

Immediate and Delayed Reactions to Radiocontrast Media: Is There an Allergic Mechanism?

Knut Brockow, MD

KEYWORDS

- Radiocontrast media • Hypersensitivity • Skin test
- Diagnosis • Immediate • Non-immediate • Mechanism

Radiocontrast media (RCM) are administered more than 75 million times per year for performing diagnosis and treatment of vascular disease and enhancement of radiographic contrast.¹ Adverse reactions after RCM administration are common.² Symptoms after RCM exposure may be regarded as hypersensitivity reactions or toxic reactions related to the well-defined toxicity of the compounds, or may be caused by factors unrelated to RCM, such as chronic idiopathic urticaria ([Fig. 1](#)).² Hypersensitivity reactions to RCM may present clinically as anaphylaxis with the potential to result in fatalities or as delayed occurring exanthemas, not unlike those to other drugs. They have been classified in regard to the time interval between administration and the first appearance of symptoms as immediate when they occur within 1 hour after RCM administration or nonimmediate when they occur 1 hour to 10 days after iodinated RCM injection.² Recently, positive skin tests have been described in case reports and in a multicenter study in patients with RCM hypersensitivity.^{3–12} In addition, laboratory data in favor of an allergic mechanism have been published.^{9,13–15} This review is focused on the current understanding of the mechanisms of immediate and nonimmediate hypersensitivity reactions to RCM and how this translates into recommendations concerning diagnostic procedures.

RADIOCONTRAST MEDIA

All RCM are highly concentrated solutions of tri-iodinated benzene derivatives.¹⁶ There are currently four types of contrast media commercially available: ionic monomers, nonionic monomers, ionic dimers, and nonionic dimers.¹⁷ The ionic contrast media are highly water soluble by means of their carboxylate group. The nonionic

Department of Dermatology and Allergy Biederstein, Technische Universität München, Biedersteiner Strasse 29, 80802 Munich, Germany
E-mail address: knut.brockow@lrz.tum.de

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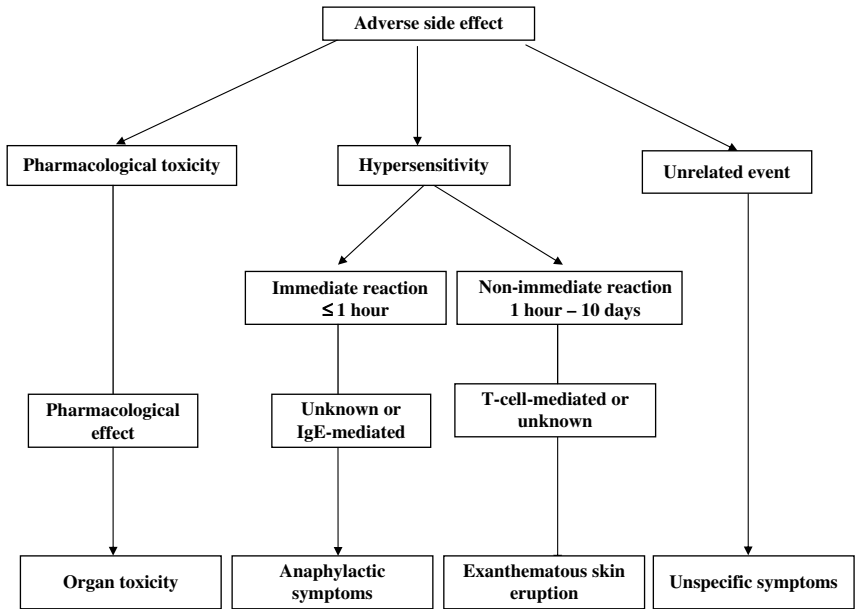


Fig. 1. Classification of adverse side effects after RCM administration. (Adapted from Brockow K, Christiansen C, Kanny G, et al. Management of hypersensitivity reactions to iodinated contrast media. *Allergy* 2005;60:157; with permission.)

products are made water soluble by introducing long side chains rich in hydroxyl groups. The majority of RCM marketed are nonionic monomers, whereas ionic monomers have been continuously withdrawn in most countries, at least for intravenous use. All compounds are nonreactive, have low protein-binding capacity, and are excreted unmetabolized in urine within 24 hours after injection.

