

What is the clinical value of negative predictive values of skin tests to iodinated contrast media?

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ABSTRACT

Background: Iodinated contrast media (ICM) can cause hypersensitivity reactions (HSR), yet data are scant about the negative predictive value (NPV) of ICM skin tests.

Objective: To determine the NPV of skin tests to ICM

Methods: We enrolled 73 patients with a history of HSRs to ICM, 136 subjects with no previous exposure to ICM, and, as controls, 47 subjects who had previously tolerated ICM. All the subjects had skin tests with the culprit and/or alternative ICM and were later questioned as to whether they were reexposed and/or reacted to the skin-test-negative ICM.

Results: Sixty (82.2%) and 13 (17.8%) patients had a history of immediate HSR and those with a history of nonimmediate HSR, respectively. The sensitivity and specificity of the skin tests were 18% and 97%, respectively, in patients with immediate HSR and were 23% and 99%, respectively, in patients with nonimmediate HSR. Of a total of 237 subjects with negative skin test results, 207 (87.3%) were asked about further ICM administration; 158 (84.9%) confirmed subsequent use either with ($n = 15$ [9.4%]) or without premedication ($n = 143$ [90.6%]). Of the 143 individuals, 140 tolerated skin-test-negative ICMs but three (1.9%) reacted to ICMs (two with mild nonimmediate reactions, one with a grade 1 immediate reaction). Of 20 patients who had previous HSR to ICM, 17 tolerated further skin-test-negative ICM without premedication. The NPV of ICM skin tests, therefore, was 97% (95% confidence interval, 75–99%).

Conclusion: The NPV of skin tests with ICM was high. None of the reactions in patients who had negative skin test results were severe, which may reassure physicians who hesitate to perform further evaluations in patients with negative skin test results.

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Iodinated contrast media (ICM) are widely used in radiology.^{1,2} Although generally considered safe, hypersensitivity reactions (HSR) to ICM range from mild to severe may still occur.^{3,4} Adverse reactions were more common after the administration of ionic high-osmolar ICM but with the replacement of ionic ICM with nonionic ICM, the incidence of adverse reactions to ICM has gradually declined.^{5,6} However, the number of reactions seen in clinical practice has remained significant because of the increased use of ICM. Although the exact mechanism that underlies the pathogenesis of ICM-induced HSR is not completely understood, recent studies indicate that a subset of immediate reactions are likely true immunoglobulin E mediated reactions; most nonimmediate skin reactions are probably caused by T cells.^{1,2,7–10} A previous reac-

tion to an ICM with either an immediate or a nonimmediate reaction is a risk factor for further reactions.¹¹ Although many studies have tried to evaluate the diagnostic potential of skin tests, only limited data with a small number of subjects are available about the negative predictive value (NPV) of skin tests.^{12–14} Therefore, we aimed to determine the NPV of skin tests to ICM.

METHODS

Two hundred fifty-six subjects referred to the allergy departments of Ankara and Ege Faculty of Medicine between June 2007 and December 2014, and who underwent skin tests (prick and/or intradermal and/or patch tests) with culprit and/or alternative ICM were included retrospectively. All the subjects were divided into two groups (patients and negative controls) according to the presence or absence of HSRs to ICM.

Patients

Seventy-three patients with a history of immediate or nonimmediate HSRs during or after ICM were included. Clinical manifestations of immediate and nonimmediate HSRs to ICM were defined according to previous data.⁷ The Ring and Messmer severity scale (grades 1–4) was used for classification of immediate reactions.¹⁵ Nonimmediate reactions were graded as mild (no treatment was required), moderate (the pa-

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tient responded to appropriate treatment without hospitalization), and severe (the reaction required hospitalization or was life threatening).^{15,16}

Negative Controls

The control group comprised subjects without a history of allergy to ICM but who underwent skin tests with ICM before radiologic investigations because of allergic diseases or a history of HSR to drugs other than ICM. One hundred thirty-six subjects in the control group had never been exposed to any ICM, and 47 subjects had tolerated ICM. Informed consent was obtained from all the subjects for skin tests. The ethics committee of Ankara University Medical School approved the survey.

