

# Skin Test–Positive Immediate Hypersensitivity Reaction to Iodinated Contrast Media: The Role of Controlled Challenge Testing

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## ■ Abstract

*Background:* Immediate hypersensitivity reactions (IHR) to iodinated contrast media (ICM) have traditionally been considered nonallergic; however, the increasingly frequent reporting of positive skin test and basophil activation test results suggests a specific allergic mechanism in some patients. Skin tests have been proposed as a useful tool for diagnosis, although their sensitivity and predictive values remain to be determined. The role of controlled challenge testing has not been assessed.

*Objective:* We aimed to evaluate the role of controlled challenge testing in skin test–positive IHR to ICM.

*Patients and Methods:* We evaluated 106 patients with IHR to ICM by performing skin tests with the agent that caused the reaction. Patients with a positive result were selected. Skin tests were extended to a series of 8 ICMs; 5 patients underwent controlled challenge test with an alternative skin test–negative ICM; a further 2 patients underwent computed tomography with an alternative skin test–negative ICM. No premedication was administered.

*Results:* Intradermal test results were positive to the ICM that caused the reaction in 11 out of 106 patients (10.4%). Five of the 11 patients tolerated a controlled challenge test with an alternative skin test–negative ICM. The 2 patients who underwent computed tomography with an alternative skin test–negative ICM tolerated the medium.

*Conclusions:* Skin tests are useful for the diagnostic workup in patients with an allergic IHR to ICM. Since ICM cannot be avoided in many patients because they are irreplaceable in some diagnostic or therapeutic techniques, an alternative safe ICM should be investigated for future procedures. We propose the use of controlled challenge tests based on skin test results to address this need in skin test–positive reactions in order to identify an alternative non–cross-reactive ICM.

**Key words:** Controlled challenge test. Allergic immediate hypersensitivity reactions. Iodinated contrast media. Skin tests.

## ■ Resumen

*Antecedentes:* Aunque clásicamente las reacciones de hipersensibilidad inmediatas (RHI) a medios de contraste iodados (MCI) se han considerado no alérgicas, la publicación creciente de pruebas cutáneas y test de activación de basófilos positivos, sugieren un mecanismo alérgico específico en algunos pacientes. Se han propuesto las pruebas cutáneas como una herramienta útil para el diagnóstico, aunque su sensibilidad y valores predictivos están aún por conocer. El papel de la prueba de provocación controlada no se ha determinado.

*Objetivo:* El objetivo fue evaluar el papel de la prueba de provocación controlada en las RHI a MCI con prueba cutánea positiva.

*Pacientes y Métodos:* Evaluamos 106 pacientes con RHI a MCI mediante prueba cutánea con el contraste que causó la reacción. Se seleccionaron los pacientes con resultado positivo: se ampliaron las pruebas cutáneas con una serie de 8 MCI; en 5 pacientes se realizó prueba de provocación controlada con un MCI alternativo con resultado negativo en la prueba cutánea; otros dos pacientes se sometieron a una tomografía computarizada con un MCI alternativo con resultado negativo en la prueba cutánea. No se administró ninguna premedicación.

*Resultados:* Las pruebas intradérmicas fueron positivas al MCI que causó la reacción en 11 de 106 pacientes (10.4%). Cinco de ellos toleraron la prueba de provocación controlada con un MCI alternativo con resultado negativo en la prueba cutánea. Los otros 2 pacientes a los que se les realizó una tomografía computarizada con un MCI alternativo con prueba cutánea negativa, también lo toleraron.

*Conclusiones:* Las pruebas cutáneas son útiles para la valoración diagnóstica en las RHI alérgicas a MCI. Dado que en muchos pacientes los MCI no pueden ser evitados al ser irremplazables para algunas técnicas diagnósticas o terapéuticas, es necesario identificar un MCI alternativo para ser utilizado con seguridad en procedimientos futuros. Proponemos el uso de la prueba de provocación controlada basada en los resultados de las pruebas cutáneas para resolver esta situación en estas reacciones con prueba cutánea positiva, para poder identificar un MCI alternativo sin reactividad cruzada.

