

Adverse Reactions to Contrast Media: Prevention and Treatment

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OVERVIEW

A non-life-threatening, moderate reaction requiring some treatment occurs in 1 to 2% of patients receiving ionic high-osmolar contrast media and in 0.2 to 0.4% of patients receiving non-ionic low-osmolar contrast media. Severe, life-threatening reactions can be expected in about 0.2% of patients after injection of ionic high-osmolar and 0.04% after non-ionic low-osmolar contrast media.

Idiosyncratic (i.e. anaphylaxis-like, anaphylactoid) reactions occur unpredictably and independently of the dose or concentration of the agent. Most anaphylaxis-like reactions relate to release of active mediators. However, these anaphylactoid reactions do not fulfill criteria for a true antigen-IgE antibody mediated reaction nor is there convincing evidence for their being a direct reaction to iodine or iodide. Chemotoxic-type effects relate to dose, the molecular toxicity of each agent and the physico-chemical characteristics of the contrast agents (e.g. osmolality, viscosity).

Reported mortality rates have varied with a commonly quoted rate around 1 in 100,000. No difference between ionic high-osmolar and non-ionic low-osmolar agents has been shown.

Late reactions of a systemic nature to contrast media are much more common than previously appreciated. Late adverse reactions are about 6% for the low-osmolar monomeric contrast media. Most of the reactions are not serious or life-threatening.

RISK FACTORS

Persons with allergic tendencies or history of asthma are at increased risk for an idiosyncratic reaction. In a review of patients with a history of asthma, this relative risk was approximately 5 times greater.

Patients with chronic obstructive pulmonary disease plus pulmonary hypertension may develop increased symptoms and there is reported increased sickling in patients with sickle cell disease. There is debate as to whether persons taking beta-blockers have an increased risk of anaphylactoid reactions.

There seems to be no direct correlation or association between allergy to povidone-iodine skin cleansing solution (Betadine®) and the predisposition to an allergic-like reaction to intravascular contrast media.

Adverse reactions to conventional ionic high-osmolar contrast media in patients who have had a previous reaction to an ionic high-osmolar contrast medium is 3 to 8 times, perhaps even 11 times, greater than the risk for the general population. Administration of lower-osmolality, non-ionic contrast media to such patients reduces the frequency of repeated reactions to about 5%. New reactions are seldom more severe than the previous reaction.

In the kidney, contrast agents are concentrated in the nephrons and collecting tubules. Pre-existing renal impairment (serum creatinine level of $>132 \mu\text{mol/L}$, 1.5 mg/dL) seems to be the most compelling risk factor for nephrotoxicity, followed by factors like dehydration, elevated uric acid level, and multiple contrast studies. Other risk factors include severe congestive heart failure, multiple myeloma and administration of a high dose of contrast. Concomitant use of certain drugs (e.g. aminoglycoside antibiotics, some cancer drugs) may also increase the risk.

A patient with diabetic nephropathy has at least 3 risk factors: reduced renal function, albuminuria and hypertension. In such patients, the incidence of contrast medium nephrotoxicity is between 15 and 25%, but may reach 90% in diabetics with more advanced renal disease. In patients with no history or signs/symptoms of renal disease, the risk of contrast-induced alteration in renal function is below 1%.

The incidence of acute nephrotoxicity in high-risk patients, especially patients with diabetic nephropathy, is significantly less with non-ionic low-osmolar contrast media.

PREVENTION

General:

Patients should be screened for conditions such as renal dysfunction. Alternative diagnostic procedures that do not require contrast media should be considered. One alternative is MR imaging with gadolinium in that systemic reactions to gadolinium are very infrequent and, at the current doses used for MR imaging, gadolinium causes no detectable nephrotoxicity.

Anaphylactoid:

Pretesting (intravascular, cutaneous) of patients to detect those who have an increased likelihood of having an anaphylaxis-like reaction to contrast media has been abandoned because it is insensitive and potentially dangerous.

