

Anaphylaxis to radiographic contrast media

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Purpose of review

Radiographic contrast media (RCM) are increasingly used in modern diagnostic medicine. Hypersensitivity reactions to nonionic RCM still occur in a significant number of exposed patients, because of the increased use of contrasted radiological investigations. Hypersensitivity reactions may be divided into immediate (<1 h of administration) and nonimmediate responses (>1 h). Immediate reactions present with anaphylaxis.

Recent findings

Although described less commonly, anaphylaxis to gadolinium contrast media have been increasingly reported in recent literature. In most patients, immunoglobulin (IgE)-mediated allergy cannot be demonstrated and the underlying mechanism remains unknown. In some patients, positive skin tests, specific IgE antibodies or specific cellular tests have been demonstrated. It may be speculated that more allergic reactions could be described, if more adequate methods were developed. Skin prick tests and intradermal tests with 1 : 10 diluted RCM are specific and confirm the diagnosis of RCM hypersensitivity.

Summary

There are not enough data yet about the value of skin tests for the selection of a 'well tolerated' RCM. Premedication of previous reactors is common among radiologists. However, breakthrough reactions are a concern and physicians should not rely on the efficacy of pharmacological premedication. Instead, radiologists should be prepared to treat severe RCM-induced allergic reactions in their practice.

Keywords

anaphylaxis, hypersensitivity, radiographic contrast medium, skin test

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Introduction

It has been estimated that about 75 million iodinated radiographic contrast medium (RCM) administrations are made per year worldwide [1]. RCM are triiodinated benzene derivatives [2]. Of the four classes available (ionic monomers, nonionic monomers, ionic dimers and nonionic dimers), ionic monomers are not used any more for intravenous application due to a higher risk of adverse reactions. MRI procedures are contrasted with gadolinium preparations, which have a different molecular structure (Fig. 1).

Considering the high frequency of applications and the high dose given, RCM and gadolinium preparations are remarkably well tolerated. However, hypersensitivity reactions occur and may be divided into immediate (<1 h) and nonimmediate (>1 h) reactions [3]. The majority of specific immediate hypersensitivity reactions to RCM present with anaphylaxis, whereas the non-immediate hypersensitivity reactions manifest as exanthemas.

In patients with nonspecific symptomatology (e.g. nausea, feeling of warmth), a hypersensitivity reaction is unlikely, and the reaction may be toxic, unrelated to the application of RCM or remain undetermined, and allergologic tests normally remain negative. The aim of this review is to provide an update on data related to immediate hypersensitivity reactions to contrast media. The majority of studies in the literature focused on diagnosis, breakthrough reactions and prophylaxis.

Incidence of iodinated contrast medium hypersensitivity and gadolinium contrast medium hypersensitivity from large prospective trials and postmarketing surveys

It has been estimated that mild immediate reactions occur in about 0.5–3% of applications of ionic dimers or nonionic RCM [3]. It is believed that patients with systemic mastocytosis are prone to developing such reactions, and cases have been described in the literature [4]. In a newer postmarketing surveillance study [5] with iopromide in which a standardized questionnaire was used to collect patient information, the rate of immediate

reactions was 1.5%. Patients with a history of previous contrast media reactions and those with an allergic diathesis had an increased risk for developing a hypersensitivity reaction (7.4 and 4.1%, respectively) when compared with patients without risk factors (1.2%). Severe immediate hypersensitivity reactions have been reported in 0.01–0.04% of intravenous procedures [3]. The risk of fatalities is about one per 100 000 RCM administrations [3]. However, due to the frequency of RCM used, these diagnostic agents rank among the drugs most often causing fatal anaphylaxis [6]. In a population-based incidence study [7] conducted in Rochester, Minnesota, USA from 1990 to 2000 looking for anaphylaxis, 0.5% of cases were accounted to RCMs. The frequency of immediate hypersensitivity reactions to RCM depends on the route of administration [3]. In a prospective study [8] on RCM hypersensitivity after endoscopic retrograde cholangiopancreatography, it was concluded that this application is rarely associated with immediate reactions, even in patients at risk. Reactions to gadolinium-containing intravenous contrast media appear to be less frequent. In a study [9] of a radiology department between 2001 and 2006, immediate hypersensitivity reactions to these agents were recorded in 0.07% in adults and 0.04% in children. Of those, 74% were classified as mild, 19% as moderate and 7% as severe. In a study [10**] analyzing gadolinium-based contrast agent adverse events reported to radiology quality assurance committees during the past 10 years, immediate reaction rates were 0.2, 0.5, 1.2 and 3.3 per 1000 injections for gadodiamide, gadopentetate dimeglumine, gadobenate dimeglumine and gadoteridol, respectively, including one death. Adverse reactions were more often described in women, as well as in abdominal MRI (0.013%) as compared with brain (0.0045%) or spine (0.0034%). Cases with severe anaphylaxis after administration of gadolinium-containing contrast media are increasingly reported [11,12,13*,14].

