A Review of Pharmacologic Interventions to Prevent Contrast-Induced Nephropathy

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The serious clinical implications of contrast-induced nephropathy (CIN) have focused researchers on prevention strategies. Increased coverage of CIN in major medical journals and at major cardiovascular meetings, including the Transcatheter Cardiovascular Therapeutics (sponsored by the Cardiovascular Research Foundation), American College of Cardiology, and American Heart Association conferences, highlight this concern. Development of CIN prevention strategies is ongoing, but efforts have been hampered by an incomplete understanding of CIN pathophysiology. The most popular theories include contrast-induced renal tubular ischemia, free radical formation, and a direct tubular toxic effect. Proponents of an ischemia model direct clinical trials evaluating the efficacy of a variety of vasodilators, while those who favor a free radical or direct toxicity theory study antioxidants and free radical scavengers, or a variety of contrast agents varying in osmolality, ionicity, and viscosity. A comprehensive review of the more important and contemporary CIN prevention trials is provided to assist the cardiologist, radiologist, or nephrologist in developing his or her own data-driven approach to CIN prevention. [Rev Cardiovasc Med. *2003;4(suppl 5):S34–S42*]

Key words: Contrast-induced nephropathy • Glomerular filtration rate • Hydration • Renal blood flow • Serum creatinine

The clinical implications of contrast-induced nephropathy (CIN) have become more greatly appreciated over the last few years. The coverage of this problem has increased in the major medical journals and the major cardiovascular meetings, including the annual Transcatheter Cardiovascular Therapeutics (TCT), the American College of Cardiology (ACC), and the American

Table 1
Previous Attempts at Preventing Contrast-Induced Nephropathy

Either No Benefit or Cause Harm	Some Benefit
• Dopamine	• Saline
• Mannitol	• Iso-osmolar, nonionic contrast (iodixanol)
• Furosemide	
• Atrial natriuretic peptide	
• Mixed endothelin antagonists	
• Calcium channel blockers	
• Fenoldopam	

Data from Solomon et al[1], Weisberg et al[29], Wang et al[30], Carraro et al[31], Moore et al.[32]

Heart Association (AHA) meetings. Efforts at developing strategies to prevent CIN have been ongoing for many years. These efforts have been hampered by an incomplete understanding of the pathophysiology of CIN. The models that are most popular include contrast-induced renal tubular ischemia, free radical formation, and a direct tubular toxic effect. Proponents of an ischemia model have driven clinical trials evaluating the efficacy of a variety of vasodilators, whereas those who have favored a free radical or direct toxicity theory have studied antioxidants and free radical scavengers or a variety of contrast agents varying in osmolality, ionicity, and viscosity. This article provides a comprehensive review of the more important and contemporary CIN prevention trials. This information will assist the cardiologist, radiologist, and nephrologist in developing his or her own data-driven approach to this problem (Table 1).

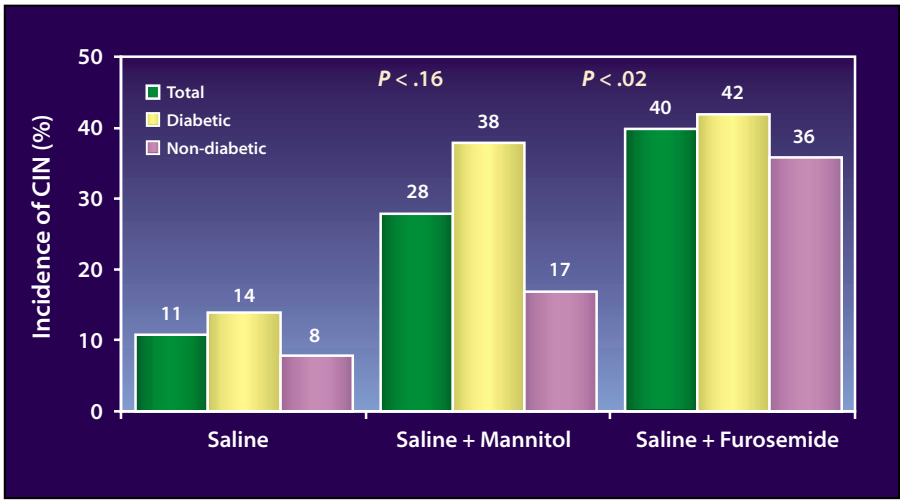
Mannitol and Furosemide

Up to the mid-1990s, a common approach to the patient at risk for CIN was a pre–contrast exposure cocktail of saline hydration with mannitol and furosemide. This was based on the concept that inducing and maintaining a post–contrast exposure diuresis would prevent the development of CIN. The pivotal trial by Solomon and colleagues[1] evaluated the utility of this approach by randomizing 78 patients undergoing coronary angiography to either saline hydration (0.45% normal saline [NS], 1 mL/kg/hr) for 12 hours before and after contrast exposure, plus mannitol (25 g intravenously during the 60 minutes prior to angiography) or hydration + mannitol + furosemide (80 mg infused intravenously 30 minutes prior to angiography). The results of this trial showed that mannitol and/or furosemide were inferior to hydration alone, with the incidence of CIN 11% in the saline group, 28% in the mannitol group, and 40% in the furosemide + mannitol group (Figure 1).

