Diagnostic approach to hypersensitivity reactions to iodinated contrast media: a single-center experience on 98 patients

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Abstract

Adverse reactions to iodinated contrast media (ICM) are reported in 1%–3% of diagnostic procedures. They represent a relevant problem involving patients' safety as well as relevant costs for healthcare systems. Premedication with antihistamines and corticosteroids is still widely used, but evidence of its efficacy is lacking and there is a risk for under-estimation of possible severe adverse reactions to ICM in those who undergo premedication.

Data from 98 patients with a previous reaction to ICM that consecutively referred to our unit between 2015 and 2018 were retrospectively analyzed. They underwent an allergologic workup comprehending skin tests and drug provocation tests (DPT) with ICM.

The skin test showed a very high negative predictive value (NPV) compared to DPT in patients with a previous immediate adverse reaction, while the NPV in patients with a previous delayed adverse reaction was lower.

After completion of the allergologic workup, 94 patients (95.9%) could tolerate a DPT with the culprit or alternative ICM.

Subsequently, 90 patients were reached by phone to assess if they had been re-exposed to ICM for radiologic procedure. Thirty-nine patients had been re-exposed, without any premedication in 13 cases: 12 of them had tolerated the ICM, while one reacted again despite a negative DPT with the same ICM. Overall, the NPV of this protocol was elevated (92.3%) for patients undergoing DPT and subsequent exposure to the same ICM in a real-life setting.

Collaboration between the prescribing physician, the radiologist and the allergist, and an accurate allergologic workup are essential to ensure maximum safety for the patient.

Keywords

Contrast media, allergy, hypersensitivity, adverse reaction, premedication

1. Introduction

Iodinated contrast media (ICM) are widely used drugs during radiological imaging and angiographic procedures [1]. They were first introduced in the 1920s and were gradually replaced by more tolerable compounds that are currently classified as follows: nonionic monomers (iopamidol, iohexol, ioversol, iopentol, iomeprol, iobitridol, and iopromide), nonionic dimers (iodixanol) and ionic dimers (ioxaglate) (Table 1).

Hypersensitivity reactions after contrast media injection are usually divided into immediate (IHR), when occurring within 1 hour, and delayed (DHR), when occurring after more than 1 hour to 7 days [2].

The prevalence of adverse reactions to nonionic ICM is about 1%–3% [3]. A consistent part of IHRs is non-IgE-driven and their rate decreased significantly (nowadays 0.7%–3%) after the introduction of nonionic hypo-isosmolar ICM [2]. Severe IHRs are usually IgE-mediated and have a frequency of 0.02%–0.04%, while DHRs could be T-cell mediated and occur in 0.5% to 3% of the administrations [3][4].

According to the European Network for Drug Allergy/European Academy of Allergy and Clinical Immunology (ENDA/EAACI) working group, in a patient with a previous adverse reaction to ICM, an allergological diagnostic workup is required to confirm hypersensitivity and to find a safe alternative ICM [5][6]. The drug provocation test (DPT) is still considered the gold standard to assess tolerability to the drug [5][6].

Nevertheless, the value of the allergologic workup is often underrecognized since scientific societies such as the European Society of Urogenital Radiology and American College of Radiology still rely on the use of premedication protocols (even recognizing their questionable efficacy) or the complete avoidance of ICM [7][8].

Recently, the Società Italiana di Allergologia, Asma ed Immunologia Clinica and the Società Italiana Radiologia Medica e Interventistica, in a joint Italian consensus document, confirmed the importance of an allergologic workup that includes a DPT [1].

In this retrospective study, we evaluated the safety and the accuracy of a diagnostic protocol that includes skin tests and DPT for patients with a previous adverse reaction to ICM.

2. Materials and Methods

2.1 Study population

We carried out a retrospective study on a population of patients who consecutively referred to our Allergology Unit from 2015 to 2018 for adverse reactions to ICM. Ninety-eight patients were evaluated and included in the study; the characteristics of our study population are shown in Table 2.

