

Allergic reactions to iodinated contrast media: premedication considerations for patients at risk

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Abstract The objectives of this article are to review allergy-type reactions to iodinated contrast media and the protocols utilized to prevent or reduce the occurrence of these adverse reactions in high-risk patients. We will begin by discussing the types or classifications of the adverse reactions to iodinated contrast media. We will then discuss reaction mechanisms, identify the patients at highest risk for adverse reactions, and clarify common misperceptions about the risk. Finally, we will discuss the actions of the medications used to help reduce or prevent allergy-type reactions to iodinated contrast media, the protocols used to help reduce or prevent contrast reactions in high-risk patients, and the potential side effects of these medications. We will also discuss the high-risk patient who has received premedication due to a prior index reaction and discuss the risk of having a subsequent reaction, termed “breakthrough reaction.” Identifying patient at high risk for an “allergy-type” reaction to contrast media is an essential task of the radiologist. Prevention of or reduction of the risk of an adverse reaction is critical to patient safety. If an examination

can be performed without contrast in a patient at high risk for an allergy-type reaction, it may be appropriate to avoid contrast. However, there are situations where contrast media is necessary, and the radiologist plays a vital role in preventing or mitigating an allergy-type reaction.

Keywords Iodinated · Contrast · Radiology · Allergic · Premedication · Glucocorticoids

Increased CT utilization

Utilization of computed tomography (CT) to evaluate outpatients, inpatients, and emergency room patients has grown tremendously in recent years. It has been estimated that more than 62 million CT scans are currently obtained each year in the USA, as compared with about 3 million in 1980 [1, 2].

With increased utilization of CT, the likelihood of encountering a patient having an adverse reaction to iodinated contrast media (ICM) has also increased. Several studies have measured the prevalence of adverse reactions, including allergy-type reactions, to iodinated contrast media. In 1990, Katayama et al. found that the prevalence of all adverse drug reactions was 3.13 % for nonionic iodinated contrast media examinations and that of severe adverse drug reactions was 0.04 % [3].

Two more recent large series studies demonstrated a 0.6 and 0.2 % rate of allergy-type reactions, and 0.01 and 0.002 % of the total number of nonionic ICM injections were classified as severe reactions [4, 5].

Although the reported rates of severe reactions to iodinated contrast media are low, they can quickly become life-threatening when they do occur, including one reported death in the large series by Hunt et al. [5].

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Types of reactions: mild, moderate, and severe

Mild reactions

Adverse reactions to ICM can be classified as mild, moderate, or severe. Mild reactions include nausea and vomiting, which may be associated with increased osmolality of contrast. Additionally, urticaria is typically mild, although it can progress and be followed by more severe systemic reactions, such as hypotension. Pain at the injection site is a minor adverse reaction and has decreased in incidence with the use of low-osmolality agents. While warmth and/or flushing are unpleasant symptoms, they are considered physiologic and are of short duration. According to the American College of Radiology (ACR) Manual on Contrast Media, they are not indicative of an adverse event. Mild reactions often do not require treatment. However, they can evolve in severity, and patients should be observed for 20–30 min, or as needed, to ensure recovery.

Moderate reactions

Moderate reactions are not immediately life-threatening, although they have potential to progress to severe life-threatening reactions, and therefore they often require treatment. Moderate reactions include moderate or symptomatic urticaria, vasovagal reaction, mild bronchospasm, and tachycardia secondary to transient mild hypotension. Moderate reactions require close monitoring until complete resolution.

Severe reactions

Severe adverse reactions are potentially or immediately life-threatening. Although rare, they can be unpredictable, so prompt recognition and treatment is needed. The patient may display a variety of signs and symptoms, such as anxiety in the setting of respiratory distress, diaphoresis with hypotension, diffuse erythema with diffuse severe urticaria, or cardiopulmonary arrest.

Severe reactions include severe vasovagal reactions with hypotension, moderate and severe bronchospasm, laryngeal (airway) edema, seizure, and severe hypotension in anaphylactic shock. Pulmonary edema may also occur, particularly in patients with underlying congestive heart failure [6].