**Palabras clave:** Prueba de provocación controlada. Reacción de hipersensibilidad inmediata alérgica. Medio de contraste iodado. Pruebas cutáneas.

## Introduction

Hypersensitivity reactions to iodinated contrast media (ICM) can be classified according to the time interval between administration and reaction as immediate (<1 hour) and nonimmediate (>1 hour).

Mild immediate hypersensitivity reactions (IHR) occur in about 0.5% to 3% of applications and severe IHRs in 0.01% to 0.04% [1]. Despite this low incidence, IHRs are a significant clinical problem, given the increasingly large amount of administrations per year worldwide. Clinical presentation ranges from mild urticaria to severe anaphylactic shock or even death in 1 per 100 000 administrations [1,2].

Although IHRs have traditionally been considered nonallergic, in recent years, evidence has increasingly pointed to an immune mechanism. The report of positive skin test and basophil activation test results to ICM suggests a specific allergic mechanism in some patients [3-12], and specific immunoglobulin (Ig) E has been detected using radioimmunoassay [13].

Skin tests have been proposed as a useful tool for the evaluation and diagnosis of IHR to ICM, and guidelines for this procedure have been published [1]. However, their sensitivity and predictive values remain to be determined [3], and the use of controlled challenge testing for evaluation of these reactions has not been assessed.

We report on 11 patients who experienced IHR to ICM and had positive skin test results with the culprit contrast agent. Seven tolerated subsequent exposure to an alternative skin test–negative ICM with no premedication. Controlled challenge test based on skin test results is proposed as a useful tool for identifying an alternative non–cross-reactive ICM.

## Methods

We analyzed all patients who attended our allergy department owing to anaphylactic IHR to ICM from May 2008 to August 2011. Anaphylactic symptoms were classified according to severity [14] as follows: grade 1, cutaneous symptoms (eg, urticaria and angioedema); grade 2, features suggesting respiratory, cardiovascular, or gastrointestinal involvement; and grade 3, severe reactions with hypoxia, hypotension, or neurological involvement. Patients reporting nonspecific symptoms such as heat sensation, nausea, or headache were excluded.

The study was approved by the local ethics committee. After signing the informed consent form, patients underwent an allergy workup. Skin tests were performed with the culprit ICM according to the recommendations of the European Academy of Allergy and Clinical Immunology [15]. In the case of an unknown causative ICM and in the case of a positive skin test result to the culprit ICM, skin tests were carried out with a series of 8 ICMs used at our institution: iopamidol, ioversol, iodixanol, iobitridol, iohexol, ioxaglate, iomeprol, and amidotrizoate. A prick test with undiluted ICM and latex (ALK-Abelló) was followed by an intradermal test with 10-fold diluted ICM. Iopamidol, ioversol, and iobitridol were also tested undiluted. These concentrations were based

on our previous experience, having proven to be nonirritant in large series of more than 100 patients exposed to ICM. Histamine and saline were used as positive and negative controls, respectively. The skin test was read after 15 minutes; the result was considered positive if a wheal  $\geq 3$  mm in diameter (prick test) or an increase in the diameter of the initial wheal by at least 3 mm surrounded by erythema (intradermal test) was observed [15].

Patients with a positive skin test result were selected. The data collected were age, gender, previous exposure to ICM, clinical presentation of the adverse reaction, culprit ICM, time to onset of the reaction, and time between reaction and testing.

An intravenous controlled challenge test was performed with an alternative skin test–negative ICM following our local protocol: no premedication was administered; increasing doses of ICM were administered in 30-minute intervals until a total dose of 120 mL was reached (day 1, 5-30-60 mL; day 2, 120 mL). The total volume for a computed tomography scan in adult patients is 120 mL. In patient 6 (aged 7 years), the intravenous controlled challenge test was performed with 6-18 mL administered at a 30-minute interval, as 24 mL was the total volume administered during coronary catheterization. Patient 3 also underwent an oral controlled challenge test with amidotrizoate (7 mL + 7 mL) administered at 30-minute intervals. During the controlled challenge test procedure, patients were carefully observed, and equipment for emergency treatment was available as recommended [16]. We also investigated subsequent exposures to ICM in radiologic explorations after the allergy workup.

