

Finding the Optimal Alternative for Immediate Hypersensitivity to Low-Osmolar Iodinated Contrast

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Objectives: Avoiding culprit agents is recommended for subjects who have had previous hypersensitivity (HSR) to low-osmolar contrast media (LOCM). However, the guidelines for choosing optimal alternatives have not been determined. We investigated the outcomes of reexposure in patients with previous immediate HSRs to provide a safe option.

Materials and Methods: The outcomes of reexposure were assessed in a cohort with previous LOCM-associated HSR based on skin testing results and the presence of a common *N*-(2,3-dihydroxypropyl) carbamoyl side chain.

Results: Among 482 skin tests, 38.7% (31/80), 45.8% (99/216), and 64.0% (119/186) of mild, moderate, and severe index, respectively, HSRs showed positivity to at least 1 LOCM, of which 62.8% showed positivity to at least 2 different LOCM. The overall recurrent HSRs were reduced from 46.6% upon reexposure to the culprit LOCM to 12.3% upon using nonculprit skin test negative LOCM ($P = 0.004$); those with severe index HSRs exhibited a significant reduction (11.3% vs 100%), but those with nonsevere HSRs to LOCM did not. In subjects with severe index HSRs, the skin test cross-reactivity between LOCM was associated with sharing the common side chain (20.7% vs 11.5%, $P = 0.003$), and the recurrence rate of HSRs was effectively reduced by avoiding the common side chain (24.0% vs 7.8%, $P = 0.039$). However, these differences were not observed in those with nonsevere index HSRs.

Conclusions: In patients who experienced a severe index HSR to LOCM, skin test negative LOCM without a common side chain could be suggested as an option for safe reexposure.

Key Words: contrast media, hypersensitivity, skin tests, drug allergy, cross reactions

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With recent advancements in the field of medical imaging technology, the consumption of iodinated low-osmolar contrast media (LOCM) as a contrast agent for computed tomography (CT) has substantially increased.¹ As a result, the incidence of LOCM-related allergic-like reactions, including idiosyncratic and immunologically mediated hypersensitivity (HSR), have also increased.²

The greatest risk factor for the development of recurrent HSR to contrast media is a previous history of HSR.^{3,4} Three main strategies have been widely applied for managing patients with previous immediate HSR according to severity: premedication,^{3,5–7} change of the culprit

LOCM,^{8,9} and skin tests.^{10,11} The decision about which among these methods is to be applied is based on the severity of the HSR.

For decades, premedication has been the primary choice of treatment across the globe for preventing HSR.^{12–14} However, premedication cannot completely prevent the recurrence of HSR, known as “break-through reactions (BTRs),” which occur in up to 17.1% of patients who experienced a previous HSR to LOCM despite premedication.^{3,15}

Another strategy to reduce the risk of recurrent HSR is changing the culprit LOCM. Our group previously reported that changing the culprit LOCM without a skin test reduced the recurrence of HSR from 31.1% to 7.6% in mild HSR cases.¹⁶ However, there is no defined guideline for choosing a safe alternative LOCM, other than avoiding the culprit agent. Therefore, it is important to determine how to choose a safe, effective alternative LOCM, which is nonreactive on systemic reexposure.

Skin testing seems to be an effective tool for the diagnosis and prevention of both immediate and delayed HSR.¹⁷ Although skin test is not routinely recommended for patients who are exposed to LOCM due to its relatively low sensitivity and poor positive predictive value,¹⁸ recent studies have recommended it for patients who have experienced previous immediate HSR, especially severe ones, as the initial step in assessing the culprit LOCM and tolerability of alternatives.^{4,10,15,17–19} All commercially available LOCM have a similar chemical structure, consisting of tri-iodinated phenyl rings with different side chains.²⁰ The cross-reactivity induced by the common *N*-(2,3-dihydroxypropyl) carbamoyl side chains in LOCM is believed to contain possible clues for the choice of safe alternatives upon subsequent reexposure.^{21,22} There is, however, currently no standard recommendation for determining the optimal choice of safe alternative LOCM based on the clinical outcomes of reexposure and the chemical structure.

The aim of this study was to evaluate the cross-reactivity between LOCM and the outcomes of LOCM readministration, based on the presence of a common carbamoyl side chain in patients who had previously experienced immediate HSR.

