

Managing Adverse Reactions to Contrast Agents



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KEYWORDS

• Adverse • Allergic • Anaphylactoid • Reaction • Iodinated • Gadolinium • Contrast

KEY POINTS

- Iodinated and gadolinium-based contrast agents have low adverse reaction rates with an overall estimated incidence of less than 1%.
- Adverse reactions are subdivided into physiologic and allergiclike (previously anaphylactoid) reactions.
- All members of the imaging staff should be familiar with signs and symptoms of contrast reactions to allow for prompt treatment.
- Treatments for both physiologic and allergiclike reactions are well accepted; radiologists must be knowledgeable of these in order to appropriately manage reactions acutely.

INTRODUCTION

Adverse reactions after the administration of low-osmolality iodinated or gadolinium-based contrast agents are estimated to have an incidence of less than 1%.^{1–5} Adverse reactions are further subdivided into physiologic and allergiclike (previously anaphylactoid) reactions.⁶ Allergiclike reactions are less common than physiologic reactions and are most often mild. Serious or severe reactions (defined as anaphylaxis grade 3) to current nonionic, low-osmolality iodinated contrast agents occur at an estimated incidence of 0.04% and have been reported in up to 0.4% of injections with previous ionic compounds.^{7,8} Comparatively, gadolinium-based contrast agents have an adverse reaction rate that is approximately 10-fold lower.^{4,9,10} Physiologic reactions,

such as headache, nausea, vomiting, and vasovagal responses, often require supportive measures at most for treatment. Allergiclike reactions, on the other hand, can range from minor discomfort to life-threatening events and may require medication therapy depending on their level of severity.

Although the incidence of adverse and true allergiclike reactions is low, the number of contrast-enhanced imaging studies performed in a typical imaging practice makes them not an infrequent occurrence; the appropriate precautions and preparations must be in place to provide prompt and appropriate treatment when they occur. The treatment regimen is based on the patients' specific symptoms and level of severity of the reaction. These treatment algorithms are well accepted and are reviewed here.

Disclosure statement: The authors have nothing to disclose.

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Magn Reson Imaging Clin N Am 25 (2017) 737–742

<http://dx.doi.org/10.1016/j.mric.2017.06.008>

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For patients with a history of a prior contrast reaction who require another contrast-enhanced examination, pretreatment strategies are also well established. Evidence for the effectiveness of these strategies has continued to grow in recent years, including risk stratification to help guide the decision-making process.^{11–14}

PHYSIOLOGIC REACTIONS

The mechanism of physiologic reactions, also known as chemotoxic reactions, is not completely understood. These reactions are thought to be related to certain molecular attributes, such as osmolarity or molecular binding of certain activators.^{5,15,16} Unlike allergiclike reactions, physiologic reactions often demonstrate dose and concentration dependence.

Adverse reactions impacting the cardiovascular system are seen with increased frequency in patients who have underlying cardiac disease.⁶ There are otherwise no specific risk factors identified that have been consistently associated with an increased incidence of physiologic reactions.

General tenets in the treatment of all adverse reactions include preservation of intravenous (IV) access, monitoring of vital signs, and administration of supplemental oxygen preferably with a mask at a rate of 6 to 10 L per minute. Familiarity with the institution-specific emergency response system and with the location of relevant medication and equipment is also paramount.

Vasovagal Reaction

A vasovagal reaction represents a complex neurologic reflex that may be triggered by a variety of stimuli and is characterized by hypotension.¹⁷ It is one of the more common physiologic reactions and can occur at any time point during the study, including before the actual administration of the contrast agent. It is often relieved by recumbence and generally requires only reassurance and elevation of the patients' legs without other intervention. If the induced bradycardia is prolonged, however, or patients become symptomatic, then a slow infusion of 0.6 to 1.0 mg of atropine IV can be administered. Rapid infusion of IV fluid resuscitation (0.9% normal saline or lactated Ringer solution) to a total volume of 500 mL to 1 L is appropriate (Table 1).

Hypertensive Crisis

Defined as systolic blood pressure greater than 200 mm/Hg, diastolic greater than 120 mm/Hg, or evidence of end organ damage, hypertensive crisis warrants consideration for transfer of patients to an

appropriate treatment facility, such as a nearby emergency department (ED), if the contrasted imaging examination was not performed in the hospital setting. Treatment can include use of labetalol or a combination of sublingual nitroglycerin and IV furosemide.