Timing of occurrence

Acute fatal or life-threatening reactions to iodinated contrast media (ICM) may occur following intravenous or intra-arterial injection but also may develop after alimentary or intracavitary administration due to absorption of ICM particles into the circulation [7]. Katayama et al. found that

70 % of adverse reactions to ionic or nonionic iodinated contrast media occurred within the first 5 min following contrast injection, 16 % occurred more than 5 min after injection, and in 14 % of cases, the time of onset was not recorded [3]. Reactions may present as generalized cutaneous manifestations, airway obstruction, angioedema, or cardiovascular collapse [7].

In addition to those reactions occurring within 1 h of administration of ICM, there is also potential for late adverse reactions to occur. Late adverse reactions to intravascular iodinated contrast media are defined as reactions which occur between 1 h and 1 week following iodinated contrast media injection [8]. The majority of the late reactions are skin reactions, including maculopapular rash, angioedema, urticaria, and erythema. Most of the skin reactions are mild or moderate. Although the pathogenesis of the late reactions is not completely understood, many may be T cell-mediated reactions [8, 9].

Reaction classification: anaphylactoid and chemotoxic reactions

The classic allergic reaction requires a sensitizing exposure; however, many patients have reactions to iodinated contrast media upon their initial exposure. In addition, patients who have had a contrast reaction may experience no reaction during their next exposure, even without premedication [10].

Serious reactions to ICM follow a clinical picture similar to type 1 hypersensitivity reaction (anaphylaxis), where the reaction begins within minutes of exposure and is mediated by a variety of chemotactic, vasoactive, and spasmogenic compounds [7].

Adverse reactions to intravascular iodinated contrast media are classified as either anaphylactoid (anaphylaxis-like) or chemotoxic reactions. Examples of these responses are listed in Table 1 [7]. The acute allergy-like reactions are usually termed anaphylactoid since they have all the features of anaphylaxis but are IgE-negative in most cases and do not appear to result from a specific antigen–antibody interaction [7, 11]. It is postulated that stimulation of the mast cells is via overload effect by the large contrast molecule on the antigen-binding sites of IgE of the mast cell, though it does not bind directly with a specific IgE antigen site [12]. Anaphylactoid, also called idiosyncratic or anaphylaxis-like, reactions to iodinated intravascular contrast media are unpredictable and dose- and concentration-independent above a certain threshold level [11].

Anaphylactoid reactions are the most common adverse reaction to ICM, therefore we will focus on these reactions in slightly greater detail. However, chemotoxic effects may cause more of the severe adverse reactions, particularly in debilitated or unstable patients [11]. Chemotoxic-type

Table 1 Classification of adverse reactions to iodinated contrast media [7, 11–13]

Anaphylactoid	Chemotoxic
• Features of anaphylaxis • IgE negative (most cases) • Idiosyncratic • Unpredictable • Independent of dose and concentration (above a certain threshold) • Most common adverse reaction to ICM	• More severe adverse reactions • Occur in debilitated or unstable patients • Related to dose • Depend on molecular toxicity and physiochemical characteristics of the • Agents: osmolality, viscosity, hydrophilicity, binding properties

effects are related to dose, molecular toxicity, and the physicochemical characteristics of the agents (i.e., osmolality, viscosity, hydrophilicity, calcium-binding properties, and sodium content) [11, 13]. For example, high osmolality can cause shift of fluids from the intracellular to the extracellular space, leading to cell dehydration and an increase in intracellular fluid viscosity, precipitating cellular dysfunction [14].

Mechanism of anaphylactoid reactions

Exact nature of anaphylactoid reactions following iodinated contrast media administration is not completely understood [10]. Possible etiologies include histamine release, leukotriene and cytokine production, complement activation, and bradykinin production. A summary of these mechanisms is provided in Table 2.

Histamine is a primary mediator of anaphylaxis/anaphylactoid reactions and is responsible for the immediate manifestations. Histamine infusion can reproduce symptoms of anaphylaxis. Preformed histamine is present in basophils and mast cells and is released rapidly when these cells degranulate after stimulus exposure.

Leukotrienes, prostaglandins, enzymes, and cytokines are additional mediators produced by mast cells and basophils [15]. These substances trigger an inflammatory cascade of mediators which cause vasodilatation, increased vascular

permeability and edema, contraction of smooth muscle cells precipitating bronchospasm, and increased mucus secretion in airways.

