

Allergological workup with half-dose challenge in iodinated contrast media hypersensitivity

To the Editor,

The diagnosis of hypersensitivity reaction (HSR) to iodinated contrast media (ICM) is challenging when based on clinical history and skin tests. ICM re-exposure is the gold standard. The ICM dose for intravenous provocation tests (IPTs) during allergological workup lacks consensus. Nine studies reported various modalities and doses for ICM challenge (10–120 mL), with negative predictive value (NPV) of skin tests vs challenge ranging from 37.5% to 100%^{1–7,10} (Table 1). A cross-reactivity classification of ICM in three subgroups was proposed by Lerondeau et al.⁸

The objective of this prospective study was to determine the NPV for skin tests as compared with IPT 50 mL, which is half the usual dose for radiologic explorations.

In a bicenter study, during 12 consecutive months, all patients with suspected HSR to ICM were included. According to recommendations,⁹ skin tests (prick tests, intradermal tests [IDTs]) were performed with the culprit ICM whenever it was known and at least 3 other ICM, and when a delayed reaction was suspected, patch tests and IDT with readings after day 2 were performed. A single-blind placebo-controlled IPT was performed during a 1-day hospital stay, with strict

supervision up to 6 hours after the challenge. All injections were intravenous, with a 2-minutes injection, beginning with the placebo (20 mL saline), followed successively with 20 and 30 mL ICM at 2-hour intervals (2-step protocol). With Grade 3 HSR, the challenge involved three successive steps: 5, 15, and 30 mL with a 1.5-hour interval. The IPT was reduced to 10 mL with glomerular filtration rate (GFR) < 30 mL/min and to 30 mL with GFR 60–30 mL/min.

One hundred and seventeen patients were included (mean age 58 years, range 20–87 years; 71% women). For 75 patients, the culprit ICM was known and was skin-tested with at least three other ICM; iomeprol, iodixanol, iohexol, and ioxitalamic acid for 112, 112, 109, and 102 patients, respectively (see Table S1). In all, 81 patients had an initial immediate HSR and 32 delayed HSR; in 4, the type of reaction was unknown. Sixteen patients reported Grade 3 HSR, and another had Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome (Figure 1A).

Overall, 110 patients had a single-blind IPT with the culprit ICM if the skin tests were negative or a substitutive ICM if positive. IPT was considered positive with saturation decreased < 90% and/or blood pressure decreased by >30% and/or a skin eruption

TABLE 1 Dose, number of patients challenged, and negative predictive value (NPV) of skin tests with iodinated contrast media (ICM) in the literature and this study

HSR type	Reference	No. of patients challenged	Challenge dose	NPV for skin tests (compared to challenge tests)
Immediate HSR	Trcka et al ²	2	49.05 mL	100%
	Salas et al ³	8 (and 14 challenges with various ICM)	100 mL	37.5%
	Prieto-Garcia et al ⁴	5	120 mL (n = 3), 24 mL (n = 1), 14 mL (n = 1)	100%
	Sese et al ¹	37	10 mL	97.3% 2/10 positive re-exposure after negative IPT 10 mL NPV of IPT 10 mL compared to real-life re-exposure: 80%
	Morales Cabeza, et al ⁵	12 (and 13 challenge with various ICM)	Day 1: 5, 30, and 60 mL Day 2: 120 mL (infusion time 5 min)	91.6%
Delayed HSR	Vernassiere et al ⁶	5	10 mL	66.6%
	Seitz CS, et al ¹⁰	4	53.5 mL	100%
	Torres et al ⁷	34 (and 42 challenge with various ICM)	100 mL (cumulative dose)	67.6%
Immediate and delayed HSR	Lerondeau et al ⁸	97	10 mL	93.8%
	Present study	110	50 mL	81.8%

HSR, hypersensitivity reaction; ICM, iodinated contrast media; NPV, negative predictive value.

