

Adverse Reactions to Contrast Material: Recognition, Prevention, and Treatment

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Adverse reactions to contrast agents range from a mild inconvenience, such as itching associated with hives, to a life-threatening emergency. Renal toxicity is a well known adverse reaction associated with the use of intravenous contrast material. Other forms of adverse reactions include delayed allergic reactions, anaphylactic reactions, and local tissue damage. Previous allergic reactions to contrast material, asthma, and allergies are factors associated with an increased risk of developing an adverse reaction. Pretreatment of patients who have such risk factors with a corticosteroid and diphenhydramine decreases the chance of allergic reactions, including anaphylaxis, renal failure, or a possible life-threatening emergency. Awareness of the different types of risk factors and prescreening for their presence allows for early recognition and prompt treatment. Prophylactic treatment before administration of contrast material can prevent potential adverse reactions. If such reactions do occur, prompt recognition allows them to be treated immediately. Using the smallest amount of contrast material possible and low-molecular, nonionic agents also decreases the relative risk of reactions. Renal insufficiency induced by contrast material may be prevented by ensuring adequate hydration and discontinuing other nephrotoxic medications before the procedure. Low-osmolar, nonionic agents are helpful in patients with known conditions associated with adverse reactions. (*Am Fam Physician* 2002;66:1229-34. Copyright© 2002 American Academy of Family Physicians.)

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The osmolality of a particular contrast agent is determined by the number of osmotically active particles formed when it is dissolved in solution. Ionic agents dissociate into ions when dissolved in water and contain an iodinated benzene ring. As a result, ionic agents have a higher osmolality than blood. Nonionic agents do not dissociate into separate particles when dissolved in water; their osmolality is therefore one half that of ionic agents. Contrast agents are categorized according to their chemical structure and relative osmolality. *Table 1* lists types of contrast agents.

Contrast agents with higher osmolality are more likely to cause adverse reactions of all kinds. Renal toxicity has long been associated with exposure to high-osmolality

agents.¹ Low-osmolality agents are associated with less discomfort, and fewer cardiovascular and anaphylactic-type reactions. However, these agents have a significantly higher cost, which prevents them from being used exclusively.

TABLE 1
Types of Contrast Agents

Type	Agents
High osmolality	
Ionic	Diatrizoate sodium (Hypaque) Iothalamate meglumine (Conray)
Low osmolality	
Ionic	Ioxaglate meglumine (Hexabrix)
Nonionic	Gadodiamide (Omniscan) Gadoteridol (ProHance) Iodixanol (Visipaque) Iopamidol (Isovue) Iopromide (Ultravist) Ioversol (Optiray)

See page 1128 for definitions of strength-of-evidence levels contained in this article.

Contrast agents with higher osmolality are more likely than those with lower osmolality to cause adverse reactions of all types.

Types of Adverse Reactions

ANAPHYLACTIC

Anaphylactic reactions are serious, potentially life-threatening reactions associated with the administration of contrast material. Acute bronchospasm, profound hypotension, and severe urticaria may occur within minutes of administration of as little as 1 mL of contrast material. These reactions are not “true” allergic reactions, because they can occur in patients who have not been exposed to contrast material previously. IgE antibodies, which are associated with allergic reactions, have not been demonstrated in most patients with anaphylactoid reactions.² The etiology of these anaphylactic reactions is unclear.

DOSE DEPENDENT

Dose-dependent, systemic adverse reactions to contrast material include nausea and vomiting, a metallic taste in the mouth, and generalized warmth or flushing. These reactions are usually nonlife-threatening, self-limited problems.

Renal failure is another form of adverse reaction that is dependent on the dose of contrast material used. Intravenous administration of contrast material is responsible for 12 percent of cases of hospital-acquired renal failure.³ Renal failure following administration of contrast material occurs in 0.1 to 13 percent of patients who receive contrast material.⁴ This range results from the lack of a set definition for contrast-induced nephrotoxicity. A generally accepted definition is the elevation of serum creatinine to greater than 25 percent of baseline within three days of receiving contrast material. Proteinuria is often found on routine urinalysis but is not

required for the diagnosis of contrast-induced nephropathy.

Patients with preexisting renal insufficiency and diabetes are at greatest risk of developing permanent renal failure following administration of contrast material. Patients with multiple myeloma are also at increased risk of developing renal failure, especially if they are dehydrated. The risk of renal failure in patients with myeloma is caused by an interaction of light chains and contrast material. How contrast materials cause renal failure is unclear, but direct cellular toxicity and intrarenal vasoconstriction are believed to be the primary causes of renal function changes.^{4,5}

DELAYED REACTIONS

Adverse reactions that occur 30 minutes or more after the administration of contrast material are considered delayed reactions. Delayed reactions are more common with the use of ionic agents.⁶ Up to 30 percent of patients receiving ionic contrast materials develop delayed reactions. Administration of nonionic agents is associated with delayed reactions in only 10 percent of patients. The symptoms of delayed reactions resemble a flu-like syndrome and include fever, chills, nausea, vomiting, abdominal pain, fatigue, and congestion.