Skin Testing for ICM-induced Immediate and Nonimmediate Reactions

Data about culprit ICM were provided by the patients or were obtained from hospital records. If we had no data about an implicated ICM, then skin tests with the ICM to be used in the radiologic investigation were performed. A skin-prick test (SPT) with the culprit and/or alternative ICM (full strength) was performed on the volar forearm. Positive (histamine, 0.01%) and negative (saline solution) controls were also included. A wheal reaction with a mean diameter of 3 mm larger than that of the negative control was considered positive after 20 minutes.^{2,7,14} If there was a negative result, then an intradermal test (IDT) was performed with 1:10 diluted ICM. An amount of 0.03–0.05 mL of the test solution was injected into the skin to produce a bleb of 3–5 mm in diameter. Readings were performed after 15 minutes (early reading) and on days 1, 2, and 3 (delayed readings).

The IDT was considered as 1+ positive if the wheal was between 3 and 5 mm, 2+ positive if the wheal was between 6 and 10 mm in size, and 3+ positive if the wheal was between 11 and 15 mm in size on the early readings or if an erythematous induration at the skin test site was present at the delayed readings.^{7,14,17,18} Patch tests (PTs) were performed by 1000-, 100-, and 10-fold dilutions of culprit ICM in saline solution, which were prepared by the researchers for PTs because there were no standardized commercially available ICM allergens.¹⁷ Solutions were soaked in a plastic chamber on a filter paper (Haye's Test Chamber; Haye's Service B.V., Haarlem, The Netherlands) and fixed on the patient's back for 3 days by using a special nonirritant, nonsensitized adhesive tape strip (Haye's Service).

The role of SPTs and early readings of IDTs in the diagnosis of immediate reactions and of PTs and delayed readings of IDTs in the diagnosis of nonimmediate reactions were evaluated. An observation or a reliable and/or documented medical history of an allergy-like reaction after administration of ICM was

used as the criterion standard, and skin test sensitivity and specificity were calculated along with the controls.

Long-Term Results

All the patients and controls with negative skin test results (either culprit or an alternative ICM) were contacted by telephone and asked whether they had been reexposed or had reacted to the negative-skin test ICM and whether they had received premedication before ICM use.

Statistics

Statistical analyses were performed by using the Statistical Package for Social Sciences for Windows version 21 (SPSS, Inc., Chicago, IL). Descriptive statistics are expressed as mean (standard deviation). Categorical data were analyzed by using the χ^2 test. The NPV was calculated as follows: $[\text{specificity} \times (1 - \text{prevalence})] / [(1 - \text{sensitivity}) \times \text{prevalence} + \text{specificity} \times (1 - \text{prevalence})]$. The 95% confidence intervals (95% CI) were calculated. Three NPVs were calculated as NPV1, NPV2, and NPV3. The NPV1 value for skin tests (SPTs and/or IDTs and/or PTs) was calculated in patients and controls in the diagnosis of ICM-related hypersensitivity reactions. The NPV2 was the proportion of patients and controls with negative skin test results to at least one ICM at the first testing and who tolerated the tested ICM after further injection without reaction. The NPV3 was the proportion of patients with negative skin test results to at least one ICM at the first testing and who tolerated the tested ICM after further injection.

RESULTS

Patient Characteristics

Characteristics of these 73 patients with a history of ICM hypersensitivity are summarized in Table 1. The median time interval between the skin test and the reaction to ICM was 48 months (range, 1–324 months). The most common immediate reactions were cutaneous (32.9%), cardiovascular (21.9%), and respiratory symptoms (24.7%). Nausea, vomiting, dyspnea, and hypotension were the main noncutaneous symptoms, but none were isolated symptoms. In 35 patients (47.9%), anaphylaxis to ICM was present. Three of them were admitted to the hospital; there were no mortalities. Skin reactions (itching, erythema, late urticaria) were the main nonimmediate reactions. In one patient, acute generalized exanthematous pustulosis (AGEP) developed twice with the same contrast media (iomeron).