Patients who have asthma or multiple systemic allergies should receive lower-osmolality, non-ionic contrast media. If a patient had a mild prior reaction to conventional ionic medium, the use of a non-ionic, low-osmolar contrast medium without additional pre-medication is considered sufficient. If a patient had a previous moderate reaction to a conventional, ionic contrast medium, it is recommended that pretreatment be instituted with corticosteroids and antihistamines and that a non-ionic, low-osmolar contrast medium be used. However, for these same patients, some radiologists just give a non-ionic contrast medium without any pretreatment.

If a patient previously had a moderate reaction to a non-ionic, low-osmolar contrast medium, pretreatment regimen with corticosteroids is advised.

By using a corticosteroid (e.g. prednisone) combined with an antihistamine (e.g. diphenhydramine) as pretreatment, the prevalence of repeat reactions is decreased. A further reduction in anaphylactoid reactions is achieved when patients receive the corticosteroid-antihistamine pretreatment regimen and non-ionic, low-osmolality contrast medium is used. An effective pretreatment regimen utilizing only corticosteroids is oral

methylprednisolone 32mg given 12 and 2 hours before the administration of contrast media.

Antihistamines alone (without corticosteroids) have not proved to be effective as a premedication regimen against moderate or severe reactions.

Nephrotoxicity:

The biguanide metformin is used to manage type 2 (non-insulin-dependent) diabetes mellitus. Renal insufficiency with failure to clear metformin leads to the accumulation of metformin and the potential for fatal lactic acidosis. The potential danger of lactic acidosis exists because of accumulated metformin and not from any interaction of contrast media and metformin. In the US, it is now recommended that metformin be stopped at the time of the study with intravascular iodinated contrast media and not be restarted for 48 hours. Normal renal function should be confirmed, e.g. by serum creatinine determination. It is not necessary to stop metformin before a MR exam with gadolinium because of the lack of nephrotoxicity from gadolinium in its usual dose.

Several measures have been recommended to prevent contrast medium-induced nephropathy. Of all these many measures, extracellular volume expansion has repeatedly been shown to be effective and is the most widely recommended. Low-osmolality, nonionic contrast media has been found to be helpful (in addition to hydration) in mitigating contrast nephrotoxicity in diabetics with renal insufficiency, but not in diabetics with normal renal function.

Patients with pre-existing renal failure, independent of cause, should not undergo radiological procedures where contrast medium is administered without being hydrated. A hydration procedure includes administration of 0.1 L/h of 0.9% saline from 4 hours before the contrast medium administration to 24 hours after for patients who are not allowed to take adequate fluids orally.

Concomitant use of nephrotoxic drugs (e.g. gentamicin, NSAIDs) should be avoided. Although the administration of contrast media to myeloma patients is not totally risk-free, it may be performed if the clinical need arises and the patient is well hydrated.

TREATMENT

Most patients with severe anaphylactoid reactions recover if they are aggressively and appropriately treated. Because 94-100% of severe and fatal reactions occur within 20 minutes of the contrast medium injection, most patients have reactions while they are still in the radiology department. Rooms in which contrast material injections are done should have the emergency drugs to treat a reaction located in the room or adjacent to it. In addition, a listing of these drugs and the doses for adults and children should be posted with the medications or in each room.

Basic response includes oxygen, physiological fluids, assurance of an adequate airway, and evaluation of heart rate and blood pressure. Oxygen delivered by mask at relatively high flow rate (10 L/min) is very important in the initial treatment. Hypoxia can be a major complicating factor. A partial 'nonrebreather' mask is optimal; nasal 'prongs' are much less effective. Oxygen should be used for all patients; a history of chronic obstructive pulmonary disease or emphysema is not a contraindication to the initiation of oxygen therapy for an acute reaction.

Intravascular fluid replacement is very important and it alone has been reported to be one of the most effective treatments for hypotension.