Cytokines and chemotactic factors recruit leukocytes, eosinophils, basophils, monocytes, and T cells, which release more mediators and cytokines. Complement system may be activated by iodinated contrast media, which causes anaphylatoxin formation (C3a, C4a, and C5a). This triggers release of histamine and other biological mediators from basophils and mast cells [16].

Iodinated contrast media may stimulate Factor XII (Hageman factor) of the clotting system, leading to kinin system activation, with production of bradykinin, which may be involved in the pathogenesis of serious CM reactions. Bradykinin can induce vasodilatation, bronchospasm, and vascular permeability. It also activates Factor XII and allows for auto-amplification of the initial stimulus. In addition, bradykinin may activate the arachidonic acid pathway, stimulating the cyclooxygenase and lipoxygenase pathways, which produce prostaglandins and leukotrienes [7, 15].

Asthmatic or patients with allergic tendencies have demonstrated increased concentrations of low-level factor XII, which may explain their increased susceptibility to ICM [7, 11, 17–19].

A genuine IgE-mediated allergic anaphylaxis to iodinated contrast material is rare. However, according to skin tests and basophil activation tests, an IgE-mediated iodinated contrast media allergy was identified in four of 96 examined patients, as reported by Trcka [20].

Table 2 Mechanisms of anaphylactoid reactions following ICM administration [7, 15, 16]

Anaphylactoid mechanisms
Histamine: primary mediator, preformed in basophils and mast cells
Leukotrienes, prostaglandins, enzymes, cytokines
Triggers inflammatory cascade toward vasodilation, increased vascular permeability, edema, bronchoconstriction
Complement activation
Anaphylotoxin formation (c3a, c4a, and c5a)
Factor XII activation
Leads to kinin activation, bradykinin production, vasodilation, bronchospasm, permeability

Mechanism of chemotoxic reactions

The chemotoxicity in contrast media is related to its chemical structure, such as the number of carboxyl and hydroxyl groups. Chemotoxicity is also related to protein binding, cell membrane effects, or enzyme interactions or blocking [14].

Patients at risk

Acute adverse reactions seem to occur most frequently in persons aged 20–50 years. However, the effects of reactions

to iodinated contrast media may be most severe in older persons, particularly in those with a cardiopulmonary reaction [13]. Patients with other chronic illnesses, for example, hematologic conditions such as sickle cell anemia, polycythemia, and myeloma, may overall have an increased risk for adverse reactions [21].

People with increased atopic tendencies are at increased risk for an anaphylactoid reaction. In the setting of a history of systemic allergies to multiple substances, the relative risk of allergy-type reaction to ICM is approximately twice that of the general population. This relative risk was found to be approximately five times greater in a retrospective review of patients with a history of asthma (although the status of the asthma was not assessed immediately before administration of the ICM) [7, 11, 13]. It is therefore important to pay particular attention to any history of allergy-type reactions to iodinated contrast media, as well as a history of multiple allergies or asthma, when screening patients for their risk of allergy-type reactions to ICM.

The effect of beta-blockers on adverse reactions to contrast media is not completely characterized and is somewhat controversial. There have been reports of anaphylactoid reactions to contrast media in patients taking beta-blockers [22]. Conversely, other studies have reported that beta-blockers did not increase the risk of anaphylactoid reactions to contrast media. However, there is concern that beta-blockers may result in a decreased response to treatment for anaphylactoid reactions to ICM [21, 22].

Reactions in children

Reactions to iodinated contrast media are less common in children than adults. Pediatric adverse responses tend to be airway rather than cardiovascular events, with predominating cutaneous and respiratory reactions. In addition, the low-osmolality contrast media causes less nausea and vomiting, as well as decreased morbidity from soft tissue extravasation [10].

In 2007, Dillman et al. examined pediatric acute allergy-type reactions related to low-osmolality nonionic iodinated contrast media and found a reaction rate of 0.18 out of 11,306 contrast media injections. Sixteen (80 %) of the acute allergy-like reactions were categorized as mild, one (5 %) was moderate, and three (15 %) were severe. During the same time period, within the same institution, they found that the incidence of acute allergy-type reactions from ICM administration in the adult population was 0.7 % out of 96,927 IV injections, which represented a statistically significant difference in their institutional pediatric and adult allergy-type reaction rates (four times more common in adults). They concluded that the etiology of the lower reaction rate in pediatric patients is unknown [23].

