

ORIGINAL ARTICLE

Drug Allergy, Insect Sting Allergy, and Anaphylaxis

Non-immediate hypersensitivity reactions to iomeprol: Diagnostic value of skin tests and cross-reactivity with other iodinated contrast media

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Abstract

Background: Iodinated contrast media produce non-immediate hypersensitivity reactions (NIHR). The goal of this prospective study was to determine the utility of skin tests and the subsequent tolerance to negative skin-tested iodinated contrasts in patients with NIHR caused by iomeprol.

Methods: Prick and intradermal tests with iomeprol, iopamidol, iopromide, and iobitridol were performed in all patients. IV challenge with the causative contrast (iomeprol in 90%) was made if skin tests were negative. In case of a positive skin test with the causal contrast, or a positive challenge test with it, IV challenge test with an alternative, negative skin-tested contrast was performed in all patients.

Results: Skin tests were positive in 47.6% (20/42) of patients with NIHR induced by iomeprol. Of the 66 challenge tests performed with negative skin-tested iodinated contrasts, tolerance was confirmed in 35 (53%): 32 iomeron, 2 iobitridol, 1 iopamidol. Cross-reactivity between iomeprol and iopamidol was 22% (4/20 in patients with positive skin tests and 5/21 in patients with negative skin tests).

Conclusions: Sensitivity of the skin tests was less than 50% NIHRs due to iomeprol, while the negative predictive value of skin tests in patients who tolerated challenges with alternative contrasts (mainly iopamidol) was 53% (35 tolerated out of 66 performed). The cross-reactivity between iomeprol and iopamidol is high.

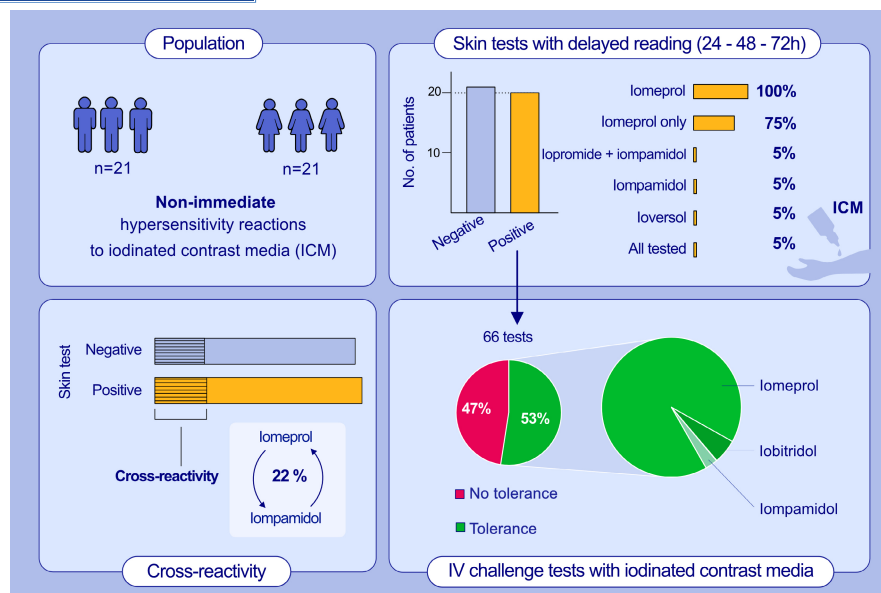
KEYWORDS

iodinated contrast media, iomeprol, iopamidol, non-immediate hypersensitivity

Non-immediate hypersensitivity reactions (NIHR) to iodinated contrast media (ICM) occur later than 1 h after ICM administration.^{1,2} Maculopapular reactions are the most frequent, followed by delayed urticaria with or without angioedema,³ although the latter seems to be caused by a different mechanism, yet not fully understood.² Much less frequently, adverse events can result in life-threatening

systemic reactions, such as Stevens–Johnson syndrome, vasculitis, drug reaction with eosinophilia and systemic symptoms (DRESS), or toxic epidermal necrolysis.³

Diagnosis of NIHR to ICM is based on skin intradermal test and patch tests with delayed readings, as well as in vitro techniques, such as the lymphoblastic transformation test (LTT).^{4,5}



