

ORIGINAL PAPER

Diagnosis of iodinated contrast media hypersensitivity: results of a 6-year period

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Summary

Background Iodinated contrast media (ICM) hypersensitivity reactions represent a serious problem. Very few clinical data concerning systematic skin testing to ICM are available.

Objective To evaluate the utility of ICM skin testing in patients with ICM hypersensitivity.

Material and methods All patients referred over a 6-year period for ICM hypersensitivity past reactions were skin tested for (a) the implicated ICM, or (b) a set of ICM if they were positive for the implicated ICM or if its name was unknown.

Results Forty-four patients, with a median age of 56 years, were studied (15 males, 29 females). The ICM skin tests were positive in 10 patients (23%): one had a positive skin prick test, seven an immediate positive intradermal test (IDT) and two a delayed positive IDT. Skin tests were more often positive in patients with immediate (9/32) as compared with those with non-immediate reactions (1/11). The time interval between the reaction and skin testing was shorter for those patients with an immediate ICM reaction and a positive skin test result (3 months [2.5–174.0]) as compared with those with an immediate ICM reaction and a negative skin test (48 months [6.8–159.0]), ($P < 0.05$). Respiratory allergy was more frequent in the positive group (6/10 vs. 7/34, $P < 0.05$).

Conclusions Skin tests with ICM are positive in a subgroup of patients with ICM hypersensitivity and may play an important role in the diagnosis of ICM allergy.

Keywords hypersensitivity, iodinated contrast media, skin testing

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Introduction

Iodinated contrast media (ICM) were introduced in the 1950s and have since then been among the most commonly prescribed drugs. Severe and fatal reactions represent a serious problem with a regard to the more than 70 million applications of ICM per year worldwide ICM [1]. All currently used ICM are composed of one (monomers) or two (dimers) tri-iodinated benzene rings and are classified on the basis of their physical and chemical characteristics. This classification divides them into ionic high-osmolality (amidotrizoate, ioxitalamate) and low-osmolality ICM. The low-osmolality ICM can be subdivided into (i) non-ionics monomers (iohexol, iopamidol, ioversol, iopramide, iomeprol, iopentol, iobitridol), ionic dimers (ioxaglate) and (ii) non-ionic dimers (iodixanol) [2].

ICM hypersensitivity reactions can be either immediate (within the first hour following the injection) or non-immediate (up to the seventh day). Mild immediate adverse reactions occur in 3.8–12.7% and in 0.7–3.1% of patients receiving intravenous injections of high-osmolar ionic and low-osmolar non-ionic ICM, respectively [3–5]. Severe immediate reactions have been reported in 0.1–0.4% and in 0.02–0.04% of patients, respectively [3–5]. Although the adverse reactions observed with the non-ionic ICM are usually less severe as compared with those induced by the ionic ICM, the death rates for the two different products are not significantly different and are estimated to be in the range of 1 in 100 000 examinations [6].

As most of the hypersensitivity reactions are seen as non-IgE mediated, investigations are not usually performed. Recently, the ENDA/EAACI group has decided to establish the value of skin tests in order to look for IgE-mediated reactions and to select an ICM alternative.

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Prospective studies are ongoing. In this paper, we present the ICM skin test results in 44 consecutive patients who were referred over a 6-year period to the Allergy Department of the University Hospital of Montpellier, France, with a past clinical history of ICM hypersensitivity.

