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Pharmacotherapeutic options to prevent radiocontrast-induced acute renal failure

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Renal insufficiency induced by intravenous, iodinated contrast media remains an important etiology of acute renal failure (ARF). This pathology is most often defined as an acute impairment of renal function manifested by an absolute increase in the serum creatinine of at least 0.5 mg/dL in patients with a baseline level of ≤2.0 mg/dL. An alternative description reported by various clinical trials is an increase in the plasma creatinine concentration by 25%–50% over baseline. The administration of radiocontrast media can lead to a reversible form of ARF that begins shortly after the dye is administered. Since ARF is both serious and costly, the best treatment for contrast-induced nephropathy is prevention.

Radiocontrast-induced nephropathy is cited as the third most common cause of ARF in the hospital setting, accounting for 10% of all cases. The reported incidence of this organ failure varies widely, from 0% to more than 50%. It is thought that the differences in the definition of nephropathy, the type and amount of contrast agent administered, the patient comorbidities, and the exact radiological procedure all account for this variability in reported incidence.

According to prospective clinical trials, small increases in serum creatinine (averaging 0.2 mg/dL) are not an uncommon finding in most patients following a radiocontrast study. Renal function markedly declines, however, in patients with 1 or more of the risk factors that are highlighted in Table 1. Independent risk factors for contrast media-induced nephropathy requiring dialysis include prior renal insufficiency, diabetes, and multiple doses of a contrast agent. The incidence of a patient developing ARF escalates with an increasing number of risk factors present.

The morbidity associated with contrast-induced ARF includes various nonrenal pathologies. A decline in excretory renal function following a contrast study increases the probability of a patient developing a nonrenal pathology that may result in death. In addition, studies have shown that in-hospital mortality is high and long-term survival is poor in patients who develop contrast-induced ARF. The development of contrast-induced ARF leads to increased hospitalization time, including time in the intensive care unit, with an obvious impact on the cost of healthcare.

**REVIEW OF RADIOCONTRAST MEDIA**

To fully comprehend the etiology of ARF from the administration of radiocontrast media, it is important to understand the purpose of contrast agents and the pharmacology behind them. The development of skeletal radiography began with Röntgen’s discovery of the x-ray. Images are produced on x-ray film when radiation passing through the body and hits the photographic film. The amount of radiation passing through the body depends on the type as well as the thickness of a tissue. Bone, being denser than air, absorbs more x-rays and therefore appears white on the film. Air, which absorbs little if any radiation, appears black on the x-ray film. The remainder of the body, including the muscles, liver, kidneys, heart, and brain, all absorb approximately the same amount of radiation due to the fact that they are of the same density. Any pathological process...
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that causes a distinct density difference compared to adjacent anatomical structures can be visualized on plain x-ray film by a natural, physiological contrast effect. Unfortunately, in many disease states the pathological tissue has nearly the same density as the adjacent structures and therefore cannot be differentiated on film. Contrast media are used to visualize the anatomy or pathologic processes that would not be seen otherwise. Radiocontrast agents can be administered either enterally or parenterally. It is the iodinated contrast agents given intravenously that carry the risk of a patient developing ARF.

Iodine-based contrast dye is utilized because an atom of iodine possesses chemical properties ideal for efficiently absorbing x-ray radiation. Iodinated contrast agents can be divided into either ionic or nonionic contrast agents. Ionic, or first-generation, agents are tri-iodated benzoic acid salts that possess high osmolality secondary to the salt dissociating in the dye solvent. These highly hyperosmolar solutions are approximately 5–8 times (1,500–1,800 mosmol/kg) the osmolality of plasma. Iopamidol (Isovue, Squibb Diagnostics), iohexol (Omnipaque, Nycomed), and metrizamide (Amipaque, Winthrop) are examples of second-generation agents. These nonionic contrast agents are significantly more expensive than the first-generation ionic contrast media. Newer, nonionic contrast agents are now available that are dimers in solution, making them iso-osmolar to the serum. Iodixanol (Visipaque, Nycomed), is an example of a nonionic, iso-osmolal contrast dye. Table 2 summarizes the differences between the 2 major types of contrast media.

The physiological effects following administration of intravenous contrast dye are numerous and can include vasoconstriction, an increase in intravascular volume, hypotension, pain upon injection, electrolyte changes and potential cardiac dysfunction, anaphylactic reactions, and nephrotoxicity. There are multiple factors that influence the pharmacodynamics of contrast media. As the concentration of iodine in the dye increases, not only does contrast improve on the x-ray film, but an increase in the risk of adverse reactions is observed. The total dose or volume of the contrast agent administered also correlates with a risk of adverse events.

The pharmacokinetics of intravenous contrast media mimic many 1-compartment, single-dose, bolus-administered medications. After injection, a very rapid peak plasma concentration is achieved and is followed by a steady decline in serum concentration. This decay can be attributed to rapid mixing in the vascular compartment along with continuous renal excretion. The distribution half-life of most contrast agents is approximately 10 minutes, and the elimination half-life is approximately 2 hours. Contrast media possess a relatively small volume of distribution of approximately 0.25 L/kg and there is no protein binding or metabolism.