Controls

The control group consisted of 183 subjects (142 women, 41 men); 136 of whom had never been exposed to an ICM and 47 had tolerated ICM. There were

Table 1 Characteristics of patients with history of hypersensitivity reactions to ICM

Total no. patients	73
Age, mean (SD), y	54.5 ± 13.0
No. men/women	19/54
Patients with comorbid nonallergic diseases, no. (%)	
Hypertension	27 (37)
Heart disease	23 (31.5)
Thyroid disease	9 (12.3)
Diabetes mellitus	8 (11)
Renal disease	4 (5.5)
Gastrointestinal system disease	4 (5.5)
Liver disease	1 (1.4)
Psychiatric disease	0
Comorbid allergic disease, no. (%)	
History of drug allergy	12 (16.4)
Asthma	9 (12.3)
Allergic rhinitis	3 (4.1)
Chronic urticaria and/or angioedema	3 (4.1)
Food allergy	2 (2.7)
Metal allergy	1 (1.4)
Venom allergy	1 (1.4)
Contact dermatitis	0
Atopy, no. (%)	9 (12.3)
Immediate reaction	60 (82.2)
Nonimmediate reaction	13 (17.8)
Immediate reaction grade, no. (%)	
1	19 (31.7)
2	21 (35)
3	17 (28.3)
4	3 (5)
Nonimmediate reaction, no. (%)	
Mild	5 (38.5)
Moderate	7 (53.8)
Severe	1 (7.7)
Contrast media responsible for the reaction, no. (%)	
Unknown	41 (56.2)
Nonionic	
Iopromide	8 (11)
Iohexol	6 (8.2)
Iomeprol	5 (6.8)
Iopamidol	3 (4.1)
Iodixanol	2 (2.7)
Ioversol	2 (2.7)
Iobitridol	1 (1.4)
Ionic	
Diatrizoate meglumine	2 (2.7)
Meglumine ioxithalamate	1 (1.4)
Meglumine gadoterate	1 (1.4)
Gadobenate dimeglumine	1 (1.4)
Route of contrast media, no. (%)	
Intravenous	61 (83.5)
Intra-arterial	11 (15.1)
Oral	1 (1.4)

ICM = Iodinated contrast media; SD = standard deviation.

significant differences between patients with a history of ICM-induced HSRs ($n = 73$) and subjects who tolerated ICM ($n = 47$) in terms of age, comorbid nonallergic diseases, asthma and allergic rhinitis, drug allergy, and use of β -blockers ($p < 0.05$). Age, prevalence of comorbid diseases, hypertension, heart disease, thyroid disease, history of drug allergy, and use of β -blockers were significantly higher in patients with hypersensitivity to ICM. Interestingly, the prevalence of asthma and allergic rhinitis were significantly higher in subjects who had previously tolerated ICM.

Skin Tests in Patients and Controls

SPT and/or IDT and/or PTs were positive in 14 (19.2%) of the 73 patients who had a history of ICM-related HSRs. Eleven of the 14 (78.6%) had a history of immediate reaction (one grade 1, two grade 2, six grade 3, and two grade 4). Three (21.4%) had a history of nonimmediate reaction (one patient from all grades). The ICM skin-test positive result group comprised 11 women (78.6%) and 3 men (21.4%) (mean [standard deviation] age, 53.2 ± 13.3 years). The implicated ICM in the past reaction was known in only eight patients (57.1%). The time between skin tests and reaction was <6 months in one patient (8.3%), 6–12 months in two patients (16.7%), and >12 months in nine patients (75%), and there were no data about the time intervals in two patients. The median time between skin test and reaction was 60 months (range, 1–192 months).

Positive SPTs were observed in 1 of 11 patients with immediate reactions (9.1%). Ten of the 11 patients had (2+) positive early readings of IDTs (90.9%). All 11 patients with immediate reactions were skin tested with only five culprit ICMs (3 iohexols, 1 iodixanol, 1 diatrizoate meglumine), and 6 patients were tested with culprit and/or alternative ICM (2 iohexols, 2 iopromides, 1 iopamidol, 1 meglumine ioxithalamate). In nonimmediate reactions, delayed readings of IDTs were (3+) positive (iopromide, iohexol, and iodixanol) in three patients with positive PT results, with iohexol and iopromide in two.