The Prospective Randomized Trial of Prevention Measures in Patients at High Risk for Contrast Nephropathy (PRINCE) study found no benefit to forced diuresis with intravenous crystalloid, furosemide, mannitol, and low-dose dopamine over hydration alone in patients exposed to contrast and at risk for CIN. These investigators did find that patients with the highest urine outputs were less apt to develop CIN.[2]

The failure of mannitol and furosemide to exert protective effects can be explained by their physiologic renal effects. Mannitol increases the intrarenal secretion of adenosine which acts as a potent renal vasoconstrictor resulting in a reduction of renal blood flow. The active transport process that is responsible for excretion of this osmotically active compound also increases tubular mitochondrial oxygen consumption. Furosemide-

Figure 1. *Comparative efficacy of saline, mannitol, and furosemide in contrast-induced nephropathy (CIN) prophylaxis. Saline hydration is superior to mannitol and furosemide, particularly in diabetic patients. Data from Solomon et al.[1]*



induced diuresis may result in hypovolemia, which may actually increase the risk of contrast-induced tubular injury.

Vasodilators

Fenoldopam

Fenoldopam mesylate is a selective dopamine-1 receptor agonist (DA_1) that produces systemic, peripheral, and renal arterial vasodilatation. It has been approved by the Food and Drug Administration as an intravenous agent for the treatment of emergent hypertension. It has the favorable characteristics of being easily titrated, and able to maintain renal blood flow (RBF) and glomerular filtration rate (GFR) with blood pressure reduction. In an anesthetized canine model, Bakris and associates[3] demonstrated that the reduction in RBF and GFR that occurs after contrast is completely blocked by prior fenoldopam administration. In a retrospective historical control study by Madyoon and coworkers,[4] the prophylactic use of fenoldopam was associated with a significant reduction of CIN compared with saline hydration alone. In a prospective historical control study by Annapoorna and Sharma,[5] fenoldopam was observed to reduce the incidence of CIN from 18.8% to 4.5% (P = .009). In a randomized and blinded pilot trial by Tumlin and colleagues,[6] the ability of fenoldopam to reduce the contrast-induced reduction in renal blood flow was observed, as well as a trend toward the reduction of CIN. In both the control and experimental groups, patients who experienced reductions in renal blood flow following contrast exposure seemed to be at higher risk of CIN.

The recently completed CONTRAST trial (Evaluation of Corlopam in Patients at Risk for Renal Failure—A Safety and Efficacy Trial) compared in a multicenter, randomized, placebo-controlled study a regimen of fenoldopam + intravenous hydration to hydration alone in preventing CIN.[7] This is the largest CIN prevention trial to date, evaluating 315 patients at 28 centers. The major inclusion criterion was a creatinine clearance < 60 mL/min in patients undergoing invasive cardiac procedures. All patients were hydrated with 0.45% NS and randomized to intravenous fenoldopam (0.05 μg/kg/min titrated to 0.10μg/kg/min) or a matching placebo study drug starting 1 hour prior to angiography and continuing for 12 hours following the procedure. The mean creatinine clearance in this study population was 29 mL/min and serum creatinine of 1.8 mg/dL. Approximately 90% of patients received a nonionic contrast, with mean volume of approximately 155 mL. The primary endpoint—CIN—defined as a ≥ 25% increase in serum creatinine from baseline within 96 hours of contrast exposure, occurred in 33.6% of fenoldopam-assigned patients versus 30.1% assigned to placebo (P = NS). The results of CONTRAST run counter to previous experiences and show no benefit of fenoldopam over intravenous hydration alone in the doses used in this randomized trial (Figure 2).

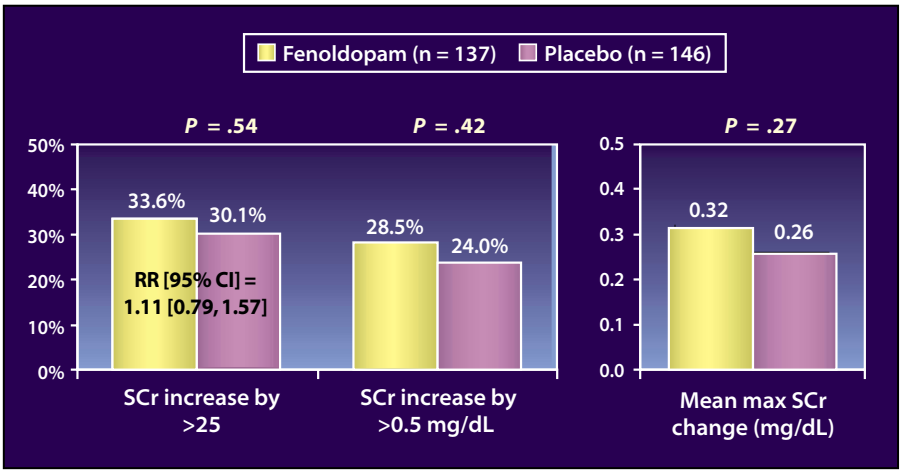
The results of CONTRAST run counter to previous experiences and show no benefit of fenoldopam over intravenous hydration alone in the doses used in this randomized trial.