PATHOLOGY

The exact mechanism that fuels the development of ARF after administration of radiocontrast media is not fully understood. There are currently 2 primary theories that may act separately or in concert with one another to promote renal insufficiency. One possibility is renal vasoconstriction mediated by the release of endothelin and adenosine. A second theory is direct tubular injury associated with the generation of oxygen free radicals.

The degree of renal vasoconstriction does not correlate with increases in serum creatinine concentrations. Vascular tone is determined through a complex equilibrium between endogenous vasoconstrictors and vasodilators. Due to the high osmolality of radiocontrast dyes, prolonged renal vasoconstriction is possible and is further mediated by the contrast-induced release of endothelin and adenosine. Antagonizing the release of protective vasodilators (eg, nitric oxide and prostaglandins), as well as concomitant disease states such as diabetes and chronic heart failure, also contribute to reductions in medullary blood flow and marked ischemia. This alteration in renal hemodynamics leads to diminished oxygen tension in the renal cortex and intensifies medullary hypoxia, resulting in ARF.

Direct renal tubular injury can act in conjunction with or can be exacerbated by renal vasoconstriction. The direct cytotoxic effects of radiocontrast agents are mediated by oxygen free radicals. These reactive oxygen species accumulate following the infusion of contrast dyes secondary to a decreased activity of protective antioxidant enzymes and hypovolemia. The renal epithelium exposed to such oxidants sensitizes the redox state of these cells and provokes apoptosis.

CLINICAL PRESENTATION

Contrast-induced nephropathy is generally benign in course and rarely leads to chronic renal failure. The renal in-

Table 1

**Risk factors associated with development of radiocontrast-induced acute renal failure**

<table>
<thead>
<tr>
<th>Pre-existing renal insufficiency</th>
<th>Diabetes mellitus with renal insufficiency</th>
<th>Dehydration</th>
<th>Hypotension</th>
<th>Nephrotic syndrome</th>
<th>Chronic heart failure</th>
<th>Multiple myeloma</th>
<th>Drugs adversely affecting renal function (NSAIDs, ACE inhibitors, aminoglycosides)</th>
</tr>
</thead>
</table>

Formulary/Source: Refs 5,8,53
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Acute renal failure (ARF) may be associated with significant morbidity and mortality, and in the United States alone, the cost of ARF-related expenses is estimated at $8 billion per year. Therefore, initiatives to educate pharmacists, physicians, and other health-care providers about how to decrease the incidence of radiocontrast-induced ARF are warranted.

sufficiency associated with the use of contrast media typically begins immediately after administration of the contrast agent. In most cases, there is an acute rise in serum creatinine from 24–48 hours after the radiographic study. As mentioned earlier, it is not uncommon to see a small increase in the serum creatinine by 0.1–0.2 mg/dL in all patients. For escalations greater than these values, the index of suspicion should be raised for the likelihood of contrast-induced nephropathy. Although the diagnosis of this pathology is based upon the unexpected rise in serum creatinine, the differential diagnosis of ARF could include renal atheroemboli if the patient is status-post angiography with diffuse atherosclerosis.

While patients experiencing this form of ARF usually present with nonoliguric renal dysfunction, oliguria is also possible. Renal function begins to stabilize in medically uncomplicated patients within 3–5 days. The decline in renal function is mild and transient for most patients; however, those with multiple pathologies or additional organ failure suffer a more severe form of renal failure.

PREVENTION STRATEGIES

Prevention is considered the best approach for contrast-induced renal failure, yet the optimal strategy to achieve this goal remains uncertain. Some possible preventive measures include the use of alternative imaging modalities, minimizing the volume of contrast agents administered, avoidance of repetitive or consecutive contrast-dependent studies, and the use of low or iso-osmolar nonionic contrast agents. However, the expense compared to other low-osmolar contrast agents may be prohibitive in certain practice settings.

Multiple pharmaceutical agents have also been explored to decrease the incidence of ARF following administration of radiocontrast dye. Numerous vascular-altering agents such as calcium channel blockers, endothelin antagonists, prostaglandin E1, atrial natriuretic peptide, dopamine, captopril, and theophylline have also been researched. Clinical trials involving these medications have produced disappointing results and have forced health-care providers to turn to other drugs such as acetylcysteine and fenoldopam in addition to aggressive hydration.

HYDRATION

Volume expansion to maintain a high urine output (minimum 0.5 mL/kg/min) and positive fluid balance was the first intervention to show a reduction in the negative renal effects of contrast media. It is known that patients presenting with dehydration have both decreased renal blood flow and glomerular filtration rates. Renal tubular exposure to the contrast agent is prolonged secondary to poor renal blood flow.

