

Hypersensitivity Reactions to Iodinated Contrast Media

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Abstract: Adverse reactions after iodinate contrast media (ICM) administration have been observed, which can be classified as immediate (i.e., occurring within one hour after administration) and delayed or non-immediate (i.e., occurring more than one hour after administration). Even though the incidence of ICM adverse reactions has been significantly reduced by the introduction of non-ionic compounds, immediate reactions still occur in about 3% of administrations. Different pathogenic mechanisms have been suggested for ICM reactions, including immunologic ones. Basophils and mast cells participate in immediate reactions through the release of mediators like histamine and tryptase, whereas a T-cell-mediated pathogenic mechanism is involved in most non-immediate reactions, particularly maculopapular rashes. Skin tests and specific IgE assays are carried out to diagnose immediate hypersensitivity reactions, while both delayed-reading intradermal tests and patch tests are usually performed to evaluate non-immediate reactions. However, *in vitro* specific IgE assays are not commercially available. As far as *in vitro* tests are concerned, a response involving ICM-related T-cell activity may be assessed by the lymphocyte transformation test.

Allergologic evaluation appears to be indicated in hypersensitivity reactions to ICM, although the sensitivity, specificity, and predictive values of allergologic tests have not yet been established.

This paper summarizes the current state of the art and addresses the research that is still needed on the pathogenic mechanisms, diagnosis, and prevention of ICM-induced hypersensitivity reactions.

Key Words: Iodinated contrast media, hypersensitivity, delayed, immediate reactions, pathophysiology, diagnosis, prevention.

INTRODUCTION

Iodinated contrast media (ICM) are widely administered in patients for performing diagnosis and treatment of vascular diseases. Indeed, only traditional angiography with ICM provides high resolution despite the progress in less invasive imaging techniques. However, adverse reactions after ICM administration have been observed, which can be divided into three types: 1) allergic and non-allergic hypersensitivity reactions, 2) toxic reactions, and 3) events unrelated to ICM exposure [1]. Hypersensitivity reactions can also be classified with regard to the time interval between administration and the first appearance of adverse manifestations as immediate, when they occur within 1 hour after ICM administration, and delayed or non-immediate, when they occur 1 hour to 1 week (sometimes longer) after ICM injection [2,3]. The frequency and mechanisms of these reactions may differ among the different types of compounds, either ionic or non-ionic. Severe immediate adverse reactions to ionic ICM have been reported in 0.04% - 0.22% of procedures, while minor reactions have been reported in as many as 7.9% of patients.

The reactions observed with the non-ionic ICM are usually less severe, but the frequency of ICM-related death seems almost identical [4]. The present review will be focused on pathogenic mechanisms of immediate and delayed reactions.

1. Chemical Structure and History of ICM

The first organic ICM were pyridones, which were introduced in the late 1920s. However, they were highly toxic and provided a poor radiographic contrast. Bi-iodinated pyridones appeared in the early 1930s, and tri-iodinated compounds in the 1950s. Both the latter compounds were less toxic than the first ones. They are usually called “high-osmolality” ICM, because their osmolality is five to eight times that of blood (Table 1) [5]. These ionic agents dissociate into two osmotically active particles (the tri-iodinated anion and cation) for every 3 iodine atoms (ratio 3:2).

In the late 1960s the first “low-osmolality” ICM was developed, which was achieved by converting tri-iodinated benzoic acid into a non-ionic molecule by replacing the carboxylic acid (COOH) radical with an amide (CONH₂) (Table 2). Consequently, this molecule does not dissociate in solution, providing 3 atoms of iodine in each active particle and a ratio iodine: active particle of 3:1. A ratio of 3:1 can also be created in ionic hexa-iodized dimers (i.e., ioxaglate) (Table 3). Agents with a ratio of 3:1 have osmolalities of about 600-

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900 mOsm/kg water. Agents with a ratio of 6:1 can be achieved by the formation of a non-ionic dimer (i.e., iodoxanol) in which each osmotically active particle contains 6 iodine atoms. The “ratio 6:1” agents are considered iso-osmolal compounds. Ioxadinol, a hypo-osmolal compound, is brought to iso-osmolality by the addition of sodium and calcium salts (Table 3). The viscosity and the iodine concentration of ICM are influenced by osmolality. ICM are hydrophilic compounds because of the presence of hydroxyl (-OH) groups of non-ionic ICM or because of ionizing carboxyl group hydrophilic chains (usually sodium or meglumine) of ionic ICM [6]. Therefore, currently used ICM can be divided into 4 classes according to their chemical structures (Fig. 1): ionic tri-iodized monomers, ionic hexa-iodized dimers, non-ionic tri-iodized monomers, and non-ionic hexa-iodized dimers [7].

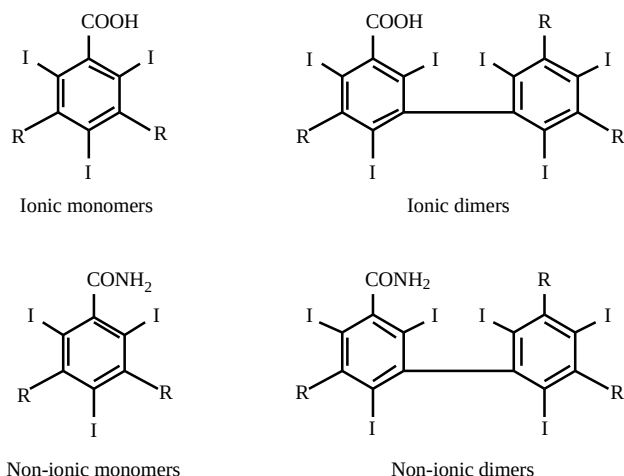


Fig. (1). Structures of different classes of iodinated contrast media.

