

Anaphylaxis in the Radiology Suite



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Learning objectives:

1. To identify the adverse effects of radiocontrast media and gadolinium agents.
2. To recognize the differences between a chemotoxic effect and hypersensitivity reaction.
3. To evaluate and manage a patient with an adverse effect of a contrast agent.

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Contrast media are crucial for modern medical imaging. Contrast agents are generally well tolerated. However, patients may present with adverse reactions, which can be divided into pharmacological effects or hypersensitivity reactions. We present a vignette of a patient with a past history of urticaria after radiocontrast media exposure for coronary angiography. He returns for evaluation for radiocontrast media because he needs another coronary angiography. There are no validated methods

for predicting such reactions yet. Mechanisms behind adverse contrast media reactions are still not well understood. Because of unknown contrast agent, the patient was successfully pretreated with corticosteroids and an H1 antihistamine. © 2020 American Academy of Allergy, Asthma & Immunology (*J Allergy Clin Immunol Pract* 2020;8:1203-9)

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CASE REPORT

A 72-year-old man was referred to the Allergy-Immunology service because of radiocontrast media (RCM) allergy and planned upcoming coronary angiography. He had reported having an intravenous pyelogram 40 years previously for a suspected kidney stone. There was no adverse reaction from the procedure. Four years ago, he underwent coronary angiography and reported “immediate-onset” generalized pruritus and urticaria. He believes he was given a “shot,” and the procedure was continued without any worsening reaction or delayed-onset rash (in the next week). He denies any other exposures to RCM. He is currently asymptomatic but had ischemic findings on a recent treadmill test. He is a nonsmoker and denies a history of allergic rhinitis and asthma. He experienced unexplained acute urticaria 9 years

Abbreviations used

ACR- American College of Radiology
 ADR- Adverse drug reaction
 BAT- Basophil activation test
 GBCM- Gadolinium-based contrast medium
 HR- Hypersensitivity reaction
 ICM- Iodinated contrast media
 IDT- Intradermal test
 RCM- Radiocontrast media

previously that lasted for 3 days and has not recurred. He denies spontaneously occurring pruritus. His daily medications include aspirin 81 mg, atorvastatin 10 mg, lisinopril 10 mg, metoprolol 25 mg (twice daily), and a multivitamin with vitamin D 1000 IU. He is asymptomatic and appears well on examination. His blood pressure is 112/64 mm Hg and resting pulse is 62 bpm. The physical examination is unremarkable. On examination, there is no oropharyngeal swelling appreciated and the chest examination is normal. The heart is in regular sinus rhythm, and no murmur is present. The skin examination reveals sun-damaged skin on the face, arms, and hands but there is no evidence of urticaria, purpura, or excoriations.

When asked, he denied being concerned about experiencing another reaction to RCM. He anticipated being skin tested for RCM allergy.

INTRODUCTION

Contrast media are used widely throughout the world to enhance medical imaging. The main contrast agents include low-osmolality iodinated or gadolinium-based contrast agents (Table I).¹ Adverse reactions to modern contrast agents are uncommon, but do happen.

Adverse reactions include physiologic/chemotoxic changes and hypersensitivity reactions. Hypersensitivity reactions can present immediately in the radiology suite, or as a delayed cutaneous reaction, typically 24 hours later. These reactions range from mild urticaria to rare life-threatening events.¹

Historically, the risk of an immediate hypersensitivity reaction was increased in the high-osmolality iodinated agents. In the 1970s, the introduction of nonionic low- or iso-osmolality iodinated contrast media (ICM) led to a decrease in hypersensitivity reactions, resulting in only about 20% of past conventional RCM reactions.² The risks are even less for gadolinium-based contrast agents.³