The decision regarding which crystalloid to employ remains unclear. A comprehensive review of the literature reveals conflicting recommendations. There are currently no studies that have directly compared the different crystalloids used for maintenance of intravascular volume. Numerous trials focusing on medications have utilized either half-normal saline or saline as the intravenous fluid (IVF) to maintain hydration in study patients. The results of one study suggest that hydration with normal saline may be superior to half-
normal saline, most notably in diabetic patients. Most practitioners initiate the fluid 4–12 hours prior to the contrast procedure at a rate of 1–3 mL/kg/h. Judicious hydration usually continues up to 4–12 hours after the procedure. Patients with chronic heart failure are at obvious risk for volume overload, and continuous peripheral oxygen saturation or pulse oximetry should be measured to maintain oxygenation greater than or equal to 92%.

ACETYLICYSTEINE

Acetylcysteine (Mucomyst, Apothecon) is a thiol-containing compound that functions as an antioxidant. It is commonly used as an oral agent for the treatment of acetaminophen toxicity as well as a nebulizer additive for its mucolytic properties. In 1999, it was reported that the use of acetylcysteine improved renal function in patients with early hepatorenal syndrome. Although this was not a controlled trial, the findings generated enough interest to warrant the evaluation of acetylcysteine in other patient populations suffering from ARF.

Several studies have now explored the use of acetylcysteine in patients with renal insufficiency undergoing radiographic studies requiring intravenous contrast media. These prospective, randomized, controlled trials have demonstrated that the administration of oral acetylcysteine in combination with appropriate crystalloid hydration and a nonionic or low-osmolar contrast agent has protective capabilities against contrast-induced nephropathy. In these studies, patients received 400–600 mg of acetylcysteine twice daily on the day before and the day of the contrast-dependent procedure. Examination of the data revealed that at 48 hours after the radiographic procedure, elevations of serum creatinine were significantly less in the treatment group compared to placebo. The results of these trials demonstrate a potential advantage in the use of acetylcysteine, since prior to these studies a proven benefit had only been demonstrated with pre-procedural hydration.

The mechanism behind this potential advantage of acetylcysteine is speculative at best. As described earlier, renal function declines after contrast agents are administered secondary to direct toxic effects of the contrast dye to the renal tubular epithelial cells and alterations in renal hemodynamics. It is hypothesized that reactive oxygen species are the basis of these direct toxic effects. Acetylcysteine may blunt the effects of these oxygen radicals and diminish their dangerous properties. Recent studies have also suggested that acetylcysteine possesses vasodilatory properties. Therefore, acetylcysteine may be capable of preventing ARF following radiocontrast administration by both halting direct oxidative tissue damage and improving renal hemodynamics.

Not all research, however, supports the use of acetylcysteine in this setting. For example, no benefit was observed in 1 trial in which patients were randomized to receive either acetylcysteine or placebo. Both treatment arms were supplied with adequate hydration throughout the study. The results revealed a similar incidence of nephrotoxicity in both arms. Although not statistically significant, diabetic patients showed a trend towards developing increased nephrotoxicity.

Given the contradictory results of acetylcysteine trials in the literature, researchers reviewed the agent’s efficacy in a 2003 meta-analysis of 7 trials that encompassed a total of 805 patients. Analysis of these studies found that compared to periprocedural hydration alone, acetylcysteine in combination with hydration significantly reduces the risk of contrast-induced nephropathy in patients with chronic renal insufficiency. It was noted that the relative risk of contrast-induced nephropathy was not related to the degree of renal insufficiency prior to the radiographic intervention or the amount of radiocontrast dye administered.

Analysis of various trials that studied acetylcysteine to determine its role in the prevention of contrast-induced nephropathy reveals multiple confounding factors. Discrepancies observed in the trials are likely secondary to variations in acetylcysteine dosing schemes, hydration regimens, volume status of the patient at baseline, dose of contrast media administered, and definition of contrast-induced ARF. Despite the incongruity among these published studies, prophylactic acetylcysteine is a relatively inexpensive pharmaceutical with a favorable side effect profile.
### Table 3