Epinephrine is an excellent, if not the best, drug for treating certain serious contrast reactions. The alpha-agonist effects of epinephrine reverse peripheral vasodilation, increase blood pressure, and decrease angioedema and urticaria. Beta-agonist actions of epinephrine reverse bronchoconstriction, produce positive inotropic and chronotropic cardiac effects, and may inhibit mediator release from inflammatory cells. Epinephrine use demands careful attention and specific application.

Antihistamines and H₂ antagonists have limited therapeutic roles in treating contrast media reactions. They are used primarily to reduce symptoms from skin reactions. High dose intravenous corticosteroids do not play a significant role in the treatment of the acute situation; they may be effective in reducing delayed recurrent symptoms. Inhaled beta₂-adrenergic agonists deliver large doses of bronchodilating beta₂-agonist drugs directly to the airways with minimal systemic absorption.

Atropine blocks vagal stimulation of the cardiac conduction system. Since low doses of atropine can be detrimental in treating bradycardia associated with contrast media-induced vagal reactions, larger doses are indicated. Our recommended initial dose is 0.6-1.0 mg IV.

TREATMENT FOR SPECIFIC REACTIONS (see Table for specific drug doses)

Nausea and Vomiting:

Though usually self-limiting, may be the first signs of a more severe reaction. For this reason, the patient should be observed closely.

Cutaneous Reactions:

Treatment is usually not necessary for only a few scattered hives or pruritus. If the urticaria is extensive or bothersome to the patient, treatment with antihistamines can be helpful.

Bronchospasm:

Bronchospasm without coexisting cardiovascular problems should be treated with oxygen and inhaled bronchodilators (β₂-agonist metered dose inhaler). Epinephrine is indicated if bronchospasm is unrelieved by the inhaled bronchodilators. Conversely, diphenhydramine (Benadryl®) may thicken bronchial secretions and/or cause hypotension either of which can make the situation worse.

Laryngeal Edema:

Epinephrine is the primary treatment for laryngeal edema. Laryngeal edema does not respond well to inhaled β-agonists and, in fact, these agents may actually worsen laryngeal edema.

Hypotension:

Normal sinus rhythm and tachycardia identify isolated hypotension and differentiate it from the so-called vagal reaction (hypotension plus sinus bradycardia). The patient's legs should be elevated. Oxygen should be started. Isolated hypotension is best treated initially by rapid intravenous fluid replacement. The vasopressor epinephrine can be administered for hypotension unresponsive to fluid therapy.

Vagal Reaction:

A vagal reaction is characterised by the combination of prominent sinus bradycardia plus hypotension. Proper recognition of this reaction and its bradycardia is vital to initiating appropriate therapy. Treatment includes elevation of the patient's legs, oxygen, rapid infusion of intravenous fluids and intravenous administration of atropine (0.6-1.0 mg) to block the vagal stimulation of the cardiac conduction system. Atropine is indicated when bradycardia is symptomatic.

Anaphylactoid Reactions:

These reactions are acute, rapidly progressing, generalized systemic reactions characterised by multisystem involvement. Initial treatment includes maintenance of airway, administration of oxygen, rapid infusion of intravenous fluids, and administration of epinephrine. A low dose [1.0ml (0.1 mg) of 1:10,000 solution] is given at a relatively slow rate (over 2 to 5 minutes) and is titrated to effect.

If there is no venous access, give epinephrine initially as a subcutaneous injection, using a larger dose, e.g. 0.3mg and then try to establish venous access. In an emergency, epinephrine can be administered via the airway (inhaled, transtracheal, endotracheal).

Because venous access in infants and children is often difficult or tenuous, subcutaneous administration of 1:1000 epinephrine is recommended (body weight determines the correct dose).

Contrast-induced Nephropathy

The finding of increased serum creatinine levels and/or lack of urinary output within the first days following contrast medium administration indicates contrast medium-induced nephrotoxicity. Also, retained renal contrast, as evidenced by unexpectedly dense kidney(s) on plain film or CT, may indicate contrast-induced nephropathy. There is no specific treatment.

