ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Special Article

Reactions to iodinated contrast media – practical aspects

Reações aos meios de contraste iodados – aspectos práticos

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ABSTRACT

Introduced in the 1950s, iodinated contrast media (ICM) remain among the most commonly prescribed drugs in radiology and have been widely used following new formulations with increased resolution and reduced toxicity. While adverse reactions to ICM are not uncommon, they are underreported and severe reactions are not always recorded. Guidelines for the management of reactions to ICM vary across different international societies, giving rise to several controversies. This paper discusses the main aspects of adverse reactions to ICM and investigation using *in vivo* assays to identify safe alternatives for future procedures. It also addresses the indications for premedication.

Keywords: Iodinated contrast media, hypersensitivity reactions, skin tests, premedication.

RESUMO

Desde a sua introdução na década de 1950, os meios de contraste iodados (MCI) têm estado entre os fármacos mais frequentemente prescritos na radiologia e vêm sendo amplamente utilizados após as novas formulações, com melhor resolução e menor toxicidade. As reações adversas a esses agentes não são incomuns, mas são subnotificadas e nem sempre há registro das reações graves. As diretrizes para manejo de pacientes com reação aos contrastes variam entre as diferentes sociedades internacionais, trazendo à discussão diversas controvérsias. Nesse artigo discutiremos sobre os principais aspectos relacionados às reações adversas aos MCI, sobre a investigação através dos testes *in vivo* em busca de alternativas seguras em caso de procedimentos futuros e também abordaremos as indicações da pré-medicação.

Descritores: Meios de contraste iodados, reações de hipersensibilidade, testes cutâneos, pré-medicação.

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Introduction

Contrast media (CM) are solutions used to increase image definition in radiology, improving diagnostic accuracy and monitoring of various diseases. The most frequent types are iodinated CM (ICM) for X-ray and tomography examinations, gadolinium-based CM for magnetic resonance examinations, in addition to dyes such as patent blue, isosulfan blue, methylene blue, and fluorescein.

More than 70 million doses of ICM are administered annually worldwide, making adverse reactions to these agents increasingly relevant.[1,2] Adverse reactions to CM include toxic reactions (generalized itching, sensation of heat, flushing, nausea, metallic taste) and hypersensitivity reactions. Hypersensitivity reactions may be allergic or non-allergic and, according to the chronology and clinical picture, are classified as immediate (i.e. those occurring up to 1 hour [or up to 6 hours] after administration) or delayed reactions (i.e. from 1 hour to a few days after exposure).[3,4] Skin tests are highly recommended to identify allergic hypersensitivity reactions and determine alternative agents, and the provocation test can be used to confirm tolerance.[3]

How are iodinated contrast media classified?

The chemical structure of ICM consists of a benzene ring linked to at least 3 iodine atoms responsible for radiopacity. Side chains are modified with hydroxyl groups and other molecules and define the properties of each CM (Figure 1).[5] ICM can be classified according to 3 properties: the charge of the iodine molecule (ionic or non-ionic), the molecular structure (monomeric or dimeric), and the osmolarity of the contrast solution (hyperosmolar, hypo-osmolar or iso-osmolar) (Figure 2).[6]

The ionization capacity of ICM is directly related to the frequency and severity of adverse reactions.6 Non-ionic and lower osmolarity ICM are associated with a lower incidence of reactions.

Are reactions to iodinated contrast media common?

In the past, high-osmolarity ICM were associated with a higher incidence of immediate reactions due to direct histamine release without the involvement of an immune mechanism. After low-osmolarity ICM were introduced in the market, the incidence of immediate reactions decreased, but evidence of reactions induced by an immune mechanism has been increasing, especially delayed reactions.[6]

Currently, immediate or delayed reactions to ICM occur at a frequency of 0.5% to 3% of infusions, and are usually mild to moderate. Mortality is low, ranging from 1 to 2 per 100,000 administrations.[3,4,7]