**Clinical trials evaluating drugs to prevent radiocontrast-induced nephropathy**

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Study</th>
<th>Patient population</th>
<th>Study design</th>
<th>Results</th>
</tr>
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<tbody>
<tr>
<td><strong>Diuretics</strong></td>
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<tr>
<td>Furosemide</td>
<td>Weinstein et al²⁰</td>
<td>18 patients with pre-existing renal insufficiency</td>
<td>Prospective, randomized trial where patients received fluids only (mean=3 L) or fluids + furosemide (mean=110 mg) 30 min prior to administration of contrast media (ionic &amp; nonionic, mean=245 mL).</td>
<td>At 24 h post-contrast, a rise in Scr and significant renal function decline (P&lt;.005 by ANOVA) occurred in the furosemide group but no change in the control was noted.</td>
</tr>
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<td></td>
<td>Solomon et al*¹⁹</td>
<td>78 patients with CRI undergoing cardiac angiography</td>
<td>Prospective, randomized trial where patients received 1/2NS 12 h pre- to 12 h post-procedure, or NS + mannitol (25 g) 1 h prior to receiving contrast, or NS + furosemide (80 mg) 30 min prior to receiving contrast.</td>
<td>At 48 h post-contrast, 11% (7/25) in mannitol arm, and 40% (10/25) in furosemide arm developed CIN (P=.05 for comparison of all 3 groups, P=.02 for furosemide vs 1/2NS)</td>
</tr>
<tr>
<td><strong>Mannitol</strong></td>
<td>Weisberg et al†²¹</td>
<td>50 patients (24 diabetics, 26 non-diabetics) with CRI undergoing cardiac catheterization</td>
<td>Prospective, randomized, double-blind trial in which patients received NS (100 mL/h) from 12 h pre-catheterization through procedure or 1 of 3 drugs during catheterization (ionic, mean=124 mL): dopamine (2 mcg/kg/min), anaritide (50 mcg 1x, then 1 mcg/min), or mannitol (15 g/dL).</td>
<td>At 48 h post-contrast, no statistically significant difference among treatment groups: 40%, 33%, 50%, and 30% of patients in NS, dopamine,anaritide, and mannitol arms respectively developed CIN.</td>
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<td><strong>Vasoactive agents</strong></td>
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<tr>
<td>Dopamine</td>
<td>Hans et al²⁸</td>
<td>55 patients with CRI undergoing abdominal aortography and angiography of LE</td>
<td>Prospective, randomized trial where patients received dopamine (2.5 mcg/kg/min) or equal volume of NS that was initiated 1 h prior to procedure and continued for 12 h.</td>
<td>No statistical difference was noted in change of baseline Scr between control and dopamine arms, except on Day 1 post-procedure.</td>
</tr>
<tr>
<td>Abizaid et al²⁹</td>
<td>Phase 1: 60 patients (67% diabetic and 27% CHF) with CAD undergoing coronary angioplasty; Phase 2: 72 patients with established CIN</td>
<td>Prospective, unblinded, randomized trial divided into 2 phases. Patients received either 1/2NS (1 mL/kg/h), dopamine (2.5 mcg/kg/min), or aminophylline (4 mg/kg 1x, then 0.4 mg/kg/h) prior to procedure (nonionic, mean=206 mL) in addition to hydration (1/2NS 1 mL/kg/h) in phase 1. In phase 2, patients received 1/2NS (1 mL/kg/h) or dopamine (2.5 mcg/kg/min).</td>
<td>Phase 1: overall incidence of CIN was 38% with no difference in patients receiving hydration vs dopamine or aminophylline. Phase 2: Scr levels were significantly higher (P&lt;.01) and a greater percentage of patients required HD (P=.04) in dopamine-treated patients.</td>
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<tr>
<td>Gare et al²²</td>
<td>66 patients with CRI and/or DM undergoing coronary angiography</td>
<td>Prospective, randomized, double-blind trial where patients received either NS (120 mL/d) + dopamine (2 mcg/kg/min) or NS alone x 48 h.</td>
<td>At 5 d following angiography, no significant difference in the change of Scr levels from baseline was noted between the 2 study arms.</td>
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<tr>
<td>Stevens et al³⁰²</td>
<td>(PRINCE Study: Prevention of Radiocontrast Induced Nephropathy Clinical Evaluation)</td>
<td>98 patients (mean baseline Scr=2.5 mg/dL, 53% diabetic, 46% CHF) undergoing coronary angiography</td>
<td>Prospective, randomized, single-blind trial where patients were assigned forced diuresis via 1/2NS (150 mL/h pre- to 6 h post-procedure then adjusted to match UOP), furosemide (1 mg/kg up to 100 mg), mannitol (12.5 g over 2 h if PCWP &lt;20 mmHg), or dopamine (3 mcg/kg/min just before and during procedure) vs hydration with 1/2NS and matching placebos.</td>
<td>At 48 h post-procedure, there was no significant difference in the mean individual change in Scr between the experimental and control arms (P=.87). 32.6% of patients in the experimental arm and 30.9% of patients in the control arm developed CIN.</td>
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</table>

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### Clinical trials evaluating drugs to prevent radiocontrast-induced nephropathy

