Preventing Nephropathy Induced by Contrast Medium

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This Journal *feature begins with a case vignette highlighting a common clinical problem.*
Evidence supporting various strategies is then presented, followed by a review of formal guidelines,
when they exist. The article end with the authors' clinical recommendations.

A 71-year-old man with type 2 diabetes and hypertension is referred for coronary angiography. His medications include metformin and a thiazide. Before the angiogram, his serum creatinine level is 1.8 mg per deciliter (160 μmol per liter), yielding an estimated glomerular filtration rate of 40 ml per minute per 1.73 m² of body-surface area. What can be done to reduce the risk that an angiographic contrast medium will worsen his kidney function?

THE CLINICAL PROBLEM

Sensitive tests of kidney function identify mild, transient changes in most patients who have been exposed to intravascular iodinated contrast mediums.[1] Clinically important injury (often called contrast-medium–induced nephropathy) is much less common. Cases of contrast-medium–induced nephropathy are usually defined by a fixed (0.5 mg per deciliter [44 μmol per liter]) or proportionate (25 percent) rise in serum creatinine levels after exposure to the contrast medium. However, the clinical importance of such changes, if they are transient, is uncertain. A serum creatinine level itself is a relatively poor measure of kidney function and is influenced by age, sex, and body composition.

In a study by Nash et al.,[2] contrast-medium–induced nephropathy was reported to be the third most common cause of acute renal failure in hospitalized patients. In this study, the contrast medium was assumed to be the cause of the renal failure if it was administered in the 24 hours before renal failure and no other major kidney insult was identified. However, exposure to contrast medium may be a contributory rather than a sole cause of acute renal failure; concomitant insults may include low blood volume, surgery, atheroembolic disease, and the presence of other nephrotoxins.

The reported incidence of contrast-medium–induced nephropathy varies among studies, due to differences in definition, background risk, type and dose of contrast medium, imaging procedure, and the frequency of other potential causes of acute renal failure. The status of renal function before administration of a contrast medium is a major determinant of deterioration in function after administration.[3] In one study, serum creatinine levels rose by more than 25 percent in 14.5 percent of patients who underwent coronary angiography (95 percent confidence interval, 12.9 to 16.1 percent).[3]

In the absence of preexisting renal disease, the incidence is much lower. In a large clinical trial, only 8 percent of patients whose baseline serum creatinine level was below 1.5 mg per deciliter (135 μmol per liter) had an increase in the serum creatinine level of more than 0.5 mg per deciliter, and none had an increase

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of more than 1 mg per deciliter (89 μmol per liter).[4]

In another study, 0.8 percent of 1826 patients required dialysis after exposure to the contrast medium; the baseline estimated creatinine clearance rate was below 47 ml per minute per 1.73 m[2] of body-surface area in all patients requiring dialysis.[3] Serum creatinine levels rose by less than 1 mg per deciliter (89 μmol per liter) in 29 percent of those requiring dialysis, indicating advanced preexisting kidney disease. Registry data suggest a 0.44 percent incidence of nephropathy requiring dialysis after percutaneous coronary intervention.[5]

RISK FACTORS

Diabetes is a risk factor for deterioration in renal function after angiography.[3,6,7] Other factors variably associated with increased rates of acute renal failure after the administration of contrast medium include age over 75 years, periprocedural volume depletion, heart failure, cirrhosis or nephrosis, hypertension, proteinuria, concomitant use of nonsteroidal antiinflammatory drugs, and intraarterial injection. In the setting of acute myocardial infarction or percutaneous coronary intervention, hypotension or use of an aortic balloon pump has been associated with a higher rate of acute renal failure after exposure to a contrast medium.[7,8] However, it is uncertain to what extent these factors independently worsen renal function, as opposed to serving as markers for coexisting conditions. High doses of contrast medium also increase the likelihood of renal dysfunction. The tolerable dose of contrast medium depends on kidney function.[3,5,9]