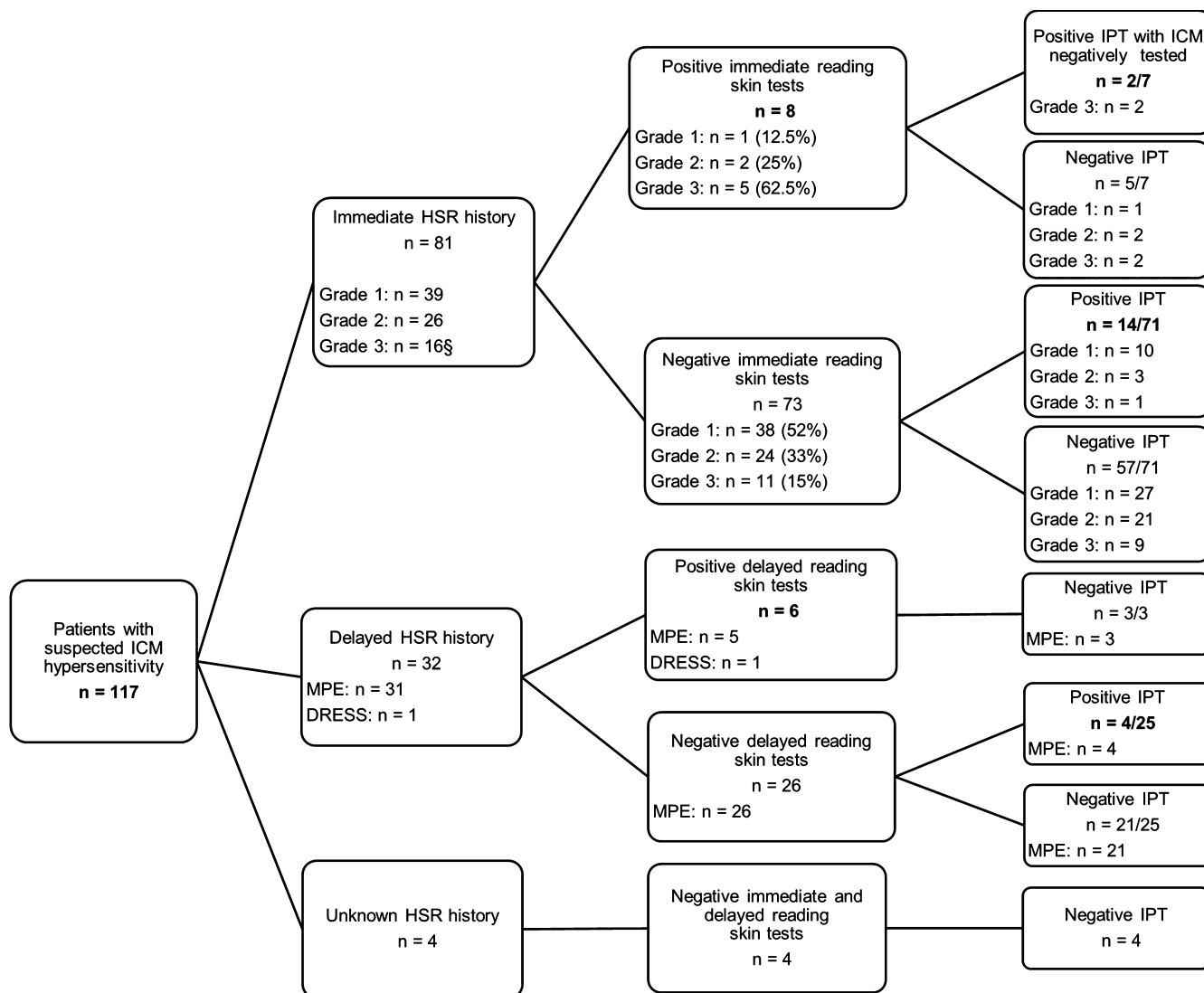


FIGURE 1 A, Allergological workup and type of hypersensitivity reaction (HSR) to iodinated contrast media (ICM), B, Skin tests, challenge and basophil activation test results. BAT, basophil activation test; DRESS, Drug Reaction with Eosinophilia and Systemic Symptoms; IOB, iobitridol; IOD, iodixanol; IOH, iohexol; IOM, iomeprol; IOP, iopamidol; IOPR, iopromide; IOV, ioversol; IOXAG, ioxaglic acid; IOXIT, ioxitalamic acid; IPT, intravenous provocation test; MA, meglumine amidotrizoate. MPE, maculopapular exanthema. §Grade 3 patients had low blood pressure (n = 12), anaphylactic shock with use of epinephrine (n = 6), bronchospasm (n = 6), loss of consciousness (n = 8), abdominal manifestations (n = 4), and rash/urticaria (n = 8). £: ICM cross-reactivity classification (by Lerondeau et al⁸): Group A: IOXIT, IOP, IOD, IOM, IOV, IOH; Group B: IOB, IOXAG; Group C: MA. Group not defined: IOPR. *skin tests with delayed readings

and/or other clinical anaphylactic manifestations occurring up to 2 hours after the IPT for immediate HSR and cutaneous eruption occurring up to 7 days after the challenge, with similar clinical characteristics as those with the initial reaction for delayed HSR. Seven patients were not challenged: 2 (patients 12 and 14) because of positivity for all skin tests for maculopapular exanthema and because of severe DRESS syndrome (Figure 1B); the five others were lost to follow-up.

For GFR, the IPT volume was reduced to 10 mL in one case and to 30 mL in four cases and was 50 mL in the remaining 105 cases.

The allergological workup was positive in 32 patients (27%): 22 and 10 with immediate and delayed HSR history (Figure 1). Fourteen patients had positive skin tests, six with delayed readings (three

patch tests and three IDT) and the other eight with immediate readings (two prick tests and six IDT) (Figure 1). For the six cases with delayed HSR, cross-reactivities with ICM occurred between Group A and Group B (patients 9–14).

The mean time between the reaction and the allergological workup was 104.4 months and was 24.6 and 38.88 months with immediate and delayed positive skin test results, respectively, and 11.76 and 4.08 months with immediate and delayed positive IPT results.

Among 110 IPT, 20 patients (18%) had a positive IPT but skin tests were negative: 16 and 4 had immediate and delayed HSR. Fourteen of the 16 patients with Grade 3 immediate HSR had an IPT, which was positive in three cases (patients 5, 7, 28; Figure 1B). Patient 28 had a severe positive IPT with atypical Grade 3 reaction

