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Proposal of a skin tests based approach for the prevention of recurrent hypersensitivity reactions to iodinated contrast media

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Summary

The purpose of the present work is to evaluate the efficacy of an approach that combines clinical history, skin tests results, and premedication, in preventing recurrent hypersensitivity reactions to iodinated contrast media (ICM). Skin Prick tests, Intradermal tests, and Patch tests were performed in 36 patients with a previous reaction to ICM. All patients underwent a second contrast enhanced radiological procedure with an alternative ICM selected on the basis of the proposed approach. After alternative ICM re-injection, only one patient presented a mild NIR. The proposed algorithm, validated in clinical settings where repeated radiological exams are needed, offers a safe and practical approach for protecting patients from recurrent hypersensitivity reactions to ICM.

Introduction

The incidence of hypersensitivity reactions to iodinated contrast media (ICM) has grown dramatically in recent years, together with the tremendous increase of ICM administration (1). At present, ICM are among the most frequently used pharmaceuticals for intravascular injection with over 75 million infusions per year worldwide (2,3).

According to the timing of onset, hypersensitivity reactions have been classified in immediate (IRs) and non-immediate reactions (NIRs). Immediate reactions occur within one hour after contrast administration; non-immediate reactions occur more than one hour after injection (4). Interestingly, at least for IRs, chemical structure, osmolarity and iodine content of the different ICM have been shown to influence the likelihood of developing a hypersensitivity reaction. For instance, high-osmolar ICM are not used any more, due to a higher risk of adverse events (4,5), while low-osmolar ICM are routinely used and regarded as relatively safe, with an overall frequency of adverse reactions that ranges from 0.7 to 3.1% (4). Low-osmolar ICM can be further distinguished into non-ionic monomers (iohexol, iopamidol, ioversol, iopromide, iomeprol, iopentol and iobitridol), ionic dimers (ioxaglate), and non-ionic dimers (iodixanol), with monomeric ICM being more frequently involved in IRs, and dimeric ICM in NIRs (6,7).

From a pathogenic perspective, ICM hypersensitivity reactions have traditionally been classified as non-allergic reactions, since (i) reaction on first exposure can occur, and (ii) contrast me-

dia-specific IgE antibodies have seldom been detected (8). However, during the last few years, several investigators have reported positive skin tests in patients with both IRs and NIRs, supporting an underlying allergic mechanism (9). In particular, it has been proposed that IRs may be elicited both by IgE-mediated mechanisms and by ICM direct induced histamine release from basophils and mast cells (9-11). On the contrary, most NIRs appear to be T-cell mediated, as suggested by the presence of dermal infiltrates of T cells in affected skin and by the proliferative T cell responses to the culprit ICM in vitro (4,12-14). Based on these immunological evidences, skin tests with diagnostic purposes have gained new consideration in recent years, and several studies addressed the role of skin prick tests (SPTs), intradermal tests (IDTs) and patch tests (PTs) in identifying hypersensitivity to ICM. In particular, the first "European multicenter skin test study" showed that up to 50% of patients with previous IRs and NIRs could be diagnosed by standardized skin tests, if evaluated within 2-6 months after the index reaction (15). However, despite these evidences, hypersensitivity to ICM still represents a major concern in clinical settings where repeated radiological examinations are required, as in case of malignant and chronic inflammatory disorders. In effect, the prognostic value of skin tests for the selection of safe alternative ICM in patients with previous adverse reactions to iodinated compounds remains poorly characterized. Moreover, the various published premedication protocols are not protective in cases of previous severe anaphylaxis, and do not completely guarantee patients against recurrent adverse reactions (16-19). In this sense, a large meta-analysis concluded that physicians should not completely rely on the efficacy of premedication alone since, in unselected patients, a large number of subjects need to be premedicated to prevent one potentially serious reaction (19).

Given these areas of uncertainty, in the present work we propose an algorithm that combines and integrates clinical history, skin tests performed according to international guidelines and premedication, for preventing recurrent hypersensitivity reactions to ICM.