EPIDEMIOLOGY

The frequency and mechanisms of hypersensitivity reactions differ between the different types of RCM. Mild immediate reactions have been reported in 3.8% to 12.7% of patients receiving intravenous injections of ionic monomeric RCM and in 0.7% to 3.1% of patients receiving nonionic RCM.^{18–20} Severe immediate adverse reactions to ionic RCM have been reported in 0.1% to 0.4% of intravenous procedures, whereas reactions to nonionic RCM are less frequent (0.02% to 0.04%).^{18–21} Fatal hypersensitivity reactions may occur in 1 to 3 persons per 100,000 contrast media administrations and are not related to one particular type of RCM.²¹

The frequency of nonimmediate reactions varies from 0.5% to 23.0%.²² This large variation may be due to the difficulty in verifying whether symptoms occurring days after exposure are, in fact, caused by the RCM. Various types of exanthema account for the majority of RCM-induced nonimmediate hypersensitivity reactions. Such exanthemas have been reported to affect 1% to 3% of RCM-exposed patients.^{23–25} Unlike immediate reactions, there seems to be a higher incidence of nonimmediate exanthemas associated with dimeric nonionic RCM but not to other types of RCM.²⁶

The main risk factor for immediate as well as nonimmediate hypersensitivity reactions is a previous reaction. Previous reactors have a 21% to 60% risk of a repeat immediate reaction when re-exposed to ionic RCM.^{2,22–24} When patients with

a previous reaction to an ionic RCM are subsequently given a nonionic RCM, the incidence of a severe immediate repeat reaction is reduced up to tenfold.² Predisposing factors for nonimmediate skin reactions are a previous hypersensitivity reaction, as well as interleukin-2 treatment and a history of drug and contact allergy.^{25,27,28} The occurrence of an immediate reaction is not a risk factor for developing a nonimmediate reaction and vice versa.

CLINICAL PRESENTATION OF RADIOCONTRAST MEDIA HYPERSENSITIVITY

Immediate RCM reactions resemble anaphylaxis. Pruritus and urticaria, sometimes accompanied with angioedema, occurs in 65% to 85% of patients with immediate reaction.^{18,27,29} Other frequent reactions are heat sensation, nausea, and vomiting; however, whether these represent real hypersensitivity or toxic reactions remains more unclear.² Gastrointestinal symptoms such as abdominal pain and diarrhea also occur. More severe reactions involve the respiratory and cardiovascular systems, with dyspnea, bronchospasm, or a sudden drop in blood pressure. Hypotension is associated with a loss of consciousness (anaphylactic shock) and with reflex tachycardia.¹⁸ The onset of immediate hypersensitivity reactions is very rapid, with about 70% occurring within 5 minutes after injection^{3,18} and 96% of severe or fatal reactions within 20 minutes after injection.³⁰ Several grading systems for the severity of hypersensitivity reactions have been published, with the classification system published by Ring and Messmer most widely used.³¹

The most frequent clinical manifestation of nonimmediate RCM reactions is a maculopapular exanthema occurring hours to several days after the RCM administration (**Table 1**).^{3,25} Other descriptions of the skin reaction include erythema, urticaria, angioedema, fixed drug eruption, macular exanthema, erythema exsudativum multiforme, scaling skin eruption, pruritus, or pompholyx.^{16,25} More untypical presentations, such as a graft-versus-host reaction,³² a symmetrical drug-related intertriginous and flexural exanthema (SDRIFE),¹⁰ or a drug-related eosinophilia with systemic symptoms (DRESS), have been described.³³ RCM are not different from other drugs such as penicillins in their ability to cause a wide spectrum of nonimmediate drug reactions. Nonimmediate RCM reactions are usually mild to moderate in