Interest in the use of this agent for preventing CIN has waned with the release of the CONTRAST trial results, though data continue to accumulate showing its renal-preserving characteristics in patients undergoing major vascular surgery and as a potential treatment for acute tubular necrosis.

Low-Dose Dopamine

Classic thinking has portrayed low-dose dopamine (2–5 μg/kg/min)

Figure 2. *Results from the CONTRAST trial. Serum creatinine (SCr) at both baseline and during the 96-hour post–drug administration period was available and analyzed at the central laboratory in 283 of 315 randomized patients (90%). Fenoldopam did not reduce the incidence of contrast-induced nephropathy relative to saline hydration.*



as a renal vasodilator. Low-dose dopamine has been used to maintain renal perfusion and function, particularly in the intensive care unit setting in patients developing, or at risk for developing, acute renal insufficiency, without any randomized clinical trial data to support its use. Clinical trial data does not support the use of low-dose dopamine to prevent or treat CIN. Gare and associates[8] evaluated the ability of low-dose dopamine (2 μg/kg/min) compared with saline alone to prevent CIN in 66 patients with mild to moderate chronic renal insufficiency and/or diabetes who were undergoing coronary angiography. Patients were randomized to low-dose dopamine + hydration (100 mL/hr of 0.45% NS) or hydration alone for 12 hours before and 36–48 hours following contrast (lopromide) exposure. The peak increase in serum creatinine (SCr) trended higher in the dopamine group and was significantly worse in the subgroup of patients with peripheral vascular disease.

In the elegant, randomized, prospective trial by Abizaid and coworkers,[9] the investigators evaluated the ability of low-dose dopamine (2.5 μg/kg/min) or aminophylline (4 mg/kg bolus followed by an infusion of 0.4 mg/kg/hr) to prevent the occurrence of CIN compared with saline. The patients from both arms who developed CIN were then randomized to treatment with low-dose dopamine or saline. All patients were hydrated for 12 hours with 1 mL/kg/hr of 0.45% intravenous saline. Iohexol was the contrast agent used for all patients. Despite the use of this low-osmolar radiocontrast agent, the overall incidence of CIN in this study was 38%, as defined by an increase of at least 25% of SCr from baseline. There was no significant difference in the development of CIN in patients who were treated with saline alone (30%) versus those who received saline + dopamine (50%) or those treated with aminophylline + saline (35%). Of the 23 patients who developed CIN, those who were then treated with low-dose dopamine had worse outcomes than those treated with saline alone (Figure 3).

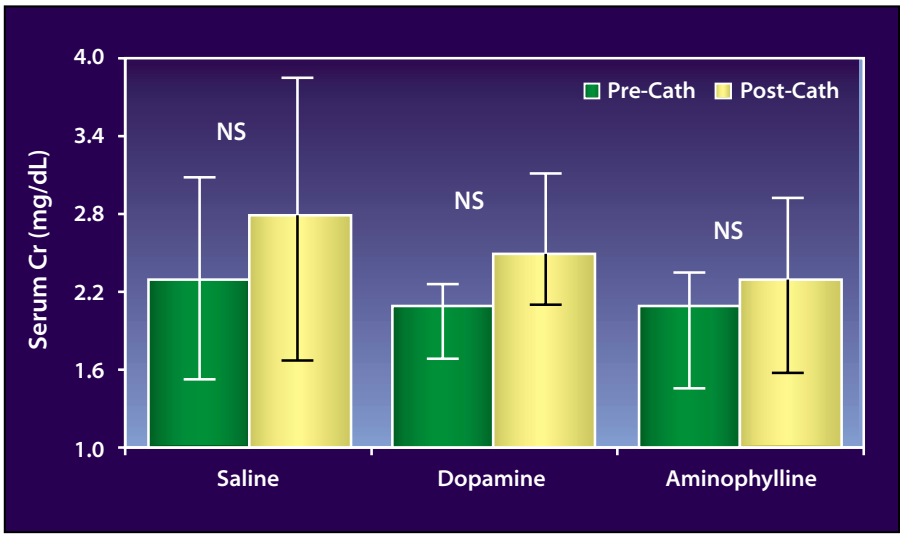


Figure 3. *Failure of dopamine and aminophylline to prevent contrast-induced nephropathy. Neither low-dose dopamine nor aminophylline reduces the incidence of contrast-induced nephropathy relative to saline hydration. Cath, catheterization; Cr, creatinine; NS, not significant. Data from Abizaid et al.*[9]

There was no significant difference in the development of CIN in patients who were treated with saline alone (30%) versus those who received saline + dopamine (50%) or those treated with aminophylline + saline (35%).

Since the results of these trials showing the lack of effectiveness of low-dose dopamine in preventing CIN, its use has become less common. The failure of low-dose dopamine to be effective in this setting may be related to its simultaneous activation of the DA_2 receptor, which, in contrast to the DA_1 receptor, has the paradoxic effect of reducing RBF and the GFR.[10] In addition, there seems to be a poor relationship between the rate of dopamine infusion and the achieved plasma concentrations.[11] This may result in plasma levels of dopamine in the alpha or beta range, despite the low-dose infusion rate.