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Study</th>
<th>Patient population</th>
<th>Study design</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fenoldopam</td>
<td>Madyoon et al †45</td>
<td>46 consecutive patients (SCr ≥1.5 mg/dL if diabetic and SCr ≥1.7 mg/dL if non-diabetic, 52% diabetic and 39% CHF) undergoing contrast study</td>
<td>Retrospective review of patients receiving fenoldopam (up to 0.5 mcg/kg/min 2 h pre- to ≥4 h post-procedure). Results compared to published cohort of similar at-risk patients.</td>
<td>At 48 h post-procedure, 13% of patients developed CIN in the fenoldopam-treated group compared to an expected 38%, and 22% of patients had a decrease of SCr from baseline.</td>
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<td></td>
<td>Chamsuddin et al46</td>
<td>29 patients (mean baseline SCr=2.5 mg/dL) receiving fenoldopam</td>
<td>Retrospective review of patients receiving fenoldopam (mean=0.46 mcg/kg/min) during contrast administration (nonionic, mean=102 mL) to determine acute and long-term effects on kidney function.</td>
<td>At 24 h, SCr decreased by an average of 0.55 mg/dL in 16 of 28 patients following contrast administration. In 9 patients, SCr did not change. 2 of the 3 increases in SCr were attributed to problems not involving contrast media.</td>
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<td>Kini et al*†44</td>
<td>260 patients (mean baseline SCr=2.1 mg/dL, 55% diabetic) undergoing PCI</td>
<td>Prospective, unblinded study of patients receiving fenoldopam 15–20 min pre-procedure and up to 6 h post-procedure (nonionic, mean=142 mL). Patients were hydrated with 1/2NS (1 mL/kg/h) up to 12 h pre-/post-procedure.</td>
<td>Incidence of CIN in all patients was 3.8% (2.8% in diabetics vs 5.1% in non-diabetics)</td>
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<td></td>
<td>Tumlin et al*47</td>
<td>45 patients with CRI undergoing contrast angiography</td>
<td>Prospective, randomized, double-blind, multicenter, placebo-controlled pilot trial where patients received 1/2NS (100 mL/h, 3 h pre- and 4 h post-procedure) or 1/2NS + fenoldopam (0.1 mcg/kg/min at least 1 h before administration of contrast dye (nonionic, mean=88 mL). SCr was measured at baseline and at 24, 48, and 72 h after procedure.</td>
<td>Primary end point was change in renal plasma flow 1 h after contrast. Secondary end point was incidence of CIN. Renal plasma flow 1 h after PCI was 15.8% above baseline fenoldopam group compared to 33.2% below baseline in control. Incidence of CIN was 41.0% in the control vs 21% in fenoldopam arm (P=.148).</td>
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<td>Stone et al‡49</td>
<td>315 patients with renal insufficiency (CrCL &lt;60 mL/min) undergoing PCI</td>
<td>Prospective, randomized, double-blind, multicenter trial where patients were assigned to fenoldopam or placebo in addition to hydration with 1/2NS (1.5 mL/kg/h). The fenoldopam and placebo were initiated 1 h prior to PCI and continued for 12 h.</td>
<td>Primary end point was incidence of contrast nephropathy and secondary end points included complications, LOS, and rehospitalization. Authors reported no difference between study arms for primary or secondary end points.</td>
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<tr>
<td>Captopril</td>
<td>Gupta et al*31</td>
<td>71 patients with DM undergoing coronary angiography</td>
<td>Prospective, randomized trial where patients received captopril (25 mg TID x 3 d starting 1 h prior to contrast) or no captopril.</td>
<td>CIN developed in 29% of patients in control group vs 6% in captopril group. At 24–72 h following contrast, GFR decreased by 9.6 mL/min in control arm vs a GFR increase of 13 mL/min in the captopril arm.</td>
</tr>
<tr>
<td>Atrial natriuretic peptide</td>
<td>Kurnik et al*124</td>
<td>247 patients (50% diabetic) with stable CRF</td>
<td>Prospective, randomized, multicenter, double-blind study where patients received 1 of 3 doses of anaritide (0.01 mcg/kg/min, 0.05 mcg/kg/min, or 0.1 mcg/kg/min) or placebo 30 min pre-procedure and continuing 30 min post-procedure. All patients received 1/2NS from 12 h before to 12 h after contrast.</td>
<td>No statistically significant difference between treatment groups when examining baseline SCr, change in SCr, or incidence of CIN.</td>
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### Radiocontrast-induced ARF