ADVERSE REACTIONS TO RCM: CLASSIFICATION, CLINICAL PICTURE, AND MECHANISMS

Classification

An acute adverse contrast reaction can present as a nonallergic, pharmacologic effect or as a hypersensitivity reaction. Physiologic/pharmacologic effects are usually due to the properties of the contrast agent: osmolality, ionicity, and viscosity. Expected chemotoxic side effects can range from mild symptoms of transient nausea, heat sensation, metallic taste, or vasovagal reaction to a rare reaction with significant morbidity, such as an arrhythmia or cardiogenic pulmonary edema (Table II).^{1,4} These reactions are due to specific physiochemical effects of the agents on the blood vessels or organs.⁵ The factors include hyperosmolality, potential for binding calcium ions, and concentration

of cations, leading to functional hypocalcemia.⁵ Compared with a hypersensitivity reaction, a physiologic side effect is dependent on dose, concentration, and infusion rate. In patients with chronic kidney disease, the use of RCM may also induced acute contrast-induced nephropathy, which is generally reversible. The RCM-induced kidney injury is most likely due to acute tubular necrosis related to the cytotoxic effects from the agent.¹

In contrast, the most serious adverse effect from gadolinium-based agents is nephrogenic systemic fibrosis, which is typically irreversible fibrotic damage in patients with acute or chronic kidney disease.⁶ Nephrogenic systemic fibrosis can present within days to months after receiving gadolinium. Recently, residual gadolinium deposits have been found in brain tissue, leading to a Food and Drug Administration safety alert in July 2015.¹ One specific agent, gadoxetate disodium, has been associated with severe transient dyspnea.¹

An acute hypersensitivity reaction is described when it occurs within an hour of contrast administration. A delayed-onset reaction would be defined as occurring 1 hour to 10 days after receiving the contrast media.

RCM are concentrated solutions of tri-iodinated benzene derivatives: ionic monomers, nonionic monomers, ionic dimers, and nonionic dimers. The frequency of reactions depends on the different types of RCM. Because ionic contrast agents are associated with a higher risk of adverse reaction,⁷ the American College of Radiology has recommended the use of nonionic contrast media.¹

Clinical presentation

Acute hypersensitivity reactions present with urticaria or pruritus at least 44% of the time, such as in our patient.⁸

Patients may also present with bronchospasm. The onset of immediate reactions is rapid, with about 70% happening within 5 minutes of contrast exposure.⁹ Rash is the most common presentation of a delayed reaction,⁸ which occurs hours to days after contrast exposure. Rare cases of severe reactions such as Stevens-Johnson syndrome and even fatalities have been reported.^{7,10}

Possible mechanisms

Hypersensitivity reactions to contrast media involve nonspecific mast cell and basophil activation, including a complement-dependent pathway.¹¹ Zhai et al¹¹ studied 27 patients who presented with at least a grade II immediate reaction after intravenous injection of nonionic contrast media. Zhai et al found significantly elevated human terminal complement complex SC5b-9 in 11 of the 27 patients, compared with 4 cases of IgE-dependent pathway. There was evidence of mast cell activation, with elevated carboxypeptidase A3 in all 27 patients.¹¹ Kim et al¹² found that 35% of 104 study patients presented with an immediate hypersensitivity reaction on first exposure.¹² Recent studies have shown that some acute hypersensitivity reactions may be caused by an IgE-mediated allergy. Laroche et al¹³ studied patients with reactions to iodinated contrast material compared with controls and found that during reaction, plasma histamine, tryptase, and urine methylhistamine levels were elevated, showing evidence of mast cell activation, along with significantly higher levels of specific IgE against ioxaglate and ioxitalamate.

In a study by Jiang et al,¹⁴ it was demonstrated that a mast cell-specific receptor, Mas-related G protein-coupled receptor

TABLE I. Contrast agents available*

Product	Iodine content (mg/mL)	Osmolality (mOsm/kg)
RCM: Nonionic monomers		
Iohexol 350	350	844
Iodixanol 270	270	290
Iopamidol 300	300	616
Iopromide 240	240	483
Product	Class	Osmolality (mOsm/kg H ₂ O)
Gadolinium based		
Gadopentetate	Linear ionic	1960
Gadoteridol	Macrocyclic nonionic	630

*In comparison to plasma osmolality of 285 mOsm/kg and cerebrospinal fluid osmolality of 301 mOsm/kg.