Pulmonary Edema

Noncardiogenic pulmonary edema is very rare and occurs in patients who have a normal cardiac function. It is not known for certain whether it represents an allergiclike or a physiologic reaction.¹⁸ In addition to providing supplemental oxygen and monitoring the patients' pulse oximetry, the head of the bed should be elevated, if possible, and IV furosemide administered. Development of pulmonary edema warrants activation of the emergency response team and consideration of patient transfer to an appropriate treatment facility.

ALLERGICLIKE REACTIONS

The exact mechanism of an allergiclike (also referred to as anaphylactoid or idiosyncratic) contrast media reaction remains unclear; however, they are treated the same as other true allergic drug reactions.⁶ They can occur within 1 hour (acute or immediate) and for up to 1 week after administration (delayed). Despite the timing of the reaction, treatment is based on the severity and types of symptoms exhibited.

Pathophysiology

Drug allergies or hypersensitivity reactions are classically broken down into 4 different categories.¹⁹ Type I reactions are immunoglobulin E (IgE) mediated and often termed immediate because of their rapid occurrence after exposure. Types II and III are IgG mediated and type IV or delayed-type reactions involve T lymphocytes. A recent meta-analysis suggests that up to 17% of iodinated contrast reactions may involve one of the true hypersensitivity pathways.²⁰ Interestingly, in patients with severe reactions, the pooled positive skin testing rate was 52%, which could aid in the selection of alternative contrast agents, should a future contrast-enhanced study be required. The data for positive skin testing and gadolinium-based contrast agents remain limited, likely owing to the overall lower rate of reactions.

Most allergiclike reactions to contrast media, therefore, must occur through a different pathway. Given the manifestations of urticaria and facial edema, histamine release is implicated; however, instead of an IgE-mediated pathway of release, histamine is thought to be triggered

Table 1
Recommended treatment of physiologic reactions to contrast agents (adults)

Reaction	Treatment	Dosage
Vasovagal reaction		
Mild	Elevate legs (>60°)	Consider 500–1000 mL 0.9% normal saline or lactated Ringer solution, rapid infusion
Moderate or severe	Atropine	IV: 0.6–1.0 mg slow infusion followed by saline flush, repeat up to 3.0 mg 500–1000 mL 0.9% normal saline or lactated Ringer solution, rapid infusion
Hypertensive crisis	Labetalol or	IV: 20 mg, administer slowly over 2 min; can double the dose every 10 min
	Nitroglycerine and Furosemide	Sublingual: 0.4 mg; may repeat every 5–10 min IV: 20–40 mg, administer slowly over 2 min
Pulmonary edema	Elevate head of bed, if possible Furosemide	IV: 20–40 mg, administer slowly over 2 min

Data from Media ACoDaC. ACR manual on contrast media: version 10.3; ACR Committee on Drugs and Contrast Media, American College of Radiology, 2017.

through mast cell and basophil degranulation.^{5,21–23} This process occurs through direct stimulation and, therefore, allows for reaction in contrast-naïve patients, which is contradictory to the pathway of classic hypersensitivity reactions.

Signs and Symptoms

Mild reactions may be self-limited and require no treatment. These reactions include limited cutaneous urticaria/erythema, itchy throat, and sneezing. Even though treatment may not be required for mild reactions, patients should be monitored for up to 1 hour after the time of contrast administration to ensure that the reaction does not worsen over time. It is important to note that most severe reactions occur within 20 minutes of injection.^{2,24}

Moderate reactions more commonly require medication therapy because of their more serious symptoms, which include diffuse cutaneous urticaria/erythema, facial edema or throat tightness without dyspnea, or bronchospasm/wheezing without hypoxia.

Severe reactions can be life threatening and require immediate treatment. Clinical manifestations are similar to those seen with moderate reactions and can include diffuse cutaneous edema/erythema, facial or laryngeal edema, and wheezing. Patients experiencing severe reactions, however, also show signs of cardiovascular compromise, such as hypoxia, hypotension, and tachycardia.

