Review Article

Prevention of Contrast Media–induced Nephrotoxicity after Angiographic Procedures

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Contrast medium–induced nephrotoxicity (ie, contrast nephrotoxicity [CN]) remains an important complication of angiographic procedures. If administration of iodinated contrast medium is deemed necessary in patients at high risk of CN, volume expansion should be offered and the lowest possible dose of nonionic isosmolar dimeric or nonionic low-osmolar monomeric contrast medium should be used. Prophylactic administration of fenoldopam or acetylcysteine has not offered consistent protection against CN. Intravenous acetylcysteine could be considered in emergency situations. Recently, sodium bicarbonate infusion has been shown to reduce the risk of CN. Hemofiltration for several hours before and after contrast medium injection may offer good protection against CN in patients with advanced renal disease. Prophylactic hemodialysis does not offer any protection against CN.

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Abbreviations: CN = contrast nephrotoxicity, GFR = glomerular filtration rate, NSAID = nonsteroidal antiinflammatory drug

THE kidney is the main route of elimination of radiographic contrast media after intravascular administration. Unfortunately, contrast medium particles, as they pass through the kidney into the urine, induce functional and structural changes. These changes include renal vasoconstriction, decrease in the glomerular filtration rate (GFR), diuresis, natriuresis, enzymuria, cytoplasmic vacuolization, and disruption of the brush borders of the cells of the proximal convoluted tubules (1). The renal vasoconstriction and decrease in GFR seem to be mediated by the endogenous vasoactive mediators endothelin and adenosine (2–4). In clinical situations such as arteriopathy, hypertension, diabetes mellitus, or use of nonsteroidal antiinflammatory drugs (NSAIDs), in which the endogenous intrarenal production of the vasodilators nitric oxide and prostacyclin is reduced, the hemodynamic effects of contrast media become exaggerated (2). The described functional and structural changes induced by contrast media are usually of no clinical significance in healthy patients with normal kidneys. However, in patients with reduced renal function or conditions causing reduction of renal perfusion, the intravascular administration of contrast media can lead to the development of nephrotoxicity (ie, contrast nephrotoxicity [CN]), which implies that impairment in renal function (an increase in serum creatinine of >25% or 0.5 mg/dL [44 μmol/L] from baseline) has occurred within 3 days after contrast medium injection and the absence of alternative etiology (1). CN is considered an important cause of hospital-acquired renal failure. This is not surprising, as diagnostic and interventional procedures requiring the use of contrast media are performed with increasing frequency (5–10). In addition, the patient population subjected to these procedures is progressively older and has more comorbid conditions (7).

The incidence of CN in patients with normal renal function before injection of contrast medium is low (<10%) (7–10). However, the incidence may increase to 25% or more in patients with risk factors, particularly preexisting renal impairment secondary to diabetes mellitus (1,7–10).

Most episodes of CN are not detected clinically because patients are usually asymptomatic and serum creatinine is not routinely measured after administration of contrast media. The majority of patients with CN tend to be nonoliguric except those with preexisting advanced chronic renal failure. The clinical course of CN in most cases is benign and resolves within 1–2 weeks (7,9). However, CN may increase the risk of nonrenal complications and prolong hospital stay. In one study (11), the mortality rate among hospital inpatients with CN was 34% but was only 7% in a matched control group that underwent a procedure involving contrast medium without developing CN (11). Therefore, prevention of this complication is important to avoid substantial morbidity and mortality that can be sometimes associated with CN (10–12).

This review will address how to

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identify patients at risk of CN before intravascular administration of contrast medium and discuss the different measures to reduce the incidence of this important complication.

RISK FACTORS FOR CONTRAST MEDIA NEPHROTOXICITY

Preexisting Renal Impairment

Patients at the highest risk for developing CN are those with preexisting renal impairment (serum creatinine level >1.5 mg/dL [130 μmol/L]), particularly when the reduction in renal function is associated with diabetes mellitus (7–10,13). The degree of renal insufficiency present before the administration of contrast medium determines to a great extent the severity of CN. McCullough et al (10), in a large study of 1,826 patients undergoing coronary angiography with high-osmolar contrast medium (diatrizoate) in 55% of patients, low-osmolar ionic dimer ioxaglate in 33% of patients, and a combination of both agents in the remaining 12%, found that creatinine clearance of 30 mL/min or less markedly increased the incidence and severity of CN. In addition, no patient with a creatinine clearance greater than 47 mL/min developed CN requiring dialysis.

