

Hypersensitivity Reactions to Iodinated Contrast Media: Is it a True Allergy?

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Opinion statement

Classically, hypersensitivity reactions to iodinated contrast media (ICM) have been termed pseudoallergic, allergy-like, or anaphylactoid. The origin of these terms to define ICM hypersensitivity reactions could be in relation to the use of traditional, classic, ionic ICMs. These ionic ICMs have a high osmolality, and the reactions have been considered as secondary to non-specific histamine release. Currently, ionic ICMs have been replaced by non-ionic compounds with low or iso-osmolality, which, although to a lesser extent, can also produce hypersensitivity reactions. In recent years, there has been growing evidence that some of these reactions, especially the more severe, can be triggered by an IgE-dependent mechanism. Also, in recent decades, there has been an increase in non-immediate reactions, especially in the form of maculopapular exanthems occurring up to several days after the administration of ICM. In these non-immediate reactions, the involvement of T lymphocytes has been clearly demonstrated. The finding of positive skin tests and other in vitro studies for ICMs would support a specific immunological

mechanism in a percentage of ICM-induced reactions. However, although there is a body of evidence suggesting that ICMs can induce true allergy reactions, the main guidelines for contrast media management, such as those proposed by US (American College of Radiology Manual on Contrast Media) or European (European Society of Urogenital Radiology Guidelines on Contrast Media) societies, continue to consider only immediate reactions and handle them as non-allergic reactions, without any allergy testing. In ICM reactions an allergic evaluation should be mandatory, not only to study the possible mechanisms involved but also to identify the ICM involved in the reaction and to find an alternative one that could be used in future radiological explorations.

Introduction

The number of medical procedures using iodinated contrast media (ICM) has dramatically increased in recent decades. Although ICMs are well-tolerated and safe compounds, adverse events, including hypersensitivity reactions, do occur in some patients.

ICM hypersensitivity reactions had been called allergy-like or anaphylactoid reactions as many of them clinically resembled IgE-mediated reactions and were believed to be due to unspecific histamine release [1, 2]. Currently, the term hypersensitivity to ICMs is considered more appropriate since it includes both true allergic reactions and reactions with similar immediate manifestations in which it is not possible to demonstrate a specific immunological mechanism [3].

Hypersensitivity reactions to ICMs can be classified according to the time interval between the ICM administration and the appearance of clinical symptoms in immediate reactions (1–6 h) and non-immediate reactions (> 1 h) [4].

Currently, ionic ICMs have been replaced by non-ionic ICMs, and this change has been associated to a decrease in the frequency of immediate hypersensitivity reactions [5]. However, immediate hypersensitivity reactions to ICMs still occur, and some of them can be severe. On the basis of allergy testing, it has been demonstrated that a variable percentage of immediate reactions to ICM especially of the most serious reactions are IgE

mediated [6, 7•, 8–10, 11•]. Nevertheless, non-immediate or delayed reactions to ICMs are the most frequent hypersensitivity reactions at present [12]. These are ICM-specific T cell-mediated non-immediate reactions, being maculopapular exanthems the most frequent clinical manifestation [7•, 13••, 14, 15].

In patients suffering from non-immediate reactions to ICMs, several studies have detected positive delayed intradermal tests as well as positive patch tests [16, 17•, 18, 19•, 20•]. The T cell involvement has also been demonstrated by positive lymphocyte proliferation tests (LTT) with the culprit contrast media [21–23].

Since allergy testing provides the opportunity to identify the culprit ICM, and to find an alternate ICM for radiological procedures that could be necessary for the future, an adequate management of patients with hypersensitivity reactions to ICM is of great importance.

Changing the ICM to another one for which the tolerance has been proven and the use of premedication have been proposed by the main guidelines for the management of contrast media reactions [24, 25]. Premedication seems to be effective to prevent recurrence of immediate hypersensitivity reactions although severe symptoms could also develop, even when prophylaxis was properly administrated.

Classification of ICM hypersensitivity reactions

The classification of drug adverse reactions most widely used differentiates between A-type and B-type reactions [26]. A-type reactions are predictable and related to the pharmacological effects of a drug, being the most common ones.

