Contrast Reaction Readiness for Your Department or Facility

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KEYWORDS

• Contrast reaction management • Iodinated contrast media • Gadolinium-based contrast agents
• High-fidelity simulation • Hypersensitivity reactions • Contrast extravasation
• Allergic-like reactions to contrast media

KEY POINTS

- Moderate and severe hypersensitivity reactions to iodinated contrast media and gadolinium-based contrast agents are rare but can be life threatening.
- Frequent training augmenting didactic lectures with hands-on or computer-based simulation, or educational online modules can improve knowledge and comfort at managing contrast reactions.
- Epinephrine administration errors are common and may be reduced by having autoinjectors available. However, frequent hands-on training is still required to ensure appropriate use.
- Treatment algorithms, visual aids, and safety checklists should be posted throughout radiology departments to improve team comfort at managing reactions and reduce errors.
- Appropriate screening may reduce the risk for hypersensitivity reactions and extravasations, although break-through reactions may still occur, usually of similar severity.

INTRODUCTION

Radiographic contrast agents, such as iodinated contrast media (ICM) and gadolinium-based contrast agents (GBCA), are useful for evaluating organs and identifying pathologic conditions. Their utilization has rapidly increased in the past few decades with approximately 48 million contrast-enhanced computed tomographic scans (CTs) and 17 million contrast-enhanced MR images performed annually in the United States.[1–3] However, adverse events, such as hypersensitivity reactions and extravasations can occur, and the radiology department's readiness to appropriately manage these will affect the patient's outcome.[4] The rarity of moderate and severe reactions results in few radiologists having first-hand experience at managing reactions.[5] Published survey data suggest that radiologists have knowledge gaps in appropriate contrast reaction management, particularly anaphylaxis.[6–8] Bartlett and Bynevelt[7] found that 57% of their respondents either did not know or gave incorrect dosing for the administration of epinephrine, which was more likely overdose (66%) versus underdose (33%). More recently, Nandwana and colleagues[9] surveyed radiology attendings, residents, fellows, and nurses, and only 29% of respondents correctly answered the rate, dose, and route of epinephrine administration for anaphylaxis. Several recent studies have used hands-on simulation contrast reaction scenarios as a surrogate to evaluate the incidence of treatment errors and have confirmed a high rate of management errors.[10–12] This review summarizes the types and incidence of adverse events to

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contrast media, treatment algorithms, and equipment needed to treat common contrast reactions, the current status of contrast reaction management training, and preventative strategies to help mitigate adverse contrast events. The scope of this review is limited to adult patients.

REVIEW OF THE TYPES AND INCIDENCE OF ADVERSE EVENTS

Hypersensitivity Reactions

The incidence of hypersensitivity, including both allergic and allergic-like reactions to low osmolar (LOCM) and iso-osmolar (IOCM) ICM, ranges from 0.2% to 0.6%: 0.4% to 0.5% mild, 0.04% to 0.1% moderate, 0.006% to 0.01% severe.[4,13,14] Death is extremely rare and estimated to be approximately 0.0006%.[14] The incidence of reactions is lower with GBCAs and estimated to be 0.08% to 0.2%: 0.02% to 0.1% mild, 0.01% to 0.02% moderate, and 0.006% to 0.0007% severe.[13,15,16] The mortality owing to GBCA reported to the Food and Drug Administration was 0.00008% between 2004 and 2009.[17] Some data suggest that the risk of adverse events is higher in ionic linear agents than in nonionic linear GBCA agents.[16,18]

Hypersensitivity reactions are now classified into acute and nonacute/delayed reactions. The acute or immediate reactions occur within 1 hour after contrast administration, and many are caused by mast cell activation that may or may not be caused by immunoglobulin E mechanisms, explaining why the term allergic-like reactions was previously used.[19,20] These reactions range from mild hives to anaphylaxis and are classified by their severity and morbidity by the American College of Radiology (ACR), as seen in **Table 1**.[21]

Delayed reactions are defined as reactions starting more than 1 hour after contrast administration but typically occurring more than 3 hours to 2 to 5 days after exposure and are suspected to be related to T-cell–mediated hypersensitivity.[19] These delayed reactions usually manifest as macular or maculopapular exanthema but rarely can be associated with more severe skin conditions, such as toxic epidermal necrolysis or Stevens-Johnson syndrome.[20] The exact incidence of delayed reactions is difficult to determine likely because of underreporting, but is estimated to be 0.5% to 9%.[22] Loh and colleagues[23] showed the most common delayed adverse reactions were cutaneous, such as rash, itching, skin redness, and swelling. Overall delayed reactions are commonly self-limited.

