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Immediate hypersensitivity to iodinated contrast media: diagnostic accuracy of skin tests and intravenous provocation test with low dose

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Abstract (<300 words)

Background: The diagnosis of HSR to iodinated contrast media (ICM) ICM is challenging based on clinical history and skin tests.

Objective: This study evaluates the negative predictive value (NPV) of skin tests and intravenous provocation test (IPT) with low-dose ICM in patients with suspected immediate hypersensitivity reaction (HSR) to ICM.

Methods: Thirty seven patients with suspected immediate hypersensitivity reaction to ICM were included retrospectively. Skin tests and a single-blind placebo-controlled intravenous provocation test (IPT) with low-dose iodinated contrast media (ICM) were performed.

Results: Skin tests with ICM were positive in 5 cases (1 skin prick test and 5 intradermal test). Thirty-six patients were challenged successfully by IPT, and only 1 patient had a positive challenge result, with a grade I reaction by the Ring and Messmer classification. Ten of 23 patients followed up by telephone were re-exposed to a negative tested ICM during radiologic examination; 2 experienced a grade I immediate reaction.

Conclusions & Clinical Relevance: For immediate hypersensitivity reaction to ICM, the NPV for skin tests and IPT with low-dose was 80% (95% CI 44-97%).

Introduction

Iodinated contrast media (ICM) is widely used and generally well tolerated. Immediate hypersensitivity reaction (HSR) (<1 hr after ICM injection) or delayed (>1 hr after ICM injection) can occur in about 1% to 3% of patients [1]; most of these reactions are not allergic [2]. Immediate HSR is more frequent with ionic than nonionic ICM: [3, 4, 5, 6] 3.8% to 12.7% and 0.7% to 3.1%, respectively. ICM are tri-iodinated benzene derivatives with different side chains, which can be classified into four groups according to their chemical structure and to their osmolality. Because of the predominant use of newer-generation nonionic ICM, HSRs are less common today than in the past [7]. The mortality of immediate HSR to ICM and cross-reactivity between ICM remain unknown. The diagnosis of HSR to ICM is challenging, based on clinical history and skin tests [8]. In this study, we evaluated the negative predictive value (NPV) of skin tests and intravenous provocation test (IPT) with low-dose ICM in patients with suspected immediate HSR to ICM.

Patients and methods

This retrospective study was conducted from January 2013 to August 2014 in the department of dermatology and allergy at Tenon Hospital and was approved by the local ethics committee. We enrolled only patients with a definite history of immediate HSR due to ICM (patients addressed for exploration to ICM allergy during shellfish or seafood allergies or for predictive allergologic skin tests without prior administration to ICM were excluded.) (Figure 1). The severity of reaction was assessed by the Ring and Messmer classification [9]. Skin tests were performed at least 6 weeks after the HSR on the volar forearm with the suspected ICM and with 4 other ICM.

Skin prick tests (SPTs) involved freshly prepared undiluted ICM commercial solutions (ioxithalamate 350 mg/mL, ioxaglate 320 mg/mL, iohexol 300 mg/mL, iomeprol 350 mg/mL, iodixanol 320 mg/mL, iopromide 300 mg/mL, ioversol 350 mg/mL, and iobitriol 350 mg/mL), and intradermal tests (IDTs) were performed successively with 100-fold, then 10-fold solution diluted in 0.9% sterile saline. Saline and chlorhydrate histamine (10 mg/mL, Stallergènes, France) were negative and positive controls, respectively. Systematic latex SPT was also performed (Alyostal prick, Stallergènes, France). Readings were performed at 20 min. SPT results were considered positive with a wheal of ≥ 3 mm in diameter observed at 20 min and IDT results if the initial wheal had increased by at least 3 mm in diameter with erythema.