## Results

We evaluated 106 patients: 60.4% female, 39.6% male, and mean (SD) age 56.7 (16.9) years. The culprit ICM was ioversol in 33.9% of patients, iopamidol in 31.1%, iomeprol in 3.8%, iohexol in 2.8%, ioxaglate in 0.9%, iobitridol in 0.9%, and unknown in 26.4%. Reactions were classified as grade 1 in 62.3% of cases, grade 2 in 27.4%, and grade 3 in 10.4%.

Prick tests with ICM and latex were negative in all patients. Eleven patients (10.4%, 5 males and 6 females; mean age, 52.6 [26.4] years) had a positive result in the intradermal test. Reactions in these patients were grade 1 in 6 patients (54.5%), grade 2 in 4 (36.4%), and grade 3 in 1 (9.1%). Two patients (18.2%) had never been exposed to ICM. Three patients were atopic. Clinical data for the patients with a positive skin test result are shown in Table 1. In the case of iopamidol, ioversol, and iobitridol, skin test results did not differ when undiluted and diluted (1:10) solutions were analyzed.

Reactions in the 95 skin test–negative patients were grade 1 in 63%, grade 2 in 26%, and grade 3 in 11%. Atopy was recorded in 24% of these patients.

The median time between reaction and testing in patients with a negative skin test result was 4 (2-22.5) months, whereas in patients with a positive skin test result, the median was 3 (1-4) months.

The results of the allergy workup in 7 skin test–positive patients are shown in Table 2. Intradermal tests were positive to the culprit ICM in all of them (Figure 1). Only patient 8 showed

Table 1. Clinical Data of the 11 Skin Test–Positive Patients

Patient	Gender	Age, y	Disease Studied	Prior Exposure to ICM	Time to Onset, min	Clinical Presentation	Time Between Reaction and Study, mo
1	Female	44	Ovarian carcinoma	Yes	5	Urticaria (grade 1)	8
2	Female	20	Ovarian adenoma	No	15	Urticaria/angioedema (grade 1)	4
3	Male	45	Colorectal carcinoma	Yes	5	Urticaria (grade 1)	1
4	Female	93	Rectal carcinoma	Yes	5	Urticaria/angioedema (grade 1)	3
5	Male	76	Gastric carcinoma	Yes	5	Anaphylaxis (grade 3)	1.5
6	Male	7	Coronary heart disease	Yes	10	Urticaria (grade 1)	3
7	Male	72	Coronary heart disease	Yes	5	Anaphylaxis (grade 2)	3
8	Female	69	Aortic dissection	Yes	5	Anaphylaxis (grade 2)	1.5
9	Female	69	Rectal-colonic carcinoma	Yes	15	Anaphylaxis (grade 2)	1.5
10	Female	58	Colon carcinoma	Yes	5	Urticaria (grade 1)	1
11	Male	27	Intracranial germinoma	No	20	Anaphylaxis (grade 1)	12

Abbreviations: ICM, iodinated contrast medium.

Table 2. Allergy Workup in 7 Skin Test–Positive Patients: Results Are Shown for the Culprit Iodinated Contrast Medium, Intradermal Test, and Controlled Challenge Test

Patient	Culprit ICM	Intradermal Tests								CCT	Subsequent Exposures (Well-Tolerated)
		Iopamidol	Ioversol	Iodixanol	Iobitridol	Iohexol	Ioxaglate	Iomeprol	Amidotrizoate		
1	Iopamidol	+	–	–	–	–	–	–	–	Ioversol –	Oral amidotrizoate
2	Iopamidol	+	–	–	–	–	–	–	–	Ioversol –	–
3	Iopamidol	+	–	–	–	–	–	–	–	Ioversol –, oral amidotrizoate –	Ioversol, oral amidotrizoate
6	Ioversol	–	+	ND	–	ND	ND	–	ND	Iopamidol –	–
8	Ioversol	–	+	–	–	+	ND	+	ND	ND	Iopamidol
9	Ioversol	–	+	ND	–	–	ND	–	ND	ND	Iopamidol
10	Iopamidol	+	–	–	–	–	–	–	–	Ioversol –	–

Abbreviation: CCT, controlled challenge test; ICM, iodinated contrast medium; ND, not done.