EXTRAVASATION OF CONTRAST MATERIAL

Tissue damage from extravasation of contrast material is caused by the direct toxic effect of the agent. Compartment syndrome may occur if enough contrast material leaks into surrounding tissue.

Patients at Risk

A patient who has renal insufficiency before the administration of contrast material is five to 10 times more likely to develop contrast-induced renal failure than patients in the general population.^{6,7} Patients with a history of anaphylactic reaction to contrast material are more likely to have a similar reaction if they are again exposed to contrast material,

TABLE 2
Conditions Associated with Adverse Reactions to Contrast Material*

- Preexisting renal insufficiency
- Previous anaphylactoid reaction to contrast material
- Asthma
- Food or medication allergies, or hayfever
- Multiple medical problems or an underlying disease (e.g., cardiac disease, preexisting azotemia)
- Treatment with nephrotoxic agents (e.g., aminoglycosides, nonsteroidal anti-inflammatory agents)
- Advanced age

*—Patients with any of these conditions are candidates for low-osmolar, nonionic contrast agents, according to the American College of Radiology Guidelines.

Information from *Manual on contrast media. Ed 4.1, 1998. Reston, Va.: American College of Radiology, 2001.*

but even these patients may not experience repeat reactions on reexposure.

Patients with a history of asthma have double the risk of developing adverse reactions compared to the general population, even if the patient's asthma is under control.⁶ Patients with multiple food or medication allergies and those with multiple medical problems (e.g., cardiac disease, preexisting azotemia) are more likely to develop complications when exposed to contrast agents.⁸

No substantive data support the myth that patients with seafood allergy are at higher risk of developing allergic reactions to contrast media. Patients treated with nephrotoxic medications (e.g., aminoglycosides and nonsteroidal anti-inflammatory agents) are at greater risk of developing renal failure. Advanced age is also considered a risk factor for developing renal insufficiency. Metformin (Glucophage), an oral agent used in the treatment of diabetes, has been associated with the development of severe lactic acidosis following administration of intravenous contrast media.⁹

Many experts recommend stopping metformin therapy at the time of the procedure, or before, and for at least 48 hours following the administration of contrast material. The medication should be resumed only after the patient's renal function has returned to baseline (as determined by the serum creatinine level).

Contrast material should not be administered to pregnant women. Alternative forms of visualization are recommended for these patients.

The extent to which mutagenesis of fetal tissue is associated with the use of contrast material is not known. Inhibition of fetal thyroid tissue has occurred after the use of contrast material before delivery.⁶ Table 2 lists conditions associated with adverse reactions to contrast material.

Avoiding Problems

GENERAL PRINCIPLES

Adverse reactions can be reduced if general principles are applied to all patients. The smallest amount of contrast agent possible should be used for each procedure. Allowing at least 48 hours to elapse between procedures in which contrast material is used enables the kidneys to recover.⁶ Table 3 outlines methods of preventing contrast-induced renal insufficiency.

TABLE 3
Methods of Preventing Contrast Material-Induced Renal Insufficiency

General principles	Use the smallest amount of contrast material possible. Discontinue other nephrotoxic medications before the procedure. Allow two to five days between procedures requiring contrast material.
Hydration	Oral: 500 mL before the procedure and 2,500 mL over the 24 hours after the procedure Intravenous: 0.9% or 0.45% saline, 100 mL per hour beginning four hours before the procedure and continuing for the 24 hours after the procedure
Calcium channel blockers	Nitrendipine (Baypress), 20 mg orally daily for three days beginning 24 hours before the procedure

A patient who has renal insufficiency before the administration of contrast material has a five to 10 times greater risk of developing renal failure than persons in the general population.

HYDRATION

It has been well documented that hydration minimizes, or decreases, the incidence of renal failure induced by contrast material. Unless contraindicated, infusion of 0.45 or 0.9 percent saline at a rate of 100 mL per hour beginning four hours before the procedure and continuing for 24 hours after the procedure, is recommended.^{10,11}

In patients able to take oral fluids, hydration can be achieved through ingestion of 500 mL of fluid before the procedure followed by 2,500 mL over the 24 hours after the procedure. There have been no prospective studies comparing different fluids for hydration.

CORTICOSTEROIDS

Nonrenal reactions to contrast material can be reduced by premedicating the patient with corticosteroids.^{12,13} [Reference 12—Evidence level A, randomized controlled trial (RCT); Reference 13—Evidence level B, uncontrolled study] This protective effect functions for ionic and nonionic contrast materials. Many physicians give corticosteroids only to patients

known to have a previous history of idiosyncratic adverse reactions.⁶

Combining corticosteroid use with a histamine H₁-receptor blocker further reduces the chance that adverse reactions will develop. Adverse reactions decreased from a range of 17 to 35 percent to a range of 5 to 10 percent when corticosteroids were combined with an H₁ blocker (diphenhydramine).^{14,15} [References 14 and 15—Evidence level B, uncontrolled study]

The following premedication protocol has been recommended for use in patients with a history of idiosyncratic reactions: methylprednisolone (one 32-mg tablet at 12 hours and two hours before the study) or prednisone (one 50-mg tablet at 13 hours, seven hours, and one hour before the study).⁶ If the previous reaction was moderate or severe or included a respiratory component, the physician can add the following: an H₁ blocker such as diphenhydramine (one 50-mg tablet one hour before the study) and an H₂ blocker (optional) such as cimetidine (Tagamet), one 300-mg tablet one hour before the study, or ranitidine (Zantac), one 50-mg tablet one hour before the study. Using an H₂ blocker without also using an H₁ blocker is not recommended.