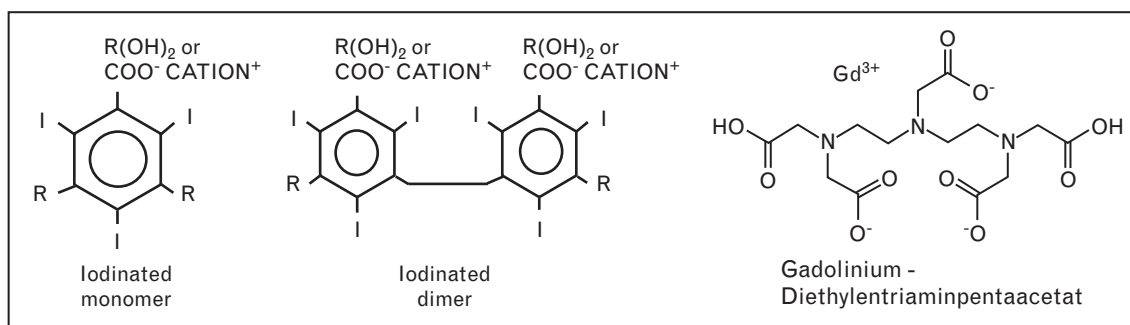
Key points

- Anaphylaxis to radiographic contrast media (RCM) and MRI agents remains a clinical problem owing to their increased use.
- Laryngeal edema is a common severe adverse reaction potentially leading to respiratory arrest, necessitating epinephrine use.
- Skin prick tests with undiluted agents and intradermal tests with 1:10 dilution are recommended in patients with anaphylaxis to RCM.
- As indirect evidence for an allergic mechanism is found only in a minority of patients, and the effect of premedication is unreliable, more research is needed on new diagnostic techniques and the optimal management of patients with contrast media hypersensitivity.

Clinical manifestations of radiocontrast media hypersensitivity

Most immediate symptoms become apparent within the first 5 min of RCM administration [15]. Symptomatology is most often limited to urticaria or nausea. In more severe reactions, the respiratory or cardiovascular systems are involved. Even after application of nonionic RCM, fatal reactions are repeatedly described [16]. A recently described hypersensitivity reaction is the Kounis syndrome, which describes the concurrence of acute coronary syndrome with mast cell activation induced by inflammatory mediators released during an allergic reaction in patients. A 45-year-old patient, 30 min after coronary angiography, developed flushing, shortness of breath and severe retrosternal chest pain [17]. An ECG revealed an anterior acute myocardial infarction and the subsequently performed coronary angiography showed subtotal occlusion of the proximal left anterior descending artery. It was concluded that the myocardial infarction had been due to the coronary artery vasospasm leading to

Figure 1 Structure of different iodinated and gadolinium contrast media classes



In ionic radiographic contrast media, the benzene ring includes a COO⁻ cation⁺ group, whereas in the nonionic products this is replaced by a nonionic R(OH)₂ group. The paramagnetic metal ion gadolinium improves the MRI signal, but has to be chelated, such as gadolinium diethylenetriamine-pentaacetate dimeglumine, the first marketed gadolinium-based contrast agent. Other MRI agents differ by their nonionic molecule or macrocyclic ring structure.

a rupture of an atheroma after the hypersensitivity reaction to RCM. Another report [18] describes a patient with an implanted stent who developed an acute myocardial infarction in the stent area following a hypersensitivity reaction to RCM.