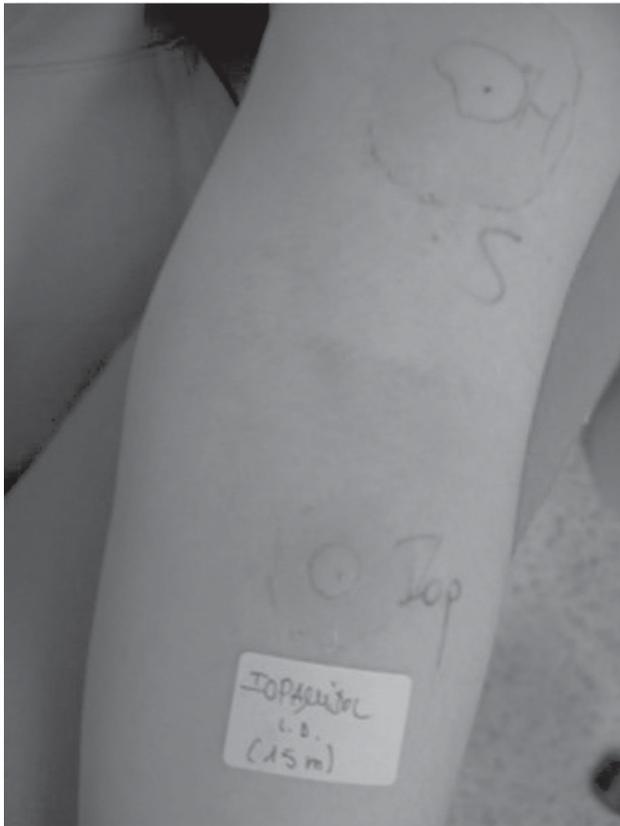


Figure 1. Positive intradermal test with iopamidol. H indicates histamine (as positive control); S, saline (as negative control); Iop, iopamidol. Reading at 15 minutes.

cross-reactivity in the skin test to 3 out of 6 ICMs tested. The results of the remaining intradermal tests were all negative.

Patients 1, 2, 3, and 10 (allergic to iopamidol) tolerated ioversol in the controlled challenge test. Patient 3 also tolerated the oral controlled challenge test with amidotrizoate, which was also given orally before the allergic reaction to iopamidol. Patient 6, who was allergic to ioversol, underwent a challenge with iopamidol and also showed good tolerance. He had a negative result in the intradermal test with midazolam. Controlled challenge was not performed in patient 4, owing to her age and comorbidity, or in the remaining patients, because they had all experienced severe reactions to the ICM. Patients 8 and 9, who were allergic to ioversol, subsequently underwent computed tomography with ICM. Iopamidol was administered without premedication. Neither patient had an adverse reaction.

After the allergy workup, patient 3 underwent a controlled challenge test with intravenous ioversol and oral amidotrizoate 10 times with good tolerance. Patient 1 also tolerated oral amidotrizoate in a computed tomography scan.

## Discussion

IHR to ICM has traditionally been considered nonallergic and caused by release of histamine and other mediators of

mast cells and basophils owing to a direct effect on the cell membrane or indirectly by activation of the complement system [1,2]. However, positive results in skin tests, basophil activation tests, and specific IgE detection have been increasingly reported, suggesting a specific allergic mechanism in some patients [3-13].

Several studies have used skin testing to evaluate patients with IHR to ICM. In a European multicenter study involving 122 patients, a positive skin test result was documented in 32 patients (26%) [3]. Dewachter et al [5] evaluated 38 patients and reported a skin test sensitivity of 73% (19 out of 26 patients tested). Goksel et al [6] reported positive skin test results in 2 out of 14 patients with IHR (14%). Kvedariene et al [11] reported positive skin test results in 9 out of 32 patients (28.1%) [11]. Trcka et al [4] found positive skin test results in 4 out of 96 patients evaluated (4.2%). We evaluated 106 patients over a 3-year period and found positive skin test results in only 11 (10.4%). Therefore, the incidence of positive results differs widely depending on the study. These discrepancies could be explained by differences in the use of ICM according to hospital and country and the fact that some ICM could be more allergenic than others. In our area, where iopamidol and ioversol are the most commonly used media, the low rate of positive skin test results (10%) could suggest lower allergenicity for these agents.