Extravasation

Contrast extravasation is another recognized adverse event related to contrast media injection and is rarely serious, although it can result in severe skin ulcerations, tissue necrosis, and compartment syndrome.[24–27] A recent systematic review of MR and CT contrast media

Table 1
Different types and severity of hypersensitivity reactions adapted from the American College of Radiology Contrast Manual

Mild	Moderate	Severe
Self-limited and no evidence of progression; treatment usually not necessary; no vital sign alterations	Symptoms may require medical treatment; however no significant vital sign alterations	Symptoms may be life threatening and require treatment to avoid morbidity or death; vital signs are abnormal
Limited hives	Diffuse hives	Diffuse hives with hypotension
Limited itchiness	Diffuse itchiness or erythema, stable vital signs	Diffuse itchiness and or erythema with hypotension
Cutaneous edema	Facial edema but no dyspnea	Diffuse edema including facial with dyspnea
Limited itchy/scratchy throat or eyes	Wheezing but no hypoxia	Wheezing with hypoxia
Nasal congestion/runny nose	Throat tightness but no dyspnea	Laryngeal edema with stridor and or hypoxia
		Anaphylactic shock (hypotension + tachycardia)

Adapted Table 1 from the 2019 Contrast Manual (categories of acute reactons); adapted information from the chapter entitled 'PATIENT SELECTION AND PREPARATION STRATEGIES BEFORE CONTRAST MEDIUM ADMINISTRATION' for the specific recommendations for premedication regimens; Adapted information from Table 4 ("EQUIPMENT FOR CONTRAST REACTION KITS IN RADIOLOGY'); with permission.

extravasations found 17 papers that reported 2191 extravasations out of 1,104,872 patients (0.2%) with a rate of 0.26% for ICM and 0.045% for GBCA.[28] The rate of extravasations is lower with gadolinium likely related to the lower volumes, lower rates of injection, and increased frequency of hand injection.

MANAGEMENT OF ADVERSE EVENTS

Acute Hypersensitivity

Appropriate management for contrast reactions varies based on the type of reaction. As a result, it is vital to have an emergency cart stocked with various supplies and medications as well as appropriate training of staff to be able to manage reactions. The management of contrast reactions is not unique to the use of iodinated contrast, and the treatment is the same, regardless of the inciting factor. Although vasovagal reactions are considered a physiologic reaction and not allergic-like hypersensitivity reaction, it is included in the treatment flowchart for completeness. It is generally considered best practice to preserve intravenous (IV) access and monitor vital signs, including pulse oximetry for all reactions, including mild reactions. **Fig. 1** provides a flowchart for managing bronchospasm versus laryngeal edema, and **Fig. 2** provides a flowchart for managing vasovagal versus anaphylaxis.

- Hives/urticaria, itchiness, or diffuse erythema
  - Mild scattered or transient hives or erythema usually does not require treatment; however, vital signs should be monitored, and IV access preserved.
  - If the hives worsen or become more numerous/widespread or bothersome, treatment with diphenhydramine 25 to 50 mg orally or fexofenadine 180 mg orally (less sedating) could be considered.
  - If the hives or diffuse erythema are accompanied by hypotension:
    - Give IV fluids normal saline 1 L bolus
    - Elevate legs $\geq 60^{\circ}$
    - Give oxygen by face mask (at least 6–10 L/min)
    - Give epinephrine (**Table 2**)
- Bronchospasm
  - Oxygen by mask, at least 6 to 10 L/min
  - Beta2 agonist inhaler 2 puffs (90 μg/puff) and can repeat up to 3 times total