Calcium Channel Blockers

Studies by Bakris and Burnett[12] have demonstrated the ability of the calcium channel antagonists verapamil and diltiazem to attenuate the renal vasoconstrictor response to radiocontrast as well as the diminution of the GFR. In a series of trials evaluating the efficacy of dihydropyridine calcium channel blockers, including felodipine, nitrendipine and nifedipine, conflicting effects were seen in their ability to prevent CIN. The ability of calcium channel antagonists to prevent CIN has not been confirmed by any preponderance of clinical data.

Prostaglandin E1 (PGE1)

Little data are available regarding the ability of PGE1 to prevent CIN. In a trial of 117 patients by Koch and associates,[13] there were no differences in creatinine clearance among the range of doses (10 ng, 20 ng, and 40 ng) of PGE1 studied.

Adenosine Antagonists

Within the renal vasculature, adenosine acts as a potent vasoconstrictor, reducing renal blood flow and increasing the generation of oxygen–free radicals as it is metabolized to xanthine and hypoxanthine. Contrast media stimulate the intrarenal secretion of adenosine that, on binding to the renal adenosine receptor, may be responsible for the vasoconstrictor response observed following contrast exposure. The ability to block the adenosine receptor with an agent such as theophylline, therefore, could result in blocking the contrast-induced renal vasoconstrictor response.

The hypothesis has been confirmed by the double-blind, placebo-controlled study of Erley and colleagues[14] that showed no significant change in GFR in patients treated with theophylline before their exposure to contrast media. In contrast, patients pretreated with placebo (saline) experienced a significant decline in GFR after the exposure to contrast agent. The results of subsequent clinical studies evaluating the rates of CIN in patients treated with theophylline compared with placebo have been inconsistent. In a recent randomized, placebo-controlled study, prophylactic intravenous administration of 200 mg theophylline reduced the incidence of CIN in patients with chronic renal insufficiency.[15] The rates of CIN in the theophylline group versus the placebo arm in this study were 4% and 16%, respectively. In another randomized, placebo-controlled study, treatment with 165 mg theophylline was accompanied by a smaller decrease in GFR, plasma erythropoietin, and renin and a smaller increase in urinary ß2-microglobulin compared with placebo.[16] Oral theophylline, in a dosage of 200 mg twice daily prescribed to diabetic patients 24 hours before and 48 hours after the exposure to contrast, provided a significantly lower degree of fall in GFR and lower SCr values compared with placebo.[17] However, three other randomized trials and one study that used a control group matched for several characteristics (ie, age, left ventricular ejection fraction, periprocedural hydration) did not show any benefit of theophylline compared with placebo in preventing CIN.

Antioxidants

N-acetylcysteine

N-Acetylcysteine (NAC) is a compound that has several attributes making it a potentially useful agent to prevent CIN. Besides its antioxidant properties, there are reports of its ability to block the expression of vascular-cell adhesion molecule 1 and the activation of nuclear factor-κ. In rats, contrast agents have been observed to increase lipid peroxidation and superoxide dismutase, a scavenger of reactive oxygen species, was found to result in preserved renal function. Owing to these properties, in addition to its safety and low cost, NAC is commonly utilized to prevent CIN. Unfortunately, clinical studies to date, most of them small single-center experiences evaluating the efficacy of NAC, have yielded mixed results.

Tepel and associates[18] randomized 83 patients with SCr levels > 1.2 mg/dL or creatinine clearance < 60 mL/min to receive intravenous hydration + NAC or hydration alone (0.45% saline at 1 mL/kg/hr) for 12 hours prior to and following contrast exposure. A 600 mg oral dose of NAC was given twice daily on the day before and day of computed tomography scanning with 75 mL of the nonionic, low-osmolar contrast agent iopromide. In this single- center trial, the mean increase in SCr in the control group was only 0.2 mg/dL and fell 0.4 mg/dL from baseline in the NAC cohort. The incidence of CIN, as defined as an increase in SCr of at least 0.5 mg/dL following contrast exposure, was 21% in the control cohort and 2% in the patients receiving NAC (P = .010). None of the patients who developed CIN in this study went on to require dialysis. The implications of this study show the ability of NAC to prevent modest increases in SCr in a noncardiac population receiving a modest amount of contrast medium. There was no observation of any ability to prevent clinically significant events, including dialysis and mortality (Figure 4).

Another single-center trial was reported by Chinese investigators in 200 patients undergoing coronary angiography.[19] All patients received 1 mL/kg/hr of intravenous NS for 12 hours before and 6 hours following angiography. The mean serum creatinine (1.26 and 1.24 mg/dL) and volume of contrast (iopamidol) exposure (120 mL and 130 mL) were similar in the control and NAC groups. There was no significant diminution of creatinine clearance in the control group, and those receiving NAC had an average increase of about 15%. The incidence of CIN, defined as > 25% increase in SCr, was 12% in the control group and 4% in those receiving NAC. These results indicate a modest impact of NAC in this lower-risk cohort of patients exposed to contrast.