MATERIALS AND METHODS

Study Participants

Individuals with a history of an immediate HSR to an LOCM, who were referred to the Allergy Clinic of Seoul National University Hospital from June 2001 through December 2019, were considered potential study participants. Those who underwent skin testing after the occurrence of HSR were retrospectively enrolled. The data collected included their age, sex, previous use of LOCM, types of premedication, detailed information on every exposure to LOCM, and the occurrence of HSR. Data were abstracted from the Contrast Safety Monitoring and Management System at Seoul National University Hospital. Their index HSR was defined as the most recent HSR occurrence before the time of the skin test. Hypersensitivity severity was classified into 3 categories based on the American College of Radiology's guidelines on contrast media: mild, moderate, and severe.¹² This study was approved by the institutional ethics board of Seoul National University Hospital (institutional review board number 1601-002-729), and informed consent was not required due to the retrospective nature of the study.

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Skin Test and Use of Side Chain for Low-Osmolar Contrast Media Classification

Skin testing was performed with 7 LOCM (iobitridol, iohexol, iomeprol, iopamidol, iopromide, ioversol, and iodixanol) to evaluate cross-reactivity among LOCM and determine potentially safer alternative LOCM. The skin prick test was performed with undiluted LOCM, and the intradermal test (IDT) was performed with a 1:10 diluted solution. Skin prick test was considered positive if the size of the wheal was at least 3 mm in diameter or at least 2 mm with erythema after 15 minutes. Intradermal test was considered positive if the size of the initial wheal after injection of 0.05 mL of LOCM increased at least 3 mm in diameter or 2 mm in diameter with erythema after 20 minutes. To assess the cross-reactivity between 2 LOCM, the copositivity rate of each pair was calculated as the percentage of cases in the intersection area that showed positivity to LOCM together whether the culprit LOCM was included or not. We classified the LOCM based on their sharing of *N*-(2,3-dihydroxypropyl) carbamoyl side chains (Supplement A). Iodixanol, ioversol, iopromide, iomeprol, and iohexol contain the identical common side chain, whereas iopamidol and iobitridol do not. This classification was based on a recent study that designated iopamidol as a group lacking the shared identical *N*-(2,3-dihydroxypropyl) carbamoyl side chain because of its subtle difference from others.²²

Reexposure to Low-Osmolar Contrast Media and Recurrence of Hypersensitivities

A recurrent HSR was defined as an immediate HSR on subsequent reexposure to LOCM while undergoing CT, after a skin test had been performed. The LOCM administered at the time of the HSR was regarded as the culprit agent. Change of LOCM was defined as the use of an LOCM that had never been documented as a culprit agent in the affected individual. A premedication protocol, based on the severity of the HSR, was used according to institutional guidelines,^{8,23} the details of which were as follows: (1) for patients with a mild index HSR, 4 mg of intravenous chlorpheniramine 30 minutes before LOCM administration; (2) for patients with a moderate index HSR, 40 mg of intravenous methylprednisolone and 4 mg of intravenous chlorpheniramine 1 hour before LOCM administration; and (3) for patients with a severe HSR, 40 mg of intravenous methylprednisolone 4 hours and 1 hour before and 4 mg of intravenous chlorpheniramine 1 hour before LOCM administration. The incidence rate of recurrent immediate HSRs was calculated by dividing the number of cases that had an HSR within 1 hour after LOCM exposure by the number of all cases undergoing enhanced CT during the study period.

Statistical Assessment

Demographic data were analyzed using descriptive statistics. Comparisons of skin test positivity in relation to severity of HSRs, time lapse from LOCM exposure, and the side chain were performed using Pearson χ^2 tests or Fisher exact tests. Statistical analyses were performed using IBM SPSS version 23.0 (IBM, Corp, Armonk, NY), and results with $P \leq 0.05$ were considered statistically significant.

RESULTS

Characteristics of the Study Subjects and Index Hypersensitivities

We assessed the results of 482 skin test panels performed on 431 patients with a history of LOCM-related immediate HSR (including 186 patients with severe index HSR) (Table 1). The mean age of these patients was 57.0 ± 13.2 years, and 269 patients (62.4%) were female. The most common culprit LOCM was iopromide (23.1%), followed by iohexol (22.8%), iobitridol (18.7%), iopamidol (16.5%), iomeprol (8.2%), ioversol (8.0%), and iodixanol (3.8%).

