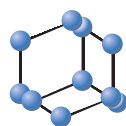


RESEARCH ARTICLE

BENTHAM
SCIENCE

Skin Tests for the Exploration of Hypersensitivity Reactions Associated with Iodinated Contrast Media



Ahmed Zaiem^{1,2,*}, Syrine Ben Hammamia^{1,2}, Fares Ben Salem^{2,3}, Ons Charfi^{1,2}, Imen Aouinti^{1,2}, Sarrah Kastalli^{1,2}, Sihem El Aidli^{1,2}, Talel Badri^{2,4}, Ghazlane Lakhroua^{1,2} and Habiba Mizouni^{2,3}

¹National Center of Pharmacovigilance, 9 Avenue du Dr Zouhaier Essafi 1006, Tunis, Tunisia; ²University of Tunis El Manar, Faculty of Medicine, 15 Rue Djebel Lakhdhar, La Rabta 1007, Tunis, Tunisia; ³Department of Radiology, la Rabta Hospital, Rue Jabbari 1007, Tunis, Tunisia; ⁴Department of Dermatology, Habib Thameur Hospital, 8 Rue Ali Ben Ayed Montfleury 1008, Tunis, Tunisia

Abstract: Background: Iodinated contrast media (ICM) are responsible for multiple side effects, especially hypersensitivity reactions. These reactions can either be authentic allergies or non-allergic hypersensitivity reactions. Skin tests (prick and intradermal tests) are simple to perform and can be of great help, especially if the ICM needs to be re-used. The aim of the study was to assess the characteristics of the patients in whom skin tests were performed and the results of these tests.

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Methods: This is a retrospective study from June 2014 to June 2019. All included patients had at least one episode of hypersensitivity reaction to ICM and underwent skin tests.

Results: We included 35 patients aged 18 to 85 years. The iopromide was the most implicated ICM. The reactions were mainly cutaneous (n=30) and immediate (n=27). The skin tests were negative, except for two patients. The re-use of ICM occurred in 11 patients: 9 with an ICM other than the one suspected and two patients with the same ICM. Among these patients, 5 did not have any premedication. Two of them had a second hypersensitivity reaction, the first with another ICM and the second with the same ICM.

Conclusion: One of the main pillars of allergic exploration is ICM skin testing, not only to prevent a recurrence, but also to allow patients to benefit from ICM re-use, which are sometimes essential.

Keywords: Iodinated contrast media, drug hypersensitivity, skin tests, *in vivo* tests, intradermal tests, prick tests.

1. INTRODUCTION

Iodinated contrast media (ICM) are diagnostic drugs used since the 1950s for radiological examinations. ICM have the capacity to absorb X-rays, thus inducing clouding of the compartments in which they are introduced. It is the iodine atom that gives them this property because of its high atomic number ($Z = 53$) [1]. The use of ICM is increasing, with an estimated 75 million injections performed worldwide annually [2].

The injection of ICM is not without risk. Hypersensitivity reactions can occur in 1 to 3% of patients [3]. These reactions can be the result of an immunological mechanism (authentic allergies) or of a non-allergic mechanism (non-specific histamine-liberation).

In vivo allergological tests, such as skin tests, are easy to perform and are not costly. They are, therefore, performed

in current practice to confirm the mechanism of hypersensitivity and thus guide the management if ICM needs to be re-used.

The aim of this study was to determine the particularities of patients who have undergone skin tests with ICM evaluating the results of these tests and proposing recommendations in case of hypersensitivity reaction.

2. METHODS

We have conducted a prospective study, at the National Center of Pharmacovigilance (NCPV) and the radiology department of the Rabta Hospital, from June 2015 to June 2019. The local hospital ethics committee approved access to the patient information database. All enrolled patients had agreed to have their data published and have signed a written informed consent form.

We have included in our study:

- All patients who have had a hypersensitivity reaction to ICM, whether immediate or subsequent, recent or old, and whether the ICM was identified or not;

*Address correspondence to this author at the National Center of Pharmacovigilance, 9 Avenue du Dr Zouhaier Essafi 1006, Tunis, Tunisia;
Tel: 0021671260699; Fax: 0021671260714;
E-mail: ahmed.zaiem@gmail.com

- Patients who have provided consent;
- Patients who have undergone allergic tests *in vivo* (prick tests and intradermal tests).