No significant difference was found between patients with positive and patients with negative skin test results in terms of demographics, reaction characteristics, and severity ($p > 0.05$); however, the rate of patients with a history of laryngeal edema was significantly higher ($p = 0.021$) among patients with positive skin test results to ICM. In addition, grade 1 reactions were less common in patients with positive skin tests ($p = 0.014$). Forty-seven of the 183 controls had previously tolerated ICM, but they did not know the name of the ICM. We tested an ICM commonly used in radiologic investigations in all the controls. For the 183 controls, skin testing was performed by using iohexol ($n = 56$ [30.6%]), iopamidol ($n = 50$ [27.3%]), iomeprol ($n = 30$ [16.4%]), iopromide ($n = 12$ [6.6%]), and others

Table 2 Results of skin tests for patients of history positive of hypersensitivity reactions to iodinated contrast media

	Positive Skin Tests in Patients (n)	Positive Skin Tests in Controls (n)	% Sensitivity (95% CI)	% Specificity (95% CI)	% NPV1 (95% CI)
SPT*	1	0	1 (0–8)	100 (97–100)	97 (93–98)
Early readings of IDTs*	10	4	16 (9–28)	97 (94–99)	97 (94–98)
Delayed readings of IDTs#	3	1	23 (8–50)	99 (96–99)	97 (94–99)
PTs#	2	0	33 (9–70)	100 (34–100)	98 (57–99)
SPT and/or early readings of IDTs*	11	4	18 (10–29)	97 (94–99)	97 (94–99)
Delayed readings of IDTs and/or PTs#	3	1	23 (8–50)	99 (96–99)	97 (94–99)
SPT and/or IDTs and/or PTs§	14	5	19 (11–29)	97 (93–98)	97 (94–98)

NPV = Negative predictive value; CI = confidence interval; IDT = intradermal test; PT = patch test; SPT = skin-prick test.

*For immediate reaction ($n = 60$).

#For nonimmediate reaction ($n = 13$).

§For immediate and nonimmediate reactions ($n = 73$).

($n = 35$ [19.1%]). None of the 47 subjects who had previously tolerated ICM demonstrated positive results in either SPTs or IDTs, but SPT and/or IDT results were found to be positive in 5 of the 136 unexposed subjects (early readings of positive IDT results [3+]) in 4 subjects and delayed readings of positive results of IDTs [2+]) in 1 subject, no positive results in SPTs). Specificity, sensitivity, and NPV1 values of skin tests in ICM-induced immediate and/or nonimmediate reactions are presented in Table 2.

Long-Term Results

All 237 subjects (59 patients) and (178 controls) with negative ICM skin test results were contacted and asked whether they had subsequently been exposed to ICM; 207 patients responded (87.3%) (Fig. 1, *a* and *b*). A skin-test-negative ICM was used in 158 of 207 subjects. In this group, 16.5% ($n = 26$) had reacted to ICM in the past, 29.1% ($n = 46$) had been exposed to but tolerated ICM, and 54.4% ($n = 86$) had never been exposed to ICM. One hundred forty-three of 158 had not received premedication before the procedure, and only three experienced an HSR. These patients had a history of HSRs with ICM (Table 3). None of the reactions with skin-test-negative ICM were severe.

In total, 140 of 143 patients and controls with a negative skin test result tolerated skin-test-negative ICMs, which resulted in an NPV2 of 98% (95% CI, 93–99%). Of these 140 subjects, 77 (55%) had no previous exposure to ICMs, 46 (32.9%) had tolerated ICM, and 17 (12.1%) had a history of HSR to ICM. Of 20 patients with a history of HSR to ICM (17 had an immediate and 3 had a nonimmediate reaction with iohexol [$n = 8$ {40%}], iopromide [$n = 3$ {15%}], iop-

amidol [$n = 2$ {10%}], iodixanol [$n = 2$ {10%}], ioversol [$n = 2$ {10%}], iopamidol [$n = 1$ {5%}], ioxilan [$n = 1$ {5%}], fluorescein [$n = 1$ {5%}], 17 tolerated further skin-test-negative ICM (Fig. 1 *a*). After taking into considering three false-negative results, the NPV3 of ICM skin tests was calculated as 97% (95% CI, 75–99%).