Risk Factors for Allergiclike Reactions

Allergiclike reactions to contrast media occur at a baseline incidence of less than 1% in the general population, but there are risk factors that have

been associated with an overall increased rate of reactions. History of a prior reaction to contrast media is the greatest single predictor of future reactions, with recurrent symptoms occurring at 5 to 6 times the rate of incidence in the general population.^{2,3} There has been no evidence to date to suggest cross-reactivity between iodinated and gadolinium-based contrast media.

Aside from a prior reaction, history of underlying allergic disease, such as asthma, bronchospasm, or atopy, have shown an increased association with contrast media reactions.^{2,3} There may also be an increased risk in women as well as young children (<5 years of age) and adults older than 60 years.^{2,3,6} The increase in incidence over the general population for these risk factors is not as high as in those patients with a prior contrast reaction. Awareness of the association is important for technologists, nurses, and clinicians involved in contrast-enhanced imaging studies; but no pre-treatment is needed in the presence of such risk factors.

It is important to note that there is no link between a history of shellfish allergy and an increased risk of allergiclike reactions to iodinated contrast media.²⁵ This historical myth continues to cause confusion, however; the true nature of patients' iodine-containing-products allergy should be clarified to prevent unnecessary avoidance of an indicated contrast-enhanced study as well as to prevent inappropriate premedication.

Premedication

The discussion of premedication before administration of contrast media is often met with some

degree of controversy. There are several issues at the root of this, including the variability of reported recurrence rates, the issue of historically greater risk of reaction to high-osmolar versus the currently used low-osmolar agents, and the overall low incidence of true allergic-type reactions. In addition, it would be prudent to test the effect of premedication in those patients with a higher baseline risk, such as those with a history of prior reaction as well as additional risk factors, such as underlying allergic disease. This type of risk stratification has been examined by some recent studies that showed breakthrough rates of 10% to 15%.^{13,26} The severity of breakthrough, should it occur, is typically the same as the initial reaction.

The preferred dosing of oral steroids for premedication begins 12 to 13 hours before the patients' examination in the elective setting.⁶ In emergent patients, additional regimens exist that use IV steroids dosed preferably at least 4 hours before examination. In rare emergent situations when this is not possible, a regimen with IV steroids administered 1 hour before the exam may be considered but its efficacy has not been proven (Table 2). Physiologic reactions are not affected by steroids or antihistamines; therefore, premedication is not indicated.

Treatment of Allergiclike Reactions

The management of allergiclike reactions starts before patients enter the examination suite. All members of the imaging team play an important role, beginning with recognition of patients' initial symptoms, which often occur at the technologist level. It is important for all imaging team members

to know how allergiclike reactions present so that they may respond to them quickly, activating a plan of action that should be rehearsed regularly.

General Considerations

A basic plan of action includes communication with the radiologist or other responsible provider of symptoms concerning for contrast reaction, initial evaluation of patients by the radiologist/provider, initiation of treatment (as appropriate), and continued monitoring and reevaluation until the reaction has resolved or stabilized. If an allergiclike contrast reaction is suspected, IV access should be preserved to allow for administration of medications, if necessary. Supplemental oxygen should be given, preferably with a mask, to allow for flow rates in the range of 6 to 10 L per minute if respiratory symptoms are present. Consider fluid resuscitation if not contraindicated by patients' comorbidities; up to 1000 mL of 0.9% normal saline administered rapidly may be appropriate.

All items necessary for carrying out initial medical treatment should be immediately available. These items may include a monitoring device to assess vital signs, supplemental oxygen, and treatment medications. They should be organized to facilitate ready access. The radiologists or other responsible providers who may be called on to evaluate and treat allergiclike reactions should be knowledgeable of the signs and symptoms as well as the treatment strategies and medications for each level of severity. Again, rehearsal of these strategies is helpful outside of actual reactions to help reinforce the process (Table 3).