Nausea and vomiting are the most common adverse reactions to contrast media in children. In both the nonsedated and sedated child, closely monitored fasting prior to the exam can be helpful. Withholding solids for 4–6 h and withholding clear liquids for 2 h prior to the exam is optimal [10].

Although uncommonly used in adult CT scans, general anesthesia is often utilized for pediatric CT exams. General anesthetics can cause anaphylactic as well as anaphylactoid reactions. Their symptoms can have considerable overlap with those of contrast media. As an example, exacerbation of obstructive symptoms can occur after the infusion of general anesthetics or iodinated contrast media in patients with diagnosed bronchial asthma or chronic obstructive pulmonary disease. The anesthetized patient at increased risk for an iodinated contrast media reaction adds complexity to the evaluation and care [24].

Seafood allergies, iodine, and contrast media reactions

Surveys have shown that many physicians and patients still have the misconception that iodine allergies are linked to seafood allergies and that both relate to an increased risk of reaction to iodinated contrast media. A survey of 231 physicians at six academic medical centers in the Midwest showed that two-thirds of participating radiologists and 89 % of cardiologists indicated that they routinely ask their patients if they are allergic to shellfish before administering iodinated contrast media [25]. In addition, 35 % of radiologists and 50 % of cardiologists surveyed would withhold ICM or require premedication for patients with shellfish allergies [26].

While shellfish contain iodine, iodine in the shellfish is not the source of people's allergy. The major allergens in shellfish are tropomyosins, which are proteins important in muscle contraction and are unrelated to iodine [26, 27]. However, the patient with an allergy to shellfish may have increased atopic susceptibility and thus should be questioned regarding the presence of additional allergies, which can predispose to anaphylactoid reactions to iodinated contrast media. The anaphylactoid reactions to ICM are primarily caused by the contrast molecule and not the iodine/iodide.

There is no direct correlation or association between allergy to povidone-iodine skin cleansing solution and the predisposition to an allergy-like reaction to intravascular iodinated contrast media. The former is considered a type of contact dermatitis, while the latter an idiosyncratic reaction [13].

Prevention of reactions in high-risk patients

"The best treatment for contrast reactions is prevention," as stated in the Radiology Life Support Manual [10]. Adequate screening for patients at risk for adverse reactions should

Table 3 Two most common (preferred) oral corticosteroid premedication protocols (elective protocols) [6]

Option 1: elective oral protocol	Option 2: elective oral protocol
1. Prednisone 50 mg by mouth, administered at 13, 7, and 1 h before ICM injection.	1. Methylprednisolone (Medrol®) 32 mg by mouth at 12 and 2 h prior to ICM injection.
2. Diphenhydramine (Benadryl®) 50 mg intravenously, intramuscularly, or by mouth administered 1 h prior to ICM administration	2. Diphenhydramine may be added

identify patients who are at high or higher risk for severe adverse effects from iodinated contrast media, such as previous life-threatening reaction, multiple allergies, active bronchospasm, or asthma, or hypotension or shock from an underlying illness [10].

Premedication with corticosteroids prior to contrast administration is most effective in reducing the occurrence of mild or moderate reactions; controlled studies have not shown the same benefit regarding severe reactions [6]. Therefore, the author believes it is best to weigh the risk and benefit of the administration of the contrast administration in high-risk patients. Sometimes the benefit of administering contrast (with premedication) outweighs the risk and, at other times, the reverse may be true.

Mechanism of corticosteroid action

Glucocorticoids passively diffuse across the cell membrane, bind to a glucocorticoid receptor inside the cell, and then are translocated into the nucleus. Inside the nucleus, this complex can interact with glucocorticoid-responsive elements, which are specific DNA sequences, and other transcription factors.

Binding of the receptor can result in enhancement, suppression, or transcription of susceptible downstream genes. The anti-inflammatory effects of glucocorticoids result from the binding and blocking of proinflammatory genes, such as interleukin 1. Transcription factors are recruited for coding anti-inflammatory gene products.

Blocking of transcription factors required for proinflammatory mediator transcription results in inhibition of cytokine synthesis. The effect on the components of the innate immunity, which are able to respond immediately without reliance on antibodies, leads to impaired migration of neutrophils, decreased macrophage function, and inhibition of both cytokine production and degranulation by mast cells [28].