GRAPHICAL ABSTRACT

This study determines the utility of skin tests and the subsequent tolerance to negative skin-tested ICM in patients with NIHR caused by iomeprol. In iomeprol-induced NIHR, skin tests sensitivity is less than 50%, though the negative predictive value of skin tests in patients who tolerated alternative contrasts (mainly iopamidol) is 53%. There is a high cross-reactivity between iomeprol and iopamidol. Abbreviations: ICM, iodinated contrast media; NIHR, non-immediate hypersensitivity reactions

The usefulness of skin tests in the diagnosis of NIHRs varies greatly between the different published series. In a recent meta-analysis, the overall positive rate of patch and intradermal skin tests in NIHR was 26%⁶ in a cluster of eight patient series involving 369 patients; however, in several of these series, no challenge tests were performed in patients with negative skin tests, to confirm or rule out the existence of true NIHR. In a later series of 50 patients with NIHR, positivity rate of intradermal test with delayed reading was 66%.⁷ Hence, skin tests cannot confirm a diagnosis in a high percentage of these patients. Furthermore, cross-reactivity between ICMs in patients with NIHR is higher than in patients with immediate reactions,¹ which makes the selection of a safe alternative ICM more difficult: In Yoon's meta-analysis,⁶ the percentage of mean cross-reactivities in NIHR was 67.9% in seven studies analyzed. In the case of iomeprol, its cross-reactivity is high in NIHR, especially with ioversol,^{7,8} iohexol, iodixanol,⁸ and iopromide.⁹ With the rest of the ICM, iomeprol cross-reactivity seems to be lower, albeit there are no series with enough "n" to determine it accurately. Therefore, given the limited utility of skin tests to diagnose these reactions and to establish the cross-reactivity of ICM, the choice of an alternative ICM in NIHR requires the confirmation of tolerance through a challenge test^{1-3,10} with the ICMs proven negative in the skin tests performed.

Based on this background, we conducted a study in 53 patients with NIHRs to ICM (iomeprol in 96% of cases) confirmed by skin tests or challenge tests, in order to verify the utility of skin testing in their diagnosis, as well as the usefulness of skin tests in the selection of a safe ICM for subsequent radiological explorations.

1 | METHODS

1.1 | Patients

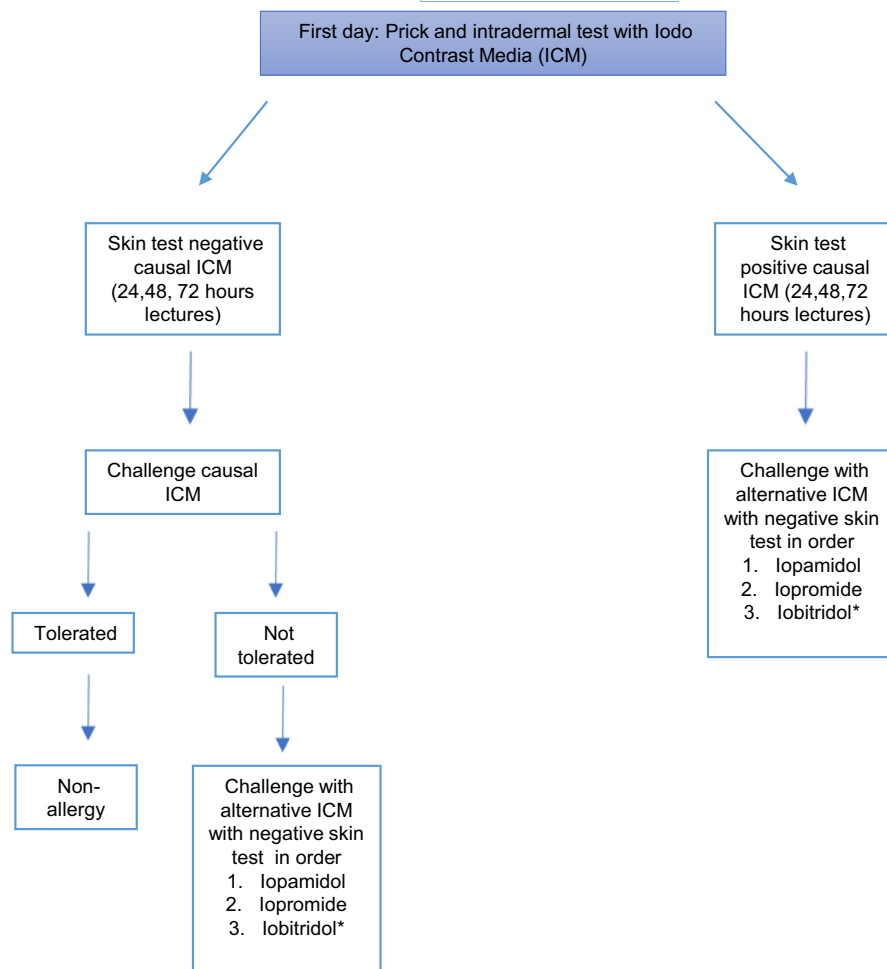
Patients referred to the Allergy Service of the Cruces University Hospital for episodes consistent with NIHRs (lapse of more than 1 h between the administration of the ICM and the suspected adverse reaction), from January 2018 to February 2022, were studied prospectively.