B-type reactions are unpredictable, and they are usually not related to the pharmacological properties of a drug. Drug hypersensitivity reactions belong to B-type reactions and include all adverse events that clinically resemble allergy [3]. Only when a definite immunological mechanism is demonstrated, reactions should be classified as drug allergy. Clinically, drug hypersensitivity reactions are classified as immediate or non-immediate depending on their symptom onset after drug administration. Immediate ICM hypersensitivity reactions occur within 1–6 h after drug administrations and include both true allergic reactions IgE mediated and reactions described as anaphylactoid or allergy-like. In the latter case, both EAACI and WAO suggest the term non-allergic drug hypersensitivity [3].

Non-immediate drug hypersensitivity reactions occur between 1 h and several days after the administration of ICMs. These reactions are often associated with a T cell-dependent type of allergic mechanism.

Epidemiology

The frequency of ICM hypersensitivity reactions differs according to the severity of the reaction and the culprit ICM (Table 1). Mild immediate reactions occur in 3.8 to 12.7% of patients receiving ionic monomeric ICMs and in 0.7 to 3.1% of patients receiving non-ionic ICMs [5, 27, 28]. Severe immediate reactions to ionic ICM have been reported with a frequency of 0.1 to 0.4% of explorations, whereas reactions to non-ionic ICM occur in 0.02 to 0.004% of administrations [5, 27–29]. Although the incidence of immediate reactions has decreased with the use of low osmolality contrast media, there are differences depending on the contrast used. Thus, iopromide and iomeprol have been associated with higher incidence rates of immediate drug hypersensitivity reactions [30–32], while iobitridol seems to be less associated with these reactions [33].

The prevalence of non-immediate reactions has increased in the last decades, to the extent that they are now more common than immediate reactions [12]. The frequency of non-immediate reactions varies widely, from 0.5 to 23% depending on the studied population, the type of the reaction, or the ICM used [7•]. Non-immediate reactions occur more

Table 1:. Classification of iodinated contrast media

Ionic		Non-ionic	
Monomeric/High osmolality	Dimeric Low osmolality	Monomeric/Low osmolality	Dimeric/Iso-osmolality
Diatrizoate	Ioxaglate	Iohexol	Iodixanol
Iothalamate		Iopamidol	Iotrolan
Metrizoate		Iopromide	
		Ioversol	
		Iomeprol	
		Iobitridol	

frequently with iodixanol compared to iohexol, iopamidol, or ioversol [31].

Pathogenesis of hypersensitivity reactions to ICM

Immediate hypersensitivity reactions

During decades, immediate reactions following ICM administration were considered non-allergic reactions and attributed to unspecific histamine release of ICMs, due to its own chemical and pharmacological characteristics. On the one hand, ICMs have a chemotoxic effect with protein-binding ability, producing histamine release dependent on the iodine concentrations. It has also been related with a direct membrane effect due to the hyperosmolality of the contrast solution, although this relation between osmolality and histamine release is controversial [6, 34]. On the other hand, an activation of the complement system, with mast cell degranulation, basophil activation, modulation of enzymes and proteolytic cascades in plasma [35], and direct formation of bradykinin, with histamine and serotonin release has been described [1].

Another factor that has contributed to consider hypersensitivity reactions as non-allergic reactions is the fact that they may occur at the first exposure to an ICM. Nevertheless, it has been speculated that sensitization to cross-reactive molecules could be the mechanisms underlying an ICM allergy reaction appearing at the first administration of an ICM [7•, 36•].

Currently, there is growing evidence that some immediate reactions induced by ICMs are IgE mediated [6, 8–10, 37, 38]. Several reports indirectly sustain the finding of specific IgE, demonstrated by the increase of the plasmatic levels of tryptase and histamine during reactions to ICMs, which correlated with the severity of the reactions [6]. Nevertheless, these findings do not substantiate the existence of an IgE-mediated mechanism, although they constitute an evidence of mast cell activation [13••]. In other studies, the support of an IgE-related mechanism comes from the basophil activation test, having been described positive basophil activation tests to ICMs in patients suffering an immediate reaction to an ICM [39, 40]. In addition, using an enzyme immunoassay and a radioimmunoassay, Mita et al. found IgE antibodies against ioxaglic acid in the sera of patients with immediate adverse reactions [41]. The description of positive skin prick tests (SPTs) and intradermal tests (IDR) with ICM endorses the hypothesis of an immediate hypersensitivity mechanism [10, 19•, 37, 38].

