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# The Role of Skin Tests and Premedication in Radiocontrast Media Hypersensitivity: A Clinical Dilemma

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## ABSTRACT

**Objective:** Controversies continue over the diagnostic approach, prediction, and premedication in radiocontrast media (RCM) hypersensitivity. One of the most important problems encountered in daily clinical practice is that patients do not recall which contrast agent has been used in previous exposures. Also, in most cases, the details of the reaction have not been recorded. Therefore, difficulties are experienced in decision-making about skin testing and premedication in patients who are suspected of RCM hypersensitivity.
To assess the clinical value of skin tests and premedication in RCM hypersensitivity.

**Materials and Methods:** A retrospective evaluation was made of the medical records of patients between October 2014 and December 2019. The skin tests were performed with the culprit agent if it was known, otherwise, with iohexol, one of the most commonly used RCM in Turkey. As premedication, oral methylprednisolone 40 mg 13-7-1 hours before the procedure and oral pheniramine 22.7 mg 1 hour before the procedure were prescribed.

**Results:** A total of 41 patients were evaluated (32 females and 9 males). Of the reactions, 35 (85.4%) were immediate and 6 (14.6%) were non-immediate. Three (7.3%) had a positive intradermal test result. It was determined that 20 patients (17 immediate, 3 non-immediate), required imaging with RCM again. Of these, 18 received premedication and two did not, although it was recommended. Of the patients who received premedication, one (5.5%) had an urticarial reaction of the same grade, while both patients (100%) who did not receive premedication developed an immediate allergic reaction that was of a similar grade to that of the previous reaction.

**Conclusion:** Skin test positivity for RCM was observed at low rates. In cases with negative skin tests and when the culprit drug cannot be identified, re-exposure to alternative RCM under premedication may reduce the risk of the reaction.

**Keywords:** Allergy, iodinated contrast media, iobitridol, iohexol, premedication

## INTRODUCTION

About 75 million doses of iodinated radiocontrast media (RCM) are consumed annually worldwide (1). Serious adverse hypersensitivity reactions happen in 0.1–0.4% of patients receiving RCM (2). The importance of skin tests and premedication in RCM hypersensitivity remains controversial.

Hypersensitivity reactions to RCM are categorized into two groups as immediate (reactions that occur up to 1 hour after drug administration) and non-immediate reactions (more than 1 hour and up to 10 days after administration) (2). Although the risk factors for RCM hypersensitivity are not clear, they include asthma, severe cardiovascular disease, multiple exposures, and previous severe reactions to RCM (3).

Premedication with antihistamines and/or corticosteroids is widely used in patients who have previously experienced RCM-related hypersensitivity reactions (4). However, the efficacy of prophylaxis regimens in these high-risk patients has not been fully evaluated, and for non-immediate hypersensitivity reactions (NIHR), the efficacy of premedication is still under debate and considered to be low (5, 6).



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Avoidance of culprit RCM should be considered in cases with a past hypersensitivity reaction (4). Skin tests should be performed with RCM involved in the index reaction. If the culprit drug is unknown, skin tests should be performed with the broadest possible panel of RCM (3, 5). However, one of the most important problems encountered in daily clinical practice is that patients do not recall which contrast agent has been used in their previous exposures, and in most cases, the details of the reaction have not been recorded.

The aim of the present study was to assess the clinical value of skin tests and premedication in RCM hypersensitivity through analysis of the clinical features, skin test results, and outcomes of subsequent RCM exposures of patients referred to our clinic for evaluation of RCM hypersensitivity.

## MATERIALS and METHODS

A retrospective evaluation was made of the medical records of the patients who were referred to the Adult Allergy and Immunology Clinic between October 2014 and December 2019 with history of RCM-related adverse reactions. The demographic characteristics of the patients, chronic diseases, allergy histories, nature and severity of the previous reactions, and the contrast agent causing the reactions were recorded. Hypersensitivity reactions were categorized as immediate (symptoms within 1 hour after RCM administration) and non-immediate (symptoms > 1 hour to 10 days after RCM exposure) as suggested by Brockow et al (4).