The study was approved by the Ethics Committee of the Cruces University Hospital.

1.2 | Skin tests

Skin prick tests and intradermal tests with undiluted ICM were performed simultaneously in all patients in the volar side of the forearm at the first visit, with reading at 24, 48, and 72 h. The flow chart of the diagnostic process is shown in Figure 1. An erythematous induration at the injection site was considered positive.¹⁻³ For reasons of public tender for centralized supply, only two ICMs have been routinely used in our health area in the last years: iomeprol (used as first choice) and iopamidol. If alternative contrasts are required, iobitridol and iodixanol are available, too. Consequently, the following ICM were tested in all patients: iomeprol (Iomeron®, Rovi, Spain), iopamidol (Iopamiro®, Rovi, Spain), iopromide (Ultravist®, Bayer, Spain), and iobitridol (Xenetix®, Guerbet, Spain). Skin tests were also performed with iodixanol (Visipaque®, GE Healthcare Bio-Sciences, Spain) or ioversol (Optiray®, Guerbet, Spain) in

FIGURE 1 Flow chart: Diagnostic process of patients with non-immediate hypersensitivity reactions to iodinated contrast media



(*lobitridol as the first option in the first four patients)

TABLE 1 Drugs and dilutions of skin tests

Drug	Trade mark	Dilution (Prick and intradermal skin tests)
Iomeprol	Iomeron®	As is
Iopamidol	Iopamiro®	As is
Iopromide	Ultravist®	As is
Iobitridol	Xenetic®	As is
Iodixanol	Visipaque®	As is
Ioversol	Optiray®	As is

patients in whom these particular ICMs were the known cause of their reaction (Table 1).

1.3 | Drug provocation test

We performed challenge tests with intravenous ICM (100ml) administered over 30min after written informed consent. Renal function was monitored in all patients prior to performing the challenge tests. No premedication was administered. Patients were contacted and visited in case of late reaction at 24, 48, and 72 h after challenge tests.

All patients were challenged according to the following criteria: If skin tests with the causative agent (iomeprol in 90%) were negative, a challenge test with the causal ICM was made. In the patients with a positive skin or challenge test to the causative ICM, a challenge test with an alternative, negative skin-tested contrast was performed (Figure 1).

Initially, the order of the challenge tests with an alternative contrast was 1st lorbitridol, 2nd lopamidol, and 3rd Iopromide. But since three of the first four challenge tests with lorbitridol were positive, we decided to change the order, placing Iopamidol as the first ICM alternative. This might contribute to avoid additional visits to the hospital in the context of pandemic situation. Given that the hospital where the TAC was going to be done did not have lorbitridol, a challenge test with Iopomide was done on patient 14.

1.4 | Statistical analysis

Quantitative results are expressed as median and interquartile range (IQR). Qualitative variables are expressed as a percentage. The comparison of mean of the quantitative variables was carried out using the Mann-Whitney U test. The qualitative variables were compared

using the Chi square test or Fisher's test. A $p < .05$ was considered statistically significant.