TABLE II. Categories of acute reactions¹

Hypersensitivity	Physiologic/chemotoxic
Mild reactions	
Pruritus	Nausea/vomiting
Urticaria	Flushing/warmth/chills
Throat pruritus	Headache/dizziness
Nasal congestion	Anxiety/altered taste
Conjunctivitis	Mild hypertension
Sneezing	Vasovagal reaction
Moderate reactions	
Diffuse urticaria	Protracted nausea/vomiting
Diffuse erythema	Hypertensive urgency
Facial edema without dyspnea	Isolated chest pain
Throat tightness, bronchospasm, no hypoxia	Vasovagal reaction that is responsive to treatment
Severe reactions	
Diffuse edema with dyspnea	Vasovagal reaction resistant to treatment
Diffuse erythema with hypotension	Arrhythmia
Laryngeal edema with stridor and/or hypoxia	Convulsions, seizures
Bronchospasm with hypoxia	Hypertensive emergency
Anaphylaxis with hypotension	Pulmonary edema

X2-mediated iopamidol, triggered mast cell calcium mobilization and degranulation, leading to an IgE-independent reaction.¹⁴

For a delayed skin eruption, the mechanism is likely comparable to that of other drug-induced T-cell-mediated reactions. The histopathologic findings are similar to those reported for other drugs known to cause T-cell-mediated cutaneous reactions.¹⁵

EPIDEMIOLOGY AND RISK FACTORS

Prevalence

The prevalence of hypersensitivity reactions (HRs) to ionic monomeric RCM has been estimated to be 3.8% to 12.7 %, whereas HRs to nonionic RCM occur in 0.7% to 3% of administrations.^{9,16}

A frequency of adverse drug reactions (ADRs) to RCM between 0.2% and 0.7%, with serious ADRs between 0% and

0.05%, was reported by An et al,⁸ with the most frequently involved RCM being iopromide and iomeprol. Another study investigated the prevalence of ADRs to low osmolality RCM according to the severity, and observed mild reactions in 0.85%, moderate reactions in 0.1%, and severe reactions in 0.02% of cases, with iobitridol, iomeprol, and iopromide as the most frequent inducers.¹⁷ Macy¹⁸ reported that of 372 serious, immediate RCM reactions between 2014 and 2017, 335 (90.1%) reactions were associated with iohexol.¹⁸

A large study carried out in China included 120,822 subjects who received RCM, observing a frequency of severe reactions in 1:17,260 (0.006 %).¹⁶ Immediate reactions occurred in 506 (0.4%), mild reactions in 90%, moderate in 7.7%, and severe in 1.4%. Patients with a history of reactions to RCM had a 22-fold greater incidence (7.2%) versus 0.32% in patients with previous exposure to RCM without any untoward effect.¹⁶ No sex differences were present, and reactions occurred with higher frequency in patients aged between 29 and 70 years, patients submitted to coronary angiography, and head and neck angiographic studies.

Although there was a progressive increase in anaphylactic reactions to RCM between 2006 and 2011, which paralleled the increased utilization of RCM in that period of time, the number of ADRs has decreased since the year 2012.¹²

The HR rate of gadolinium-based contrast material is approximately 0.05% to 0.33% and the risk of death is 0.1 to 2.7 per million.¹⁹ Reactions to both RCM and gadolinium are even more rare, because there is no evidence of cross-reactivity between iodinated and gadolinium-based agents. At Northwestern Memorial Hospital in Chicago, Illinois, a review of 302,858 contrast injections between 2011 and 2017 showed that of more than 37,073 subsequent contrast reactions, only 9 (0.024%) patients presented with HRs to both types of agents.²⁰

Risk factors

The clinical features that have been associated with an increased risk for ADRs to RCM are summarized in Table III. The main risk factor for an HR to RCM is a previous ADR.⁵ Some of them, such as atopy, comorbid allergic disease, asthma, female sex, repeated RCM administration, severe cardiovascular disease, allergy to other drugs, and mastocytosis, have been recognized in the literature. Other factors, including psychiatric disorders, food allergy, and concomitant intake of proton pump inhibitors, have been proposed more recently. There is no evidence that a history of shellfish or topical iodine solution allergy puts the patient at risk for RCM reactions.

