Finding the optimal alternative for immediate hypersensitivity to low-osmolar iodinated contrast

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October 1, 2020

Abstract

Background: For subjects who had previous hypersensitivity (HSR) to low-osmolar contrast media (LOCM), changing contrast media is recommended. However, determining the safest alternative LOCM is uncertain. We investigated the cross-reactivity among LOCMs and the outcomes of re-exposure in patients with previous immediate HSRs. Methods: The outcomes of re-exposure were assessed in the cohort with previous LOCM-associated HSR by the skin testing results and the presence of a common N-(2,3-dihydropoxypropyl) carbamoyl side chain. Results: Among 431 patients with previous HSR who underwent 482 skin tests, 250 cases (51.9%) showed positivity to intradermal tests, which was positively associated with the severity of HSR. The cross-reactivity among LOCMs was higher between LOCMs sharing common side chain compared to those not sharing (21.5% vs. 13.3%, P = .008). The recurrent HSRs was significantly reduced from 46.6% on re-exposure to culprit LOCM to 12.3% with changing LOCM based on the skin test results (P = .004). The overall recurrence rate was not further reduced when the LOCM was changed based on presence or absence of common side chain (15.1% vs. 11.8%, P = .428). However, for those who had severe index HSRs, skin test non-reactive LOCMs exposures, without the common side chain, resulted in a significant reduction in recurrent HSRs compared to LOCMs with the common side chain (24.0% vs. 7.8%, P = .049). Conclusion: In patients who experienced a severe index HSR to LOCM, avoidance of re-exposure to LOCMs with a common side chain or a positive skin test result is safer.

Abbreviations

CT – Computed tomography

LOCM – Low-osmolar iodinated contrast medium

HSR – Hypersensitivity reaction

SPT – Skin prick test

IDT – Intradermal test

Introduction

With the recent advancement in the field of medical imaging equipment, the use of iodinated low osmolar contrast media (LOCM) as a contrast agent for computed tomography (CT) has substantially increased.[1] As a result, LOCM-related adverse reactions, usually classified as toxic and rarely 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] Two main strategies have been widely used for managing patients with previous immediate hypersensitivity according to severity: premedication,[3, 5-7] and change of the culprit LOCM.[8,9] The decision

of which among these methods is to be used is based on the severity of the HSR. For decades, premedication has been the primary choice of care across the world for preventing HSR .[10-12] However, premedication cannot completely prevent the recurrence of HSR, so called 'breakthrough reactions (BTRs)', which occur in up to 17.1% of patients who experienced a previous HSR to LOCM despite premedication.[3,13] A previous study reported that changing the culprit LOCM to other one without skin test reduced the recurrence of HSR from 31.1% to 7.6% in mild HSR cases.[9] However, there is no defined guideline for choosing a safe alternative LOCM to prevent the recurrent HSR other than avoiding the culprit agent. Therefore, it is of interest how to choose the right and safe alternative LOCM which is non-reactive on systemic re-exposure.

Skin testing to all patients who showed a prior HSR to LOCM is not routinely recommended because of its relatively low sensitivity and an unreliable positive predictive value.[15] One option for screening safe alternative(s) for re-exposure to contrast media is skin testing with LOCM.[14,15] However, its clinical usefulness is not clearly validated yet and the choice of alternative LOCMs is still unsolved problem since certain combinations of alternate LOCM had no prophylactic effect.[8] The cross-reactivity by the common N-(2,3-dihydropoxypropyl) carbamoyl side chains found in LOCMs are believed to be a possible clue into choosing safe alternatives for subsequent re-exposure.[18,19] There is, however, currently no standard recommendation for deciding the optimal choice of safe alternative LOCMs based on clinical evidence, such as outcomes of re-exposure to contrast media. The aim of this study was to evaluate the cross-reactivity between LOCMs and the outcomes of LOCM re-administration based on the presence of common carbamoyl side chain in patients who had immediate HSR.