Materials and methods

Patients. From our Database of Hypersensitivity reactions to ICM, we identified 36 consecutive patients who were tested within 2 to 6 months after the adverse reaction, in accordance with the timing indicated by international guidelines (15). Patients included in this study were referred between March 2010 and January 2014. Hypersensitivity reactions were classified as IRs when occurring within one hour after ICM injection, and as NIRs when occurring from one hour to 7 days after ICM administration (4). Immediate reactions were graded according to the Ring and Messmer classification: generalized cutaneous and/or mucocutaneous symptoms like pruritus, skin eruption, urticaria and angio-oedema (grade 1); mild systemic reactions including skin manifestations, abdominal symptoms, respiratory symptoms, cardiovascular symptoms (tachycardia) (grade 2); life-threatening systemic reactions including shock (grade 3); cardiac and/or respiratory arrest (grade 4) (20). Non-immediate reactions were defined as mild when no treatment was required, moderate when the patient responded readily to an appropriate treatment without hospitalization, and severe when the reaction required treatment in hospital, was life-threatening or resulted in death (4). All subjects signed written, informed consent for the investigations described. Since all tests were performed for diagnostic purposes, an ethical committee approval was not required for this observational analysis.

Skin testing. All patients were evaluated within 2 to 6 months after the adverse reaction and were tested with a panel of at least 3 ICM used at the Radiology Department of our Institutes in addition to the culprit agent, when known. The panel of ICM included: iohexol (Omnipaqueâ 300 mg I/mL), iomeprol (Iomeronâ 400 mg I/mL), iopromide (Ultravistâ 370 mg I/mL), iodixanol (Visipaqueâ 270 mg I/mL), iobitridol (Xenetixâ 300 mg I/mL). Skin prick tests with undiluted ICM, IDTs with 100-fold diluted, 10-fold diluted, and undiluted ICM, and PTs with undiluted ICM were performed, and interpreted according to the International Guidelines and the European multicenter study protocol respectively (15,21).

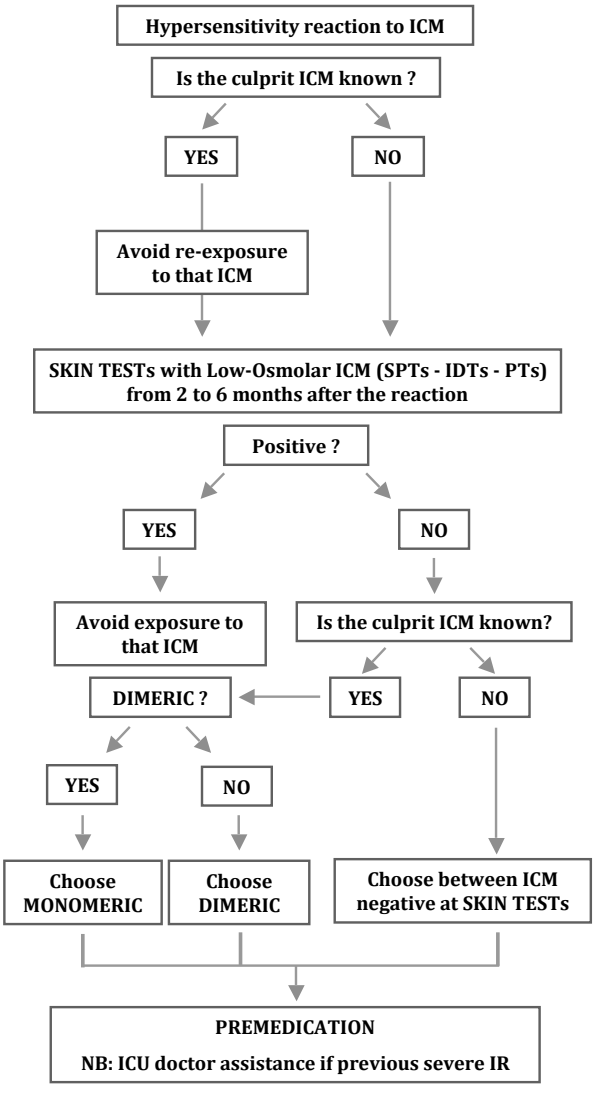
Algorithm for the selection of alternative iodinated contrast media. Alternative ICM for subsequent radiological procedures were chosen according to an algorithm based on skin tests results and patient history, proposed in **figure 1**: (i) avoidance of the previous culprit ICM, when known, was mandatory, even in presence of negative skin tests for that compound; (ii) contrast media with positive results on skin tests were avoided as well; (iii) in the absence of positive skin tests and/or known culprit ICM, non-ionic dimeric ICM were preferred over monomeric ICM, because the former are typically less implicated in immediate life threatening reactions (6,7); (iv) in the presence of positive skin tests for all the tested ICM, especially when prior hypersensitivity reaction was severe, iodinated contrast enhanced exam was discouraged, and a possible alternative procedure was suggested.