Table 1
Clinical manifestations of immediate and nonimmediate hypersensitivity reactions to radiocontrast media (most frequent reactions in bold)

Immediate Reactions	Nonimmediate Reactions
Pruritus	Pruritus
Urticaria	Exanthema (mostly macular or maculopapular drug eruption)
Angioedema/facial edema	Urticaria, angioedema
Abdominal pain, nausea, diarrhea	Erythema multiforme minor
Rhinitis (sneezing, rhinorrhea)	Fixed drug eruption
Hoarseness, cough	Stevens-Johnson syndrome
Dyspnea (bronchospasm, laryngeal edema)	Toxic epidermal necrolysis
Respiratory arrest	Graft-versus-host reaction
Hypotension, cardiovascular shock	Drug-related eosinophilia with systemic symptoms (DRESS)
Cardiac arrest	Symmetrical drug-related intertriginous and flexural exanthema (SDRIFE)
	Vasculitis

severity and self-limiting.³ Rare cases of severe reactions have been reported, such as cutaneous vasculitis, Stevens-Johnson syndrome, toxic epidermal necrolysis, and papulopustular eruptions.^{34–40} Systemic symptoms with more immediate-type manifestations such as hypotension, fever, abdominal pain, dyspnea, and biphasic reactions have been reported occasionally.^{12,41,42}

PATHOPHYSIOLOGY OF IMMEDIATE REACTIONS TO RADIOCONTRAST MEDIA

The mechanisms of the allergy-like reactions to RCM have been a matter of speculation for decades (**Table 2**). Anaphylaxis to RCM may be theoretically due to (1) a direct membrane effect possibly related to the osmolality of the contrast media solution or the chemical structure of the contrast media molecule (pseudo-allergy),¹⁷ (2) an activation of the complement system,⁴³ (3) direct bradykinin formation,⁴³ or (4) an IgE-mediated mechanism.

A higher histamine release after incubation of high osmolal ionic monomeric RCM in comparison with low osmolal nonionic RCM has been reported for rat and human mast cells^{44,45} and for human basophils.⁴⁶ On the other hand, Stellato and colleagues reported heterogeneity of human basophils and human mast cells isolated from lung, skin, and heart concerning their ability to release histamine and tryptase after incubation with RCM. For mast cells, they found no correlation between the osmolality of RCM and histamine release.⁴⁶ Similarly, an activation of the complement system has been described, with a decrease of CH50 in the presence of RCM *in vitro*.⁴⁴ *In vivo*, the anaphylatoxins C3a and C4a were reported to be increased in a fraction of patients with immediate life-threatening reactions to RCM, without significant differences between RCM-intolerant and tolerant patients.⁴⁷ The increase has been attributed to a secondary activation of the complement system by tryptase. In other studies, complement activation has also been demonstrated in patients who did not develop immediate reactions.⁴⁸ All of these concepts regarding direct histamine release, complement activation, or bradykinin formation remain controversial as long as pathologic changes are reported for reactors as well as for nonreactors.^{49,50} Factors for a patient-specific predisposition explaining why some patients react and others do not must still be elucidated.

Increasing evidence suggests that immediate hypersensitivity reactions may indeed be caused by an IgE-mediated allergic mechanism. The following data support this concept:

Immediate hypersensitivity reactions to contrast media are associated with histamine release from basophils and mast cells.^{43,47} Extensive mast cell activation as the cause of the clinical symptoms has been convincingly demonstrated by Krause and Niehues.⁴⁵ They demonstrated that patients with hypersensitivity reactions after contrast medium exposure had increased plasma levels of both histamine and tryptase, and that the levels correlated with the severity of the reaction. Other investigators have reported high levels of tryptase in connection with severe or fatal reactions.^{11,51,52}

Especially in Japan, pretesting with an intravenous injection of a small amount (usually 0.5–1 mL) of RCM as a means of predicting severe or fatal reactions was performed in the 1970s and 1980s. This approach was abandoned after it was found that it was not useful in predicting severe reactions to ionic or nonionic contrast media, and after severe cardiovascular reactions to these minute amounts of RCM were described.^{53,54} The possibility of reacting to low amounts is typical for an IgE-mediated reaction.