All patients signed an informed consent for the diagnostic procedure. All patients were treated according to the Helsinki declaration ethical principles.

The adverse reactions to ICM were classified according to the literature (IHR, <1 hour after ICM administration; DHR >1 hour after ICM administration) [2].

Ring and Messmer severity scale (grades 1–4) was used for classification of IHRs [9], while DHRs were graded as mild (no treatment was required), moderate (the patient responded to appropriate treatment without hospitalization), and severe (the reaction required hospitalization or was life-unreatening) [10].

MS Excel (Microsoft Corporation, Redmond, WA, USA) was used for statistical analysis.

2.2 Skin tests and in vitro tests

Patients underwent skin tests for ICM according to ENDA criteria with the culprit (when known) and with the ICM commonly used in our geographic area (iohexol, iopromide, iodixanol, iopamidol, ioversol) [5].

Briefly, we performed skin prick tests on the volar surface of the forearm with undiluted ICM; positive (histamine 0.01%) and negative controls (saline solution NaCl 0.9%) and latex prick test (Alk-Abellò, Hørsholm, Denmark) were also included. If the ICM prick tests were negative, intradermal tests (IDT) with a 1:10 dilution were performed.
The result was considered positive in case of a wheal reaction with a mean diameter of ≥3 mm with surrounding erythema 15 minutes after the prick test and 20 minutes after IDT; we also reevaluated the skin reactions 48/72 hours after IDT [2].
Basal tryptase level (ThermoFisher Scientific, Uppsala, Sweden) was assessed in patients who had experienced more severe reactions (grade ≥ 3 IHR and moderate/severe DHR).

2.3 Drug provocation tests (DPT)

The ICM for the DPT was chosen according to the results of skin tests and the characteristics of the index reaction. In case of a mild (grade I according to Ring and Messmer in case of a previous DHR), recent (<12 months) reaction with negative skin tests for the culprit (when known), tolerance toward the culprit ICM was proposed. DPT with an alternative ICM was performed in those who did not agree to be challenged with the culprit ICM and in all the other patients not included in the aforementioned situation.
The dose ICM to be tested was decided according to international literature (total volume 95 mL) [11][12], independently of the subject body weight [6]. In case of non-allergologic contraindications to ICM administration (e.g., kidney failure), the patient was excluded from the diagnostic protocol and the case was discussed with the referring physician.
The challenge required a 6-hour in-hospital stay, with supervision of trained medical staff and emergency equipment and an on-call emergency team available.
Briefly, in patients with a previous IHR, the DPT started with a placebo consisting of 50 mL of saline solution, and then the chosen ICM was administered intravenously with an infusion volume of 5 mL, 30 and then 60 mL (cumulative dose, 95 mL), respectively, at 30-minute intervals. An infusion pump was used for this purpose (Infusomat Space Neutrapur; B. Braun, Melsungen, Germany).
In case of DHR, the contrast media was administered in two separate sessions with an interval of 7–14 days in between; 50 mL of saline solution followed by 5 and 30 mL of ICM on the first day, and 30 and 60 mL of ICM on the second session.
Subsequent telephone follow-up was carried out in order to determine whether the patients had been re-exposed to ICM in real-life settings as well as the outcome.

3. Results

3.1 Characteristics of adverse reactions to ICM in our population

The main aspects of the adverse reactions to ICM in our population are shown in Table 3.
Of note, iomeprol was the most commonly reported culprit ICM, at least partially due to its frequent use in our region. In almost one third of the patients, the reactions occurred on the first exposure to ICM and were mainly immediate, but this rate might have been underestimated since information on previous exposure was scarce. Culprit ICM was unknown in almost half of the cases.
We recorded a high rate of grade 1 IHRs. Globally, the use of antiallergic premedication, including steroids and/or antihistamines, without any previous allergologic consultation was common, from 22% in those who had experienced an IHR to 50% in those who had experienced a DHR.
The delay between the adverse reaction and the allergologic evaluation was lengthy, but a gradual reduction of this time interval was noted during the 3 years observation period (an average of 110.7 months in 2015 vs 87.5 months in 2017–18).
Three patients exhibited more than one adverse reaction against ICM, and in these cases the same clinical features (IHR or DHR) relapsed regardless of the use of a different compound.