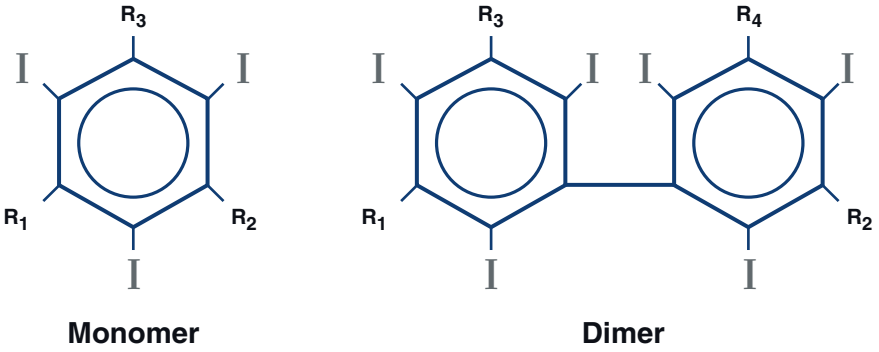

Figure1
Chemical structure of iodinated contrast media

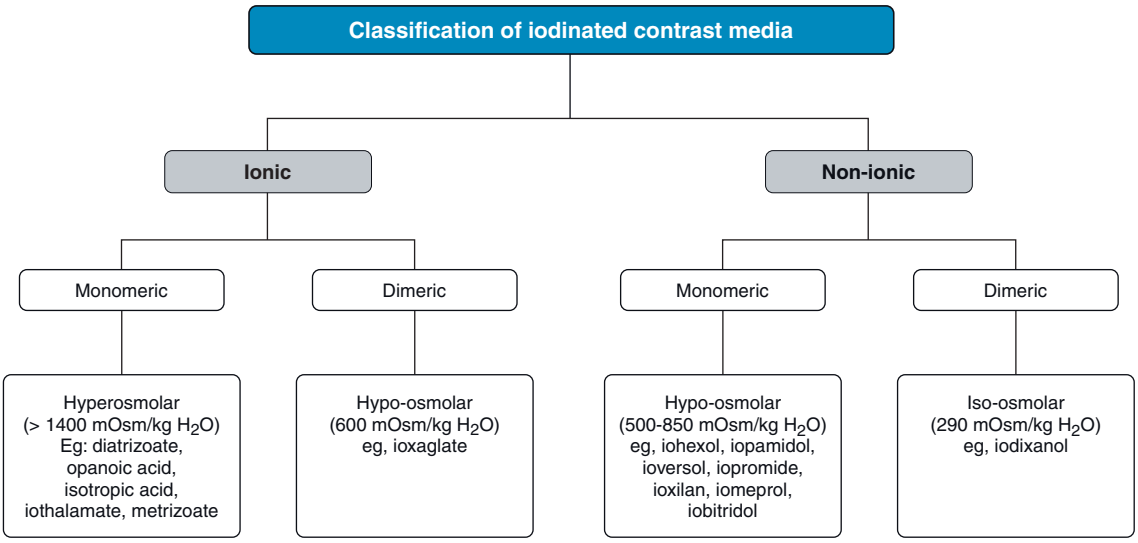

Figure 2
Classification of iodinated contrast media according to ionization capacity, molecular structure, and osmolarity[6]

What are the main risk factors?

Previous reactions to contrast-enhanced exams are the main risk factor for new reactions, increasing the risk by approximately 5 times for re-exposure to the same CM.[2,4,7,8] An immediate hypersensitivity reaction is not a risk factor for a delayed reaction and vice versa. Immediate hypersensitivity reactions to CM are substantially less frequent in intra-arterial and extravascular (e.g., gastrointestinal, genitourinary) administration.[3] Other less significant risk factors for immediate and delayed reactions are shown in Table 1.[6]

It should be noted that a history of allergy to crustaceans, mollusks, and fish, as well as contact dermatitis due to products containing iodine, are not risk factors for ICM reactions.[6]

There is no evidence that people with systemic mastocytosis have a higher risk of immediate hypersensitivity reactions to ICM than the general

Table 1
Risk factors for immediate and delayed hypersensitivity reactions

Previous reaction to ICM
Repeated administration of ICM
Renal failure
Female sex
Drug allergy
Cardiopulmonary disease
IL-2 treatment
Atopy
Use of beta-blockers, ACE inhibitors or proton pump inhibitors (immediate reactions)

ICM = iodinated contrast medium, IL-2 = interleukin 2, ACEI = angiotensin-converting enzyme inhibitors.
Adapted from Rosado-Ingelmo, et al.[6].

population,[3,4] but due to the variety of anaphylaxis triggers in mastocytosis, the basal serum tryptase of patients with anaphylaxis to ICM should be measured as a screening method.[4]

How are reactions classified?