Table 2

Arguments for and against radiocontrast media allergy

Reaction Type	Con	Pro
Immediate hypersensitivity reactions	No sensitization phase Repeated reactions do not always recur and do not always increase in severity No increase of plasma leukotrienes after RCM administration Only anecdotal reports of RCM-specific IgE antibodies Low affinity of IgE to RCM RCM are not able to form haptens	Preclinical sensitization to cross-reactive substance possible Previous reaction highest risk factor for subsequent reaction, case reports with increasing severity Mast cell mediator release correlates with severity of reaction, positive basophil activation test to RCM in patients Low levels of IgE antibodies to ioxaglic acid in one study Specific IgE to RCM higher in reactors than in controls in one study Positive skin tests in patients but not in controls in optimal concentrations
Nonimmediate hypersensitivity reactions	No sensitization phase RCM are not able to form haptens Not all patients show positive skin tests Atypical manifestations reported Repeated reactions do not always recur or increase in severity — — — — —	Preclinical sensitization to cross-reactive substance possible PI concept Positive skin tests in patients but not in controls in optimal concentrations, skin test positivity may be lost over time Maculopapular exanthema and time course resembles drug allergy Previous reaction highest risk factor for subsequent reaction, case reports with breakthrough reactions Histopathology shows T-cell pathology and T-cell activation in acute reaction and in skin test Enhanced frequency in interleukin-2 treated patients Positive lymphocyte transformation test and lymphocyte activation test Demonstration of RCM-specific T cells Generation of RCM-specific T-cell lines and T-cell clones

Further indirect evidence for an IgE-mediated reaction has been reported in rare cases with severe reactions. Several groups have reported positive skin test results for patients with severe immediate reactions to either ionic or nonionic RCM.^{47,52,58–61} Some of these patients were shown to react not only to the culprit contrast medium but also to other contrast media.^{47,55,56} Recently, the frequency of positive skin tests was investigated in more than 200 patients with RCM hypersensitivity and in 82 controls in a European multicenter study.³ When a nonirritative skin test concentration was used, the intradermal test (IDT) was positive in 26% of patients but remained negative in 96.3% of controls. The relatively high percentage of skin test–positive patients may be influenced by the selective inclusion of patients with typical features of RCM hypersensitivity and involvement of allergy departments experienced in drug hypersensitivity. One patient with a severe anaphylaxis to an unknown ionic RCM experienced urticaria, rhinoconjunctivitis, and glottis edema 5 minutes after an IDT with a nonionic CM. The percentage of positive skin test results was even 50% in the 28 patients who could be tested within 2 to 6 months after the reaction. At later time points, the frequency of positive tests decreased significantly, possibly owing to loss of sensitization over time as reported for other drug allergies.⁶²

Basophil activation tests were found to be positive in patients with immediate hypersensitivity reactions as another indirect indication for an IgE-mediated allergy.⁶³

Two groups have performed immunoassays to search for contrast medium–specific IgE to ionic RCM in the sera from patients with moderate-to-severe immediate reactions after exposure to RCM.^{15,48} Laroche and colleagues studied specific IgE to ionic RCM in 20 patients with immediate reactions. Significantly higher levels of specific IgE against ioxaglate and ioxitalamate were reported in a comparison with control patients. Mita and colleagues reported ioxaglate-specific IgE in 43% of patients (16/34) with a history of reaction to this RCM and in 20.6% of patients (14/68) who reacted to this RCM and in whom serum was sampled in the next 24 hours, but in none of the 10 RCM-tolerant control patients. These RCM-specific IgE levels were not much higher when compared with the levels in controls (usually less than twofold higher than the cut-off level), and the dissociation constant K_D (18.7 mM) was very low, which has been regarded as an argument against specificity. These studies were performed with ionic RCM coupled to a solid phase. Contemporary assays for nonionic RCM used today have not been described, because it is extremely difficult to bind nonionic RCM to a solid phase, limiting research in this field.

