Design and Rationale of CONTRAST—A Prospective, Randomized, Placebo-Controlled Trial of Fenoldopam Mesylate for the Prevention of Radiocontrast Nephropathy

Gregg W. Stone, MD, * James A. Tumlin, MD,† Hooman Madyoon, MD,‡ Norman E. Lepor, MD,§ Peter A. McCullough, MD, ê¶ Vandana S. Mathur, MD,¶ Patrick T. Murray MD,# William W. O'Neill MD**

*Lenox Hill Hospital, New York, NY, †Emory University, Atlanta, GA, ‡St. Joseph's Medical Center, Stockton, CA, §Cedars-Sinai Medical Center, Los Angeles, CA, êUniversity of Missouri-Kansas City School of Medicine, Truman Medical Center, Kansas City, MO, ¶University of California San Francisco, San Francisco, CA, #University of Chicago, Chicago, IL, **William Beaumont Hospital, Royal Oak, MI

Radiocontrast-induced nephropathy develops in approximately 10% to 20% of patients following administration of iodine-based dye and is one of the most prognostically detrimental complications that invasive cardiologists and radiologists encounter. Preexisting renal dysfunction and diabetes mellitus are two of the most powerful predictors of the likelihood of developing acute renal insufficiency after contrast delivery. To date, only adequate preprocedural hydration and postprocedural hydration to offset dehydration from contrast-induced diuresis have been shown to be effective in preventing this condition. Fenoldopam mesylate, a systemic vasodilator currently FDA-approved for short-term, in-hospital management of severe hypertension, has been shown to increase renal plasma flow in patients with and without chronic renal insufficiency. As a selective agonist of the dopamine-1 receptor, fenoldopam may preserve outer medullary renal blood flow and thereby attenuate radiocontrast-induced nephropathy. Small studies with fenoldopam prior to iodine-based dye administration have demonstrated low rates of radiocontrast nephropathy, and a larger, randomized trial has found that renal blood flow 1 hour after angiography rose in the fenoldopam group compared to a decline in the placebo group. The CONTRAST study has been designed to determine whether fenoldopam is indeed effective in diminishing the occurrence of radiocontrast-induced nephropathy. [Rev Cardiovasc Med. *2001;2(suppl 1):S31–S36*]

Key words: Radiocontrast-induced nephropathy • Coronary balloon angioplasty • Stent implantation • Atheroablation • Fenoldopam mesylate

Radiocontrast-induced nephropathy (RCN), which, depending on the population and definition, develops in approximately 10% to 20% of patients following administration of iodine-based dye,[1,2] is one of the most prognostically detrimental complications that invasive cardiologists and radiologists encounter. Preexisting renal dysfunction and diabetes mellitus are

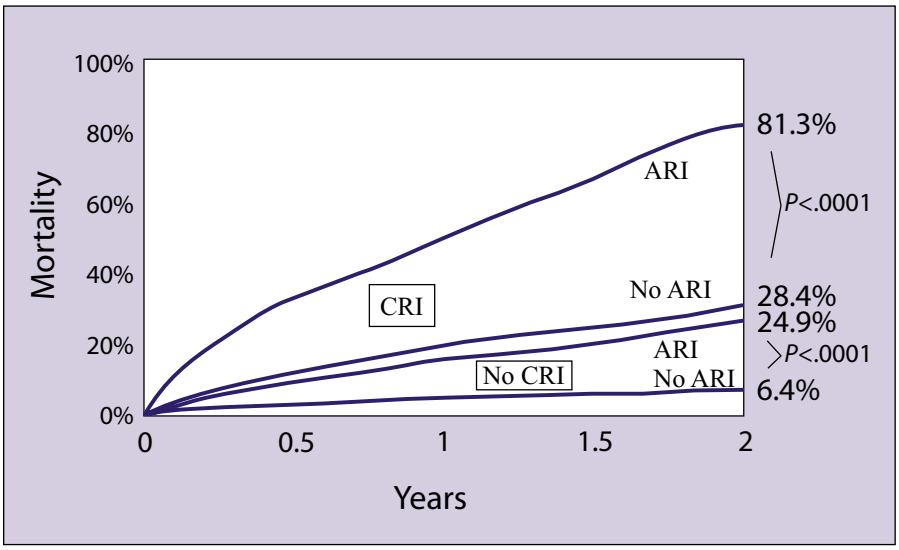

Figure 1. *Cumulative late mortality in 7205 patients at median follow-up of 1.4 years, stratified by the presence or absence of chronic renal insufficiency (CRI) and the development or absence of acute renal insufficiency (ARI) after percutaneous intervention.*