TABLE 1. Baseline Characteristics of Study Populations

Age, y	57.0 ± 13.2
Sex, female, n (%)	269/431 (62.4%)
Severity of index HSR	
Mild	80 (16.6%)
Moderate	216 (44.8%)
Severe	186 (38.6%)
Reaction on first exposure, n (%)	51/282 (18.1%)
Culprit LOCM, n (%)	364 cases
Iopromide	84 (23.1%)
Iohexol	83 (22.8%)
Iobitridol	68 (18.7%)
Iopamidol	60 (16.5%)
Iomeprol	30 (8.2%)
Ioversol	29 (8.0%)
Iodixanol	14 (3.8%)
Median days between index HSR and skin test (IQR)	25.9 (8.00–116.4)
Skin test positivity	
Skin prick test (%)	3.1%
Intradermal test (%)	51.8%

IQR, interquartile range; HSR, hypersensitivity reaction; LOCM, low-osmolar iodinated contrast medium.

With respect to the severity of the index HSR, there were 80 mild cases (16.6%), 216 moderate cases (44.8%), and 186 severe cases (38.6%).

Outcomes of Skin Test With Low-Osmolar Contrast Media and Time Interval

The skin test positivity for any LOCM was only 3.1% (15/482) in skin prick test, but this increased to 51.8% (250/482) when the IDT was performed. The skin test positivity for culprit LOCM in first exposure to LOCM populations was lower than that of patients for whom the HSR occurred on repeated LOCM applications (25.5% vs 34.3%). The mean number of reactive LOCM per test was 2.29 ± 1.34 in cases showing positivity in skin tests. Of the LOCM, iohexol showed the highest positive rate (70.0%), whereas iopamidol showed the lowest positive rate (44.1%, Fig. 1A). The positive rate was not different between monomers and dimer (56.6% vs 58.3%, respectively). The occurrence of previous severe HSRs was associated with a higher likelihood of a positive skin test (Fig. 1B). Among the mild HSR group, 38.7% (31/80) of patients had positive results. Furthermore, 45.8% (99/216) of patients with previous moderate HSR demonstrated positivity, whereas 64.0% of those with severe HSR (119/186) showed positive results ($P = 0.002$ among the 3 groups, Fig. 1B). Skin test positivity was dependent on the time interval between the index HSR and the skin test: 67.2% (39/58) <4 weeks, 60.7% (34/56) in 4–8 weeks, and 46.0% (160/348) >8 weeks, respectively ($P = 0.007$, Fig. 1C).

Cross-Reactivity Classified by a Common *N*-(2,3-Dihydroxypropyl) Carbamoyl Side Chain

To evaluate cross-reactivity among LOCM, we calculated the copositivity between different LOCM pairs. Among the 250 patients with skin test positivity, 157 cases (62.8%) showed copositivity to at least 2 different LOCM (Supplement B). The most common copositivity was observed in the iohexol-iomeprol pair (36.3%). The copositivity proportion in the LOCM pairs sharing common side chains was 21.5%, which was significantly higher than the 13.3% that was observed in the LOCM pairs without common side chains ($P = 0.008$) (Fig. 2). This significant difference was observed in the severe index HSR group (20.7% vs 11.5%, $P = 0.003$), but not in the nonsevere cases.