Decrease in repeat reaction rate with steroid premedication

Greenberger et al. found that using a corticosteroid and antihistamine preparation regimen prior to conventional high-osmolality iodinated contrast media administration in high-risk patients resulted in a decrease in repeat reaction incidence to 11 % from historical numbers of 17–30 % [29].

Further reduction in anaphylactoid reactions in patients with a previous contrast reaction was achieved when patients were administered a corticosteroid and antihistamine pretreatment regimen, as well as examined with the use of nonionic low-osmolality iodinated contrast media [30].

In premedicating high-risk patients with the regimen of prednisone 50 mg PO at the intervals of 13, 7, and 1 h prior to injection of contrast, 9 % had an adverse reaction if they received an ionic high-osmolality iodinated contrast media and only 0.5 % had an adverse reaction if they received a nonionic low-osmolality iodinated contrast media [30]. The ACR Manual on Contrast Media notes that an H-1 antihistamine, such as

Table 4 Emergency intravenous premedication protocols in decreasing order of desirability [6, 32]

Option 1: most desirable (<i>for the emergency protocol</i>)	Option 2: less desirable (<i>used in known allergies to methylprednisolone, aspirin, or NSAIDs, particularly if asthmatic</i>)	Option 3: least desirable (<i>in setting of inadequate time interval to achieve corticosteroid effect</i>)
1. Methylprednisolone sodium succinate (Solu-Medrol®) 40 mg IV every 4 h until study is performed, or hydrocortisone sodium succinate (Solu-Cortef®) 200 mg IV every 4 h until study performed	1. Dexamethasone sodium sulfate (Decadron®) 7.5 mg IV every 4 h until study performed, or betamethasone 6 mg IV every 4 h until study performed	1. Omit steroids entirely (not desirable)
2. Diphenhydramine (Benadryl®) 50 mg IV administered 1 h prior to ICM injection	2. Diphenhydramine (Benadryl®) 50 mg IV administered 1 h prior to ICM injection	2. Administer diphenhydramine 50 mg IV (<i>Antihistamines alone have not been proven to reduce occurrence of reactions</i>)

diphenhydramine, is also administered 1 h prior to injection of contrast [6]. H-2 blockers have been discussed for premedication in high-risk patients; however, a study evaluating addition of the H-2 antihistamine cimetidine to the premedication protocol reportedly resulted in a slight increase in the repeat reaction rate [6, 31].

Elective premedication protocol

There are two frequently used elective premedication oral regimens, which are listed in Table 3 and adapted from the ACR Manual of Contrast Media, version 7, 2010 [6, 18, 30].

Emergency premedication protocol

In the high-risk patient who requires an emergency CT with iodinated contrast media administration, there are three protocols which have been used (presented in decreasing order of desirability). These are listed in Table 4, adapted from the ACR Manual of Contrast Media, version 7, 2010 [6, 32].

The second, less desirable option, presented in the second column, should be used in patients with known allergy to methylprednisolone, aspirin, or nonsteroidal anti-inflammatory drugs, particularly if they are asthmatic [6].

The third and least desirable option listed in the ACR contrast manual is to omit the steroids entirely and give diphenhydramine 50 mg IV when there is an inadequate time interval of less than 4–6 h to achieve corticosteroid effect. Antihistamines alone have not been proven to reduce the occurrence of moderate or severe reactions [6].

Timing of preventative medications

The ACR Manual on Contrast Media (version 7, 2010) states that oral administration of steroids is preferable to IV administration and that prednisone and methylprednisolone are equally effective. It is preferred that steroids are started at least 6 h prior to the injection of iodinated contrast media, regardless of the route of steroid administration. It is unclear if the administration of steroids less than 3 h prior to ICM injection can still reduce adverse reactions. For the emergency room patient, it is generally recommended to administer IV the steroid dose and repeat it every 4 h until the study is performed [6, 32].

Administration of an H-1 antihistamine (e.g., diphenhydramine) orally or intravenously may reduce the frequency of urticaria, angioedema, and respiratory symptoms when utilized in conjunction with the corticosteroid premedication protocols [6]. Compared to epinephrine in the first-response medications of acute anaphylaxis, antihistamines have a

Table 5 Risk factors for moderate or severe breakthrough reactions [33]

Moderate or severe breakthrough reaction risk factors

- Severe allergy to any substance (including ICM)
- Allergies to four or more allergens
- Any drug allergy
- Chronic corticosteroid use
- History of moderate or severe index reaction

slow onset of action and cannot block events that occur after histamine has already bound to its receptors [7].