Material and methods

In our study, we included all the patients who, over a 6-year period (from April 1999 to September 2005), were consecutively referred to the Allergy Department of the University Hospital of Montpellier, France, for a compatible past clinical history of a hypersensitivity reaction to ICM. Clinical data were registered using the ENDA drug allergy questionnaire before performing skin tests [7]. Patients were tested to the implicated ICM or to a set of ICM if they were positive for the implicated ICM or if its name was unknown. The ICM used were as follows: amidotrizoate, ioxitalamate, iopamidol, iohexol, ioversol, iopromide, iomeprol, iopentol, iobitridol, iodixanol and ioxaglate. Skin tests for ICM were performed firstly as prick tests and then, if negative, were followed by intradermic tests (IDT). Prick tests were considered positive if after 15 min, the size of the weal was at least 3 mm in diameter with undiluted ICM. For IDT, positivity was considered when the size of the initial weal increased by at least 3 mm in diameter after 15–20 min at a 1:10 dilution, as this concentration has been accepted as non-irritant [8–11]. Late reactions were also considered and measured as previously described [1]. Demographic parameters, clinical presentation, score of the reaction, chronology of the reaction, allergy clinical history, airborne allergen skin prick test (SPT) results, time delay from ICM hypersensitivity reaction to first consultation, implicated ICM, tested ICM and ICM skin test results were all analysed. 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 [12]. The Ring and Messmer [13] classification was used for immediate reactions. Non-immediate reactions were classified as mild, moderate and severe, as previously suggested [1]. Anaphylaxis was defined as a severe, life-threatening generalized or systemic hypersensitivity reaction [14]. The median and interquartile ranges for age and time delay were calculated. The Fisher exact test was used for statistical comparisons between patients with positive ICM skin tests and those who were negative. All data were collected in a Drug Allergy and Hypersensitivity Database using FileMaker Pro 7 software.

Results

Forty-four patients have been studied over the last 6 years in the Allergy Department of the University Hospital of

Montpellier, for a compatible past clinical history of hypersensitivity reaction to ICM. This study included 15 males (34%) and 29 females (66%), with a median age of 56 years (interquartile range, 40–67 years). As far as chronology is concerned, 32 patients (72.7%) had immediate reactions, 11 non-immediate (25%) and the result was unknown for one patient (2.3%). The male/female ratio for the immediate and non-immediate reactions was 1:1.5 and 1:4.5, respectively. The median time that elapsed before the reaction and the allergy work up (time delay) was 48 months (interquartile range, 3–138 months), and the reasons for ICM use were CT scans in 27 patients (61%), coronary angiography in six (13.6%) and urography in six (13.6%).

Clinical presentations for the immediate reactions were as follows: isolated skin eruption (maculopapular exanthema, urticaria, angioedema, undefined skin eruption) in 13 patients (40%) and anaphylaxis in 19 (60%). For non-immediate reactions, clinical presentations were as follows: isolated skin eruption in eight patients (73%), anaphylaxis in two (18%) and dyspnoea alone in one patient (9%). As expected, anaphylaxis was more frequent for those patients with immediate reactions ($P < 0.05$). The severity scoring for the immediate reactions was Grade I in 11 patients, Grade II in 13, Grade III in five and Grade IV in three. The non-immediate reactions were classified as mild in nine patients, moderate in one and severe in another.

SPTs to airborne allergens were positive in 12 patients (27.3%), negative in 24 (54.5%) and not performed in eight (18.2%). Concerning other relevant medical background details, 10 patients (22.7%) had rhinitis (seven atopic), three (6.8%) had asthma (one atopic), three (6.8%) had nickel contact allergy, four (9%) a confirmed drug allergy (two β -lactams, one fraxiparinus, pyrazinamide) and two (4.5%) were allergic to hymenoptera venom. As far as previous ICM exposure is concerned, 20 patients (45.5%) had had at least one previous ICM examination before the reaction and 21 (47.7%) had not. Three could not recall precise details. Sixteen patients (36.4%) had two or more previous reactions to ICM and 25 just one (57%). From these 41 patients, the implicated ICM in the last reaction was known in 17 (38.6%): nine iomeprol, four ioxaglate, one ioxitalamate, one ioversol, one iohexol and one iopamidol. Table 1 summarizes the results.

Patients were skin tested as described above. The number of skin tests performed for each ICM was as follows: 38 for iomeprol (86.4%), 34 for amidotrizoate (77.3%), 32 for ioxaglate (72.7%), 30 for iopromide (68.2%), 29 for iopamidol (66%), 18 for ioversol (41%), 16 for iobitridol (36.4%), 13 for ioxitalamate (29.5%), six for iohexol (13.6%), six for iopentol (13.6%) and six for iodixanol (13.6%).