Methods

Study participants

Individuals with a history of an immediate HSR to a LOCM, who were referred to the Allergy Clinic of Seoul National University Hospital from June 2001 through December 2019, were 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 pre-medication, detailed information on every exposure to LOCM, and occurrence of HSR. Data was abstracted from the Contrast Safety Monitoring and Management System (CoSM^{2}oS) in Seoul National University Hospital. Their index HSR was defined as the most recent HSR occurrence prior to the time of the skin test. HSR severity was classified into three categories based on the American College of Radiology's guidelines on contrast media: mild, moderate, and severe.[20] This study was approved by the institutional ethics board of Seoul National University Hospital (IRB No.:1601-002-729) and informed consent was not required due to the retrospective nature of the study.

Skin test and use of side chain for LOCM classification

Skin testing was performed with seven LOCMs (iobitridol, iohexol, iomeprol, iopamidol, iopromide, ioversol, and iodixanol) to evaluate cross-reactivity among LOCMs and determine potentially safer alternative LOCMs. The skin prick test (SPT) was performed with undiluted LOCM and the intradermal test (IDT) was performed with a 1:10 diluted solution. SPT 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. IDT 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 two LOCMs, the co-positivity rate of each pairs was calculated as the percentage of cases in the intersection area that showed positivity to both LOCMs.

We classified the LOCMs 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 while iopamidol and iobitridol do not. This classification was based on a recent study which designated iopamidol as a group without sharing the identical N-(2,3-dihydroxypropyl) carbamoyl side chain because of its subtle difference from others.[19]

Re-exposure to LOCM and recurrence of HSR

A recurrent HSR was defined as an immediate HSR on subsequent re-exposure 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,[3] the details of which were previously described.[21] The incidence rate of recurrent immediate HSRs was calculated by dividing the number of cases that had an HSR within one 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. A comparison of skin test positivity in relation with severity of HSRs, time lapse from LOCM exposure, and according to the side chain were performed using Pearson's chi-squared test or Fisher's exact test. Statistical analyses were performed using IBM SPSS version 23.0 (IBM, Corp., Armonk, NY, USA), and results with P *[?]* 0.05 were considered statistically significant.

Results

Characteristics of the study subjects and index HSRs

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). In 17.6% of the patients, the initial HSR occurred on their first exposure to LOCM. The mean age of these patients was 57.0 ±13.2 years, and 269 (62.4%) patients were female.

According to the severity of the index HSR, there were 216 moderate cases (44.8%), 186 severe cases (38.6%), and 80 mild cases (16.6%). The most common culprit LOCM was iopromide (23.1%), followed by iohexol (22.8%), iobtridol (18.7%), iopamidol (16.5%), iomeprol (8.2%), ioversol (8.0%), and iodixanol (3.8%).

The outcome of skin test with LOCM and time interval

Skin test positivity to any LOCM was only 3.1% (15/482) in the skin prick test but increased to 51.8% (250/482) when the IDT was performed. The mean number of reactive LOCMs per test was 2.29 ± 1.34 in cases showing positivity in skin tests. Of the LOCMs, iohexol showed the highest positive rate (70.0%), while iopamidol showed the lowest positive rate (44.1%, Figure 1A). 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 (Figure 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, while 64.0% of those with severe HSR (119/186) showed positive results ($P = 0.002$ among three groups, Figure 1B). Skin test positivity was dependent upon 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. ($P = 0.007$, Figure 1C).

Cross-reactivity classified by common N-(2,3-dihydroxypropyl) carbamoyl side chain

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

Outcomes of re-exposure to LOCM

Of 431 patients of LOCM skin tests, 355 cases were subsequently re-exposed to LOCM and the consequences of LOCM re-exposure were assessed based on the skin test results. The overall BTR rate was 12.3% in the

244 cases in which the LOCM was changed, which is significantly lower than the 46.6% BTR rate observed upon re-exposure to the culprit LOCM (Figure 3-A, P-value = 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 to those who had re-exposure to the same culprit LOCM (11.3% vs. 100%, P-value < 0.001). However, reduction of recurrence due to the changing of the contrast media was not significant in patients who had non-severe 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 re-exposure, 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 (Figure 3-B). However, this did not reach statistical significance (P -value = 0.428). When cases were divided into two groups according to the severity of their index HSR, analysis revealed that, in patients that had 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% ($P = 0.049$). However, this difference was not observed in those who had a non-severe HSR to LOCM. In addition, changing between a monomer and dimer did not demonstrate an advantage in reducing the risk of HSR (Data not shown).

