

ORIGINAL ARTICLE

Clinical value of negative skin tests to iodinated contrast media

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Abstract

Background Several studies have shown that skin tests are useful tools for the diagnosis of iodinated contrast medium (ICM) allergy, but the real number of false negative results is not known.

Objective To evaluate the negative predictive value of ICM skin tests.

Material and Methods One hundred and fifty-nine patients tested in our department because of a previous ICM reaction over the last 9 years were called and asked standardized questions about ICM re-exposure.

Results Twenty-nine patients had been re-exposed to ICM. There were 20 (69.0%) females and the median age was 55 (34–60) years. The median time interval between the reaction and skin testing was 11.9 (1.6–21.5) years. Twenty-four patients (82%) had an immediate reaction, four a non-immediate (13.8%) reaction and no data were available for one patient. Two patients had positive ICM skin tests previously and were re-exposed to a negatively skin-tested ICM and did not react. Only two patients presented a mild reaction during ICM re-injection: one immediate (generalized urticaria lasting for 3 days) and one non-immediate maculopapular reaction. The patient with urticaria was re-tested and re-challenged (negative). The other patient was unable to return for re-testing.

Conclusion Skin testing for ICM hypersensitivity has a negative predictive value of 96.6% (95% CI: 89.9–103.2) and none of the reactions in skin-test-negative patients were severe. Multi-centric large surveys are still needed for confirmation.

Keywords allergy, drug allergy and hypersensitivity database, hypersensitivity, iodinated contrast media, negative predictive value, skin tests

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Introduction

Iodinated contrast media (ICM) are among the most commonly used injectable drugs utilized in radiology. Modern ICM can be introduced in the body via different routes, such as intravenously (i.v.), intra-arterially, intrathecally and orally [1]. All the ICM currently used in modern medicine are obtained by chemical modifications of a 2,4,6-triiodinated benzene ring. They are classified on the basis of their physical and chemical characteristics, including their chemical structure, osmolality, iodine content and ionization in solution [2]. They are divided into high-osmolality ionic monomers (amidotrizoate and ioxitalamate) and low-osmolality ICM. The low-osmolality ICM can be subdivided into (i) non-ionic monomers (iohexol, iopamidol, ioversol, iopramide, iomeprol, iopentol and

iobitridol), (ii) ionic dimers (ioxaglate) and (iii) non-ionic dimers (iodixanol) [3].

ICM are considered as safe drugs: in fact, the reported adverse reactions are generally mild and self-limiting. Nonetheless, considering that >75 million ICM-enhanced X-ray procedures are conducted yearly and world wide, and that some severe or even life-threatening immunological reactions may occur [4], a validated drug allergy work up is needed in order to fully assess the potential side-effects generated by such useful molecules. ICM hypersensitivity reactions can be either immediate (occurring within the first hour following the injection) or non-immediate (occurring up to the seventh day following the injection) [4]. Mild immediate adverse reactions occur in 3.8–12.7% and in 0.7–3.1% of patients receiving

i.v. injections of high-osmolar ionic and low-osmolar non-ionic ICM, respectively [5–7]. Severe immediate reactions have been reported in 0.1–0.4% and in 0.02–0.04% of patients, respectively [5–7]. Although adverse reactions observed with the non-ionic ICM are usually less severe when compared with those induced by the ionic ICM, their respective death rate is not significantly different and is estimated to be in the range of 1 in 100 000 examinations [8]. Non-immediate hypersensitive reactions occur at various rates and they appear to be T cell mediated. Thus, they depend on the injected product and not on the osmolality, iodine content, or ionization of the drug [9].

Skin testing has been used to confirm an ICM sensitization in patients with such reactions [9–11]. However, the specificity and sensitivity of these tests still need to be established for this particular group of allergens [9]. In a recent collaborative study by the European Network for Drug Allergy (ENDA) [11], 220 patients with either previous immediate (122) or non-immediate (98) hypersensitivity reactions to ICM were skin tested. In up to about 50% of the patients tested within 6 months after the reaction, a diagnosis could be reached by performing skin tests. However, the negative predictive value of these tests remains unknown and this crucial aspect is addressed in this paper. We now present the ICM skin test results of all consecutive patients who were referred to the Allergy Department of the University Hospital of Montpellier, France over the last 9 years with a past clinical history of ICM hypersensitivity and who were re-challenged after negative skin tests.