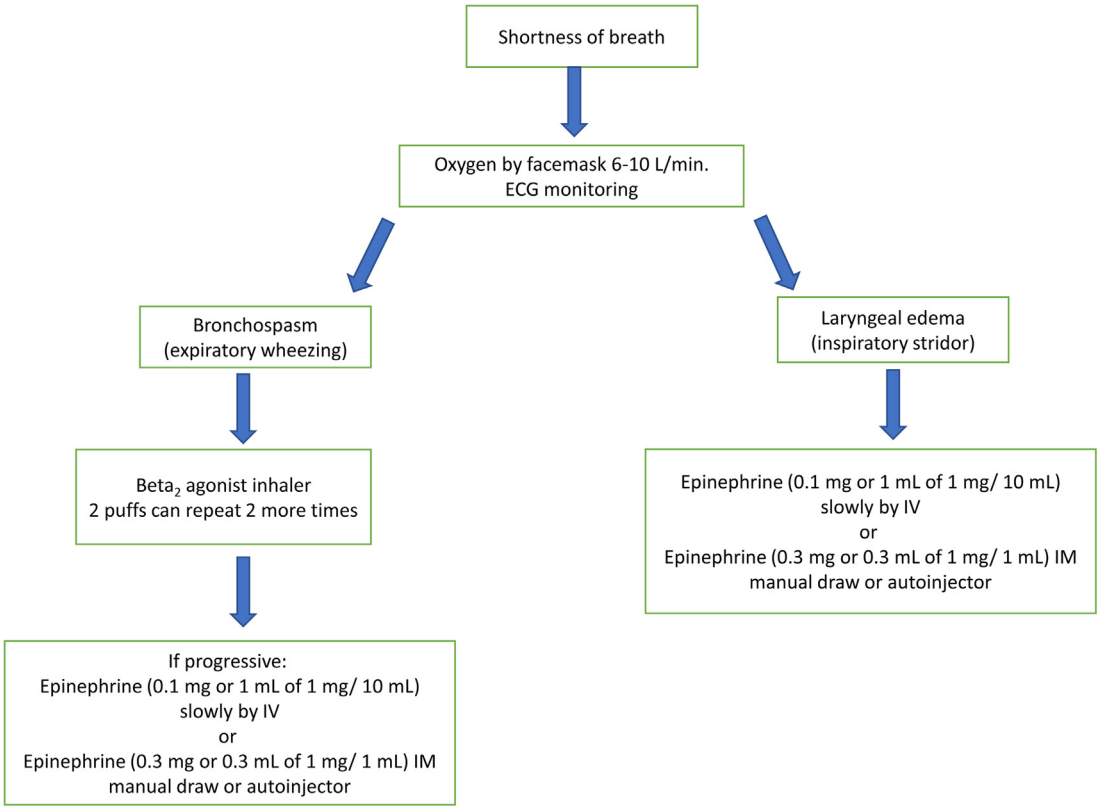

Fig. 1. The management of bronchospasm versus laryngeal edema.

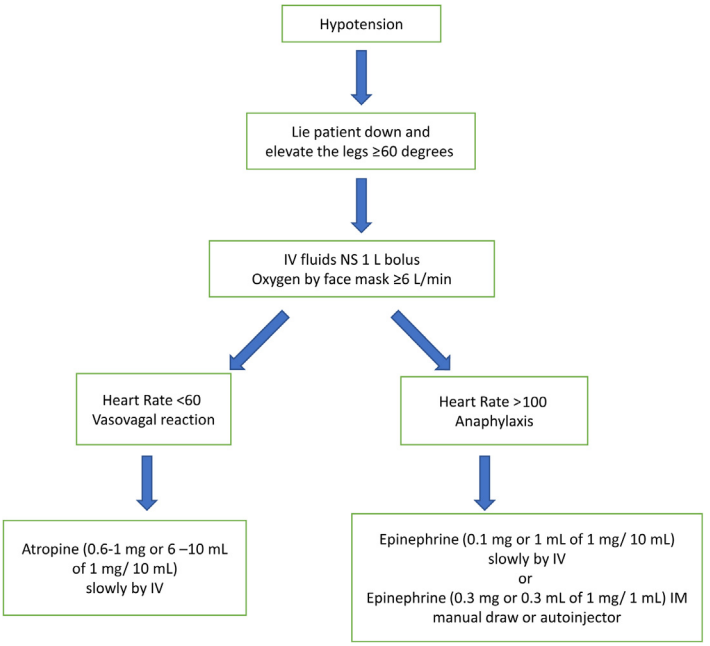

Fig. 2. The management of hypotension related to vasovagal versus anaphylaxis.