Premedication. Premedication was adopted in all patients with a previous history of hypersensitivity to ICM undergoing a new radiological examination, regardless the entity of the initial reaction. Premedication was performed according to a protocol approved and adopted by the American College of Radiology for the last 5 years: Methylprednisolone (Medrol®) 32 mg by mouth 12 hours and 2 hours before ICM injection, and Hydroxyzine Hydrochloride (Atarax®) 25 mg by mouth 1 hour before ICM injection (22). Intensive care unit doctor assistance was requested when the first hypersensitivity reaction was immediate and life threatening.

Follow-up. After ICM re-exposure, patients were monitored for one hour and discharged if no IRs occurred. Patients were then instructed to report any type of NIR occurring in the following 7 days, and to take pictures of eventual non-immediate skin eruptions; moreover, in case of adverse events occurring in this time frame, patients were immediately evaluated at our Institutes. Finally, patients were called a week after ICM injection and asked for possible hypersensitivity reactions, clinical conditions and drug assumption (mainly corticosteroids and/or antihistamines) in the previous 7 days.

Statistics. Statistical analysis was performed using GraphPad Prism software 6.0. Continuous variables are expressed as mean (range minimum-maximum value), unless otherwise specified.

Figure 1 *- Algorithm for the selection of an alternative ICM.*



Iodinated Contrast Media: ICM, Skin Prick tests: SPTs, Intradermal tests: IDTs, Patch tests: PTs, Immediate reaction: IR.

Results

Clinical characteristics of the patients' cohort

Thirty-six patients (mean age 58 years; range 22-75) (9 males and 27 females) were included in this study. Their clinical characteristics are summarized in **table 1** and **2**. Nineteen subjects (mean age 58 years; range 22-75) experienced an IR; seventeen patients (mean age 57 years; range 35-75) had a NIR. The overall male:female ratio was 1:3, with an increased incidence of both IRs and NIRs among females. Adverse reactions of both immediate and non-immediate type were related to computed tomography (CT) scan in the majority of cases. The remaining cases of adverse reactions occurred during angiography (two cases of Irs and one case of NIR) and urography (one case of IR). The culprit ICM was known in 27/36 cases (75%) (14 cases of Irs and 13 cases of NIRs) and unknown in 9/36 cases (25%) (5 cases of Irs and 4 cases of NIRs): Iopromide was the most frequently involved ICM both in Irs and NIRs.

An allergic background was present in 6/19 patients (32%) who experienced an IR and 7/17 patients (41%) with a previous NIR. Drug hypersensitivity represented the most frequently reported past allergic manifestation in both groups, followed by rhino-conjunctivitis and allergic contact dermatitis. Sixty-eight percent and 59% of subjects with immediate and non-immediate reactions, respectively, were not allergic. Seventy-five percent of the patients who experienced an adverse reaction to ICM in our cohort (14/19 patients with previous Irs and 13/17 with NIRs) had an underlying oncological disease and required periodical follow-up radiological exams.