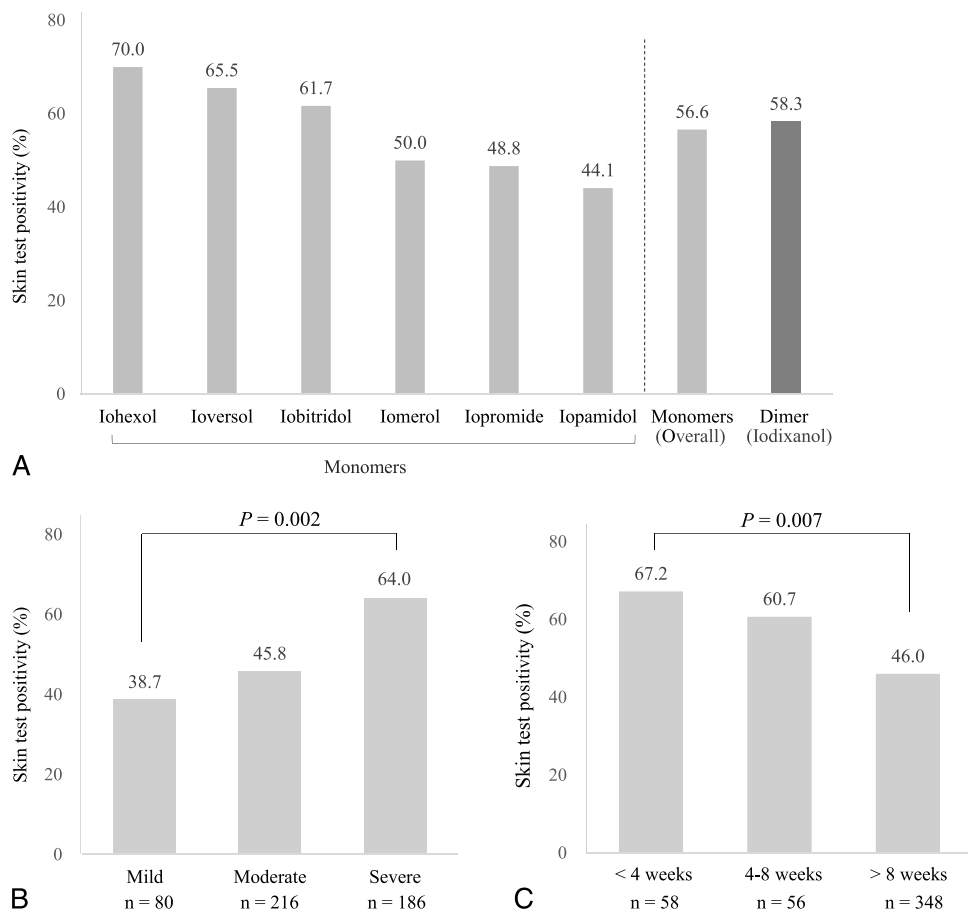


FIGURE 1. Skin test positivity according to culprit low-osmolar iodinated contrast medium (LOCM) (A), skin positivity according to index HSR severity (B), and test interval (C).

Outcomes of Reexposure to Low-Osmolar Contrast Media

Of 431 patients with LOCM skin tests, 355 cases were subsequently reexposed to LOCM. The overall BTR rate was 12.3% in the 238 cases in which the LOCM was changed, which is significantly lower than the 43.8% BTR rate observed upon reexposure to the culprit

LOCM (Fig. 3A, $P = 0.004$). The subgroup analyses by severity showed that patients who had a severe index HSR exhibited a significantly lower rate of recurrent HSR when changing the LOCM compared with those who had reexposure to the same culprit LOCM (11.3% vs 100%, $P < 0.001$). However, the reduction of recurrence due to the changing contrast media was not significant in patients who had

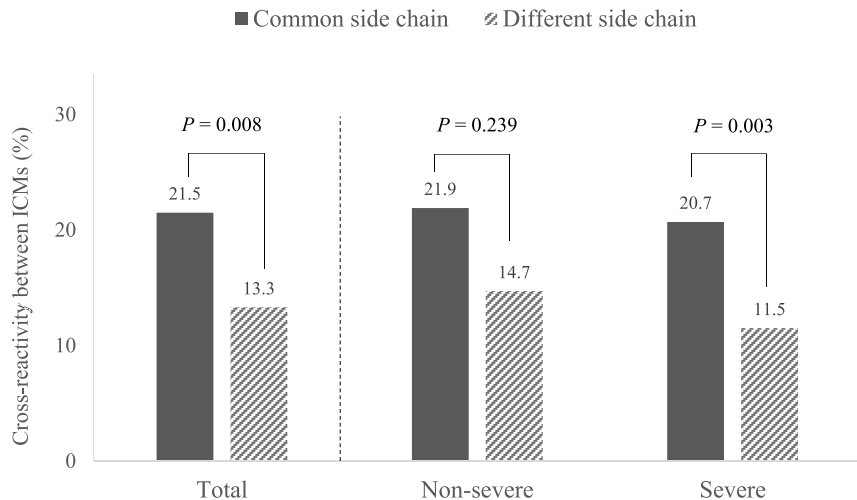


FIGURE 2. Skin test positivity in the total patient, in patients with a nonsevere hypersensitivity (HSR) and in patients with a severe index HSR. Nonsevere HSR: combination of mild and moderate HSR.