The interval between the reaction and skin testing has proven to be relevant in terms of results [3,11]. In the European multicenter study, the percentage of positive skin test results increased from 26% to 50% in patients evaluated 2 to 6 months after the reaction [3]. For the same time period, the percentage of positive results in our study would increase to only 14.5%.

In some studies, 30% to 50% of skin test-positive patients had never been exposed to ICM, as in 2 of our cases (18.2%) [3,5], illustrating that specific anaphylaxis may follow the first administration of ICM. Most of our patients have chronic diseases, mainly oncologic and cardiovascular diseases, which require repeated exposures to ICM.

An allergy workup should be performed in patients with IHR to ICM. Information concerning which ICM caused the reaction should be obtained before the workup so that it can be included in the workup. Prick testing showed insufficient diagnostic sensitivity; intradermal testing seems to be much more sensitive. Intradermal testing should be performed with a 10-fold dilution of ICM [3]. Dewachter et al [5] performed an intradermal test with undiluted ICM. Since they did not test controls, it remains unclear whether the ICM tested could be irritant at that concentration. The fact that the test was performed with undiluted ICM could also explain the unexpected high percentage of skin test-positive results found. Furthermore, the authors found that 179 out of 188 intradermal tests to alternative ICM were negative, thus indicating specificity, and argue that the culprit ICM was known in their patients, whereas in other studies it was unknown in a high percentage of patients. In our experience, some agents (iopamidol, ioversol, and iobitridol) can be tested undiluted, as they proved to be nonirritant in a large series (106 patients).