In terms of severity of historic HSRs to ICM among patients who tolerated further ICM with or without premedication: those with premedication were 7 (41.2%) grade 1, 6 (35.3%) grade 2, 4 (23.5%) grade 3, and those without premedication were 2 (33.3%) grade 1, 3 (50%) grade 2, 1 (16.7%) of grade 3. An alternative skin-test-negative ICM was used in radiologic examinations in 3 of 14 patients with positive ICM skin test results, and no reaction was observed. A second AGEF attack developed in one patient who had previously had ICM-induced AGEF after accidental exposure to the same contrast media, which was positive in late-reading IDT and PTs. ICM was not given to the remaining 11 patients.

DISCUSSION

In the present study, the overall sensitivity and specificity of skin tests were 18% and 97%, respectively, in patients with immediate HSR, and the sensitivity and specificity of skin tests were 23% and 99%, respectively, in patients with nonimmediate HSR to ICM. The NPV1 was 97% (95% CI, 94–98%) for the diagnosis of hypersensitivity reactions to ICM. Data about sensitivity and specificity results differ widely, depending on the differences in the use of ICM, and by country. The sensitivity and specificity rates of our study for immediate and nonimmediate reactions were in agreement with previous data.^{10,11,19,20} A recent meta-analysis of 21 studies reported that the pooled positive rates of