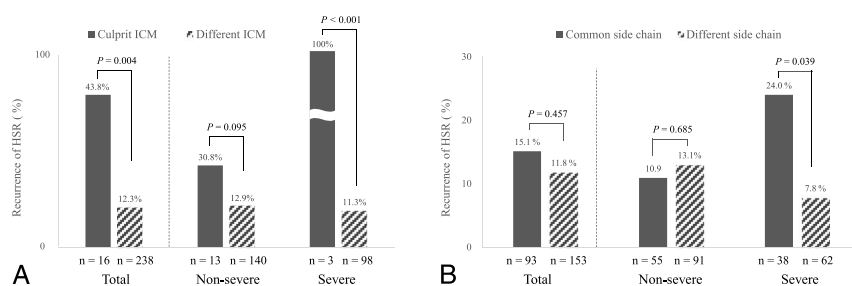


FIGURE 3. Recurrent of hypersensitivity (HSR) reaction rate (A) outcomes of low-osmolar iodinated contrast medium (LOCM) reexposure according to culprit LOCM. Change (B) outcomes of LOCM reexposure according to common side chain change.

nonsevere HSR to LOCM. The recurrence of HSR was evaluated based on the presence of the *N*-(2,3-dihydroxypropyl) carbamoyl side chain. Among cases that used an alternative LOCM on reexposure, the reaction rate was 15.1% when the alternative LOCM had an identical side chain to the culprit LOCM. This was slightly higher than the 11.8% rate observed when the alternative LOCM had a different side chain than

the culprit LOCM (Fig. 3B). However, this was not statistically significant ($P = 0.457$). When cases were divided into 2 groups according to the severity of their index HSR, analysis revealed that in patients with severe index HSRs, the use of an alternative LOCM with a different side chain significantly reduced the BTR rate from 24.0% to 7.8% ($P = 0.039$). However, this difference was not observed in those who