This evidence collectively challenges the dogma that all immediate hypersensitivity reactions to RCM are pseudo-allergic reactions, and that diagnostic testing is of no value. The fact that as many as 50% of patients had a positive skin test when tested 2 to 6 months after the reaction indicates that in a subgroup of contrast media–induced immediate hypersensitivity reactions may be immunologic reactions involving contrast media–reactive IgE antibodies. In patients with negative skin tests, the mechanism involved remains speculative. An important argument against an allergic mechanism is that patients can react to a contrast media on first exposure, and the reaction does not always recur. This lack of a clear sensitization phase is similar to the situation described in anaphylaxis to muscle relaxants,⁶³ in which it has been proposed that previously nonexposed patients may have already been sensitized. The chemical structures responsible for the sensitization remain unknown. On the other hand, the

positive immediate skin tests reported by several investigators, the detection of contrast media-specific IgE antibodies in sera from immediate reactors to ionic contrast media, as well as the positive basophil activation test in immediate reactors with positive IDTs to the implicated nonionic contrast media strongly support the concept of an IgE-mediated mechanism, at least in a fraction of patients (see **Table 2**).

PATHOPHYSIOLOGY OF NONIMMEDIATE REACTIONS TO RADIOCONTRAST MEDIA

During the past decade, much information on the pathogenesis of nonimmediate reactions induced by RCM has become available. These data indicated that the majority of these reactions are T cell mediated (see **Table 2**). The current evidence for an allergic mechanism in many of these patients is summarized as follows:

The clinical presentation of the majority of nonimmediate RCM reactions is a maculopapular exanthema and is comparable with other drug-induced, T cell-mediated hypersensitivity reactions, such as to penicillins. The reported onset of skin eruptions 2 to 10 days after the first exposure to a contrast medium and 1 to 2 days after re-exposure to the same substance is typical for nonimmediate allergic drug reactions.

The histopathology of exanthematous reactions to RCM and positive skin test sites provides evidence for a T cell-mediated mechanism.^{9,14} The histopathologic findings are identical to those reported for other drugs known to cause T cell-mediated allergic skin reactions. A dermal lymphocyte-rich infiltrate is accompanied by intraepidermal spongiosis and sometimes hydropic degeneration of the basal cell layer.²⁸ Immunohistologic studies of positive skin test sites have shown that the perivascular infiltrate consists mainly of CD4+ and CD8+ (CD45RO+) T cells.^{9,14} The dermal perivascular mononuclear cell infiltrate in most patients with maculopapular exanthemas shows higher levels of CD4 lymphocytes than CD8 T lymphocytes, with moderate expression of CD25 and a higher expression of HLA-DR and CLA.¹⁴ There is a high presence of eosinophils. Skin biopsies obtained at the site of positive skin tests to the culprit RCM showed similar results to those seen in the initial acute phase biopsy, with higher expression of CD69 in lymphocytes.^{8,14,64}

The enhanced frequency of RCM-related side effects in interleukin-2-treated patients is indicative of a T cell-mediated pathology,⁶⁵ because interleukin-2 has been reported to reduce the threshold for T-cell activation and to increase the possibility for clinical symptoms.

The observation that previous reactors are at high risk for a new reaction is typical for an allergic reaction. In the majority of cases reported, readministration of the culprit contrast medium to patients with a previous nonimmediate exanthema results in a repeat reaction.^{37,38,66–68} In most (but not all) cases, a more severe reaction with subsequent RCM exposure has been reported. After provocation tests, a reappearance of the exanthemas after intravenous administration of the culprit contrast medium has been reported in patients with previous contrast medium-induced eruptions.^{69,70}