Table 2 summarizes clinical manifestations of Irs and NIRs to ICM in the patients' cohort. Immediate reactions consisted of 12 grade 1, 3 grade 2 and 4 grade 3 reactions; NIRs were mild and moderate in 16 and 1 cases, respectively. Mucocutaneous involvement was the presenting feature in 95% of Irs and 100% of NIRs. Respiratory symptoms manifested only as part of an IR in 37% of patients. Gastrointestinal and neurological involvement accounted for a minor proportion of allergic manifestations. Four subjects (11%) experienced anaphylactic shock requiring epinephrine injection.

Skin testing

Skin tests were performed on average 16 weeks (range 8-25) after the reaction, and results are reported in **table 3** and **4**. SPTs were negative in all patients. IDTs were positive in 7/19 patients with a previous IR and 4/17 patients with a previous NIR. In

Table 1 *- Clinical characteristics of the patients' cohort.*

	Immediate Reactions	**Non-immediate Reactions**	**Total**
Number of Patients	19	17	36
Female, n (%)	14 (74%)	13 (76%)	27 (75%)
Age, mean (range)	58 (22-75)	57 (35-75)	58 (22-75)
Allergic history, n (%)	6 (32%)	7 (41%)	13 (36%)
Rhinoconjunctivitis	3	2	5
Drug allergies	4	2	6
Allergic contact dermatitis	2	1	3
Food allergy		1	1
Hymenoptera venom allergy		1	1
Not allergic, n (%)	13 (68%)	10 (59%)	23 (64%)
Ongoing disease requiring ICM exam, n (%)			
Oncological disease	14	13	27 (75%)
Chronic pulmonary disease	2		2 (5%)
Cardiovascular disease	1	4	5 (14%)
Autoimmune disease	1		1 (3%)
Other	1		1 (3%)
Implicated contrast medium, n			
Iomeprol (non-ionic monomer)	2	2	4 (11%)
Iopamidol (non-ionic monomer)	1		1 (3%)
Iopromide (non-ionic monomer)	8	6	14 (39%)
Iodixanol (non-ionic dimer)	3	5	8 (22%)
Unknown	5	4	9 (25%)

the group of patients who experienced an IR, IDTs were positive in 2 cases with ICM diluted 1:100, 4 cases with ICM diluted 1:10, and 2 cases with ICM diluted 1:1; 6 subjects developed a skin reaction at 20 minutes (immediate reading) and 2 at 48 hours (delayed reading). In the group of patients who experienced an NIR, IDTs were positive in 4 cases with ICM diluted 1:10; two subjects developed a skin reaction at 20 minutes and 2 at 48 hours. PTs were positive at 48 hours in one patient with a previous NIR. The rate of positive skin tests in our cohort was 7/19 (37%) in the group of patients with a previous IR and 5/17 (30%) in the group of patients with a previous NIR. The overall rate of positive skin tests in our cohort was 12/36 (33%). When known, the culprit ICM elicited a positive skin test in 5/14 cases of IRs, and 2/13 cases of NIRs.

Re-exposure to iodinated contrast media

All patients underwent a new contrast enhanced radiological procedure. Patients with previous IRs and NIRs were re-exposed to the alternative ICM on average 8 months (range 1-12 months) and 5 months (range 1 week-21 months), respectively, after the index adverse event (**table 3** and **4**). All patient were premedicated, and ICM dosage was not adapted because of the past clinical history of adverse reaction. 18/19 patients with previous IRs (95%) and 17/17 patients with previous NIRs (100%) tolerated

Table 2 *- Adverse reactions to ICM: severity of the reaction and clinical manifestations.*

	Immediate Reactions n = 19	**Non-immediate Reactions n = 17**	**Total n = 36**
Severity of the reaction			
Grade I	12		
Grade II	3		
Grade III	4		
Grade IV			
Mild		16	
Moderate		1	
Severe			
Mucocutaneous involvement, n (%)	18 (95%)	17 (100%)	35 (97%)
Urticaria	6	6	
Mucocutaneous Angioedema	6		
Exanthema	1	11	
Erythema	4		
Conjunctivitis	1		
Respiratory involvement, n (%)	7 (37%)		7 (19%)
Rhinitis	2		
Dispnea	1		
Bronchospasm	1		
Laryngeal edema	3		
Gastrointestinal involvement, n (%)		2 (12%)	2 (5%)
Nausea/vomiting		2	
Neurological involvement, n (%)	1 (5%)		1 (3%)
Paresthesia	1		
Anaphylactic Shock*, n (%)	4 (21%)		4 (11%)