2. Pharmacokinetics

All ICM have pharmacokinetics very similar to that of the compounds called “extracellular tracers” [6,8]. After intravenous injection, the molecules mix with circulating plasma volume and 70% of the injected dose diffuses from plasma to extracellular space within 2-5 minutes. Reverse diffusion also occurs from extracellular space to plasma. A

complete equilibrium between plasma and interstitial space is reached about 2 hours after injection [9]. The degree of internalization of these agents into intact cells is very low both *in vivo* and *in vitro* [10,11]. Kidneys, brains, livers, and a few other glandular organs are thus reported to retain small amounts of these agents [12,13]. With the exception of biliary contrast agents, all compounds display limited protein binding [14]. The majority of ICM are not metabolized before elimination, but new compounds, such as iodinated polymers for X-ray perfusion imaging and iopromide- or metrizamide-containing liposomes allowing enhancement of the liver image, have been developed [15]. The kidneys are the main route of elimination of ICM from plasma into urines [16]. ICM are filtered through glomeruli without tubular reabsorption, except for iodamide, a contrast medium that undergoes a tubular secretion [17]. In the presence of normal renal function, the half-life is about 1-2 hours for each of the four groups of ICM, and 75% of the administered dose is excreted in urines within 4 hours. Most of the injected dose is recovered intact in urines within the first 24 hours [10,15]. In patients with renal failure, the excretion of ICM is prolonged, and approximately one-third of ICM may be eliminated through extra-renal routes (gastrointestinal and biliary systems) [18]. Low osmolar ICM are less nephrotoxic than high osmolar ICM in patients with pre-existing renal failure [19]. Moreover, the iso-osmolal dimeric ICM are less nephrotoxic in comparison with other low osmolar ICM [20,21].

3. Prevalence of Hypersensitivity Reactions to ICM

Minor immediate reactions were reported in as many as 15% of patients receiving high-osmolality ICM and 3% of patients receiving low-osmolality ICM [22]. Severe immediate adverse reactions to ionic ICM have been reported in 0.04% - 0.22% of intravenous procedures, while reactions to non-ionic ICM are less frequent: 0%-0.04% (Table 4) [4,23,24]. In addition, reactions observed with non-ionic ICM are usually less severe than those with ionic ICM, 3.1% versus 12.7% [4]. Fatal reactions are extremely rare (1-3 per 100,000 administrations) and they are not related to one particular type of ICM [25]. In comparison, the frequency of delayed reactions varies from 0.5% to 23.0% [26]. This wide range seems to be due in part to false-positive diagnoses [27]. The incidence has been higher in Japan than in Europe for the past few decades. This difference could be explained

Table 1. Composition, Iodine Concentration, Viscosity, and Osmolality of “High Osmolality” Iodinated Contrast Media

Trade names	Non-proprietary names and composition g/100 mL		Iodine concentration (mg/mL)	Viscosity at 37°C mPa.s	Osmolality at 37°C (mOsm/kg water)
Radioselectan™ 76%	Aminotrizoate sodium	10.00	146	1.4	710
	Aminotrizoate meglumin	66.00			
Telebrix™ 35	Ioxitalamate sodium	9.66	350	7.5	2,130
	Ioxitalamate meglumin	65.09			
30	Ioxitalamate meglumin	66.03	300	5.2	1,710
12	Ioxitalamate sodium	21.80	120	1.1	640

Table 2. Composition, Iodine Concentration, Viscosity, and Osmolality of “Tri-Iodinated, Low Osmolality” Iodinated Contrast Media

Trade names	Non-proprietary names and composition g/100 mL		Iodine concentration (mg/mL)	Viscosity at 37°C mPa.s	Osmolality at 37°C (mOsm/kg water)
Iomeron™ 150	Iomeprol	30.60	150	1.4	301
200	Iomeprol	40.80	200	2.0	362
250	Iomeprol	51.00	250	2.9	435
300	Iomeprol	61.20	300	4.5	521
350	Iomeprol	71.40	350	7.5	618
400	Iomeprol	81.60	400	12.6	726
Iopamiron™ 200	Iopamidol	40.83	200	2.2	413
300	Iopamidol	61.24	300	4.7	616
370	Iopamidol	75.52	350	9.4	796
Ivepaque™ 150	Iopentol	32.90	150	1.7	310
200	Iopentol	43.80	200	2.8	410
250	Iopentol	54.80	250	3.9	520
300	Iopentol	65.80	300	6.5	640
350	Iopentol	76.80	350	12.0	810
Optiject™ 240	Ioversol	50.90	240	3.0	500
Optitray™ 300	Ioversol	63.60	300	5.5	645
350	Ioversol	74.00	350	9.0	780
Omnipaque™ 180	Iohexol	38.8	180	2.0	360
240	Iohexol	51.8	240	3.3	510
300	Iohexol	64.7	300	6.1	640
350	Iohexol	75.5	350	10.6	780
Ultravist™ 300	Iopromide	63.34	300	4.6	607
370	Iopromide	76.90	370	9.5	774
Xenetix™ 250	Iobridol	58.84	250	4.0	585
300	Iobridol	65.81	300	6.0	695
350	Iobridol	76.78	350	10.0	915

by a high frequency of skin testing before ICM administration in Japan, which could have led to a large number of sensitized patients because of such practice. In Japan, this practice has now declined. Most of the delayed reactions occur during the first 24 hours after ICM exposure [28,29]. Unlike immediate reactions, there seems to be a higher incidence of delayed reactions associated with dimeric non-ionic, but not with the other types of ICM [30,31]. Severe delayed reactions to ICM are extremely rare. Only 6 cases have been reported, 5 of them in adults, including 3 cases of toxic epidermal necrolysis (TEN) after iohexol administration and 2 fatal cases. Of the latter, one was a Stevens-Johnson syndrome (SJS) after iopamidol injection in a patient with sys-

temic lupus erythematosus and the other was a vasculitis following a high dose of iohexol [32-36]. A SJS has been also reported in a child suffering from Hodgkin's disease [37].

4. Clinical Manifestations

Many clinical manifestations of immediate ICM reactions resemble anaphylaxis. The most frequent systemic reactions include nausea, mucocutaneous manifestations (pruritus, urticaria), and heat sensation [4]. Gastrointestinal events such as abdominal pain and diarrhea may also occur. More severe reactions involve the respiratory and cardiovascular systems, with dyspnea and bronchospasm similar to

Table 3. Composition, Iodine Concentration, Viscosity, and Osmolality of “Hexa-Iodinated, Low Osmolality” Iodinated Contrast Media

Trade names	Non-proprietary names and composition g/100 mL		Iodine concentration (mg/mL)	Viscosity at 37°C mPa.s	Osmolality at 37°C (mOsm/kg water)
Visipaque™ 270	Iodixanol	55.0	270	5.8	290
320	Iodixanol	65.2	320	11.4	290
Hexabrix™ 200	Ioxaglate sodium Ioxaglate meglumine	12.27 24.54	200	2.2	370
320	Ioxaglate sodium Ioxaglate meglumine	19.65 39.30	320	7.5	600

Table 4. Incidence of Immediate Adverse Reactions to Iodinated Contrast Media

Reference	Ionic contrast media			Non-Ionic contrast media		
	Patient number	Overall reactions (%)	Severe reactions (%)	Patient number	Overall reactions (%)	Severe reactions (%)
Palmer 1988 [23]	79,278	3.8	0.09	30,268	1.2	0.02
Wolf <i>et al.</i> 1989 [24]	6,006	4.2	0.32	7,170	0.7	0.01
Katayama <i>et al.</i> 1990 [4]	169,284	12.7	0.22	168,363	3.1	0.04

those seen in asthma and/or with a sudden drop in blood pressure. The shock is related to vasodilatation and a massive increase in microvascular permeability. Hypotension is associated with loss of consciousness and with reflex tachycardia [38]. Anaphylactic reactions should be distinguished from other medical situations frequently seen in interventional radiology, such as vasovagal reactions.