The ICM skin tests were positive in 10 patients (23%): one had a positive SPT (to ioxaglate) and nine a positive

Table 1. Clinical characteristics of the patients skin tested to iodinated contrast media (ICM)

	ICM skin test (+)	ICM skin test (–)	Total
Number	10	34	44
Gender M/F	5/5 (1 : 1)	10/24 (1 : 2.4)	15/29 (1 : 1.9)
Age* – years (interquartile)	50.5 (34–58)	56.5 (43–70)	56 (40–67)
Implicated examination			
CT scan	6	21	27
Coronary angiography	2	4	6
Urography	1	5	6
Unknown	1	4	5
Chronology			
Immediate [†]	9	23	32
Non-immediate	1	10	11
Unknown	0	1	1
Time delay* – months (interquartile)			
Immediate	3 (2.5–174)	48 (6.8–159)	42 (3–123)
Both immediate and non-immediate	3 (3–117)	48 (10–144)	48 (3–138)
Clinical presentation			
Skin only [‡]	4	18	22
Respiratory only	0	1	1
Anaphylaxis	6	15	21
Immediate reactions classification			
Grade I	3	8	11
Grade II	3	10	13
Grade III	1	4	5
Grade IV	2	1	3
Non-immediate reactions classification			
Mild	1	8	9
Moderate	0	1	1
Severe	0	1	1
Previous ICM exposure: yes/no/no data	3/5/2	17/16/1	20/21/3
More than one reaction: yes/no/no data	2/6/2	14/19/1	16/25/3
Airborne allergen skin tests: + / – /no data	4/6/0	8/18/8	12/24/8
Respiratory symptoms (A/R)	1/5	2/5	3/10
Drug allergy confirmed by DPT	2	2	4
Contact allergy	1	2	3
Hymenoptera venom allergy	0	2	2

*Median.

[†]Immediate, occurring within the first hour after ICM injection.[‡]Skin eruptions of any type, generalized in most cases.

M, male; F, female; A, asthma; R, rhinitis; DPT, drug provocation test.

IDT test. Five patients had two or more positive skin tests: iomeprol and ioxaglate in one, ioversol and iomeprol in one, iopamidol, ioversol, iobitridol and ioxaglate in one and iopromide and iomeprol in a fourth patient. A fifth one had nine delayed positive skin tests to different ICM. Iomeprol was the most frequent positive ICM (seven patients). All the six patients where the ICM was known had a positive skin test to the implicated ICM. The data concerning these 10 patients are presented in Table 2.

In the positive skin test patient group, the male/female ratio was 1:1 as opposed to those with negative ICM skin tests, which were more often in females (1:2.4). No differences were found regarding age. In those with a positive skin test, 9/10 (90%) had an immediate ICM reaction compared with the 23/33 (70%) of those who

were skin test negative. Skin tests were more often positive in patients with immediate (9/32) as compared with those with non-immediate reactions (1/11). If we look only at the patients who had an immediate ICM reaction, those from the positive ICM skin test patient group were referred to the Allergy Department earlier (median time 3 months [2.5–174.0]) than those who were skin test negative (median time 48 months [6.8–159.0]), ($P < 0.05$). No significant difference was found between the two groups for clinical presentation and the score of the reaction. In the positive skin test patients, the scores for the immediate reactions were Grade I in three, Grade II in three, Grade III in one and Grade IV in two. The non-immediate reaction was classified as mild. The implicated ICM on the previous reaction was iomeprol and ioxaglate for two patients each

Table 2. Clinical data concerning the iodinated contrast media (ICM) skin test-positive patients

Age*, gender	Chronology	Score	Time delay (months)	Medical history	Atopy	Implicated ICM	ICM skin test-positive results		
							SPT	IDT [†] (20 m)	IDT [‡] (48 h)
59, F	IM	4	276	A	No	ND	–	Iomeprol	–
40, M	IM	1	72	DA	No	ND	–	Iomeprol, Ioxaglate	–
32, F	IM	1	2	–	No	Iomeprol	–	Iomeprol	–
74, M	NIM	Mild	132	R/DA	No	ND	–	–	Amidot, Iopam, Iohexol, Iovers, Ioprom, Iomepr, Iopent, Iodixa, Ioxaglat [§]
32, F	IM	2	1	R	Yes	Ioversol	–	Ioversol, Iomeprol	–
24, F	IM	2	3	–	No	Iomeprol	–	Iomeprol	–
46, M	IM	3	348	R	Yes	ND	–	Iopamidol, Ioversol, Iobitridol, Ioxaglate	–
55, F	IM	1	3	–	No	Iohexol	–	–	Iohexol
55, M	IM	2	3	R	Yes	Ioxaglate	–	Ioxaglate	–
63, M	IM	4	3	R	Yes	Ioxaglate	Ioxaglate	Iopromide Iomeprol	–

*In years.