Discussion

In order to reduce the likelihood of an HSR recurrence, a change of LOCM is currently recommended during subsequent re-exposure for patients who experienced a prior allergy-like immediate-onset HSR. Additionally, selecting the appropriate premedication may have further reduction effect.[21,22] However, there is no failsafe way to determine which LOCM is the best alternative for these patients. This study suggests that performing skin tests combined with grouping LOCMs based on the presence of N-(2,3-dihydropoxypropyl) carbamoyl side-chains might help physicians choose safe alternatives that will not be reactive on subsequent systemic re-exposure. LOCM cross-reactivity was assessed based on skin test reactivity and the presence of a shared N-(2,3-dihydroxypropyl) carbamoyl side chain. Our study results demonstrate that switching from the culprit LOCM to an alternative without identical side chains helps 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 re-administration in patients who have experienced a previous immediate HSR (Figure 4).

Risk factors for the recurrence of LOCM-induced HSR include a previous history of contrast media hypersensitivity, the presence of an allergic disease, hyperthyroidism, and a family history of contrast media hypersensitivity.[23] 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.[5,24,25] Therefore, its efficacy has not been fully validated for the prevention of recurrent HSR to LOCM.[21] 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 BTR including anaphylaxis, although most cases were mild HSR, in our previous study.[21] Therefore, premedication and change of culprit LOCM may not be sufficient enough to prevent the recurrence of immediate HSRs, particularly in those cases in which the patient experienced a 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.[15] Although skin tests do not elucidate a primary preventive effect on HSR, the question of whether or not they will aid in the diagnosis and therapeutic decision-making for patients who had a previous HSR still remains . In the present study, the rate of recurrent HSR to LOCM following a contrast media change based on a skin test was 11.9% in patients with a history of moderate and severe HSR. This is much lower than that reported in previous studies by the same group who had premedication and a change of LOCM that was independent of a skin test (14.3%).[21] In a recent study based on skin tests conducted on 69 patients who had a previous HSR, it was found that a change in LOCM following 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 LOCMs.[26]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% vs. negative to culprit LOCM: 12.0%). Moreover, changing the LOCM to one that does not have an identical side chain to the culprit was helpful for reducing the recurrence of HSR in patients who had severe index HSRs, regardless of culprit LOCM positivity.

Compared to previous work,[19,26] the current study investigated the effects of changing LOCM based on its N-(2,3-dihydroxypropyl) carbamoyl side chain. Since, in our study, we conducted skin tests on 186 patients who had severe immediate HSRs and 75.5% of the initial culprit LOCMs were clearly validated, our study provides enough data to analyze the results according to alternative LOCMs. We found that the cross-reactivity rate of the skin tests varied based on the presence of the common side chain. Furthermore, the outcome of re-exposure to those alternate LOCMs 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 investigated the cross-reactivity between LOCMs and alternatives LOCMs that were suggested as safe based on presence of the N-(2,3-dihydroxypropyl) carbamoyl side chain.[17,18]However, in these studies, either the data representing the outcomes of re-exposure to LOCM was absent or there was no information on the culprit and/or re-exposed contrast media in cases that had immediate HSRs.[19] Our study presents the results of re-exposure to LOCMs 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 non-reactive LOCMs in skin test and common side chain change were not fully preventive to recurrent HSR. Although all preventive measures (e.g., premedication and the change of LOCM based on side chain) were taken, 7.8% of patients still experienced a recurrence of HSR when re-exposed to LOCM. For these vulnerable patients, further safety protocols, such as an intravenous challenge or desensitization, should be considered. There is only a small number of research investigating the effect of intravenous challenges of LOCMs performed on high-risk patients before re-exposure. A recent study suggests that intravenous provocation tests with a skin test-negative LOCM is safe in both immediate and delayed HSR.[27] The provocation protocol started at 0.05 mL and following this, patients received 0.5, 1.0, 5.0, 7.5, 10.0, and 25.0 mL every 30 minutes (total 49.05 mL). Further studies involving re-challenges based on the common side chain are needed to confirm the optimal alternative for immediate hypersensitivity to LOCMs.

