Renal and Hemodynamic Effects of Intravenous Fenoldopam Versus Nitroprusside in Severe Hypertension

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The renal and hemodynamic effects of intravenously administered fenoldopam mesylate, a novel dopamine-1 receptor agonist, were compared with those of sodium nitroprusside in 28 patients (18 male; 26 black, two white; average age, 49±3 years) with an average blood pressure of 219/137 mm Hg, most of whom presented with acute target organ damage. Fenoldopam and nitroprusside lowered blood pressure safely to an average pressure of 176/105 mm Hg; highly significant dose-response relations were found for the 13 patients receiving fenoldopam and the 15 receiving nitroprusside. Volume and sodium, potassium, and creatinine concentrations were measured in freely voided urine specimens both before and during intravenous therapy. In the fenoldopam-treated patients, there were significant increases in urinary flow (92±21 to 168±37 ml/hr, p<0.003), sodium excretion (227±73 to 335±90 μeq/min, p<0.001), and creatinine clearance (70±11 to 93±13 ml/hr, p<0.003). In the nitroprusside-treated group, however, all these parameters decreased, but not significantly. For direct comparison of the two agents, the increments in urinary flow rate (+76±20 vs. -16±15 ml/hr, fenoldopam vs. nitroprusside), sodium excretion (+109±28 vs. -39±28 μeq/min), and creatinine clearance (+23±6 vs. -11±7 ml/min) were significantly greater (p<0.001 for each) in the fenoldopam-treated group. Significant differences were also obtained when these parameters were calculated as percentage increase over baseline. Fenoldopam and nitroprusside are effective therapies for severe, accelerated, or malignant hypertension, but fenoldopam had additional salutary renal effects in these patients. (Circulation 1990;81:970–977)

For many years, primary (or idiopathic) hypertension was called “essential hypertension” because it was thought that the elevation in blood pressure was necessary to maintain perfusion of vital organs, particularly the kidney. Corroborative evidence included the fact that acute lowering of blood pressure often resulted in deterioration of renal function. This side effect of therapy is often still noted today, particularly when the blood pressure is being reduced from very high levels, as in the setting of hypertensive urgencies and emergencies. Although many pharmacological options are currently available for the acute reduction of blood pressure in hypertensive emergencies, nitroprusside is still considered the drug of choice because of its rapid onset of action, short serum half-life, and long history of efficacy. The major disadvantage of nitroprusside is the conversion to its very toxic metabolites, cyanide and thiocyanate. This problem is often manageable by limiting the dose and duration of infusion. Despite short-term, low-dose administration, however, nitroprusside has been associated with deterioration in renal, cerebral, and cardiac function.

Fenoldopam mesylate is a novel vasodilator that acts by dopamine-1 receptor activation. Its vasodilatory actions are greatest in the renal bed, but resistance in other vascular beds (especially splanchnic, coronary, and cerebral) is also reduced. Previous work in normal subjects and in mildly hypertensive patients has shown that, during fenoldopam infusion, the lowering of blood pressure is accompanied by enhanced renal blood flow. Natriuresis, diuresis, and an increase in the glomerular filtration rate (measured either as inulin or creatinine clear-


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ance) have also been demonstrated. These renal effects, coupled with a short plasma half-life, suggest that fenoldopam might be a useful drug for the acute reduction of severe hypertension. The present study was designed to compare the effects of fenoldopam with those of nitroprusside on various hemodynamic and renal parameters.

Methods

Twenty-eight patients were enrolled from the emergency department or Hypertension Clinic of the University of Chicago. All patients had supine diastolic blood pressures in excess of 120 mm Hg during at least 20 minutes of quiet rest, had received no antihypertensive medication for at least 24 hours, and were initially thought to have some form of acute target organ damage due to severe hypertension. All patients signed informed consents to enroll in a research project approved by the Clinical Investigation Committee of the University of Chicago. Because of the known beneficial effects on renal function via increased cardiac output due to afterload reduction in congestive heart failure, patients with symptoms, signs, or chest x-ray evidence of congestive heart failure were excluded from this analysis.