In most cases, the onset of adverse ICM reactions is very rapid, with about 70% occurring within 5 minutes after injection [4]. ICM reactions occur following intra-vascular administration, as well as through other routes [39]. For example, Hugo *et al.* [40] reported eight cases of anaphylaxis after ICM administration in 262,000 arthrograms.

Several classifications of adverse reactions to ICM have been published. They distinguish 4 or 5 grades of severity [23,38,41,42]. The most useful is the classification published by Ring and Messmer, which is used by anesthesiologists for reactions to drugs and is more appropriate for grading severe reactions based on clinical signs [42].

The most frequent clinical manifestation of delayed ICM reactions is maculopapular rash [1]. Other skin reactions include erythema, urticaria, angioedema, fixed drug eruption, macular exanthem, scaling skin eruption, pruritus, and pompholyx. Delayed reactions are usually mild to moderate in severity and self-limiting. Rare cases of severe reactions have been reported, such as cutaneous vasculitis, SJS, and TEN [32-37]. Systemic symptoms typical of immediate-type manifestations (such as hypotension, abdominal pain, and dyspnea) and others, such as fever, have been reported occasionally [43-45].

5. Risk Factors

Immediate Reactions

Asthma and a previous history of moderate or severe reactions to ICM are the most important risk factors for generalized reactions. Previous reactors have a 21%-60% risk of reactions when re-exposed to the same or similar ICM. In the study of Katayama *et al.* [4], the prevalence of adverse reactions in patients with histories of hypersensitivity reactions to ICM was lower in the non-ionic group than in the ionic one (3.1% and 12.7%, respectively).

In patients with a history of allergy, the prevalence of adverse reactions to ICM is twice as high as in those without allergy. Asthma is the most important predisposing factor of severe reactions [38]. The female gender is indicated as a risk factor for anaphylactic reactions in a series of more than 5,000 patients who received ICM: females experienced a two-fold increase in the frequency of adverse reactions and they also suffered the most severe reactions [46]. However, whether the female gender is a risk factor is still a matter of debate, because another study on 60,891 patients indicated that the male gender was the greater risk factor [47].

Other risk factors include histories of cardiac diseases. In a case-control study of 34,371 procedures, β -blocker exposure and cardiovascular disorders were two statistically significant risk factors for severe anaphylactic reaction to ICM (OR 3.62) [48]. However, the broad definition of cardiovascular disease used in this study made any mechanistic explanation difficult. On the other hand, we observed that histamine release during coronaro-angiography was significantly

higher in patients with coronary artery disease ($P = 0.003$) [49]. It had been previously established that β -blockers may increase the release of mediators from both mast cells and basophils, but we found no difference of histamine release between treated and non-treated patients in our series of patients undergoing coronarography [49].

Delayed Reactions

Previous reactions to ICM are the most important risk factor for a new delayed reaction to ICM.

Treatment with recombinant interleukin-2 (IL-2) has also been shown to predispose subjects to ICM hypersensitivity. In these patients, reactions could occur several hours or days after IL-2 infusion [50].

A previous history of delayed hypersensitivity to other molecules could be a risk factor in developing a delayed reaction to ICM. In a recent study [51], 8 out of 15 patients with delayed reactions to ICM had either contact dermatitis

(balsam of Peru, metals, fragrances) or delayed cutaneous reactions to drugs (antibiotics, atorvastatin, pyridoxine).

6. Pathophysiology

6.1. Immediate ICM Reactions

There are conflicting reports about the mechanisms responsible for the release of histamine from mast cells by ICM [52]. Hypersensitivity reactions to ICM are generally considered non-allergic hypersensitivity manifestations and in most cases no antigen-antibody reaction can be demonstrated. They appear to result from release of vasoactive mediators such as histamine, serotonin, and bradykinin after exposure to ICM [53]. Histamine can be released from basophils and mast cells. Histamine release may depend on (i) a chemotoxic effect, (ii) a direct membrane effect related to the osmolality of the ICM, (iii) the heterogeneity of cell release, (iv) activation of the complement system, or (v) an IgE-mediated mechanism (Fig. 2).