OTHER DRUGS

Mannitol. Mannitol (Resectisol) has been used in an attempt to increase or maintain the glomerular filtration rate (GFR) during radiographic studies using contrast media. Very little supporting evidence shows that mannitol maintains GFR during hypoperfusion. A study that compared hydration with saline alone versus saline plus mannitol showed that saline alone was more protective.⁵

Furosemide. Furosemide (Lasix) has not been shown to prevent contrast-induced renal failure. A significant decline in renal function occurred in patients treated with furosemide before contrast administration.¹⁶ Negative fluid balance caused a decrease in renal cortical and medullary blood flow, leading to hypoxia.

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Calcium Channel Blockers. Oral administration of calcium channel blockers was shown to minimize reduction of GFR. In a prospective study,¹⁷ patients were treated with 20 mg per day of nitrendipine for three doses starting 24 hours before the procedure. Some sparing of GFR was noted in these patients compared with patients who did not receive calcium channel blockers.¹⁷

Treating Problems

DOSE-DEPENDENT SYSTEMIC REACTIONS

Nausea and vomiting, a metallic taste in the mouth, and generalized warmth or flushing that are associated with contrast material injection are usually nonlife-threatening, self-limited problems. Slow intravenous injection (over two minutes rather than over 10 seconds) decreases the incidence of headache and metallic taste. The rate of infusion, rapid or slow, does not make a difference in the development of nausea or vomiting.¹⁸ General supportive care of the patient usually suffices in the management of these reactions.

RENAL FAILURE

Monitoring patients for the development of renal failure after the administration of contrast material requires observation of the patient's renal function for at least three days. A rising serum creatinine level is usually the first sign of an impending change in renal function, but elevation of the serum creatinine level may not occur for 72 hours. However, the serum creatinine level often rises within the first 24 hours and peaks in three to five days. The patient's creatinine level usually returns to baseline by seven to 10 days after the procedure.

Electrolytes should be checked daily to ensure that hyperkalemia is not occurring. The patient's intake and output should be measured as a gross indication of renal function. Most cases of contrast-induced renal failure resolve with supportive measures such as adequate hydration and adjustment of electrolyte abnormalities. The above measures are

usually adequate for renal support; rarely is dialysis or transplantation required.

ANAPHYLACTIC REACTIONS

The principles of advanced cardiac life support should be followed in the treatment of anaphylactic reactions to contrast material. Stabilization of the patient's airway, cardiac function, and blood pressure is the fundamental element of treating anaphylactic reactions. In patients who develop bronchospasm, laryngeal edema, or severe urticaria or angioedema, epinephrine should be administered immediately (0.3 to 0.5 mg subcutaneously every 10 to 20 minutes). Patients with bronchospasm should be given 50 mg of hydrocortisone or 50 mg of methylprednisolone.

Radiology personnel who have direct contact with patients should be familiar with and certified in providing emergency care. Radiology departments must be equipped and their personnel trained to respond to life-threatening reactions at any time.

DELAYED REACTIONS

Symptoms of delayed reactions (nausea, vomiting, abdominal pain, fluid overload, and fatigue) usually resolve spontaneously and require only supportive management.

EXTRAVASATION

Application of ice packs and heating pads, and elevation are used to alleviate the symptoms associated with extravasation of contrast material. Tissue damage is more likely to occur with extravasation of ionic contrast material than with nonionic contrast agents.

Choosing a Contrast Agent

Some physicians suggest that nonionic, low-osmolality agents be used universally because fewer adverse reactions are associated with them. Unfortunately, the higher cost of nonionic agents prohibits their widespread use. Nonionic contrast agents cost up to 10 times more than high-osmolality ionic agents. Guidelines have been developed by the Amer-

Nonionic contrast agents should be considered for use in patients with previous contrast reactions, renal insufficiency, asthma, multiple allergies, and diseases that could be aggravated by contrast materials.

ican College of Radiology for the use of low-osmolality, nonionic agents.¹⁹ According to these guidelines, nonionic agents should be used in patients who are at increased risk of adverse reactions. This group includes patients who had previous contrast reactions, or who have asthma, multiple allergies, or diseases that could be aggravated by contrast materials (Table 2). Low-osmolar, nonionic agents should be used in patients known to have renal insufficiency. In addition, when a complete history is difficult to obtain and in patients who are concerned about the use of contrast material or are at risk for aspiration, low-osmolality agents should be considered.¹⁹ [Evidence level C, consensus and expert guidelines]

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