

GUIDELINES FOR CONTRAST MEDIA PRE-MEDICATION

Purpose

To produce pre-medication guidelines for CDHA to minimize patient risk from acute allergic-like contrast reactions while performing necessary diagnostic and interventional examinations.

Overview

1. **Define Acute Allergic-Like Contrast Reactions**

Contrast materials employed in routine clinical practice include non-ionic iodinated contrast agents¹ (x-ray, CT, fluoroscopy) and gadolinium-based contrast agents (MRI). The major complication arising from the use of contrast materials in patients with normal renal function is an acute adverse reaction². Acute adverse reactions can be classified as allergic-like or physiologic and stratified by severity (Table 1). Although clinically similar in presentation, allergic-like reactions are not considered true allergies given the absence of an IgE-mediated immune response in most cases (1).

2. **Describe the Frequency with which Acute Allergic-Like Contrast Reactions Occur in the General Population**

Reported reaction rates for acute allergic-like reactions are:

- a) ***Non-ionic iodinated contrast media*** (2-6)
 - All reactions: 0.2-3%
 - Severe reactions only: 0.005-0.01%
- b) ***Gadolinium-based contrast media*** (3, 7-9)
 - All reactions: 0.03-0.2%
 - Severe reactions only: 0.002-0.01%

3. **Identify Patients at Risk**

Risk factors for acute allergic-like contrast reactions include:

- a) ***Non-ionic iodinated contrast media***
 - **Prior allergic-like reaction to a non-ionic iodinated contrast agent**

¹ Non-ionic iodinated contrast agents are also known as lower osmolality agents. These contrast agents came into widespread clinical use in the early 1990s due to a lower prevalence of adverse reactions with respect to their ionic or high osmolality precursors (4). Only non-ionic iodinated contrast agents are currently used at CDHA and any reference to iodinated contrast agents within this document refers solely to the non-ionic or lower osmolality variety.

² Please refer to the existing CDHA Policy and Procedure document entitled “Guidelines for Prevention of Contrast Induced Nephropathy” for a complete discussion of contrast induced nephropathy which is a delayed non-allergic contrast reaction.

- Risk of a subsequent reaction is up to five times higher with respect to those who have never received IV contrast or who have received IV contrast previously without a reaction (4).

b) Gadolinium-based contrast media

- Prior allergic-like reaction to a gadolinium-based contrast agent
 - The risk is approximately 8 times higher in patients with a history of a prior reaction (1). Subsequent reactions may also be more severe.

Limited data suggests that patients with an history of asthma, atopy, and drug or food allergy may be at a mildly elevated risk of an acute allergic-like reaction to non-ionic iodinated contrast media and gadolinium-based contrast media (1, 4). However, objective criteria to identify which patients might benefit from pre-medication based on allergy type, related symptoms, and their severity have not been developed. In the absence of reliable evidence-based data, screening for asthma, atopy, and drug or food allergy will not be incorporated into our CT/MRI requisition process given potential side-effects from corticosteroids and the lack of a defined benefit to patient safety.

No cross-reactivity has been identified in those with an history of a prior allergic-reaction to either non-ionic iodinated contrast media or gadolinium-based contrast media (1). Accordingly, an history of an allergic-like reaction to one type of agent is not included as a risk factor for a reaction to the other.

4. Review the Evidence for Pre-Medication

a) *Does pre-medication work?*

i. No previous reaction history

- A randomized controlled trial of pre-medication with corticosteroids to prevent adverse reactions to non-ionic iodinated contrast media in 1155 patients reported a significant reduction in the overall frequency of reactions with oral corticosteroids in comparison to placebo (1.7% vs 4.9%; $P < 0.005$) (10). A reduction in the frequency of the most severe reactions (0.3% vs 1.4%; $P = 0.11$) was not statistically significant, but this may have been on the basis of the small sample size (10).