*Anaphylactic Shock was defined according to international Consensus statements[23].

the alternative ICM selected according to the previously cited criteria, reported in the algorithm in **figure 1**. A single patient, who had a previous grade 1 IR to an unknown ICM, developed a self-limited localized slightly itchy erythema 48 hours after exposure to iobitridol. Notably, according to our algorithm, a non-ionic dimeric ICM would have been the alternative of choice in this case; however, non-ionic dimers were not available when skin tests were performed and were, therefore, not tested.

Discussion

The incidence of hypersensitivity reactions to ICM has increased along with the large use of these compounds for both diagnostic and interventional procedures (2). However, our knowledge about the implicated allergic and non-allergic mechanisms has not grown in parallel and clinicians actually lack accurate techniques for the diagnosis of hypersensitivity to ICM. Moreover, the introduction of nonionic low-osmolar products drastically reduced life-threatening reactions but did not prevent them, and anaphylaxis still remains a major concern both for patients and radiologists. This is particularly true for clinical conditions where repeated ICM injections are required for evaluation or follow-up, as in case of neoplastic, cardiovascular or chronic inflammatory disorders. Indeed, in these common clinical settings, allergists are oftentimes asked to readily provide an

Table 3 *- Outcomes of patients with previous IRs re-exposed to alternative ICM.*

Pt.	Radiological procedure	Type of IR	Culprit ICM	Skin test results1	Alternative ICM	Months after reaction	Outcome
1	CT scan	Grade 1	Iodixanol	IDT 1:10 Iodixanol at 48 hrs	Iopromide	3	No reactions
2	CT scan	Grade 1	Unknown	Negative	Iodixanol	4	No reactions
3	CT scan	Grade 1	Unknown	Negative	Iodixanol	7	No reactions
4	Urography	Grade 1	Unknown	Negative	Iodixanol	6	No reactions
5	CT scan	Grade 1	Unknown	Negative	Iobitridol	11	NIR (Mild)
6	CT scan	Grade 1	Iomeprol	Negative	Iodixanol	5	No reactions
7	CT scan	Grade 1	Iopromide	Negative	Iodixanol	9	No reactions
8	CT scan	Grade 1	Iopromide	IDT 1:100 Iopromide	Iodixanol	2	No reactions
9	CT scan	Grade 1	Iopromide	IDT 1:10 Iopromide and 1:1 Iomeprol. IDT 1:1 iomeprol at 48hrs	Iodixanol	6	No reactions
10	CT scan	Grade 1	Iopromide	Negative	Iodixanol	3	No reactions
11	CT scan	Grade 1	Iodixanol	IDT 1:1 Iopromide	Iomeprol	1	No reactions
12	CT scan	Grade 2	Iopromide	Negative	Iodixanol	7	No reactions
13	CT scan	Grade 3	Iopromide	Negative	Iodixanol[2]	9	No reactions
14	CT scan	Grade 3	Iopamidol	Negative	Iodixanol[2]	7	No reactions
15	CT scan	Grade 3	Iodixanol	Negative	Iopromide[2]	6	No reactions
16	CT scan	Grade 3	Iomeprol	IDT 1:10 Iomeprol and Iopromide	Iodixanol[2]	2	No reactions
17	Angiography	Grade 3	Unknown	IDT 1:10 Iopromide	Iodixanol[2]	12	No reactions
18	Angiography	Grade 3	Iopromide	Negative	Iodixanol[2]	9	No reactions
19	CT scan	Grade 3	Iopromide	IDT 1:100 Iopromide	Iodixanol[2]	10	No reactions

[1]Skin tests included IDTs and PTs: only positive results are reported.
[2]ICU doctor assistance was requested in presence of a history of severe IR to a previous ICM. All patients underwent premedication before re-exposure to the alternative ICM.
Computed tomography: CT; Iodinated contrast medium: ICM; Immediate reaction: IR; Intradermal test: IDT.

alternative ICM, because radiological exams need to be repeated every 6 to 12 months.