two of the most powerful predictors of the likelihood of developing acute renal insufficiency after contrast delivery.[3,4] In a consecutive series of 439 patients with baseline serum creatinine at or above 1.8 mg/dL undergoing angioplasty at the Washington Hospital Center, 37% had a further rise in serum creatinine of 25% or more within 4 hours.[5] In-hospital mortality was 14.9% for patients with further renal function deterioration versus 4.9% for patients with no creatinine increase (P = .001). Thirty-one patients required hemodialysis; their in-hospital mortality was 22.6%. The cumulative 1-year mortality was 45.2% for those who required dialysis, 35.4% for those who did not require dialysis, and 19.4% for patients with no creatinine increase (P = .001). Thus, while the prognosis is most adverse in the minority of patients requiring dialysis, even lesser degrees of acute renal insufficiency have a negative impact on late survival.

Extending this analysis to the entire Washington Hospital Center database of 7205 unique patients (excluding those with recent myocardial infarction) undergoing coronary balloon angioplasty, atheroablative procedures, or stent implantation, acute renal insufficiency developed in 31.8% of patients versus 4.5% of patients without chronic renal dysfunction (P < .0001). By Kaplan-Meier analysis, 9.8% of patients had died at 2 years, including 44.0% of patients with baseline renal insufficiency versus 8.2% without chronic renal dysfunction. A powerful interaction was observed between the presence of chronic renal insufficiency and the development of acute renal insufficiency on late survival, as shown in Figure 1. Clearly, a poignant need exists to prevent RCN.

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The mechanism of contrast-induced nephropathy is incompletely understood, but involves dye-induced reduction in renal blood flow (especially to the outer renal medulla), reduced oxygen delivery, and impaired autoregulation, ultimately resulting in acute tubular necrosis.[6-9] Iodinated contrast may also be directly toxic to renal tubular cells by generating oxygen radicals.[10] In an attempt to reverse this pathophysiology, prior studies have evaluated forced diuresis with mannitol or furosemide.[3,11,12] and parenteral vasodilators, including aminophylline and atrial natriuretic peptide.[13-15] Other than adequate preprocedural hydration and postprocedural hydration (to offset dehydration from contrast-induced diuresis), none of these measures have convincingly been shown to be effective.[11,12] Similarly, whereas a recent 83-patient randomized trial has found that oral acetylcysteine started 48 hours prior to contrast-enhanced computerized tomographic scans reduced RCN,[16] this finding has not been duplicated with other agents that affect generation of free oxygen radicals.[10] Finally, intravenous dopamine, which at low doses has been shown to increase renal blood flow, has not been found to reduce (and may paradoxically increase) the incidence of RCN.[15,17]

Rationale for Fenoldopam

Fenoldopam mesylate is a systemic vasodilator currently approved by the FDA for short-term, in-hospital management of severe hypertension.[18] It has been shown to increase renal plasma flow in patients with and without chronic renal insufficiency.[19-21] Unlike dopamine, which as a nonselective dopamine-1 (DA_1) and DA_2 receptor agonist has been shown to increase renal blood flow primarily

to the renal cortex,[22] fenoldopam specifically binds to only the DA_1 receptor and thus increases renal blood flow to the outer medulla as well as the cortex.[23] Experimental studies in dogs have shown that fenoldopam protects against the decline in renal blood flow that occurs after intravenous contrast administration.[24] These observations suggest that, unlike dopamine, fenoldopam may preserve outer medullary renal blood flow and thereby attenuate RCN.[25]

Small single-center experiences with fenoldopam prior to iodine-based dye administration have demonstrated low rates of RCN compared to what would have otherwise been expected from historical controls.[26] More recently, Tumlin and colleagues reported the findings from a four-center, prospective, double-blind, randomized trial in which 45 patients with chronic renal insufficiency were randomized to fenoldopam at 0.10 µg/kg/min versus matching placebo.[27] Renal blood flow 1 hour after angiography, the primary end point of the study, *rose* 15.8% above baseline in the fenoldopam group compared to *declining* 33.2% below baseline in the placebo group ($P < .05$). Though the trial was underpowered to demonstrate a reduction in RCN, at 48 hours RCN occurred in 41% of control patients versus 21% in the fenoldopam-treated group ($P = 0.15$). The peak serum creatinine 72 hours after contrast infusion was significantly reduced in the fenoldopam group compared to placebo (3.6 + 1.0 mg/dL versus 2.8 + 0.35 mg/dL; $P < .05$).