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<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Endothelin antagonist</td>
<td>Wang et al*125</td>
<td>158 patients (68% diabetic with CRI mean baseline SCr=2.8 mg/dL) undergoing PCI</td>
<td>Prospective, randomized, multicenter, double-blind trial where patients were to receive either a mixed endothelin A and B antagonist or placebo in addition to hydration before and after contrast administration. SCr measured at baseline, 24 h, 48 h, and 3-5 d post-procedure.</td>
<td>Mean SCr 48 h after PCI was higher and incidence of CIN was higher (56% vs 29%, P=.002) in endothelin antagonist arm compared to placebo. Negative effect apparent in both diabetic and non-diabetic patients. Hypotension more common in endothelin antagonist arm.</td>
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<td><strong>Radical scavenger</strong></td>
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<td>Acetylcysteine</td>
<td>Tepel et al*25</td>
<td>83 patients with CRI mean baseline SCr=2.4 mg/dL undergoing CT with contrast</td>
<td>Prospective, randomized, placebo-controlled trial where patients received acetylcysteine (600 mg PO BID) or placebo on day before and day of contrast (nonionic, 75 mL). All patients received 1/2NS (1 mL/kg/h) as hydration 12 h before and after contrast administration.</td>
<td>Incidence of CIN was higher in placebo arm compared to treatment group (21% vs 2%, P=.01) with NNT=6.</td>
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<td>Briguori et al*38</td>
<td>183 patients with impaired renal function mean baseline SCr=1.52 mg/dL undergoing contrast procedure</td>
<td>Prospective, randomized trial where patients were assigned to 1/2NS (1 mL/kg/h) and acetylcysteine (600 mg PO BID) or 1/2NS alone (1 mL/kg/h) 1 d before and day of contrast dye administration.</td>
<td>Development of CIN was higher in placebo group compared to experimental group (11% vs 6.5%, P=.22). Logistic regression analysis revealed that the volume of contrast dye administered (P=.035, OR=2.58, 95% CI, 1.1–4.9) was a predictor of CIN.</td>
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<td>Diaz-Sandoval et al**39</td>
<td>54 patients with impaired renal function (SCr ≥1.4 mg/dL, mean baseline SCr=1.6 mg/dL) undergoing coronary angiography</td>
<td>Prospective, randomized, double blind, placebo-controlled study where patients received acetylcysteine (600 mg PO BID, 1 dose before contrast and 3 doses after) or placebo in addition to 1/2NS (1 mL/kg/h 2–12 h pre- and 12 h post-procedure).</td>
<td>Incidence of CIN was greater in placebo arm compared to treatment arm (45% vs 8%, P=.005) with NNT=3.</td>
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<td>Durham et al*42</td>
<td>79 patients with impaired renal function (SCr &gt;1.7 mg/dL, mean baseline SCr=2.3 mg/dL) undergoing PCI</td>
<td>Prospective, randomized, placebo-controlled study where patients received acetylcysteine (1,200 mg PO 1 h before and 3 h after procedure) or placebo in addition to hydration (1/2NS 1 mL/kg/h 2–12 h) as hydration 12 h before and up to 12 h after contrast).</td>
<td>Nephropathy developed in 24% of subjects, 26.3% receiving acetylcysteine, and 22.0% placebo (P=NS). Among subjects with DM, there was no significant difference in nephropathy between groups.</td>
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<td>Shyu et al*36</td>
<td>121 patients with CRI (stable SCr between 2.0–6.0 mg/dL) undergoing coronary angiography</td>
<td>Prospective, randomized, double-blind, placebo-controlled trial in which patients were assigned to receive 1/2NS (1 mL/kg/h 12 h before and after procedure) in addition to acetylcysteine (400 mg PO BID on day before and day of procedure) or placebo. SCr and BUN measured before, 48 h and 7 d after procedure (nonionic, 188 mL).</td>
<td>Occurrence of CIN was greater in the control group than in the treatment arm (24.6% vs 3.3%, P&lt;.001, RR=0.13, 95% CI, 0.08–0.20) with NNT=5.</td>
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<td>Kay et al**37</td>
<td>200 patients with CRI (stable CrCl &lt;60 mL/min) undergoing coronary angiography</td>
<td>Prospective, randomized, placebo-controlled trial where participants were assigned acetylcysteine (600 mg PO BID on day before and day of procedure) or placebo in addition to NS (1 mL/kg/h 12 h before and 12 h after contrast exposure).</td>
<td>At 48 h, the incidence of CIN was higher in placebo arm compared to treatment group (12% vs 4%, P=.03, RR=0.32, 95% CI, 0.10–0.96) with NNT=13.</td>
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</tbody>
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**Clinical trials evaluating drugs to prevent radiocontrast-induced nephropathy**

**Continued on page 178**
### Radiocontrast-induced ARF

#### Intervention from page 177

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Study</th>
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<tr>
<td>Acetylcysteine</td>
<td>Allaqaband et al*48</td>
<td>123 patients with CRI (baseline Scr &gt;1.6 mg/dL or CrCL &lt;60 mL/min undergoing contrast-dependent cardiovascular procedures)</td>
<td>Prospective, randomized trial in which patients received hydration (1/2NS 1 mL/kg/h 12 h before and 12 h after procedure), or acetylcysteine hydration (1 mL/kg/h 24 h before and 24 h after procedure) and hydration, or fenoldopam (0.1 mcg/kg/min) plus hydration 4 h before and 4 h after procedure.</td>
<td>At 48 h post-contrast, 15.3% in the hydration arm, 17.7% in the acetylcysteine arm, and 15.7% in the fenoldopam arm developed CIN (P&lt;.919).</td>
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</table>

### Adenosine antagonist

| Theophylline          | Kolonko et al22                 | 58 healthy patients (exclusion criteria included pregnancy, CHF, DM, HTN, Scr >1.4 mg/dL) | Prospective, randomized study in which participants were randomized to 165 mg theophylline IV or 0.9% saline 30 min prior to contrast administration (ionic, 40 mL). | At 24 h, a small but transient decrease in GFR and rise in Scr were noted in the placebo group but not observed in the theophylline treatment arm. |

