physicians should be aware of the possibility of premedication failing and of breakthrough reactions, even in cases in which the previous reactions were mild.

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1. Introduction

Radio-contrast media (CM) are intravascular pharmaceuticals that are used in approximately 75 million procedures annually [1]. In addition to computed tomography, many recent radiological and cardiologic interventional procedures require contrast media to obtain more accurate information and, indeed, the use of contrast media is crucial for diagnosis in many cases. However, contrast media are composed of highly concentrated solutions of tri-iodinated benzene derivatives, which can cause various types of immediate (≤ 1 h) and non-immediate (> 1 h) adverse reactions [2]. Although low-osmolar, non-ionic CM have been used since the mid-1970s to reduce such side-effects, adverse reactions to them have also been reported (in 2.0–3.1% of cases) [3,4]. Furthermore, large-scale observational studies have demonstrated that severe immediate adverse reactions such as anaphylactic shock occur in 0.1–0.4% of patients receiving ionic CM and 0.02–0.04% of patients receiving non-ionic CM [5]. Considering the large num-

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Table 1
Clinical characteristics of and previous adverse reactions in the study subjects.

Subject number	Gender	Age	Underlying disease	Previous adverse reaction			Risk factors ^b
				Type ^a	Severity	Contrast media	
1	M	59	UTI	S	Mild	Iomeprol	
2	F	54	Pancreatic mucinous cystic tumor	S	Mild	Iopromide	
3	M	21	Nutcracker syndrome	S, G	Mild	Iopromide	
4	F	40	Breast cancer	S	Mild	Iopromide	
5	F	43	Breast cancer	S, N	Mild	Iopromide	
6	F	55	Angina	S	Mild	Iopromide	
7	F	77	Cholangiocarcinoma	S	Mild	Iomeprol	
8	F	35	Takayasu's arteritis	S	Mild	Unknown	
9	F	49	Brain aneurysm	S	Mild	Iopamidol	
10	M	68	CVA	S	Mild	Unknown	
11	M	25	Hypertension	S, G	Mild	Iopromide	
12	M	47	Angina	S	Mild	Iodixanol	
13	F	67	Hepatocellular carcinoma	S	Mild	Iomeprol	
14	F	57	Acute pancreatitis	S	Mild	Iopromide	AR
15	F	35	Gross hematuria	S	Mild	Iopromide	
16	F	50	Renal cell carcinoma	S	Mild	Unknown	
17	M	69	Angina	S	Mild	Iodixanol	BB
18	F	30	Asthma	R	Severe	Iopromide	BA
19	F	43	Cervix cancer	S, R, C	Severe	Iopromide	
20	F	58	Hepatocellular carcinoma	S, C	Severe	Iopromide	
21	F	74	Duodenal cancer	S, C	Severe	Iopromide	
22	F	68	Hepatocellular carcinoma	S, C	Severe	Iopamidol	
23	F	24	Spine tumor	S, R, C	Severe	Iomeprol	
24	F	68	Hepatocellular carcinoma	S, C	Severe	Iopamidol	
25	M	72	Angina	C, N	Severe	Iopromide	
26	M	55	Colon cancer	S, R, C	Severe	Iopromide	
27	F	38	Rectal cancer	S, R, C	Severe	Iopromide	
28	F	48	Unstable angina	S, R	Severe	Iodixanol	
29	F	56	Colon cancer	S, C	Severe	Iopromide	
30	F	59	Carotid aneurysm	S, C	Severe	Iopamidol	

^a S: skin manifestations such as urticaria, angioedema, pruritus, facial flushing, or redness; G: gastrointestinal manifestations such as nausea or vomiting; N: neurological manifestations such as dizziness or syncope; R: respiratory manifestations such as rhinorrhea, dyspnea, laryngeal edema, bronchospasm, or hypoxemia; C: cardiovascular manifestations such as hypotension, arrhythmia, or cardiac arrest.
^b AR: allergic rhinitis; BB: concomitant use of beta-blockers; BA: bronchial asthma.

ber of patients who receive CM annually, this incidence rate has a significant impact in clinical practice.

Premedication with corticosteroid, either alone or in combination with antihistamines and/or H2 blockers, is commonly used in patients that have previously experienced CM-related immediate adverse reactions [5]. However, the efficacy of combination prophylaxis regimens in these high-risk patients has not been fully evaluated to date, and supporting data are still lacking [6], especially in cases of non-ionic CM-induced reactions. Moreover, the outcome of using premedication to prevent CM hypersensitivity reactions has never been evaluated in an Asian or Korean population.

In this study, we evaluated 30 patients who had experienced prior immediate-type CM-related adverse reactions and who received premedication to prevent non-ionic CM hypersensitivity. We analyzed the effectiveness of premedication and the features of breakthrough reactions according to the patients' clinical characteristics.