For these reasons, premedication actually represents the most widely adopted measure for preventing recurrent hypersensitivity reactions to ICM. However, several works demonstrated that current premedication procedures appear to reduce symptoms, but may not prevent repeated reactions (16-19). Moreover, studies performed by Greenberger and colleagues found that repeated reactions to ICM decreased from 17-30% to 11% by using a corticosteroid and antihistamine preparation, but were not abolished (18). In other words, premedication alone has been proven to be insufficient for a complete prevention of recurrent reactions to ICM, and we are actually unable to predict those patients that will react despite pretreatment.

International guidelines also suggest avoidance of the culprit ICM as an additional preventive measure (4), but the causative

Table 4 *- Outcomes of patients with previous NIRs re-exposed to alternative ICM.*

Pt.	Radiological procedure	Type of NIR	Culprit ICM	Skin test results[1]	Alternative ICM	Months after reaction	Outcome
1	CT scan	Mild	Iodixanol	Negative	Iopromide	2	No reactions
2	CT scan	Mild	Iomeprol	Negative	Iodixanol	7	No reactions
3	CT scan	Mild	Unknown	Negative	Iodixanol	9	No reactions
4	CT scan	Mild	Iopromide	Negative	Iodixanol	6	No reactions
5	CT scan	Mild	Iopromide	Negative	Iodixanol	3	No reactions
6	CT scan	Mild	Iopromide	IDT Iomeprol, Iodixanol, Iopromide 1:10 at 48 hrs	Iohexol	21	No reactions
7	CT scan	Mild	Iodixanol	IDT 1:10 Iodixanol at 48 hrs	Iopromide	8	No reactions
8	CT scan	Mild	Unknown	PT Iohexol at 48 hrs	Iodixanol	5	No reactions
9	Angiography	Mild	Iodixanol	Negative		6	No reactions
10	CT scan	Mild	Iodixanol	Negative	Iopromide	3 weeks	No reactions
11	CT scan	Mild	Iopromide	Negative	Iodixanol	4	No reactions
12	CT scan	Mild	Iopromide	Negative	Iodixanol	1 week	No reactions
13	CT scan	Mild	Iopromide	Negative	Iodixanol	2 weeks	No reactions
14	CT scan	Mild	Iodixanol	Negative	Iopromide	1	No reactions
15	CT scan	Moderate	Unknown	IDT 1:10 Iopromide	Iodixanol	7	No reactions
16	CT scan	Moderate	Unknown	IDT 1:10 Iopromide	Iodixanol	4	No reactions
17	CT scan	Moderate	Iomeprol	Negative	Iodixanol	8	No reactions

[1]Skin tests included IDTs and PTs: only positive results are reported. All patients underwent premedication before re-exposure to the alternative ICM. Computed tomography: CT; Iodinated contrast medium: ICM; Non-immediate reaction: NIR; Intradermal test: IDT; Patch test: PT.

iodinated compound is still rarely reported by radiologists and, thus, typically ignored in everyday clinical practice.

Thus, different approaches have been evaluated in order to identify safe alternative ICM. For instance, drug provocation test was reported to reliably diagnose NIRs to ICM, and was proposed as an additional tool for identifying alternative compounds, although reasonable safety concerns still remain to be completely addressed (24,25). Similarly, a large European multicentric study reported high specificity of skin tests in the diagnosis of immediate and non-immediate ICM reactions, but their usefulness in the selection of alternative and safe compounds was not evaluated (15). In trying to address this issue, a recent pivotal study reported a negative predictive value for ICM skin tests of 97%; of note, patients in this series were not premedicated before re-exposure to ICM (26). However, this promising result has to be interpreted in light of two main limits: (i) the absence of reports about the culprit ICM, and (ii) the long median time interval between the reaction and skin tests (11.5 years). In effect, since avoidance of the culprit ICM reduces the likelihood of a second hypersensitivity reaction, awareness of the implicated substance should integrate skin tests' results for deciding which alternative compounds to inject. On the other hand, skin tests with ICM should be performed from 2 to 6 months after the reaction in order to obtain the highest sensitivity (4,15). At later time points, in fact, loss of sensitization is known to significantly decrease the frequency of positive responses (15,27). Moreover, the negative predictive value of skin tests with ICM was calculated by analyzing immediate and non-immediate reactions together, although differences in terms of pathogenic mechanisms between the two types of reactions are well known in the literature (9-14).