2 | RESULTS

Within the period of study, 59 patients were referred to the Allergy Service of Cruces University Hospital because of suspected NIHR (onset of reaction beyond 1 h) after intravenous administration of ICM. Six patients were eliminated from the study since, despite negative skin tests with all ICMs, they did not accept the challenge test with the causal agent (iomeprol in the six patients); tolerance to iopamidol was proven instead in all of them. Sensitization to the causal ICM was ruled out in 11 patients (10 iomeprol, 1 iopamidol) by performing skin and IV challenge tests with the radiographic contrast involved.

Finally, 42 patients were included in the study (21 women) with a median age of 62.5 years (IQR 56–73) (Table 2). The ICMs involved in the reaction were iomeprol in 38 (90%); ioversol and iodixanol in 1 patient each one; in two cases, the ICM was unknown (5%). ICM were administered for CT scanning in 39 patients, cardiac catheterization in two, and urography in one. In 39 patients, the reaction consisted of disseminated erythematous macular or maculopapular skin rash, with subsequent residual desquamation in 3 of them. In three patients, the reaction consisted of a fixed multilocal exanthema. In all cases, the adverse event subsided with oral corticosteroids and antihistamines.

The time elapsed from the reaction to the allergy study ranged from 1 to 132 months (median 2.5 months; IQR 1–6). Thirty three patients (78.6%) were studied within 6 months after reaction. Regarding the period from administration to the onset of symptoms, six patients (14.6%) began in the first 1–6 h after ICM intravenous infusion; eleven patients (26.8%), between 6 and 12 h; eighteen patients (42.9%) between 12 and 24 h; and seven patients (16.7%) more than 24 h after. 6/41 (14.3%) of these allergic patients had two previous ICM reactions before the study.

Skin tests in IDR were positive for some of the ICM tested in 20 patients (47.6%), in delayed readings in all cases. All these 20 patients were positive to iomeprol (100%), 15 of them exclusively (75%). In addition, one was positive to iopamidol (5%); one to ioversol (5%); one to iopromide (5%); another one to iopamidol and iopromide (5%); and the remaining patient (5%) to all the ICMs tested (iomeprol, iopamidol, iopromide, and iobitridol). Skin tests were positive in 12 cases at 24 h; in 5 cases at 48 h and in 3 cases at 72 h.

In the 22 allergic patients with negative skin tests to all the ICM tested, IV challenge tests were performed, with the causal ICM in twenty, and with iomeprol in the two patients for whom the contrast was unknown. The IV challenge test was positive in all of them (including the two patients with unknown ICM): 21 with iomeprol (95%) and 1 with iodixanol (5%). In all patients, the positive response appeared within the first 24 h, and the clinical picture resembled the one suffered after the radiological examination.

Sixteen of these patients tolerated a subsequent challenge test with iopamidol, including the patient with a positive challenge test with iodixanol; another one tolerated iobitridol. However, five patients with negative skin tests tolerated neither iomeprol nor iopamidol. Of these, three refused to continue the study; another one tolerated iopromide; and the remainder did not tolerate iobitridol and left the study too. The last patient did not tolerate neither iomeprol nor iobitridol but tolerated iopamidol.

In the 20 patients with positive skin tests to any of the ICM tested, IV challenge tests were carried out with an alternative ICM to which skin test results were negative. Among 17 patients with negative skin tests to iopamidol, 15 tolerated a challenge test with iopamidol, and another one did not tolerate it and left the study. The remaining one tolerated a challenge test with iobitridol. Of the three other patients with positive skin tests to iopamidol, one tolerated iopromide. The patient with positive skin tests to iomeprol, iopamidol, and iopromide did not tolerate iobitridol and dropped out of the study. The patient with a positive skin test to all four ICMs also refused to continue.

Among the cases with proven ICM hypersensitivity, the time elapsed since the reaction to the study was shorter in patients with a positive skin test (median 2 months; IQR 1–3.5 months) compared with those with a negative skin test (median 5 months IQR 2–8.5 months) ($p < .05$). But, if we divide the time span since the reaction into more or less than 6 months, despite a higher frequency of positive skin tests in the group studied within the first 6 months versus the rest (51.5% vs 33%), the difference was not statistically significant ($p = .46$).