PROGNOSIS

Contrast-medium–induced nephropathy is usually transient, with serum creatinine levels peaking at 3 days after administration of the medium and returning to baseline within 10 days after administration.[8,10] Appreciable nephropathy is unlikely to develop if the serum creatinine level does not increase by more than 0.5 mg per deciliter within 24 hours.[11] Few studies report kidney function beyond a few days after exposure to the contrast medium. In one report, 5 of 21 elderly patients with an initial sudden rise in serum creatinine levels after angiography had a final creatinine level of at least 0.5 mg per deciliter above baseline.[12] Thirteen to 50 percent of patients re-

quiring dialysis after exposure to a contrast medium may depend on dialysis permanently.[3,13]

A decline in kidney function after the administration of a contrast medium is associated with a prolonged hospital stay, adverse cardiac events, and high mortality both in the hospital and in the long term.[3,6,8,14-16] However, the association between these outcomes and the decline in function may be explained at least in part by coexisting conditions, acuteness of illness, or other causes of acute kidney failure, such as atheroembolism.

PATHOGENESIS

The pathogenesis of contrast-medium–induced nephropathy in humans is not clear. In vitro studies and studies in animals suggest a combination of toxic injury to the renal tubules and ischemic injury partly mediated by reactive oxygen species.[17,18] Low blood flow in the medulla, which has a high demand for oxygen, might result from increased perivascular hydrostatic pressure, high viscosity, or changes in vasoactive substances such as endothelin, nitric oxide, and adenosine.[10,19] Factors impairing medullary vasodilation, such as nonsteroidal antiinflammatory drugs, may worsen contrast-medium–induced nephropathy.

STRATEGIES AND EVIDENCE

EVALUATION OF RISK

The first steps in reducing the risk of kidney injury are to look for risk factors and review the indications for the administration of contrast medium. Most risk factors can be detected by history taking and physical examination. Factors such as dehydration can be at least partially corrected before exposure to the contrast medium.

The risk of a decline in kidney function after the administration of contrast medium rises exponentially with the number of risk factors present.[8,12,14] Validated risk-prediction models, such as the one shown in Table 1, have been developed for patients undergoing percutaneous coronary intervention.[7]

It is not necessary to measure the serum creatinine levels of every patient before exposure to a contrast medium, but measurements should be made before intraarterial use of the medium and in patients with a history of kidney disease, proteinuria, kidney surgery, diabetes, hypertension,

Table 1. Predicting the Risk of an Acute Decline in Kidney Function after Percutaneous Coronary Intervention.*

Risk Factor	Score
Systolic pressure <80 mm Hg for >1 hr and patient requires inotropic support or an intraaortic balloon pump within 24 hr after the procedure	5
Use of intraaortic balloon pump	5
Heart failure (New York Heart Association class III or IV), history of pulmonary edema, or both	5
Age >75 yr	4
Hematocrit <39% for men or <36% for women	3
Diabetes	3
Volume of contrast medium	1 for each 100 ml
Serum creatinine level >1.5 mg/dl (133 μmol/liter) or	4
Estimated GFR† <60 ml/min/1.73 m² body-surface area	2, 40 to <60 ml/min/1.73 m² 4, 20 to 39 ml/min/1.73 m² 6, <20 ml/min/1.73 m²

Total Risk Score‡	Risk of an Increase in Serum Creatinine Levels of >0.5 mg/dl (44 μmol/liter) or >25 Percent	Risk of Dialysis
	percent	
≤5	7.5	0.04
6 to 10	14.0	0.12
11 to 15	26.1	1.09
≥16	57.3	12.6

* Adapted from Mehran et al.[7]
† Estimated glomerular filtration rate (GFR) = $186 \times$ (serum creatinine in mg/dl)$^{-1.154} \times$ age$^{-0.203} \times 0.742$ if female $\times 1.21$ if black.
‡ The total risk score is determined by adding the scores for each factor.

or gout.[20] The creatinine clearance rate or the glomerular filtration rate should be estimated from the serum creatinine level, according to either the Cockcroft–Gault[21] or the Modification of Diet in Renal Disease[22] formula (Table 1) to identify more accurately patients with values below 50 ml per minute per 1.73 m², who are at increased risk for nephropathy.[8] Alternative imaging methods not requiring contrast medium should be considered for use in patients with any risk factors. If contrast medium has to be given, serum creatinine levels should be measured 24 to 48 hours after administration of the contrast medium. Because of the risk of lactic acidosis when contrast-medium–induced nephropathy occurs in a patient with diabetes who is receiving metformin, it is prudent to withhold this agent until the glomerular filtration rate is greater than 40 ml per minute per 1.73 m² and for the 48 hours before exposure of the patient to the contrast medium.[23]