3.2 Skin tests and laboratory results

Skin prick tests to ICM and latex were negative in all our patients. Basal tryptase values were normal in all the tested subjects.

In our population, IDTs for ICM resulted positive in 10 patients (10.2%), the majority of whom were positive to iomeprol (n = 6) (Table 4); of note, one patient showed a delayed positivity to IDT to all tested ICM. Seven skin positive results correlated to IHRs and the other three to DHRs.

In two of these cases, the culprit ICM was not known. In the case of the patient with multiple IDT positive results, the culprit ICM was iopromide. In all the other cases there was concordance among the result of the IDT and the culprit ICM (skin test positive for iomeron in 6/32 [18.75%] patients that previously reacted to iomeron; skin test with ioversol was positive in the only individual that reacted to ioversol, but ioversol was only tested in this patient).

A complete overview of the results of these 10 patients is shown in Table 4.

Focusing on the cases evaluated within 1 year since the last reaction (n = 47, 48.0%), the rate of positive skin tests increased to 14.9% (n = 7); however, this difference was not statistically significant compared with the whole population. Even in the cases of grade 3 HR (with hypotension or worse), the rate of positive skin tests showed an increasing trend (n = 3 on 13 patients, 23.1%) without reaching statistical significance.

3.3 ICM provocation test

After the skin tests, all patients underwent a DPT with intravenous ICM. Only four of them received the culprit ICM, and two reacted again, despite negative skin tests (iomeron n = 1, iobitridol n = 1).

Eight patients, on a total of 94, who were challenged with an alternative ICM (8.5%), exhibited an adverse event that did not differ from the index reaction regarding the time of onset and the severity.

Hence, we recorded 10 overall adverse events during DPT (two with culprit, eight with alternative ICM) consisting in two immediate erythematous rashes, one immediate and one delayed urticaria, four delayed cutaneous angioedema, one delayed lymphoadenomegaly, and one delayed disphagia. Epinephrine administration was not needed in any of these cases. Results of the DPTs are shown in Table 5.

Seven patients who had experienced a previous DHR did not tolerate the ICM challenge test (7/16 = 43.8%), despite negative skin tests.

After failure of the first DPT, seven patients accepted to undergo a second DPT with a different ICM; the index reaction was a DHR in most cases (Table 5). All of these patients, except one, tolerated the DPT with a second different ICM. Overall, the protocol was completed by 94 patients (95.9%).

Therefore, assuming DPT as the gold standard, in our study population, the negative predictive value (NPV), calculated as no. of true negatives / [no. of true negatives + no. of false negatives], for skin tests was 96.2% in IHRs and 58.8% in DHRs($p < 0.0001$, Fisher's exact test) when administering an ICM different from the culprit.

In the patients who underwent DPT with the culprit ICM, NPV was low (50%) despite negative skin tests.

Figure 1 summarizes the study protocol and outcomes.

3.4 ICM real-life re-exposure and follow-up

All patients were discharged with the indication to use only the tolerated ICM in case of future need of ICM-enhanced radiologic examination, without premedication.

Ninety subjects were reached by phone in the following months and asked standardized questions regarding their re-exposure to ICM as well as the outcome. Thirty-nine of them had undergone ICM re-administration, with anti-histamine/corticosteroid premedication in 26 cases, even if this was advised against after our allergologic evaluation.

