Special Article

Controversies in Drug Allergy: Radiographic Contrast Media

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The risk for developing immediate or delayed hypersensitivity reactions to radiocontrast media (RCM) interferes with the diagnosis and treatment of a number of patients requiring imaging diagnostic methods for many common diseases. A group of experts met in Orlando, Florida, in March 2018 to analyze the similarities and differences in the management of RCM reactions in different areas of the world. This paper presents a summary of the recommendations provided by this consensus group, highlighting controversial issues and unmet needs that require further research. © 2019 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2019;7:61-5)

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Worldwide more than 75 million X-ray examinations are performed per year using radiographic contrast media (RCM). RCMs are categorized based on ion content (Table I), and currently nonionic RCMs are preferred more in clinical practice owing to their lower hypersensitivity profile.[1-4]

The prevalence of hypersensitivity reactions to monomeric ionic RCM has been reported to vary between 3.8% and 12.7%, and severe reactions occur in 0.02% to 0.04% of intravenous applications.[5] For nonionic RCM, the observed prevalence is 0.7% to 3%.[6]

Two types of hypersensitivity reactions to RCM have been recognized: immediate and nonimmediate (delayed).[7] Immediate reactions can be caused by IgE and non-IgE mechanisms. Immediate, anaphylaxis-like reactions may be caused by an effect of the RCM on the mast cell membrane leading to mediator release or, possibly, by direct complement activation. IgE-mediated allergic hypersensitivity reactions may have been underreported in the past,[1-4,8-13] due to the lack of allergy testing.

Macular or maculopapular exanthema seems to account for the great majority of RCM-induced nonimmediate reactions. Although the mechanisms of these exanthematous reactions have not been fully elucidated, T-cell involvement has been suggested in delayed hypersensitivity to RCMs (Figure 1).[14] Previous reactions to RCM are the main risk factor for developing hypersensitivity reactions to RCM. Other factors that have been associated with an increased risk to develop hypersensitivity reactions to RCM are atopy and asthma (Table II).

CONTROVERSIAL AREAS

The role of the basophil activation test

The usefulness of the basophil activation test (BAT) to study reactions to RCM has been investigated in some centers, but still remains a research tool and needs further validation.[2] For RCM, BAT sensitivity varies from 46% to 62%, and although specificity is high (88% to 100%), the results do not correlate with symptom severity. Further research is required before routine usage of this diagnostic method can be recommended.[12,15]

Abbreviations used
BAT- Basophil activation test
DPT- Drug provocation test
RCM- Radiographic contrast media

The role of skin testing

Skin tests with RCM for diagnostic purpose are not routinely performed outside specialized centers, although diagnostic sensitivity and specificity of prick tests with undiluted RCM and intradermal tests with 1:10 dilution seem to be quite high. A multicenter study demonstrated that up to 50% of the immediate reactors and up to 47% of nonimmediate reactors were skin test positive when patients were tested within 2 to 6 months after the initial reaction, whereas the skin test positivity decreased to 18% and 22% when tested after this time interval.[11,16,17]

The initial evaluation for immediate reactions includes skin testing with culprit RCM if the involved RCM is known. After this step, if the test is positive or the RCM is unknown, a broad panel of RCM is tested. In patients who develop nonimmediate reactions, prick and intradermal tests with late readings, as well as patch tests, are used in Europe (Table III).[10,16-22]

The differences in recommendations on skin testing are reflected in the different guidelines published by various national and international scientific societies such as the 2010 Practice Parameters from the American Academy of Allergy, Asthma and Immunology, the American College of Allergy, Asthma and Immunology and the Joint Council of Allergy, Asthma and Immunology,[23] the American College of Radiology Contrast Media Manual,[24] and the International Consensus Document on Drug Allergy.[25]

There are additional issues that are not currently elucidated and make difficult to comment on test results. For example, in a study by Schrijvers et al,[26] 29% of patients were atopic and that could influence skin testing results. Although the mechanism of immediate reactions seems mediated by IgE, transient positivity has been observed and needs to be better understood.

