KIMMIE L. BUI, MD
Department of Diagnostic Radiology, Cleveland Clinic

JOSEPH D. HORNER, DO
Department of Diagnostic Radiology, Cleveland Clinic

BRIAN R. HERTS, MD
Associate professor of radiology, Cleveland Clinic Lerner College of Medicine; section head, Abdominal Imaging, Department of Diagnostic Radiology, Cleveland Clinic

DAVID M. EINSTEIN, MD
Program director, Radiology Residency Program, Department of Diagnostic Radiology, Cleveland Clinic

Intravenous iodinated contrast agents: Risks and problematic situations

ABSTRACT

Many of today's diagnostic imaging studies use intravenous contrast media to adequately evaluate disease processes. Although these agents are generally safe, their use poses some risks and, in some situations, is problematic. The risks include contrast-induced nephropathy.

KEY POINTS

The most important risk factor for anaphylactoid reactions is a previous reaction, but it is not an absolute indicator. Severe reactions can occur with any type of iodinated contrast agent and without any specific risk factor. Doses of corticosteroids and antihistamines before the imaging study decrease the frequency of repeat contrast reactions, but do not eliminate them.

The highest risk of contrast-induced nephropathy is in patients with renal insufficiency and diabetes. Hydration is the most important preventive measure.

In view of an increased risk of lactic acidosis, patients should not take metformin (Glucophage) for 48 hours after a contrast-enhanced study.

In pregnant patients, alternative imaging studies should be considered before exposing the mother and fetus to iodinated contrast and ionizing radiation.

Breastfeeding can be continued safely after the mother has received intravenous iodinated contrast.

A 56-YEAR-OLD MAN who was recently diagnosed with laryngeal carcinoma needs a contrast-enhanced computed tomographic (CT) scan of the neck to assess the extent and stage of the tumor. The patient is diabetic and currently takes metformin (Glucophage). How should the referring physician instruct the patient with regard to obtaining the CT scan?

CONTRAST IS GENERALLY SAFE, BUT DOES POSE RISKS

Intravenous iodinated contrast has become an integral part of many diagnostic imaging studies. In most cases, its use is straightforward and free of problems, and it has a good safety record. Nevertheless, it does pose some risks, including contrast-induced nephropathy and adverse reactions. In addition, its use is problematic in some situations, such as in pregnant or breastfeeding patients or, as in the situation described above, patients taking metformin.

INDICATIONS FOR INTRAVENOUS CONTRAST

Intravenous contrast makes vessels, highly vascular organs, and other structures more conspicuous on radiographic studies. It has many indications, including intravascular disease, primary neoplasms, metastatic disease, infection, inflammation, and urinary tract disease (except for nephrolithiasis). It aids in the general evaluation of most soft-tissue structures, abscesses, and lymphadenopathy.

TYPES OF IODINATED CONTRAST MEDIA

Iodinated contrast media are categorized according to their osmolality and whether they are ionic.

- **High-osmolar contrast media** are approximately 2,000 mOsm/kg H_2O; all of the available high-osmolar media are ionic.
- **Low-osmolar contrast media** are 600 to 800 mOsm/kg H_2O; some are ionic and some are nonionic.
- **Iso-osmolar contrast** is 290 mOsm/kg H_2O; only one product is available, and it is nonionic.

In patients with underlying renal insufficiency, low-osmolar contrast media are less nephrotoxic than high-osmolar ionic contrast media, although they have no significant renal benefit in patients with normal renal function. In addition, nonionic low-osmolar agents have a lower rate of adverse reactions than high-osmolar ionic contrast media and cause less patient discomfort during intravenous injection. For these reasons, we routinely use low-osmolar nonionic contrast at our institution.

ADVERSE CONTRAST REACTIONS

Adverse reactions are classified as either idiosyncratic (anaphylactoid) or nonidiosyncratic.

Idiosyncratic reactions resemble allergic or hypersensitivity reactions, but are not mediated by immunoglobulin E. Unpredictable and independent of dose, they usually occur within the first 20 minutes after contrast injection. They are categorized as mild, moderate, or severe.

- Mild reactions are relatively common and self-limited. They include mild urticaria, rhinorrhea, and dizziness.
- Moderate reactions are not immediately life-threatening but may progress to more serious, life-threatening situations, and they usually require treatment. They include symptomatic or diffuse urticaria, mild bronchospasm, facial edema, and mild laryngeal edema.
- Severe reactions are potentially life-threatening. They include hypotension, arrhythmias, moderate or severe bronchospasm, moderate or severe laryngeal edema, pulmonary edema, and respiratory arrest.