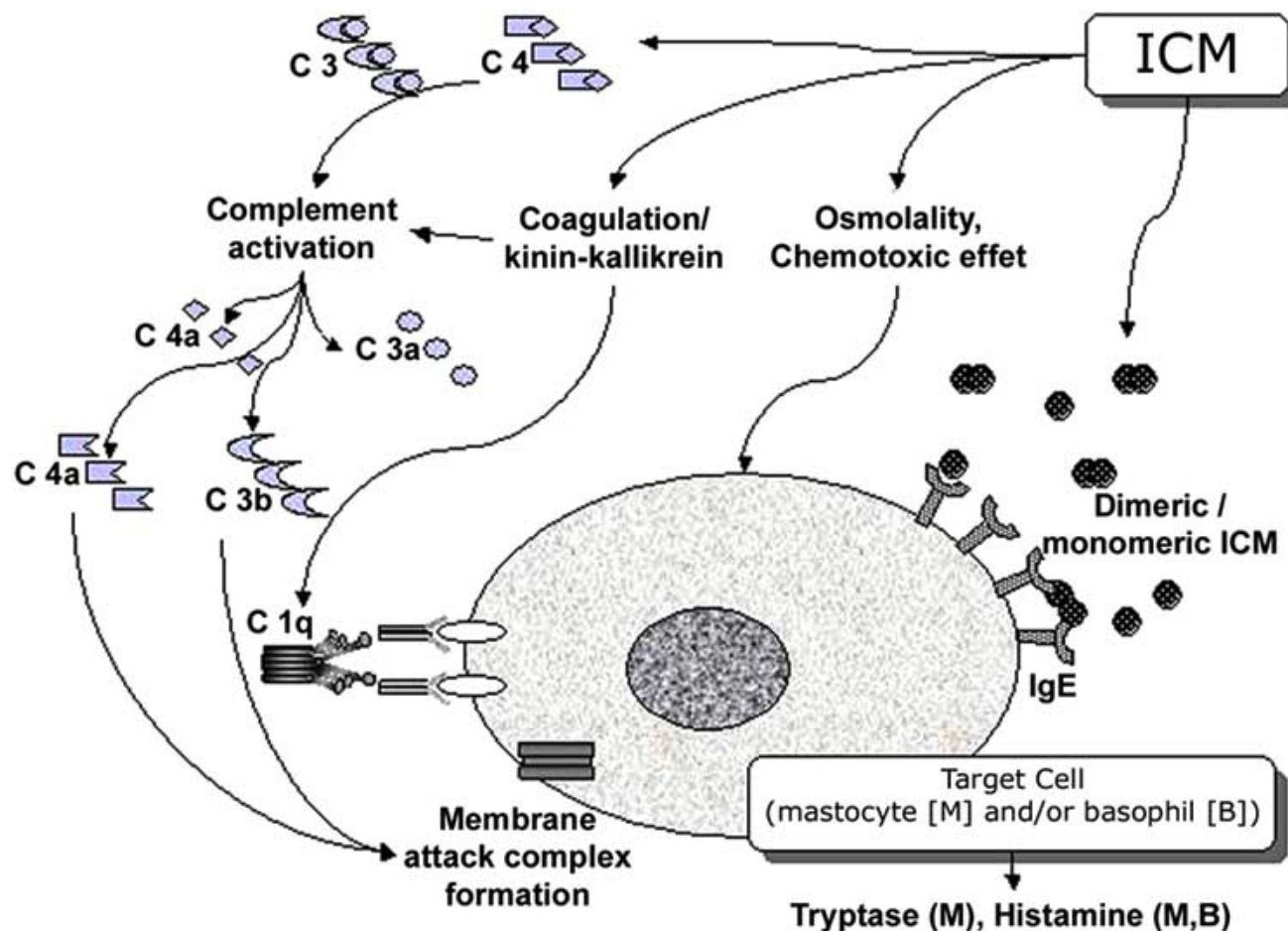


Fig. (2). Mechanisms of histamine and tryptase release in immediate reactions to iodinated contrast media (ICM).

Basophils (B) and mastocytes (M) can release histamine (B,M) and tryptase (M) by different mechanisms, such as the chemotoxic effect of ICM, the direct membrane effect related to the osmolality of ICM, activation of coagulation and complement systems, and the IgE-mediated mechanism.

Chemotoxic Effect

The clinical effects of ICM do not result only from high osmolality, but also from their own specific pharmacology, which mediates chemotoxic effects. Paton [54] reviewed the chemical structures of some histamine-releasing agents and concluded that the presence of basic groups (NHCO) or the big size and complexity of the molecule favor histamine release. Studies in human basophils from non-allergic, non-atopic non-reactors to ICM have shown that the percentage of histamine release is dependent on iodine concentrations [55]. The protein-binding capability of ICM is poor. However, protein binding occurs and might inhibit some enzyme systems like acetylcholinesterase, which leads to excessive and prolonged cholinergic activity. It could explain side effects such as flushing, bronchospasm, urticaria, and abdominal pain [56,57]. For example, ioxaglate has a lower osmolality than iohexol, but it produces more flushing, which may be related to acetylcholinesterase inhibition [55].

More recently, 11 ionic and non-ionic ICM were compared regarding their effects on various biochemical parameters *in vitro*, such as histamine release in mast cells, hydrophilicity, and protein binding. Although all compounds influenced the parameters tested, non-ionic dimers seemed to be more effective than non-ionic monomers [58].

Osmolality

In a non-isotonic environment, cells can swell or shrink. Hyperosmolality is considered an important factor for adverse reactions to ICM [59]. However, discrepant results have been published on the role of osmolality in histamine release [60]. ICM with comparable osmolalities can induce different levels of histamine release.

Ionic hyperosmolar solutions like saline appear less potent in inducing histamine release than non-ionic solutions, and this release process does not appear to be toxic or lytic. It does not depend on IgE-binding to basophils [61]. The extent of histamine release seems dependent on the dose and time of exposure and on the cellular type [62]. Amon *et al.* [63] investigated the effect of 6 commonly used ICM on peritoneal and lung mast cells in animals. Solutions with low osmolalities released little histamine, in contrast to solutions with high osmolalities. Conversely, Stellato *et al.* [64] found no association between the osmolality of ICM and histamine and tryptase release from human basophils and human mast cells isolated from lung, skin, and heart tissue.

Heterogeneity of Mediator Release in Cell Populations

The degree of release depends on the cells tested. For example, Ennis *et al.* [65] showed that cardiac mast cells were more sensitive to ICM than were mast cells from lungs, livers, and kidneys. Moreover, histamine release depends not only on the tissue origin of mast cells, but also on underlying mechanisms related to diseases. This is illustrated by an experiment in which isolated peritoneal and lung mast cells were exposed to different ICM from normotensive and hypertensive rats. Mast cells derived from hypertensive rats released significantly more histamine than those from normotensive rats [65]. Stellato *et al.* [64] showed heterogeneous histamine and tryptase release from human basophils and human mast cells isolated from lung, skin, and heart tissue

after exposure to ICM. As previously mentioned, they found no correlation between the osmolality of ICM and histamine release. A study with isolated mast cells from healthy subjects showed an ICM-induced release of both histamine and tryptase and of newly synthesized mediators, such as leukotrienes and prostaglandins [67]. The *in vitro* release of preformed mediators from basophils (histamine) and from mast cells isolated from ischemic and control hearts (histamine and tryptase) was evaluated using either immunological (anti-IgE) or non-immunological stimuli (Ca⁺⁺ ionophore). The authors observed that mast cell density and tryptase content were higher in ischemic than in control hearts. In addition, the anti-IgE-induced release was also increased in the isolated cells from ischemic hearts [67]. We have studied *in vivo* the release of histamine and tryptase from basophils and mast cells provoked by ICM during coronary angiograms. The plasma concentration of histamine and tryptase was determined before and after sequential administration of an ionic ICM, ioxaglate, and a non-ionic ICM, iopamidol [49]. The release of histamine observed in arterial blood after ICM injection was higher in case of ischemic heart disease, suggesting that in this disease the increased release of mediators previously observed in heart mast cells also exists in systemic blood basophils. The increased release of histamine from basophils in coronary artery disease may have a pathophysiological significance, regardless of the context of ICM injection. It has been suggested that histamine participates not only in myocardial damage and arrhythmia, but also in the patho-mechanisms of ischemia and atherosclerosis [68-70].