Assessment for immediate hypersensitivity reactions (IHR) was performed 20 minutes after a skin prick test (SPT) with an undiluted solution of RCM, histamine and saline as positive and negative control, respectively. In cases with negative SPT, an intradermal test (IDT) with a 1:10 dilution in a saline solution was performed and assessed after 20 minutes. Delayed readings of IDT at the 48th, 72nd, and 96th hours were performed for the evaluation of NIHRs. Positive responses were considered if a blister larger than 3 mm surrounded by erythema appeared with a negative response to control saline. (7). If the contrast agent used in the previous reaction was known, primary skin tests were performed with that agent and iohexol as an alternative agent; otherwise, skin tests were performed only with iohexol, one of the most commonly used contrast agents in Turkey.

In the follow-up, RCM was administered only for those who needed these medications later but with premedication. The culprit agent was not recommended for the patients and a skin test negative alternative agent was administered. Iohexol was administered if the previous agent was unknown and the skin test with iohexol was negative. In cases with severe reactions, the contrast agent was generally not recommended again according to a comprehensive risk-benefit analysis (8). As premedication, oral methylprednisolone 40 mg 13-7-1 hours before the procedure and oral pheniramine 22.7 mg 1 hour before the procedure were prescribed (9).

The medical records of these patients were re-evaluated, and during routine follow-up visits, patients were asked questions pre-defined for this study (if they had a procedure with RCM after allergy workup, did they receive premedication? and did any reactions occur?).

The statistical analyses were performed using SPSS version 20.0 software (IBM Corp, Armonk, NY, USA). Conformity of the data to a normal distribution was assessed with the Kolmogorov-Smirnov test. Data with an abnormal distribution were expressed as median (range), and those with a normal distribution as mean ± standard deviation (SD) values. Approval for the study was granted by the Ethics Committee of Hacettepe University (Approval Number: 2020/08-31).

## RESULTS

A total of 96 patients with a history of RCM hypersensitivity were evaluated. A total of 55 patients were excluded; 12 due to non-specific symptoms in the anamnesis, 12 due to insufficient data, and one who was diagnosed with latex allergy during the process. Of the remaining 71 patients, skin tests could not be applied in 20 as they were taking antihistamines, steroids, or antidepressants or refused to have the test and, 10 had reactions with gadolinium-based radiocontrast agents. Consequently, the data of 41 patients were analyzed. Figure 1 presents the flow chart of the study.

### Characteristics of The Patients

A total of 41 patients with RCM hypersensitivity were included in the study, comprising 32 (78%) females and 9 (22%) males with a mean age of 53.5 ± 12.9 years. Previous reactions were immediate in 35 (85.4%) and non-immediate in 6 (14.6%) patients. Immediate reactions

revealed 8 (22.8%) generalized erythema, 16 (45.7%) urticaria / angioedema, 8 (22.8%) dyspnea ± pruritus, and 3 (8.6%) anaphylaxis. In non-immediate reactions, 3 (50%) patients had delayed urticaria, 2 (33.3%) maculopapular rash, and 1 (16.6%) patient had delayed anaphylactoid reaction (Figure 1). According to the verbal information received from the patients and the medical records, iohexol (n=10, 24.4%), iobitridol (n=5, 12.2%), and iopromide (n=4, 9.8%) were the most commonly used RCMs whereas the culprit agent was unknown in 22 (53.6%) patients. The median time between the reactions of the patients and the skin tests was 10 (min: 2-max: 24) months. Table I presents the characteristics of the study population.

The most common non-atopic comorbidities were hypertension (n=10, 24.4%), coronary artery disease (n=6, 14.6%) and hypothyroidism (n=6, 14.6%). Atopic diseases were drug allergy (n = 20, 48.8%), followed by asthma (n=13, 31.7%), rhinitis (n=6, 14.6%), chronic urticaria (n=3, 7.3%) and Hymenoptera venom allergy (n=1, 2.4%).