A large number of studies on patients with contrast medium-induced nonimmediate skin reactions have reported positive delayed skin tests when the patients were tested with the culprit contrast medium.¹⁶ In the large European multicenter study, 37% of patients with nonimmediate reactions were positive in delayed IDTs or patch tests.³ The majority of the patients reacted not only to the culprit contrast medium but also to other structurally similar contrast media. More

than 30% of the skin test-positive patients in the study had been administered an RCM for the first time; therefore, there is a lack of a sensitization phase, which can again only be explained by the fact that these previously nonexposed patients may have already been sensitized. Different patterns of RCM cross-reactivity indicate that several chemical entities might be involved. No positive skin tests have been obtained with the contrast medium excipients tris(hydroxymethyl)aminomethane (trometamol) and ethylenediaminetetraacetic acid (EDTA), and only rare patients have been reported to react to inorganic iodide.⁷¹

The presence of contrast medium-specific T cells in patients with nonimmediate exanthematous skin eruptions was confirmed in recent *in vitro* and *ex vivo* findings. Peripheral blood mononuclear cells (PBMCs) from patients showed an enhanced *in vitro* proliferation in the presence of the culprit contrast medium when added to the culture (mainly in the range of 10–100 mg iodide/mL).⁹ Flow cytometric analysis showed an increase in the different T-lymphocyte activation markers (CD69, CD25, and human leukocyte antigen D-related) and in the skin homing receptor (cutaneous lymphocyte-associated antigen) in CD4+ lymphocytes, whereas perforin expression was increased in the CD8+ cytotoxic lymphocytes.¹⁴ Approximately 0.5% to 3% of T cells expressed the early T-cell activation marker CD69 after incubation with contrast media.¹³ On the other hand, the precursor frequency of peripheral T cells specific for RCM was estimated to range from 0.05% to 0.6% by CFSE staining assays in PBMCs.¹³ It has been speculated that the reactive cell population consisted of a minority of drug-specific T cells and a higher number of cytokine-activated bystander T cells amplifying the reaction.⁷² A high level of cross-reactivity between different RCM was confirmed by CD69 up-regulation and lymphocyte proliferation, as well as in generated T-cell lines and T-cell clones from patients with RCM hypersensitivity.¹³ When analyzing different T-cell clones, different patterns of cross-reactivity were identified, with broad, more restricted, or no cross-reactivity depending on the clone. These *in vitro* experiments confirm the presence and crucial importance of drug-specific T cells in nonimmediate reactions to RCM.

Another argument against an immunologic reaction in nonimmediate hypersensitivity reactions has been the lack of a hapten. Nonionic RCM are chemically nonreactive and unable to bind covalently to proteins;³⁰ however, it has been shown that drugs without haptenic properties are able to stimulate T cells noncovalently in an HLA-restricted pattern.^{73,74} This concept has been termed the *p-i concept* (pharmacologic interaction of drugs with immune receptors) and does not require drug metabolism or protein processing. Pichler and colleagues provided evidence for this concept reminiscent of other drug-receptor cross-talks. This model can be applied for RCM reactions and would explain the cross-reactivity observed between different compounds.

DIAGNOSIS

Because different mechanisms are involved in RCM hypersensitivity, the allergologic work-up of immediate and nonimmediate reactions must be regarded separately.

Immediate Hypersensitivity Reactions

Immediately after the reaction, elevated plasma histamine and serum or plasma levels of histamine and tryptase have been found, especially in patients with severe or fatal immediate reactions.^{48,53,54} In cases in question for anaphylaxis, blood samples for histamine analysis should be drawn as soon as possible after the reaction and for

tryptase 1 to 2 hours after the onset of symptoms.⁴⁸ Tryptase values should be compared with baseline levels.

Further allergologic work-up is recommended between 2 and 6 months after the reaction (**Table 3**) because positive skin tests are more seldom found afterward.³ Patients are only rarely skin prick test (SPT) positive with undiluted RCM. Afterward, IDTs with readings after 20 minutes are recommended with the RCM (300–320 mg I/mL) diluted 10-fold in sterile saline, because this concentration has been shown to give a low frequency of false-positive reactions in controls (0% to 4%).³ Because cross-reactivity is frequent, a panel of several different RCMs should be tested in an attempt to find a skin test-negative product, which might be tolerated in future RCM examinations.