  - In severe cases or if the bronchospasm is progressive or unresponsive to the inhaler, epinephrine (see **Table 2**)
- Laryngeal edema
  - Oxygen by face mask, at least 6 to 10 L/min
  - Epinephrine (see **Table 2**)
- Vasovagal
  - Elevate legs $\geq 60^{\circ}$
  - Give IV fluids normal saline 1 L bolus
  - Give oxygen by face mask 6 to 10 L/min
  - If the patient remains symptomatic, consider atropine 0.6 to 1 mg IV
- Anaphylaxis
  - Early initiation of the resuscitation team and/or calling 911 is critical
  - Assess airway and begin oxygen by face mask, 6 to 10 L/min
  - Elevate legs $\geq 60^{\circ}$
  - Give IV fluids normal saline 1 L bolus
  - Give epinephrine (see **Table 2**)
- Delayed reaction

  Management of cutaneous delayed reactions should be symptomatic with oral antihistamines and topical steroids and emollients.[29,30]
- Extravasation

  Management of this complication is controversial. Most cases of contrast extravasation occur with small volumes and are self-limiting, although larger volume can result in severe skin necrosis and ulceration.
  - Verify estimated volume of extravasation and examine the patient.
  - In most cases conservative management is enough.
    - Apply either ice packs or warm compresses

Table 2
Various forms of epinephrine administration for hypersensitivity reactions

Route of Delivery	Concentration of Epinephrine	Dose, mg (mL Volume)
Intramuscular (IM) manual[a]	1 mg in 1 mL	0.3 (0.3 mL)
Intramuscular autoinjector[a]	1 mg in 1 mL	0.3 (prefilled)
IV[b]	1 mg in 10 mL	0.1 (1 mL)

[a] Inject into the lateral thigh.
[b] Inject slowly into an IV line with fluids running or followed by a slow flush.

- Elevate the limb
- Check pulses and sensory function for neurovascular compromise
- Monitor patient vital signs as well as site of extravasation
- Can mark skin to determine size of involvement

- If symptoms worsen, consult a surgeon if concerned about compartment syndrome.

REQUIRED EQUIPMENT

Table 3 summarizes the suggested medications and supplies needed for managing contrast reactions. Please refer to your own radiology department's contrast management policy for the minimum equipment and medications required because these may vary depending on institutional policies and practices.

CONTRAST REACTION MANAGEMENT TRAINING

Although moderate and severe hypersensitivity reactions are rare, usually the first and potentially only responders are the radiologists and the radiology staff. Questionnaire surveys and hands-on simulation testing have demonstrated that contrast reaction management knowledge gaps exist for radiologists, radiology nurses, and technologists.[5,9,31] Trainees and radiologists in practice for less than 5 years or more than 15 years appear to benefit the most from contrast reaction management training.[32] At many academic centers, the first responders are radiology residents.[33] Several survey studies demonstrate that traditional annual didactic lecture remains the preferred format for contrast reaction management training at most US radiology residencies.[33–35] Studies have shown that online educational modules for contrast reaction management can improve knowledge and comfort at managing reactions with short-term knowledge assessment.[5,36] High-fidelity simulation training has been shown to be superior to didactic lecture alone.[37] Multiple studies have shown the value of high-fidelity simulation training for such high-acuity low-frequency scenarios at improving not only knowledge but also comfort at managing contrast reactions.[32,38,39] Ali and colleagues[40]