2. Methods

2.1. Study subjects

We retrospectively reviewed patients who, in a 3-year period, were referred to the allergy clinics of the Seoul National University Hospital and Seoul National University Bundang Hospital for the prevention of CM-induced hypersensitivity reactions, due to a history of CM-related adverse reactions. The patients' clinical characteristics, including the characteristics of prior reactions, severity of prior reactions, contrast media associated with prior reactions, underlying disease, allergic disease history, and concomitant use

of beta-blockers, were examined. This study included patients who had experienced only immediate-type (<1 h) hypersensitivity reactions and excluded patients with other types of previous reactions, such as delayed hypersensitivity reactions, vasovagal reactions, and chemotoxicity-related reactions. Prior CM-induced adverse reactions were classified as being either 'mild' or 'severe'. Severe reactions were defined by the presence of one or more of the following systemic symptoms: dyspnea, sudden drop in blood pressure, cardiac arrest, loss of consciousness. This study was approved by the institutional review boards of both hospitals.

2.2. Contrast media and procedures

All patients evaluated in this study had undergone intravascular radiological procedures, including various kinds of contrast CT scans, angiographies, and radiological interventions requiring the use of CM. Patients who had undergone non-vascular procedures, such as urological or intrabiliary procedures, were excluded. The CM used in these procedures included Ultravist™ (Iopromide), Iomeron™ (Iomepril), Pamiray™ (Iopamidol) (all low-osmolar, non-ionic), and Visipaque™ (Iodixanol) (iso-osmolar, non-ionic). Patients treated with high-osmolar and ionic CMs were excluded.

2.3. Premedication

Premedication formulations comprised combinations of modified forms of previously described systemic steroids, antihistamines, and H2 blockers [5,7,8]. In most patients, systemic steroids (prednisolone, 50 mg or methylprednisolone, 40–50 mg) were administered three times (13, 7, and 1 h prior to the procedure). As a result of factors including infection with hepatitis B virus, poor

Table 2

Radiologic interventions and outcomes of premedication.

Subject number	Premedication				Procedure	Contrast media	Breakthrough adverse reaction
	Steroid	Antihistamine	H2-blocker	Total steroid dose (mg) ^a			
1	PD ^b 30 mg × 1	+	+	30	Kidney, bladder CT	lopromide	NAE ^c
2	MP ^d 20 mg × 2	+	+	50	Pancreatobiliary CT	lopromide	NAE
3	MP 50 mg × 1	+	+	62.5	Kidney bladder CT	lopromide	NAE
4	MP 20 mg × 3	+	+	75	Chest CT	lopromide	NAE
5	MP 30 mg × 3	+	+	112.5	Chest CT	lopromide	NAE
6	MP 30 mg × 3	+	+	112.5	CT angiography	lopromide	NAE
7	MP 30 mg × 3	+	+	112.5	Pancreatobiliary CT	lomeprol	NAE
8	PD 40 mg × 3	+	+	120	CT angiography	lopromide	Facial flushing
9	MP 40 mg × 3	+	–	150	Coil embolization	lopamidol	Facial flushing
10	MP 40 mg × 3	+	+	150	CT angiography	lomeprol	Urticaria
11	PD 50 mg × 3	+	+	150	CT angiography	lopromide	NAE
12	PD 50 mg × 3	+	+	150	CT angiography	lomeprol	NAE
13	PD 50 mg × 3	+	+	150	Liver CT	lomeprol	NAE
14	PD 50 mg × 3	+	+	150	Pancreatobiliary CT	lopromide	Facial flushing, edema
15	MP 50 mg × 3	+	+	187.5	Renal angiography	lodixanol	NAE
16	MP 50 mg × 3	+	+	187.5	Kidney bladder CT	lopromide	NAE
17	MP 50 mg × 3	+	+	187.5	CAG ^e	lodixanol	NAE
18	MP 40 mg × 1	+	+	50	Brain CT angiogram	lopromide	NAE
19	MP 20 mg × 3	+	+	75	Abd/pelvis CT	lopromide	NAE
20	MP 20 mg × 3	+	+	75	Liver CT	lopromide	NAE
21	MP 20 mg × 3	+	+	75	Pancreatobiliary CT	lopromide	NAE
22	MP 30 mg × 3	+	+	100	TFCA ^f	lopamidol	NAE
23	MP 40 mg × 2	+	+	100	Spinal angiography	lopamidol	NAE
24	MP 30 mg × 3	+	+	112.5	TFCA	lopamidol	NAE
25	MP 40 mg × 3	+	+	150	CAG	lodixanol	NAE
26	PD 60 mg × 3	+	–	180	Abd/pelvis CT	lopromide	NAE
27	MP 50 mg × 3	+	+	187.5	Abdominal CT	lopromide	Anaphylactic shock
28	MP 50 mg × 3	+	+	187.5	CAG	lodixanol	NAE
29	MP 50 mg × 3	+	+	187.5	Abdominal CT	lopromide	NAE
30	MP 50 mg × 3	+	+	187.5	Coil embolization	lopamidol	NAE