The APART (Acetylcysteine to Prevent Angiography-Related Renal

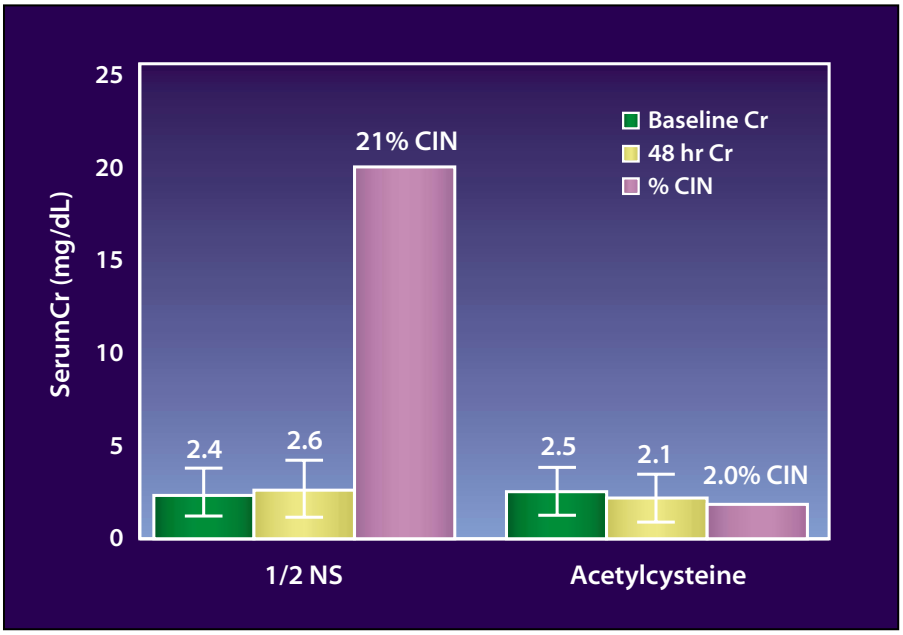


Figure 4. *Antioxidant therapy reduces the incidence of contrast-induced nephropathy (CIN). Though the incidence of CIN was reduced in the acetylcysteine arm, there is no significant increase in serum creatinine (Cr) from baseline in the control arm. A criticism of this trial is the unexpectedly high event rate (21%) in the placebo group based on an estimate of risk in a patient population with a mean creatinine of 2.4 mg/dL. This high event rate would make a positive effect of acetylcysteine more likely than it should have been. NS, normal saline. Data from Tepel et al.*[18]

Tissue Injury) trial was another single-center study that did show a significant benefit of NAC by preventing the increase in SCr observed in the control group.[20]

Briguori and associates[21] studied 183 patients and found no significant benefit in preventing CIN. Caputo and coworkers randomized 79 patients and found a trend toward more CIN in the patients receiving NAC (26%) versus the control cohort (23%).

The Rapid Protocol for the Prevention of Contrast-Induced Renal Dysfunction (RAPPID study) prospectively randomized 80 patients undergoing coronary angiography or interventions at three London hospitals.[22] The experimental group received a rapid protocol of intravenous NAC (150 mg/kg) prior to contrast exposure, followed by 50 mg/kg intravenously over 4 hours postcontrast. All patients received 1 mL/kg/hr of NS for 12 hours pre- and postcontrast. Iodixanol was the contrast agent used in all patients, with average contrast exposure of 238 mL in the NAC group and 222 mL in the control group and mean SCr of 1.85 mg/dL and 1.75 mg/dL, respectively. An increase in SCr of 0.09 mg/dL was observed in the control group at 96 hours following contrast exposure and decreased by a mere 0.08 mg/dL in the cohort receiving NAC. The incidence of CIN, as defined by a 25% or greater increase in SCr at the 48 or 96 hour endpoint, occurred in 4.9% of patients receiving NAC and 20.5% in the control group ($P = .045$).

A meta-analysis of 7 trials that included a total of 805 patients was recently reported, showing a 44%-56% reduction in CIN using a fixed-effects and random-effects statistical model (Figure 5).[23] The common criterion among the 7 trials was randomization to NAC + hydration versus hydration alone. Unfortunately, there is tremendous heterogeneity among the trials, including differences in the degree of baseline cardiac risk factors (CRF) and the mode of NAC administration. In addition, there is a strong tendency for this type of analysis to report positive findings due to publication bias, which generally favors the publication of positive over negative reports in the medical literature. Other suspect findings of this analysis include the secondary conclusion that the degree of CRF before the procedure and the amount of radiocontrast given did not affect the risk of developing CIN.

The accumulation of clinical trial data indicates that NAC may have modest protective effects in preventing CIN. Without larger multicenter, prospective, placebo-controlled randomized trials, the uncertainty of this effect will remain. It is anticipated, however, that because of its low cost and safety—more than its effectiveness—it will remain part of protocols to prevent CIN. However, the above-mentioned clinical trials evaluated the use of NAC where both the experimental and control groups were aggressively hydrated. It is, therefore, imperative that all patients at risk for the development of CIN receive aggressive preprocedure intravenous hydration with a compound such as NAC as an

It is imperative that all patients at risk for the development of CIN receive aggressive preprocedure intravenous hydration with a compound such as NAC as an adjunct to hydration, not as a replacement.

adjunct therapy, not as a replacement. In addition, postprocedure surveillance for CIN with monitoring of serum electrolytes, blood urea nitrogen, and SCr, 48–96 hours following contrast exposure, should be mandatory. This certainly becomes more difficult in the outpatient setting, where it is less practical to guarantee a well-hydrated state in patients exposed to contrast and where a more cavalier attitude to postcontrast exposure surveillance of renal function and electrolytes seems to exist.

