

EDITORIAL

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Should allergic reactions to radio-contrast media be investigated by an allergist?

This editorial discusses the findings of the paper in this issue by Scherer et al. [7] published in the March issue

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Hypersensitivity reactions to radio-contrast media (RCM) during radiological investigations are generally divided into immediate-type reactions, occurring within 1 h, and delayed reactions, occurring typically at 6–12 h. Cross-reactivity between different RCM is more commonly found with delayed reactions, suggesting a common moiety and mechanism. In the past, adverse reactions were much more common after the administration of ionic high osmolar contrast media, and the incidence of these reactions declined significantly after they were replaced by non-ionic low-osmolar agents. However, the number of reactions seen in clinical practice has remained significant because of the increasing use of radiological investigations involving contrast. In the United Kingdom, the management of adverse reactions to RCM has remained the domain of radiologists. Radiology departments have guidelines on the management of patients with a history of allergic reactions to iodinated intravascular contrast media. In patients with a history of a severe reaction, further doses are not administered and imaging occurs without the use of contrast. In less severe cases, contrast media is administered if deemed necessary to the investigation. In these cases, a doctor is always present and the patient is observed for 30–60 min post-administration.

Our understanding of the patho-mechanism of adverse reactions is evolving and complement activation is no longer considered to play a major role [1]. The prospect of identifying the cause of RCM reactions and safe alternatives has emerged with a number of recent publications, suggesting that many, if not the majority of adverse reactions to RCM, have an immunological basis [2–4]. In up to 50% of patients with immediate-type reactions, there is evidence suggesting contrast medium-specific IgE from intradermal testing [2] or *in vitro* studies of

basophil activation [5]. Patch tests and delayed reading intradermal tests are most often positive in patients with maculo-papular late reactions. In these patients, there is evidence of the involvement of T lymphocytes from the generation of specific T cell clones [6]. Potentially, skin testing with a single member of each of the four tri-iodinated benzene-derived contrast media groups may provide a pattern of responses that could be used to predict whether the patient is hypersensitive to a single agent or is multiply sensitized. This information should help to identify agents that could be administered safely.

A previous reaction to a contrast medium with either an immediate or delayed reaction is a risk factor for further reactions. The type and severity of reaction are usually similar and can occur despite pre-medication with corticosteroids and antihistamines. This calls into question the common practice of pre-dosing with these agents. In some cases, the reaction has simply been delayed until after the patient has returned home. There may be an argument for avoiding pre-medication and simply being aware of a possible adverse reaction and treating it appropriately. In patients with a positive skin test to the implicated contrast medium, cross-reactivity is frequently observed with either ionic or non-ionic products. Cross-reactivity on skin testing usually to RCM of a similar chemical structure is most frequently observed in patients with delayed reactions resulting in multiple positive delayed intradermal tests or patch tests. In the majority of cases, however, a contrast medium to which there is a negative test can be identified. The structural moiety responsible for the generation of an immunological response remains unidentified.

Scherer et al. [7] have shown that skin prick tests to RCM are never positive, even if the patient has a history of an immediate clinical reaction. It is, therefore, essential to undertake intradermal testing. In their study of nine patients with an immediate-type reaction to contrast media, two had an immediate positive intradermal response and one of nine a positive intradermal test when

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read at 24–48 h. Conversely, all subjects with a delayed adverse reaction to RCM had an evidence of delayed-type hypersensitivity from either late-reading of an intradermal test or patch test. Therefore, IDTs must also be read at 24–48 h for delayed-type hypersensitivity, and in order to increase the sensitivity of skin testing, the authors have made a case for undertaking patch testing in every case. A European multicentre study of 220 patients with a history of RCM reactions suggested that skin testing is most likely positive if conducted between 2 and 6 months after the reaction [2]. In their study, approximately 50% of patients with immediate reactions had positive intradermal tests if conducted within the 4-month window, although the concept of loss of skin test reaction without a loss of clinical reactivity is difficult to grasp. Delayed reading of intradermal tests together with patch tests were positive in approximately 50% of patients with delayed reactions.

Scherer et al. [7] have also provided limited evidence for the positive and negative predictive value of skin tests. One patient known to have positive skin tests to loporomide developed flexural exanthemata after a challenge administration. Interestingly, premedication with antihistamines and corticosteroids delayed the clinical reaction for 2 days. He tolerated an intravenous challenge with two other RCM to which he had negative skin tests. There are also other reports of the utility of skin tests in predicting clinical reactions [8] but unfortunately, skin testing fails to predict a clinical reaction in all cases. This was highlighted by a patient who skin-tested negative by both patch and delayed reading of an intradermal test to loporomide. On a challenge, he reacted with a maculopapular exanthem and developed recall phenomenon on previous skin test sites, confirming the immunological nature of the reaction. The literature provides insufficient data on the outcome of challenge in patients with both negative and positive skin tests, and therefore the predictive value of these tests remains unknown [9]. Reassuringly however, skin tests were almost always negative in volunteers who had never been exposed to RCM or those who had tolerated RCM previously, thereby excluding an irritant effect at the concentrations used [2].

Two patients positive on skin testing to a large number of RCM also experienced maculopapular exanthemata after an oral challenge with Lugol's solution containing potassium iodide. The authors therefore concluded that hypersensitivity reactions to free iodine can occur in some patients, particularly those with positive delayed intradermal tests to most RCMs. This is the first time that free iodine has been implicated as a cause of hypersensitivity reactions to RCM and is at odds with current concepts [7].

The importance of the study by Scherer and colleagues is that it describes the heterogeneity of contrast media reactions and suggests that patients with these reactions can be divided into 1) IgE mediated identified from clinical history

and intradermal testing, 2) T cell-mediated delayed-type reactions identified from history and delayed reading of intradermals or patch tests and (3) patients intolerant of all iodine-containing compounds who demonstrate positive patch or delayed intradermal tests to the majority of contrast media.

Recent studies represent an important step in the validation of skin tests for the diagnosis of RCM hypersensitivity, but they have also shown that a negative skin test cannot completely exclude a hypersensitivity reaction. Therefore, before advocating skin tests as a valid investigation, their negative predictive value should be determined by challenging allergic patients to contrast media to which they have a negative skin test response. It is quite feasible that patients with true positive skin tests to the culprit and cross-reacting RCM are more likely to have reliable negative tests to different RCM, and in this group it may be possible to recommend challenge testing. A further important consideration is the likely pattern of cross-reactivity between and within each class of RCM, which include ionic and non-ionic monomers and dimers. Some of this information could be derived from laboratory tests, such as lymphocyte transformation and basophil activation tests. Identification of the structural moiety that elicits both immediate and delayed reactions will further enhance our ability to predict potential cross-reactivity and allow the development of reliable *in vitro* tests.

Finally, recent publications will lead to a hope that clinical guidelines can be developed on the management of patients with adverse reactions to contrast media. These studies have established that many of these reactions are due to hypersensitivity reactions. However, it is essential for investigators to understand that the presence of IgE or T cell clones on *in vivo* and *in vitro* testing is insufficient for diagnosis. Further useful information can be obtained by maintaining a database of all patients who have undergone provocation testing. Once positive and negative predictive values and cross-reactivity have been determined, it will be possible to draw up guidelines and an algorithm for the management of these challenging patients.

A general approach to the investigation of drug allergy has been recently published [10].

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