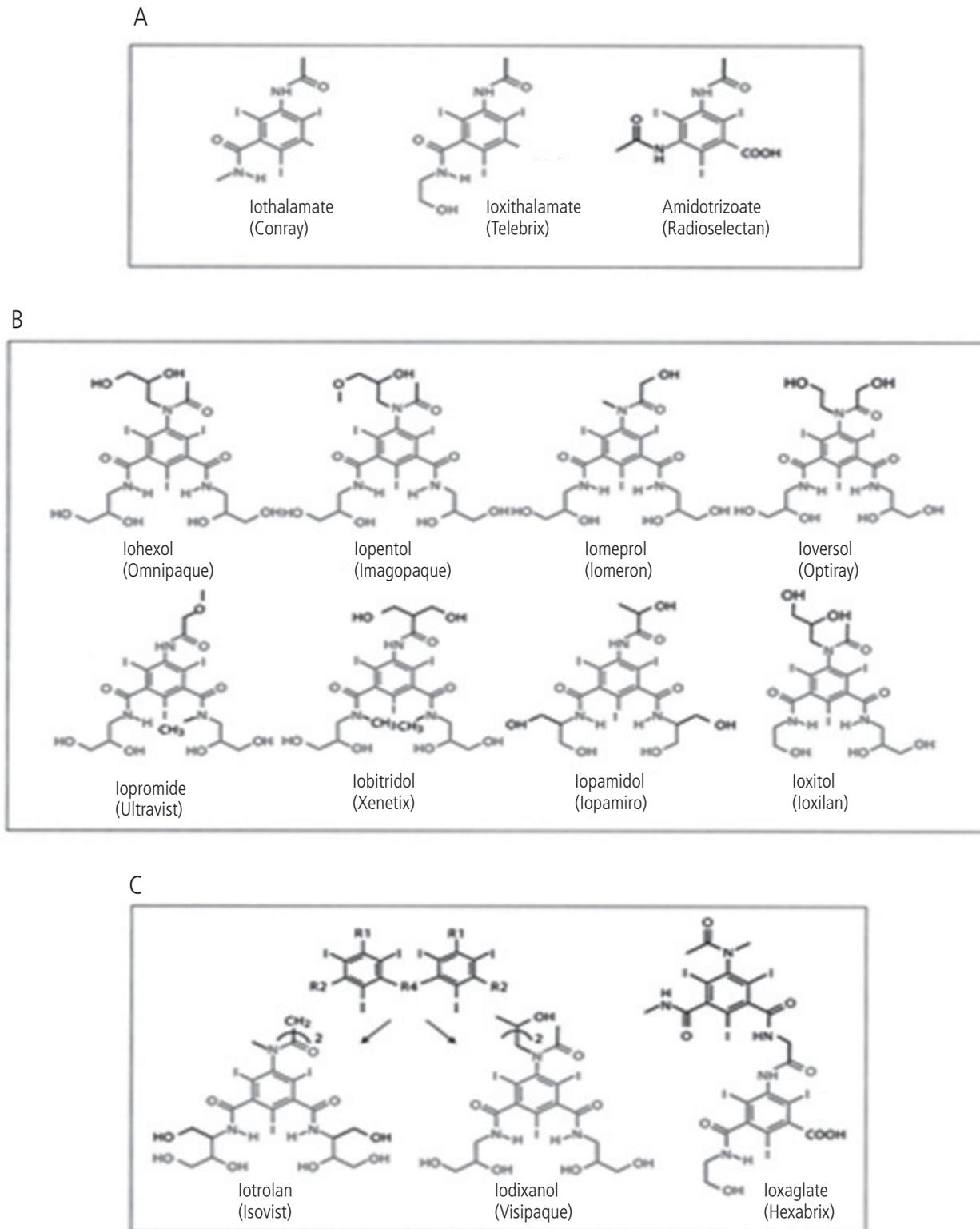


Figure 2. Chemical structure of ICM. A, Ionic monomers; B, Nonionic monomers; C, Nonionic dimers.

Skin tests are considered a useful tool for identifying a specific allergic mechanism [3], although published data concerning subsequent tolerability of skin test–negative ICM are lacking, and the role of controlled challenge testing to evaluate these reactions has not been assessed. Few patients have been re-exposed to a different skin test–negative ICM [5-8]. To our knowledge, only 1 publication shows that controlled challenge testing based on skin test results was used in 2 patients in order to identify an alternative well-tolerated ICM [4].

A panel of several ICMs should be investigated using skin tests to evaluate cross-reactivity, since a comparison of the chemical structures of ICMs cannot identify potential cross-reactivity in individual patients. In fact, iopamidol and ioversol, which are the most commonly used ICMs in our hospital (and therefore the ones we chose for controlled challenge testing) are both nonionic monomers with a very similar chemical structure (Figure 2). No cross-reactivity was detected between these substances in our patients.

The current approach to IHR to ICM in patients with negative skin test results involves premedication with H<sub>1</sub> and H<sub>2</sub> antihistamines and corticosteroids for future administrations, as well as a different ICM to that involved in the previous reaction, as was the case with our skin test–negative patients. However, if skin test results are positive, premedication cannot be considered efficient for preventing subsequent reactions, and an alternative skin test–negative ICM could be eligible for future testing. However, tolerability is uncertain, since the negative predictive value of skin testing remains unknown. ICMs cannot be avoided in some patients and are irreplaceable agents in certain diagnostic and therapeutic techniques, especially in cardiovascular diseases; therefore, an alternative and safe ICM must be identified for these allergic patients. We propose controlled challenge testing based on skin test results to identify an alternative and safe non–cross-reactive ICM for future diagnostic or therapeutic procedures. As in the evaluation of other drug allergies, the risk of controlled challenge testing should be taken into account when patients experience a severe or life-threatening reaction to the ICM or they have other risk factors or comorbidities [16].

This study does not provide data on subsequent tolerability to ICMs by skin test–negative patients. Therefore, the negative predictive value of skin testing and the underlying mechanism in these patients is not clear. We present a diagnostic approach to skin test–positive patients using controlled challenge testing. We report 7 patients presenting IHR to ICM with positive skin test results to the culprit ICM who tolerated subsequent exposure to an alternative skin test–negative ICM with no premedication. Our approach identified an alternative non–cross-reactive ICM to be used safely in future diagnostic or therapeutic procedures in 5 patients. More studies based on controlled challenge testing are needed to determine the predictive values and sensitivity of skin tests.

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