Non-immediate hypersensitivity reactions

Although the clinical manifestations and severity are wide and heterogeneous, there is evidence of a common T cell-mediated mechanism in most of the reactions [14, 15]. The T cell participation has been histologically demonstrated, throughout the observation of a lymphocytic perivascular infiltration on biopsies of affected skin in patients with non-immediate ICM reactions [34]. Thus, an infiltration of CD4+ and CD8+ T cells expressing activation markers as CD25, CD69, CLA, and HLA-DR has been described [14]. In addition, positive LTT (lymphocyte transformation test) with ICMs in patients with non-immediate ICM reactions has been reported [14]. In vivo studies also support

this hypothesis, having been described positive delayed skin tests with the ICM involved and with other structurally related ICMs [13••].

Clinical manifestations

Hypersensitivity reactions to ICMs include a wide range of clinical symptoms, which can be classified in immediate reactions and non-immediate reactions, as previously said. In both types of reactions, the skin is the most frequently affected organ.

Immediate reactions

Immediate reactions generally occur in the first hour after the administration of ICMs. The most frequent reactions include erythema, pruritus, and urticaria—sometimes accompanied with angioedema—which can appear in 85% patients having an immediate reaction [7•]. Other clinical manifestations are rhinitis, hoarseness, cough, sneezing, or rhinorrhoea. Also, gastrointestinal symptoms, like nausea, vomiting, pain, or diarrhea, can appear. More severe symptoms are those involving the respiratory system, like dyspnoea due to laryngeal edema or bronchospasm. In addition, the cardiovascular system can be affected, with hypotension and dizziness. All these symptoms may develop into very severe reactions, such as anaphylactic shock, cardiac or respiratory arrest [7•, 42], or even death [43, 44]. Other reactions, like Kounis syndrome [45, 46], have been described. Finally, biphasic and protracted anaphylaxis has been described to develop from 4.1 to 10.3% of cases [32, 42] (Table 2).

Several grading systems for the severity of hypersensitivity reactions to ICM have been published [47], being the most used classification that of Ring and Messmer [48].

Table 2. Clinical manifestations of immediate and non-immediate hypersensitivity reactions to ICM

Immediate reactions	Non-immediate reactions
Pruritus	Maculopapular exanthema
Urticaria	Urticaria, angioedema
Angioedema	Fixed drug eruption
Abdominal pain, nausea, diarrhea	Stevens-Johnson syndrome
Rhinitis (sneezing, rhinorrhoea)	Toxic epidermal necrolysis
Dyspnoea (bronchospasm, laryngeal oedema)	Drug-related eosinophilia with systemic symptoms (DRESS)
Tachycardia	
Hypotension	Acute generalized exantematous pustulosis (AGEP)
Anaphylaxis	Symmetrical drug-related intertriginous and flexural exanthema (SDRIFE)
	Vasculitis

Non-immediate reactions

The most frequent manifestation is the maculopapular exanthema (30–90% of cases) occurring in the first 3 days after the ICM administration, followed by delayed urticaria (40–60%) with or without angioedema [13••]. These reactions usually are mild to moderate in severity and self-limiting [34]. Other delayed skin reactions include erythema, fixed drug eruption [49, 50], pruritus, scaling skin eruption, and multiform exudative erythema. More severe manifestations have been reported, such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug-related eosinophilia with systemic symptoms (DRESS), symmetrical drug-related intertriginous and flexural exanthema (SDRIFE), graft versus host reaction, vasculitis, or acute generalized exanthematous pustulosis (AGEP) [51, 52], although they are infrequent.