Breakthrough reactions

A breakthrough reaction indicates a reaction that occurs after iodinated contrast media injection in patients who have already been premedicated with corticosteroids in order to prevent an allergy-type reaction. These are likely patients already identified as being at high risk for a reaction. It is thought that patients who have experienced prior breakthrough reactions may be at greater risk than the general population for a subsequent moderate or severe reaction after a repeat low-osmolality iodinated contrast media injection. There also may be a concern that subsequent reactions will be progressively more severe, although this theory has been contested.

In the study performed by Davenport and Cohan, injections of low-osmolality iodinated contrast media resulted in 0.7 % recorded ICM reactions. Of these ICM reactions, 18 % were breakthrough reactions. In the premedicated patients who previously had a breakthrough reaction, the majority (88 %) of low-osmolality ICM injections did not result in a repeat breakthrough reaction.

The breakthrough reactions in the patients with mild index reactions were never severe and were usually (91 % of the cases) mild. In the patients with moderate or severe index reactions, the breakthrough reaction was also often moderate or severe (in 42 and 67 % of cases, respectively). Conclusions drawn from this study are that patients with a mild index reaction have an extremely low risk of a severe breakthrough reaction. However,

Table 6 Disease processes which increase risk of corticosteroid adverse effects [6, 34]

Benefits of contrast should be balanced against the low risk of corticosteroids

- Uncontrolled hypertension or severe congestive heart failure
- Uncontrolled diabetes
- Gastrointestinal diseases, such as acute diverticulitis, acute peptic ulcer disease, or acute ulcerative colitis (risk of perforation)
- Active tuberculosis or systemic fungal infections

patients with a moderate or severe index reaction are at high risk of experiencing another moderate or severe reaction, should a breakthrough reaction occur. The likelihood that a breakthrough reaction will be of similar severity to the index reaction is only reassuring in patients with mild index reactions. This study found that certain risk factors (listed in Table 5) are associated with a higher risk of moderate or severe breakthrough reaction: severe allergy to any substance, including iodinated contrast media, allergies to four or more allergens, any drug allergy, and chronic use of oral corticosteroids [33].

In 2007, Dillman et al. reported a pediatric breakthrough reaction rate in 10 % (representing two patients) of the pediatric patients in the study who had an acute allergy-type reaction. In their study, these pediatric patients had been appropriately premedicated with corticosteroids and an antihistamine due to a known history of allergy-type reaction to ICM. Both of the patients experienced mild acute allergy-type breakthrough reactions (one urticaria and the other generalized rash). However, the severity of their index reactions were not reported [23].

Adverse effects of corticosteroids

The risk of administering the short-term doses of oral corticosteroids used for allergic reaction prevention or reduction is extremely low. However, caution must be observed when administering a short course of steroids in the setting of certain disease processes, as listed in Table 6 [6, 34], and the benefits of the contrast should be balanced against the low risk of corticosteroid administration.

Anaphylactoid reactions to oral glucocorticoids have been rarely reported. In comparison, there are more frequent reports of serious adverse reactions associated with the use of intravenous corticosteroids [6].

Administration of intravenous corticosteroids

There are specific guidelines to follow for the intravenous administration of corticosteroids (also refer to Table 7) [34,

35]. Although the dosages used in the emergent corticosteroid preparation regimen fall into the low-dose category (described in Table 7), it is important to understand the importance of correct dosages when advising other physicians on the corticosteroid preparations in radiology and the potential adverse effects of larger doses or incorrectly administered dosages. For example, high doses of methylprednisolone (or doses exceeding 125 mg/dose) should not be administered by IV push but rather should be administered over 15–30 min, depending on the dose, due to the risks of hypotension, cardiac arrhythmias, and sudden death [34].

Conclusion

With increased utilization of CT, the radiologist continues to play a critical role in the prevention or reduction of the risk of allergy-type reactions to iodinated contrast material. While the majority of the reactions are mild [3, 4], moderate and severe reactions can quickly become life-threatening.

We have reviewed the types of reactions to iodinated contrast media, both anaphylactoid and chemotoxic. We have also reviewed the pathophysiology of the anaphylactoid reaction, the most common adverse reaction to ICM, which leads to vasodilation, increased vascular permeability, and bronchoconstriction via cellular mediator activation [7, 11, 15, 16].