Adverse reactions to CM can be classified as toxic or hypersensitive. The former are associated with the chemical properties of the media, are dose and infusion rate dependent, and include vasovagal reaction, convulsions, arrhythmias and toxicity in some organs, especially the kidneys.[4,6,7] Hypersensitivity reactions occur independently of the dose and infusion rate and may occur in response to small amounts of contrast. They are classified based on the chronology, involved mechanism, or phenotype. According to onset time after contrast infusion, they are divided into immediate or delayed hypersensitivity reactions, and the lesion type should also be considered.[4,6,7]

Although immediate hypersensitivity reactions may have an immunological mechanism (IgE-mediated), non-immunological mechanisms (direct histamine release or non-immunological complement activation) are more common, especially among high-osmolarity ICM. The clinical manifestations of immediate hypersensitivity reactions are urticaria and/or angioedema, either isolated or associated with bronchospasm, vomiting and/or hypotension, which characterizes anaphylaxis. Seventy percent of immediate hypersensitivity reactions occur within 5 minutes of infusion, and the greater the number of organs affected and/or severity of the reaction, the greater the possibility of an IgE-mediated reaction.[2,4]

Immune-mediated (T-cell) immediate hypersensitivity reactions are based on the structure of the ICM, and their spectrum ranges from maculopapular exanthema, fixed drug eruption, drug-related symmetrical intertriginous and flexural exanthema, and late-onset urticaria to severe cutaneous reactions, such as drug reaction with eosinophilia and systemic symptoms, acute generalized exanthematous pustulosis, Stevens-Johnson syndrome, and toxic epidermal necrolysis. Uncomplicated maculopapular exanthema is the most common adverse reaction to dimeric nonionic ICM, being implicated in > 50% of cases.[4,9]

Who should be investigated?

Because previous reactions to contrast-enhanced exams are the main risk factor for new immediate or delayed reactions, it is important to investigate patients with suspected hypersensitivity reactions. Nonspecific reactions, such as generalized pruritus, burning sensation, transient erythema, flushing, skin reaction at the injection site, atopy, asthma, allergy to other medications, food allergy, patients classified as allergic to iodine (eg, crustaceans, povidone, and mollusks) are not indicated for ICM allergy investigation when there is no history of reaction to them.[4,6]

Investigation: when, how, and where?

The ideal time for investigating immediate hypersensitivity reactions or delayed hypersensitivity reactions should be 2 to 6 months after the reaction and at least 6 months after a drug reaction with eosinophilia and systemic symptoms and sequential reactivation of herpes virus. Studies show that sensitivity decreases from 50% to 18% 6 months after the reaction test.[3]

For immediate hypersensitivity reactions, a skin prick test with undiluted ICM 300-320 mg/ml and immediate reading in 20 minutes is recommended. If negative, proceed with an intradermal test at 1/10 dilution. Use the involved ICM whenever possible.[3,4]

In delayed hypersensitivity reactions, delayed-reading (48/72 h) intradermal tests (1/10) and patch tests (undiluted ICM) are the initial approach (Table 2). Do not perform intradermal testing for drug reactions with eosinophilia and systemic symptoms, fixed drug eruptions, or bullous reactions due to the risk of reactivation. Testing with an alternative ICM is mandatory if these tests are positive or if the incriminating ICM is unknown (Figures 3 and 4).[3,4]

In vitro tests (basophil activation test and lymphoproliferative test) are not standardized and are still unavailable outside of clinical research. Provocation tests are controversial due to their risk, but can be performed to rule out mild delayed reactions, offer alternatives, assess the risks and benefits, and exclude contraindications.[4] It is important to note that tests must always be performed in a prepared environment (hospital or level 3 office) by a team trained to handle reactions.

Is there cross-reactivity between iodinated contrast media?