^a Total steroid dose (prednisolone equivalent; mg).^b PD: prednisolone.^c NAE: no adverse-event.^d MP: methylprednisolone.^e CAG: coronary angiography.^f TFCA: transfemoral cerebral angiography.

glucose control, low body weight, and need for urgent examination, some patients received a lower dosage or experienced a shortened dosing schedule. Antihistamine (pheniramine maleate, 45.5 mg, i.v. or chlorpheniramine, 2 mg, p.o.) was administered to all patients 1 h before the procedure. H2 blocker (cimetidine, 300 mg, p.o., ranitidine, 50 mg, i.v., or famotidine, 20 mg i.v.) was administered to all but two patients 1 h prior to the procedure.

2.4. Statistical analysis

To compare the recurrence rates in patients with mild previous reactions and those with severe previous reactions, Fisher's Exact test was performed using SPSS Version 13.0 software. A *p* value < 0.05 was considered to be statistically significant.

3. Results

3.1. Subject characteristics

Thirty patients who were premedicated due to prior adverse reactions were included in this study. The mean age ± SD of the patients was 50.9 ± 15.3 years. Eight patients (26.7%) were male. The prior reactions in 17 patients were classified as mild, and those in the remaining 13 patients severe. Skin manifestations such as urticaria, angioedema, pruritus, and flushing were noted in all subjects except two with severe prior reactions. Among the 13 patients with severe previous reactions, 11 had experienced cardiovascular problems such as hypotension, arrhythmia, and cardiac arrest and 7 had experienced respiratory manifestations

such as dyspnea, laryngeal edema, bronchospasm, and hypoxemia (Table 1).

3.2. Outcome of premedication

Premedication failed to prevent hypersensitivity reactions in 5 of the 30 patients who had experienced previous immediate-type CM-related adverse reactions (overall recurrence rate after premedication was 16.7%). While premedication failed to prevent an adverse reaction in only one of the 13 patients who had previously experienced a severe reaction such as anaphylaxis, immediate adverse reactions recurred in 4 of 17 patients with mild previous reactions, in spite of premedication. The recurrence rate after premedication was significantly higher in patients with mild previous reactions than in those with severe reactions (23.5% vs. 7.7%; *p* < 0.001). All breakthrough reactions occurred in cases in which the same CM as that which caused the previous reaction (or an unidentified CM) was used. Recurrence of adverse reactions did not occur in any patients who received a different CM from that which was associated with previous adverse reactions. All failures of premedication occurred in patients receiving a low-osmolality CM. Premedication successfully prevented reactions to iso-osmolar CM (Table 2).

3.3. Breakthrough adverse reactions

Despite receiving premedication, five patients experienced immediate breakthrough adverse reactions. These were similar to the previous reactions they had experienced in terms of their

characteristics and severity. Four patients (Nos. 8, 9, 10, and 14) who experienced immediate mild previous reactions exhibited similar mild cutaneous manifestations, such as facial flushing or urticaria, that were no more severe than those they had previously suffered. One patient (No. 27) who had previously experienced anaphylactic shock following abdominal CT underwent a similar type of anaphylactic shock requiring emergency management and additional treatment with epinephrine, antihistamine, and steroid (Table 2).

4. Discussion

Premedication with corticosteroids, antihistamines, and H2 blockers has commonly been used to treat patients who have previously experienced CM-related immediate adverse reactions [5,7,8]. However, data supporting the effectiveness of premedication at preventing adverse reactions in such patients are insufficient, and the outcomes of the use of premedication to prevent CM hypersensitivity reactions have not been properly demonstrated, especially in the case of procedures involving non-ionic CM [6]. Therefore, the present study was conducted to evaluate our experiences of using premedication to prevent non-ionic CM hypersensitivity in patients who had previously experienced a CM-related immediate-type adverse reaction.

History of previous adverse reactions to CM is the most important risk factor for an adverse reaction to CM [5,9,10]. Katayama et al. reported the incidence of adverse reactions among patients with a history of CM exposure and reactions to ionic and non-ionic CM to be 44.0% and 11.2%, respectively. Notably, in the same study, only 9.0% and 2.2% of the patients with a history of exposure to, but no previous reaction to, ionic and non-ionic CM, respectively, experienced an adverse reaction when subsequently receiving a CM [3]. Although the exact recurrence rate is unknown, it has been reported to range from 16% to 30% and may be as high as 44% in patients receiving high-osmolar, ionic CM with no premedication [11].