Material and methods

Patients

From April 1999 to June 2008, 159 patients were referred to the Allergy Department of the University Hospital of Montpellier, France, with a compatible clinical history of hypersensitivity reaction to ICM. The patients were part of the Drug Allergy and Hypersensitivity Database (DAHD[®]), a case-control cohort. Clinical data were registered using the ENDA drug allergy questionnaire before performing skin tests [12]. Hypersensitivity reactions were classified as immediate reactions (when they occurred within 1 h after ICM administration) and non-immediate reactions (when apparent from 1 h to 7 days after ICM exposure) [9]. The Ring and Messmer [13] classification was used for classifying the severity of immediate reactions: grade 1: generalized cutaneous and/or mucocutaneous symptoms (pruritus, skin eruption, urticaria, angio-oedema); grade 2: mild systemic reactions including skin manifestations (not obligatory), abdominal symptoms (nausea, cramping),

respiratory symptoms (rhinorrhoea, hoarseness, dyspnoea), cardiovascular symptoms (tachycardia); grade 3: life-threatening systemic reactions including shock; and grade 4: cardiac and/or respiratory arrest. Non-immediate reactions were classified as mild, moderate and severe as suggested previously [9]: mild when no treatment was required, moderate when the patient responded readily to an appropriate treatment and no hospitalization was needed and severe when the reaction required treatment in hospital, was life-threatening or resulted in death.

Skin testing

Patients were tested with the implicated ICM and a set of ICM if they were positive for the implicated ICM or if its name was unknown. In order to know which ICM was involved, either patients already knew which drug had supposedly caused the reaction and provided us the name, or we contacted the hospital in which the reaction had occurred. The ICM used were: amidotrizoate, ioxitalamate, iopamidol, iohexol, ioversol, iopromide, iomeprol, iobitridol, iodixanol and ioxaglate. Skin tests were performed firstly as prick tests with the undiluted commercially available solution and then, if negative by intradermal tests (IDT) at a 1 : 10 dilution. Prick tests were considered positive if, after 15 min, the size of the weal was at least 3 mm in diameter. For IDT, positivity was considered when the size of the initial weal increased by at least 3 mm in diameter after 15–20 min, considering as non-irritant a maximum dilution of 1/10 [11]. All data were collected using FileMaker Pro 7 software.

In the absence of radiological alternatives, the current attitude within our institution for positive skin test patients is to inject a low-osmolality ICM, which produces negative skin tests, in the presence of an ICU doctor [10]. This is the information with which these patients left the department. The same instructions were given to negative skin test patients [10].

Survey

All of the patients with negative skin tests (either the suspected ICM or an alternative ICM in the case of a positive skin test for the suspected ICM) were phoned and asked standard questions: whether they had or had not undergone another ICM administration after their visit to our department, and in this case, if they had undergone premedication and what the outcome was (Fig. 1). In the case of a positive reaction, new skin tests were proposed.

Statistics

Qualitative data were expressed in frequency and percent. Quantitative data were expressed in median and