Complement Activation

The complement is part of the innate immune system and constitutes one of the main mechanisms of antibody-mediated immunity. The deposit of the complement factors on normal cells and tissues is limited. They must be activated at sites of tissue injury. The role of complement activation in ICM reactions has been evaluated in a considerable number of studies [71]. Krause *et al.* [58] have shown a decrease in CH50 (complement hemolysis 50%) after ICM exposure, indicating the activation of the complement system. Other authors have suggested that the decrease in CH50 by ICM is due to a direct suppression of complement activity, rather than to an activation-induced consumption [72]. For this reason, measurement of activated complement proteins (C_{3a}, C_{4a}, C_{5a}) seems to be more reliable than that of CH50. Histamine release may be stimulated after formation of the anaphylatoxins C_{3a} and C_{5a} by lysosomal enzymes or proteolytic enzymes, such as trypsin or plasmin [73,74]. Increase of blood histamine and activation of the complement system have been shown in both reactors and non-reactors to ICM, without any significant difference between the two groups [75-77]. Eaton *et al.* [77] have shown that non-ionic ICM in the plasma of donors had lower complement-activating potential than ionic ICM. In addition, the ionic ICM reduced haemolytic activity and raised C_{3a}. In other *in vivo* studies, complement activation was not found in all patients [78-80]. Furthermore, ICM may induce proteolysis without participation of the multicomponent C₃/C₅ convertases by activation of the plasma proteolytic systems, in particular the coagulation and kinin-kallikrein systems, and by various cross-over amplification and depletion of C₁-esterase inhibitor [81]. We

performed a multicenter prospective study in which 20 patients with mild to severe reactions to ICM had an increased blood level of both histamine and tryptase, which correlated with the severity of the reactions. In this study, simultaneous increases of C_{3a} and C_{4a} concentrations were observed only in patients with life-threatening reactions, indicating activation of a direct, immunologically mediated pathway [82]. More recently, we compared the total IgE and complement fractions in patients with coronary artery disease and high histamine concentration (>6.8 nM) (group 1) with both patients with coronary artery disease and normal plasma histamine level (group 2) and patients without coronary artery disease and normal plasma histamine (group 3). We did not find any difference of total IgE and C_{3c} and C_4 complement fractions among the 3 groups [83]. Finally, the interactions between ICM and the complement system are still controversial, which may be due to experimental conditions and characteristics of the studied populations.

IgE-Mediated Mechanism

An immunologic pathogenic mechanism has been suggested by Brasch *et al.* [84], who reported that rabbits immunized with ICM analogues bound to carrier protein produced high titers of antibodies against ICM. Later, they compared the presence of IgE against ICM in patients suffering severe reactions with that in control subjects [85]. The sera from the patients had significantly higher levels of ICM binding activity, suggesting the presence of anti-ICM antibodies. Twenty years later, it was demonstrated that the administration of iopamidol with an immunogen in mice produces an increased level of total IgE, but no anti-hapten IgE [86]. Mita *et al.* [87] detected IgE antibodies specific to ioxaglate in patients who had previously reacted to this ICM. In a multicenter prospective study [82], we assessed 20 patients with mild to severe immediate reactions to ioxaglate and

ioxatamate and control subjects. We found that the former had a high level of serum tryptase, which corresponded to the severity of the reactions. Later, we studied the IgE after ICM exposure during coronary catheterization and found no difference in total IgE serum levels between coronary-artery-disease patients and the other patients [83]. No patient had a severe allergy-like reaction and only one patient had a detectable anti-ioxaglate IgE level. The affinity of drug-IgE binding was extremely low, suggesting that it may have been the result of a low specific interaction (Fig. 3). The low affinity of ICM for IgE means that in order for the molecule to bind IgE, a high concentration of ICM has to be reached [88]. Such a concentration may be theoretically reached when the ICM is injected in the coronary artery, since the concentration of injected ICM is as high as 50 mM and its diffusion is mainly restricted to the artery lumen. In addition, the dimeric chemical structure of ioxaglate is compatible with an IgE-mediated mechanism. However, given the low affinity of the ICM binding to IgE, the specificity of this binding is questionable. In fact, the pathogenic role of the IgE antibodies seemed to be marginal in our prospective study, as most of the reactors had no detectable IgE in serum [82].

6.2. Delayed ICM Reactions

Delayed reactions are heterogeneous in their pathophysiological pathways, clinical symptoms, and severity. Nevertheless, growing evidence indicates that a cell-mediated pathogenic mechanism is involved in most delayed reactions (Fig. 4) [89-92].

T-Cell Activation

The role of T-cells in contact dermatitis has been proven [93,94]. In contrast, their role in delayed ICM reactions has not been well elucidated. The arguments in favor of this