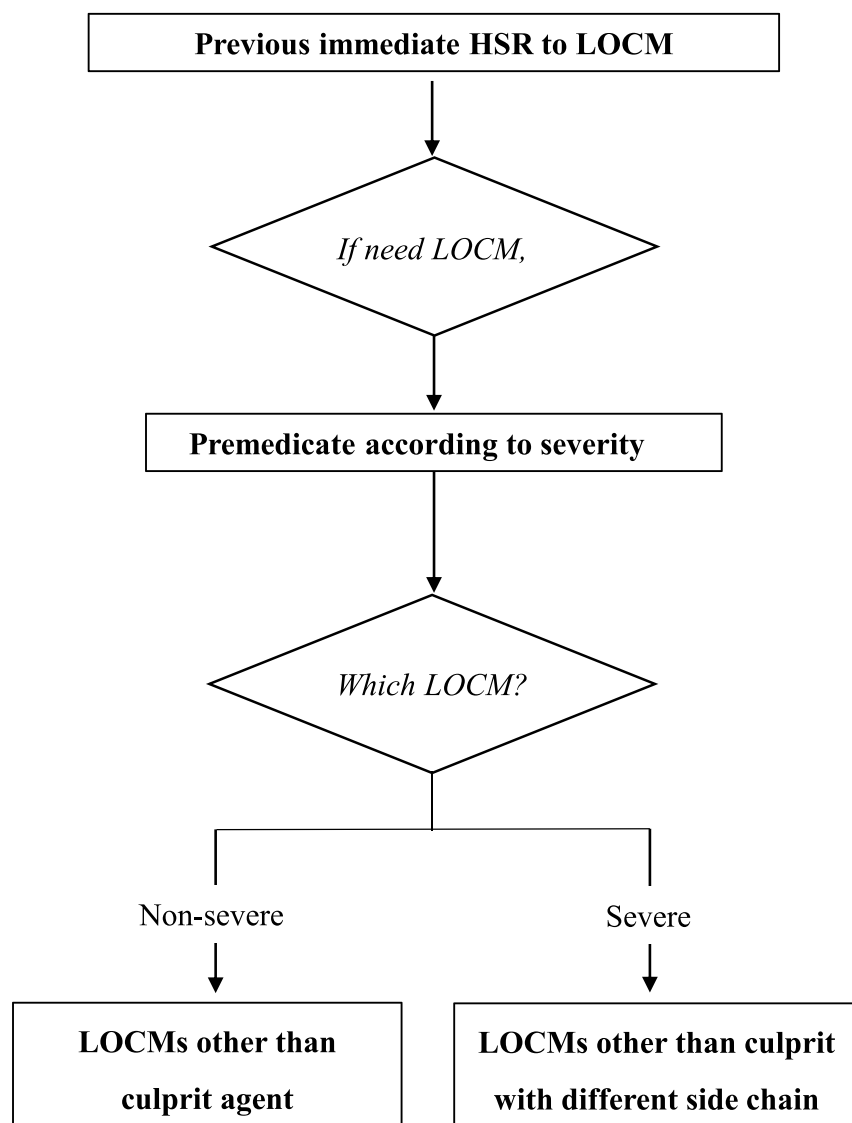


FIGURE 4. Algorithm for patients with previous hypersensitivity reactions to low-osmolar iodinated contrast medium and clinical suggestions of readministration.

had a nonsevere HSR to LOCM. In addition, changing between monomers and dimer did not demonstrate an advantage in reducing the risk of HSR (data not shown).

DISCUSSION

To reduce the likelihood of an HSR recurrence, a change of LOCM is currently recommended during subsequent reexposure for patients who experienced a prior allergy-like immediate HSR. In addition, selecting the appropriate premedication may have a further reductive effect.^{8,9} However, there is no ideally safe way to determine which LOCM is the best alternative for these patients. This study suggests that performing skin tests combined with grouping LOCM based on the presence of *N*-(2,3-dihydroxypropyl) carbamoyl side chain might help physicians choose safe alternatives that will not be reactive on subsequent systemic reexposure. Low-osmolar contrast media cross-reactivity was assessed based on skin test reactivity and the presence of a common *N*-(2,3-dihydroxypropyl) carbamoyl side chain. Our study results demonstrated that switching from the culprit LOCM to an alternative with a different side chains helped to reduce the risk of recurrent HSR, especially in cases of severe index HSR. Based on our findings, we suggest using a clinical algorithm that involves skin testing and switching the LOCM based on its side chain as the approach for readministration in patients who have experienced a previous immediate HSR (Fig. 4).

Risk factors for the recurrence of LOCM-induced HSR include a previous history of HSR to contrast media, presence of allergic diseases (eg, asthma, urticaria), hyperthyroidism, family history of contrast media HSR, genetic factor, and cardiovascular disease.^{24,25} The benefit of changing culprit LOCM within the same class was first described in guidelines released in 2017.¹² This study included 16 cases of culprit LOCM reinjection that had been performed before the update of guidelines, which produced results that confirmed the drastic difference in recurrence by avoiding culprit LOCMs in severe cases. Although high doses of steroids in combination with antihistamines are widely used to prevent HSR in high-risk groups, this strategy was originally conceived to prevent infusion reactions related to high osmolar contrast media injections.^{6,26,27} Therefore, its efficacy has not been fully validated for the prevention of recurrent HSR to LOCM.^{8,28,29} It must be highlighted that, despite premedication and changing the culprit LOCM, 14.3% (11/77) of the patients with previous HSR to LOCM still had recurrent BTRs including anaphylaxis, although most cases were mild HSR, in our previous study.⁸ Therefore, premedication and change of culprit LOCM may not be sufficient to prevent the recurrence of immediate HSRs, particularly in cases with severe index HSR.

A previous study demonstrated that using skin tests as a screening tool for primary prevention in the general population is of little value.¹⁸ Although skin tests do not have a primary preventive effect on HSR, the question of whether they will aid in diagnosis and therapeutic decision making for all patients who had a previous HSR still remains. In the present study, the rate of recurrent HSR to LOCM after a contrast media change based on a skin test was 11.9% in patients with a history of moderate and severe HSR. This proportion is much lower than that reported in previous studies by our group in patients who had premedication and changed LOCM without of skin test (11/77, 14.3%).⁸ In a recent study based on skin tests conducted on 69 patients who had a previous HSR,¹⁸ it was found that a change in LOCM after the skin test was helpful only in cases in which the patient showed skin test positivity to the culprit LOCM, and skin tests were not beneficial if there was no skin test reactivity to the culprit LOCM. In our study, the recurrence of HSR did not change based on whether the patient showed skin test positivity to the culprit LOCM (positive to culprit LOCM: 10.3% [16/155] vs negative to culprit LOCM: 12.0% [20/167]). Changing the LOCM to one that does not have a side chain identical to that of the culprit was helpful for reducing the recurrence of HSR in patients with severe index HSRs, regardless of culprit LOCM positivity. Although the reductive effect was not statistically

significant in those with nonsevere index HSRs in this study, physicians should consider choosing an LOCM without a common side chain if possible because the role of side chains in nonsevere reactions cannot be completely ruled out.