The frequency of cross-reactions between ICM vary in different studies (20%-75%) and are not related to iodine, excipient, or ionic charge. They are more common in late reactions with ICM that have the N-(2,3-dihydroxypropyl) carbamoyl side chain.[3,6,11,12]

Safe alternatives for re-exposure must be selected with caution due to the possibility of cross-reactivity between different products.[13]

The role of cross-reactions between different ICMs was highlighted in an article by Lerondeau et al. and confirmed by Schrijvers et al., who classified ICMs into 3 groups (A, B and C) based on the frequency of cross-reactivity between agents in the same group and the low cross-reactivity between the 3 groups (Table 3).[12,14] Therefore, sensitized patients should be tested with an alternative ICM from a different subgroup than the offending ICM.[12]

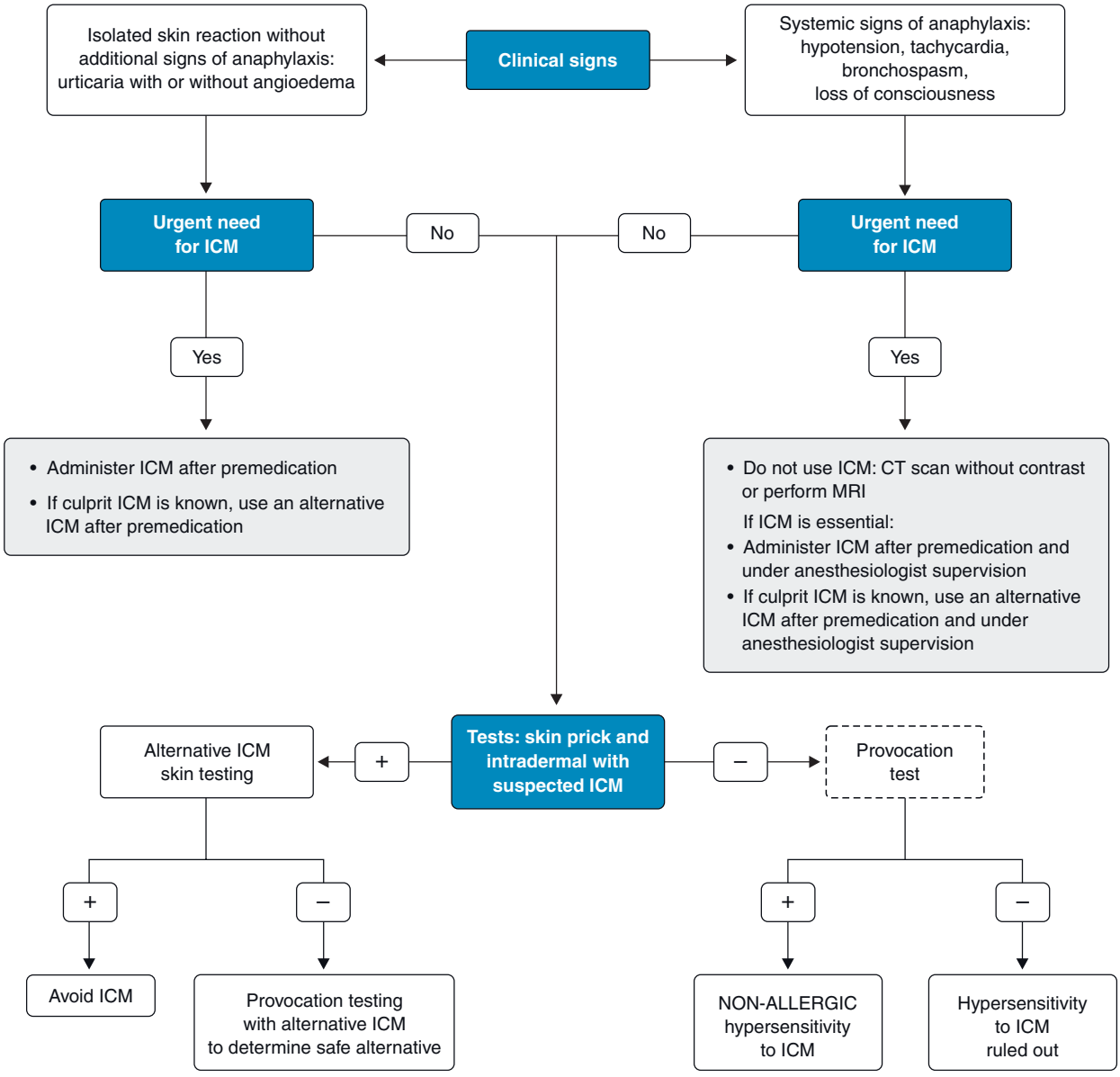

Figure 3

Algorithm for diagnosing and managing immediate hypersensitivity reactions to iodinated contrast media

ICM = iodinated contrast media, CT = computed tomography, MRI = magnetic resonance imaging, Positive skin tests = > 3 mm. Adapted from Torres, et al.[4]

When should premedication be used?