Patient number	Type of HSR	Culprit ICM	Time between original reaction and testing (months)	Skin tests ± (group)£	IPT ± (group) type of HSR (step of IPT)	BAT ± (group)
Immediate positive skin tests						
1	Grade 1	IOB	116	IOB+ (B) IOM- (A), IOH- (A), IOD- (A)	IOD- (A)	Not done
2	Grade 2	IOPR	7	IOPR+ (group not defined) IOXAG- (B), IOM- (A), IOH- (A), IOD- (A), IOXIT- (A)	IOD- (A)	Not done
3	Grade 2	IOP	4	IOP+ (A) IOXAG- (B), IOM- (A), IOH- (A), IOD- (A), IOXIT- (A)	IOD- (A)	IOXIT- (A), IOM- (A), IOD- (A), IOXAG- (B), IOB- (B), MA- (C)
4	Grade 3	IOXAG	14	IOXAG+ (B) IOM- (A), IOH- (A), IOD- (A), IOXIT- (A)	IOD- (A)	IOM- (A), IOH- (A), IOXIT- (A), IOD- (A), IOXAG- (B), IOB- (B), MA- (C)
5	Grade 3	IOV	2	IOV+ (A) IOXAG- (B), IOM- (A), IOH- (A), IOD- (A), IOXIT- (A)	IOD+ (A) Grade 1 (after third step)	IOD+ (A), IOM+ (A), IOB+ (B) IOXIT- (A), IOXAG- (B), IOH- (A), MA- (C)
6	Grade 3	IOP	13	IOPR+ (group not defined) IOXAG- (B), IOM- (A), IOH- (A), IOD- (A), IOXIT- (A)	Not done (lost to follow-up)	Not done
7	Grade 3	IOM	6.5	IOM+ (A), IOPR+ (group not defined) IOXAG- (B), IOH- (A), IOD- (A), IOXIT- (A), IOV- (A), IOP- (A), IOB- (B)	IOD+ (A) Grade 1 (after third step)	Not done
8	Grade 3	IOPR	35	IOPR+ (group not defined) IOM- (A), IOH- (A), IOB- (B)	IOB- (B)	Not done
Delayed positive skin tests						
9	MPE	IOH	181	*IOM+ (A), IOH+ (A), IOD+ (A), IOXIT+ (A), *IOXAG- (B), IOPR- (group not defined)	IOXAG- (B)	Not done
10	MPE	IOM	21	*IOH+ (A), *IOXAG- (B), *IOM- (A), IOD- (A), IOXIT- (A),	IOM- (A)	Not done
11	MPE	IOXAG	12.5	*IOM+ (A), IOH+ (A), IOD+ (A), *IOXAG- (B), IOXIT- (A),	IOXIT- (A)	Not done
12	MPE	IOPR	2	*IOM+ (A), IOH+ (A), IOD+ (A), IOXIT+ (A), IOV+ (A), IOP+ (A), IOPR+ (group not defined), IOXAG+ (B), IOB+ (B), MA- (C)	Not done	Not done
13	MPE	IOD	11	*IOXIT+ (A), *IOM- (A), IOH- (A), IOD- (A),	IOH- (A)	Not done
14	DRESS	IOB	7.5	*IOM+ (A), IOH+ (A), IOD+ (A), IOXAG+ (B), IOB+ (B), *IOXIT- (A)	Not done	Not done
Immediate positive IPT for patients with negative skin test						
15	Grade 1	IOM	24.5	IOXAG- (B), IOM- (A), IOH- (A), IOD- (A), IOXIT- (A)	IOM+ (A) Grade 1 (after second step)	Not done