DIAGNOSTIC METHODS: *IN VIVO* AND *IN VITRO*

Skin tests

Although skin tests with RCM are not commonly performed in North America, skin testing in Europe happens in specialized testing centers, where patients with a history of immediate reactions to RCM will receive skin prick tests with undiluted RCM, and then an intradermal test (IDT) with a 1:10 dilution with reading after 20 minutes.²⁹ In a Korean study, it was found that less than 20% of hospitals in Korea and abroad perform skin testing in patients with previous ADRs to ICM.³⁰

Brockow et al³¹ observed that at least 50% of HRs to RCM are caused by an immunologic mechanism, and proposed that skin testing is a useful method for the diagnosis of an IgE-mediated allergy to RCM and may play an important role in the selection

TABLE III. Risk factors for HRs to RCM

Atopy ²¹
Asthma ²²⁻²⁴
Female sex ^{22,24}
Severe cardiovascular disease ²³
Repeated administration of RCM ^{25,26}
Previous reaction to RCM ²⁴
Intravascular RCM injection ^{16,27}
Drug allergy ²²
Mastocytosis ²⁸
Comorbid allergic disease ²¹
Psychiatric disorders ²²
Food allergy ²²
Proton pump inhibitor comedication ²⁵

TABLE IV. Cross-reactivity of RCM³²

Group A	Group B
Iodixanol	Ioxaglate
Iopamidol	Iobitridol
Iomeprol	
Iohexol	
Ioversol	
Ioxitalamate	

of a safe alternative RCM in previous reactors.³¹ In this study, the specificity of skin testing was as high as 96% to 100%. However, the culprit contrast agent could not be identified in 83 of the 200 cases reported, so it was not clear whether the contrast agent responsible for the reaction was tested.³¹ Skin test for an acute RCM reaction seems to have high specificity (about 94.6%), with lower sensitivity (about 20%), 77.8% to 80% negative predictive value, and 0% to 40% positive predictive value.²²

Another study by Lerondeau et al,³² which included 38 patients with immediate reactions to RCM, found that skin prick testing result to radiocontrast was negative for all 38 tested subjects, and found positive patch test results in 3 patients (7.8 %), positive IDT result with reading at 20 minutes in 24 patients (63.1%), and positive IDT result with reading at 24 hours in 8 patients (21.0%), with 2 positive challenges (5.2%).³²

The French 5-year CIRTACI study was a prospective multicenter investigation dealing with immediate HRs to ICM and gadolinium-based contrast media (GBCM).³³ It included 319 patients with immediate HRs to ICM or GBCM from 31 hospitals. Two hundred forty-five skin tests were performed (ICM 209 and GBCM 36). Patients with a positive reaction to IDT with a 1:10 dilution of contrast media were considered allergic. There were 41 positive test results to ICM (19.6%) and 10 positive skin test results to GBCM (27.8%). Forty-two patients (17.1%) showed a positive IDT result to pure ICM and were considered potentially allergic, whereas 152 patients (62%) had negative skin test results. Nonallergic reactions occurred in 134 patients (54.6%). Cutaneous reactions in patients with allergy were present in 10%, and in those patients more than 50% had life-threatening reactions, while cardiovascular signs were strongly associated with allergy. Interestingly, allergy correlated with clinical severity of the reaction and with plasma histamine and tryptase levels.³³ Although no skin testing with RCM was done in

the case reported in this article, from the European experience it has been suggested that skin testing is helpful in patients with a history of immediate reactions to confirm hypersensitivity and to choose alternative RCM with a negative skin test result.³⁴ However, Lee et al³⁵ found that routine IDT to iodinated contrast agents in patients without a known adverse reaction did not predict HRs, because testing had low sensitivity and positive predictive value.³⁵

***In vitro* tests**

Confirmation of mast cell activation following an immediate reaction to RCM is often done by measuring serum tryptase levels,³⁶ although determination of serum chymase and carboxypeptidase 3 levels has been also proposed for such task (not yet commercially available).¹¹ Elevated tryptase level has been reported, especially in patients with severe or fatal acute reactions.³⁷