Perhaps protocols standardizing oral and/or intravenous hydration and the use of compounds such as NAC and lower-risk radiocontrast agents such as iodixanol, along with recommendations for postcontrast CIN surveillance, can be developed and applied to protect patients at risk.

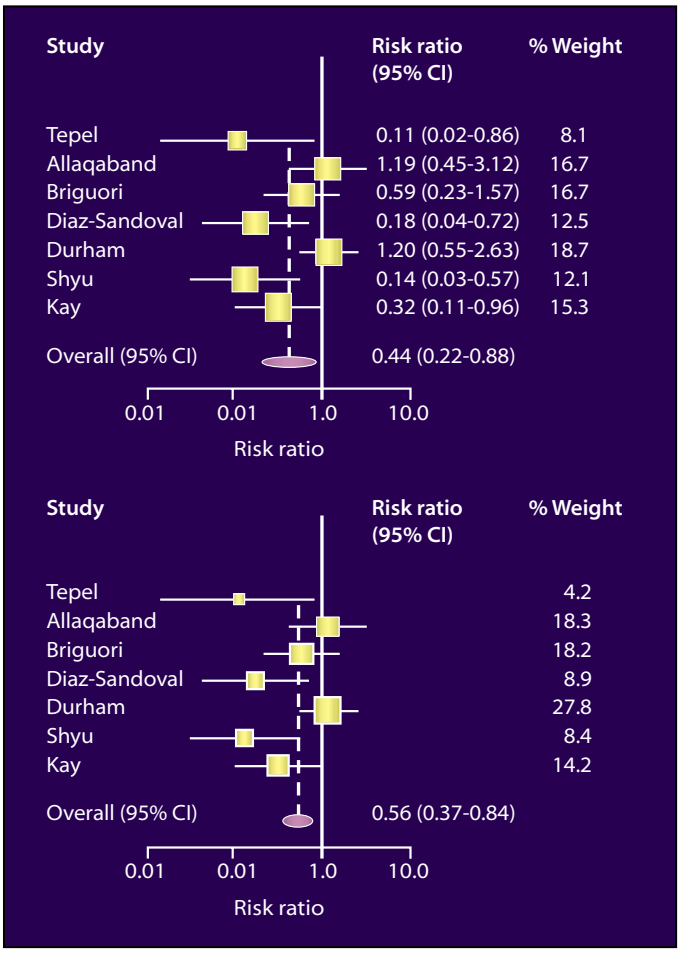


Figure 5. *Summary of meta-analysis data for 7 randomized, controlled trials comparing N-acetylcysteine plus hydration to prevent contrast-induced nephropathy versus hydration alone. Reproduced with permission from Birck et al.*[23]

Other Approaches

The possible role of the renin-angiotensin axis in the genesis of contrast-induced medullary ischemia prompted Gupta and coworkers[24] to evaluate the efficacy of the angiotensin-converting enzyme inhibitor captopril in a randomized study of 71 diabetic patients undergoing coronary angiography. Captopril 25 mg was given three times daily, starting 1 hour before angiography. According to the results, GFR increased in the captopril group and decreased in the control group. The increase in SCr in the captopril group was significantly less prominent than in the control. This was accompanied by significantly lower rates of CIN in the captopril-treated group compared with control. However, because of the lack of a placebo group and the small sample size used in the study, one cannot conclude currently that captopril is effective in prevention of CIN in diabetic patients.

Perhaps protocols standardizing oral and/or intravenous hydration and the use of compounds such as NAC and lower-risk radiocontrast agents such as iodixanol, along with recommendations for postcontrast CIN surveillance, can be developed and applied to protect patients at risk.

Insulin-like growth factor (IGF) has been reported to improve experimental ischemic renal failure. Fuchs and colleagues[25] investigated a possible beneficial role of IGF-1 in a rat model of CIN. In this study, IGF-1 did not prevent either the fall in creatinine clearance or the medullary thick ascending limb necrosis. Atrial natriuretic peptide in three different doses failed to prevent CIN in the randomized, placebo-controlled study by Kurnik and associates.[26]

Several studies examined the effect of hemodialysis immediately after exposure to contrast media in preventing renal function deterioration in patients with preexisting renal disease. All these studies concurred that prophylactic hemodialysis does not diminish the risk of CIN[27] and may even increase it.[28] Other approaches that are contemplated

to undergo investigation as to their ability to prevent CIN include simultaneous dialysis and hypothermia.

Hemofiltration initiated 4–6 hours prior to a scheduled coronary procedure, with resumption after procedural completion and continuation for an additional 18–24 hours in the intensive care unit, was compared to standard hydration by Marenzi and coworkers.[33] One hundred and fourteen patients with a mean SCr of 3.0 mg/dL and an average creatinine clearance of 27 mg/dL were randomized to either hydration or hemofiltration. The low osmolar contrast agent iopentol was used in all patients with an average exposure per patient of about 250 cc. There was a decreased incidence of contrast-induced nephropathy (> 25% increase in SCr from baseline) from 50% to 5% ($P < 0.001$) with hemofiltration. In-hospital mortality was 14% in the control group and 2% in the hemofiltration group ($P = .02$) and 1 year mortality was reduced from 30% in the hydration group to 10% in the hemofiltration group ($P = .01$). The implications from this clinical trial include the failure of this low-osmolar contrast agent to prevent CIN in this high-risk patient population and confirmation of the protective ability of hemofiltration. Unfortunately, the expense and complexity of hemofiltration will prevent its widespread utilization. Nonetheless, this study proves that reduction of both in-hospital and 1-year mortality through the prevention of CIN are possible. This certainly underscores the importance of CIN prevention efforts and counters the claims that the occurrence of CIN is only a marker of mortality risk and doesn't have mortality implications on its own.