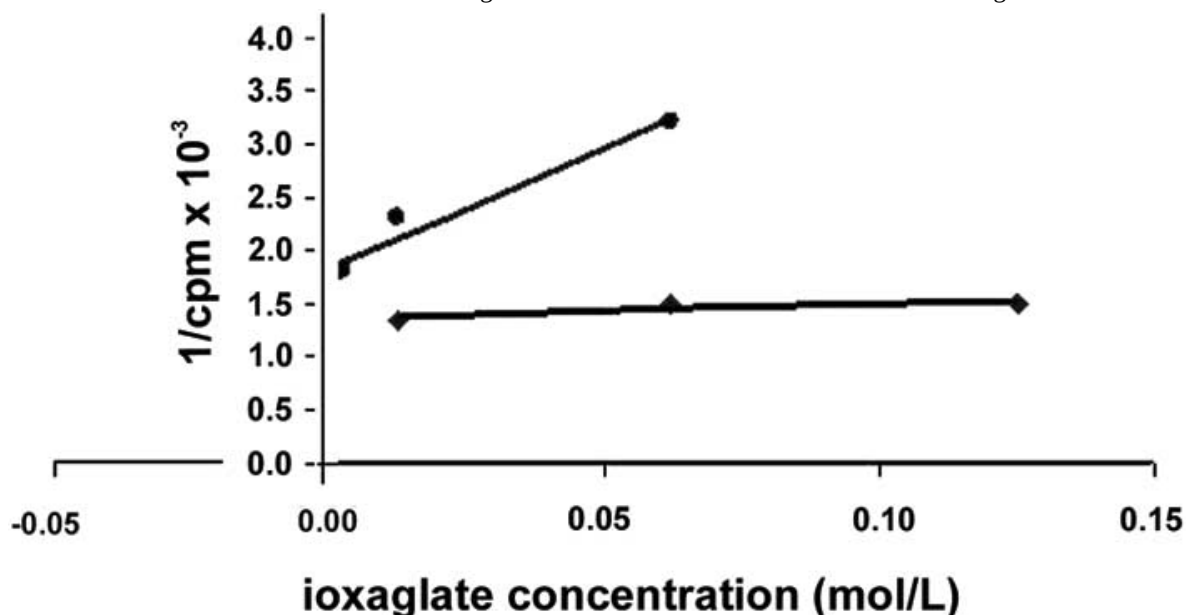


Fig. (3). The Dixon plot of the inhibition of IgE binding to ioxaglate-sepharose by ioxaglate. The patient serum was incubated with increasing concentrations of ioxaglate in the presence of either 25 mL or 50 mL of ioxaglate-sepharose solid phase. IgE-bound to drug-sepharose were detected by adding an anti-IgE 125I-iodinated tracer. The dissociation constant corresponded to the intercept of the 2 curves obtained by plotting (1/cpm) in function of the concentration of ICM added (X, mol/L).

mechanism are (i) the clinical manifestations of delayed ICM reactions similar to other drug-induced side effects mediated by T-cells [95], (ii) positive patch tests and delayed intradermal tests to the culprit ICM [51,92,96-98], (iii) histological findings of skin showing the presence of infiltrates of T-cells [92,99-101], (iv) *in vitro* T-cell proliferation with ICM [92], and (v) the reappearance of delayed eruptions after provocation tests [51,102,103].

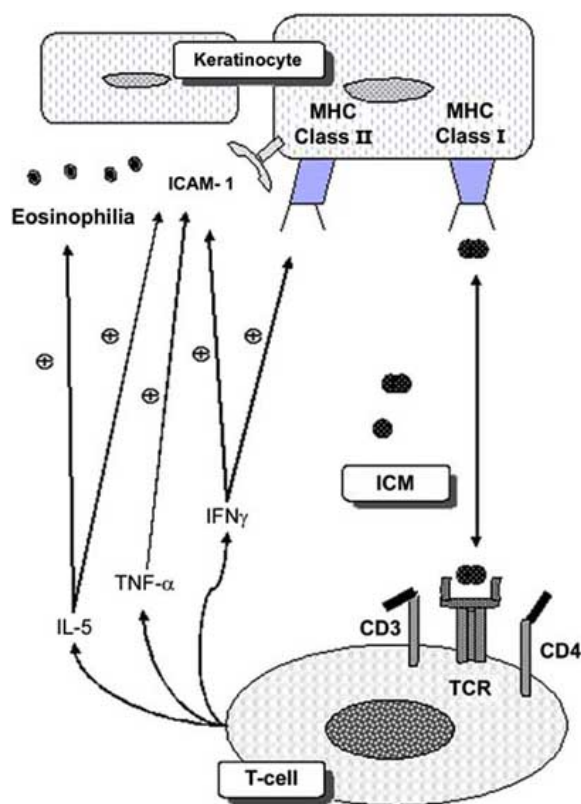


Fig. (4). Pathways associated with the presentation of iodinated contrast media (ICM) to T-cells.

ICAM-1 plays an important role in cell interaction and migration of T-cells within the epidermal compartment. Infiltrating T-cells interact with the drug through their T-cell receptors (TCR). Full T-cell stimulation requires an ICM-dependent interaction of TCR with the major histocompatibility complex (MHC). Stimulated T-cells release cytokines, including, IL-5, TNF- α , and IFN- γ . Enhanced IL-5 production stimulates the differentiation and the recruitment of eosinophils. TNF- α and IFN- γ mediate the keratinocyte expression of the intercellular adhesion molecule (ICAM-1) and MHC class II antigens, which subsequently enable drug presentation to CD4⁺ T cells. Stimulated keratinocytes express MHC antigens and ICAM-1.

T-cells have receptors belonging to the major histocompatibility complex, which recognize antigens on cell surfaces. T cells recognize small peptide antigens and are also involved in immune reactions to small chemicals [104]. Most drugs that provoke delayed reactions must undergo bioacti-

vation to haptens, which are recognized by sensitized lymphocytes [105]. Haptens are small molecules (<1.0 kDa) that are chemically reactive and thus able to undergo stable, covalent binding to larger proteins or peptides [106-108]. Unlike some drugs (penicillins, sulfonamides), non-ionic ICM are chemically non-reactive and unable to bind covalently to proteins, and they are found almost completely unmetabolized in urines. Like lidocaine (a drug without haptenic properties), ICM are unable to form haptens, and they may therefore stimulate T-cells by another mechanism. In effect, Zanni *et al.* [109,110] have shown that lidocaine-specific T cell lines were generated in patients with contact dermatitis after topical application of lidocaine. They concluded that local anesthetics are directly recognized by $\alpha\beta^+$ T cells in an HLA-DR restricted way, as neither drug metabolism nor protein processing is required for T cell stimulation. This model can be applied to ICM reactions and can also explain the cross-reactions among different ICM. Recently, it has been proposed that a number of drugs, including ICM, might stimulate memory T-cells directly via their T-cell receptor, in absence of a peptide antigen. That could lead to direct T-cell stimulations by drugs, bypassing the innate immune system [111].

It has also been demonstrated that the processing-free HLA class II-restricted T-cell response termed "direct metabolism-independent T-cell stimulation" can occur following drug binding by specific T-cells in cutaneous adverse drug reactions [112].

The majority of delayed ICM reactions occurs in the first 24 hours after ICM administration. A rapid reaction is possible only if a pool of T cells is able to interact with the ICM [101]. Some authors have proposed the formation of antigens (iodo-proteins) during radiographic procedures in amounts sufficient to elicit a hypersensitivity reaction, in subjects with a previous sensitization to immunologically similar iodo-proteins [113,114]. Cross-reactions can occur among distinct chemical classes of ICM [51,115,116].

One study [117] indicates that only ionic ICM have antigenic properties, as shown by lymphocyte stimulation tests. In this study, irradiated mixtures of radiographic contrast media and serum proteins were not more effective than ICM alone in inducing a lymphocyte response.