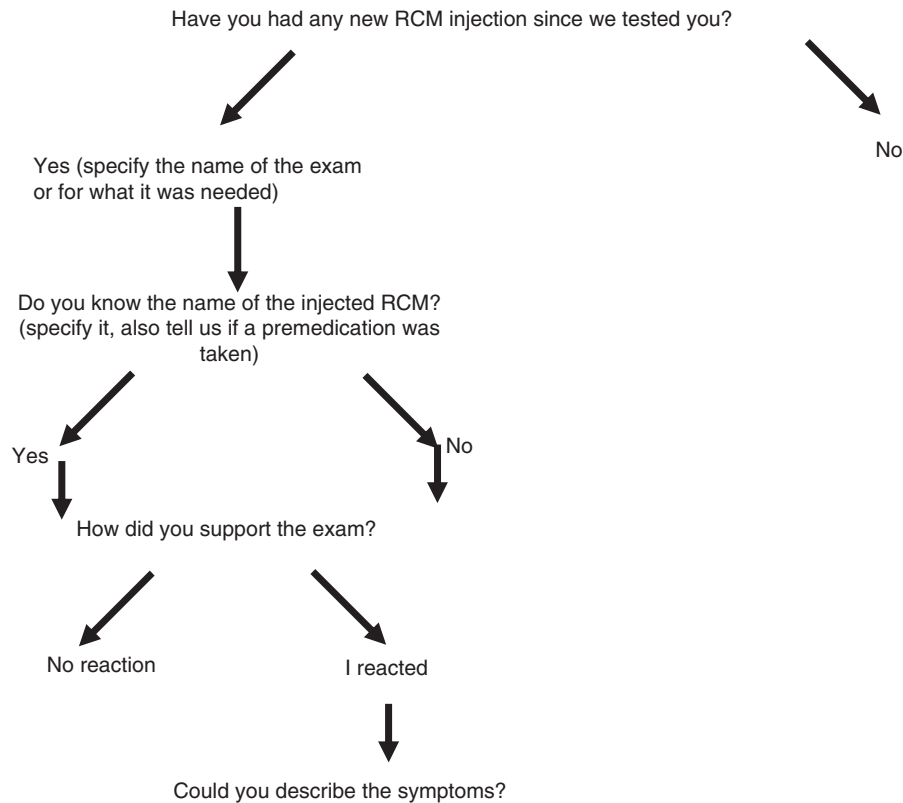


Fig. 1. Telephone interview.

[25th–75th] percentiles. The negative predictive value was defined as the proportion of patients with negative skin test results to at least one ICM at first testing who had a further injection with that ICM without reacting. The 95% confidence interval (95%CI) was computed.

Results

All patient characteristics

One hundred and fifty-nine patients have been studied over the last 9 years (Fig. 2). One hundred and twenty answered the phone call (75.5% participation rate). Seventy-one of them (59.2%) were females of a median age of 56 [45–65] years. The majority of the reactions were immediate (101 out of 120, 84.2%), and in two cases, it was not possible to assess whether the reaction was immediate or non-immediate. For immediate reactions, 42 (41.6%) were of grade 1, 34 (33.7%) of grade 2, 20 (19.8%) of grades 3 and five (4.9%) of grade 4. Only one (5.9%) of the 17 non-immediate reactions was moderate, all the others were mild (16–94.1%). In our cohort, the ICM was used in order to perform 70 (58.3%) CT scans, 12 (10%) i.v. urographies, eight (6.7%) coronarographies,

nine (7.5%) angiographies, four hysteroographies, three arthroscans and 14 undefined radiological exams.

Patients with a positive iodinated contrast media skin test and a negative alternative

The ICM skin tests were positive in 21 patients (17.5%). Seventeen of them (80.9%) had a history of immediate reaction (four with grade 1, eight grade 2, four grade 3 and one grade 4). Three of them (14.3%) had a history of non-immediate reaction (all mild) and one (4.8%) could not recall the exact chronology of the reaction. Prick tests were all negative. IDT were positive at 20 min for 15 patients with an immediate history and the patient with unknown chronology. A delayed positive IDT was observed for two patients with an immediate history and the three patients with a non-immediate history. There were nine females (42.9%) and 12 males (57.1%), median age 53 [34–60] years. The ICM was used for 14 (66.6%) CT scans, two (9.5%) coronarographies, two (9.5%) angiographies and one (4.8%) for arthroscan and hysteroigraphy. It was not known for one patient. The implicated ICM in the first reaction was known in only 13 patients (61.9%). The median time interval between the reaction and skin testing was 11.9 [1.6–21.5] years. Concerning the medical