16	Grade 1	IOM	25.5	IOXAG- (B), IOM- (A), IOH- (A), IOD- (A), IOXIT- (A)	IOM+ (A) Grade 1 (after second step)	IOM- (A), IOH- (A), IOXIT- (A), IOD- (A), IOXAG- (B), IOB- (B), MA- (C)
17	Grade 1	IOXAG	14	IOXAG- (B), IOM- (A), IOH- (A), IOD- (A), IOXIT- (A)	IOXAG+ (B) Grade 1 (after second step)	Not done
18	Grade 1	IOM	14.5	IOM- (A), IOH- (A), IOD- (A), IOXIT- (A),	IOM+ (A) Grade 1 (after second step)	Not done
19	Grade 1	unknown	155	IOM- (A), IOH- (A), IOD- (A), IOXIT- (A), IOP- (A)	IOD+ (A) Grade 1 (after third step)	Not done
20	Grade 1	unknown	276	IOM- (A), IOH- (A), IOD- (A), IOXIT- (A)	IOM+ (A) Grade 1 (after third step)	Not done
21	Grade 1	unknown	187.5	IOXAG- (B), IOM- (A), IOH- (A), IOD- (A), IOXIT- (A)	IOP+ (A) Grade 1 (after second step)	Not done
22	Grade 1	IOM	1.5	IOM- (A), IOH- (A), IOD- (A), IOPR- (group not defined)	IOM+ (A) Grade 1 (after second step)	Not done
23	Grade 1	IOM	10	IOM- (A), IOH- (A), IOD- (A)	IOM+ (A) Grade 1 (after third step)	Not done
24	Grade 1	IOB	5.6	IOXAG- (B), IOM- (A), IOH- (A), IOD- (A), IOB- (B)	IOB+ (B) Grade 1 (after third step)	Not done
25	Grade 2	IOM	4	IOXAG- (B), IOM- (A), IOH- (A), IOD- (A), IOXIT- (A)	IOM+ (A) Grade 1 (after second step)	IOM- (A), IOH- (A), IOXIT- (A), IOD- (A), IOXAG- (B), IOB- (B), MA- (C)
26	Grade 2	unknown	319	IOM- (A), IOH- (A), IOD- (A), IOP- (A)	IOM+ (A) Grade 1 (after third step)	Not done
27	Grade 2	IOB	0.3	IOM- (A), IOH- (A), IOD- (A), IOPR- (group not defined), IOB- (B)	IOB+ (B) Grade 1 (after second step)	Not done
28	Grade 3	IOPR	1	IOM- (A), IOD- (A), IOXIT- (A), IOV- (A), IOPR- (group not defined), IOB- (B)	IOPR+ (group not defined) Grade 3 (after third step)	Not done
Delayed positive IPT in negative skin test patients						
29	MPE	unknown	303	*IOXAG- (B), IOM- (A), IOH- (A), IOD- (A)	IOD+ (A) MPE 12 hours after IPT	Not done
30	MPE	IOD	8	*IOXAG- (B), IOM- (A), IOH- (A), IOD- (A), IOXIT- (A)	IOD+ (A) MPE 10 hours after IPT	Not done
31	MPE	IOM	5	*IOM- (A), IOH- (A), IOD- (A), IOXIT- (A)	IOM+ (A) MPE 2 hours after IPT	Not done
32	MPE	IOD	2	*IOM- (A), IOH- (A), IOD- (A),	IOD+ (A) MPE 24 hours after IPT	Not done