Evaluation of allergic reactions to contrast media

Allergy testing provides the opportunity to verify the immunologic mechanism implied, to identify the culprit ICM and to find an alternate ICM for radiological procedures in the future. The diagnosis of patients with hypersensitivity reactions to ICMs includes a clinical history, skin tests, *in vitro* tests, and drug provocation tests (DPTs).

The evaluation should be performed by an allergist, preferably not much longer after the reaction, because the incidence of positive skin tests seems to decrease as the time from the acute phase of the reaction to evaluation increases; this is especially critical in IgE-mediated reactions [19]. Potential confounding factors should be excluded (latex, chlorhexidine exposure, and other drugs). During acute systemic reactions, the determination of serum tryptase determination could be useful to confirm anaphylaxis. It should always be compared to baseline levels.

Clinical history

A detailed clinical history is essential. It should include the ICM involved in the reaction, the time from the reaction to the study, the symptoms presented, and the previous and subsequent tolerance to other ICMs. However, these data are not always easy to obtain, and the contrast involved is frequently unknown to the patient, and even it is not recorded in the radiological examination report.

Skin tests

Skin tests with ICM are well documented [13••, 19•, 53]. ICMs are used undiluted for skin prick and patch tests and at 1:10 dilutions in 0.9% NaCl for intradermal tests. Skin tests should be performed in accordance with European Network of Drug Allergy/European Academy of Allergology and Clinical Immunology recommendations [54].

Whenever known, skin tests should be performed with the ICM involved in the reaction. Moreover, since cross-reactivity between contrasts is frequent, it is highly recommended to test a panel of different ICMs in order to provide guidance to find alternative ICMs that could be administered to the patient in further ICM radiological examinations.

In the case of immediate reactions, skin prick and intradermal tests should be performed with an ICM battery, with readings at 20 min. Positivity rates of skin tests are very variable in the different studies, ranging from 4.2 to 73% [8, 10, 18, 19•, 37, 38, 55]. The ultimate cause of this wide variation is not well known, but it could be explained by differences in the studied populations, the ICM concentrations used, the type of reactions assessed, and the time lapse between the reactions and the allergy evaluation. The percentage of positive results is higher in the more severe reactions, when the ICM involved in the reaction is tested, and when skin testing is performed in the first 6 months following the reaction [11•, 19•].

In non-immediate reactions, intradermal tests and patch tests should be also performed with an ICM battery, and readings should be taken at 48 and 96 h. Occasionally, when the previous reaction was very delayed, readings should be also taken at 7 days. The percentage of positive results varies from 18 to 60%, depending on the studies [16, 17•, 18, 19•, 20•]. The sensitivity of the intradermal tests is higher than that of the patch tests [16, 17•]. As in the case of immediate reactions, the positivity rate is higher when the involved contrast is tested [11•].

Some authors consider that skin tests may be helpful for identifying the non-tolerated ICM and for finding alternative ICMs [18, 38]. However, several studies have shown a low negative predictive value of skin tests in ICM-delayed reactions [6, 9, 10, 16, 17•, 56]. In this sense, Torres et al. evaluated patients with non-immediate reactions to ICMs, finding that the DPT was positive in 34.6% of patients with negative skin tests [17•]. In another study, Vernassiere et al. showed that DPTs were positive in 41.7% of patients with negative skin tests [16].

In vitro diagnostic tests

In vitro tests focus on the study of different biomarkers (e.g., specific IgE, activation markers on effector cells, mediator release, and others after the stimulation with the suspected drug or their metabolites. As above mentioned, ICMs can induce both immediate and non-immediate reactions, and therefore, the in vitro tests used for their evaluation should adapt to the mechanism involved.

In vitro tests for immediate reactions to ICM

ICM-specific IgE can be involved in immediate reactions, although non-IgE-dependent mechanisms or even non-immunological mechanisms may also be involved.