Thirteen patients had undergone ICM re-administration without corticosteroid and/or anti-histamine premedication, and only these were considered for the purpose of predictive value calculation. Among these, one experienced an adverse reaction (immediate urticarial rash, 7.7%).
The NPV of our diagnostic protocol was 92.3%, compared with real-life re-exposure.
Considering all the 39 patients that had undergone ICM re-exposure, a total of 4 reactions (10.3%) (Table 7) were reported, which was a rate higher than that observed in not-premedicated patients (reaction rate in premedicated patients was 3 on 26, 11.5%; p = ns, Fisher's exact test).

4. Discussion

This retrospective study reports a single-center experience on 98 patients with a previous adverse reaction to ICM who underwent an allergological workup.
The study protocol, adapted from the EAACI/ENDA consensus document [5], was demonstrated to be safe since no severe adverse events nor epinephrine administration occurred during the workup.

4.1 Skin tests

Regarding the skin tests, in our population, only a minority (10.2%) of the subjects exhibited a positive skin test. This result agrees with previous data reported by Schnyders et al. (13.4%) [13] and Sesè et al. (13.5% in IHRs only) [14]; other authors reported a higher prevalence of positive skin tests to ICM (29.1% to 64.7%) [12][15][16].
It is known that most of the IHRs to ICM are not IgE-mediated, and this is the main reason for the low sensitivity of the skin tests [2]. However, the low rate of positive skin tests could also depend on other factors. First of all, the exact ICM involved in the index reaction was unknown in about half of our patients. Although we tested the five most frequently used ICM in the last 5 years, we could have not included the culprit, especially for those who experienced the reaction several years before.
This high rate of missing information regarding the culprit has been reported in other European countries as well, for example in the cohort of Sesè et al. (32.4%) [14], and is a reasonable value considered the real-life setting.
Secondly, the severity of the reaction could influence the outcome of skin tests; other authors have described a higher rate of positivity among patients who experienced severe reactions [17] with a reported percentage of positivity of more than a half in case of anaphylaxis and 82% in case of anaphylactic shock [16][18]. Our data confirm these findings since focusing on grade ≥3 IHRs with at least hypotension, the rate of positive skin test showed an increasing trend in respect to patients with a grade <3 reaction (25.1% vs 9.0%, p = ns).
Thirdly, it has been demonstrated in a multicenter trial that skin testing within six months from the latest reaction confers higher sensitivity to the test [15].
Our results highlight the importance of a short time delay between the reaction to ICM and the execution of the allergologic workup, and in particular of skin tests. In this study, the median time delay was elevated (89.0 months [range, 1–600 months]); only 42.8% and 30.6% of the patients, respectively, underwent an allergologic workup within 12 or 6 months from the last reaction.
Shortening this delay could have a positive impact on the predictive value of skin tests, as in our population; when performed within 1 year (n = 47) and 6 months (n = 31), the rate of positive skin test increased respectively to 14.9% (7 of 47) and to 12.9% (4 of 31), even if this difference did not reach statistical significance. These findings are similar to those already reported [15][14], [19].
Even considering DHRs alone, previous studies report a higher rate of positive skin tests in case of DHR [12], [20], and our results confirm this trend.
Of note, we reported 30 reactions on first exposure, two of which associated with positive skin tests; they were both IHRs, the culprit emerged and resulted positive in one case, while it was unknown in the other one. Reactions on first exposure to ICM have been already reported before [13]; in other series, most of them were DHRs, which occurred more than 1 hour after ICM administration [21].

Of interest, in our study, only two subjects out of 30 experienced a DHR on first exposure; they exhibited negative skin tests performed more than 6 months after the adverse event, tolerated the DPT, but one relapsed after re-exposure.
IHR to ICM on first exposure have been also described. The rate of positive skin tests was 43% in subjects with such features in a study by Brockow [4].