These patients had two consultations: the first in NCPV to collect information, and the second to perform the skin tests within a minimum of 6 weeks relative to the event (whenever possible, if the event was recent).

The data were collected based on standardized clinical observation records for adverse drug reactions used in the NCPV [4].

The reactions were considered immediate if they occurred within 1 hour. After an hour, the reactions were considered delayed reactions. The immediate reactions were classified in grades I, II, III, and IV according to the Ring and Messmer Classification [5]. The reactions were considered serious or not, according to the definition of the International Council for Harmonisation (ICH) Harmonised Tripartite Guideline [6].

Depending on the availability of ICMs, the patients were tested with one or more products (iopromide 370 mg/mL or 300 mg/mL, iodixanol 320 mg/mL, iohexol 350 mg/mL and iopamidol 370 mg/mL). The solutions for the tests were prepared the same day of the test: pure, 1/10, and 1/100 dilutions.

The prick-tests were performed with pure solutions. If negative, intradermal tests (IDT) were performed at 1/100

and then at 1/10 dilutions (IDT 1/100 and IDT 1/10, respectively).

The prick-tests were read after 20 minutes. The test was considered positive if a papule appeared and was 3 mm larger than the negative control's diameter [7].

The IDT were read after 30 minutes. The test was considered positive in the case of 3 mm increase in the diameter of the initial papule. If the papule is not round, the length and width of the papule are measured, added together, and divided by two [7].

If the patient has previously presented a late hypersensitivity reaction, a late reading within 48 to 72 hours was performed.

For patient safety considerations, skin tests were carried out in hospital departments where the framework allows adequate medical support if necessary (availability of an experienced anesthetist and necessary medical equipment). Monitoring was recommended at least two hours after skin tests were completed.

All the patients were followed up at our consultation and contacted by phone in order to assess the consequences of a new re-exposure to ICM.

3. RESULTS

We included 35 patients: 22 women and 13 men. The main epidemiologic characteristics of the patients are summarized in Table 1.

Table 1. Epidemiologic characteristics of the patients.

Patient	Age	Sex	History of Allergy	Medical History	Previous ICM Injection	HS Reaction Prior to the Notified Event	Type of HS Prior to the Notified Event
1	31	F	No	-	No	No	-
2	33	F	No	Neo	No	No	-
3	68	F	AR, DH (paracetamol)	Diabetes, HBP	No	No	-
4	18	F	No	Neo, HBP	Yes (ioh, iopr)	Yes (ioppr)	Immediate/Grade I
5	62	F	CA	Diabetes, HBP	Yes (ioh)	No	-
6	44	F	DH (anti-HBV vaccine)	-	Yes (ioh)	Yes(ioh)	Late
7	59	M	No	-	No	No	-
8	46	F	No	-	No	No	-
9	44	M	No	-	No	No	-
10	52	M	No	HBP	Yes(NI)	No	-
11	81	M	No	HBP	No	No	-
12	29	M	No	Neo	Yes (ioh)	Yes (ioh)	Immediate/Grade I
13	66	M	No	-	Yes(NI)	No	-
14	64	F	No	Diabetes	No	No	-
15	43	F	AR	-	No	No	-
16	61	M	No	Neo	No	No	-
17	41	M	No	-	Yes (ioppr)	No	-
18	31	F	No	-	No	No	-
19	54	F	AR, Asthma	-	Yes(NI)	No	-
20	51	F	Ur	Neo	Yes(NI)	No	-
21	31	M	No	-	No	No	-

Patient	Age	Sex	History of Allergy	Medical History	Previous ICM Injection	HS Reaction Prior to the Notified Event	Type of HS Prior to the Notified Event
22	32	F	Asthma	Neo	No	No	-
23	38	F	FA	Neo	Yes(NI)	No	-
24	54	F	AR	Neo, HBP	No	No	-
25	52	F	AC, AR	-	No	No	-
26	71	M	DH (paracetamol)	-	Yes (NI)	No	-
27	43	F	DH (Carboplatine)	Neo	Yes (NI)	No	-
28	37	F	DH (Furosemide)	HBP, CRF	No	No	-
29	40	F	AR	-	Yes (NI)	No	-
30	49	F	No	Epilepsy, Diabetes	No	No	-
31	85	M	No	Arrhythmia, Dyslipidemia, Diabetes	Yes (ioh)	No	-
32	52	F	No	HLC	No	No	-
33	63	M	AR	-	Yes (NI)	No	-
34	62	M	No	Diabetes HBP, CRF	No	No	-
35	61	F	DH (penicillin)	Neo	No	No	-