After signed informed consent from the patient, a single-blind placebo-controlled IPT was performed with the suspected ICM when the skin test result remained negative and the reaction was not life-threatening and with another ICM if the skin test result was positive with the suspected ICM, if the patient requested a particular ICM or if the adverse reaction was severe (grade III or IV by the Ring and Messmer classification [9]). The challenge was performed during a 1-day hospital stay, with intravenous access and strict supervision of blood pressure, heart rate, and oxygen saturation before, during and up to 6 hr after the challenge. It was a single-blind placebo-controlled challenge; first 10 mL of saline (placebo) had been intravenously administered and two hours later 10 mL of ICM. No premedication was administered. The IPT result was considered positive if oxygen saturation decreased below 90% and/or if blood pressure decreased of more than 30 % and/or a skin eruption (urticaria, angioedema or maculopapular rash) occurred up to 2 hr after the challenge.

Patients were followed up by telephone survey after skin tests to determine whether they had been re-exposed to ICM during subsequent radiologic examination after our tests and to learn the outcome (Figure 1). The NPV for skin tests and IPT was defined as the proportion of patients with a negative skin-test result to at least one ICM, an uneventful IPT and

uneventful re-exposure to ICM during subsequent radiologic examination. The 95% confidence interval (95% CI) was calculated with the Pearson-Clopper method in R 3.0.1.

Results

In total, 37 patients (24 women, mean age 49.3 years at the time of the reaction) completed the tests. The clinical severity of the reaction was grade I for 26 (70%), grade II for 4 (11%), and grade III for 7 (19%); 35 (95%) reported skin or mucosal symptoms, including pruritus (n=11), facial erythema (n=6), generalized erythema (n=20), urticaria (n=7) and angioedema (n=5). Atopy history was reported for 6 patients (16%) and spontaneous chronic urticaria for another 5 (14%); 6 (16%) had a confirmed drug or food allergy (one with contact urticaria to fish). For 25 patients (67.6%), the suspected culprit ICM was known, for 34 (92%), the ICM injection was intravenous whereas 3 had intra-arterial ICM injection (during coronarography procedure, patients N° 22, 25 and 26 Table 1) with severe immediate HSR (grade III). Because of the severity of the reactions an intravenous challenge (IPT) had been decided. The 3 patients had successfully provoked with the culprit ICM for one (with successfully re-exposure) and with another ICM for 2 other patients.

The median delay between the reaction and skin testing was 2.0 years (range 0.25–34 years). For 15 patients (40%), skin tests with ICM were performed during the year after the HSR. A total of 5 patients (4 with grade I reaction and 1 with grade III reaction) had at least one positive skin-test result, from an SPT in 1 case and an IDT in 5 others (patient N°5 had positive IDT test results for two ICM; iomeprol and iohexol); 3 of them had been tested in the next 12 months the reaction while 2 other patients had been tested respectively 15 years and 2 years later. The characteristics of the immediate HSR, skin tests and IPT are in Table 1.

The rate of a positive skin-test result was 13.5% (95% CI 4–29%) and increased to 20% (95% CI 4-48%) for patients who consulted during the year after the HSR. The 5 patients with a positive skin-test result were challenged successfully by IPT with a negative tested ICM. Among the 32 patients with negative skin-test results, 31 were challenged successfully, 15 with the culprit ICM. One grade I reaction occurred 2 hr after challenge (generalized pruritus, erythema and eyelid oedema lasting < 1 hr) and was considered a positive IPT result. At 2 hr after IPT, 2 patients reported generalized and isolated pruritus that regressed with antihistamine therapy and was not considered a positive IPT result. Among the 29 negatively tested and challenged patients (Table 1; patient N° 9 to 26), culprit ICM was known in 18 of them. 14 of the 18 patients were provoked with the culprit ICM tested negatively (patient N° 9 to 22) and 4 patients were provoked with an alternative (patient N° 23 to 26). In the 33% of cases where the ICM was not known, 6 were provoked with iodixanol, 3 with iomeprol, 2 with iohexol and one with ioxaglate. Iodixanol was chosen as often as possible, but some patients requested a particular ICM. Ten of 23 patients followed up by telephone were re-exposed to a negative tested ICM during radiologic examination; 2 experienced an immediate reaction: one had an itchy rash a few minutes after ICM injection that lasted 30 min, and one had an eruption 3 hr after the procedure that lasted < 1 hr. None of 5 patients with positive skin test to ICM were re-exposed to contrast media during radiologic examination. No premedication was used for these 2 patients before or during the radiologic procedure.