[†]IDT, intradermic test after 20 min.[‡]IDT, intradermic test after 48 h.[§]: Positive tests, amidotrizoate, iopamidol, iohexol, ioversol, iopromide, iomeprol, iopentol, iodixanol, ioxaglate.

M, male; F, female; IM, immediate; NIM, non-immediate; A, asthma; R, rhinitis; DA, drug allergy; SPT, skin prick test; ND, no data.

and ioversol and iohexol for one. The remaining four positive cases did not know to which ICM they reacted and the reaction was more than 6 years ago.

SPTs to airborne allergens were positive in 4/10 (40%) patients of the positive ICM skin test group and in 8/34 (23%) of the negative group. Concerning the medical background of the positive ICM skin test patient group, rhinitis was present in five patients (four atopics), one patient was asthmatic (non-atopic), two had a confirmed drug allergy by drug provocation test and one had a contact allergy. For those who were ICM skin test negative, five patients had rhinitis (three atopics), two had asthma (one atopic), two a confirmed drug allergy, two a contact allergy and two were allergic to hymenoptera venom. If we compare both groups, respiratory allergy was more frequent in the positive skin test patient group (6/10 vs. 7/34, $P < 0.05$).

Discussion

For many years, it was considered that the pathomechanism supporting the majority of ICM reactions could not be explained by any of the four Gell and Coombs allergy types and especially the type I reaction. In fact, it has been accepted that most of the reactions are of an 'anaphylactoid' nature, which is the consequence of the mast cell and basophil histamine and/or other vasoactive mediator release mechanisms. However, the exact mechanism is far from being completely understood. More recently, the old IgE theory was revitalized after the publication of certain papers correlating histamine release and the se-

verity grade of the reaction [15], the results of specific IgE measurements in reactors [16, 17] and some case reports of positive skin tests. Regarding skin tests, prick and IDT have both been performed for many years in the diagnosis of immediate hypersensitivity reactions to ICM, but positive tests have rarely been reported and mostly involving patients with severe reactions only [9, 10, 17, 18]. In the literature, there are some references considering the non-irritant threshold for ICM at 1:10 dilution [8–11]. This is also our opinion and we have performed skin tests with ICM in 10 controls who had tolerated ICM, without any positive result at this dilution (data not shown). Moreover, at this concentration, five patients who reported an immediate reaction and who were negative to the known implicated ICM (tested with other agents) and all the 11 patients who reported a non-immediate ICM hypersensitivity reaction (negative immediate reading) were also tested negative. A large study of exposed non-reacting controls is nevertheless lacking [19]. This is why the ENDA/EAACI group has decided to establish the value of skin tests in order to look for IgE-mediated reactions and to select an ICM alternative. A prospective multi-centre study is currently ongoing.

Despite the recommendations for patients with previous ICM reactions (especially for those with immediate severe episodes) to avoid future exposure and to perform an alternative procedure, the clinical situation is rarely that simple and pharmacological prophylaxis is very frequently proposed. This is why the classic approach to previous ICM reactors consists of pre-medication and the use of low osmolality ICMs. Corticosteroids and

antihistamines are the most frequently used prophylactic agents, but their efficacy is still debated. The limited number of well-conducted studies does not allow us to establish the efficacy of pre-medication [1, 2].

In the present study, 10 patients referred to our Drug Allergy Department had a positive ICM skin test at 1:10 dilution. All the six patients for whom the ICM was known had a positive skin test to the implicated ICM. On the basis of our results, we conclude that those with a previous history of ICM should be skin tested, as a proportion of the ICM reactions could really be allergic (Type I and Type IV) and, if so, pre-medication should not be prescribed as it could possibly mask the signs of a serious, possibly delayed, reaction. Indeed, severe ICM-induced anaphylactic reactions have occurred in previous reactors despite such prophylactic use of corticosteroids [20, 21]. Five patients had two or more positive ICM skin tests, suggesting that cross-reactivity can occur between ICMs, even within different groups. Cross-reactivity has been previously described [22]. This should be remembered before choosing an alternative ICM not based on skin testing.