Abbreviations: AC: Allergic Conjunctivitis, AR: Allergic Rhinitis, CRF: Chronic Renal Failure, DH: Drug Hypersensitivity, F: Female, FA: Food Allergy, HBP: High Blood Pressure, HLC: Hydatid Liver Cyst, iod: iodoxanol, ioh: iohexol, iopa: iopamidol, iopr: iopromide, M: Male, Neo: Neoplasia, NI: Nonidentified, Ur: Urticaria.

Table 2. Main characteristics of the notified events.

Patient	Notified Events	ICM	Delay	Grade	Intrinsic Imputability Score	Type	Seriousness (WHO)
							Hospitalisation
1	Ur, FA, Fever	iopr	16 h	NV	I1	L	Yes
2	Ur	iopr	10 mn	I	I2	Im	No
3	Ur, GE	iopr	10 mn	I	I2	Im	No
4	Ur, FA, D	ioh	10 mn	II	I2	Im	No
5	D	NI	1 mn	II	NV	Im	No
6	Ur	ioh	4 h	NV	I1	L	Yes
7	Ur	iopr	5 mn	I	I2	Im	No
8	Ur, GE, FA	iopr	1 mn	I	I2	Im	No
9	FA, D	NI	10 mn	II	NV	Im	No
10	Ur, GE, FA	iopr	5 mn	I	I2	Im	Yes
11	Pr, Suff	NI	1 mn	I	NV	Im	No
12	Ur	iodi	5 h	NV	I1	L	No
13	LC	NI	1 mn	I	NV	Im	No
14	OM, D, T	iopa	1 mn	II	I2	Im	No
15	Ur, D	iopr	1 mn	II	I2	Im	No
16	Ur, FA	NI	3 h	NV	NV	L	Yes
17	GE, FA, D, Tac	ioh	10 mn	II	I2	Im	Yes
18	Ur	iopr	1 mn	I	I2	Im	Yes
19	N, Hypot	iopr	1 mn	II	I2	Im	Yes
20	Ur, FA	iopr	5 mn	I	I2	Im	No
21	Pr, D, RsB	iopr	1 mn	II	I2	Im	No
22	Ur	iopr	10 mn	I	I2	Im	No
23	GE, Pr, D, N	NI	1 mn	II	NV	Im	No
24	Ur, GE	iopr	10 mn	I	I2	Im	Yes
25	FA, OM	ioh	1 mn	I	I2	Im	No
26	Ur, GE	NI	24 h	NV	NV	L	No
27	Ur	iopr	10 mn	I	I2	Im	No
28	Ur	iopr	24 h	NV	I1	L	No
29	AS	NI	5 mn	III	NV	Im	Yes

Patient	Notified Events	ICM	Delay	Grade	Intrinsic Imputability Score	Type	Seriousness (WHO)
							Hospitalisation
30	Ur	NI	1 mn	I	NV	Im	No
31	D	ioh	24 h	NV	I3	L	No
32	Ur, D	lopr	1 mn	II	I2	Im	No
33	Ur, GE	lopr	1 mn	I	I2	Im	No
34	Ur, GE	NI	10 mn	I	NV	Im	No
35	FA	iopr	3 h	NV	I1	L	No

Abbreviations: AS: Anaphylactic Shock, Hypot: Arterial Hypotension, C: Cough, D: Dyspnea, FA: Facial Angioedema, GE: Generalized Erythema, h: hour, Im: Immediate, iod: iodixanol, ioh: iothexol, iopa: iopamidol, iopr: iopromide, L: Late, LC: Loss of Consciousness, mn: minute, N: Nausea, NI: Not identified, NV: Non valid, OM: edema of the mucosa, Pr: Pruritus, RsB: Retrosternal Burn, Suff: suffocation feeling, Tac: Tachycardia, Ur: Urticaria.