This study has some limitations to be considered. First, when an alternative LOCM was selected based on whether or not it had an identical side chain to the culprit, the study did not employ enough differing culprit LOCM-alternative LOCM pairs. This might be affected by some unknown bias in the selection of LOCMs as the process of switching to an alternative LOCM was not ideally randomized. Second, since this study was conducted only on patients who had skin tests performed, it is difficult to clarify the role of the skin test, itself, on choosing a safe alternative. Nevertheless, this study has valuable and immediate clinical implications and provides practical information for selecting safe LOCM alternatives.

In conclusion, our study demonstrates that skin test-negative LOCMs still induce HSR. Furthermore, we demonstrated that selecting an LOCM based on the presence of a common side chain will give additional safety benefits upon re-exposure to LOCM in those patients who experienced severe index HSRs.

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Table 1. Baseline characteristics of study populations

Age, year	57.0 ± 13.2
Sex, female (n, %)	269/431 (62.4%)
Severity of index HSR	
Mild	80 (16.6%) 216 (44.8%) 186 (38.6%)
Moderate	
Severe	
Reaction on first exposure (n, %)	42/239 (17.6%)
Culprit LOCM (n, %) Iopromide	364 cases 84 (23.1%) 83 (22.8%) 68 (18.7%)
Iohexol	
Iobitridol	
Iopamidol	60 (16.5%) 30 (8.2%) 29 (8.0%) 14 (3.8%)
Iomeprol	
Ioversol Iodixanol	
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

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

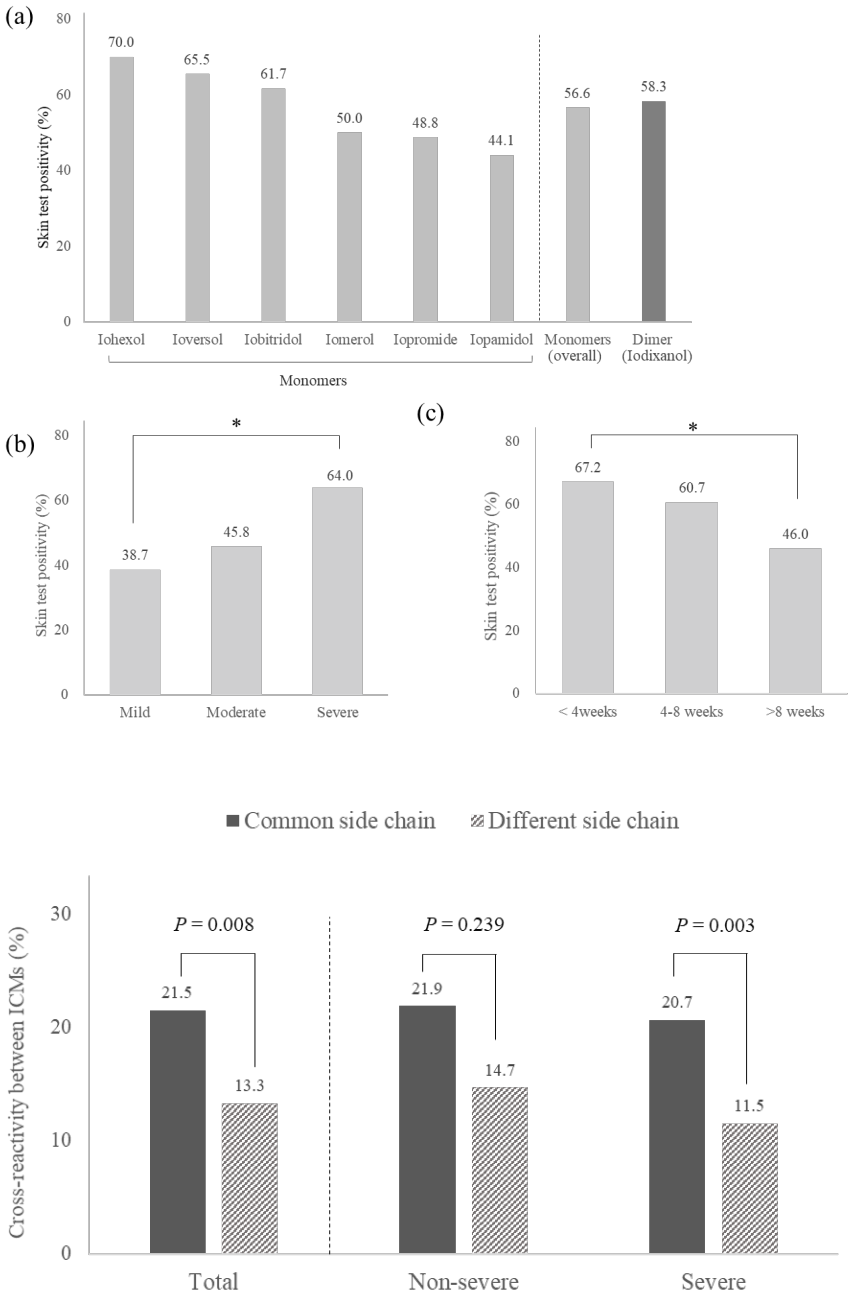
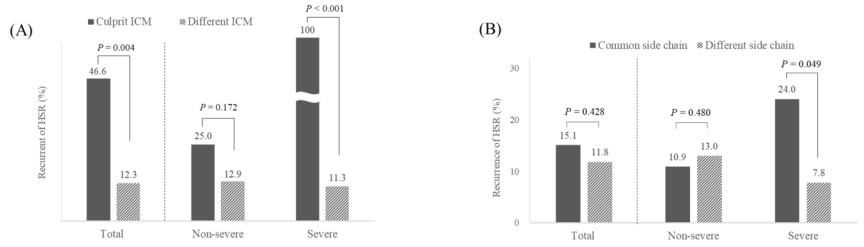