For an immediate HSR to ICM, the NPV for skin tests and IPT with low-dose was 80% (95% CI 44-97%).

Discussion

In our study, the rate of a positive skin-test result for immediate HSR was 13.5%. This result agrees with the literature: 17% (95% CI 10-26%) from a recent meta-analysis [10] and 10.4% from another study [11]. The long delay between the reaction and the skin test could induce a loss of sensitization and explain the lower rate of positive skin-test results we found. Our rate of positive skin-test results increased to 20% when skin tests were performed during the year after the HSR, as was reported in other studies [8, 11, 12, 13, 14].

In our study, the culprit ICM remained unknown for 32.4% patients as compared with 39.1% in the Caimmi *et al.* study [14]. Overall, 36 of our 37 patients were challenged successfully by IPT with low-dose ICM and only one had a grade I reaction. Two other patients probably experienced a nonspecific histamine release [2] because the reaction disappeared with antihistaminic treatment and was no more serious than the first reaction.

Ten of our 23 patients followed up underwent rechallenge with a negative tested ICM on radiologic examination; 2 experienced a grade I reaction. We cannot make a firm statement regarding the nature of these reactions, allergic or not, but no severe reactions were reported. To date, only 3 studies reported successful ICM challenge in 2 and 5 patients with immediate HSR [11, 15]; the studies involved increasing doses of ICM administered at 30-min intervals up to a total dose, which varied from 120 mL for 4 patients to 49.05 mL for 2 patients and 24 mL for 1 patient. Salas *et al.* reported eight patients with confirmed immediate HSR, 5 (62.5%) by skin tests and 3 (37.5%) by ICM challenge in 90 patients suspected of immediate HSR to ICM [16]. In this study the dose of ICM administrated for each patient varied between 5 until 100 mL [16].

For delayed HSR, one study found successful ICM challenge in 4 patients with a total dose of 53.5 mL ICM [17] and another study reported a positive ICM challenge (up to 10^{-1} of the

usual dose) in 5/12 patients with negative skin-test results [18]. Torres *et al.* reported in 78 of 161 patients a confirmed delayed HSR; 34 (43.6%) by skin testing and 44 (56.4%) by drug provocation test (up to cumulative dose of 100 mL) [19]. A recent study on cross-reactivity among ICM in 97 patients (38 immediate, 50 delayed and 9 not recorded HSR) with at least one positive skin-test result and/or nontolerated challenge (up to 10^{-1} of the usual dose) identified 3 subgroups of ICM in which cross-reactions were frequent; group A (iodixanol, iopamidol, iomeprol, iohexol, ioversol, and ioxitalamate), group B (ioxaglate and iobitridol) and group C with an isolated ICM amidotrizoate. This new ICM classification seemed been statistically significant in delayed HSR [20]. The volume of ICM injected during a radiologic examination varies from 10 to 200 mL. The injected ICM volume was lower in our study than in other studies (i.e., 10 mL) to avoid the risk of acute kidney injury [21]. Renal failure after ICM injection ranges from 2% to 50% depending on the study and the associated comorbidities [22, 23]. Our NPV rates for skin tests and IPT with low-dose was 80% (95% CI 44-97%), and are close to the 96.6% found in the Caimmi *et al.* study [14] of 29 patients with a history of HSR that was immediate, delayed and unknown for 24, 4 and 1 patients, respectively, who were challenged during a radiologic procedure after a negative skin-test result.