EXTRAVASATION

Extravasation occurs more frequently with power injection of high flow rates for CT. Risk factors include fragile veins, IV catheters that have been indwelling for many days, and multiple punctures during IV placement. Extravasation of nonionic, low-osmolality contrast is much better tolerated than extravasation of conventional ionic contrast media.

Evaluate for signs of skin injury (blanching, discoloration) and for nerve or vascular compromise. If the patient is asymptomatic, treatment is elevation, cool

compresses, and observation. If skin or neurovascular compromise is evident, elevation and cool packs plus consultation with plastic surgery is advised.

Follow-up contact with the patient during the next 24 hours is recommended.

REFERENCES

Much of this material is extracted from: Thomsen HS and Bush WH: Adverse effects of contrast media: Incidence, Prevention, and Management. Drug Safety 1998; 19:313-324. (With permission)

ACR Manual on Contrast Media (4th Edition) Segal AJ, Editor. American College of Radiology, Reston, VA, 1998.

Bush WH, Krecke KN, King BF, Bettmann MA: Radiology Life Support (RAD-LS): A Practical Approach. London/New York, Arnold/Oxford University Press, 1999, 146 pp.*

*A quiz set of questions and answers about contrast media physiology and treatment of reactions is the Arnold website. <http://www.arnoldpublishers.com/rad-ls/>

Treatment Table**

ACUTE REACTIONS TO CONTRAST MEDIA: TREATMENT OUTLINE

URTICARIA:

Mild urticaria and pruritis: observation

H-1 antihistamine (e.g. diphenhydramine, 25-50 mg PO/IM/IV)

Severe urticaria: add :

IV fluids (normal saline, lactated Ringer's)

Epinephrine (1:10,000): 1 ml (0.1 mg), IV slowly (e.g., over 2-5 min.)...or...epinephrine (1:1000), 0.1-0.2 ml (0.1-0.3 mg), subcutaneously

H-2 antihistamine

(e.g. cimetidine injectable, 300 mg, diluted to 20 ml, slowly IV)

(pediatric: 5-10 mg/kg, diluted to 20 ml, slow IV)

...or...

(e.g. ranitidine injectable, 50 mg, diluted to 20 ml, IV slowly)
(pediatric: use not established)

BRONCHOSPASM (isolated):

Oxygen by mask (10 L/min)

Beta-2-agonist metered dose inhaler (2-3 deep inhalations):

(e.g. metaproterenol, terbutaline, or albuterol)

[or use nebulizer if available: albuterol 0.5% solution, 0.5 ml in 3 ml of normal saline, breathe through nebulizer tube for 8-10 min.)]

Epinephrine:

Normal blood pressure, stable bronchospasm:

Subcutaneous: 1:1000, 0.1-0.2 ml (0.1-0.2 mg); may give 0.3 mg

[pediatric: 0.01 mg/kg up to 0.3 mg max. (e.g. .01-0.2 mg subcutan.)]

Progressive bronchospasm or decreased blood pressure:

IV: 1:10,000, 1 ml (0.1 mg), slowly (e.g., over 2-5 min.)
(pediatric: 0.01 mg/kg, IV)

**From: Bush W.H. Treatment of Acute Contrast Reactions. In: Bush WH, Krecke KN, King BF, Bettmann MA (Eds). Radiology Life Support (Rad-LS). London/New York, Arnold/Oxford University Press, 1999, pp. 31-51.

HYPOTENSION (isolated):

Elevate patient's legs

Oxygen by mask (10 L/min)

IV fluids (primary therapy): rapidly, normal saline or lactated Ringer's solution

If hypotension unresponsive: vasopressor, e.g., epinephrine or dopamine, get appropriate assistance (e.g. call CODE)

Epinephrine: IV injection, 1:10,000 dilution, 1 ml (0.1 mg), slowly over 2-5 min.