Most of the allergy-type reactions occur in the first 5 min following contrast injection. However, there are also instances of delayed reactions, which occur between 1 and 7 days following contrast administration [3, 8].

We have reviewed the risk factors for allergic reactions to ICM, such as asthma and multiple allergies, as well as those factors which do not convey increased risk, such as an allergy to shellfish alone [7, 11, 13, 26].

We have also reviewed the corticosteroid and antihistamine preparation regimens recommended for use prior to administration of iodinated contrast media in high-risk patients. Studies performed by Greenberger et al. found that using a corticosteroid and antihistamine preparation in high-risk patients resulted in a decrease of repeat reaction incidence to 11 % from the historical numbers of 17–30 % [29]. While the H-1 antihistamine (diphenhydramine) is used in

Table 7 Guidelines for IV administration of corticosteroids (methylprednisolone and hydrocortisone) [34, 35]

Methylprednisolone sodium succinate (Solu-Medrol®)	Hydrocortisone sodium succinate (Solu-Cortef®)
- Doses only less than 1.8 mg/kg or less than 125 mg/dose may be given IV push over 3–15 min. Higher doses must be administered over 15 or 30 min depending on the dose. - Note, doses for contrast reaction prophylaxis in emergency setting are 40 mg IV every 4 h until exam is performed (refer to Table 4)	- For an IV Bolus: must dilute to 50 mg/ml and administer over 30 s. However, doses ≥ 500 mg must be administered over 10 min. - For an IV infusion: dilute to 1 mg/mL and administer over 20–30 min - Note, doses for contrast reaction prophylaxis in emergency setting are 200 mg IV every 4 h until exam is performed (refer to Table 4)

conjunction with corticosteroids to help reduce the occurrence of allergy-type reactions to ICM, antihistamines cannot block events that occur after histamine has already bound to its receptors, such as in the treatment of acute anaphylaxis or anaphylactoid reactions [7].

Although adverse effects associated with short-term administration of corticosteroids are rare, there are certain disease processes where caution is required. Awareness on the potential complications is important for radiologists, particularly with intravenous administration of the corticosteroids, in order to reduce or avoid potential adverse effects [6].

The potential for allergy-type reactions to ICM cannot be completely eliminated by the administration of corticosteroid and antihistamine preparations, as breakthrough reactions are known to occur. Therefore, knowledge on the appropriate risk factors for such reactions is valuable in helping our patients as well as helping to educate fellow physicians. As is often the case in medicine, risk versus benefit analysis can be useful to those patients at high risk for a reaction.

Conflict of interest None.