ii. Previous reaction to non-ionic contrast

- A retrospective study of 30 patients with an history of acute allergic-like contrast reactions ($n = 17$, mild; $n = 13$ severe) to non-ionic iodinated contrast media found that **16.7%** ($n = 5/30$) had a breakthrough reaction after a subsequent contrast injection following pre-medication with corticosteroids, H1 antihistamines, \pm H2 blockers (11). The breakthrough reactions mirrored the previous reactions with respect to severity and clinical manifestations ($n = 4$, mild; $n = 1$, severe) (11).

b) *What if a patient has had a previous reaction to an IONIC iodinated contrast material?*

i. Effect of changing to non-ionic contrast

- A study evaluating the safety of iodinated contrast media reported overall adverse reaction rates in patients with a history of a contrast reaction to an ionic agent of 44.0% ($n = 2,548/5,785$) and 11.2% ($n = 1,087/9,667$) for those receiving ionic and non-ionic agents, respectively (4). In the ionic group, the severe reaction rate was 0.73% ($n = 42/5,785$) in

comparison to 0.18% (n = 17/9,667) in the non-ionic group (4). The reductions with non-ionic agents were highly significant ($P < 0.0001$).

These data clearly illustrate the benefits of switching to non-ionic iodinated contrast agents in patients with a history of acute allergic-like reactions to ionic agents. Further benefits may also be seen with pre-medication in this population (12):

ii. Effect of changing to non-ionic and pre-medicating

- A study of 191 patients with a prior reaction to an ionic iodinated contrast agent reported an adverse reaction rate of **0.7%** (n = 1/146) in patients pre-medicated with prednisone and diphenhydramine prior to receiving a non-ionic iodinated contrast agent (12). The single reaction was moderate in severity. None of the 26 patients with a history of severe reaction experienced a repeat reaction (12).

c) *Does pre-medication entirely eliminate the risk of an acute allergic-like contrast reaction?*

- A “breakthrough” reaction occurs when a patient with a history of an acute allergic-like reaction subsequently experiences a repeat reaction after receiving the same class of contrast material following pre-medication.
- The frequency with which breakthrough reactions occur is unknown, but has been reported for both non-ionic iodinated contrast agents (13, 14) and gadolinium-based contrast agents (15). The ACR Manual on Contrast Media summarizes the existing literature in part as follows (1):
 - *“Breakthrough reaction severity, signs, and symptoms are most often similar to the index reaction;*
 - *The majority of low-osmolality contrast injections in pre-medicated patients with a prior breakthrough reaction will not result in a repeat breakthrough reaction;*
 - *Patients with a mild index reaction have an extremely low risk of developing a severe breakthrough reaction;*
 - *Patients with a moderate or severe index or breakthrough reaction are at higher risk for developing another moderate or severe reaction should breakthrough occur;(14)*

5. Define the Pre-medication Strategy

The CDHA pre-medication strategy is designed to identify patients at increased risk of acute allergic-like contrast reactions prior to the time of imaging so that appropriate steps can be taken to minimize the risk of harm. Separate pre-medication strategies have been described in the literature for the following patient groups:

- a) The “*non-emergent*” population consists of outpatients, stable ER patients, and stable inpatients whose imaging can be delayed for the full 12 hour oral steroid preparation.
- b) The “*emergent*” population consists of ER and acutely ill inpatients clinically requiring imaging within a shorter time-frame.

6. Define “Non-Emergent” and “Emergent” Pre-medication Regimens

The following pre-medication regimens have been described in the non-emergent and emergent settings to “reduce the frequency and/or severity of acute allergic-like contrast reactions” and are adapted from ACR Manual on Contrast Media (1):

a) *Non-emergent Pre-medication*

- Methylprednisolone 32mg PO at 12 hours and 2 hours before contrast injection, plus diphenhydramine (Benadryl[®]) 50 mg PO/IV/IM 1 hour before contrast injection (10, 16).
- Note: If oral medications cannot be taken, hydrocortisone 200 mg IV may be substituted for oral prednisone and given 4 – 6 hours before contrast injection (17). Diphenhydramine 50 mg IV should also be administered 1 hour before contrast injection.