In the case of IgE-mediated reactions, even if the most widely used method is the immunoassay [57••], it is not available IgE immunoassays for evaluating ICM immediate reactions. Currently, the only available in vitro diagnostic test is the basophil activation test (BAT), a functional test that mimics the IgE-mediated basophil activation during the acute phase of the reaction. The activation (measured by the expression of CD63 or CD203c) is determined in a flow cytometer after the specific drug/metabolite stimulation [57••, 58]. ICMs have demonstrated the ability to induce CD63 expression, but only when basophils are previously treated with cytokines such as IL3 or IL1 β [59]. Therefore, IL3 is frequently included in the stimulation buffer used in BAT.

BAT has been shown to be potentially useful for evaluating the ICM hypersensitivity in several studies [37, 39, 60, 61] with a sensitivity that varies from 58 to 62%, a specificity of 98–100%, and a positive predictive value (PPV) of 93.8–100% [37, 39]. Interestingly, these data showed a good correlation with the DPTs, since the negative predictive values (NPV) were high (79.3–87%) [62]. However, the results of BAT do not correlate with the severity of the symptoms [37, 39]. This fact must be taken into account, especially in the diagnosis of severe reactions [6, 55]. Although more studies are needed, the good specificity showed by the BAT could help reduce the number of false positive results, decreasing the unnecessary prescription of alternative drugs. In addition, its high NPV allows the label of patients as allergic when they really are; therefore, the need to use the DPT to confirm the diagnosis decreases [62]. This fact is particularly valuable when evaluating life-threatening reactions or high-risk patients.

In-vitro tests for non-immediate reactions to ICM

The LTT is the most widely used approach to assess ICM hypersensitivity, although there is a limited number of studies [15, 21, 63]. This test is based on the T cell capacity to proliferate after recognition of the specific drug, either by direct binding to the MHC–TCR complex or binding after uptake and processing by antigen presenting cells (APCs) [22]. The sensitivity of the LTT in ICM non-immediate reactions is heterogeneous, ranging between 37 and 75% [15, 21, 63], probably due to differences in the number of patients, clinical characteristics, and the in vitro method [15]. Different studies indicate that LTT sensitivity can be improved by using T cell lines/clones [23] or APCs, as autologous monocyte-derived dendritic cells (moDCs). In the latter case, the improvement observed ranged from 16 to 83% [63] and was related to the maturation of moDCs induced by the ICMs [63]. Although not evaluated in ICM-induced hypersensitivity, LTT sensitivity has been shown to increase when assessing patients with maculopapular exanthema (MPE) or AGEP or DRESS [57••, 58], as well as when determining the drug-induced proliferation in effector T cell subsets [64, 65].

All these results indicate that in spite of the promising results observed in some cases, which provide complementary information to the in vivo tests, there is still a need to clinically validate the different in vitro tests in larger series of patients.

Drug provocation test

DPTs are important to establish the diagnosis of allergic reactions to ICMs and to offer an alternative ICM [10, 17•, 37, 56]. In mild reactions, the DPT is necessary to rule out or confirm the diagnosis of allergy to iodinated contrasts. In the case of severe reactions, the DPT is important to provide guidance in selecting an alternative MCI that can be administered to patients if radiological investigations based on ICM are required. DPTs can only be performed if the patient's clinical situation or the severity of the reaction does not contraindicate them. In immediate reactions, studies indicate that the DPT is a recommendable and quite safe method to provide an alternative ICM [10, 37, 38].

DPTs are usually done by administering increasing doses in patients with negative skin tests with ICMs. In immediate reactions, the ICM is administered at intervals of between 20 min and an hour, with progressive increases of the injected doses until reaching the minimum of the iodinated contrast required to perform a basic radiological examination (approximately 100 ml). DPTs are formerly contraindicated when the initial reaction was an anaphylaxis [13••].

In non-immediate reactions, progressive increases of the injected ICM dose over several days in patients with negative skin test are used to confirm tolerance to an ICM. Sometimes, incremental doses are administered in two sessions separated by a week [13••]. Some authors consider that a exposure test with 1/10 of the required dose would be sufficient to exclude an allergy to an ICM, with a minimal percentage of reactions appearing after the administration of the full dose, which will be administered during the radiological exploration [36•, 66]. DPTs are contraindicated in subjects with severe reactions, such as AGEP, SSJ, NET, or DRESS [67].