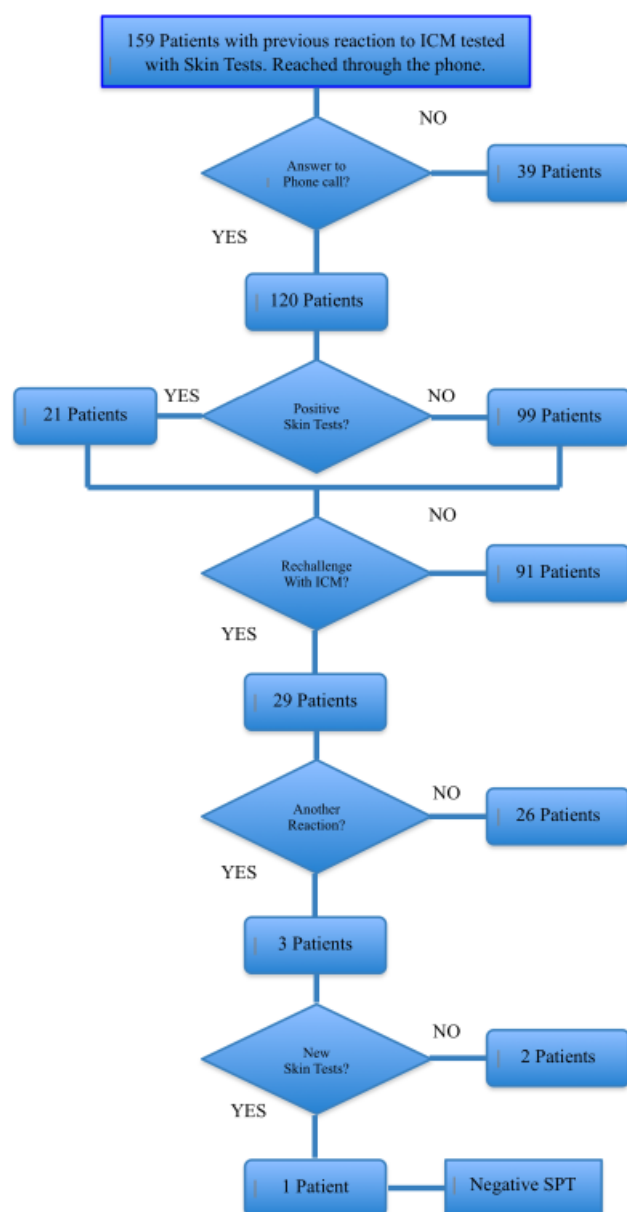


Fig. 2. Flow chart of patients.

background of the positive ICM skin test patient group, none of them suffered from other allergies.

Follow-up survey

Whole population analysis. Amongst the 120 patients who were contacted and who answered the questionnaire, 29 had been re-challenged (Table 1). None of them had undergone premedication before the ICM injection. Doses used followed the requirements of the radiological procedure and were not adapted because of the past clinical history of ICM reaction. Four patients had asthma (13.8%)

and two had a confirmed drug hypersensitivity (6.9%): one to amoxicillin and cefuroxime, and another to non-steroidal anti-inflammatory drugs.

As for the time that elapsed between ICM injection and allergic reaction, 24 patients (82%) had an immediate reaction and four a non-immediate reaction (13.8%). One patient could not recall the chronology of the reaction (3%). Clinical presentations for the immediate reactions were as follows: isolated skin eruption (maculopapular exanthema, urticaria, angio-oedema) in nine patients (37.5%), anaphylaxis in 14 patients (58.3%) and isolated dyspnoea in one patient (4.2%). The severity scoring for the immediate reactions was of grade 1 in 10 patients, grade 2 in five and grade 3 in nine. For non-immediate reactions, clinical presentations were: isolated maculopapular eruption in one patient, delayed urticaria/angio-oedema in two patients, isolated dyspnoea in one patient. The non-immediate reactions were all classified as mild. The median time interval between the reaction and skin testing was 11.5 [1.7–21.5] years.