Table 3
Equipment and medications needed for contrast reaction management

Medications	Supplies	Advanced Life-Support Supplies[a]
Epinephrine 1 mg in 1 mL vial (for IM injections)	Needles and syringes (eg, 1 mL needle for IM administration of epinephrine with 20-G needle)	Automatic external defibrillator
Epinephrine 1 mg in 10 mL box (for IV administration)[b]	Face mask/oxygen	Oral and or nasal airways
Epinephrine autoinjectors IM (0.1 mg for infants; 0.15 mg for children; 0.3 mg for adults)[c]	Stethoscope	Suction tubing and catheters
Atropine 1 mg in 10 mL box (for IV administration)	Pulse oximetry	Protective barriers for mouth to mouth and or bag-valve-mask device
1 L normal saline IV fluid bags	Sphygmomanometer	
Beta-2 agonist inhaler	IV catheters	
H_1 antihistamine (oral or IV)		

[a] These items will likely be found on code/crash carts in hospital settings and may exceed the required equipment for limited outpatient imaging facilities.
[b] Epinephrine 1 mg in 10 mL is typically in code/crash carts in hospital settings.
[c] Epinephrine autoinjectors may not be stocked because of the high cost associated compared with manual IM epinephrine.

Adapted Table 1 from the 2019 Contrast Manual (categories of acute reactons); adapted information from the chapter entitled 'PATIENT SELECTION AND PREPARATION STRATEGIES BEFORE CONTRAST MEDIUM ADMINISTRATION' for the specific recommendations for premedication regimens; Adapted information from Table 4 ("EQUIPMENT FOR CONTRAST REACTION KITS IN RADIOLOGY'); with permission.

also expanded the hands-on simulation training to include other less common events, such as seizures, hypocalcemia, and panic attacks.

Hands-on simulation training continues to be used less commonly than didactic lecture, although the percentage of programs surveyed that use it appears to be increasing in the literature: 18% in 2010, 30% in 2013, and 37.8% in 2015.[33–35] Cost has been reported to be a limiting factor, and 1 study estimated to be around $256.76 per resident for the first year and $203.46 for each subsequent year of hands-on simulation training compared with less than $5 for didactic lecture.[41] They also noted the differences in nonmonetary costs as well, such as faculty time and effort developing and administering the program as well as trainee time away from clinical duties to participate in the course. Other published self-reported barriers to hands-on simulation training include insufficient availability, no trained faculty, and time constraints.[35] The timing and frequency of training are important because studies have shown a decline in both confidence and knowledge of managing contrast reactions by 6 to 9 months, suggesting that a 6-month refresher should be considered.[32,42] It may be more cost-effective to supplement hands-on simulation training with either traditional in-person didactic lecture, online education modules, or computer-based simulation.

It is important to train not only radiologists but also radiology nurses and technologists who are also key members of the response team. Effective teamwork and interprofessional communication are critical to ensure patient safety. High-fidelity and computer-based simulation has been shown to be useful for training interprofessional teams of radiologists, technologists, and nurses for both contrast reaction management and team communication skills as tested with a high-fidelity simulation scenario, although a single session appeared inadequate for mastery of such complex teamwork skills, suggesting refreshers are necessary.[31]

Although training is critical, it is important to have treatment algorithms posted throughout the radiology department so that no one is relying on their memories during these high-stress situations. Gardner and colleagues[12] demonstrated that fewer errors in management were committed by groups of participants who had a visual aid flowchart than those who did not during a high-fidelity severe contrast reaction scenario. Safety checklists, which are critical in the airline industry, have also been shown to be an effective tool at reducing treatment errors during testing with a high-fidelity severe contrast reaction simulation scenario.[43] These types of visual aids and checklists should be included in any contrast reaction kit box or code cart found in the radiology suites to use as reference during reaction management. It is imperative that the treating members, including radiologists, technologists, and nurses, have familiarity with and working knowledge of the checklists and visual aids to be able to use them most effectively.