Cross-reactivity

Different studies have observed frequent cross-reactions between ICMs [13••, 17•, 19•, 36•, 55]. The cross-reactivity between ICMs does not follow the current chemical classification (Table 1). However the association most frequently found has been between iodixanol and its monomer iohexol [17•, 19•, 20•]. In addition, these ICMs can also show cross-reactivity with iopentol, ioversol, and iomeprol [20•]. It seems that other contrasts, like iobitridol, may have less cross-reactivity [13••, 20•]. A recent published study in a group of 96 patients sensitized to ICMs observed a 67% of cross-reactivity among ICMs, with more than one ICM giving a positive skin test result or a positive skin test result and positive challenge [36•]. These authors propose three subgroups of ICM in which cross-reactivity was frequent: group A (iodixanol, iopamidol, iomeprol, iohexol, ioversol, and ioxitalamate), which share two identical carbamoyl side chains—with the exception of ioxitalamate; group B (ioxaglate and iobitridol) which are non-structurally related; and group C, with an isolated ICM (amidotrizoate) [36•].

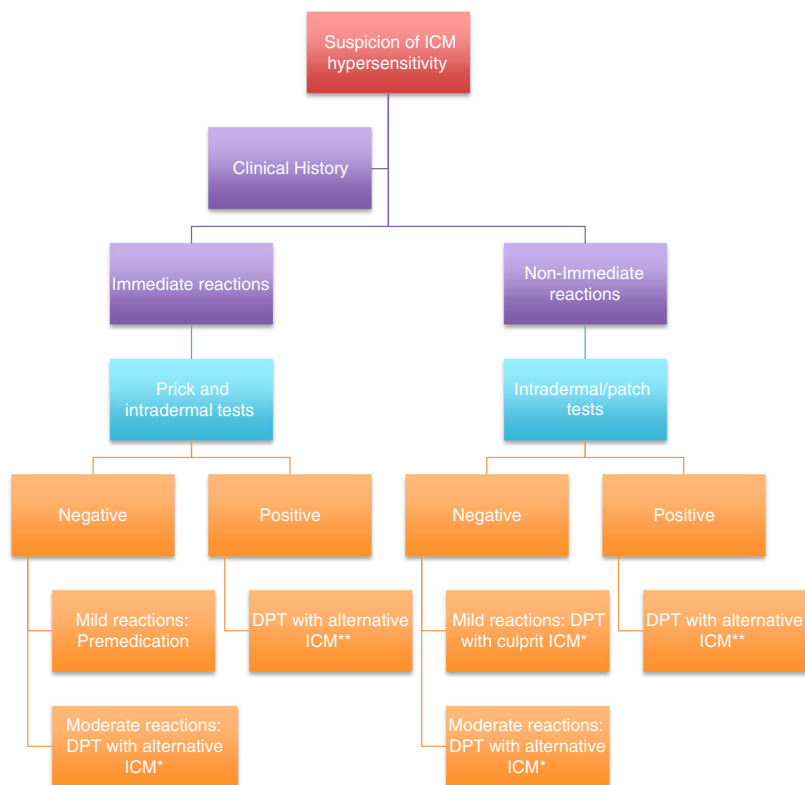
Reactions to ICMs frequently (49.5%) occur at first exposure [19•], suggesting that there may be a prior sensitization to other components that may be responsible for the allergy. It has been suggested that a previous exposure to molecules containing carbamoyl side chains might be the inducer of cross-reactivity [36•].

Prevention of ICM reactions: is premedication useful?

Although the general recommendation is to avoid a new exposition to ICMs in patients with a history of acute allergic-like or immediate hypersensitivity reactions to ICM, many patients require the administration of ICMs for an accurate diagnosis. An alternative ICMs could be selected in order to reduce the incidence of reactions; however, reactions have been reported after re-exposure [68–70], even when the ICM had been selected according to the negative result of skin testing [17•, 56].