The basophil activation test (BAT) has been proposed for the *in vitro* diagnosis of ADRs to RCM. Its sensitivity varies from 46% to 62%, and its specificity ranges from 88% to 100%, although BAT results do not seem to correlate with symptom severity. The current recommendation is that BAT, when available, be used in high-risk groups before skin testing.³⁸

Salas et al³⁹ observed that less than 10% of cases evaluated after having an immediate reaction to RCM were finally confirmed as having hypersensitivity, with both skin test and drug provocation tests being necessary to confirm the diagnosis. They suggested that BAT is a promising method for the diagnosis that may complement *in vivo* tests.³⁹

Specific IgE to RCM, for example to ioxaglate acid, has been rarely demonstrated by using radioimmunoassays and is not routinely investigated.⁴⁰

Cross-reactivities between intravenous contrast agents

Various studies suggested the existence of immunologic cross-reactions between the different RCM.^{31,34} In Clement et al's study,³³ cross-reactions between different RCM were demonstrated in 31.4% of skin tests done with diluted RCM and in 62.7% of skin tests done with pure, undiluted solutions. In patients with allergy, cross-reactions were present in 26.8%. Lerondeau et al³² proposed 3 groups of RCM according to their cross-reactivity as determined by means of skin test (Table IV): Group A: ioxitalamate, iopamidol, iodixanol, iomeprol, ioversol, and iohexol. Group B: iobitridol and ioxaglate. Group C: amidotrizoate. A different approach, not fully coincident with Lerondeau et al's classification, was proposed by Rosado Ingelmo et al⁴¹ as follows: RCM with strong association: iodixanol and iohexol; RCM with frequent association: iodixanol, iohexol, iopentol, ioversol, and iomeprol; RCM with limited association: ioxaglate, iopamidol, iobitridol, and iopromide.

According to various investigators, immunologic cross-reactivity between RCM is commonly observed, and reported proportions of patients with cross-reactions range from 20% up to 75%.^{31,42-44} Nevertheless, there is some evidence that iobitridol has a comparatively low tendency to cross-react with other RCM.^{42,43,45,46} The major allergen in shellfish is tropomyosin, a protein important in muscle contraction, and is not related to iodine, so there is a lack of cross-reactivity between shellfish allergy RCM HRs.⁴⁷

Intravenous provocation

In a study by Trautmann and Brockow,⁴⁸ subjects were diagnosed with an RCM hypersensitivity with IDT to the culprit agent. The subjects also underwent skin testing to alternative agents, and controlled provocation testing of skin-test-negative RCM was used

as final proof of tolerance. Lee et al³⁵ studied 2843 patients in Seoul, Korea. Fifteen patients had a positive IDT result before scheduled imaging with RCM. However, none of the 15 patients with positive skin test result experienced any reaction, but 19 other patients experienced reactions after an intravenous challenge, even though they had a negative IDT result.³⁵

MANAGEMENT

The patient in our case has experienced a grade 1 severity reaction to RCM, considered mild because of the absence of respiratory, cardiovascular, or gastrointestinal involvement.⁴⁹ Alternatively, using criteria of the American College of Radiology (ACR), he had a moderate reaction from a mild, moderate, and severe classification system.¹ The latter has the following comment about moderate reactions: "Some of these have the potential to become severe if not treated." The patient has a very strong indication for coronary angiography and is receiving metoprolol and lisinopril. Pretreatment with prednisone and diphenhydramine was advised. The basis for such an approach comes from the ACR Committee on Drugs and Contrast Media Manual, previous allergy-immunology practice parameters,⁵⁰ series of patients receiving lower osmolality media,⁵¹ and extrapolation of results of pretreatment in high-risk patients who received high-osmolality RCM.⁵² The patient was not advised to withhold his current medications. Although there is a case-control study identifying an increased number of reactions to RCM if patients received beta-adrenergic antagonists,²³ prospective studies have not demonstrated an increase.^{16,52} The ACR Committee on Drugs and Contrast Media Manual states that "Patients on beta-blocker therapy do not need to discontinue their medication(s) prior to contrast medium administration."¹