PREVENTION

Protocols for Administration of Fluids

The administration of fluids is recommended to reduce the risk of contrast-medium–induced nephropathy. However, data are lacking that specify the optimal fluid regimen. In one trial, serum creatinine levels increased by more than 0.5 mg per deciliter in nine patients (34.6 percent) given water orally as compared with one (3.7 percent) given intravenous saline for 24 hours beginning 12 hours before administration of the contrast medium, but the trial was stopped early after an unplanned interim examination of the data.[24] Prolonged intravenous fluid therapy is difficult to administer for ambulatory procedures. A small trial comparing the use of intravenous fluids for 12 hours (before and after administration of the contrast medium) with oral fluids plus a single intravenous bolus of fluid showed a lesser mean decline in the glomerular filtration rate at 48 hours after administration of the contrast medium

(−18.3 vs. −34.6 ml per minute per 1.73 m²) in the group receiving intravenous fluids,[25] although another trial did not confirm this result.[26] In a study comparing isotonic saline with 0.45 percent saline, each given at 1 ml per kilogram of body weight per hour for 24 hours starting the morning of the procedure involving the contrast medium, a rise in the serum creatinine level of more than 0.5 mg per deciliter within 48 hours after administration of the contrast medium was less likely in patients who were given isotonic saline (0.7 percent vs. 2.0 percent, P=0.04).[27]

It has been hypothesized that alkalinization of tubular fluid might be beneficial by reducing the levels of pH-dependent free radicals. In one report, the creatinine level was less likely to rise more than 25 percent within two days after the administration of contrast medium in patients who were given an infusion of isotonic sodium bicarbonate than in those given a saline infusion.[28] However, there are methodologic concerns about these results. The trial was terminated early because of a lower-than-expected rate of "events" in the bicarbonate group, but the timing of the interim analysis and the stopping rules were not prespecified, and the P value for the difference in event rates (P=0.02) was higher than is standard for stopping a trial early.

N-acetylcysteine

N-acetylcysteine has the potential to reduce the nephrotoxicity of contrast mediums through antioxidant and vasodilatory effects.[29] In an initial trial, serum creatinine levels rose by more than 0.5 mg per deciliter in 2 percent of patients who received *N*-acetylcysteine as compared with 21 percent of patients in the control group (P<0.01).[30] This event rate in the control group is unexpectedly high for patients who received low-dose intravenous low-osmolality contrast medium. For the most part, subsequent trials have involved patients with reduced kidney function who underwent coronary angiography. Some have shown a benefit and others have shown a lack of effect; many are limited by low power and a lack of blinding.[31-34] Recent meta-analyses[31-34] suggest some benefit to *N*-acetylcysteine (pooled odds ratio, 0.54 to 0.73 for contrast nephropathy, defined variably across studies). However, this estimate must be interpreted with caution, given the heterogeneous results of the individual trials, the possibility of publication bias, and the underrep-resentation of small negative studies. Also, the effect of *N*-acetylcysteine on outcomes other than minor changes in serum creatinine levels is unknown. More data are needed before *N*-acetylcysteine can be strongly recommended for the prevention of contrast-medium–induced nephropathy.