Figure 2. Skin test positivity in the total patient, in patients with a non-severe HSR and in patients with a severe index HSR

*Non-severe HSR: Combination of mild and moderate HSR

Figure 3. Recurrent of hypersensitivity reaction (HSR) rate (A) Outcomes of LOCM re-exposure according to culprit LOCM change (B) Outcomes of LOCM re-exposure according to common side chain change



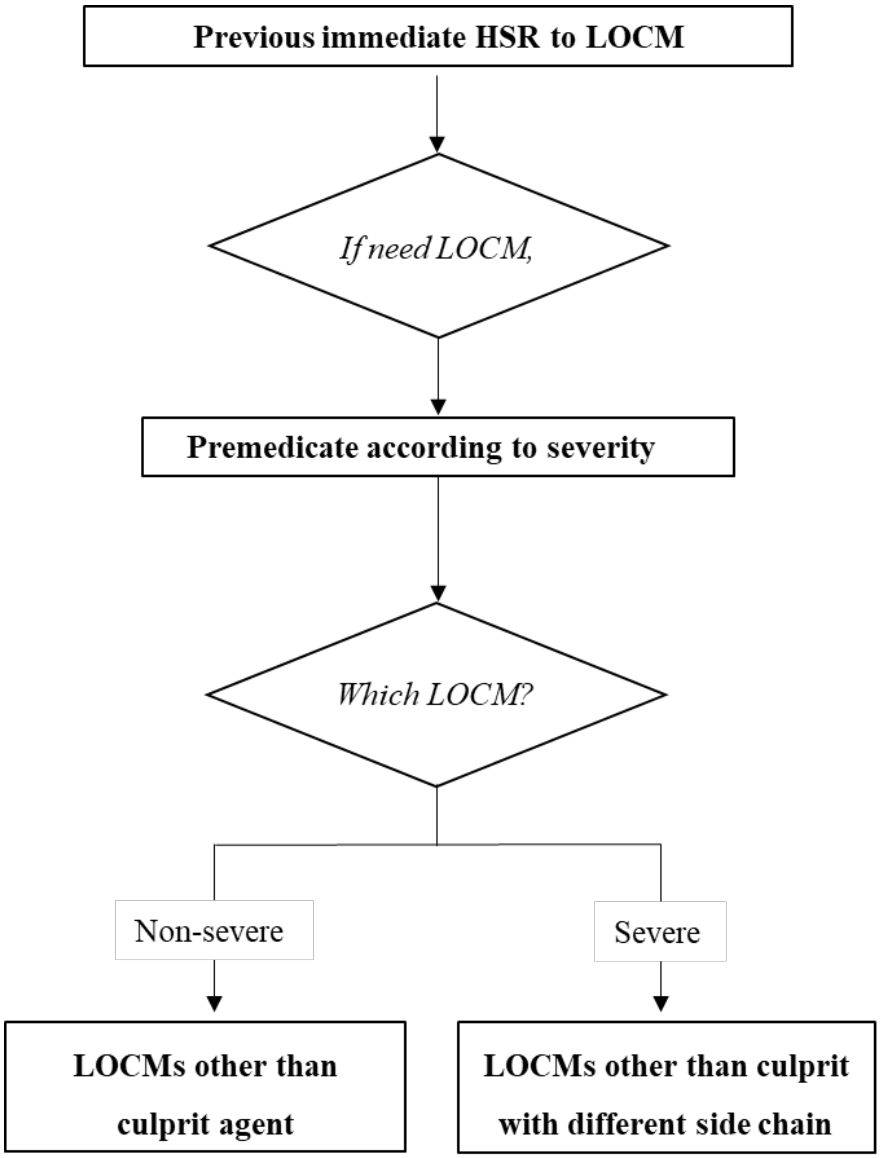
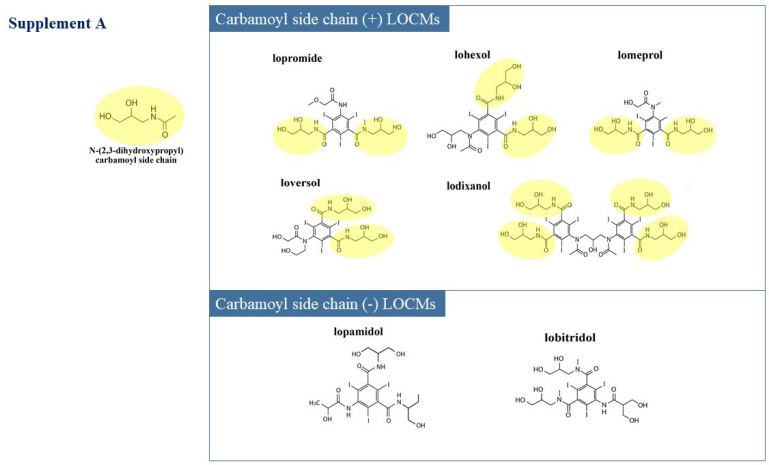


Figure 4. Algorithm for patients with previous hypersensitivity reactions to LOCM and clinical suggestions of re-administration



Supplement A .

Supplement B

(A) Total

	Iodixanol	Ioversol	Iopromide	Iomeprol	Iohexol	Iopamidol
Iodixanol						
Ioversol	20.4					
Iopromide	16.6	20.4				
Iomeprol	17.8	21.7	21.7			
Iohexol	20.4	15.3	23.6	36.3		
Iopamidol	7.6	10.9	19.1	14.0	14.0	
Iobitridol	12.8	10.8	12.1	16.6	14.6	22.1

(B) Non-severe index hypersensitivity

	Iodixanol	Ioversol	Iopromide	Iomeprol	Iohexol	Iopamidol
Iodixanol						
Ioversol	17.4					
Iopromide	20.9	21.1				
Iomeprol	20.9	6.9	18.7			
Iohexol	19.8	27.7	21.2	35.4		
Iopamidol	9.3	13.0	18.1	11.1	11.1	
Iobitridol	15.1	12.5	15.3	15.3	13.9	13.1

(C) Severe index hypersensitivity

	Iodixanol	Ioversol	Iopromide	Iomeprol	Iohexol	Iopamidol
Iodixanol						
Ioversol	13.9					
Iopromide	12.5	16.9				
Iomeprol	19.4	18.1	19.4			
Iohexol	19.4	23.6	22.2	41.7		
Iopamidol	5.6	8.3	18.1	11.1	11.1	
Iobitridol	9.8	6.9	15.3	15.3	13.9	13.1