Clinical Experience with the Use of Fenoldopam for Prevention of Radiocontrast Nephropathy in High-Risk Patients

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A protocol for using fenoldopam, an FDA-approved intravenous agent for the treatment of severe hypertension with a newly available renal vasodilatory effect, was adopted to prevent radiocontrast nephropathy in high-risk patients undergoing angiographic procedures. Fenoldopam is a selective dopamine-receptor agonist with renoprotective properties. The results of 46 consecutive procedures were retrospectively reviewed in both diabetic and nondiabetic patients and compared to a prior published cohort of similarly at-risk patients. The incidence of radiocontrast nephropathy was 13% in the group treated with fenoldopam, compared to an expected 38% based on historical controls. The percentage change in serum creatinine was also very favorable. In this clinical experience of a high-volume coronary and peripheral vascular laboratory, the use of fenoldopam in high-risk patients appeared to minimize the likelihood of radiocontrast nephropathy.
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As an interventional cardiologist working in a busy coronary and peripheral vascular lab performing a large volume of diagnostic and interventional angiographic procedures, I realized the impact of radiocontrast nephropathy (RCN) on my ability to treat my patients adequately. Lack of effective treatment for prevention of RCN in high-risk patients, along with the growing trend both to diagnose and definitively treat vascular occlusion nonsurgically, led to adoption of a protocol for using fenoldopam for prevention of RCN.

The incidence of a 1 mg/dL increase in serum creatinine following cardiac catheterization is estimated to be about 5%.[2] These patients are often elderly, diabetic, and have preexisting renal insufficiency or congestive heart failure, which increases the risk for RCN.[1] In patients with multiple preexisting risk factors, incidence of radiocontrast nephropathy may increase up to 80% (diabetics with a serum creatinine of greater than 4 mg/dL).[3] The morbidity and mortality associated with this increase in creatinine has been shown to be significant. In a recent study of more than 12,000 patients undergoing percutaneous coronary interventions, hospital mortality in patients who developed dialysis-requiring RCN was 25%, and 1-year mortality was 55%.[4] Furthermore, in the survivors, renal function failed to return to normal in as many as 30%.[4]

The morbidity and mortality associated with this increase in creatinine has been shown to be significant.

Although it is possible to identify patients who are at high risk for RCN, it is not possible to predict *a priori* which of the patients with a rise in creatinine will go on to develop dialysis-requiring RCN and its attendant morbidity and mortality. Consequently prevention seems to be the mainstay of therapy for these patients at high risk.

Other than use of saline, previously examined drug strategies for RCN prevention have been shown either to have no benefit (mannitol[5]) or to aggravate RCN (diuretics,[5] dopamine[6,7]).

Studies in animal models have shown that fenoldopam fully attenuates the radiocontrast-induced renal blood flow reduction that seems to be the root cause of RCN.[8] Based on the evidence that fenoldopam reverses radiocontrast-induced reduction of blood flow to the kidney, the agent was studied as a potential prophylactic strategy for prevention of RCN. A dose-dependent increase in renal blood flow occurs at very low doses of 0.01 mg/kg/minute and plateaus at around 0.3 mg/kg/min. There is another 5% to 10% increase in renal blood flow up to 0.5 mg/kg/minute. The drug has a very short half-life of 5 minutes, allowing rapid titration in the cardiac catheterization laboratory to optimal levels and rapid reverse titration of effect when necessary.

Patients and Methods

Presented here is a retrospective review of the results of 46 consecutive cases treated with fenoldopam (*Corlopam*®) according to our clinical protocol. These patients were enrolled in the protocol if they were diabetics with serum creatinine levels at or above 1.5 mg/dL or nondiabetics with serum creatinine levels at or above 1.7 mg/dL. Fenoldopam was diluted to 40 µg/mL by adding 10 mg (1 mL ampules) of drug in 250 mL of normal saline or dextrose in water. The infusion was initiated 2 hours prior to radiocontrast exposure as a continuous intravenous infusion, starting at a dose of 0.1 µg/kg/min. The dose was titrated up in increments of 0.1 µg/kg/min every 20 minutes to a maximum dose of 0.5 µg/kg/min, as long as systolic blood pressure remained above 100 mm Hg and diastolic blood pressure remained within 20 mm Hg of baseline. The final dose was maintained throughout the procedure and for a minimum of 4 hours postprocedure. Blood pressure and heart rate were measured 15 to 20 minutes following every dose adjustment, using a standard blood pressure cuff. Every effort was made to give adequate intravenous hydration prior to contrast. All patients received low-osmolar, nonionic radiocontrast (primarily iohexol).