There were 27 cases of immediate reactions and 8 cases of late reactions (Table 2).

The incriminated ICM were iopromide (n=18), iothexol (n=5), iodixanol (n=1) and iopamidol (n=1). The ICM was not identified in 10 patients. The intrinsic imputability score was valued when the ICM was identified (n=25).

The time between the occurrence of the reaction and skin testing ranged from 6 weeks to 43 years (median: 30 weeks).

Among the 35 patients who had skin tests, 34 had shown no systemic clinical signs of intolerance as specified (discomfort, fever, or rash). One patient (patient 22) had “hyperventilation syndrome” with a feeling of warmth and tightness in the chest. However, no objective clinical signs (correct blood pressure, normal cardiopulmonary auscultation) were noticed. These signs resolved spontaneously, without symptomatic treatment, in less than 15 minutes.

Prick tests and 1/100 IDT were negative in all patients. 1/10 IDT were positive in two patients (patients 4 and 23). For patient 4, 1/10 IDT were positive with both iopromide and iothexol: 11mm papule (initial 8mm) with iopromide and 12mm papule (initial 8mm) with iothexol. For patient 23, 1/10 IDT were positive with iothexol: 16mm papule (initial 10mm).

Among the patients with negative skin tests, 11 patients re-used ICM: 9 patients with another ICM than the one suspected and two patients with the same ICM (patients 27 and 31) (Table 3). Five had no premedication. The others had premedication based on corticosteroids or antihistamines.

Two of the non-premedicated patients developed a second hypersensitivity reaction. Patient 8 re-used another ICM and presented a reaction of the same grade as the first, with clinical signs considered less intense. Patient 31 used the same ICM again and presented the same reaction as the first time (late dyspnea).

4. DISCUSSION

Among the 35 cases of hypersensitivity reactions to ICM explored by skin tests, 27 were immediate, and 8 were delayed. Two patients had positive skin tests. Eleven patients re-used the ICM with the absence of recurrence of signs in 9 cases.

Regarding the epidemiologic and past medical possible risk factors, only three patients in our series had a history of

previous hypersensitivity reactions. In literature, the only risk factor cited is the previous occurrence of a hypersensitivity reaction to ICM [8, 9]. It increases the risk of having another reaction by about 5 times [10]. Other risk factors are reported, such as asthma and other atopies [8, 9], neoplasias [11], beta-blockers [8], and interleukin 2 immunotherapy [12-14].

In our study, the majority of clinical signs of immediate hypersensitivity reactions involved the skin and mucous membranes. Respiratory signs were present in 10 patients, cardiovascular signs in two patients, and digestive signs in two other patients. For immediate hypersensitivity reactions, the majority of patients had grade I or grade II reactions. Only one patient had a grade III reaction (anaphylactic Shock). This is in line with the data in the literature, which found that severe reactions are rare and especially after the most common use of low osmolality and nonionic ICM [15].

The ICM involved in immediate events were all low osmolar and nonionic ICM. It was iopromide in fifteen patients, iothexol in three patients, and iopamidol in one patient. ICM was not identified in eight patients. In a Turkish cross-sectional study, the incidence of hypersensitivity reactions due to nonionic ICM was 0.72% [16]. A Korean study assessing the safety of seven ICM use found that iopromide and iothexol were the drugs with the most side effects [17].

Seven of the eight late reactions showed dermatological signs, including one patient with associated fever. Only one patient presented dyspnea. In literature, dermatological signs are the most frequent expressions of late reactions, represented mainly by urticaria, maculopapular rash, or exanthematous pustulosis [2, 12].

Several studies suggest that the incidence of late reactions within the interval of 1 hour-24 hour was 4% or less, and the incidence of skin reactions within 7 days of injection was 1-3% [12]. In our study, the average interval was 12h (3 h-24 h). This shortened delay is explained by the fact that the longer the delay, the more difficult it was to link them to the ICM injection.

Among the eight patients who developed late reactions, three patients received iopromide, and two received iothexol. Only one patient received iodixanol. It has been reported in the literature that iodixanol has more late skin side effects compared to other low osmolality ICM without explaining this trend [8].