The role of cross reactions between different RCMs has been highlighted in a paper by Lerondeau et al,[27] and confirmed by Schrijvers et al,[26] and should help identify safe alternative(s) for re-exposure relating to nonimmediate reactions. Present evidence suggests that cross-reactivity seems less understood in case of skin test–proven immediate sensitization compared with nonimmediate RCM reactions.

Figures 2 and 3 present algorithms suggested by some experts for the skin test–based management of patients with immediate and nonimmediate reactions to RCM.

The role of the drug provocation test

Provocation tests with RCM have been used mainly in patients with a history of severe reactions to identify alternative RCMs. Increasing amounts of a skin test–negative RCM with a different structure are administered under direct monitoring where emergency care equipment is ready. For example, doses of 5, 15, 30, and 50 mL at 30- to 45-minute intervals for immediate reactions and at 1-hour intervals for nonimmediate reactions, with observation times at 3, 6, and 24 hours.

However, dose titration is empiric, and there are no data to support that the procedure is safer than giving 1/10 and 9/10 of a target dose. Furthermore, more than 3 doses may induce desensitization and provide a false sense of security.

Figure 2 presents an algorithm suggested by some experts for the management of patients with immediate reactions to RCM that includes a role for the drug provocation test (DPT).

The role of premedication

Premedication with corticosteroids, antihistamines, and sympathomimetics to prevent severe reactions to RCM was proposed years ago by Greenberger and Patterson[28] in North America (Table IV) and is the standard of care in all US institutions. The premedication regime has provided a significant reduction of severe reactions using a pretreatment protocol with prednisone and diphenhydramine or prednisone, diphenhydramine, and ephedrine.

A recent large study increasing the median of days of oral corticosteroid to 6 had substantial increased costs, side effects as well as longer hospital stay.[29]

Although premedication protocols are used around the world by radiologists, in Europe the value of premedication is considered controversial, because it provides patients and physicians a false sense of security. Cases of "breakthrough reactions" despite premedication in untested patients have been reported.[30,31] Although it has gained wide acceptance, it is not generally recommended by European colleagues because they consider that the evidence is weak and although it may be useful to reduce mild immediate nonallergic reactions, its efficacy for immediate moderate-to-severe and nonimmediate reactions has not been confirmed.[30,32]

CONSENSUS RECOMMENDATIONS

Current recommendations of this panel can be summarized as follows:

1. Skin testing for RCM immediate hypersensitivity may potentially identify safe alternative(s) for re-exposure. However, this still needs to be confirmed with additional prospective studies. The opinion of most members of the expert panel is that the evaluation of patients with RCM-induced anaphylaxis or exanthema should always include appropriate skin tests ensuring that patients with IgE-mediated or delayed-type allergy are not missed. Allergy testing may also identify alternative RCM that could be tolerated in future radiologic investigations.
2. Considering that DPT involves the risk of severe reactions, the expert group recommends that this is performed only in selected cases using a skin test–negative RCM to identify alternative RCMs for further radiologic investigations.
3. Although recommendations on premedication are not standardized, anesthesiology specialists in the USA have been using premedication guidelines for the last 20 years with good outcomes. Its use can be reserved to decrease reaction frequency or severity in high-risk patients (eg, those who have experienced previous anaphylactic reactions to RCM, mastocytosis) including those who experienced severe immediate-type reactions without evidence of an IgE-mediated mechanism. It is important to highlight that physicians using RCM routinely should be trained to early recognize and treat anaphylaxis appropriately.[33,34]
4. Because skin tests and BAT are negative in the majority of control subjects, the negative predictive value is likely to be high. However, the positive predictive value is unknown, although some experts suggest that it is high especially for

TABLE I. Radiocontrast media currently available for diagnosis

Class	Combination	Iodine content (mg/mL)	Osmolality (mOsm/kg)
Ionic monomers with high osmolality	Sodium iothalamate 54%	325	1843
	Meglumin diatrizoate 65%	306	1530
Ionic dimers with low osmolality	Meglumin ioxaglate 39.5%	320	580
	Sodium ioxaglate 19.6%	320	580
Nonionic monomers	Iopamidol 61.2%	300	616
	Iohexol 64.6%	300	640
	Ioversol 63.6%	300	645
	Iopromid 62.3%	300	610
Nonionic dimers	Iotrolan 64.1%	300	320
	Iodixanol 65.2%	300	290