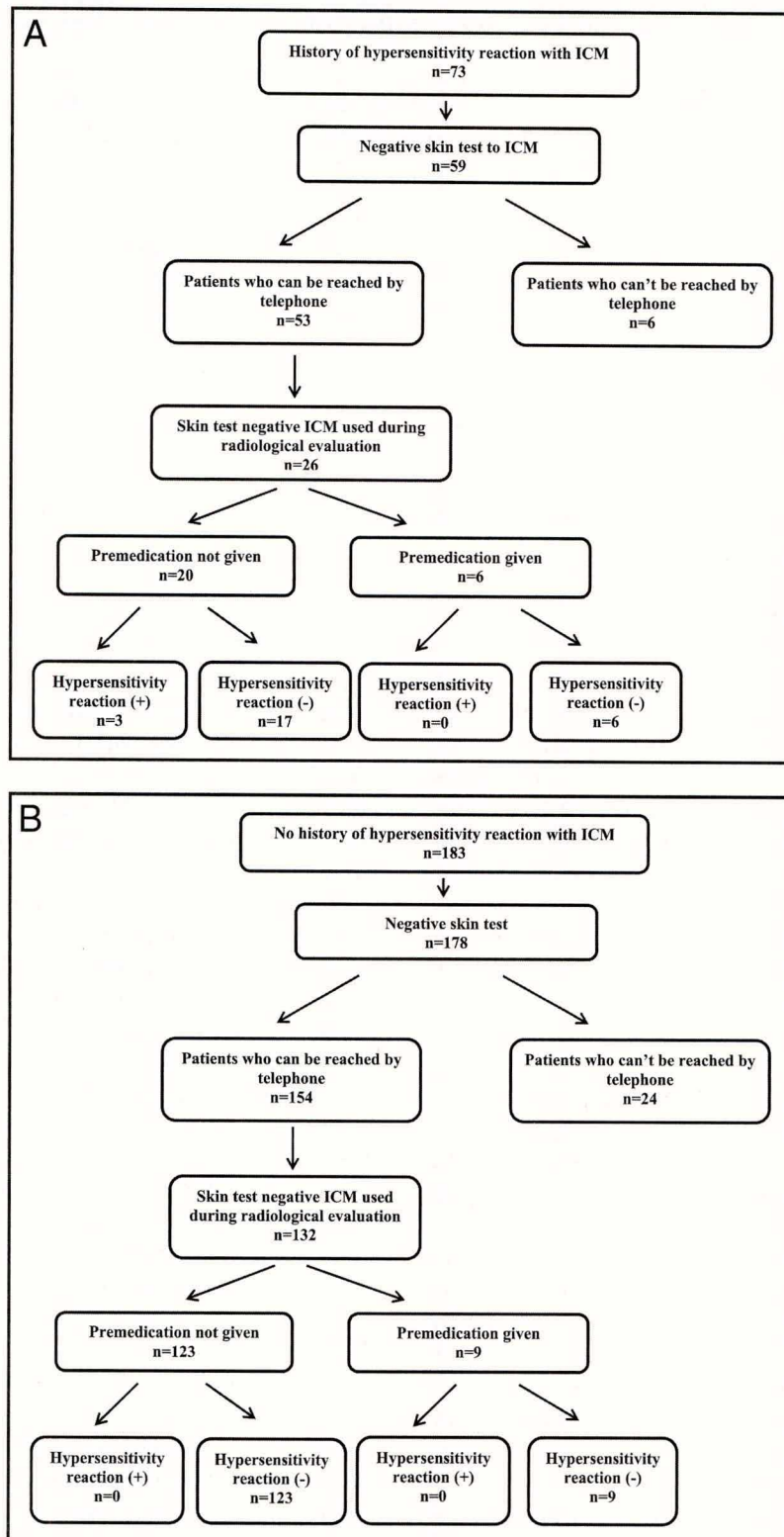


Figure 1. Hypersensitivity reactions in subjects who were reexposed to a skin-test-negative ICM. (a) Patients; history of hypersensitivity reaction to ICM. (b) Controls; no history of hypersensitivity reaction to ICM. ICM = Iodinated contrast media.

skin test results were 17% and 26% in patients with immediate and nonimmediate HSRs to ICM, respectively.¹³ The time between skin testing and reaction seemed to be relevant in terms of positive results.

Early and delayed reading IDT performed 1–6 months after the reaction showed higher positive rates than those performed after 6 months for patients with immediate and patients with nonimmediate HSRs, respectively.¹⁰

Table 3 Details of three patients who reacted to skin-test-negative ICM

Age, y/Sex	Type of ICM Examination	Name of Culprit ICM	Type of Reaction	Skin Tests* with Culprit or Alternative ICM	ICM Reinjected	Reaction
39/M	CT	Ioversol	Immediate, grade 1	Ioversol/iohexol negative	Iohexol	Generalized erythema
33/F	CT	ND	Nonimmediate, moderate	Negative	Iohexol	Delayed maculopapular exanthem, fever
36/F	CT	ND	Immediate, grade 1	Negative	Ioxilan	Pruritus, delayed maculopapular eruption

ICM = Iodinated contrast media; CT = computed tomography; SPT = skin prick test; IDT = intradermal test; PT = patch test; ND = not determined.

*SPT and/or IDT and/or PT.

The longer time between skin testing and reaction in our study (median, 48 months) may explain the lower rate of sensitivity. When considering the relatively low number of positive skin test results, the meta-analysis indicates that skin tests have a diagnostic limitation in immediate and nonimmediate ICM HSRs.¹³ However, skin tests could be useful tools for diagnosis in patients with severe immediate HSR, because positive skin test results increased up to 52% in anaphylaxis.^{9,13}

Skin tests may also be helpful for finding alternatives for patients with HSR to ICM.⁵⁻⁷ Use of ICM is unavoidable in some diagnostic or therapeutic techniques; therefore, a safe ICM should be found for future procedures. It has remained unclear whether a skin-test-negative ICM could be safely administered due to the limited data about NPV.¹⁹ Scherer *et al.*²¹ documented one patient who tolerated skin-test-negative ICM. Caimmi *et al.*¹² reported that skin testing for ICM hypersensitivity had an NPV of 96.6% (95% CI, 89.9–103.2%) and none of the reactions in patients with a negative skin test result were severe. The study consisted of 29 patients with immediate and those with nonimmediate HSR; only two patients presented a positive IDT result to ICM, but no control subjects.¹² Later, a total of seven patients who had formerly had positive skin test results and with a history of immediate HSR to ICM underwent a controlled challenge or subsequent exposure with a skin-test-negative ICM without premedication, and all showed good tolerance.²⁰