The CONTRAST Trial

Based on the encouraging prior investigation,[27] a double-blind, placebo-controlled, multicenter, randomized study, the CONTRAST study (Evaluation of Corlopam in Patients at Risk for Renal Failure—A Safety and Efficacy Trial) has been designed to determine whether fenoldopam is indeed effective in diminishing the occurrence of RCN. In CONTRAST, approximately 300 patients undergoing invasive cardiology procedures and at risk for RCN at approximately 20 to 30 U.S. centers will be enrolled and randomized 1:1 to pretreatment with parenteral fenoldopam versus matching placebo (Figure 2). Randomization will be stratified according to the presence or absence of diabetes mellitus (drug- or insulin-treated). Patient inclusion and exclusion criteria appear in Table 1. The principal entry criteria is for moderately severe but stable baseline renal insufficiency to be present as calculated by the Cockcroft-Gault formula, thereby minimizing the confounding effects of age, gender, and body mass on serum creatinine, guaranteeing enrollment of a uniform population. Other agents that may interfere with fenoldopam or that have not been proven to reduce RCN are prohibited. The exact choice of iodinated contrast (ionic or nonionic and osmolarity) will be left to the discretion of the operator, given the lack of clear evidence that specific contrast properties materially affect the occurrence of RCN.[28,29]

Fenoldopam protects against the decline in renal blood flow that occurs after intravenous contrast administration.

Following randomization and within 2 to 4 hours of catheterization, the patient will be hydrated with 0.45% sodium chloride at a rate of 1.0 mL/kg/hr, as previously recommended,[11,12] an infusion which will be continued to the end of the study period. One hour prior to the anticipated initiation of catheterization, the patient will be started on the study

Figure 2. *Summary of the CONTRAST protocol. Abbreviations as in Figure 1.*

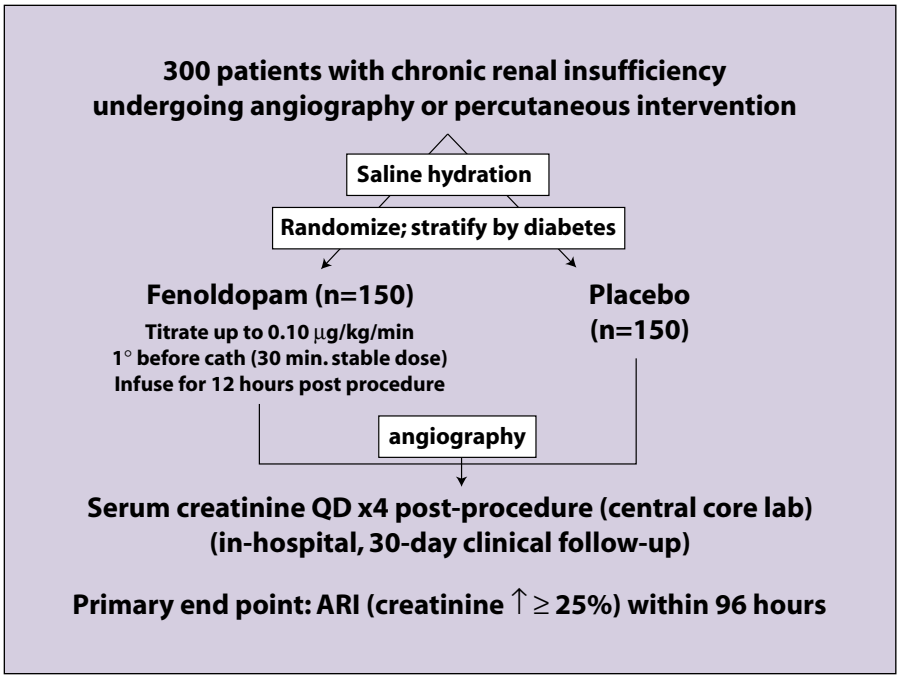

Table 1

Patient Inclusion and Exclusion Criteria in the CONTRAST Trial

Inclusion criteria (all of the following must be present for enrollment):

1. Baseline calculated creatinine clearance must be 20 to 50 cc/min.
2. Patient is undergoing an invasive cardiology diagnostic or interventional procedure in which use of ≥75 cc of iodinated contrast is anticipated.
3. Patient is ≥18 years of age.
4. Patient is willing and able to give informed consent.
5. Female patients of childbearing potential must have a negative serum or urine human chorionic gonadotropin (hCG) pregnancy test.