Table 3. Results of skin tests and possible reuse of ICM.

Patient	Time to Achieve Skin Tests (Weeks)	Culprit ICM	ICM Tested	Prick-test	IDT	ICM Reused	Premedication	Recurrence
1	14	iopr	iod/ ioh/ iopr	N	N	-	-	-
2	31	iopr	iod/ ioh/ iopr	N	N	iod	No	No
3	65	iopr	iod/ ioh/ iopr	N	N	iod	No	No
4	92	ioh	iod/ ioh/ iopr	N	P (ioh, iopr)	-	-	-
5	406	NI	iod/ ioh/ iopr	N	N	-	-	-
6	16	ioh	iod/ ioh/ iopr	N	N	iod	Anti-H1	No
7	7	iopr	iod/ ioh/ iopr	N	N	-	-	-
8	6	iopr	iod/ ioh/ iopr	N	N	iod	No	Grade I reaction
9	417	NI	iod/ ioh/ iopr	N	N	ioh	Anti-H1	No
10	6	iopr	iod/ ioh/ iopr	N	N	-	-	-
11	203	NI	iod/ ioh/ iopr	N	N	iopr	No	No
12	30	iod	iod/ ioh/ iopr	N	N	-	-	-
13	18	NI	iod/ ioh/ iopr	N	N	-	-	-
14	72	iopa	iod/ ioh/ iopr	N	N	-	-	-
15	11	iopr	iod/ ioh/ iopr	N	N	-	-	-
16	26	NI	iod/ ioh/ iopr	N	N	iod	Anti-H1	No
17	25	ioh	iod/ ioh/ iopr	N	N	-	-	-
18	19	iopr	iod/ ioh/ iopr	N	N	-	-	-
19	8	iopr	iod/ ioh/ iopr	N	N	-	-	-
20	6	iopr	iod/ ioh/ iopr	N	N	iod	Anti-H1	No
21	52	iopr	iod/ ioh/ iopr	N	N	-	-	-
22	18	iopr	iod/ ioh/ iopr	N	N	-	-	-
23	54	NI	iod/ ioh/ iopr	N	P (ioh)	-	-	-
24	40	iopr	iod/ ioh/ iopr	N	N	ioh	Anti-H1	No
25	43	ioh	iod/ ioh/ iopr	N	N	-	-	-
26	8	NI	iod/ ioh/ iopr	N	N	-	-	-
27	8	iopr	iod/ ioh/ iopr	N	N	iopr	Corticosteroids	No
28	103	iopr	ioh/ iopr	N	N	-	-	-
29	123	NI	iod/ ioh/ iopr	N	N	-	-	-
30	988	NI	iod	N	N	-	-	-
31	52	ioh	iopa/iod/ ioh/ iopr	N	N	ioh	-	Delayed reaction (dyspnea)
32	104	iopr	ioh/ iopr	N	N	-	-	-
33	11	iopr	iod/ ioh/ iopr	N	N	-	-	-
34	2236	NI	iod/ ioh/ iopr	N	N	-	-	-
35	20	iopr	iopr	N	N	-	-	-

Abbreviations: iod: iodixanol, ioh: iohexal, iopa: iopamidol, iopr: iopromide, N: Negative, NI: Not identified, P: positive.

The intrinsic causality score was “doubtful” in five patients and “likely” in one patient. The delay of the onset of late reactions makes it difficult to attribute these reactions to ICM. Minor reactions in the first few days after the injection of ICM may go unnoticed. It is therefore important to warn the patient about the risk of having these kinds of reactions and recommend consulting at the slightest clinical sign.

The timing of skin testing is critically important. Yoon reported that one of the factors significantly influencing the positivity of skin tests was the time taken to perform these tests in relation to the event, and an optimal time between one to six months has been proposed [18]. In our study, the time taken to perform skin tests was variable, with a median

of 30 weeks. The two positive skin tests were performed, respectively, one year and two years after the event (beyond the recommended optimal time).

No significant reaction was noted during skin tests to ICM in both the literature and our study. These tests are considered to represent a safe means of diagnosis with a low systemic reaction rate [18, 19].