Nonidiosyncratic reactions reflect the physiologic effects of contrast media and direct organ toxicity. Predictable and dose-dependent, they include sensations of warmth, metallic taste in the mouth, bradycardia, vasovagal reactions, and neuropathy.

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Risk factors for contrast reactions

No accurate method exists for predicting contrast reactions. However, some risk factors have been identified.

A previous reaction to contrast is the most important risk factor. The incidence of recurrent reactions is estimated to range from 8% to 25%.

A strong history of allergic tendencies or multiple allergies predisposes patients to developing anaphylactoid reactions (urticaria). Active asthma increases the frequency of bronchospasm following contrast administration. Vasovagal reactions are relatively common and in part related to anxiety. An allergy to shellfish was previously thought to be a risk factor, but this is not proven and is now thought to be unreliable.

Of note, severe or life-threatening reactions are rare, but can occur without any specific risk factor and with any type of contrast agent.

PREMEDICATION REDUCES RISK OF RECURRENT ANAPHYLAXIS

Giving corticosteroids and antihistamines before the imaging study (premedication) is generally recommended for patients who have a history of a previous anaphylactoid reaction to contrast media, multiple allergies, or asthma (frequent or severe attacks, or recently symptomatic). Premedication decreases the frequency of contrast reactions by a factor of 10 in some studies, but no regimen completely prevents recurrent reactions.

There are many regimens, but none has been found to be superior. In general, a corticosteroid should be started at least 6 hours before the scan to give it time to take effect. At our institution, we give prednisone 50 mg by mouth 13 hours before the scan, and another 50 mg of oral prednisone and 50 mg of oral diphenhydramine (Benadryl) 1 hour before the scan. Outpatients are required to have a designated driver, owing to the sedating effect of diphenhydramine.

In patients with a history of a severe reaction, an unenhanced CT scan or alternate

studies that do not require iodinated contrast should be considered, such as magnetic resonance imaging, nuclear medicine, or ultrasonography.

CONTRAST-INDUCED NEPHROPATHY: LOW RISK IF RENAL FUNCTION IS NORMAL

Contrast-induced nephropathy has been estimated to occur in 2% to 7% of all patients who have a CT scan with contrast. The estimates vary depending on the definition used (there is no standard definition).

The pathogenesis of contrast-induced nephropathy is not completely understood. Some etiologic factors that have been suggested include renal hemodynamic changes and direct tubular toxicity by the contrast material. Generally, the serum creatinine concentration begins to rise within the first 24 hours, reaches a peak by 3 to 7 days, and returns to baseline within 1 to 2 weeks. In rare cases, patients need temporary or permanent dialysis.

Risk factors for contrast-induced nephropathy are many. The more important ones include:

- Preexisting renal insufficiency (particularly if the serum creatinine concentration is ≥ 1.5 mg/dL)
- Diabetes mellitus with renal insufficiency (which poses the highest risk)
- Dehydration (particularly in patients with multiple myeloma)
- Concurrent use of nephrotoxic drugs
- High dose of contrast
- Age greater than 70 years
- Cardiovascular disease.

Patients with normal renal function are at very low risk for contrast-induced nephropathy.

At our institution, based on the guidelines established by the American College of Radiology, all patients 70 years of age and older who are undergoing a contrast study must have had a serum creatinine measurement within the previous 6 months. A new baseline serum creatinine measurement should also be considered in any patient with factors predisposing to renal insufficiency, such as a history of renal tumor, a kidney transplant, a family history of kidney failure, diabetes, multiple myeloma, collagen vascular disease, nephrotoxic medications (nonsteroidal anti-inflammatory drugs, chemotherapy, aminoglycosides), or metformin.

RECOMMENDATIONS FOR PREVENTING CONTRAST-INDUCED NEPHROPATHY

Adequate hydration is the most important method for preventing contrast-induced nephropathy. As with premedication regimens, there is no standard for hydration.

One protocol for patients at high risk who can tolerate oral hydration is to have them drink 500 mL (17 oz) of fluid before the study and 2,500 mL (85 oz) over the next 24 hours.

If the patient cannot drink enough fluid, then intravenous hydration is recommended. There are several recommended regimens; our protocol for inpatients with renal insufficiency is to give normal saline at 1 mL/kg/hour for 12 hours before and 12 hours after the scan. For outpatients with only mild renal insufficiency or mild risk factors for contrast-induced nephropathy, 3 hours of intravenous hydration prior to the study is used, for practical purposes.

Of note, these protocols are not applicable to patients with congestive heart failure, owing to the risk of volume overload.