OTHER APPROACHES TO PROPHYLAXIS

Several other interventions have been proposed to reduce the risk of contrast-medium–induced nephropathy, but data to support them are limited. Forced diuresis with furosemide, mannitol, dopamine, or a combination of these given at the time of exposure to the contrast medium has been associated with similar or higher rates of contrast-medium–induced nephropathy when compared with prophylactic fluids alone.[35-38] Deleterious effects may be explained by negative fluid balance in some instances. In generally small randomized trials, the use of various vasodilators, including dopamine, fenoldopam, atrial natriuretic peptides, calcium blockers, prostaglandin E_1, or a nonselective endothelin-receptor antagonist, has not been shown to reduce the risk of contrast-medium–induced nephropathy in comparison with fluid therapy.[38-43] A small randomized trial showed a lower frequency of an increase of more than 0.5 mg per deciliter in serum creatinine levels in patients given captopril for three days as compared with those given placebo,[44] but confirmatory trials are required. In another small trial, serum creatinine levels were significantly less likely to increase (by >25 percent or >0.5 mg per deciliter) within two to five days of administration of the contrast medium in patients who received ascorbic acid as an antioxidant than in those who received placebo.[45] The baseline serum creatinine level was lower in the placebo group, and both groups reached a similar level after exposure to the contrast medium.

Theophylline and aminophylline have also been proposed as agents that may reduce the risk of contrast-medium–induced nephropathy. A recent meta-analysis found that the mean rise in serum creatinine levels was significantly lower (by 0.17 mg per deciliter [15 μmol per liter]) at 48 hours after administration of the contrast medium among patients receiving either of these medications than among those receiving placebo.[46] However, the clinical importance of this finding is questionable, and there was heterogeneity among studies with regard to changes in serum creati-

nine levels. Overall, no prophylactic agent has been shown conclusively to prevent clinically important contrast-medium–induced nephropathy.

Hemodialysis or Hemofiltration

The role of hemodialysis in patients at high risk for contrast-medium–induced nephropathy remains uncertain. Among patients with advanced kidney disease (mean creatinine clearance, 26 ml per minute), an increase in serum creatinine levels of at least 25 percent was significantly less common in patients randomly assigned to prophylactic hemofiltration before and after the administration of contrast medium than in those assigned to receive fluid alone (5 percent vs. 50 percent, P<0.001).[19] In-hospital death was also significantly less frequent in the hemofiltration group.[47] However, the serum creatinine level is directly altered by the intervention, and the relationship between the intervention and the reduced mortality rate is unclear. Thus, the results require confirmation. Given the resources to deliver the intervention, this approach would apply only to the most ill.

Choice of Contrast Mediums

Iodinated contrast mediums can be classified by osmolality (e.g., high-osmolar contrast mediums, such as sodium diatrizoate; low-osmolar mediums, such as iohexol; and iso-osmolar mediums, such as iodixanol). In a meta-analysis of comparative trials, an increase in serum creatinine levels of more than 0.50 mg per deciliter after administration of the contrast medium in patients with reduced kidney function was less frequent with low-osmolar than with high-osmolar mediums (odds ratio, 0.50; 95 percent confidence interval, 0.36 to 0.68).[48] Because of the small number of events, no conclusion could be reached about the effects of osmolality on the need for dialysis.

Iso-osmolar contrast mediums have been proposed as an alternative. One randomized trial involving patients with diabetes who have renal impairment showed a significantly lower frequency of increases in creatinine levels of at least 0.5 mg per deciliter with the iso-osmolar agent iodixanol, than with a low-osmolar agent.[49] However, the rate of renal deterioration in the group receiving a low-osmolar contrast medium was higher than expected. Similarly, in an open-label trial, a maximal increase in serum creatinine levels of greater than 25 percent within a week

after the administration of contrast medium was less common with iodixanol than with iohexol (3.7 percent vs. 10 percent), but a lack of consistent timing for measuring creatinine levels in the two groups may have biased the results.[50] In contradistinction, other trials have revealed no significant differences between iodixanol and low-osmolar agents in the rates of renal failure requiring intervention or prolonging hospitalization[51] or in mean changes in creatinine levels after administration of contrast medium.[52] Further studies are needed before iso-osmolar contrast mediums can be recommended in place of low-osmolar mediums.

Exceeding a volume of contrast medium of 5 ml per kilogram of body weight divided by the serum creatinine level in milligrams per deciliter strongly predicts nephropathy requiring dialysis.[5] Table 2 summarizes recommendations regarding interventions commonly used to prevent contrast-medium–induced nephropathy.

AREAS OF UNCERTAINTY

The pathogenesis of contrast-medium–induced nephropathy remains uncertain. The value of possible preventive strategies (including N-acetylcysteine, vasodilators, and iso-osmolar contrast mediums) in reducing the risk of contrast-medium–induced nephropathy and associated morbidity also remains uncertain.