In a new study, the NPV for skin tests and intravenous provocation tests was reported to be 80% for immediate HSR to ICM.²² In our first trial, NPV was 80%, with early readings of IDTs for immediate reactions and was 85% with delayed readings of IDTs for nonimmediate reactions in 41 patients who reacted to ICM.¹⁴ The present study was a continuum of our first experience with larger numbers of patients. In total, 140

of 143 patients with negative skin test results tolerated skin-test-negative ICMs without premedication, which resulted in a 98% NPV overall. Of 20 patients with previous HSR to ICM, 17 tolerated further skin-test-negative ICM administration, which resulted in a 97% NPV3. These numbers seemed to be acceptable to evaluate the NPV of skin tests with ICM. We believe that this very high NPV is important to reassure physicians who might hesitate to perform further evaluations when using ICM in patients with negative skin test results. Our data were supported by a recent meta-analysis in that skin-test-negative ICMs were more tolerable in immediate HSR than in nonimmediate HSR, with pooled per-patient recurrence rates of HSR of 7% with immediate HSR and 35% with nonimmediate HSR.¹³ In addition, it was found that skin tests may be beneficial even in false-negative cases because recurrent HSR to skin-test-negative ICM was milder than the initial HSR.¹³

Premedication with corticosteroid and antihistamines is recommended for patients with a known HSR to ICM.²³ However, premedication alone may not be sufficient for prevention of HSRs, particularly in patients with severe HSRs.^{7,11} We did not specifically address premedication, but our 15 patients who were premedicated did not react to ICMs; however, we cannot draw firm conclusions regarding the preventive effect of premedication because of our limited number of patients and because all such patients received skin-test-negative ICM. A previous reaction to an ICM is the main risk factor for further reactions.^{5,11} However, several other risk factors (age, sex, atopy and accompanying atopic or nonatopic diseases, dose, group, or route of ICM) have been reported.^{4,5,24,25} Concordant with these studies, in the present study, older age, comorbid diseases, a history of drug allergy, and the use of β -blockers were significant risk factors.

Our study had disadvantages and advantages. As a retrospective study, we had to rely on the patients' statements, which might have a high likelihood of recall bias. The literature about the usefulness of skin tests in the diagnosis of ICM-induced HSR is mostly limited to case reports.^{2,13,18} We had a good number of patients with ICM hypersensitivity; however, in keeping with a retrospective study, culprit ICM could be tested in half of the subjects. Only 20 of 73 patients with a history of ICM reaction underwent subsequent procedures, which was also a disadvantage. Despite a good response rate, we could not contact all the patients; however, this did not seem to have affected the results because the demographic and clinical characteristics of both populations were similar. All related studies used a history of ICM-HSR as a criterion and calculated sensitivity as percentage of positive skin-test result among these patients. As an advantage, we had subjects tolerated ICM and healthy subjects never been exposed to any ICM. To our knowledge, only the recent European Network of Drug Allergy/European Academy of Allergy and Clinical Immunology study used such subjects as controls in establishing the value of skin tests.⁷

Although it is valid from a statistical point of view to use all control subjects and patients with negative skin tests in the calculation of NPV, this may also be considered a disadvantage. Therefore, we calculated two NPVs by considering both controls plus patients with a history of ICM-HSRs and only patients with a history of ICM-HSRs. The NPV2 and NPV3 values were similar between the two calculations. Moreover, we worked with the highest number of patients to date. Nevertheless, studies with larger patient groups with a history of ICM hypersensitivity and positive skin-test result to the culprit drug but negative to alternative ICMs will further enhance our ability to evaluate the NPV of skin tests.

CONCLUSION

The NPV of skin tests with ICMs is high (98%), and none of the subjects with negative skin test results had severe reactions. Therefore, we believe that these data will be helpful to reassure physicians who hesitate to perform radiologic evaluations in patients with a diagnosis of allergic disease and a history of HSR to other drugs and/or ICM but who have negative skin test results.

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