No commercial assay is available for routine measurement of serum levels of RCM-specific IgE antibodies. The reliability of other in vitro tests, such as the basophil activation test, has not yet been established. Results from individual patients and the author's unpublished study indicate that the basophil activation test may be helpful,⁶² however, currently, it may only be used on an experimental scientific basis. Provocation is generally not recommended because intravenous applications of as low as 0.5 to 1 mL of RCM have led to severe anaphylaxis.⁷⁵

Nonimmediate Hypersensitivity Reactions

In patients with RCM-induced nonimmediate skin reactions, systemic involvement has been described;⁶⁴ therefore, hematology and clinical chemistry should be determined in more severe exanthemas. A skin biopsy is sometimes needed for differential diagnosis.

Based on available data, further allergologic work-up should be performed within 6 months after the reaction.³ Both delayed IDTs (**Fig. 2**) and patch tests are frequently positive when read after 48 and 72 hours (and optionally at other time points, such as at 24 hours or 96 hours in cases of local pruritus or erythematous plaques). Because some patients test positive with only one of these tests, it is recommended to use both tests in parallel to enhance test sensitivity (see **Table 3**). Patch tests should be conducted with undiluted contrast media, whereas 10-fold diluted products in physiologic saline are recommended when performing delayed IDTs. In cases of non-severe reactions, an IDT and late readings with undiluted RCM may be discussed to increase sensitivity; however, this approach has not yet been evaluated in a sufficient number of controls. A panel of several different RCM should be tested to identify skin test-negative substances.

A response involving RCM-related T-cell activity may be assessed in vitro by the lymphocyte transformation test.^{9,14} In addition, CD69 up-regulation (lymphocyte

Table 3
Presently recommended skin test concentrations for radiocontrast media

Test	Concentration ^a	Readings	
		Immediate Reaction	Nonimmediate Reaction
Skin prick test	Undiluted	20 min	20 min, 48 h, 72 h ^b
Intradermal test	1/10 diluted	20 min	20 min, 48 h, 72 h ^b
Patch test	Undiluted	—	20 min, 48 h, 72 h ^b

^a Undiluted RCM with an iodine concentration of 300–320 mg/mL.

^b If the patient notices a positive reaction (pruritus, erythema) at the skin test site at other time points, additional readings may be performed (eg, after 24 or 96 hours).



Fig. 2. Positive skin test reactions after 72 hours in the IDT in a patient with nonimmediate RCM hypersensitivity. The patient developed a disseminated maculopapular exanthema 1 day after contrasted CT with ioversol (Optiray). Ioversol tested positive in a 1/10 dilution with vesicle formation. Several other positive skin test reactions indicate cross-reactivity between RCM.

activation test) has been observed in patients with a positive lymphocyte transformation test.^{14,72} These tests appear to be promising tools to identify drug-reactive T cells in the peripheral blood of patients with RCM-induced drug hypersensitivity reactions; however, because the sensitivity and specificity remain unknown, the tests cannot be recommended for routine use at present. Further research on the specificity and sensitivity is indicated.

Provocation tests with progressive increases of the injected RCM dose over several days are useful to confirm a negative skin test result before the patient is exposed to the full dose of contrast media.^{7,76} Safe readministration of a skin test-negative contrast media has only been published for individual case reports and in a series of 15 patients with nonimmediate skin eruptions.⁷ In that study, nonserious skin symptoms after exposition of the dimeric agents iodoxanol ($n = 4$) or ioxaglate ($n = 1$) were described despite negative skin tests for these agents in five patients. It remains unknown whether false-negative skin tests are a phenomenon specific for dimeric contrast media. Skin test results are currently being validated in a European multi-center follow-up study by provocation tests and data on re-exposure. Until these results are available, a positive skin test to a given RCM dictates that this RCM should not be chosen for a future exposure, but a negative test does not necessarily guarantee tolerance. In this situation, graded provocation tests are helpful depending on the time course of the primary reaction (eg, one-tenth of the full dose on day 1, one half of this dose on day 2, and the full dose on day 3 at the radiology department).⁷ This procedure has also been performed in the author's department without problems. Although a previous nonimmediate exanthematous reaction does not pose a higher

risk for a subsequent immediate anaphylactic reaction, due to the potential risk involved, provocation tests should generally be performed only in centers with experience in performing monitoring and emergency treatment.