After collection of a freely voided urine specimen, the patients were hospitalized in an intensive care unit. Blood pressure and pulse rate were recorded in duplicate every 5 minutes by an oscillometric device that had been carefully calibrated (correlation coefficient versus mercury sphygmomanometer = 0.995) for accuracy at extremely high blood pressures (Dinamap, Criticon, Inc., Tampa, Florida). Because of known pharmacological differences between the two drugs, and to maximize patient safety, the identity of the infused drug was known to the administering physicians. Five patients received fenoldopam and six patients received nitroprusside during an open-label trial; the remainder of the patients were randomized at the time of presentation between the two treatments according to a predetermined schedule. A post-hoc analysis revealed no significant differences in demographics, hemodynamic, or renal responses between the open-label and randomized patients. The infusion of either hypotensive agent was begun (at 0.1 µg/kg/min for fenoldopam, or 0.5 µg/kg/min for nitroprusside), and increased or decreased (by 0.05–0.1 µg/kg/min for fenoldopam, or 0.25–0.5 µg/kg/min for nitroprusside) at 20-minute intervals until the diastolic blood pressure was between 100 and 110 mm Hg. After maintenance of the diastolic blood pressure in this range during a constant dose infusion for at least 1 hour and collection of another freely voided urine specimen, standard oral antihypertensive medications were given (typically, atenolol 100 mg and furosemide 20 mg); thereafter, the infusion was tapered and eventually discontinued. Patients were then observed in the hospital for 48–72 hours, during which blood pressures were monitored and a 24-hour urine specimen was collected for creatinine clearance and protein excretion. Seven to 10 days after hospital discharge, blood pressure and serum creatinine were rechecked in the Hypertension Clinic.

The demographic characteristics of the patient population studied are shown in Table 1. There were no statistically significant differences between the two groups in any characteristic (by χ² analysis). All patients, except two, were black. All but six patients had previously been told of hypertension (average duration of diagnosis, 7.6 years; range, 0–24 years), but had stopped taking prescribed medications for a variety of reasons (“ran out” in 14, “blood pressure normalized” in six, nausea and vomiting in one, and severe diarrhea in one). All presented to the emergency department or clinic because of a symptom related to hypertension (headache in 14, blurred vision in seven, epistaxis in four, gross hematuria in four, and impending stroke in three). All patients manifested some evidence of acute target organ damage from hypertension (Table 1): subnormal renal function (assessed either by serum creatinine or creatinine clearance, and compared with prior data from the clinic chart), cardiomegaly by chest x-ray, electrocardiographic criteria for left ventricular hypertrophy, and funduscopic abnormalities worse than Keith-Wagener-Barker Grade II were equally common in each group. Eleven patients in each group presented with “accelerated or malignant” hypertension, defined as fundal hemorrhages or exudates, papilledema, gross hematuria, or acute deterioration in renal function.

Measurements of renal function were made in a standardized fashion by analysis of freely voided urine passed at recorded time intervals. Patients were allowed to drink water ad libitum, but supple-

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Table 1. Demographic Characteristics of Patients Studied

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Treatment group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fenoldopam</td>
</tr>
<tr>
<td>n</td>
<td>13</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>51±5</td>
</tr>
<tr>
<td>Male</td>
<td>7</td>
</tr>
<tr>
<td>Black</td>
<td>12</td>
</tr>
<tr>
<td>&quot;Accelerated/malignant&quot; hypertension</td>
<td>11</td>
</tr>
<tr>
<td>Serum creatinine &gt;1.5 mg/dl</td>
<td>6</td>
</tr>
<tr>
<td>Creatinine clearance &lt;100 ml/min</td>
<td>10</td>
</tr>
<tr>
<td>Retinopathy &gt; grade II</td>
<td>7</td>
</tr>
<tr>
<td>Hematuria at presentation</td>
<td>8</td>
</tr>
<tr>
<td>Left ventricular hypertrophy by electrophysiology</td>
<td>12</td>
</tr>
<tr>
<td>Cardiac enlargement on x-ray film</td>
<td>10</td>
</tr>
<tr>
<td>History of stroke</td>
<td>2</td>
</tr>
</tbody>
</table>

NS, not statistically significant.
mental intravenous fluids were avoided. When subjects voided more than once during therapy, the renal parameters obtained during the last part of the infusion (i.e., during the more than hour-long maintenance dose) of either fenoldopam or nitroprusside are reported.