Routine premedication for patients with allergic or undetermined reactions to ICM is a common practice and is endorsed by some American associations. However, European guidelines advise against it, emphasizing the importance of investigation, considering both the risk of breakthrough reactions in patients with a history of severe reactions, as well as the false sense of security from using it. Exchanging ICM within the same hypo-osmolar group or using premedication for mild-to-moderate immediate reactions is recommended. However, no evidence exists that premedication is efficacious for moderate or severe IgE-mediated reactions. In such cases, performing a skin test and using an alternative ICM with a negative test is safer. Premedication is not indicated for delayed reactions.

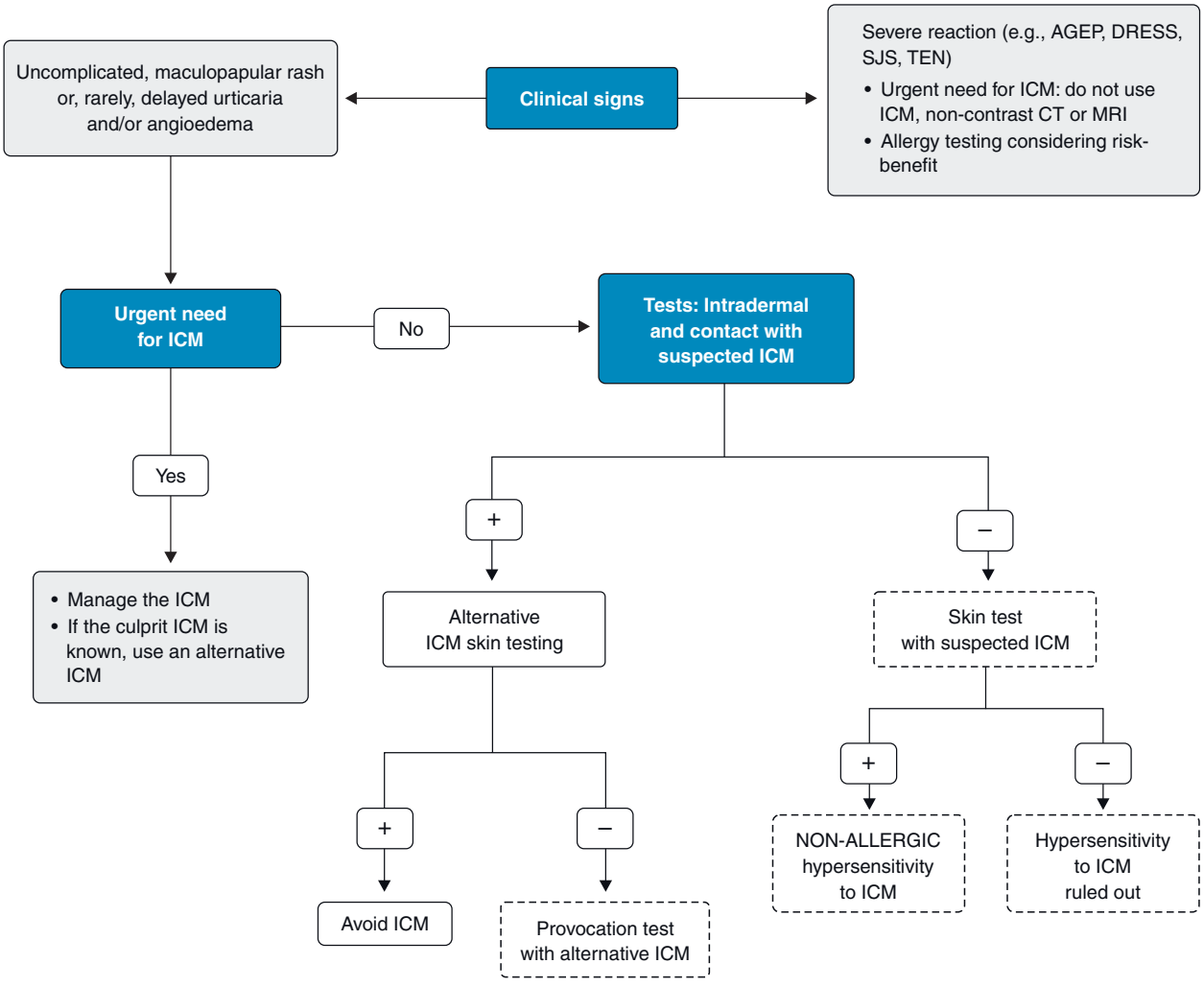

Figure 4

Algorithm for diagnosis and management of non-immediate hypersensitivity reactions to iodinated contrast media