PREVENTION OF IMMEDIATE REACTIONS

In patients with risk factors, such as bronchial asthma or a previous contrast media-induced immediate adverse reaction, radiologists routinely administer nonionic RCM because of their lower incidence of total reactions.⁷⁷ If a patient with a previous immediate hypersensitivity reaction to a RCM needs a new contrasted examination, the culprit preparation should not be readministered. In patients with a history of previous anaphylaxis, skin tests (SPT and IDT) with RCM and a reading after 20 minutes are recommended.¹⁶ In a patient with a positive reaction, a panel of several different contrast media should be tested in an attempt to find a skin test-negative product;³ however, only a few case reports have described the successful use of skin tests or in vitro tests for selection of a safe, alternative contrast media in patients with a previous immediate reaction.^{54,57,58} The results from multicenter studies with re-exposure of RCM are needed to clarify the negative predictive value of these tests. In the majority of cases with immediate reactions, skin tests will remain negative and the pathomechanism will not be identified; therefore, on theoretical grounds, a structurally unrelated RCM should be chosen for the next examination.

The prophylactic use of premedication in patients at high risk of immediate RCM reaction is becoming more controversial.^{78–80} Corticosteroids and H1- and H2-antihistamines are the most frequently used agents.^{81,82,83} Despite different protocols and administration routes, severe reactions may still develop in patients who receive corticosteroid premedication.^{82,83} The estimated recurrence rate of RCM reaction after corticosteroid administration has been estimated to be almost 10%.⁸² In a recent systematic review, it was concluded that, in unselected patients, the usefulness of premedication is doubtful because a large number of patients would need to receive premedication to prevent one potentially serious reaction.⁷⁹ In addition, sufficient data supporting the use of premedication in patients with a history of allergic reactions are lacking. Physicians treating these patients should not rely on the efficacy of premedication.⁷⁹

PREVENTION OF NONIMMEDIATE REACTIONS

Patients with previous nonimmediate skin exanthemas to RCM are at risk for developing new eruptions on re-exposure to the same RCM.^{37,38,66–70} Consequently, another product should be chosen if re-exposure is required. Due to frequent cross-reactivity between different RCM, a change of product is no guarantee against a repeat reaction.

Patch tests and delayed IDTs are recommended to confirm an allergic reaction to the culprit RCM.³ Although it has not yet been proven whether skin testing is a suitable tool for the selection of an alternative CM that can be safely used, in the case of positive skin tests, the substances that are able to elicit test reactions should be avoided. Currently, the administration of skin test-negative contrast media in previous reactors should be done with caution because reactions have been observed after administration of skin test-negative dimeric contrast media in five patients.⁷ A fractionated provocation test, which is performed in the author's department before the final procedure, may be indicated.

In current practice, steroid prophylaxis is often given to patients with previous serious nonimmediate adverse reactions if new contrast media exposure is required.

An even stronger pretreatment protocol that has been used involved intramuscular 6-methyl-prednisolone (40 mg daily) and oral cyclosporine (100 mg twice daily) 1 week before and 2 weeks after each of four angiograms in a patient with two previous episodes of maculopapular reactions after RCM administration, the last despite steroid premedication.⁶ No studies have been conducted to establish the optimum pretreatment regimen. Repeated nonimmediate reactions, including a case of toxic epidermal necrolysis, have been reported despite corticosteroid premedication.^{6,38,41,68} There are not enough data to support the efficacy of pharmacologic prevention in patients with nonimmediate reactions to RCM.

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