b) *Emergent Pre-medication (In Decreasing Order of Desirability)*

- i. Methylprednisolone sodium succinate (Solu-Medrol[®]) 40 mg IV or hydrocortisone sodium succinate (Solu-Cortef[®]) 200 mg IV 4 – 6 hours before contrast injection, plus diphenhydramine 50 mg IV 1 hour before contrast injection (17).
- ii. Dexamethasone sodium sulfate (Decadron[®]) 7.5 mg IV or betamethasone 6 mg IV 4 – 6 hours before contrast injection if there is a known allergy to methylprednisolone, aspirin, or non-steroidal anti-inflammatory drugs, especially if asthmatic. Diphenhydramine 50 mg IV should also be administered 1 hour before contrast injection.
- iii. If the scan must be performed immediately, give diphenhydramine 50 mg IV. IV steroids have not been shown to be effective when administered less than 4 – 6 hours prior to contrast injection.

Note: Diphenhydramine should not be given to a hypotensive patient (18).

7. When to Employ the Premedication Guidelines

Separate algorithms to identify patients at increased risk of acute allergic-like contrast reactions have been developed for non-ionic iodinated contrast agents and gadolinium-based contrast agents. Detailed responses to the “Risk for Contrast Media Reaction Questionnaire” document are required for appropriate utilization of these algorithms. Please refer to the attached algorithms for complete details.

Procedure

A “Risk for Contrast Media Reaction Questionnaire” will be sent to referring physicians for those patients identified on the CT or MRI requisition as having had a prior reaction.

Pre-medication is only required for select patients undergoing contrast-enhanced examinations. The radiology resident or staff radiologist protocoling the study will assess the patient’s risk for an acute allergic-like contrast reaction using specific algorithms developed for both non-ionic iodinated contrast media and gadolinium-based contrast media administration using the submitted patient questionnaire. If

pre-medication is required, the referring clinician will be instructed as to whether the patient requires “non-emergent” or “emergent” pre-medication (see the regimens listed in II.6 above).

Stable outpatients requiring pre-medication according to the “non-emergent” regimen above will need to obtain prescriptions for methylprednisolone and diphenhydramine from the referring clinician. This information will be faxed to the referring clinician and mailed to the patient. Stable ER and stable inpatients requiring pre-medication may also undergo the “non-emergent” regimen. The radiology resident or staff radiologist protocoling the study will liaise with the referring physician to determine the most appropriate pre-medication regimen on an individual basis.

Patients requiring pre-medication who are unable to undergo the standard 12 hour oral preparation due to the acuity of their clinical conditions (some ER patients, acutely unwell inpatients) may receive “emergent” pre-medication as outlined above. Again, the radiology resident or staff radiologist protocoling the study will liaise with the referring physician to determine the most appropriate pre-medication regimen on an individual basis.

Please note that corticosteroids may not be appropriate for all patients given established absolute and relative contraindications.

Some patients will require direct supervision of their examinations by the radiology resident or staff radiologist with epinephrine on hand. The specific scenarios are outlined in the pre-medication algorithms.

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CONTRAST REACTION PROPHYLAXIS: PRE-MEDICATION REGIMENS

a) Non-emergent Pre-medication

- Methylprednisolone 32mg PO at 12 hours and 2 hours before contrast injection, plus diphenhydramine (Benadryl[®]) 50 mg PO/IV/IM 1 hour before contrast injection.
- Note: If oral medications cannot be taken, hydrocortisone 200 mg IV may be substituted for oral prednisone and given 4 – 6 hours before contrast injection (17). Diphenhydramine 50 mg IV should also be administered 1 hour before contrast injection.

b) Emergent Pre-medication (In Decreasing Order of Desirability)

- i. Methylprednisolone sodium succinate (Solu-Medrol[®]) 40 mg IV or hydrocortisone sodium succinate (Solu-Cortef[®]) 200 mg IV 4 – 6 hours before contrast injection, plus diphenhydramine 50 mg IV 1 hour before contrast injection.
- ii. Dexamethasone sodium sulfate (Decadron[®]) 7.5 mg IV or betamethasone 6 mg IV 4 – 6 hours before contrast injection if there is a known allergy to methylprednisolone, aspirin, or non-steroidal anti-inflammatory drugs, especially if asthmatic. Diphenhydramine 50 mg IV should also be administered 1 hour before contrast injection.
- iii. If the scan must be performed immediately, give diphenhydramine 50 mg IV. IV steroids have not been shown to be effective when administered less than 4 – 6 hours prior to contrast injection.