In an autopsy report of fatal anaphylaxis, clinical features were described in a patient who died 4 h after receiving ioxaglic acid [19]. In this patient, 18-h postmortem analysis of plasma revealed elevated tryptase (182 $\mu\text{g/l}$) and histamine (145 ng/ml) levels. Laryngeal edema and an increase in lung weight were observed, but other remarkable changes were lacking. Thus, in fatal RCM anaphylaxis, evidence of severe mast cell mediator release has been found, but clinical signs were mainly limited to laryngeal and lung edema.

Pathomechanism and diagnosis

Immediate hypersensitivity reactions to RCM are associated with histamine release from basophils and/or mast cells. As this histamine release has not been convincingly explained by an activation of the complement system, a bradykinin-induced mechanism or a direct membrane effect, the possibility of an immunoglobulin (IgE)-mediated mechanism has been most extensively discussed [20]. The facts that contrast media are small-size molecules, which should involve haptization to become immunogenic, that patients can react on first exposure, that RCM-specific IgE antibodies have seldom been detected and that positive skin tests can be found in the minority of patients favor a nonallergic mechanism. However, recent results have challenged this dogma and led to the speculation that possibly IgE-mediated reactions could be demonstrated by direct or indirect means, if better methods could be developed.

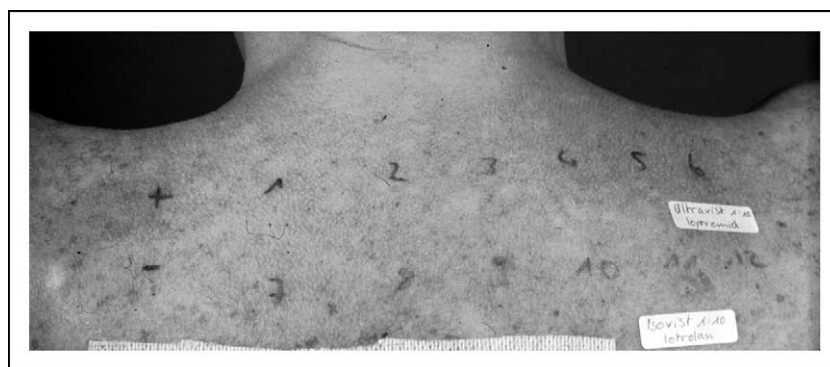
The frequency of positive skin test has been investigated in a European multicenter study [15] in patients with

RCM hypersensitivity and in 82 controls. Intradermal skin tests were performed at dilutions of up to 1:10 (Fig. 2). In 26% of patients, positive skin tests were documented. Controls had negative skin tests in 96%, demonstrating specificity. The percentage of positive skin tests was higher in patients that could be tested within 2–6 months after the reaction, consistent with a decrease of immunoreactivity over time. Almost half of the patients had never been exposed to RCM before. It was concluded that a reaction on first exposure does not rule out an immune-mediated reaction, as a considerable fraction of these patients (43%) were skin test positive.

Dewachter *et al.* [21] performed intradermal tests with undiluted RCM in 38 patients with immediate hypersensitivity reactions and reported an even higher sensitivity of 73%. Also in this study, 30% of the reactions occurred after the first exposure to an RCM. As no controls have been tested, the question remains whether some of these skin test reactions could be unspecific irritative responses. However, the authors reported that 179 of 188 intradermal tests with alternative RCM remained negative in the patients.

In a single-center study on prevalence, risk factors and on the value of skin tests in the diagnosis of immediate RCM hypersensitivity by Goksel *et al.* [22] investigating patients who underwent computed tomography during a 1-year period, a structured questionnaire was employed and skin tests with 1:10 diluted RCM were performed in 24 RCM reactors and in 37 controls. The sensitivity and specificity of intradermal tests were found to be 20 and 91.4%, respectively. The prevalence of RCM hypersensitivity in the patients' history was 2.9% and that of actual hypersensitivity reactions 0.7%. In this study, female sex, history of doctor-diagnosed asthma, drug allergy, food allergy and psychiatric disease were significant risk factors.