References

- Brenner DJ, Hall EJ (2007) Computed tomography—an increasing source of radiation exposure. *N Engl J Med* 357:2277–2284
- Larson D, Johnson L (2011) National trends in CT use in the emergency department: 1995–2007. *Radiology* 258:164–173
- Katayama H, Yamaguchi K, Kozuka T et al (1990) Adverse reactions to ionic and nonionic contrast media. *Radiology* 175:270–276
- Wang C, Cohen R (2008) Frequency, outcome, and appropriateness of treatment of nonionic iodinated contrast media reactions. *AJR* 191:409–415
- Hunt C, Hartman P (2009) Frequency and severity of adverse effects of iodinated and gadolinium contrast materials: retrospective review of 456,930 doses. *AJR* 193:1124–1127
- ACR Committee on Drugs and Contrast Media (2010) ACR Manual on Contrast Media, Version 7, p 5–6, 20–21
- Morcos SK (2005) Acute serious and fatal reactions to contrast media: our current understanding. *Br J Radiol* 686–693
- Webb J, Stacul F (2003) Late adverse reactions to intravascular iodinated contrast media. *Eur Radiol* 13:181–184
- Bigby M, Jick S (1986) Drug induced cutaneous reactions. A report from the Boston Collaborative Drug Surveillance Program on 15,438 consecutive inpatients, 1975–1982. *J Am Med Assoc* 256:3358–3363
- Bush WH Jr, Krecke KN, King BF Jr, Bettmann MA (1999) *Radiology life support*, 1st edn. Arnold, London, pp 1–51
- Bush WH Jr, Swanson DP (1991) Acute reactions to intravascular contrast media: types, risk factors, recognition, and specific treatment. *AJR Am J Roentgenol* 157:1153–1161
- Lasser EC (2004) Chasing contrast molecules: a 45 year quixotic quest. *Acad Radiol* 11:1190–1196
- Thomsen HS, Bush WH Jr (1998) Adverse effects of contrast media: incidence, prevention, and management. *Drug Saf* 19(4):313–324
- Almen T (May 1994) The etiology of contrast medium reactions. *Investig Radiol*
- Cotran RS, Kumar V, Collins T (eds) (1999) *Robbins pathologic basis of disease*, 6th edn. W.B. Saunders Company, Imprint of Elsevier Science, Philadelphia, pp 67–199
- Vik H, Froya A (1995) Complement activation and histamine release following administration of roentgen contrast media. *Acta Radiologica* 36(suppl 399):83–9.e
- Lasser EC (1985) Etiology of anaphylactoid responses: the promise of nonionics. *Invest Radiol* 20(1 Suppl):S79–S83
- Lasser EC (1987) A coherent biochemical basis for increased reactivity to contrast material in allergic patients: a novel concept. *AJR Am J Roentgenol* 149:1281–1285
- Lasser EC (1988) A general and personal perspective on contrast material research. *Invest Radiol* 23(Suppl 1):S71–S74
- Trecka J (2008) Anaphylaxis to iodinated contrast material: nonallergic hypersensitivity or IgE-mediated allergy? *AJR Am J Roentgenol* 190:666–670
- Namasivayam S, Kalra M (2006) Adverse reactions to IV iodinated contrast media: a primer for radiologists. *Emerg Radiol* 12:210–215
- Lang D, Allpern M. Increased risk for anaphylactoid reaction from contrast media in patients on betaadrenergic blockers or with asthma. *Ann Intern Med* 115: 270–276
- Dillman J, Strouse P (2007) Incidence and severity of acute allergic-like reactions to IV nonionic iodinated contrast material in children. *AJR* 188:1643–1647
- Liccardi G, Lobefalo G (2008) Strategies for the prevention of asthmatic anaphylactic and anaphylactoid reactions during the administration of anesthetics and/or contrast media. *J Investig Allergol Clin Immunol* 18(1):1–11
- Beatty AD, Lieberman PL, Slavin RG (2008) Seafood allergy and radiocontrast media: are physicians propagating a myth? *Am J Med* 121:158.e1–4
- Schabelman E, Witting M (2010) The relationship of radiocontrast, iodine, and seafood allergies: a medical myth exposed. *J Emerg Med* 39(5):701–707
- Leung PS, Chen YC, Chu KH (1999) Seafood allergy: tropomyosins and beyond. *J Microbiol Immunol Infect* 32:143–154
- Chatham WW. Glucocorticoid effects on the immune system. <http://www.uptodate.com.offcampus.lib.washington.edu/contents/glucocorticoid-effect-on-the-immune-system>. Accessed 24 Feb 2011
- Greenberger PA, Patterson R, Radin RC (1984) Two pretreatment regimens for high-risk patients receiving radiographic contrast media. *J Allergy Clin Immunol* 74:540–543
- Greenberger PA, Patterson R (1991) The prevention of immediate generalized reactions to radiocontrast media in high-risk patients. *J Allergy Clin Immunol* 87:867–872
- Greenberger PA, Patterson R (1985) Prophylaxis against repeated radiocontrast media reactions in 857 cases. Adverse experience with cimetidine and safety of beta-adrenergic antagonists. *Arch Intern Med* 145:2197–2200
- Greenberger PA, Halwig JM, Patterson R, Wallemark CB (1986) Emergency administration of radiocontrast media in high-risk patients. *J Allergy Clin Immunol* 77:630–634
- Davenport MS, Cohan RH. Repeat contrast medium reactions in premedicated patients: frequency and severity. *Radiology* 253(2): 372–379
- Lexicomp. Methylprednisolone: drug information. <http://www.uptodate.com.offcampus.lib.washington.edu/contents/methylprednisolone-drug-information>. Accessed 24 Feb 2011
- Lexicomp. Hydrocortisone (systemic): drug information. <http://www.uptodate.com.offcampus.lib.washington.edu/contents/hydrocortisone-systemic-drug-information>. Accessed 24 Feb 2011