The importance of diabetes mellitus per se without renal impairment as a risk factor for CN remains to be clarified (9). In a large study of 1,196 patients (13), the incidences of CN associated with the administration of low-osmolar contrast medium in patients with normal renal function were 7.2% in diabetic patients and 8.5% in nondiabetic patients. However, multivariate logistic regression analysis in this study identified diabetes mellitus as an independent risk factor for CN. In another study (14), the risk was limited to insulin-dependent diabetic patients. Although the importance of diabetes mellitus without renal impairment as a risk factor for CN is not certain, caution is still warranted in diabetic patients because endothelial dysfunction may exist that predisposes the patient to CN through alterations in the production of vasoactive mediators in the kidney, particularly nitric oxide (2,9,15).

Type of Contrast Medium

The type of contrast medium is an important risk factor for the development of CN. It is well-recognized now that low-osmolar contrast media are less nephrotoxic than high-osmolar contrast media in patients with preexisting renal impairment (7–9,13,14). It has also been suggested recently that the isosmolar nonionic dimer iodixanol is less nephrotoxic than low-osmolar contrast medium (16,17). A recent study of diabetic patients with preexisting renal impairment undergoing angiography reported a 3% incidence of CN with iodixanol and a 26% incidence with the low-osmolar nonionic monomer iohexol (16). A previous study by Chalmer et al (17) in patients with baseline renal impairment, one third of whom had diabetes, also observed less reduction in renal function with iodixanol in comparison with iohexol. However, a low incidence of CN with iodixanol was not observed in other studies. Stone et al (18) reported a 33.3% incidence of CN with iodixanol and a 25.3% incidence with other types of low-osmolar contrast media, but the difference was not statistically significant (18). Incidences of CN of 12% and 21% with iodixanol were observed in two further studies (19,20). A recent review of numerous clinical trials describing the renal tolerance of different contrast media concluded that patients with preexisting renal insufficiency are at high risk of CN with all classes of contrast media, including the isosmolar dimer (21). Further studies are required to elucidate whether the isosmolar dimer has less associated nephrotoxicity in comparison with other types of contrast media in patients with renal impairment.

Dose of Contrast Medium

The nephrotoxic effect of contrast medium is dose-dependent, and the higher the dose, the higher the risk of CN (8,9,13,22,23). Cigarroa et al (22) correlated the dose of contrast medium to baseline serum creatinine level and found that, if the amount of contrast medium injected in patients with preexisting renal impairment undergoing angiographic examinations with high osmolar diatrizoate 370 mgI/L is limited to 5 mL per kilogram of body weight (maximum 300 mL) divided by serum creatinine level in mg/dL (1 mg/dL = 88.4 μmol/L), the development of CN is rare (22). This formula provides some guidance about the volume of contrast medium that can be given to patients with renal impairment without inducing CN. It is reasonable to postulate that, with the administration of low-osmolar contrast media, which are less nephrotoxic than high-osmolar contrast media, the limit according to this formula can be expanded by a factor of 1.5. The extent of reduction of renal function induced by high-osmolar contrast medium is twice that of low-osmolar contrast medium at a comparable dose (9,13). In addition, the incidence of CN with high-osmolar contrast medium is almost twice that with low-osmolar contrast medium in patients with renal impairment (9,13).

The importance of the dose was also observed in a study by McCullough et al (10) in patients undergoing coronary angiography. They found that 100 mL was the cutoff dose below which there was no CN requiring dialysis. In addition, Rudnick et al (13) also reported that the dose of contrast medium is a significant independent risk factor for CN. The importance of dose and type of contrast medium was also shown in animal studies in vivo under controlled laboratory conditions with use of the model of acute renal ischemia in the rat. The increase in serum creatinine induced by contrast medium was dose-dependent and the nonionic monomer iopromide induced significantly less reduction in renal function compared with high-osmolar diatrizoate (23). Multiple injections of contrast medium within 72 hours in patients with renal impairment are also likely to increase the risk of CN. The clearance of contrast medium from the body in patients with reduced renal function will be prolonged, and it is feasible that repeat injections within 72 hours would result in a cumulative renal insult (8,13).

Other risk factors for CN may include dehydration, congestive cardiac failure, multiple myeloma, concurrent use of nephrotoxic drugs, hypertension, hyperuricemia, and proteinuria. Dehydration or congestive cardiac failure can lead to reduction in renal perfusion, enhancing the ischemic insult of contrast media (1,2). Multiple