Several studies have demonstrated that the most common errors made during high-fidelity simulation training and testing of severe contrast reactions are related to the concentration, dose, route, and administration of epinephrine.[10–12] Masch and colleagues[44] demonstrated that not having IV access resulted in faster time to medication delivery of epinephrine; however, similar rates of errors of administration still occurred, most commonly administering the intramuscular autoinjector for less than 5 seconds resulting in inadequate dosing. An additional 5 participants autoinjected their thumbs instead of the patient. Asch and colleagues[45] demonstrated fewer errors in epinephrine administration when an autoinjector was used rather than drawing up and administering intramuscular epinephrine. The most common error was the wrong dose of epinephrine followed by attempting to administer the intramuscular concentration (epinephrine 1 mg in 1 mL) intravenously. No errors occurred in the autoinjector group, and the difference between this study and the study by Masch may have been the type of autoinjector used in the simulation scenario: the Auvi-Q (Kaleo, Richmond, VA) versus EpiPen (Mylan, Canonsburg, PA).[44,45] Both experienced and inexperienced caregivers have demonstrated a preference for the Auvi-Q (Kaleo, Richmond, VA) likely because the injector verbalizes instructions, which minimizes potential errors.[46] Having epinephrine autoinjectors stocked in radiology suites may improve patient safety by quicker delivery of the medication as well as reduction in epinephrine administration errors. However, there is a financial consideration because the autoinjectors are approximately 100 times more expensive than the manual device, and only have approximately a 1-year shelf life. Also, the autoinjectors require adequate training to avoid misadministration.[45]

PREVENTION OF HYPERSENSITIVITY REACTIONS

Screening

Identifying which patients will benefit the most from IV contrast administration includes understanding the clinical question to be answered and determining the best imaging test. For most patients, IV contrast is well tolerated, and no

special precautions need to be taken. Certain subsets of patients need further consideration and require screening before contrast media administration, particularly those with a history of prior adverse reaction to contrast media.[21] Additional considerations, such as risk of nephrotoxicity, lactic acidosis, nephrogenic systemic fibrosis, or gadolinium deposition, are beyond the scope of this article. Patients with a prior history of severe allergy to the same type of contrast agent have an overall 5- to 6-fold increased risk for a subsequent reaction.[3]

Historically, patients with seafood allergies were thought to have greater risk of reaction to ICM. A systematic review of the literature shows that patients with seafood allergies had similar rates of reactions as patients with allergies to other substances.[47] Iodine cannot be an allergen because it is found throughout our bodies in thyroid hormones and amino acids. Tropomyosins are the major allergen for most patients with seafood allergies.[47] Patients who are allergic to povidone iodine skin preparation react to other allergens in the solution, not the iodine. In addition, this type of reaction is a contact dermatitis rather than a hypersensitivity reaction.[48] Therefore, there is no need to screen patients for seafood allergies or povidone iodine skin preparation allergies, and it is important to clarify when patients report an "iodine allergy" if it is to ICM.

Patients with a history of asthma have a modest increased risk of hypersensitivity reactions; however, well-controlled asthmatics do not appear to be at increased risk for adverse reactions.[49] Patients who have a prior history of reaction to ICM are at no increased risk for GBCAs because they are chemically distinct contrast agents without any known cross-reactivity.[13,50] In general, patients who have unrelated medication or food allergies have a modest 2- to 3-fold increased risk over the general population, but the ACR does not recommend restricting contrast media use and does not consider it alone as an indication for premedication.[21]

Premedication

The greatest risk factor for a hypersensitivity reaction is a prior hypersensitivity reaction to the same type of contrast media. Physiologic reactions, including flushing, metallic taste, nausea, vomiting, and vasovagal reactions, are not hypersensitivity reactions and therefore do not require premedication. Premedication with corticosteroids before contrast administration has been shown to be effective at reducing mild hypersensitivity reactions in average-risk patients to low-osmolality ICM, but no case-controlled studies have shown efficacy at reducing risk in high-risk patients or for moderate and severe hypersensitivity reactions.[48,51–53] A systematic review of the literature for studies that randomized pretreatment against placebo or no treatment before patient receiving ICM suggests that H_1 antihistamines mainly showed efficacy against cutaneous reactions, while corticosteroids prevent respiratory symptoms; however, no case-controlled study tested the combination of the 2 in high-risk patients.[54] No studies to the authors' knowledge have been published evaluating the efficacy of premedication for oral ICM or GBCAs, and the benefits are extrapolated from the ICM literature.