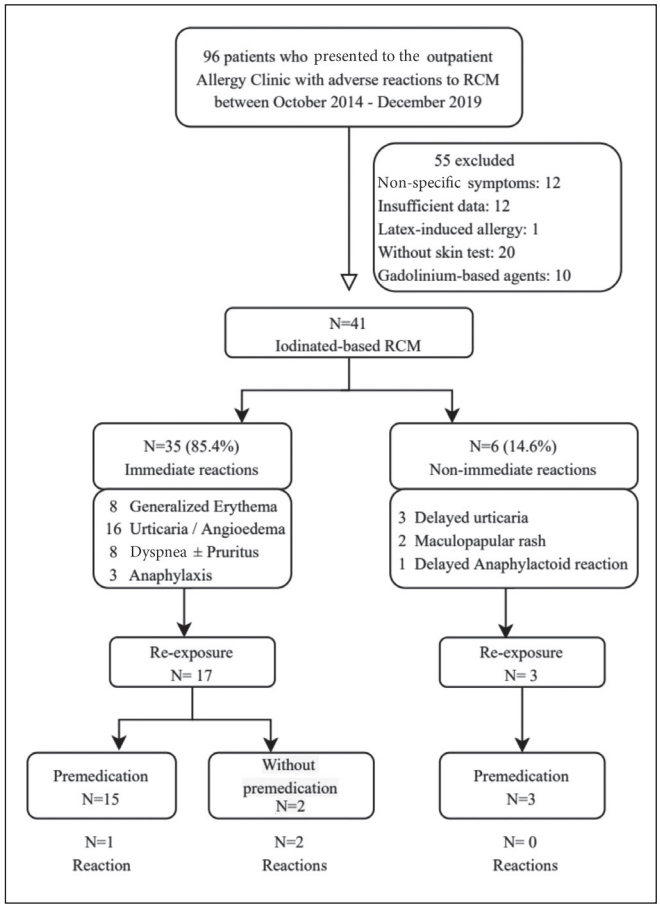


**Figure 1.** Flow chart of the study.

A history of allergic diseases in first-degree relatives was reported by 9 patients.

### Positive Skin Test Results

The skin test was performed as described in the methods section, using the RCM: iobitridol (Xenetix®), iohexol (Omnipaque®), iopromide (Ultravist®). Three of the 41 patients included in the study had a positive IDT result, one of which was delayed reading of IDT. Among these patients with a positive skin test, only P2 has required RCM again. No reaction was observed with the alternative agent applied with premedication. Table II presents the data of these three patients.

### Re-Exposure to RCM

It was determined that 20 patients, 17 of whom had experienced immediate reactions and 3 non-immediate reactions, required imaging with RCM again. As planned in the method section, 16 patients received iohexol, three patients iobitridol, and one patient received iopromide among the patients who were re-exposed to RCM. Of these, 18 received premedication (oral methylprednisolone 40 mg 13-7-1 hours before the procedure and oral pheniramine 22.7 mg 1 hour before the procedure),

**Table I: Characteristics of the study population.**

| Variables | Total (n=41) |
|---|---|
| Age, year (mean ± SD) | 53.5 ± 12.9 |
| Gender, female, n (%) | 32 (78) |
| Comorbidities, n (%) | |
| Hypertension | 10 (24.4) |
| Coronary Artery Disease | 6 (14.6) |
| Hypothyroidism | 6(14.6) |
| Diabetes Mellitus | 5 (12.2) |
| Malignancy | 5 (12.2) |
| Atopic Diseases, n (%) | |
| Drug allergy | 20 (48.8) |
| Asthma | 13 (31.7) |
| Rhinitis | 6 (14.6) |
| Chronic Urticaria | 3 (7.3) |
| Venom allergy | 1 (2.4) |
| Atopic family history, n (%) | 9 (22) |
| Previously reacted RCM, n (%) | |
| Iohexol | 10 (24.4) |
| Iobitridol | 5 (12.2) |
| Iopromide | 4 (9.8) |
| Undetermined | 22 (53.6) |