Eosinophil Activation

Eosinophil degranulation is thought to play a pivotal role in the pathogenesis of allergic disorders. A transient silent eosinophilia was noted in the peripheral blood in patients after the administration of ICM. The duration of an eosinophilia is approximately 6 days [118]. The incidence of eosinophilia is irrespective of dosage or type of ICM [118-120]. Moreover, several studies have shown the presence of eosinophils in the dermal infiltrates of ICM-induced skin lesions [51,102,121,122]. *In vitro* and *in vivo* studies suggest that enhanced IL-5 production by helper T cells stimulates the late stages of eosinophil differentiation [123]. Mikami *et al.* [124] showed that the number of peripheral eosinophils and the level of serum IL-5 at the eruption-active stage were high in skin lesions of patients with drug hypersensitivity. Histological and immunohistological examination revealed CD4⁺ T cells and eosinophils.

The Effector Cells: T Lymphocytes

In delayed cutaneous adverse drug reactions due to other drugs, immunohistochemical studies of maculopapular exanthems (MPE) have shown that the cell infiltrate in drug-induced MPE is mainly composed of CD2+, CD3+ T cells (40-70%), with a predominance of CD4+ cells [125,126]. Conversely, CD8+ cells are the predominant epidermal T-cells in most severe skin drug reactions [127,128]. In patients with ICM-induced skin reactions, the cellular population consist mainly of CD3+, CD4+ T cells [92].

In addition to their cytotoxic function, drug-specific T cells induce skin inflammation through the release of different cytokines (i.e., IL-1, IL-5, IL-6, TNF- α , IFN- γ) and chemokines (i.e., CCL-11, CCL24) [129-132]. The increase of IFN- γ induces class II antigens of the major histocompatibility complex, which subsequently enables drug presentation to CD4+ T cells [133]. The release of other cytokines and chemokines causes infiltration of eosinophils and other inflammatory cells. In an *in vitro* study of 9 patients [134], ICM administration provoked the modification of cytokine release, with an increase of IL-2, IL-4 and IL-6. These results suggest that ICM administration induces a sequential T helper response, first of type 1, then of type 2. Patients with late adverse reactions had the highest histamine values.

ICAM-1

The epidermal keratinocyte is a key cell in the initiation and propagation of cutaneous immune reactions. Since keratinocytes have been shown to express human leukocyte antigens at inflammatory sites [125], these cells may act as antigen-presenting cells. Moreover, keratinocytes regulate T-cell activation in a direct manner with regard to the responsiveness to adhesion molecules such as ICAM-1 (CD54) [135]. ICAM-1 plays an important role in cell interactions and migration of T-cells within the epidermal compartment. Following the action of ICAM-1, keratinocytes are capable of internalizing compounds within 20-60 minutes [136]. The triggers for the induction of ICAM-1 expression are TNF- α , IFN- γ , and IL-5, which interact synergistically. Yamauchi *et al.* [121] reported focal expression of HDL-DR and ICAM-1 in keratinocytes in the epidermis of a patient with an eruption caused by iopamidol.

7. Diagnosis

7.1. Immediate Hypersensitivity Reactions

During or Immediately After the Reaction

Histamine and tryptase. These are the mediators most widely studied. These mediators have been found in some patients with severe ICM reactions, but not in those with milder symptoms [82,87,137-139]. Plasma histamine peaks within 5-10 minutes after the onset of the reaction and returns to normal in less than 1 hour [82]. Values in excess of 2,000 nmol/L can be observed in patients with grade 4 reactions [82]. Mast-cell involvement can be evaluated by measuring plasma tryptase levels [140]. The peak concentration is observed 15-30 minutes after the reaction, and the half-life in plasma was 90 minutes to 2 hours. Blood samples must be collected 1-2 hours after the onset of symptoms; in order to enable comparison with baseline levels, additional samples

should be collected 1-2 days after the reaction [1]. Like those of histamine, tryptase levels seem to be correlated with the severity of the reaction [82].

After Recovery

Specific IgE antibodies. A few investigators have reported the presence of ICM-specific IgE in the sera of patients with immediate reactions [83,87,137,141]. However, phenyl-sepharose drug IgE-radioimmunoassays sometimes indicate that non-specific rather than specific IgE are involved [83,88]. No commercial assay is available for routine measurement of serum levels of ICM-specific IgE antibodies.

Skin tests. In clinical practice, the way to diagnose an IgE-mediated hypersensitivity is to perform skin prick tests (SPT) and/or intradermal tests (IDT), but positive tests have rarely been reported in immediate reactions and only in severe ones [82,137,142-144].

The reliability of other *in vitro* tests, such as the basophil activation test, has not yet been established [1].

7.2. Delayed Hypersensitivity Reactions

During or Immediately After the Reaction

Hematology and clinical chemistry. Asymptomatic eosinophilia following ICM administration has been reported [119,120]. In patients with severe skin reactions, other organs could be involved [145], especially in patients who were treated with IL-2 [146]. Thus, the assessment of liver and renal functions should be considered. Tests detecting lymphocyte activation markers must be considered research tools [1].

Skin biopsy. Histological examinations of biopsy specimens from ICM-induced skin reactions have occasionally been reported. Most of them have been conducted during severe skin reactions. In these cases, the affected skin showed perivascular T-cell infiltration, epidermal spongiosis, and necrosis, as well as hydropic degeneration of the basal layer [100,102,121,122,145]. In mild cases, the histological examination showed only a slight lymphocytic perivascular dermal infiltration [51]. Unfortunately, as usual in maculopapular rashes due to other drugs, biopsy findings in ICM-induced skin reactions have few distinguishing features. Thus, histological examination is not obligatory, and the results must be interpreted in the context of the whole clinical report.

After Recovery

Skin tests. Three main types of skin test are in use: (i) SPT, (ii) IDT, and (iii) patch tests. The first two tests are used for diagnosis of both IgE-mediated and T-cell mediated reactions, whereas the patch test is used to diagnose T-cell mediated reactions only [95]. Several investigators have shown positive SPT or IDT to the culprit ICM in reactors [95-97]. However, in a recent study [51], only 2 of 15 patients had positive patch tests, and none had positive SPT, while 8 had delayed positive results on IDT. Thus, it seems that IDT are more reliable than patch tests and SPT in delayed skin reactions, but larger studies are needed to reach a definitive conclusion.