There have been many attempts to identify the pharmacologic "silver bullet" that would prevent contrast-induced nephropathy in the at-risk patient population. Unfortunately, no single pharmacologic compound has been able to show in a consistent fashion its ability to improve on the results seen with hydration alone.

A common clinical scenario is the patient with risk factors for CIN who is undergoing a contrast-requiring diagnostic or therapeutic procedure and who has not received appropriate preprocedure hydration. This is certainly an issue in both the inpatient and outpatient settings. The question of whether fenoldopam, NAC, or other agents would have a role in the treatment of at-risk patients undergoing contrast-requiring procedures who have not received hydration at the time of contrast exposure remains unanswered. In this clinical situation, minimizing contrast exposure and using a contrast agent with the lowest CIN potential, such as iodixanol, would be prudent. Unfortunately, there are no clinical trial data available that would confirm an optimal strategy in the volume-depleted patient, underscoring the need to insure that patient volume status is optimized prior to contrast exposure and that patients at risk have

Main Points

- Neither the study by Solomon and colleagues nor the Prospective Randomized Trial of Prevention Measures in Patients at High Risk for Contrast Nephropathy (PRINCE) found a benefit in mannitol and/or furosemide compared with hydration alone for preventing contrast-induced nephropathy (CIN).
- Several studies showed that fenoldopam blocks the reduction in renal blood flow and glomerular filtration rate (GFR) that occurs after contrast exposure, thereby reducing the incidence of CIN; however, the CONTRAST trial showed that fenoldopam is not superior to hydration alone in preventing CIN.
- Although low-dose dopamine has classically been portrayed as a renal vasodilator, clinical trial data do not support its use in the prevention or treatment of CIN. Studies have shown no significant difference in development of nephropathy in patients receiving dopamine or aminophylline versus those receiving saline only.
- Erley and associates showed there was no significant change in GFR in patients treated with theophylline before exposure to contrast media. In contrast, patients pretreated with saline experienced significant decline in GFR after exposure.
- N-acetylcysteine (NAC) has several qualities that make it a potentially useful agent in preventing CIN; however, clinical studies evaluating the efficacy of NAC have yielded mixed results.
- There is no "silver bullet" that prevents CIN in the at-risk population. No single pharmacologic compound has been able to show in a consistent fashion its ability to improve on the results seen with hydration alone.

an assessment of SCr and potassium 48–96 hours following contrast exposure.

In summary, there have been many attempts to identify the pharmacologic "silver bullet" that would prevent contrast-induced nephropathy in the at-risk patient population. Unfortunately, no single pharmacologic compound has been able to show in a consistent fashion its ability to improve on the results seen with hydration alone. With the mixed results observed with NAC, we await an appropriately powered multicenter, randomized clinical study similar in design to the CONTRAST trial to evaluate its efficacy. Other presentations in this supplement underscore the important role of contrast agent selection in the prevention of CIN. ■