Exclusion criteria (patient is excluded if any of the following are present):

1. Patient is currently undergoing dialysis.
2. Patient has a known allergy to imaging contrast agents.
3. Patient has a known allergy to fenoldopam mesylate or any of its ingredients, such as metabisulfite or sulfites.
4. Patient has a contraindication for the use of dopaminergic agents (eg, history of increased intraocular pressure or glaucoma).
5. Patient is receiving mannitol or IV diuretics.
6. Patient is unwilling to receive blood or blood products.
7. Patient has an active history of drug or alcohol abuse.
8. Patient is in acute renal failure or has unstable renal function, as evidenced by clinical findings or a change in serum creatinine of ≥0.5 mg/dL or ≥25% within the preceding 10 days.
9. Patient has an SBP < 100 mmHg.
10. Patient has had a myocardial infarction within 72 hours prior to the start of study drug administration.
11. Patient has decompensated heart failure, as defined by the requirement for IV diuretic, inotropic, or vasodilator support.
12. Patient requires respiratory support.
13. The addition, discontinuation, or dose-adjustment of trimethoprim, cimetidine, metoclopramide, bromocriptine, levadopa, nonsteroidal anti-inflammatory drugs (NSAIDs) or catechol O-methyltransferase (COMT) inhibition (eg, encapone or tolcapone) may reasonably be anticipated at any time during the study.
14. Patient is receiving or will receive acetylcysteine or dopamine.
15. Patient has received a contrast agent within 10 days prior to study drug administration, or a second imaging study is planned within the next 10 days.
16. Female patient is pregnant or lactating.
17. Patient has any serious medical condition which, in the opinion of the investigator, is likely to interfere with study procedures.
18. Patient has participated in other clinical trials for investigational drugs and/or devices within 30 days prior to enrollment.

drug infusion at 0.05 µg/kg/min. The study drug will be titrated upward to 0.10 µg/kg/min if the previous dose is tolerated for 20 minutes without excessive hypotension or reflex tachycardia. The infusion will be continued throughout the invasive procedure and for 12 hours after the last contrast injection.

The primary efficacy end point will be the development of RCN, defined as an increase in serum creatinine of 25% or more from baseline within the 24- to 96-hour period following completion of study drug administration. Serum creatinine will be assessed precatheterization and at 1, 24 (or at time of hospital discharge), 48, and between 72 and 96 hours following completion of study drug administration. All blood samples will be sent to a central core laboratory for analysis. Additional end points include hospital length of stay, urinalysis, mortality, and requirement for dialysis or rehospitalization within 1 month after the procedure.

With 134 patients enrolled in each group (268 total subjects), the study will have 80% power to detect the difference between a 30% incidence of RCN in the placebo group and a 15% incidence in the fenoldopam mesylate group, using a two-group, continuity-corrected chi-square test with a 0.05 two-sided significance level. Thus 300 total patients will be randomized to assure more than 80% power and to allow for 10% protocol noncompliance or study withdrawal.

With complete enrollment anticipated in the fall of 2001, the CONTRAST trial, to date the largest multicenter prospective trial yet performed to examine therapies for preventing RCN, will contribute significantly to our understanding of the development and prevention of this grave condition. ■

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Main Points

- After administration of iodine-based dye, 10% to 20% of patients will develop radiocontrast-induced nephropathy.
- Studies attempting prevention of the condition by forced diuresis with mannitol or furosemide and parenteral vasodilators, including aminophylline and atrial natriuretic peptide have found these agents ineffective.
- Preprocedural hydration and postprocedural hydration (to offset dehydration from contrast-induced diuresis) are the only proven measures effective for prevention.
- Fenoldopam mesylate is approved by the FDA for short-term, in-hospital management of severe hypertension; it has been shown to increase renal plasma flow in patients with and without chronic renal insufficiency.
- Fenoldopam specifically binds to the DA_1 receptor and thus increases renal blood flow to the outer medulla as well as the cortex; experiments with dogs have shown that fenoldopam protects against the decline in renal blood flow that occurs after intravenous contrast administration.
- The CONTRAST study is designed to determine whether fenoldopam is indeed effective in diminishing the occurrence of radiocontrast-induced nephropathy.

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