4.2 ICM provocation test

The choice of ICM for DPTs has been based on results of skin tests, severity and temporal proximity of the index reaction, patient's consent to use the culprit ICM when indicated and potential cross-reactivity between different ICM.
Cross-reactivity between ICM depends on their chemical structure, but is less common in IHRs than in DHRs [6]. Recently, Rosado Ingelmo et al. reported an elevated risk of cross reactions between iohexol, iopentol, ioversol, iopentol, and iodixanol, with the most relevant risk between iodixanol and its monomer iohexol, previously described by other authors [6], [12],[22].
There have been several attempts to classify ICM considering their cross-reactivity in skin tests, with little differences between authors. In a recent metanalysis [21], Yoon et al. confirmed the higher cross-reactivity of ICM during skin tests in case of DHRs, but even the higher rate of failure during DPTs in spite of negative skin tests.
Skin tests are currently considered the most reliable tool to choose the alternative ICM to be used for DPT, and a more reliable tool than premedication itself [20]. Consequently, DPT has been recognized as essential to establish the diagnosis of ICM allergy, to assess tolerance, and to find a safe alternative ICM [12].
Of interest, the main feature of the patients who did not tolerate the selected ICM was an index DHR (see Table 5). The diagnostic accuracy of skin tests was significantly higher in patients who experienced a previous IHR compared with those who experienced a previous DHR (NVP, 96.2% vs 58.8%, respectively; $p < 0.0001$, Fisher's exact test).
Even if the sensitivity of the skin test with ICM is fairly good, we cannot exclude that a real-life challenge with a bolus administration could result in a more serious—and potentially life-threatening—adverse event in those who fail to tolerate the selected ICM. For this reason, DPT is an essential part of the proposed diagnostic protocol.
We know that DPTs are time- and resource-consuming, and can be performed only in hospital settings, in selected Allergy Units with adequate facilities and trained staff. Nevertheless, even if the NPVs for skin tests with ICM is fairly good, DPTs are still essential for a correct diagnosis. With our protocol, 10.3% of the patients reacted at the DPT after a negative skin test, but no severe adverse reactions were reported. We cannot exclude that some of these patients could have experienced a more severe (or even life-threatening reaction) if a real-life exposure with a bolus of ICM was performed instead of the step-wise administration of the DPT. Moreover, skin tests alone demonstrated a very low NPV in those patients who had experienced a previous DHR to ICM.
In vitro tests, such as the basophil activation test (BAT), could be useful to further improve the accuracy of the protocol. However, BAT is nowadays still a not completely standardized procedure and is not currently available in most laboratories.

4.3 ICM real-life re-exposure and follow-up

Overall, thirty-nine subjects were re-exposed to ICM after our allergologic workup, but only in 13 cases a corticosteroid/anti-histamine premedication was not used. In order to avoid bias, these were the only patients considered for the calculation of NPV, which resulted to be very high (92.3%). Just one of these patients experienced an adverse reaction to ICM in a real-life setting, which was mild.

The fact that a premedication was used in 26 of the 39 patients that had undergone ICM re-exposure, despite this was advised against after our allergologic work-up, confirms that radiologist still rely very much on premedication, despite a low grade of evidence on its efficacy.
Surprisingly, the rate of reaction in premedicated patients was higher than that in not-premedicated patients in our study population, even if the difference was not statistically significant (11.5% vs 7.7%, p = ns). In each of these cases, reaction was mild, which required no epinephrine administration or hospitalization.
As this observation could be attributed to the small size of the population, it once again confirms the scarce utility of antiallergic premedication.
Moreover, it has been demonstrated that premedication protocols are associated with elevated costs (mostly due to the delay of the diagnostic procedure) and adverse effects (mostly due to corticosteroids), which greatly exceed the possible benefits [23, 24]. The number needed to treat has been estimated to be 69 to prevent any reaction, 569 to prevent a severe reaction, and 56.900 to prevent a lethal reaction [23].
Despite the elevated NPV of our study protocol, four patients (on a total of 39) who had tolerated the chosen ICM reacted to the same compound in the real-life setting. The total dose of administered ICM was not significantly different between the DPT and the radiologic exam. Possibly, a difference in the means of its administration should be taken into account; for the radiologic examination, the ICM is administered all at once, while in our study protocol it was administered in a three-step protocol that took about 120 minutes to be completed. One can speculate that a slower administration, as in our study protocol, could reduce the incidence of mild reactions due to direct histamine-releasing effects, while it should not modify the risk of immune-mediated adverse reactions.