It was surprising to note that one patient with an immediate reaction (urticaria) had a non-immediate positive IDT. Although it seems a paradox as immediate reactions are mostly IgE mediated, we should bear in mind that they need the collaboration of activated T cells, that are necessary for the development of the humoral response as was previously shown for penicillin allergy [23]. This finding is in agreement with previous works, which documented the participation of T cells in immediate drug reactions with positive lymphocyte transformation tests [24]. Positive patch tests are also documented in urticaria drug reactions [25]. Previous exposure/reaction really does seem to be one of the most important risk factors as described before [3]. It is remarkable that 45.5% of the patients had a previous history of an ICM examination before the reaction and that 36.4% had more than one ICM hypersensitivity episode. No differences exist between the two patient groups in the present study.

About 2/3 of all the patients were female and it is interesting to analyse the different male/female ratios found for the positive and negative skin test patient groups (1:1 vs. 1:2.4) as well as for the patients with immediate and non-immediate reactions (1:1.4 vs. 1:4.5). This concurs with the data from the Katayama et al. [3] trial and with the Mikkonen et al. [26], study which reported that the female gender is a risk factor for non-immediate reactions. We did not find any differences between the groups regarding age.

The time that elapsed before the reaction and allergy workup for the positive ICM skin test immediate reactors was lower and statistically different ($P < 0.05$) compared with those who were skin test negative and who also had immediate reactions. This can probably be explained by

the fact that the sooner a skin test is performed, the more likely it is to obtain a positive result, as already defined from experience with penicillin skin tests [27]. No differences were found for the clinical severity scoring and in fact three positive skin test patients had a Grade I reaction, suggesting that true allergic reactions do not occur only in high clinical score cases.

SPTs for airborne allergens were positive in 27.3% of the patients (40% for those who were ICM skin test positive and 23.5% for those who were ICM skin test negative), suggesting a possible role for the atopy. As far as respiratory symptom history is concerned, 6/10 (60%) positive ICM skin test patients had rhinitis or asthma as compared with 7/34 (20.6%). This difference was statistically significant ($P < 0.05$). Despite this, respiratory atopic disease (mostly allergic rhinitis) was present in fewer patients, but still significantly different when comparing the two patient groups: 4/10 (40%) vs. 4/34 (11.7%). Four patients (9%) had a previous history of confirmed drug allergy, two cases in each group. This prevalence could result from some predisposition higher than in the general population, although the size of the sample does not allow us to make reliable conclusions within the study. The vast majority of published articles on ICM reactions concentrates on prevalence and risk factors. This was not the aim of this study when taking into consideration the limited number of patients tested.

Another limitation of this study results from the low molecular weight of ICMs and the theoretical need of haptenization for these compounds to become allergens. Thus, false-negative results may have been obtained and this clearly is an issue for patients having had Grade III and IV reactions and needing another ICM injection. In the absence of radiological alternatives, the current attitude within our institution for negative skin test patients is to inject a low-osmolality ICM in the presence of an ICU doctor. This was the case for 10/34 of our negative skin test patients who produced no reaction (data not shown). False-positive results may also have occurred and the literature does not adequately address the positive predictive value of ICM skin tests. In the absence of radiological alternatives, the current attitude within our institution for positive skin test patients is to inject a low-osmolality ICM, that produces negative skin tests, again in the presence of an ICU doctor. This was the case for two of our 10 positive skin test patients who produced no reaction: one was positive to iomeprol (IDT at 10-fold dilution) and the other to ioxaglate (prick test), iopromide and iomeprol (IDT at 10-fold dilution).

Our main objectives were as follows: (a) to show that ICM allergy exists and is not necessarily related to the severity of the reaction; (b) to remember that cross-reactivity may occur; and (c) to determine that skin tests may play an important role in the study of ICM hypersensitivity in order to prevent new reactions.

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