### Calcium channel blocker

| Nifedipine           | Khoury et al26                  | 85 patients undergoing scheduled CT or IVP                                          | Prospective, randomized, single-center study in which patients either received nifedipine (10 mg 1 h prior to contrast) or no treatment. | Baseline Scr compared to max levels 24 h and 48 h after administration of contrast revealed a +0.03 mg/dL difference with nifedipine, and +0.08 mg/dL with control (P<.54). |

### Other

| Prostaglandin E1     | Koch et al27                   | 130 patients with renal insufficiency (Scr ≥1.5 mg/dL, mean baseline Scr=2.2 mg/dL undergoing contrast procedure) | Prospective, randomized study where patients were randomized to 3 different doses of PGE1 (10, 20, 40 ng/kg/min) or placebo from 1 h pre- to 5 h post-contrast. Hydration consisted of 1 L NS and 1 L D5W. | All treatment groups had increases in Scr from baseline; however, PGE1 did lower the rate of increase in patients with CRI compared to placebo (P=.0136 placebo vs 20 ng/kg/min group). |

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SCr=serum creatinine; 1/2NS=0.45% NaCl solution; NS=0.9% NaCl solution; CIN=contrast-induced nephropathy; CRI=chronic renal insufficiency; LE=lower extremities; CHF=congestive heart failure; CAD=coronary artery disease; HD=hemodialysis; DM=diabetes mellitus; UOP=urine output; PCWP=pulmonary capillary wedge pressure; PCI=percutaneous coronary intervention; CrCl=creatinine clearance; LOS=length of stay; GFR=glomerular filtration rate; CRI=chronic renal failure; CT=computed tomography; HTN=hypertension; IVP=intravenous pyelogram; PG=prostaglandin; D5W=5.0% dextrose solution

*Contrast-induced nephropathy defined as increase in serum creatinine of >0.5 mg/dL with 48 h of contrast.
†Contrast-induced nephropathy defined as increase in serum creatinine of ≥25% over baseline within 48 h of contrast.
‡Contrast-induced nephropathy defined as increase in serum creatinine of ≥25% over baseline within 96 h of contrast.

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Formulary/Source: Refs 19–32, 35–39, 42, 44–49
Continued from page 178

profile. Since there exists a strong link between contrast-induced nephropathy and increased morbidity and mortality, the potential use of acetylcysteine in this setting warrants further investigation.

FENOLDOPA M

Fenoldopam (Corlopam, Neurex) is a parenteral, selective dopamine-1 agonist approved for the use of systemic hypertension. The agent dilates renal and systemic arteries and increases renal blood flow, reducing renal vascular resistance without altering glomerular filtration rate. Fenoldopam also increases renal blood flow in a dose-dependent manner and appears to preferentially vasodilate different glomerular arterioles. This mechanism explains the substantial increase in blood flow to the medullary regions without affecting the glomerular filtration rate. Urine volume increases as does sodium and water excretion secondary to a non-vascular effect on the distal tubules, which promotes a sodium nature. The drug is metabolized in the liver by conjugation and has no CYP450 drug interactions. These clinical observations stimulated interest to conduct studies using fenoldopam as a prophylactic agent for contrast-induced nephropathy.

Of the many previous interventions studied, none had shown a decrease in the incidence of developing radiographic contrast-induced nephropathy in diabetic patients with elevated baseline serum creatinine concentrations. However, a recent clinical trial elucidated the renoprotective properties of fenoldopam in both diabetic and non-diabetic patients undergoing percutaneous coronary intervention with creatinine values ≥2.0 mg/dL.44 Madyoon and colleagues45 were the first to publish their clinical experience with fenoldopam to prevent contrast-induced nephropathy. In this retrospective review, high-risk patients were given adequate hydration and received a continuous infusion of fenoldopam 2 hours prior to the procedure. Patients remained on the medication for at least 4 hours after the procedure. The dose was initiated at 0.1 mcg/kg/min and titrated up by 0.1 mcg/kg/min increments every 15 to 20 minutes to a maximum of 0.5 mcg/kg/min. Systolic blood pressure was measured regularly and maintained at greater than or equal to 100 mmHg. An important limitation of fenoldopam is the potential for significant hypotension; therefore, patients receiving fenoldopam should have their blood pressure monitored regularly during the course of treatment. Table 4 outlines the general algorithm that was followed in this study to initiate a fenoldopam infusion for patients at risk of developing contrast-induced nephropathy.*

Madyoon and colleagues documented contrast-induced ARF in only 13% of the high-risk patients receiving fenoldopam, which was substantially lower than the 38% observed in previous controls (statistical comparison not performed). At 48 hours after the procedure, a decrease from baseline serum creatinine was documented in 22% of the patients. The addition of fenoldopam to pre-procedural hydration has resulted in positive clinical outcomes as reported by several other clinical trials.46,47