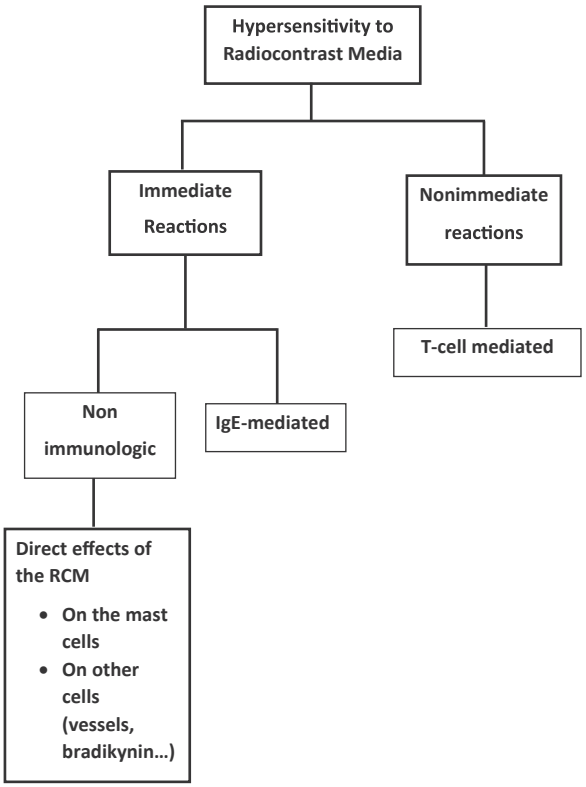

FIGURE 1. Mechanisms of hypersensitivity reactions to radiocontrast media. *RCM*, Radiocontrast media.

TABLE II. Risk factors for hypersensitivity reactions to RCM

Risk factor	OR (95% CI)
Atopy	5.0[37]
Asthma	8.74 (2.36-32.35)[38] 2.0 (0.8-5.1)[39]
Female gender	1.6 (1.3-2.0)[39]
Severe cardiovascular disease	7.71 (1.04-57.23)[38]
Repeated administration of RCM	NA[40]
Previous reactions to RCM	15.9 (7.8-32.3)[39]
Drug allergy	1.4 (1.0-1.9)[39]
Mastocytosis	NA[41]

CI, Confidence interval; *OR*, odds ratio; *RCM*, radiocontrast media.

TABLE III. Skin test concentrations recommended for iodinated radiocontrast media*

Test	RCM concentration	Readings: Immediate reactions	Readings: Nonimmediate reactions†
Skin-prick test	Undiluted	20 min	48 h, 72 h
Intradermal test	1:10	20 min	48 h, 72 h
	1:1‡	Not recommended	≥24 h
Patch test	Undiluted	Not recommended	48 h, 72 h

RCM, Radiocontrast media.
*Modified from Brockow and Sánchez-Borges.[18]
†For nonimmediate reactions, readings at 96 h and 7 d could also be applied.
‡For nonimmediate reactions, intradermal tests with the undiluted RCM and readings at >24 h are associated with a higher sensitivity.

immediate reactions.[25,35,36] Although provocation testing outside the context of radiological imaging to verify negative in vivo and in vitro test results has been used, it is not recommended because no controlled studies have provided evidence of utility and can put patients at risk for a reaction outside a controlled environment.

5. There is no standardized premedication regime, with differences between the North American and European recommendations. Allergists and radiologists differ in the approach, and consensus multidisciplinary strategies (and even care pathways) should be established to overcome differences between specialists. Recently, there has been some concern related to adverse effects induced by systemic corticosteroids, even when taken for short periods of time.[29] However, the expert group considers that premedication in those patients with a high risk for severe repeat reactions and a negative allergy workup may help many patients and the benefits of premedication generally outweigh the potential harm. For patients who have suffered Drug reaction with eosinophilia and systemic symptoms (DRESS) or Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) associated with RCM, the contrast media is contraindicated and a non−cross-reactive alternative will need careful evaluation. Premedication is contraindicated in these patients and further exposure to the same contrast can be lethal.