Our study had several limitations. First, because of its retrospective nature, some data on serum tryptase levels and precise clinical descriptions were missing. Second, the culprit ICM was unknown for 32% of the patients, which was a major limitation in interpreting the skin tests. Finally, after completing the study, we had data for only a few patients who were re-exposed on radiologic examination. Further multicentre prospective studies with larger samples of patients are needed to conclude on the interest of challenge with low-dose ICM as a complement to skin tests. According to our results, when results of skin tests and challenge with low-dose ICM are negative, premedication with antihistamines may be needed to prevent a nonspecific histamine release during ICM re-exposure.

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Conflict of interest's statement: No relevant competing interests

Figure legends:

Figure 1: Flow chart of the study

Table 1: Characteristics of the 37 patients with immediate hypersensitivity reaction (HSR) to iodinated contrast media (ICM).

N°	Culprit ICM	Time between original reaction and testing (years)	Severity of immediate HSR (grade I/II/III)*	Skin prick tests														Intradermal tests (10-fold diluted in saline)**																Intravenous provocation test ICM/positive or negative result	Re-exposure to ICM on radiologic examination/positive or negative re-exposure			
				lomeprol		lodixanol		loxaglate		loxithalamate		loversol		lobitriol		lopromide		lohexol		lomeprol		lodixanol		loxaglate		loxithalamate		loversol		lobitriol		lopromide				lohexol		
				W	E	W	E	W	E	W	E	W	E	W	E	W	E	W	E	W	E	W	E	W	E	W	E	W	E	W	E	W	E					
Positive skin test																																						
1	lobitriol	1	I	ND	ND	0	0	0	0	0	0	ND	ND	0	0	ND	ND	0	0	ND	ND	0	0	0	0	0	0	ND	ND	7	20	ND	ND	0	0	lodixanol/-	NK	
2	lopromide	0.83	I	0	0	0	0	ND	ND	ND	ND	ND	ND	ND	ND	0	0	0	0	0	0	0	0	ND	ND	ND	ND	ND	ND	ND	8	8	ND	ND	lodixanol /-	No		
3	loxaglate	2	I	0	0	0	0	9	20	0	0	ND	ND	ND	ND	ND	ND	0	0	ND	ND	0	0	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	lodixanol /-	No	
4	loxaglate	15	I	0	0	0	0	0	0	0	0	ND	ND	ND	ND	ND	ND	0	0	0	0	0	0	9	35	0	0	ND	ND	ND	ND	ND	ND	0	0	lohexol/-	No	
5	lomeprol	1	III	0	0	0	0	0	0	ND	ND	ND	ND	ND	ND	ND	ND	0	0	10	20	0	0	0	0	ND	ND	ND	ND	ND	ND	ND	ND	10	20	loxaglate/-	No	
Negative skin test																																						