Although several studies support the use of fenoldopam as a renoprotective agent in patients at risk for developing contrast-induced nephropathy, until recently, no clinical trials had been performed that compared fenoldopam to other interventions such as hydration and/or acetylcysteine. One study examined the incidence of contrast-induced nephropathy among 3 groups of patients: 1 received only saline, another received acetylcysteine, and the last group received fenoldopam.48 Results of the trial showed that the occurrence of contrast-induced ARF was 17.7% in the acetylcysteine group, 15.3% in the hydration group, and 15.7% in the fenoldopam group (P=.919). The au-

Table 4

Sample protocol for fenoldopam administration to patients at risk for ARF following radiocontrast procedure*

- Obtain CMP to check for electrolyte abnormalities.
- Begin IV hydration with 0.9% saline at 1–3 mL/kg/h maintaining positive fluid balance but maintaining SpO₂ >92%.
- Prepare fenoldopam drip by diluting 10 mg fenoldopam in 250 mL of 0.9% saline (concentration of 40 mcg/mL).
- 2 h prior to procedure, initiate fenoldopam infusion at 0.1 mcg/kg/min.
- Increase fenoldopam infusion by 0.1 mcg/kg/min q 15–20 min to a maximum of 0.5 mcg/kg/min.†
- Monitor BP with each dosage increase and maintain SBP ≥100 mmHg.
- Monitor BP q 30 min during fenoldopam administration.
- Maintain fenoldopam infusion at highest obtained dose throughout procedure.
- Continue fenoldopam infusion for at least 4 h following procedure.
- Fenoldopam infusion may be continued until UOP >0.5 mL/kg/h should patient become anuric after the procedure.

CMP=complete metabolic profile; SpO₂= peripheral oxygen saturation; BP= blood pressure; SBP= systolic blood pressure; UOP= urine output

* Multiple protocols exist; this regimen represents 1 algorithm studied in the literature.
† A more rapid titration is possible: Increase infusion q 15 min by 0.1 mcg/kg/min to a maximum of 0.3 mcg/kg/min.
thors concluded that acetylcysteine and fenoldopam offered no prophylactic value against radiocontrast-induced ARF when compared to hydration alone.

The results of the CONTRAST trial were presented at the American College of Cardiology 2003 Scientific Sessions.49 Their study is the first randomized, double-blind, multicenter, placebo-controlled trial to examine the efficacy of fenoldopam in preventing contrast-induced ARF following a contrast-dependent, interventional cardiology procedure. After randomizing patients to either fenoldopam or placebo, the authors reported that fenoldopam was no more effective than hydration alone in averting the deterioration of renal function following administration of contrast media (33.6% vs 30.1%; P=.61; RR=1.11, 95% CI, 0.79–1.57).49 The conclusions of this study suggest that fenoldopam should not be used as a prophylactic measure to prevent the development of contrast-induced nephropathy.

RENAL REPLACEMENT THERAPY

Although not a pharmacotherapeutic modality, prophylactic hemodialysis is another proposed method of protection against contrast-induced nephropathy in high-risk patients. Two randomized studies have previously shown no benefit to patients receiving renal replacement therapy following the radiographic study to actively remove the contrast media from circulation.46,47 A clinical trial published in 2003, however, reports novel results. Marenzi et al48 found that deterioration of renal function could be attenuated with pericardial hemodialysis in patients with chronic renal failure undergoing percutaneous coronary intervention. The discrepancy among conclusions in these clinical trials warrants further study and analysis.

CONCLUSION

The optimal strategy to eliminate contrast-induced ARF remains uncertain. Further research in this area is warranted since no satisfactory animal model of contrast-induced ARF exists. It is apparent that the etiology of this disease state is multifactorial and close inspection of the current literature reveals that a poor control of relevant variables in clinical trials has led to the reporting of widely conflicting conclusions.

A key step to safer contrast-assisted interventions is to identify patients at high risk for contrast-induced nephropathy. If the necessity of a contrast-dependent imaging study cannot be postponed, aggressive crystalloid hydration to maintain a positive fluid balance and high urine output should be initiated prior to the procedure and should also be continued after the exam. In addition to adequate hydration, all medications that could potentiate the nephrotoxicity of contrast media by adversely affecting renal blood flow should be discontinued prior to the procedure. In high-risk patients, the use of a nonionic, iso-osmolar contrast agent also serves as a preventive measure.

The application of periprocedural drugs has been considered in the past; however, due to inconsistent results from many clinical trials, the potential use of these agents should be dependent on careful consideration of their risks, benefits, and economic value. Given the need for alternative, evidence-based interventions to reduce the incidence of contrast-induced nephropathy, it is conceivable that combination drug strategies such as acetylcysteine (to reduce chemotoxicity) in combination with a medication that promotes renal vasodilation may be an area for future research.

REFERENCES