Results

The mean age of the population was 68.8 ± 12.1 years. The mean weight was 84.1 ± 18.9 kg, and 30.4% were female. The serum creatinine at preprocedure baseline was 2.4 ± 1.0 mg/dL (range, 1.5 to 7.3 mg/dL). The patients had a number of major comorbid conditions identified by history prior to angiographic procedures; 63% had myocardial infarction or angina; 61% had renal disease; 48% had peripheral vascular disease or claudication; 52% had drug-treated diabetes; 39% had congestive heart failure; and 20% had cerebrovascular

Table 1
Patient Baseline Comorbidities

• Baseline serum creatinine (mg/dL)	2.37 ± 1.05
• MI or angina	63%
• CVA or TIA	20%
• DM (drug-treated):	52%
• Known history of renal disease	61%
• CHF	39%
• Vascular disease or claudication	48%

Table 2
Baseline Characteristics

	Fenoldopam Group	Comparator Group
Number of Patients	46	50
Baseline Serum Creatinine (mg/dL)	2.4 ± 1.0	2.5 ± 0.1
% with Diabetes Mellitus	52% (drug-treated)	48% (drug- or diet-treated)
Treatment Strategy	Fenoldopam (100%) + saline (41%)	Saline (100%) + dopamine (30%) + mannitol (20%) + atrial natriuretic peptide (20%)
Contrast Volume (mL)	141 ± 85	124 ± 6
Contrast Type	Low-osmolar, nonionic	High-osmolar, ionic

events. (Diagnostic procedures are shown in Table 1.) Mean duration of fenoldopam infusion was 8.7 hours ± 4.8 hours.

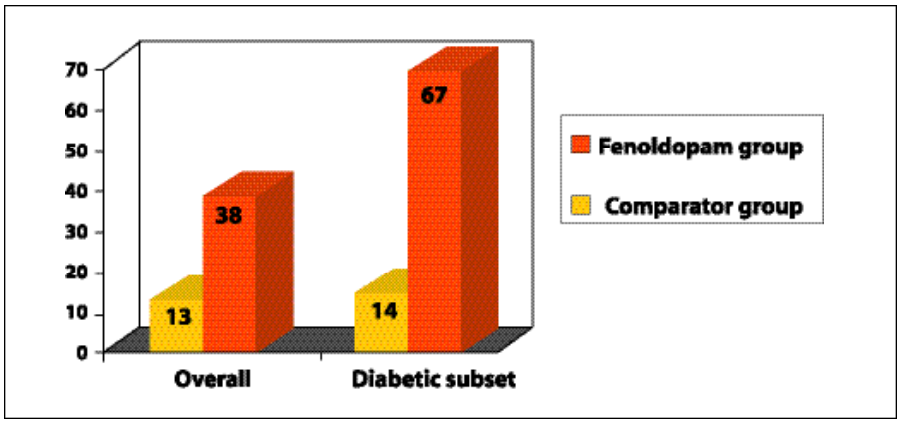
Even though there were blood pressure fluctuations, they did not impact the use of this medication or result in any serious sequelae. Mean systolic blood pressure fell by 26 mm Hg (from 148 mm Hg), and mean diastolic fell by 12 mm Hg (from 76 mm Hg) in the fenoldopam-treated patients. Seven patients (15%) required temporary discontinuation of treatment with fenoldopam because of blood pressure lower than specified by our protocol, but without ill sequelae.

We compared our results with those of a representative benchmark paper[9] with similarly at-risk patients as a comparison group. In the comparator group, patients were randomized to receive saline, dopamine, mannitol, or atrial natriuretic peptide (ANP) starting prior to cardiac catheterization and continuing for 2 hours postprocedure. All patients received 66% diatrizoate meglumine or 10% diatrizoate sodium. Table 2 compares the baseline characteristics of our patients to the comparator group.

The incidence of acute renal failure, defined as a 25% increase in serum creatinine at 48 hours postprocedure, was 13% (6 of 46) in the fenoldopam group compared to 38% (19 of 50) in the comparator group (Figure 1). The incidence of acute renal failure in the comparator group subsets was as follows: saline only, 40%; saline plus dopamine, 33%; saline plus ANP, 50%; and saline plus mannitol, 30%. The incidence of acute renal failure in diabetics was 14% in the fenoldopam group compared with 67% in the comparator group (Figure 1).

The percent increase in serum creatinine at 48 hours from baseline was only 16% in the fenoldopam group compared to an increase of 118% in the control group (Figure 2). At 48

Figure 1. *Percent reduction of radiocontrast nephropathy with fenoldopam compared to historical untreated controlled population. Acute renal failure defined as serum creatinine > 25% over baseline within 48 hours.*



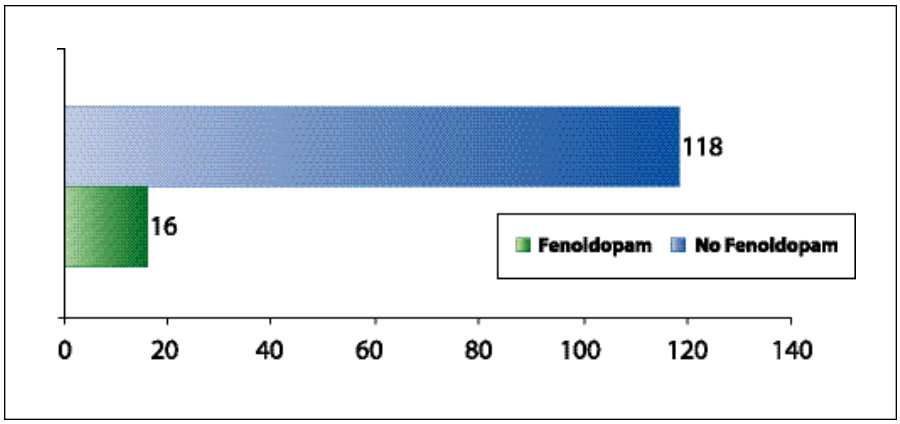


Figure 2. *Percent change in serum creatinine at 48 hours from baseline. Data from Weisberg et al.*[9]

hours, 22% of fenoldopam-treated patients had a reduction in their serum creatinine compared to their preprocedure baseline serum creatinine.