5. Conclusions

We have reported here the results of the application of a protocol to diagnose ICM allergy and find a safe alternative in subjects with previous adverse reactions to ICMs.
This protocol is based on skin test and LTT, which is considered the gold standard for the diagnosis of ICM allergy but is potentially dangerous for the risk of severe adverse events.
Our protocol demonstrated to be safe as no serious adverse event or epinephrine administration was reported in any of our 98 patients.
It also demonstrated to be accurate as 92.3% of our patients subsequently tolerated ICM administration in a real-life setting without any antiallergic premedication.
On the other hand, some critical issues arouse that could limit the efficacy of the protocol; the late presentation of the patient to the allergist after an adverse reaction to ICM and the missing information about the culprit ICM represent important reasons of diagnostic failure.
Therefore, we believe that this protocol could be proposed to be used for the management of patients with previous reactions to ICM, where a BAT is not available.
The choice of premedication does not represent a valid alternative the allergologic workup, as an increasing body of evidence demonstrates discouraging data regarding premedication; a high number needed to treat is needed to prevent severe-lethal reactions and an unfavorable cost/harm ratio, since unnecessary premedication increases adverse events (glycometabolic failure and infections, to name a few), hospital stay and costs [23].
Hence, the use of premedication with antihistamines and steroids before the administration of an ICM should be evaluated on the single case, when the allergologic workup is not possible (e.g., radiologic examination is urgent) or contraindicated (e.g., renal failure).
A strong interplay between the prescribing physician, the radiologist, and the allergist is a key factor to ensure maximum safety for the patient.

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Tables

Table 1: Biochemical classification of ICM

	Monomers	Dimers
Ionic	Replaced by more tolerable compounds	Ioxaglate
Nonionic	Iopamidol, iohexol, ioversol, iopentol, iomeprol, iobitridol and iopromide	Iodixanol

Table 2. Characteristics of our study population.

Number of patients	98
Sex distribution	53 female (54.1%), 45 male (45.9%)
Median age	65.6 years (range, 23–90 years)
Atopic	34 (34.7%)
Asthma/COPD comorbidity	16 (16.3%)

Table 3. Features of the adverse reactions to ICM.

	Total	Immediate	Delayed
Timing of the index reaction (%)	98	82 (83.7%)	16 (16.3%)
Severity		Grade 1 n = 47 (58.1%)	Mild n = 15 (93.7%) Moderate n = 1 (6.3%) Severe) n = 0

			Grade 2 n = 24 (29.6%) Grade 3 n = 10 (12.3%) Grade 4 n = 0	
On first exposure to ICM (missing information n = 40, 40.8%)		30 (30.6%)	28 (34.1%)	2 (12.5%)
Use of "antiallergic" premedication (missing information n = 16, 16.3%)		26 (26.5%)	18 (22.0%)	8 (50.0%)
Culprit ICM (three patients reported adverse reactions with more than one ICM)	Iomeprol	32 (32.7%)	24 (29.3%)	8 (50.0%)
	Iopamidol	4 (4.1%)	2 (2.4%)	2 (12.5%)
	Iopromide	14 (14.3%)	11 (13.4%)	3 (18.8%)
	Iobitridol	5 (5.1%)	5 (6.1%)	0
	Iodixanol	4 (4.1%)	3 (3.7%)	1 6.3%)
	Unknown	43 (43.9%)	39 (47.6%)	4 (25.0%)
Latency from latest ICM reaction to allergologic workup (missing information n = 2, 2.0%)	Median delay (months)	90.8 (range 1–600)	107.7 (range 1–600)	12.4 (range 1–48)
	Within 12 months	47 (48.0%)	35 (42.7%)	12 (75.0%)
	Within 6 months	31 (31.6%)	23 (28.0%)	8 (50.0%)

Table 4. Features of patients with positive skin test.