Over the last several decades, many premedication protocols have been developed to prevent hypersensitivity reactions in patients that are considered at high risk due to a previous adverse reaction to CM. However, most studies have focused on high-osmolar, non-ionic CM, and/or patients with no previous history of adverse reactions [6,11]. Although a few studies have sought to evaluate the efficacy of premedication in patients with a history of previous hypersensitivity reactions or who underwent procedures involving low-osmolar, non-ionic CM [12–16], the specific effects of premedication on reactions to low-osmolarity non-ionic CM in patients who had previously experienced adverse reactions remain underexplored. Furthermore, different studies have employed different premedication regimens, rendering comparisons of premedication outcomes between studies problematic. Greenberger et al. conducted a large-scale prospective study that revealed the efficacies of combination premedication protocols (prednisolone and dipheniramine and/or ephedrine and/or cimetidine). These premedication protocols reduced the reaction rate to 9.1% for conventional CM and to 0.7% for low-osmolar CM [12]. However, all subjects in their study had experienced previous reactions to conventional CM.

The use of low- and iso-osmolar, non-ionic CM has become increasingly popular. Recent investigations into the effects of premedication on adverse reactions to low-osmolarity CM have reported higher recurrence rates after premedication [16,17]. Freed et al. evaluated the clinical characteristics of 53 patients who experienced breakthrough reactions, despite steroid premedication, following procedures involving low-osmolar CM [16]. They reported that breakthrough reactions occurred in a substantial

minority of patients (approximately 10%), despite premedication and the use of low-osmolarity CM, and that the reactions were of a similar severity to those the patients had previously experienced [16]. Recently, Davenport et al. revealed that breakthrough reactions induced by low-osmolar CM, in spite of premedication, were usually similar to the index reactions and more likely to be moderate or severe in patients with a history of chronic oral corticosteroid use or drug allergy or reactions to multiple allergens [17].

In the present study, five patients (16.7%) experienced hypersensitivity reactions after receiving non-ionic CM, despite premedication. This reaction rate was higher than that reported in previous studies [12,16]. Indeed, the rate of recurrence of adverse reactions in premedicated patients receiving non-ionic CM with a history of non-ionic CM-induced adverse reactions is still not precisely known. Moreover, recent studies have suggested that the mechanism of CM hypersensitivity has an immunological dimension in a considerable proportion of patients [18,19]. Current premedication protocols were originally designed for the prevention of immediate adverse reactions, which were traditionally classified as pseudoallergic reactions and were more prevalent with ionic CM [11,12]. If an IgE-mediated immunologic reaction contributes to CM immediate hypersensitivity, it is possible that current premedication protocols are not sufficiently effective. Although our study involved a small patient group and did not evaluate the mechanisms behind the observed reactions (through skin tests or other *in vitro* tests), our data suggest that the rate of recurrence of non-ionic CM hypersensitivity reactions after premedication could be even higher than expected.

Interestingly, the severity and manifestation of the reactions the patients experienced were similar to those of their previous reactions. These data are in accordance with previous reports. However, the recurrence rate after premedication was significantly higher in patients with mild previous reactions than those with severe reactions. Premedication protocols successfully prevented adverse reactions following subsequent procedures in most of our patients with severe previous reactions, while 23.5% of our patients with mild previous reactions experienced similar mild reactions, in spite of premedication. The influence of the severity of previous reactions on the rate of recurrence of hypersensitivity reactions has not previously been explored in great detail. It is not clear why premedication failed more frequently in patients with mild previous reactions. However, our data suggest the possibility that the current premedication protocol is more effective in preventing adverse reactions in patients with severe, systemic hypersensitivity reactions rather than in those with only cutaneous reactions.

Our study has several limitations, including a small study group and a retrospective design lacking a control group with non-identical premedication protocols. However, it is the first study to evaluate the efficacy of premedication in preventing adverse reactions to non-ionic CM in an Asian population. In addition, our results provide important clinical insights, notably into the influence of previous reactions on the characteristics and incidence of breakthrough reactions. To evaluate the effectiveness of premedication and prevention strategies more fully, further large-scale, prospective studies, and studies focusing on the pathogenic mechanisms behind non-ionic CM-induced adverse reactions, are required.

In summary, although premedication with corticosteroid and H1 antihistamines and/or H2 blockers effectively prevented non-ionic CM-related adverse events in the majority of patients who previously experienced severe reactions to CM, several patients experienced breakthrough reactions. Therefore, physicians who care for patients that require CM administration despite a history of previous adverse reactions should consider using a premedication protocol, but should be aware of the possibility that premedication may fail, even in cases in which the previous reaction was mild.

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