Discussion

Fenoldopam was associated with a low (13%) incidence of acute renal failure in this retrospective study. Of the patients on fenoldopam, 22% actually had a reduction of serum creatinine 48 hours postprocedure compared to baseline. Compared to a similarly at-risk patient population, in the Weisburg study,[6] the incidence of acute renal failure and the rise in serum creatinine at 48 hours postprocedure were reduced by 66% and 87%, respectively.

The renal-protective effect of fenoldopam that has been shown in animal studies and small series is now being observed in a larger series of patients. The published series of 20 patients revealed that 14 were noted to have reductions in serum creatinine 24 hours postprocedure.[10]

The main limitation of this study is that it is uncontrolled and observational in nature. I adopted a clinical protocol for the use of fenoldopam in high-risk patients and retrospectively analyzed their outcomes. The published reference population, which was very similar to that of this study, was used as a historical control. The reference population had an incidence of acute renal failure that was comparable to that described elsewhere in RCN literature.[11]

One of the differences between the fenoldopam group and the control group in the comparator study was our use of low-osmolar dye versus high-osmolar dye in the historical cohort. Even though a lower incidence of RCN was observed in one study in patients with baseline renal insufficiency with one particular contrast agent, this has not been proven for other contrast agents.[12] The use of a larger volume of contrast and lack of saline hydration in the majority of our patients may balance this potential difference.

The excellent results in our patient population, 59% of whom were not able to be hydrated with saline either because of medical contraindications to volume administration or because of logistical considerations, suggest that fenoldopam may be especially useful in these situations. The clinical findings above are consistent with the known ability of fenoldopam to reverse the pathophysiologic mechanism of RCN: the reduction of renal medullary tubular perfusion and subsequent tubular injury and possible necrosis.

On closer study of the 6 patients (13% of the total population) who developed RCN based on the current definition, it was found that a majority of these patients had particular comorbidities that would place them

Main Points

- Preexisting renal insufficiency or congestive heart failure increases the risk for radiocontrast nephropathy in patients undergoing angiography.
- Hospital mortality in patients who developed radiocontrast nephropathy requiring dialysis was 25%, and one-year mortality was 55%.
- Fenoldopam provides a dose-dependent increase in renal blood flow.
- The drug's short half-life of 5 minutes allows rapid titration in the cardiac catheterization laboratory to optimal levels and rapid reverse titration of effect when necessary.
- More than one in five fenoldopam-treated patients had a reduction in their serum creatinine compared to their preprocedure baseline serum creatinine.
- Fenoldopam may be especially useful in patients who are not able to be hydrated with saline either because of medical contraindications to volume administration or because of logistical considerations.

at particular risk. These include decompensated congestive heart failure, concomitant use of intravenous diuretics, procedure-related renal infarction, and limb ischemia requiring amputation with associated myoglobinemia. In summary, of the patients who developed radiocontrast nephropathy despite use of fenoldopam, two patients had developed acute renal failure prior to angiography; one patient had ongoing rhabdomyolysis, underwent vascular surgery and became septic; one patient had preexisting end-stage renal disease with a baseline creatinine of 7.3 mg/dL; one patient received no saline hydration and was aggressively diuresed postprocedure; and one patient with diabetic nephropathy received 325 mL of contrast.

Conclusion

Early experience with fenoldopam is encouraging, showing that it is effective for prevention of RCN. Fenoldopam is a unique vasodilator that reduces systemic vascular resistance and lowers blood pressure in hypertensive patients (doses of 0.1 µg/kg/min or higher) but can increase renal blood flow (at dose from 0.01 µg/kg/min). In the normotensive, renal blood flow increases within 30 minutes with little or no effect on systemic hemodynamics.[13-15] Because it is titratable with a short half-life of 5 minutes and is easy to use without any special monitoring, adoption of fenoldopam as a strategy for renoprotection and blood pressure management in the interventional laboratory is straightforward. Despite the fact that our patients were very ill with multiple major comorbid conditions and underwent complex coronary and peripheral interventions, fenoldopam proved to be very safe and was not associated with any major complications.

As the demographic trends show a steady increase in the prevalence of diabetes and patients with kidney disease,[16] populations that have both a disproportionately high burden of cardiac and vascular disease as well as high risk for RCN, the strategies for prevention of RCN are expected to have significant positive impact on improving patient care and reducing health care costs. ■

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