		Total	IHR	DHR
No. of patients with skin test positive for any ICM		10 (10.2%)	7 (8.5%)	3 (18.8%)
No. of patients with skin test positive for >1 ICM		1 (1.0%)	0	1 (6.25%)
No. of patients with skin test positive for any ICM and ICM reaction despite premedication		4 (4.1%)	2 (2.4%)	2 (12.5%)
No. of patients with skin test positive for any ICM and ICM reaction on first exposure		2 (2.0%)	2 (2.4%)	0
Elicitor	Iomeprol	6*	4*	2
	Iopamidol	0	0	0
	Iopromide	1	1	0

	Iobitridol	1*	1*	0
	Iodixanol	0	0	0
	Ioversol°	1	1	0
	All	1[#]	0	1[#]

*In two of these patients (one with skin test positive for iomeprol, one for iobitridol), the culprit ICM was unknown.
[#]In this case, a delayed positive reaction to all the ICM was observed after IDT.
°A single patient with previous IHR to ioversol underwent skin tests with this ICM, which were positive.

Table 5. Features of the subjects who did not tolerate the first challenge with culprit or alternative ICM.

Patient no.	Index reaction	Symptoms	ICM	Skin tests	DPT witch culprit	1st challenge	Symptoms	2nd challenge	Symptoms
3	DHR	Dysphagia	Iopromide	Negative	No	Iomeprol	Dysphagia	Iodixanol	No
11	DHR	Urticaria	Iopromide	All positive	No	Iomeprol	Urticaria	STOP	-
17	DHR	Generalized angioedema	Iomeprol	Iomeprol (culprit) positive	No	Iodixanol	Generalized angioedema	Iopromide	No
21	DHR	Angioedema	Iopamiro	Negative	No	Iodixanol	Angioedema	Iopromide*	Angioedema
25	DHR	Angioedema	Iomeprol	Negative	No	Iopromide	Urticaria/Angioedema	STOP	-
27	DHR	Angioedema	Iomeprol	Negative	No	Iopromide	Angioedema	STOP	-
43	IHR	Cutaneous rash	Iomeprol	Negative	No	Iopromide	Cutaneous rash	Iodixanol	No
54	DHR	Face angioedema	Iomeprol	Iomeprol positive (unknown culprit)	No	Iodixanol	Face angioedema	Iopromide	No
57	IHR	Cutaneous rash	Iobitridol	Negative	Yes	Iobitridol	Cutaneous rash	Iomeprol	No
82	IHR	Urticaria	Iomeprol	Negative	Yes	Iomeprol	Urticaria	Iodixanol	No

STOP = no more DPTs; *= 2nd DPT was not tolerated, no more DPTs were proposed.

Table 6. Summary of negative DPTs (with alternative ICM)

Total of negative DPT with alternative ICM	Culprit ICM	Alternative ICM used for DPT
88	Known, n = 46 (52.3%)	Iopromide n = 32 (36.4%)
		Iodixanol n = 27 (30.7%)
	(Unknown, n = 42, 47.7%)	Iomeprol n = 25 (28.4%)
		Iobitridol n = 4 (4.5%)

Table 7. Characteristics of the reactions after ICM re-exposure.

		No. of reactions upon ICM re-exposure	Type of reaction upon ICM re-exposure	Premedication*
Total		4/39 (10.2%)		3/26 (11.5%)
Culprit reaction	IHRs	3/33 (9.1%)	2 IHRs + 1 DHR	2
	DHRs	1/6 (16.7%)	DHR	1

*Premedication was not indicated after our diagnostic workup

Figures

Figure 1. Study protocol and outcomes. * = only not-premedicated patients were considered.

Figure 1

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