Figure 2 Intradermal skin tests



Specific positive intracutaneous skin tests to iopromide and iotrolan in a patient with anaphylaxis to iopromide, with no skin test reaction to the other radiographic contrast media of the series.

Scherer *et al.* [23^{••}] reported positive intradermal skin tests to a 1:10 dilution of RCM in three of nine patients (33%) with immediate RCM hypersensitivity. After oral provocation with Lugol's solution, containing high amounts of potassium iodide, one of nine patients with negative skin test reacted twice with acute urticaria. The authors concluded that the free iodine from the RCM may have caused urticaria in this patient despite negative skin tests to RCM and that iodine is rarely the eliciting agent in hypersensitivity reactions to RCM.

A further study [24] evaluated 96 patients with immediate RCM hypersensitivity by skin tests using 1:10 RCM dilutions and by in-vitro basophil activation tests. Positive reactions were found in four of 96 patients (4.2%) with the intradermal tests and in three of these patients with the basophil activation tests, which in these patients strongly suggested an IgE-mediated allergy. In two of these patients, alternative nonionic monomer contrast RCM were tolerated in controlled challenge tests.

In another case report [25] on one patient with amido-trizoate hypersensitivity, a positive basophil activation test and positive intradermal test (to a 1:100 dilution) was described.

Thus, these studies conclude that evidence of an allergic mechanism in immediate RCM hypersensitivity by positive skin tests may be more common than previously thought and that it can occur after the first administration. Intradermal tests up to 1:10 dilution help to establish the diagnosis. The sensitivity in studies differs between 4 and 73%, whereas the specificity of undiluted preparations is not yet sufficiently demonstrated. The basophil activation test may be a useful additional diagnostic tool. Whether other tests, such as the cysteinyl leukotriene release from basophils, aid to diagnose RCM hypersensitivity remains unproven [26].

It has not yet been shown whether skin testing is a suitable tool for the selection of an alternative RCM that can be safely used. Caimmi *et al.* [27^{••}] studied the clinical value of negative skin tests to RCM in 29 patients with previous hypersensitivity reaction, who had been re-exposed without any premedication. In two of 29 patients, a positive intradermal test was seen. After provocation of an RCM, which gave a negative skin test, both patients showed no symptoms. Three patients reacted to the RCM injection despite negative skin test. One patient reacted with a generalized urticaria, lasting for 3 days after receiving iomeprol, but was re-exposed later under the suspicion of an unrelated chronic idiopathic urticaria and tolerated iomeprol the second time. The second patient developed a generalized exanthema after 24 h. A third patient presented with nausea, dyspnea

and tremors, which was attributed to a vagal/anxiety reaction. Thus, the negative predictive value of intradermal skin tests in RCM hypersensitivity was calculated to be 97%.

In patients with severe anaphylaxis after application of gadolinium contrast media, positive skin tests appear to be rare. Hasdenteufel *et al.* [14] described two patients with an anaphylactic shock after first exposure to gadoterateme-glumine. In one of these patients, the skin prick test with the undiluted preparation was positive, and another patient showed a positive response to a 1:10 diluted intradermal test, whereas other preparations tested were negative. In a following report on two further cases, Galera *et al.* [13[•]] described two further patients with a positive intradermal test to undiluted and 1:10 diluted gadoteridol and 1:10 diluted gadobenatime-glumine. In 10 exposed controls, skin prick tests with undiluted gadolinium preparations were negative, but half of them had irritative positive intradermal tests to the undiluted gadolinium agents. These case reports show that in parallel to the situation in RCM, skin prick tests or intradermal tests with 1:10 diluted preparations may be helpful in the diagnosis of immediate gadolinium hypersensitivity.