Unmet needs

There are several issues that need further research to improve the knowledge in this field and consequently the quality of

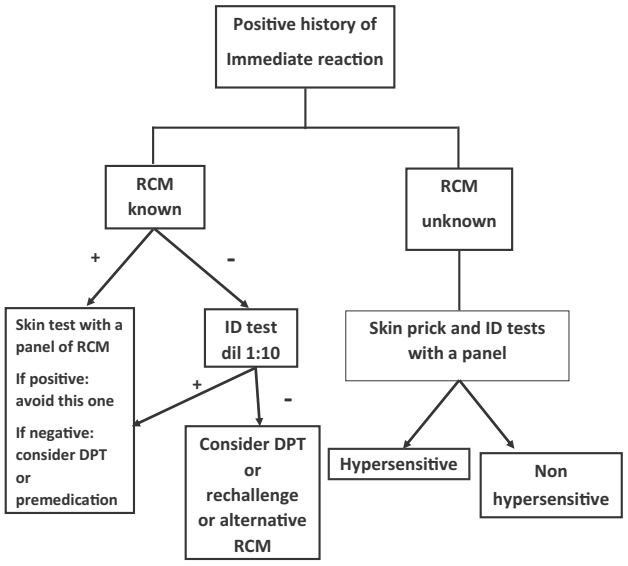

FIGURE 2. Skin test–based management of patients with immediate reactions to radiocontrast media. *DPT*, Drug provocation test; *RCM*, radiocontrast media.

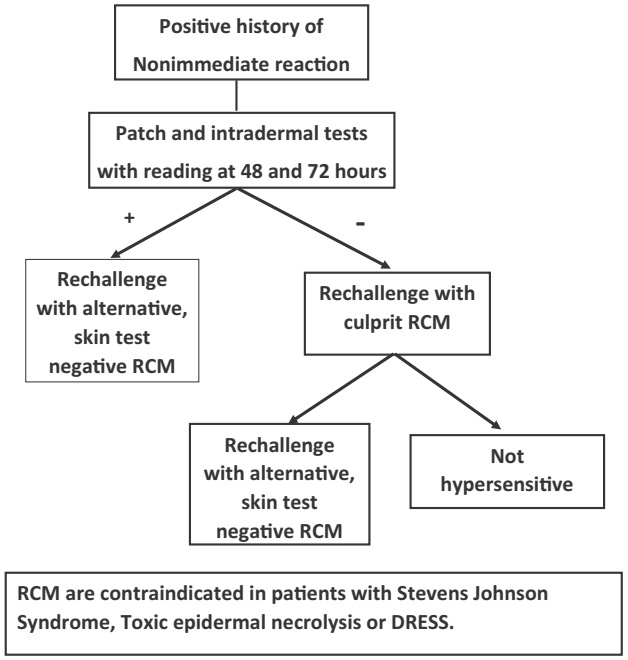

FIGURE 3. Skin test–based management of patients with nonimmediate reactions to radiocontrast media (RCM). RCM are contraindicated in patients with Stevens-Johnson syndrome, toxic epidermal necrolysis, or DRESS. *DRESS*, Drug reaction with eosinophilia and systemic symptoms.

patient's care. Prospective investigations are needed that help clarify the clinical usefulness of skin testing with RCM to confirm or exclude an RCM allergy diagnosis and to select alternative RCMs in patients with a history of reactions. Beyond tryptase, good diagnostic tools to evaluate the mechanism of RCM hypersensitivity reactions in real time are needed. Finally, controlled prospective multicentric studies with large numbers of patients to assess the impact (efficacy/safety) of different premedication protocols on clinical outcomes are needed.

TABLE IV. Premedication for prophylaxis of reactions to radiocontrast media*

Time before injection (h)	Pretreatment	Recommended dose
13	Corticosteroid: prednisone	50 mg PO
7	Corticosteroid: prednisone	50 mg PO
1	Corticosteroid: prednisone	50 mg PO
1	Anti-H1 antihistamine: diphenhydramine	1 mg/kg PO or IM

IM, Intramuscular route; *PO*, oral administration.
*Modified from Greenberger and Patterson.[28]

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