- In our study, 33 of the 35 patients had negative skin tests. The low rate of positivity of these tests can be explained by:

- The majority of patients included in our series had a grade less than or equal to 2 according to the classification

of Ring and Messmer for immediate reactions. In the literature, there is a correlation between the severity of a reaction and the positivity of the test [18].

- The limited number of ICM tested. In fact, the ICM used were variable depending on their availability in the hospital. One patient, who had a hypersensitivity reaction to iopamidol in 2016, was not tested with the injected ICM, which was not available when the tests were performed. To increase the sensitivity of skin tests, especially when the ICM injected is not known, some teams performed skin tests with the higher possible number of ICMs, in order to increase the chance of testing the injected ICM [20].

- The time taken to perform skin tests in relation to the event (17 patients had skin tests beyond 6 months): the sensitivity of skin tests decreases over time [18].

- The specificity of skin tests was estimated at 96-100%. A positive skin test suggests an immunoallergic mechanism [21]. In our series, among the patients with negative skin tests, 11 patients had a re-injection of ICM: nine patients with a different ICM from the one previously injected, and two patients with the same ICM. Of these nine patients, two developed a hypersensitivity reaction:

- The first presented the same reaction again, with another ICM, although this ICM was tested negative. This result suggests a nonspecific histamine release which is the most frequently observed mechanism (90% of reactions) [8].

- The second patient presented the same delayed reaction (dyspnea) with the same ICM, although the test was negative. The sensitivity of skin tests seems to be low with late reactions.

- Skin tests with a large panel of ICM could explore cross-reactions which are considered if skin tests and/or provocation tests were positive with two or more ICM tested. A classification of ICM was proposed based on the frequency of cross-reactions [1]. However, cross-reactions should be considered carefully since:

- A positive skin test to one or more ICM does not mean a cross hypersensitivity reaction. The methodology of skin testing is of crucial importance. A skin test performed with nondiluted ICM can give false positives, and therefore wrongly identify cross-reactivity.

- Similarly, a provocation test or even a re-use of an ICM tested negatively can induce a new hypersensitivity reaction related to a nonspecific histamine release and therefore to a nonallergic mechanism.

- Only a formally positive tryptase assay, performed on an emergency sample simultaneously at the time of the reaction, can confirm the immunoallergic mechanism and, therefore, cross-reactivity.

- The use of skin tests in hypersensitivity reactions to ICM is not consensual. The French Radiology Society [9], as well as the European Society of Urogenital Radiology [22], indicates an allergological assessment based on skin tests. However, the American College of Radiology suggests

not performing skin tests because of the high rate of nonspecific histamine-release reactions. The true allergy to ICM (IgE-mediated reactions) is rare, affecting 4% of patients with anaphylaxis [8].

Concerning premedication, Tramer reported that corticosteroids reduce the incidence of respiratory signs from 1.4% to 0.4% and cardiovascular and respiratory signs (combined) from 0.9% to 0.2% [23]. Furthermore, antihistamines may be effective in preventing angioedema, and the combined use of antihistamines and corticosteroids could reduce the frequency of dermatological signs [23]. However, the benefit from premedication for severe and serious reactions with non-ionic ICM, of low osmolality, has not been proven [8].

CONCLUSION

Skin tests are simple and safe to perform and can be of great help to radiologists in case of hypersensitivity reactions to ICM. The skin tests made it possible to better choose the ICM, which could be re-used during a subsequent radiological examination. Premedication may also be useful to reduce the incidence of hypersensitivity in case of re-use of ICM.

LIST OF ABBREVIATIONS

ICH	= International Council for Harmonisation
ICM	= Iodinated Contrast Media
IDT	= Intra Dermal Test
NCPV	= National Center of Pharmacovigilance

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Charles Nicolle Hospital committee approved access to the patient information database.

HUMAN AND ANIMAL RIGHTS

No animals were used for studies that are base of this research. All the humans used were in accordance with the ethical standards of the committee responsible for human experimentation (institutional and national), and with the Helsinki Declaration of 1975, as revised in 2013 (<http://ethics.iit.edu/ecodes/node/3931>).

CONSENT FOR PUBLICATION

Written informed consent was obtained from all patients.

STANDARDS OF REPORTING

STROBE guidelines have been followed in this study.

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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