Lymphocyte transformation tests (LTT). A response involving ICM-related T-cell activity may be assessed *in vitro* by the LTT. In a recent study [92], which assessed 12 patients with adverse reactions to ICM, the LTT was positive in 3 out of the 4 patients evaluated with this method. In this study, however, slight positive responses were also observed in 2 out of 10 control subjects not exposed to ICM. Positive LTT to several ICM, which confirmed patch-test and delayed intradermal-test positivity, have also been described in a recent case report [97]. There are also reports of single cases of cell-mediated hypersensitivity to ICM, in which LTT were negative [147,148]. It has to be considered that the LTT is a rather cumbersome test, lasting about 1 week, as it requires live cells and relies on the measurement of the proliferation of drug-specific T cells in a cell culture system with various variables. The LTT, therefore, cannot be recommended for routine use at present, but further research in this area is indicated [1].

8. Prophylaxis

Prevention of Immediate Reactions

In current practice, interventional cardiologists and radiologists prefer to avoid the use of ionic ICM for preventing generalized reactions to ICM in patients with risk factors, such as bronchial asthma, and/or with a history of reactions to ICM. In the latter patients, a structurally different non-ionic ICM should be chosen. Wolf *et al.* [149] studied the use of ionic and non-ionic ICM alone and in combination with steroids. They concluded that non-ionic ICM alone were safer for intravenous use. In accordance with Wolf *et al.* [149], a European consensus report for the prevention of generalized reactions to ICM recommended non-ionic ICM in patients at high risk and the presence of a resuscitation team during their administration [2]. In patients with severe reactions, it recommended gadolinium as an alternative to ICM for angiography [150].

So far, the successful use of skin tests, provocation tests, and *in vitro* basophil activation tests for the selection of alternative ICM in patients with histories of immediate hypersensitivity reactions has only been reported in a few cases [35,142,143].

Premedication

The prophylactic use of corticosteroids in patients at high risk of immediate reactions is controversial. The most used corticosteroids are prednisolone, prednisone methylprednisolone, and hydrocortisone. The protocols and the administration routes are variables [2]. Severe reactions may still occur in patients who receive corticosteroid premedication [4]. Theoretically, premedication may help to lessen reactions caused by non-specific histamine release, but may not be as effective in preventing IgE-mediated reactions. The estimated recurrence rate of reactions despite corticosteroid administration has been reported to be almost 10% [151]. Patients with repeat reactions despite premedication frequently have a history of food allergy or hay fever [151,152]. Despite the controversial evidence of its efficacy, steroid prophylaxis should be considered, except in patients with diabetes mellitus or systemic infections.

Histamine is a primary mediator of anaphylaxis. H1 and H2 antihistamines have been used as adjunctive treatments for the prevention of ICM reactions [2]. They are administered alone or in association with corticosteroids [153,154]. Their protective effect against ICM reactions has not been proven.

Prevention of Delayed Reactions

Contrast Medium Selection

Patients with previous ICM-induced delayed skin eruptions are at risk for developing new eruptions if re-exposure to the same compound takes place [1]. Consequently, another ICM should be chosen if re-exposure is required. Due to frequent cross-reactivity among different ICM, changing the responsible compound is no guarantee against repeat reactions.

Several investigators performed patch tests and delayed-reading IDT to diagnose a cell-mediated hypersensitivity to the culprit ICM in such patients. However, it remains to be established whether such tests are also reliable tools for identifying a safe alternative ICM. In a recent study by Vernassiere *et al.* [51], skin tests had a low negative predictive value with regard to delayed reactions to ICM.

Premedication

The recent guidelines from the Contrast Media Safety Committee of the European Society of Urogenital Radiology [26] stated that patients with previous serious delayed adverse reactions can be given oral steroid prophylaxis if new ICM exposure is required. However, delayed hypersensitivity reactions have been reported despite corticosteroid premedication [1].

A prophylactic protocol has recently been devised by our group for subjects with a cell-mediated hypersensitivity to ICM [97]. We successfully used intramuscular 6-methylprednisolone (40 mg daily) and oral cyclosporine (100 mg twice daily) 1 week before and 2 weeks after each of 4 angiograms with iobitridol in a patient who had suffered 2 iopamidol-associated maculopapular eruptions (the second of whom occurred despite steroid premedication) and displayed positive delayed-reading intradermal tests, patch tests, and LTT to several ICM, including iopamidol and iobitridol.

However, further investigations are needed in order to establish a practical and effective prophylactic protocol for preventing further hypersensitivity reactions to ICM in patients who have suffered them.

CONCLUSION

Even after introduction of non-ionic compounds, adverse reactions to ICM represent a challenge to the treating physician. In recent years, great advances have been made regarding the pathogenic mechanisms and diagnosis of ICM hypersensitivity. Allergologic evaluation appears to be indicated in patients with severe immediate hypersensitivity reactions, as well as in those with non-immediate skin reactions following administration of ICM, although several questions still remain. Skin testing of immediate reactors has been positive only in patients with severe reactions, in whom positive IDT may be indicative of an occasional IgE-

mediated reaction. For patients with non-immediate skin reactions to ICM, there is solid evidence that skin testing may be useful. If a patient with a previous ICM-induced hypersensitivity reaction requires a new administration, a structurally different ICM should be given, means of resuscitation should be available during the radiological examination, and prophylactic regimens have to be considered. However, several aspects of ICM hypersensitivity are not yet fully understood and have to be addressed in further studies. These include the pathogenic mechanisms of non-IgE-mediated hypersensitivity reactions; the sensitivity, specificity and predictive value of specific IgE assays, skin testing, and LTT; and the value of premedication procedures in patients with different types and severities of hypersensitivity reactions.

ABBREVIATIONS

CCL	=	CC chemokine ligand
CH50	=	Complement hemolysis 50%
ICAM-1	=	Intercellular adhesion molecule-1
ICM	=	Iodinate contrast media
IDT	=	Intradermal test
IFN- γ	=	Interferon- γ
IgE	=	Immunoglobulin E
IL	=	Interleukin
kDa	=	Kilodalton
LTT	=	Lymphocyte transformation test
mOsm/kg	=	Milliosmolar/kilogram
MPE	=	Maculopapular exanthem
nM	=	Nanomolar
nmol/L	=	Nanomole per litre
SJS	=	Stevens-Johnson syndrome
SPT	=	Skin prick test
TEN	=	Toxic epidermal necrolysis
TNF- α	=	Tumor necrosis factor- α

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