Cross-reactivity in iomeprol-allergic patients occurred in 12/41 cases (29.3%). The cross-reactivity between iomeprol and iopamidol was 9/41 (22%) (4/20 in patients with positive skin test and 5/21 in those with negative skin tests). In our series, 3/5 patients with NIHR to iomeprol did not tolerate iobitridol.

In the 42 patients studied, a total of 66 challenge tests were performed with the ICMs to which skin tests were negative. Of these, 31 were positive (47%) and 35 (53%) tolerated. In all the positive challenge tests, the reaction was similar to that presented by the patients. In all cases, except two, the symptoms began in the first 24 h after the challenge test.

According to these results, the skin tests have a sensitivity of 47.6%. Assuming that the specificity of skin tests in our series and in other series is 100% (8), the negative likelihood ratio is 0.524.

3 | DISCUSSION

Iodinated contrast media are the third leading cause of drug-induced skin reactions after antibiotics and nonsteroidal anti-inflammatory drugs.¹¹ The most frequent symptoms of NIHR to ICM are cutaneous and the prevalence of this type of reactions for non-ionic monomeric ICMs ranges from 0.5 to 23%.¹²

This kind of adverse events, like other drug-induced reactions, raises several questions for the allergist who performs its evaluation:

TABLE 2 Clinical and demographic data of the patients

N°	Causal ICM	Gender	Age (years)	Lap reaction (months)	Skin tests	Tolerated ICM	ICM not tolerated	Symptoms
1	lomeprol	M	59	6	Negative	lopamidol	lomeprol	MPE
2	lomeprol	M	44	5	Negative	lopamidol	lomeprol	MPE
3	lomeprol	F	80	1	Negative	Lost	lomeprol, iopamidol, iobitridol	MPE
4	lomeprol	F	68	6	Negative	lopamidol	lomeprol	MPE
5	lomeprol	F	73	20	Negative	lopamidol	lomeprol, iobitridol	MPE ^a
6	iodixanol	M	60	1	Negative	lopamidol	iodixanol	MPE
7	lomeprol	M	59	2	Negative	lopamidol	lomeprol	MPE
8	lomeprol	F	63	2	Negative	lopamidol	lomeprol	MPE
9	lomeprol	M	18	2	Negative	Lost	lomeprol, iopamidol	MPE
10	lomeprol	F	59	1	Negative	lopamidol	lomeprol	MPE
11	lomeprol	F	45	6	Negative	lopamidol	lomeprol	MPE
12	lomeprol	F	38	6	Negative	lopamidol	lomeprol	MPE
13	lomeprol	F	76	27	Negative	lopamidol	lomeprol	MPE
14	lomeprol	M	63	3	Negative	lopromide	lomeprol, iopamidol	FE
15	Unknown	F	72	10	Negative	lopamidol	lomeprol	MPE
16	Unknown	M	46	132	Negative	Lost	lomeprol, iopamidol	MPE
17	lomeprol	M	75	1	Negative	lopamidol	lomeprol	FE
18	lomeprol	F	76	5	Negative	lopamidol	lomeprol	MPE
19	lomeprol	M	56	21	Negative	iobitridol	lomeprol	MPE
20	lomeprol	M	77	2	Negative	lopamidol	lomeprol	MPE
21	lomeprol	M	84	2	Negative	lopamidol	lomeprol	MPE
22	lomeprol	M	67	8	Negative	Lost	lomeprol, iopamidol	FE
23	lomeprol	M	68	1	lomeprol	lopamidol		MPE
24	lomeprol	F	86	2	lomeprol	lopamidol		MPE
25	lomeprol	F	59	2	lomeprol	lopamidol		MPE
26	loversol	F	64	1	lomeprol, ioversol	lopamidol		MPE
27	lomeprol	M	63	2	lomeprol	iobitridol		MPE
28	lomeprol	F	60	1	lomeprol	lopamidol		MPE
29	lomeprol	M	75	10	lomeprol	lopamidol		MPE
30	lomeprol	M	65	1	lomeprol	lopamidol		MPE
31	lomeprol	F	65	9	lomeprol	lopamidol		MPE
32	lomeprol	M	56	8	lomeprol	lopamidol		
33	lomeprol	F	52	1	lomeprol	lopamidol		MPE
34	lomeprol	F	62	3	lomeprol, iopamidol, iopromide	Lost	iobitridol	MPE ^a
35	lomeprol	M	52	4	lomeprol	lopamidol		MPE
36	lomeprol	F	87	1	lomeprol, iopamidol, iopromide, iobitridol	Lost		MPE ^a
37	lomeprol	F	89	1	lomeprol, iopamidol	lopromida		MPE
38	lomeprol	M	58	1	lomeprol	lopamidol		MPE
39	lomeprol	F	48	3	lomeprol, iopromide	lopamidol		MPE
40	lomeprol	M	50	3	lomeprol	lopamidol		MPE
41	lomeprol	F	58	4	lomeprol	Lost	lopamidol	MPE
42	lomeprol	M	57	1	lomeprol	lopamidol		MPE