Positive intravenous provocation test																																						
6	lomeprol	1	I	0	0	0	0	ND	ND	ND	ND	ND	ND	0	0	ND	ND	0	0	0	0	0	0	ND	ND	ND	ND	ND	ND	0	0	ND	ND	0	0	lodixanol/+ (generalized pruritus, erythema and eyelid oedema)	No	
Positive re-exposure																																						
7	lohexol	1	I	0	0	0	0	ND	ND	ND	ND	ND	ND	ND	ND	0	0	0	0	0	0	0	ND	ND	ND	ND	ND	ND	ND	ND	ND	0	0	0	0	lohexol/-	lohexol/+ (itchy rash a few minutes after the exposure)	
8	NK	13	II	ND	ND	0	0	0	0	0	0	ND	ND	ND	ND	ND	ND	0	0	ND	ND	0	0	0	0	0	0	ND	ND	ND	ND	ND	ND	0	0	lodixanol /-	lodixanol/+ (rash 3 hr after exposure)	
Negative skin tests and intravenous provocation tests +/- negative re-exposure																																						
9	lobitriol	4	I	ND	ND	0	0	0	0	0	0	ND	ND	0	0	ND	ND	ND	ND	ND	ND	0	0	0	0	0	0	ND	ND	0	0	ND	ND	ND	ND	lobitriol/-	NK	
10	lobitriol	0.5	I	0	0	ND	ND	ND	ND	ND	ND	ND	ND	0	0	0	0	0	0	0	0	ND	ND	ND	ND	ND	ND	ND	ND	0	0	0	0	0	0	lobitriol/-	NK	
11	lodixanol	8	I	0	0	0	0	0	0	0	0	ND	ND	0	0	ND	ND	0	0	ND	ND	0	0	0	0	0	0	ND	ND	0	0	ND	ND	0	0	lodixanol /-	NK	
12	lodixanol	13	I	0	0	0	0	ND	ND	ND	ND	ND	ND	0	0	ND	ND	0	0	0	0	0	0	ND	ND	ND	ND	ND	ND	0	0	ND	ND	0	0	lodixanol /-	NK	
13	lodixanol	1	I	0	0	0	0	0	0	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	0	0	0	0	0	0	0	ND	ND	ND	ND	ND	ND	ND	ND	ND	lodixanol /-	NK	
14	lohexol	2	I	0	0	0	0	0	0	ND	ND	ND	ND	ND	ND	ND	ND	0	0	0	0	0	0	0	0	0	ND	ND	ND	ND	ND	ND	ND	0	0	lohexol/-	lohexol/-	
15	lomeprol	1	I	0	0	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	0	0	0	0	0	0	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	0	0	0	0	lomeprol/-	NK
16	lomeprol	0.41	I	0	0	0	0	0	0	0	0	ND	ND	ND	ND	ND	ND	0	0	0	0	0	0	0	0	0	ND	ND	ND	ND	ND	ND	ND	0	0	lomeprol/-	NK	
17	lomeprol	0.67	I	0	0	0	0	0	0	0	0	ND	ND	ND	ND	ND	ND	0	0	0	0	0	0	0	0	0	ND	ND	ND	ND	ND	ND	ND	0	0	lomeprol/-	No	
18	loversol	0.25	I	0	0	ND	ND	ND	ND	ND	ND	0	0	ND	ND	0	0	0	0	0	0	ND	ND	ND	ND	ND	ND	0	0	ND	ND	ND	ND	0	0	loversol/-	loversol/-	
19	loversol	6	I	0	0	0	0	0	0	0	0	0	0	ND	ND	ND	ND	0	0	0	0	0	0	0	0	0	0	0	0	ND	ND	ND	ND	0	0	loversol/-	NK	
20	loxaglate	12	I	0	0	0	0	0	0	0	0	ND	ND	ND	ND	ND	ND	0	0	0	0	0	0	0	0	0	0	ND	ND	ND	ND	ND	ND	0	0	loxaglate/-	NK	
21	lopromide	1	II	0	0	0	0	0	0	ND	ND	ND	ND	ND	ND	0	0	ND	ND	0	0	0	0	0	0	0	ND	ND	ND	ND	ND	0	0	ND	ND	lopromide/-	lopromide/-	
22	lobitriol	0.25	III	0	0	0	0	0	0	0	0	ND	ND	0	0	ND	ND	0	0	0	0	0	0	0	0	0	0	ND	ND	0	0	ND	ND	0	0	lobitriol/-	lobitriol/-	