IV solution, 1 mg in 250 ml D5W, start at 4 microgm/min (1 ml/min)

VAGAL REACTION (hypotension and bradycardia):

Elevate patient's legs

Oxygen by mask (10 L/min)

IV fluids: rapidly, normal saline or lactated Ringer's Solution

Atropine: 0.6-1.0 mg IV, repeat q 3-5 min. as needed to 3 mg total (adults)

[pediatric: 0.02 mg/kg IV; starting dose: min. 0.1 mg, max. 0.6 mg dose; may repeat to 2 mg total dose]

ANAPHYLACTOID REACTION (generalized systemic reaction):

Suction, as needed

Elevate patient's legs if hypotensive

Oxygen by mask (10 L/min)

IV fluids: normal saline or Ringer's Solution

Epinephrine:

(a generalized reaction usually has hypotension or incipient hypotension as a significant component, therefore, IV route for administration is advised)

IV: 1:10,000, 1 ml (0.1 mg), slowly (e.g., incrementally over 2-5 minutes)

(pediatric: 0.01 mg/kg, IV, to 0.1 mg dose)

* Limit amount of epinephrine in patients taking noncardioselective beta-adrenergic blocking drugs.

Alternate drug therapy for severe reaction in patient taking beta-adrenergic blocking medication:

Isoproterenol, 1:5000 solution for injection (0.2 mg/ml), IV, 0.5-1.0 ml diluted to 10 ml with normal saline; 1 ml (20 microgm) increments

(note: may cause hypotension or arrhythmias)

Glucagon, 1 to 5 mg IV bolus, followed by IV infusion of 5-15 microgm/min. (note: may cause hypotension)

Antihistamines:

H-1 blocker:

(e.g. diphenhydramine 25-50 mg), IV (Caution: may exacerbate or cause hypotension; may thicken bronchial secretions)

H-2 blocker:

(e.g. cimetidine injectable 300 mg, diluted to 20 ml, slowly IV)

(pediatric: 5-10 mg/kg, diluted, slowly)

...or...

(e.g. ranitidine injectable 50 mg, diluted to 20 ml, slowly IV)
(pediatric: use not established)

Beta-2-agonist metered dose inhaler (MDI)[for persistent bronchospasm]:
(2 or 3 inhalations)

(e.g. metaproterenol, terbutaline, or albuterol)

[or use nebulizer if available: albuterol 0.5% solution, 0.5 ml in 3 ml of normal saline, breathe through nebulizer tube for 8-10 min.]

Corticosteroids:

hydrocortisone 200 mg IV; methylprednisolone 80 mg IV

ANGINA:

Oxygen by mask (10 L/min.)

IV fluids: very slowly

Nitroglycerin: 0.4 mg, sublingually, may repeat q 15 min.

Morphine: 2 mg, IV

HYPERTENSION:

Oxygen: (10 L/min)

IV fluids: very slowly; primarily to maintain IV access

Nitroglycerin :

orally, 0.4 mg tablet, sublingual

topically, 2% ointment: apply 1-2 inch strip to skin

If secondary to autonomic dysreflexia:

nifedipine 10 mg capsule, punctured or chewed and the contents swallowed

[NB: Nifedipine sublingually, because of its very poor sublingual absorption and reported serious adverse effects, is no longer recommended as the first line drug for treatment of all hypertensive crises]

If secondary to pheochromocytoma: phentolamine 5 mg, IV slowly

SEIZURES:

Protect the patient

Airway: suction as needed; monitor airway for obstruction by tongue

Oxygen by mask (10 L/min.)

If caused by hypotension +/- bradycardia, treat per protocols.

Uncontrolled: consider diazepam, 5 mg, IV

HYPOGLYCEMIA:

Oxygen by mask (10 L/min.)

IV fluids: D₅W

IV glucose: Dextrose 50% solution, IV push

Oral glucose: e.g. glass of orange juice plus sugar or glass of milk