Premedication with systemic corticosteroids and H1 antihistamines has been widely administered to reduce the recurrence of immediate hypersensitivity reactions in high-risk patients. So far, a gold standard of the premedication regimens has not been established, and in addition, its effectiveness is controversial. Based on two studies [71, 72], a premedication regimen with prednisone-diphenhydramine combination was suggested, and it is currently recommended in guidelines [25]. The benefit of adding H2 antihistamines is not demonstrated, and they are not routinely administered. One report found that the combination of H1 and H2 antihistamines was more effective in preventing adverse reactions to ICMs than either H1 antihistamines or glucocorticoids [73], while other reports found that the addition of cimetidine did not reduce the number of ulterior reactions [74, 75].

Lee et al. [76] reported the result of a study to evaluate the benefit of a severity-tailored prophylaxis in patients at risk of recurrent hypersensitivity reactions to ICMs. Chlorpheniramine and methylprednisolone were recommended according to a severity index, and an alternative ICM based on a negative skin test was used for patients with near-fatal anaphylactic shock



DPT: drug provocation test
 *when the culprit ICM is known
 ** DPT with a negative skin test ICM

Fig. 1. Management of hypersensitivity reactions to ICM. DPT drug provocation test. Single asterisk indicates when the culprit ICM is known. Double asterisk shows DPT with a negative skin test ICM

or life-threatening reactions. A total of 82.9% of the patients did not develop hypersensitivity reactions in a new administration of an ICM; most reactions were mild (89%), and there were only 1.9% of moderate to severe reactions. In the group of patients with mild reactions, the prophylaxis with antihistamines plus corticosteroids did not produce significant beneficial outcomes compared with the pretreatment with antihistamines only; in patients with severe reactions, the frequency of breakthrough reactions was increased when a lower corticosteroid dose administered before the re-exposure. In general, using an alternative ICM protected for developing a reaction. The authors concluded that for patients with mild reactions, antihistamines can be a safe alternative option on re-exposure and that the steroid dose should be stratified according to the severity of the previous reaction.

A recently published large retrospective cohort study [77] assessing the outcomes of using premedication in high-risk patients with a previous history of acute allergic-like reactions to low osmolar ICM found that 85.4% of high-risk patients tolerated low osmolar ICM during a CT; moderate and severe reactions occurred in 2.5 and 0.9% of patients, respectively. Corticosteroids were administered in 36% of patients, including all patients with prior severe reactions. The rate and the dose of corticosteroids administered were significantly higher in patients that did not present a reaction after re-exposure than in patients that did present a recurrence. Kim et al. [78] and Freed et al. [79] reported a recurrence rate of 17 and 10%, respectively, with the premedication use, which is in agreement with that study [77].

However, although premedication seems to be effective to prevent recurrences of immediate hypersensitivity reactions, severe symptoms could be developed, even when an adequate prophylaxis is administered.

In relation to non-immediate hypersensitivity reaction to ICMs, there are no studies to establish the usefulness of premedication and recurrences of severe reactions have been described despite premedication [80, 81].

Finally, in Fig. 1, an algorithm for management hypersensitivity reactions is proposed.

Conclusions

Hypersensitivity reactions to ICMs may be either true allergy or “allergy-like” reactions.

Currently, there is growing evidence that a percentage of immediate reactions, especially the more severe, are true allergy reactions mediated by IgE antibodies.

Non-immediate reactions are currently the reactions most frequently related to ICMs, and these reactions are mediated by specific T lymphocytes.

Allergy testing is useful to identify in some cases the ICM involved and to find an alternative to patients who probably need more radiological examinations with contrasts in the future. The premedication may be useful to avoid the recurrence of immediate reactions not IgE-

mediated, but it would not be indicated in severe anaphylactic reactions or in non-immediate reactions.

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Compliance with Ethical Standards

Conflict of Interest

Esther Moreno declares that she has no conflict of interest. M. Teresa Gracia-Bara declares the she has no conflict of interest. Cristobalina Mayorga declares the she has no conflict of interest. Milagros Lázaro declares the she has no conflict of interest. M. Valle Campanón declares the she has no conflict of interest. Ignacio Dávila declares the he has no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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Papers of particular interest, published recently, have been highlighted as:

- Of importance
- Of major importance

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