All in all, standardized guidelines for preventing recurrent adverse reactions to ICM are lacking, adequate tools for the selection of safe alternative iodinated compounds need to be refined,

and premedication alone does not offer complete protection to patients with hypersensitivity to these substances.

In the present work, we validated an algorithm that efficiently protected 95% of patients with a previous IR and 100% of patients with a previous NIR from recurrent reactions to ICM. The algorithm was based on (i) the avoidance of the culprit ICM (when known in the majority of cases), (ii) the selection of an alternative ICM by integrating clinical history and skin tests results, and (iii) the premedication of all patients. Of note, all patients underwent skin tests within 2 to 6 months after the index adverse reaction, in accordance with the international guidelines (4,15).

Thanks to this approach, we were able to safely re-expose all patients to ICM early after the index adverse event, because the vast majority of subjects in our cohort had clinical priorities related to follow-up of oncological or chronic inflammatory diseases. The algorithm was equally efficacious both in case of a previous immediate and non-immediate adverse reaction to ICM. In particular, the combined use of SPTs, immediate and delayed reading IDTs and PTs, guided the selection of an alternative compound, both in case of positive and negative result. In fact, positive skin tests identified ICM that were avoided in subsequent radiological exams, while negative skin tests identified potentially safe ICM, unless involved in the previous adverse reaction. The knowledge of the culprit ICM was, therefore, crucial in the algorithm, since that substance was avoided in the following radiological procedures. Hence, radiologists are strongly encouraged to record the name of the injected iodinated compound, especially if patients need to undergo repeated exams. In light of these considerations, it is reasonable to think that the false negative patient had, indeed, a second adverse reaction to the same ICM, because the initial culprit ICM was unknown.

Moreover, it is noteworthy to observe that the proportion of patients who tolerated the alternative ICM (95% of patients with a previous IR and 100% of those with a previous NIR) was very similar to what reported by Caimmi without premedication. Of course, it is possible that premedication might have suppressed part of minor reactions in our cohort of patients. Alternatively, since both immediate and non-immediate reactions are known to occur despite pretreatment with corticosteroids and antihistamines, we might speculate that the selection of the alternative ICM, rather than premedication, played a major role in preventing recurrent hypersensitivity reactions. A third additional and comprehensive hypothesis is that both the selection of an alternative ICM and premedication concurred in efficaciously protecting patients from a subsequent adverse reaction.

Finally, the presence of positive skin tests results for ICM other than the culprit ones, might indicate either a real multiple sensitization, or cross-reactivity between different iodinated compounds. Indeed, cross-reactivity between different ICM is a clinically important problem and a well-defined phenomenon that primarily resides in the presence of contrast media-specific T cells (14). In this sense, skin tests might have been of further help in identifying potentially additional harmful ICM for individual patients.

Dissecting the protective contribution of premedication as well as the negative predictive value of skin tests is far beyond the purposes of the present study, but the reported results are in accordance with those of the literature and support the notion that premedication alone is not sufficient to control further reactions to ICM. Rather, the identification of a safe alternative ICM appears to be equally important for reducing the likelihood of a new hypersensitivity reaction.

Conclusions

In conclusion, we herein provide clinicians with a practical algorithm for approaching patients who need to be re-exposed to ICM despite a history of immediate or non-immediate hypersensitivity reactions to iodinated compounds. In particular, given the lack of established guidelines for the management of these subjects, the proposed algorithm represents a reliable and easily replicable tool for safely re-exposing patients to ICM in clinical settings where repeated radiological examinations are required.

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