Although the practice of prophylaxis premedication in high-risk patients is commonly considered the standard of care in the United States, it is not performed in other countries because of the lack of level 1 evidence that it reduces the reaction risk in high-risk patients or the incidence of moderate or severe reactions to LOCM, IOCM, or GBCA.[55] There are also minimal direct risks to premedication, including asymptomatic hyperglycemia and transient leukocytosis.[56–58]

Premedication does not prevent all future reactions, because breakthrough reactions do occur at reported rates between 1.2% and 3.4% for IOCM and or LOCM.[16,59] Breakthrough reactions may partially depend on the indication for the premedication as Mervak and colleagues[59] found a rate of 2.1% for those patients with had a prior contrast reaction compared with 0% for those premedicated for other indications. These ICM breakthrough reactions tend to be of the same severity of as the index reactions, and patients with a mild index reaction are at very low risk of developing a severe breakthrough reaction.[59–61] Breakthrough reactions have also been seen with GBCA, and in 1 study, 56% were of similar severity; however, 33% were more severe than the index reaction.[62] Repeat breakthrough reactions to ICM also occur at a reported rate of 12% and are usually of the same severity.[59] Therefore, it may be more prudent to avoid repeat exposure to contrast media for severe contrast reactions given the higher likelihood of a severe breakthrough reaction rather than rely on corticosteroid premedication.[55] The estimated number of patients needed to treat to prevent 1 severe reaction in patients with a prior reaction is 569 and to prevent 1 lethal reaction is 56,900.[59] In addition, in the in-patient setting, the orally premedicated patients had longer hospital stays and more hospital infections than those not premedicated.[63]

Two common oral premedication regimens and 1 shortened IV premedication regimen are listed in **Box 1**.[51–53,64] Data suggest that a less than 2-hour

Box 1
Three possible premedication regimens

- Prednisone 50 mg by mouth 13 hours, 7 hours, and 1 hour plus optional diphenhydramine 50 mg by mouth 1 hour before contrast administration
- Methylprednisolone 32 mg by mouth 12 hours and 2 hours plus optional diphenhydramine 50 mg by mouth 1 hour before contrast administration
- Hydrocortisone 200 mg IV 5 hours and 1 hour plus diphenhydramine 50 mg IV 1 hour before contrast administration

Data from Refs.[51,53,65]

oral regimen is not effective compared with placebo.[51] A 5-hour IV premedication regimen was found to be noninferior to a 13-hour oral regimen and could be considered for patients in whom timely diagnosis and treatment are critical, such as the inpatient or emergency room setting.[65]

PREVENTION OF CONTRAST EXTRAVASATION

Warming contrast has been shown to decrease the rate of extravasation for the more viscous iopamidol 370 than iopamidol (Bracco, Milan, Italy) 300.[66] Risk factors for extravasation include older age, female gender, using an existing cannula, using a site other than the antecubital fossa, and using a power injector with a high-injector rate.[28] Using the largest vein available may also reduce the risk of extravasation, such as the larger veins in the antecubital fossa rather than the hands.[67] Other risk mitigating techniques, such as starting a new IV line and avoiding the use of high-injection rate with a power injector, in higher at-risk populations, including elderly women, could also be considered.[28]

SUMMARY

Moderate and severe contrast reactions are rare but can be life threatening. Appropriate contrast reaction management is necessary for the best patient outcome. Radiologists, radiology nurses, and technologists have knowledge gaps on how to manage contrast reactions, which can be closed with appropriate and frequent training that augments traditional didactic lecture with more hands-on or computer-based simulations or online educational modules. Visual aids, treatment algorithm flowcharts, and safety checklists should be posted throughout the radiology suites to help reduce management errors and increase the teams' comfort at managing these rare events. Errors in epinephrine administration may also be reduced by having epinephrine autoinjectors available in radiology suites, although hands-on and frequent training is advisable, and high cost may hinder adoption. Appropriate screening can be used to reduce the risk for hypersensitivity reactions and extravasations. Corticosteroid prophylaxis is frequently used in the United States to prevent hypersensitivity reactions to ICM and GBCAs in high-risk patients with prior contrast reactions, although breakthrough reactions still occur, usually of similar severity to the index reaction.

DISCLOSURE

The authors have nothing to disclose.

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