Hydration is the most important method for preventing contrast-induced nephropathy

N-acetylcysteine (Mucomyst), an antioxidant, can also be considered for patients at high risk (especially those with diabetes and renal insufficiency). *N*-acetylcysteine can be given orally, 600 mg twice daily the day before and on the day of the contrast study. Alternatively, it can be given intravenously (150 mg/kg over 30 minutes just before the study, followed by 50 mg/kg for 4 hours after the study). The effectiveness of *N*-acetylcysteine in the prevention of contrast-induced nephropathy is controversial.

Waiting at least 72 hours between contrast studies, if possible, also reduces the risk of contrast-induced nephropathy.

Iso-osmolar contrast. Recent studies have demonstrated that at doses typically used for a CT scan, iso-osmolar contrast (iodixanol; Visipaque) is less nephrotoxic than low-osmolar contrast in patients at high risk for contrast-induced nephropathy (ie, those with renal insufficiency who are diabetic).

We use iso-osmolar contrast in a lower dose with vigorous hydration when patients have a serum creatinine concentration in the range of 1.8 to 2.5 mg/dL. If the serum creatinine concentration is higher than 2.5 mg/dL, we do not use intravenous contrast except in rare circumstances. Instead, we consider using an alternative study such as nonenhanced CT scanning, magnetic resonance imaging, nuclear scintigraphy, or ultrasonography.

CAN DIALYSIS WAIT?

Contrast agents are cleared by dialysis. Some controversy exists as to whether dialysis patients need to undergo dialysis within 48 hours after the contrast study or if they can wait for their next dialysis session, which could be up to 72 hours later. The primary concerns about waiting for dialysis are the osmotic load of the contrast material and the theoretical direct toxicity on the heart and the blood-brain barrier. If patients have preexisting renal insufficiency that requires temporary or intermittent dialysis, then these patients are at risk for contrast-induced permanent renal damage, and alternative studies should be considered.

Check renal function before restarting metformin

HOLD METFORMIN TO REDUCE RISK OF LACTIC ACIDOSIS

Metformin is an oral antihyperglycemic agent used to treat patients with type 2 diabetes mellitus. It is excreted unchanged by the kidneys, with approximately 90% of the absorbed drug eliminated within the first 24 hours. Furthermore, it increases the intestinal production of lactic acid. Therefore, any factor such as renal insufficiency that decreases metformin excretion thus increases serum lactate levels and increases the risk of lactic acidosis.

Contrast material is nephrotoxic and, in patients with renal insufficiency, can lead to metformin accumulation, resulting in lactic acidosis. The risk of contrast-induced renal toxicity can be decreased by hydration and by limiting the amount of contrast used. It is unclear if *N*-acetylcysteine is helpful in preventing lactic acidosis associated with metformin use.

Metformin should be withheld for 48 hours after the contrast study, and an alternate glucose-controlling drug should be considered during this time. The US Food and Drug Administration recommends that the renal function be reevaluated and determined to be normal before restarting metformin. This is likely best done by the referring physician.

THINK TWICE IF THE PATIENT IS PREGNANT

In the doses used in clinical practice, iodinated contrast agents cross the human placenta and enter the fetus. No well-controlled studies have examined the teratogenic effects of these agents on the fetus, so there is not enough evidence to presume that they are completely safe. In addition to the potential risk of contrast media, there is the bigger risk associated with ionizing radiation.

For these reasons, the medical necessity of the imaging study needs to be considered. If the study is still strongly indicated, then contrast can be used as needed.

PATIENTS CAN CONTINUE BREASTFEEDING

Less than 1% of the contrast dose administered to the mother is excreted into breast milk, and of that ingested by the infant, less than 1% is absorbed from the infant's gastrointestinal tract. Thus, the expected contrast dose absorbed by the infant from breast feeding is very low (about 0.01% of the mother's intravenous dose and less than 1% of the suggested infant dose).

The recommendation is that it is safe for the mother and infant to continue breastfeeding after the mother receives intravenous contrast. If the mother is concerned, she can stop breastfeeding for 24 hours and pump and discard breast milk from both breasts during that time.

CASE REVISITED

In our case, the referring physician checked the patient's creatinine the day before the study because of his diabetes. It was within normal limits, and a contrast-enhanced CT scan utilizing nonionic low-osmolar contrast

was performed the following day. The patient was instructed to stop taking his metformin following the study and for the next 48 hours. During this time, he used pioglitazone (Actos) for substitute glycemic control. Another creatinine was checked after 48 hours. It was not significantly changed, and the referring physician notified the patient to restart metformin.

SUGGESTED READING

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ADDRESS: *David M. Einstein, MD, Department of Radiology, Hb6, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195; e-mail einsted@ccf.org.*