GUIDELINES

The European Society of Urogenital Radiology and the American College of Radiology recommend assessment of risk factors including dehydration, heart failure, age greater than 70 years, and concurrent use of nephrotoxic drugs, along with measurement of serum creatinine levels in those at risk for reduced kidney function.[23,53] In the presence of risk factors, consideration of alternative imaging techniques, discontinuation of nephrotoxic drugs, and use of low-osmolar or iso-osmolar contrast mediums in limited doses are recommended. Maintaining adequate hydration and the administration of additional fluids are also recommended, but the details of the regimens are not defined. Multiple infusions of contrast medium within a short period of time and the use of mannitol or diuretics are to be avoided. The American guidelines mention the

Table 2. Summary Recommendations of Interventions Commonly Used to Reduce the Risk of Contrast-Medium–Induced Nephropathy.*

Intervention	Details	Evidence	Comments	Recommendation
Intravenous saline therapy	Intravenous 0.9% saline at 1 ml/kg/hr for 24 hr, beginning 2–12 hr before administration of contrast medium	Several small randomized trials that compared intravenous saline with oral fluids alone, shorter regimens of intravenous fluid, or 0.45% saline	Optimal duration of intravenous therapy not fully established by existing trials	Generally recommended
Contrast medium				
Type	Low osmolality	Meta-analysis of several randomized controlled trials comparing low-osmolar with high-osmolar contrast mediums	Further data on the relative nephrotoxicity of iso-osmolar contrast mediums are required	Low-osmolality mediums recommended
Dose	Lowest required to complete the procedure	Cohort studies that associate higher doses with greater risk	A dose >5 ml × kg of body weight ÷ serum creatinine level in mg/dl associated with higher risk	Lowest dose possible recommended
Intravenous sodium bicarbonate	Intravenous sodium bicarbonate 154 mmol/liter at 3 ml/kg/hr before administration of contrast medium, then 1 ml/kg/hr for 6 hr after administration	A single randomized controlled trial that suggested a lower risk of an increase of >25% in creatinine levels with bicarbonate as compared with 0.9% saline given at the same rate of infusion and duration	Methodologic flaws in the trial	Not generally recommended unless efficacy confirmed by further trials
N-acetylcysteine	Most commonly, 600 mg by mouth every 12 hr for four doses, beginning before administration of contrast medium	Multiple randomized trials and meta-analyses	Inconsistent trial results for unknown reasons: optimal dose not clear	Not generally recommended pending further data to confirm efficacy

* Several other agents, such as captopril, have been studied in small trials, but data are insufficient to support their use at present.

use of *N*-acetylcysteine or other potential prophylactic drug therapies without specifically recommending these approaches.

SUMMARY AND RECOMMENDATIONS

Patients with normal kidney function and no recognized risk factors for contrast-medium–induced nephropathy do not require routine testing or prophylactic intervention before angiography. For patients likely to have reduced kidney function, such as the man described in the vignette, we recommend measurement of the serum creatinine level and estimation of the glomerular filtration rate. If the glomerular filtration rate is less than 50 ml per minute per 1.73 m², particularly in combination with other risk factors, consideration should be given to alternative imaging approaches. If infusing contrast medium is thought to be warranted, a low-osmolar agent should be used at the minimal dose necessary,

and measurement of the serum creatinine level should be repeated 24 to 48 hours after the administration of the contrast medium. Nonsteroidal antiinflammatory drugs and diuretics should be withheld for at least 24 hours before and after exposure to contrast medium, if possible. Metformin should be withheld for 48 hours before the administration of contrast medium and until it is certain that contrast-medium–induced nephropathy has not occurred. Additional fluids should be given; although the optimal regimen is uncertain, available data support a regimen of 0.9 percent saline at 1 ml per kilogram per hour intravenously from up to 12 hours before administration of contrast medium and for up to 12 hours after, with careful observation of fluid balance. The use of *N*-acetylcysteine is not recommended routinely, given the inconsistent results of clinical trials.

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