Table 2 Premedication regimens			
Elective	Regimen 1		Regimen 2
Steroid	Prednisone, 50 mg PO 13, 7, and 1 h before examination		Methylprednisolone, 32 mg PO 12 and 2 h before examination
Antihistamine	Diphenhydramine 50 mg PO, IV, IM 1 h before examination		Diphenhydramine 50 mg PO, IV, IM 1 h before examination
Emergent	Most Preferred	Less	Least
Steroid	Methylprednisolone sodium succinate, 40 mg or Hydrocortisone sodium succinate, 200 mg IV q 4 h until examination	Dexamethasone sodium sulfate, 7.5 mg IV q 4 h until examination	Methylprednisolone sodium succinate, 40 mg or Hydrocortisone sodium succinate, 200 mg IV 1 h before examination
Antihistamine	Diphenhydramine 50 mg PO, IV, IM 1 h before examination	Diphenhydramine 50 mg PO, IV, IM 1 h before examination	Diphenhydramine 50 mg PO, IV, IM 1 h before examination

Data from Media ACoDaC. ACR manual on contrast media: version 10.3; ACR Committee on Drugs and Contrast Media, American College of Radiology, 2017.

Table 3
Recommended treatment of allergiclike reactions to contrast agents (adults)

Reaction	Treatment	Dosage
Urticaria (hives)		
Mild	Self-limited: Persistent: Diphenhydramine Fexofenadine	No treatment PO: 25–50 mg PO: 180 mg
Moderate	Diphenhydramine Fexofenadine	PO: 25–50 mg IM or IV: 25–50 mg, give IV over 1–2 min PO: 180 mg
Severe	Diphenhydramine	IM or IV: 25–50 mg, give IV over 1–2 min
Bronchospasm		
Mild	Beta-agonist inhaler (albuterol)	Two puffs (90 µg per puff), repeat up to 3 times
Moderate	Beta-agonist inhaler (same dose as earlier), epinephrine	IM: 0.3 mg (0.3 mL of 1:1000 concentration), repeat up to 1 mg IV: 0.3 mg (3 mL of 1:10,000 concentration) slow infusion with saline, repeat up to 1 mg
Severe	Epinephrine	IM: 0.3 mg (0.3 mL of 1:1000 concentration), repeat up to 1 mg IV: 0.3 mg (3 mL of 1:10,000 concentration) slow infusion with saline, repeat up to 1 mg
Laryngeal edema		
All forms	Epinephrine	IM: 0.3 mg (0.3 mL of 1:1000 concentration), repeat up to 1 mg IV: 0.3 mg (3 mL of 1:10,000 concentration) slow infusion with saline, repeat up to 1 mg
Anaphylaxis	Epinephrine	IM: 0.3 mg (0.3 mL of 1:1000 concentration), repeat up to 1 mg IV: 0.3 mg (3 mL of 1:10,000 concentration) slow infusion with saline, repeat up to 1 mg

Abbreviation: IM, intramuscularly.

Data from Media ACoDaC. ACR manual on contrast media: version 10.3; ACR Committee on Drugs and Contrast Media, American College of Radiology, 2017.

Urticaria/Erythema

Often self-limited, mild urticaria may only require reassurance and extended monitoring to ensure that symptoms do not progress. Should the hives and pruritus be more extensive, administer an antihistamine. Acceptable routes of administration are by mouth, IV, and intramuscularly (IM), tailored in accordance with the severity of patients' symptoms. If patients do not fully respond to treatment, consider referral to the nearest ED or contact an emergency response team/911.

Bronchospasm

Bronchospasm, presenting as wheezing, may also be self-limited in mild reactions. Place patients on supplemental oxygen, monitor pulse oximetry, and administer an inhaled beta agonist. If the wheezing does not resolve, consider referring patients to the nearest ED or contact an emergency response team/911.

Moderate cases of bronchospasm may require administration of epinephrine IM/IV after an inhaled beta agonist. If the symptoms are severe, do not administer an inhaled beta agonist, but instead give epinephrine immediately and contact 911.

Laryngeal Edema

Although cases of laryngeal edema could be mild in severity, with patients complaining only of self-limited throat itching, laryngeal edema is more typical of moderate to severe reactions and should prompt treatment with epinephrine and referral to the nearest ED via emergency response/911.

Anaphylaxis

It is exceedingly rare but constitutes a medical emergency. Contact 911 immediately, administer epinephrine, start IV fluids, and begin resuscitation per advanced cardiac life support guidelines when appropriate.

SUMMARY

Adverse reactions to contrast media are uncommon. Of these, true allergiclike reactions are notably rare as well as more frequently mild in severity. Treatment, if required, is based on the signs and symptoms and severity of the reaction. Premedication plays a role primarily in patients who have a history of prior reaction and require an additional contrast-enhanced examination that will expose them to the same or a similar agent.

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