Compared with previous work,^{13,18} the current study investigated the effects of changing LOCM based on its *N*-(2,3-dihydroxypropyl) carbamoyl side chain. Contrast molecules are small, typically less than 1000 kDa in molecular weight, and have been generally shown to act as haptens. However, it is not clear which iodinated structure acts as an epitope in IgE-mediated HSR.²⁹ The side chain determinants of the tri-iodinated benzenic ring might be associated with hydrophilicity, which is important to improve the tolerance to contrast media by preventing diffusion.³⁰ The elucidation of the underlying mechanism of the immediate HSR related to LOCM seems important; however, the physicochemical properties of LOCM that induce allergic-like immediate HSR remain controversial. Based on our results, we suggest that the *N*-(2,3-dihydroxypropyl) carbamoyl chain might be an epitope contributing to true allergic reaction and show cross-reactivity between LOCM sharing common side chains. Indeed, carbamoyl side chain seems to play a certain role in severe HSR. These findings also corresponded to a recent study in which the proportion of allergic HSR was higher in grade 3 and 4 HSRs compared with grade 1 and 2 HSRs.⁴ Further studies are needed to confirm this hypothesis.

We conducted skin tests on 186 patients who had severe immediate HSRs, and 75.5% of the initial culprit LOCM were clearly validated; our study provides enough data to analyze the results according to alternative LOCM. We found that the cross-reactivity rate of the skin tests varied based on the presence of a common side chain. The outcome of reexposure to alternate LOCM that were selected based on their side chain was favorable, especially in those with severe index HSRs who were more likely to have an allergic reaction. Two other studies have investigated the cross-reactivity between LOCM and alternatives LOCM that were suggested to be safe based on presence of the *N*-(2,3-dihydroxypropyl) carbamoyl side chain.^{21,22} However, in these studies, either the data representing the outcomes of reexposure to LOCM were absent or there was no information on the culprit and/or reexposed contrast media in cases that had immediate HSRs. Our study presents the results of reexposure to LOCM according to the presence or absence of the common side chain, and we used a larger sample size. As a result, we are able to draw a more definitive conclusion.

The present study also showed that the use of nonreactive LOCM in skin tests and common side chain changes were not fully preventive against recurrent HSR. Although all preventive measures (eg, premedication and a change of LOCM based on the side chain) were taken, 11.8% (18/153) of patients still experienced a recurrence of HSR when reexposed to LOCM. For these vulnerable patients, further safety protocols, such as intravenous challenge or desensitization, should be considered. There is only a small number of research investigating the effect of intravenous challenges of LOCM performed on high-risk patients before reexposure. A recent study suggested that intravenous provocation tests with a skin test negative LOCM are safe in both immediate and delayed HSR.³¹ The provocation protocol started at 0.05 mL, and after this dose, patients received 0.5, 1.0, 5.0, 7.5, 10.0, and 25.0 mL every 30 minutes, for a total of 49.05 mL. Further studies involving rechallenges based on the common side chain are needed to confirm the optimal alternative for immediate HSR to LOCM.

This study has some limitations to be considered. First, the process of switching to an alternative LOCM was not ideally randomized. Second, because this study was conducted only on patients who had skin tests performed, it is difficult to clarify the role of the skin test itself in choosing a safe alternative. Another limitation of this study is the lack of detailed information about LOCM use, such as contrast volume and injection rate and temperature of LOCM, which might have affected the recurrence of HSR. Fourth, because only a 1:10 dilution was used for IDT, some of true allergic cases might have been missed. Therefore,

further studies are warranted to establish an ideal concentration of LOCM for skin testing. Lastly, this study suggested that taking the *N*-(2,3-dihydroxypropyl) side chain into account might help to prevent recurrent HSR in patients with severe index HSR. Further studies are needed to confirm whether carbamoyl side chain plays a role as an epitope related with HSR. Nevertheless, this study has valuable and immediate clinical implications and provides practical information for selecting safe LOCM alternatives.

In conclusion, this study demonstrated that skin test negative LOCM still induce HSR and that selecting an LOCM based on the presence of a common side chain will provide additional safety benefits upon reexposure to LOCM in patients with severe index HSRs.

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