Prevention

If a patient with a previous immediate hypersensitivity reaction to RCM needs a repeated examination, the culprit preparation should be avoided [3]. Skin tests (skin prick test with undiluted and intradermal tests with 1:10 diluted RCM) and optionally the basophil activation test are recommended for the diagnosis [20], although in our hands they are only positive in a fraction of patients with typical clinical reactions.

The preventive value for the selection of a well tolerated, alternative RCM still has to be further defined. It may be limited to those patients in whom skin test-positive RCM can be avoided. In one study [27^{••}], however, the negative predictive value of reapplication of RCM in combination with skin tests has been reported to be high.

It is common practice to use premedication in patients at high risk for an immediate RCM reaction [28]. Corticosteroids and H₁ and H₂ antihistamines are the most frequently used agents. However, severe reactions still develop in patients who receive RCM or gadolinium preparations after premedication [29,30]. In a study from the Department of Radiology of the University of Michigan over a 9-year period, Davenport *et al.* [31] reported on 190 breakthrough reactions to intravenous nonionic RCM in 175 patients despite premedication with corticosteroids and antihistamines. In cases in which the index reaction severity was known, 81% of the breakthrough

reactions were of a similar severity and 8% of a higher severity to that of the index reaction. When the index reaction was severe, the breakthrough reaction tended to be moderate or severe. In addition, repeat breakthrough reactions were analyzed, which occurred in only 23 of 197 examinations in 58 patients. Moderate or severe breakthrough reactions were reported significantly more often in patients with a history of chronic corticosteroid use, drug hypersensitivity or patients with severe or several allergies. In a further study [32] on premedication from Korea, the overall recurrence rate of immediate hypersensitivity reactions was five of 30 patients (17%). In a systemic review [33] it has been concluded that in unselected patients, the usefulness of premedication is doubtful. Also, it was criticized that data supporting the use of premedication patients with a history of allergic reactions are lacking.

Acute therapy of immediate radiocontrast hypersensitivity reactions by the radiologist

Radiologists should be prepared to treat anaphylaxis, even though severe immediate hypersensitivity reactions to RCM or gadolinium preparations are rare [34]. Epinephrine might be used too seldom. In one radiology practice retrospectively reviewing their medical database over a 5-year period, epinephrine was only used in nine of 457 000 cases [35]. The most common clinical indication was laryngeal edema in six patients. In these series, four of nine patients had some form of cardiovascular side-effect attributed to epinephrine given intravenously.

To evaluate radiologists' knowledge of the appropriate management of severe RCM-induced immediate reactions, a telephone survey was performed in 13 Canadian English-speaking and 13 USA university-affiliated radiology departments. Given a severe RCM-induced hypersensitivity reaction case scenario, radiologists were asked about their medication of choice and specifically on their use of epinephrine [36]. Although 91% of radiologists identified epinephrine as the most important initial medication, no radiologist gave the ideal response on the treatment scenario and only 41% provided an acceptable administration route, concentration and dose.

In a further study [37], a similar simulation model was used to test the radiology resident preparedness for pediatric life-threatening events. Out of 19 radiology residents, only one resident chose the correct sequence of interventions (calling coteam, providing oxygen and then providing epinephrine) in one of two scenarios.

Thus, these studies show that the radiologists' preparedness for immediate hypersensitivity and their knowledge of adequate epinephrine use appear deficient and should be improved by training.

Conclusion

Anaphylaxis to RCM and to gadolinium preparations remains a clinical problem owing to the high number of administrations performed. Allergologic evaluation including skin tests, prick and intradermal tests with 1:10 diluted RCM and optionally the basophil activation test is recommended in patients with a clear history of anaphylaxis to RCM. However, at the moment, the value of these tests is limited due to the fact that only a fraction of patients will show a positive result. More research leading to new diagnostic methods with higher sensitivity is urgently needed. Physicians dealing with patients receiving RCM should not rely on premedication, as there is a risk of repeat reactions. Another approach is to train physicians who use RCM to recognize and treat anaphylactic reactions appropriately. Radiology departments should be trained and staffed with the necessary equipment for resuscitation.

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References and recommended reading

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- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 000–000).

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