References

1. Solomon R, Werner C, Mann D, et al. Effects of saline, mannitol and furosemide on acute decreases in renal function induced by radiocontrast agents. *N Engl J Med*. 1994; 331:1416–1420.
2. Stevens M, McCullough P, Tobin K, et al. A prospective randomized trial of prevention measures in patients at high risk for contrast nephropathy. *J Am Coll Cardiol*. 1999; 33:403–411.
3. Bakris G, Lass N, Glock D. Renal hemodynamics in radiocontrast medium–induced renal dysfunction: a role for dopamine-1 receptors. *Kidney Int*. 1999;56:206–210.
4. Madyoon H, Croushore L, Weaver D, Mathur V. Use of fenoldopam to prevent radiocontrast nephropathy in high-risk patients. *Catheter Cardiovasc Interv*. 2001;53:341–345.
5. Annapoorna K, Sharma S. Managing the high-risk patient: experience with fenoldopam, a selective dopamine receptor agonist, in prevention of radiocontrast nephropathy during percutaneous coronary intervention. *Rev Cardiovasc Med*. 2001;2(suppl 1):S19–S25.
6. Tumlin JA, Wang A, Murray PT, Mathur VS. Fenoldopam mesylate blocks reductions in renal plasma flow after radiocontrast dye infusion: a pilot trial in the prevention of contrast nephropathy. *Am Heart J*. 2002;143:894–903.
7. Stone G, McCullough P, Tumlin J, et al. A prospective randomized placebo-controlled trial evaluating fenoldopam mesylate for the prevention of contrast-induced nephropathy. The CONTRAST trial. Abstract presented at the 52nd Annual ACC Scientific Session, Chicago, IL, March 2003.
8. Gare M, Haviv Y, Ben-Yehuda A, et al. The renal effects of low-dose dopamine in high risk patients undergoing coronary angiography. *J Am Coll Cardiol*. 1999;34:1682–1688.
9. Abizaid AS, Clark CE, Mintz GS, et al. Effects of dopamine and aminophylline on contrast-induced acute renal failure after coronary angioplasty in patients with preexisting renal insufficiency. *Am J Cardiol*. 1999;83:260–263, A5.
10. Juste RN, Moran L, Hooper J, Soni N. Dopamine clearance in critically ill patients. *Intensive Care Med*. 1998:1217–1220.
11. Mathur V. Pathophysiology of radiocontrast nephropathy and use of fenoldopam for its prevention. *Rev Cardiovasc Med*. 2001;2(suppl 1);S4–S8.
12. Bakris G, Burnett J. A role for calcium in radiocontrast-induced reductions in renal hemodynamics. *Kidney Int*. 1985;27:465–468.
13. Koch J, Plum J, Grabensee B, Modder U. Prostaglandin E1: a new agent for the prevention of renal dysfunction in high risk patients caused by radiocontrast media? PGE1 Study Group. *Nephrol Dial Transplant*. 2000;15:43–49.
14. Erley C, Duda S, Schlepkow S, et al. Prevention of radiocontrast media induced nephropathy in patients with pre-existing renal insufficiency by hydration in combination with the adenosine antagonist theophylline. *Nephrol Dial Transplant*. 1999;14:1146–1149.
15. Huber W, Iigman K, Page M, et al. Effect of theophylline on contrast material induced nephropathy in patients with chronic renal insufficiency: controlled randomized, double-blinded study. *Radiology*. 2002;223:772–779.
16. Kolonko A, Wiecek A, Kokot F. The nonselective adenosine antagonist theophylline does prevent renal dysfunction induced by radiographic contrast agents. *J Nephrol*. 1998; 11:151–156.
17. Kapoor A, Kumar S, Gulati S, et al. The role of theophylline in contrast-induced nephropathy: a case-control study. *Nephrol Dial Transplant*. 2002;17:1936–1941.
18. Tepel M, Van der Giet M, Schwarzfeld C, et al. Prevention of radiographic contrast agent induced reductions in renal function by acetylcysteine. *N Engl J Med*. 2000;342:180–184.
19. Kay J, Chow W, Chan T, et al. Acetylcysteine for prevention of acute deterioration of renal function following elective coronary angiography and intervention: a randomized trial. *JAMA*. 2003;289:553–558.
20. Diaz-Sandoval L, Kosowsky B, Losordo D. Acetylcysteine to prevent angiography related renal tissue injury. (The APART trial). *Am J Cardiol*. 2002;89:356–358.
21. Briguori C, Managanelli F, Scarpato P, et al. Acetylcysteine and contrast agent associated nephrotoxicity. *J Am Coll Cardiol*. 2002; 40:298–303.
22. Baker C, Wragg A, Kumar S, et al. A rapid protocol for the prevention of contrast-induced renal dysfunction: The RAPPID study. *J Am Coll Cardiol*. 2003;41:2114–2118.
23. Birck R, Krzossok S, Markowetz F, et al. Acetylcysteine for prevention of contrast nephropathy: meta-analysis. *Lancet*. 2003; 362:598-603.
24. Gupta R, Kapoor A, Tewari S, et al. Captopril for prevention of contrast-induced nephropathy in diabetic patients. A randomized study. *Indian Heart J*. 1999;51:521–526.
25. Fuchs S, Yaffe R, Beeri R, et al. Failure of insulin-like growth factor 1 to improve radiocontrast nephropathy. *Exp Nephrol*. 1997;5:88–94.
26. Kurnik BR, Allgren RL, Genter FC, et al. Prospective study of atrial natriuretic peptide for the prevention of radiocontrast-induced nephropathy. *Am J Kidney Dis*. 1998;31: 674–680.
27. Vogt B, Ferrari P, Schonholzer C, et al. Prophylactic hemodialysis after radiocontrast media in patients with renal insufficiency is potentially harmful. *Am J Med*. 2001; 111:692–698.
28. Berger ED, Bader BD, Bosker J, et al. Contrast media-induced kidney failure cannot be prevented by hemodialysis [German]. *Dtsch Med Wochenschr*. 2001;126:162–166.
29. Weisberg LS, Kurnik PB, Kurnik BR. Risk of radiocontrast nephropathy in patients with and without diabetes. *Kidney Int*. 1994;45:259–265.
30. Wang A, Bashore T, Holcslaw T, et al. Philadelphia: American Society of Nephrology; 1998:137A.
31. Carraro M, Mancini W, Artero M, et al. Dose effect of nitrendipine on urinary enzymes and microproteins following non-ionic radiocontrast administration. *Nephrol Dial Transplant*. 1996;11:444–448.
32. Moore RD, Steinberg EP, Powe NR, et al. Nephrotoxicity of high-osmolality versus low-osmolality contrast media: randomized clinical trial. *Radiology*. 1992;182:649–655.
33. Marenzi G, Marana I, Lauri G, et al. The prevention of radiocontrast-agent-induced nephropathy by hemofiltration. *N Engl J Med*. 2003; 349:1333-1340.