Abbreviations: F, female; FE, fixed exanthema; ICM, iodinated contrast media; M, male; MPE, maculopapular exanthema.

^aDesquamation residual.

Was the ICM actually causal for the reaction suffered by the patient? What are the precise diagnostic methods to complete these patients' study? What is the safe alternative contrast for those patients in whom a particular ICM is proven responsible for the reaction?

The first question that clinicians ask ourselves when assessing a patient with suspected NIHR versus ICM is whether the given contrast was the causative agent of his reaction. Skin tests are the diagnostic element most frequently used in the diagnosis. In our series, skin tests showed a sensitivity of 46.3% (19/41), similar to that reported in patients with NIHR in other series (38%,⁸ 43.6%,²), and superior to that of meta-analysis (22%).⁶ This higher value can be driven by three facts: First, the ICM causing the reaction was known in 95% (all except two) of patients, and consequently, it could be evaluated in skin tests. In other series, the percentage of unknown ICM was much higher: 14.3%; 24%; 9%; 11%.⁷ Second, the short time elapsed between the reaction and the study: all except 10 patients were studied within 6 months after the reaction. In previous works,^{1,8} the highest time span from the reaction to allergy workup is set at 6 months, given the greater effectiveness of skin tests within this period. In our series, the time elapsed since the reaction to the study was shorter in patients with a positive skin test (median 2 months) compared with those with a negative skin test (median 5 months), which supports the usefulness of conducting the allergy workup close to the date of the reaction. Third, skin tests were performed in all cases with an undiluted (1:1) concentration, whose convenience is higher in NIHR than the 1:10 concentration used in some of the previous series.¹

The second question we ask ourselves is how to perform the challenge tests. Different guidelines for these purposes have been defined: in progressive doses over 2 days,³ in two sessions separated by a week,¹⁴ or in a single day with different dose escalation patterns.^{6,15,16} In our series, we decided to run the challenge in a single session in order to minimize the risks of repeated visits to the hospital, since most patients were studied throughout the COVID-19 pandemic, they suffered from severe diseases (50% oncological) and their reactions due to ICM were moderate. In all the positive challenge tests, the reaction was similar to that suffered by the patients. None of our patients had a worse reaction after challenge than those that motivated their referral. Except in two cases, the symptoms started in the first 24 h after the provocation test; in a shorter period of time, therefore, than the initial reaction. In all cases, they subsided with corticosteroids and oral antihistamines. That is, in these types of reactions and patients, the symptoms after the challenge test were not severe. We think consequently that this challenge regimen can be a safe and rapid alternative in patients with similar clinical characteristics to those in our series.

The third and final question to answer is what contrast the patient will be able to tolerate in future radiological examinations. To achieve this, once again skin tests guided our decisions: we carried out challenge tests with alternative, negative skin-tested ICMs. In our series, a total of 65 challenge tests were performed with ICM to which patients had negative skin tests, with a negative predictive

value of 52.3% (34/65). In other series, this percentage of tolerability or recurrence in NIHR to ICM is highly variable. In Yoon's meta-analysis,⁶ 35% of patients had recurrence after challenge test with negative skin-tested ICMs. In different series, recurrence rate varies from 0% (0/22) by Hasstendeufel,¹⁷ to 32.3% (11/34) in the series by Torres et al¹ and 42% (5/12) in the Vernassière's series.¹⁸ These figures indicate that skin tests alone do not have the diagnostic value to seek out accurately the ICM that patients might tolerate in subsequent radiological examinations. Therefore, challenge tests are essential when defining the ICM to be used safely.