23	loversol	5	I	ND	ND	0	0	ND	ND	ND	ND	0	0	ND	ND	ND	ND	ND	ND	ND	0	0	ND	ND	ND	ND	0	0	ND	ND	ND	ND	ND	ND	iodixanol /-	NK		
24	loversol	12	II	0	0	0	0	0	0	ND	ND	0	0	ND	ND	ND	ND	0	0	0	0	0	0	0	ND	ND	0	0	ND	ND	ND	ND	0	0	iodixanol /-	NK		
25	lohexol\$	0.5	III	0	0	0	0	0	0	0	0	ND	ND	ND	ND	ND	ND	0	0	0	0	0	0	0	0	0	ND	ND	ND	ND	ND	ND	0	0	lomeprol/-	No		
26	loxaglate\$	0.67	III	0	0	0	0	0	0	0	0	ND	ND	ND	ND	ND	ND	0	0	0	0	0	0	0	0	0	ND	ND	ND	ND	ND	ND	0	0	lomeprol/-	No		
27	NK	2	I	0	0	0	0	0	0	ND	ND	ND	ND	ND	ND	ND	ND	0	0	0	0	0	0	0	0	ND	ND	ND	ND	ND	ND	ND	0	0	iodixanol/- (pruritus)	iodixanol/-		
28	NK	18	I	0	0	0	0	0	0	ND	ND	ND	ND	0	0	0	0	0	0	0	0	0	0	0	0	ND	ND	ND	ND	0	0	0	0	0	0	lohexol/-	lohexol/-	
29	NK	3	I	0	0	0	0	0	0	0	0	ND	ND	ND	ND	ND	ND	0	0	0	0	0	0	0	0	0	ND	ND	ND	ND	ND	ND	0	0	lomeprol/-	lomeprol/-		
30	NK	34	I	0	0	0	0	0	0	ND	ND	ND	ND	0	0	ND	ND	ND	ND	0	0	0	0	0	0	0	ND	ND	ND	ND	0	0	ND	ND	ND	ND	iodixanol/-	NK
31	NK	26	I	0	0	0	0	0	0	ND	ND	ND	ND	0	0	ND	ND	0	0	0	0	0	0	0	0	ND	ND	ND	ND	0	0	ND	ND	0	0	iodixanol/- (pruritus)	No	
32	NK	2	I	0	0	0	0	0	0	ND	ND	ND	ND	ND	ND	ND	ND	0	0	0	0	0	0	0	0	ND	ND	ND	ND	ND	ND	ND	ND	0	0	lomeprol/-	No	
33	NK	31	I	0	0	0	0	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	0	0	0	0	0	0	0	0	ND	ND	ND	ND	ND	ND	ND	ND	0	0	iodixanol /-	No	
34	NK	0.67	II	0	0	0	0	0	0	ND	ND	ND	ND	ND	ND	ND	ND	0	0	0	0	0	0	0	0	ND	ND	ND	ND	ND	ND	ND	ND	0	0	iodixanol /-	No	
35	NK	33	III	0	0	0	0	0	0	ND	ND	ND	ND	ND	ND	ND	ND	0	0	0	0	0	0	0	0	ND	ND	ND	ND	ND	ND	ND	ND	0	0	lomeprol/-	lomeprol/-	
36	NK	18	III	0	0	0	0	0	0	ND	ND	ND	ND	ND	ND	ND	ND	0	0	0	0	0	0	0	0	ND	ND	ND	ND	ND	ND	ND	ND	0	0	loxaglate/-	NK	
37	NK	2	III	0	0	0	0	0	0	0	0	ND	ND	ND	ND	ND	ND	0	0	0	0	0	0	0	0	0	ND	ND	ND	ND	ND	ND	ND	0	0	lohexol/-	No	

Table 1: Characteristics of the studied population

Grade I: generalized cutaneous and/or mucocutaneous symptoms; grade II mild systemic reactions: grade III: life-threatening systemic reactions, grade IV: cardiac and/or respiratory arrest. *No grade IV severity reaction in this study.

ICM: iodinated contrast media. Skin tests: W: wheal size of skin test in mm, E: erythema size of skin test in mm, ND: not done. Re-exposure to ICM: NK: not know, No: no re-exposure. ** Intradermal tests 100-fold diluted in saline were not showed, but none were positive. \$ Patients with intra-arterial ICM administration during original reaction.

Sese et al. Figure 1: Flow chart of the study