As presented earlier, there is growing literature regarding potential utility of skin testing to identify RCM that would be less "allergenic."^{33,53-55} The skin testing is carried out undiluted and then 1:10 dilution of radiographic contrast material. Irritant reactions are infrequent in controls. It should be noted that positive reactions are more likely to be present within 6 months of reactions.³³ Often, the report of the radiologist does not identify which media was used. A further caution is in interpretation of the skin test results and making the analogy to IgE-mediated reactions. Anaphylaxis would be expected from IgE-mediated skin testing of undiluted and 1:10 dilutions of aeroallergens and Hymenoptera species.⁵⁵

PREMEDICATION

The use of steroids and antihistamines as premedication is common in the United States, but has not gained wide acceptance in Europe. The most widely used premedication protocols used in the United States were studied as prevention of reactions to ionic contrast media. The Lasser protocol includes 2 doses of methylprednisolone 32 mg administered orally 12 hours and 2 hours before imaging.⁵⁶ The Greenberger protocol includes 3 doses of prednisone 50 mg administered orally at 13, 7, and 1 hour before imaging, along with diphenhydramine 1 hour before imaging for patients with a past history of RCM reactions.⁵⁷ In 1980, Saavedra-Delgado et al⁵⁸ published a dose-response study that showed that 3 doses of prednisone 50 mg given at 6-hour intervals had a greater effect on whole blood histamine and leukocytes, supporting the Greenberger protocol.⁵⁸ Lasser et al's

premedication study⁵⁶ was with allcomers, excluding those with severe reactions or diabetes mellitus. However, Kolbe et al⁵⁹ studied patients with a past history of contrast reactions and then repeated studies in 4 groups: no premedication, premedication with diphenhydramine alone, corticosteroid alone, or both corticosteroid and diphenhydramine. Repeat reactions occurred in 7.5% (5 of 66) of those without any premedication. The rate of breakthrough reaction after diphenhydramine was similar to that of no premedication at 8%.⁵⁸ In 2015, Abe et al⁶⁰ found that changing to an alternative contrast agent was more effective than premedication. The most recent updated practice parameters on anaphylaxis and GRADE (Grading of Recommendations, Assessment, Development and Evaluations) analysis (2019) looked at the question of premedication for RCM and determined that very low-quality evidence suggests that glucocorticoid and/or antihistamine premedication does not provide benefit in terms of reducing risk for patients with a history of previous RCM reactions.⁶¹ The authors recommended additional well-designed trials to clarify the need for premedication before using an alternative agent.

Our patient had no adverse reaction to the coronary angiography with pretreatment of prednisone 50 mg 13 hours, 7 hours, and 1 hour before angiography. He also received diphenhydramine 50 mg 1 hour before his procedure.

CONCLUSIONS

What best to do for contrast media reactions is still controversial. In this case, which is not uncommon, a patient comes in with the history of an acute adverse reaction to a contrast agent. However, the contrast material is not known and the patient often does not come for an evaluation for a possible adverse reaction until long after the incident. In this case, he presented to the allergy clinic 4 years after angiography because he was referred for consultation for a planned repeat coronary angiography. As noted earlier, testing between 2 and 6 months from the incident yields the best test results. Because his reaction was about 4 years ago, steroid and antihistamine premedication was recommended and the patient did well. At the Brigham and Women's Hospital, the radiology report includes the specific radiocontrast agent used. If there was a reaction associated with the procedure, the report is added to report the details of the index reaction, which makes it easier to find out details months to years later, when the patient may need to undergo another imaging procedure. It is important to capture the culprit agent in the medical record so an alternative agent may be used for subsequent imaging. Patients also do not always remember if the reaction happened during a computerized tomography scan or magnetic resonance imaging. Some patients think they are to avoid all contrast agents after a reaction; however, iodinated and gadolinium-based agents are not molecularly similar and do not cross-react. Skin testing may also be helpful to evaluate for cross-reactivities, but more importantly, to identify possible alternative contrast agents for future use. In this case, the patient denied any additional delayed rash, but we remind patients to report any delayed-onset reactions.

There is disagreement that future contrast agent-associated reactions may be prevented with a combination of skin testing, using alternative agents, and possibly premedication. Prospective studies are still needed to help clarify the role of skin testing with the use of drug provocation challenges.

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