In view of the results of the skin tests, would it be possible to ask about the challenge test as the only diagnostic and confirmatory procedure in the study of these patients?

From a practical point of view, skin tests are able to detect the causal agent in 50% of cases, which in our series has managed to avoid 21 challenge tests. Of the 41 patients with confirmed allergy to iomeprol, 38 had negative skin tests with iopamidol and of these, 32 tolerated challenge tests with iopamidol. Thus, altogether the skin tests have been useful in 35/41 patients (85.4%); in three of them to avoid a positive challenge test, and in the remaining 32 to confirm an alternative safe ICM. In short, we consider that skin tests continue to be the first diagnostic method to be used in patients with NIHR to ICM, although with limited diagnostic capacity.

In NIHR to ICM, the pattern of cross-reactivity appears to be broader than in patients with immediate hypersensitivity reactions.^{7,18} In two recent studies,^{7,9} ICMs have been classified into three groups based on the frequency of cross-reactivity between drugs in the same group and the low cross-reactivity between the three groups. Lerondeau et al⁷ described three groups of ICM by multiple correspondence analyses: group A (iodixanol, iopamidol, iomeprol, iohexol, ioversol, and ioxitalamate); group B (ioxaglate and iobitridol), the members of which share two identical N-(2,3-dihydroxypropyl) carbamoyl side chains (except ioxitalamate); and group C (amidotrizoate).

Schjivers⁹ later proposed a classification of ICM into three groups: group A, which included iodixanol, iomeprol, ioversol, iohexol, and iopromide, all sharing a N-(2,3-dihydroxypropyl) carbamoyl side chain; group B, which consisted of iobitridol, sodium ioxaglate, ioxitalamate, and iopamidol; and group C, with sodium amidotrizoate. In our series, the frequency of cross-reactivity between iomeprol and iopamidol is about 25%. Based on this, it seems consistent to consider iomeprol and iopamidol as drugs belonging to the same group, at least with regard to NIHR with ICM.

In different previous works, iobitridol has been indicated as an ICM with a low frequency of cross-reactivity. In the Gracia-Bara study, 92% of the patients with negative skin tests to iobitridol tolerated its administration¹⁴; in Hasstendeufel's study on 22 patients with NIHR to iodixanol, tolerance to iobitridol was verified when it was used as an alternative contrast (10 cases)¹⁷; and in Gaudin's series,¹³ 77% of the patients showed negative skin test to iobitridol, and so, it was proposed as an alternative contrast although challenge tests were not performed.

In our series, we carried out challenge tests with iobitridol only in five patients, and three of them did not tolerate it. Although the number of challenge test with iobitridol is very low, our modest results warn about a possible greater cross-reactivity than reported, in the case of iomeprol-induced NIHR. More studies with a larger number of cases are required to validate the cross-reactivity of iobitridol in NIHRs induced by iomeprol.

Our study has several limitations. We did not use patch tests in our patients, which, according to the meta-analysis, can increase the percentage of patients with positive skin tests by 7%. Nor did we use in vitro tests such as the lymphoblastic transformation test that could improve the diagnosis accuracy.² Finally, we did not perform provocation tests with all ICMs with a negative skin test. Then, we cannot know the possible tolerance to these contrasts, which might allow a better comparison of our data and more accurate descriptive statistics. Our study is also limited by dealing with almost exclusively one causal ICM, without being able to extend its data to other ICMs. At the same time, however, it has made possible to gather a substantial number of patients with NIHR caused by iomeprol, and to establish the diagnostic utility of skin tests and their actual cross-reactivity with other ICMs.

AUTHOR CONTRIBUTIONS

All authors were involved in diagnosis and treatment of the patients, conception and design of the study, data acquisition, analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content, and approval of the final version of the document.

ACKNOWLEDGMENTS

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest in relation to this work.

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How to cite this article: Gamboa P, Sánchez de Vicente J, Galán C, et al. Non-immediate hypersensitivity reactions to iomeprol: Diagnostic value of skin tests and cross-reactivity with other iodinated contrast media. *Allergy*. 2022;77: 3641-3647. doi: [10.1111/all.15433](https://doi.org/10.1111/all.15433)