**Table II: Patients with positive IDT results.**

| Patients | Age/G | Culprit RCM | Time | Previous reaction | RCM with positive test | RCM re-exposed | Premedication | Re-Reaction |
|---|---|---|---|---|---|---|---|---|
| P1 | 39/F | iohexol | NIHR | Maculopapular rash | Iohexol | No | No | No |
| P2 | 63/F | UD | IHR | Anaphylaxis | Iohexol | Iobitridol | Yes | No |
| P3 | 50/F | UD | IHR | Urticaria | Iohexol | No | No | No |

**UD:** Undetermined, **G:** Gender, **F:** Female, **NIHR:** Non-immediate hypersensitivity reaction, **IHR:** Immediate hypersensitivity reaction

and two did not, although it was recommended. Reactions were observed in three patients after re-exposures. Of the patients who received premedication, one (5.5%) had an immediate urticarial reaction of the same grade, while both of the patients (100%) who did not receive premedication developed an immediate allergic reaction that was of a similar grade to that of the previous reaction (Figure 1). Among the 41 patients in the study, none of the patients have had reactions with more than one contrast agent according to their anamnesis. However, one of the three patients who had a reaction after re-exposure to RCM reacted with iohexol, which was a skin test-negative alternative although the previous culprit agent was iopromide. In the other two patients who experienced the reaction, one of which was a reaction under premedication, iohexol had been administered after a negative skin test, since the previous culprit agents were unknown.

## DISCUSSION

In this study, the value of skin tests and premedication was retrospectively investigated and the question of whether the frequency of reactions can be reduced by giving standard premedication, even when the RCM agent to which the patient previously reacted is not known, was addressed.

Although hypersensitivity reactions to RCM are clinically rare, the incidence is increasing in allergy clinics due to the increasing use of contrast agents worldwide. However, controversies continue over the diagnostic approach, prediction, and premedication. The latest guidelines suggest that skin tests should be performed first with a panel of RCM including the culprit agent (3, 8). However, the most common problem encountered in daily clinical practice is that patients do not know the contrast agent used in their previous reaction or have difficulty in accessing this information. Considering the low sensitivity of the skin tests, there are difficulties in diagnosing RCM hypersensitivity and finding a safe alternative agent. Based on recent discussions in skin testing, the current study results showed that premedication may reduce the frequency of reactions where the culprit agent is undetermined or the skin tests are negative.

The findings of the current study converge with previous findings. In a study by Lee et al. IDT was calculated to have sensitivity of 0%, specificity of 99.47%, a negative predictive value (NPV) of 99.33%, and a positive predictive value (PPV) of 0% for prediction of hypersensitivity to an iodinated contrast agent (10). This low positivity rate shows it has low clinical value in the prediction of a hypersensitivity reaction to RCM. A meta-analysis by Yoon et al. indicated the limitation of the skin tests in immediate and non-immediate reactions but it was also stated that it can be helpful in patients with severe immediate reactions (11). Schrijvers et al. determined skin test positivity with the culprit drug in 13.4% of 597 patients over 13.5 years (12). In the current study, only 3 (7.3%) of 41 patients had positive skin test results, which was a lower rate than in other studies in the literature. The reason for this difference may be that the time between the reaction and skin tests was longer than recommended in our study, and it may therefore have caused a decrease in skin test reactivity due to IgE clearance. Also, it may be due to the low number of patients and the difficulties of accessing the culprit agent.

Many risk factors are suspected for RCM allergy, with the most important being a history of previous adverse reactions to RCM (4). Goksel et al. showed a 2-fold increase in the prevalence of RCM hypersensitivity in females, and other significant risk factors were reported as asthma, and drug and food allergies (13). In accordance with the previous studies, there was a female predominance in the current study. In one of the latest series of international consensus, it was emphasized that the most important risk factor for developing hypersensitivity reactions to RCM

was previous allergic reactions, and other factors that have been associated with an increased risk were atopy and asthma (3). In the current study, 61% of the patients had allergic diseases, the most common of which were drug allergy (48.8%), and asthma (31.7%).