Positive iodinated contrast media skin test patients re-challenged with an alternative iodinated contrast media. At the first visit, two out of the 29 patients presented a positive IDT. An ICM which gave a negative skin test was utilized for the re-challenge and no reaction occurred. The first patient was a 38-year old man with an imprecise history of reaction to ICM and a positive IDT to ioxaglate, iopamidol and amidotrizoate. He was administered iomeprol for his arthroscan. The second, a 73-year old man, had an immediate grade 2 reaction and a positive IDT to iopamidol. He was administered iobitridol for an angioscan (Table 1). The ICM involved in these previous reactions were unknown for both patients. Skin prick tests to airborne allergens were negative in both patients.

Patients reacting although they had a negative iodinated contrast media skin test. Three patients reacted during the ICM injection (Table 1). One patient had a sudden generalized urticaria starting within 1 h after an iomeprol i.v. injection for an angioscan and lasting for 3 days. Another one presented a generalized exanthema appearing 24 h after the drug was administered, and the third patient presented nausea, dyspnoea and tremors that we have actually attributed to a vagal/anxiety reaction. We repeated ICM skin tests for the patient presenting with an immediate long-lasting urticaria. She was tested for iomeprol, ioxaglate, iopamidol, ioversol, iopromide, amidotrizoate, iobitridol, iohexol and iodinaol. Prick tests and IDT were all negative at 20 min. Three hours after these tests, the patient had a CT angioscan, which was needed to check arterial fistules. No cutaneous or systemic manifestation occurred after the injection of iomeprol 300. In her clinical history, she had actually dealt with hives from time to time. The patient with the

Table 1. Patients characteristics

Patient #	Age	Sex	Type of ICM exam	Name of culprit ICM	Type of reaction	Delay* (months)	Skin tests	ICM re-injected	Side-effects
6	38	M	ND	ND	ND	ND	Positive [†]	Iomeprol	None
7	62	F	CT scan	ND	Immediate grade 3	408	Negative	Iomeprol	None
13	52	M	Fistulography	Ioxaglate	Immediate grade 3	5	Negative	Iodixanol	None
25	59	F	i.v. urography	ND	Immediate grade 2	312	Negative	Iomeprol	None
30	59	M	CT scan	Iopamidol	None immediate mild	5	Negative	Iomeprol	None
37	76	M	i.v. urography	ND	Immediate grade 3	432	Negative	Iomeprol	None
40	81	F	Angioscann	Iomeprol	Immediate grade 1	2	Negative	Iomeprol	Generalized urticaria
42	69	M	Angiography	ND	Immediate grade 3	144	Negative	Iomeprol	None
50	53	M	CT scan	ND	Immediate grade 1	12	Negative	Ioxaglate	Nausea, dyspnoea, tremor
65	56	F	CT scan	Iomeprol	None immediate mild	3	Negative	Iomeprol	None
68	58	F	i.v. urography	ND	Immediate grade 1	180	Negative	Iomeprol	None
69	47	F	Arthroscan	ND	Immediate grade 3	60	Negative	Iopromide	None
71	31	F	CT scan	ND	Immediate grade 3	132	Negative	Iomeprol	None
77	37	M	i.v. urography	ND	Immediate grade 2	180	Negative	Iomeprol	None
93	64	M	CT scan	ND	Immediate grade 1	24	Negative	Iomeprol	None
107	45	F	CT scan	ND	Immediate grade 1	2	Negative	Iomeprol	None
108	52	F	CT scan	ND	Immediate grade 3	132	Negative	Ioxaglate	None
109	54	F	CT scan	ND	Immediate grade 1	96	Negative	Iobitridol	None
110	28	F	CT scan	ND	Immediate grade 2	60	Negative	Iomeprol	None
111	53	F	i.v. urography	ND	Immediate grade 2	444	Negative	Iomeprol	None
112	46	F	CT scan	ND	Immediate grade 3	420	Negative	Iohexol	None
113	27	F	CT scan	ND	None immediate mild	120	Negative	Iomeprol	None
114	61	F	CT scan	ND	Immediate grade 1	408	Negative	Iomeprol	None
115	29	F	Phlebography	ND	Immediate grade 1	240	Negative	Iomeprol	None
116	57	F	CT scan	ND	Immediate grade 1	156	Negative	Iomeprol	None
117	56	F	CT scan	ND	None immediate mild	12	Negative	Iobitridol	Delayed maculopapular exanthem
118	77	F	Angiography	ND	Immediate grade 1	240	Negative	Ioxaglate	None
119	73	M	Angiography	ND	Immediate grade 3	360	Positive [‡]	Iobitridol	None
120	57	F	i.v. urography	ND	Immediate grade 3	192	Negative	Iomeprol	None