ICM = iodinated contrast media, CT = computed tomography, MRI = magnetic resonance imaging, DRESS = drug reaction with eosinophilia and systemic symptoms, AGEP = acute generalized exanthematous pustulosis, SJS = Stevens-Johnson syndrome, TEN = toxic epidermal necrolysis.
Adapted from Torres, et al.[4].

Table 2
Concentrations used in skin tests for iodinated contrast media

Test	Concentration[a]	Reading	
		Immediate reaction	Delayed reaction
Skin prick test	Undiluted	20 min	
Intradermal test	1/10 dilution[b]	20 min	20 min, 48 h, 72 h
Patch test	Undiluted		20 min, 48 h, 72 h

[a] Undiluted iodinated contrast media at a concentration of 300-320 mg/mL. In more severe reactions, intradermal tests should be performed with higher dilutions.
[b] In non-severe delayed reactions, if the result of the intradermal test at 1/10 dilution is negative, the test can be repeated using the undiluted ICM, but in this case, if there is a reaction in the 20-minute reading, it should be interpreted as an irritant[4].
Adapted from Brockow[10].

The most widely used and referenced protocol in the literature for premedication recommends diphenhydramine as an antihistamine (Table 4).[4,6,8,15] However, since this medication is not available in oral form in Brazil, we suggest using a second generation H1 antihistamine.

No evidence exists that protocols lasting < 4-5 hours (oral or IV) are efficacious, but they may be considered in emergency situations when there are no alternatives. In these cases, methylprednisolone 40 mg or hydrocortisone 200 mg IV are used immediately and every 4 hours until the administration

Table 3
Cross-reactivity between iodinated contrast media

Group A	Group B	Group C
Iodixanol	Ioxaglate	Amidotrizoate
Iopamidol	Iobitridol	
Iomeprol		
Iohexol		
Ioversol		
Iopromide		
Ioxitalamate[a]		

[a] The only iodinated contrast medium in group A without the N-(2,3-dihydroxypropyl) carbamoyl side chain.
Adapted from Lerondeau B, et al.[12].

Table 4
Suggested premedication protocols for immediate reactions according to age group

Adults	Prednisone 50 mg, oral dose, 13 h, 7 h and 1 h before the procedure. If oral administration is unfeasible, opt for IV methylprednisolone[a] 40 mg at the same time intervals AND Diphenhydramine[b] 50 mg, oral or IV, administered 1 h before the procedure.
Children	Prednisone 0.5 to 0.7 mg/kg per dose up to 50 mg per oral dose, 13 h, 7 h, and 1 h before the procedure. If oral administration is unfeasible, opt for IV methylprednisolone[a] 0.5 mg/kg, up to a maximum of 40 mg per dose AND Diphenhydramine[b] 1.25 mg/kg, ≤ 50 mg, oral or IV, administered 1 h before the procedure.

IV = intravenous.
[a] Option: Hydrocortisone 200 mg IV.
[b] Oral diphenhydramine is not available in Brazil, therefore a 2nd generation H1 antihistamine is suggested.
Adapted from Wang C, et al.[8].

of ICM and diphenhydramine 50 mg IV 1 hour before using the ICM.[8]

Conclusions

The approach to patients with contrast reactions is challenging. Clinical history and in vivo tests are the cornerstones of diagnosis, but in vitro tests are not yet widely available. A previous reaction to an ICM is the main risk factor for future reactions. The frequent lack of description of the involved ICM and the time elapsed between the reaction and the investigation hinder this entire process. When tests are positive, skin tests with an alternative CM should be performed, since cross-reactions may occur. Provocation tests may be indicated after risk-benefit assessment. Premedication may be indicated for mild-to-moderate reactions, but not for delayed or severe immediate reactions.

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