Premedication is an effective method that may prevent the development of hypersensitivity reactions in high-risk patients (6). Premedication with corticosteroids and antihistamines was proposed by Greenberger and Patterson in North America many years ago with the aim of preventing severe reactions to RCM (9). The efficacy of premedication is known but also contradictory. There are several studies on RCM hypersensitivity reporting the efficacy of premedication for skin test negative patients and also for the patients whose culprit agent is unknown (8, 14). On the other hand, there are studies that indicate breakthrough reactions may develop despite premedication (15). In the study by Park et al, the recurrence rate of mild hypersensitivity reactions was 31.1% when patients were re-exposed to the same RCM without premedication. When the RCM was changed, the recurrence rate of reactions was 12%, and by using the combination of changing the RCM and antihistamine premedication the rate was 7.6%. Therefore, they suggested that a combination of changing the culprit agent and antihistamine premedication led to the best preventive outcome for patients with mild immediate hypersensitivity reactions (16). On the other hand, Freed et al. evaluated the clinical features of 53 patients who experienced breakthrough reactions despite premedication with steroids and found that the risk of having a breakthrough reaction was approximately 10% (15). Davenport et al. demonstrated that breakthrough reactions to RCM despite premedication were generally similar to index reactions and were more likely to be more severe in patients with a history of chronic corticosteroid use or drug allergy (6, 17). In the current study, there was one patient who had urticarial lesions after re-exposure to RCM despite premedication, and the reaction was of a similar grade to the previous reaction.

There is no precise evidence of premedication in patients with NIHR and it is considered to be harmful, especially in patients with a severe history of NIHR (e.g. TEN, DRESS) (8). However, three of the six patients with NIHR in our study had a history of delayed urticaria, two of maculopapular rash, and one of delayed anaphylactoid reaction. One of the reasons why they benefited from premedication may be our classification of reactions up to 1 hour as immediate and after 1 hour as non-immediate in accordance with Brockow's recommendations, while this limit was accepted as 6 hours in the latest position paper of the European Academy of Allergy and Clinical Immunology (EAACI) (2, 8). Brockow's medical algorithm has classified reactions according to a limit of 1 hour, and it has been suggested that premedication should be considered in patients whose skin tests are negative with an RCM panel (2). We preferred to recommend premedication in NIHR patients because of our limitation in performing skin tests with a large panel and the relatively more common cross-reactivity risk in NIHR than in IHR (12, 18, 19).

This study has certain limitations. Firstly, the data on the culprit RCM was missing in many patients, and therefore it may not be accurate to interpret skin test negativity in some cases. Although the guidelines recommend testing first with the culprit agent and a panel of RCM, the retrospective findings of this study reflect the real-life experience and show that in the majority of patients the culprit RCM is unknown in clinical practice due to improper registration (3). Secondly, the other limitation was our time interval between the reaction and allergological evaluation. It is recommended that skin tests be performed ideally within the first 6 months after a clinical reaction (8). In our study, this median period was determined to be 10 months, and it may have caused a decrease in skin test reactivity due to IgE clearance. Thirdly, we did not perform drug provocation tests due to risk-benefit analysis. This situation may cause us to perceive non-allergic reactions as allergic, and this may have shown premedication to be more effective than usual. Another limitation was that we did not perform patch testing. Instead, we assessed the delayed readings of the intradermal tests for non-immediate reactions.

In conclusion, skin test positivity for RCM was observed at low rates and it was assessed that premedication can decrease the frequency of reactions. In appropriate cases where the culprit agent is known, an allergological examination for the alternative agent should be performed as recommended in the guidelines. However, in cases where the culprit agent cannot be identified and skin tests are negative, re-exposure to alternative RCM under premedication may reduce the risk of reaction.

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