FIGURE 1B

(erythema, loss of consciousness, low blood pressure) more than 2 hours after 10 mL iopromide injection but normal tryptase levels (6.1 and 6 µg/L at 2 and 24 hours after the reaction); a non-IgE HSR could be suspected.

As previously reported, many patients with a positive allergological workup 7 of 14 with positive skin test and 12 of 18 with positive IPT did not report previous ICM administration before the initial reaction.

Few studies have evaluated the basophil activation test (BAT) in ICM immediate HSR.^{2,3} BAT was performed in six patients with immediate HSR by quantifying the upregulation of CD63 and CD203c in response to serial dilutions of various ICM; the results were known only after allergological workup. BATs were negative for one patient with negative allergological workup (data not shown), and two had a positive IPT result with iomeprol (patients 16, 25; Figure 1B).

Two had a positive skin test with iopromide (patient 3) and ioxaglic acid (patient 4) with negative BAT for ioxaglic acid; iopromide was not done. One patient had a positive skin test with ioversol, positive IPT, and BAT with iodixanol (patient 5); ioversol was not done. BAT confirmed positive allergological workup in one of six patient and could be useful to determine ICM cross-reactivity, more than for the diagnosis.

Our NPV for skin tests was 81.8%, without any adverse renal effects after IPT with ICM. Because of the various modalities of IPT among available studies, comparing the NPV for skin tests is difficult (Table 1). The different NPVs observed in our two studies, 97.3% NPV with 10 mL IPT vs 81.8% with 50 mL IPT, can be explained by the types of HSR included (only immediate HSR in the first study vs immediate and delayed HSR in the second). The main explanation is the higher number of positive IPT with 50 mL vs 10 mL.

Our study confirms that ICM IPT with 50 mL is useful and well tolerated. However, the modalities need to be better standardized.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Supplemental table S1: Culprit iodinated contrast media and skin tests performed

Culprit ICM/number		Skin tests performed									
		IOXAG	IOM	IOH	IOD	IOXIT	IOV	IOP	IOPR	IOB	MA
	IOXAG/7	7	7	7	7	7	0	0	0	1	0
	IOM/23	19	23	22	23	20	3	1	3	3	0
	IOP/5	4	5	5	5	5	0	5	0	0	0
	IOH/3	3	3	3	3	3	0	0	1	0	0
	IOV/6	3	6	6	6	5	6	0	0	1	0
	IOXIT/1	1	1	1	1	1	0	0	0	0	0
	IOPR/14	7	13	12	13	10	3	1	14	4	2
	IOD/8	5	8	7	8	8	1	1	0	2	0
	IOB/8	6	8	8	8	5	0	1	2	8	0
	NK/42	9	38	38	38	38	0	6	4	7	0
	Total	64	112	109	112	102	13	15	24	26	2

Legends: ICM: iodinated contrast media, IOB: iobitridol, IOD: iodixanol, IOH: iohexol, IOM: iomeprol, IOP: iopamidol, IOPR: iopromide, IOV: ioversol, IOXAG: ioxaglic acid, IOXIT: ioxitalamic acid, MA: meglumine amidotrizoate, NK: ICM not known.