Note: Diphenhydramine should not be given to a hypotensive patient.

RISK FOR CONTRAST MEDIA REACTION QUESTIONNAIRE

PATIENT NAME: _____
 DOB (DD/MM/YYYY): _____
 HCN: _____
 ADDRESS: _____
 HOME PHONE: _____

On the CT/MRI requisition that you submitted for the patient above, you indicated the patient has a history of a reaction to a CT/MRI contrast agent. Please complete as much as possible of the questionnaire below so that the examination can be booked.

After reviewing the questionnaire, we will inform your office if your patient requires pre-medication. A letter listing your patient's name and their identifying information, the examination they are scheduled to undergo, and the pharmacologic regimen for pre-medication (if required) will be sent to your office. If your patient requires pre-medication, we would ask that you kindly make arrangements to provide your patient with the required prescriptions.

PATIENT'S RISK FACTORS	YES	NO
Previous allergic-like reaction to iodinated contrast media?	<input type="checkbox"/>	<input type="checkbox"/>
If yes, please indicate :		
a) Year of reaction: _____		
b) Route of administration: _____		
c) Name of contrast agent, if known: _____		
d) Signs and symptoms: _____		
Previous allergic-like reaction to gadolinium-based contrast media?	<input type="checkbox"/>	<input type="checkbox"/>
If yes, please indicate :		
a) Year of reaction: _____		
b) Route of administration: _____		
c) Name of contrast agent, if known: _____		
d) Signs and symptoms: _____		

TABLE 1 - CLASSIFICATION OF ACUTE CONTRAST REACTIONS (REPRODUCED FROM THE ACR MANUAL ON CONTRAST MEDIA)

I. MILD

- Signs and symptoms are self-limited without progression.

<i>a. Allergic-like</i>	<i>b. Physiologic</i>
Limited urticaria / pruritis	Limited nausea / vomiting
Limited cutaneous edema	Transient flushing / warmth / chills
Limited “itchy” / “scratchy” throat	Headache / dizziness / anxiety / altered taste
Nasal congestion	Mild hypertension
Sneezing / conjunctivitis / rhinorrhea	Vasovagal reaction that resolves spontaneously

II. MODERATE

-Signs and symptoms are more pronounced and commonly require medical management. Moderate reactions may become severe if untreated.

<i>a. Allergic-like</i>	<i>b. Physiologic</i>
Diffuse urticaria / pruritis	Protracted nausea / vomiting
Diffuse erythema, stable vital signs	Hypertensive urgency
Facial edema without dyspnea	Isolated chest pain
Throat tightness or hoarseness without dyspnea	Vasovagal reaction that requires and is responsive to treatment
Wheezing / bronchospasm, mild or no hypoxia	

III. SEVERE

-Signs and symptoms are often life-threatening and can result in permanent morbidity or mortality if not managed appropriately.

<i>a. Allergic-like</i>	<i>b. Physiologic</i>
Diffuse edema, or facial edema with dyspnea	Vasovagal reaction resistant to treatment
Diffuse erythema with hypotension	Arrhythmia
Laryngeal edema with stridor and/or hypoxia	Convulsions, seizures
Wheezing / bronchospasm, significant hypoxia	Hypertensive emergency
Anaphylactic shock (hypotension and tachycardia)	

REFERENCE

Committee on Drugs and Contrast Media of the American College of Radiology. Manual on Contrast Media, Version 9.0. Available at http://www.acr.org/~media/ACR/Documents/PDF/QualitySafety/Resources/Contrast%20Manual/2013_Contrast_Media.pdf. Accessed March 14, 2014.