*Delay between reaction and skin testing.

[†]Immediate positive IDT to ioxaglate, iopamidol, amidotrizoate.[‡]Immediate positive IDT to iopamidol.

F, female; i.v., intravenous; M, male; ND, not determined; ICM, iodinated contrast media; CT, computed tomography; IDT, intradermal tests.

late-appearing maculopapular exanthema was unable to return for further tests. Considering the one single false negative, the negative predictive value of ICM skin tests was therefore 96.6% (95% CI: 89.9–103.2).

Discussion

Several studies have now shown that skin tests are useful tools for the diagnosis of ICM allergy [9, 11, 14–17]. However, both false negative and false positive results may exist and may be a problem for patients needing a further ICM injection. These issues have simply not been worked out properly. One possibility of addressing the question was to contact all the patients referred to our department for a suspicion of ICM hypersensitivity with negative skin tests and to ask whether they had been re-challenged with an ICM or not. For the last 9 years in our hospital, further to a decision made with the radiologists

and anaesthetists, in the absence of radiological alternatives, negative skin test patients are injected with a low-osmolality ICM in the presence of an ICU doctor. Among the 120 patients referred to our department for a history of ICM hypersensitivity, 29 needed a new ICM injection. Only three mild reactions occurred: one immediate urticaria (again negative after new ICM skin tests), one vasovagal reaction and one generalized late-appearing exanthema. We could not re-test the third patient who was too ill and was therefore considered as a false negative. Thus, the negative predictive value of skin testing for ICM hypersensitivity is high, above 95%, and none of the reactions in skin-test-negative patients were severe. However, further studies in larger numbers of subjects are still required.

In a recent ENDA collaborative study [11], 220 patients with either previous immediate (122) or non-immediate (98) hypersensitivity reactions were skin tested and up to

about 50% of the patients in both groups could be diagnosed by standardized skin tests, if the testing was conducted within 2–6 months after the reaction. In our study, the time delay between reaction and skin testing was much longer. For this reason, most of the patients could not recall the name of the ICM injected and this is of importance because immunological reactions to ICM may be ICM specific, and cross reactivity to all ICM has never been shown [11]. Nine of our cases had a previous reaction of grade 3 severity (life-threatening systemic reactions including shock) and, without our skin testing and re-challenge, they would never have benefited from a proper radiological intervention. Our pragmatic step-wise approach is indeed of interest. It is also relevant to note the fact that two of our patients had an immunologically proven ICM reaction (with positive IDT) and could benefit from the proper radiological intervention with an ICM, which gave a negative skin test. Although we are aware that this limited study should be extended, we can definitely advise a careful work up and a re-challenge in those patients for whom no alternative ICM exists.

We did not address the issue of premedication. Indeed, the 29 patients followed up in this study and re-injected were not premedicated. The literature on secondary prevention by premedication is not clear enough to draw conclusions [18]. The worst scenario would be to premedicate all patients with a previous reaction without testing, as severe anaphylaxis may occur. In this paper, we only advocate to test patients with a clinical reaction resembling allergy and to perform the ICM injection if the exam is absolutely needed in a safe environment using an ICM, which gave negative skin tests.

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