Data are reported as mean±SEM. When serial measurements of a given parameter were obtained (e.g., dose-response curves), the data were first compared by one-way analysis of variance, followed by paired Student’s t tests, if the first analysis disclosed significant differences. The remainder of the statistical analyses was performed within treatment groups by paired t tests, and between treatment groups by Student’s (nonpaired) t tests; differences were considered significant at the p<0.05 level.

Results

The hemodynamic effects of infusion of either fenoldopam or nitroprusside are shown in Figure 1: the average initial blood pressures (before the infusions were begun) in the two groups were 214±5/136±4 mm Hg for the fenoldopam group, and 222±5/137±3 mm Hg for the nitroprusside group. The average heart rates before therapy were 87±4 min⁻¹ in the patients treated with fenoldopam, and 85±4 min⁻¹ in the patients treated with nitroprusside. These differences between treatment groups were not statistically significant in systolic (p>0.30), diastolic (p>0.40) blood pressures, or in pulse rates (p>0.30). Both drugs were successful in attaining and maintaining the goal blood pressure (diastolic between 100 and 110 mm Hg) for at least 1 hour during drug infusion at a constant dose. More pertinent to the comparison of the renal effects of the two drugs were the average blood pressures (measured every 10 minutes) between micturitions. The right hand panel of Figure 1 shows the average blood pressures and heart rates during the time period that the kidneys were making urine, for which the rates of excretion were calculated. There were no significant differences between either the blood pressures (180±5/106±4 for fenoldopam, and 174±5/105±3 for nitroprusside) or heart rates (93±3 min⁻¹ for fenoldopam; 89±5 min⁻¹ for nitroprusside). The increase in heart rate was statistically significant (by paired t test, compared with baseline) in both groups: fenoldopam (p<0.02) and nitroprusside (p<0.05). Thus, both agents were effective in reducing blood pressure, and a small increase in heart rate was seen with each.

Side effects attributable to the drugs were minor and not significantly different between groups: fenoldopam caused one patient to note transient “warmth,” and another experienced a “slight headache” that resolved spontaneously in 20 minutes. One patient experienced a large natriuresis and diuresis, after which no further antihypertensive therapy was required; this has been noted previously in another series.¹ Nitroprusside caused one patient to persistently feel “warm,” another reported (and was observed to be) “flushing,” and three others experienced severe headaches.

The average doses of hypotensive agent required to keep the diastolic blood pressure between 100 and 110 mm Hg were 0.30±0.04 μg/kg/min (range, 0.20–0.70) for fenoldopam, and 1.89±0.55 μg/kg/min (range, 0.25–8.0) for nitroprusside. There were no significant relations between pretreatment blood pressure and the maintenance dose of either drug by either linear or log-linear regression analysis.

There was a clear dose-response relation between blood pressure (measured after 20 minutes, i.e., two to three half-lives, at a given rate of infusion) and ascending fenoldopam dose, as shown in Figure 2. This dose-response relation was statistically significant (by analysis of variance testing) at the p<0.001, 0.0001, and 0.05 levels for systolic, diastolic blood pressures, and pulse rates, respectively. Too few patients required higher doses to extend the analysis of this dose-response relation beyond the 0.25 μg/kg/min dose (n=9). There was also a similar dose-response relation for nitroprusside: the blood pressure decreased from 222±5/137±3 (at 0.0 μg/kg/min) to 199±6/122±4 (at 0.5 μg/kg/min) to 180±5/107±3 mm Hg (at 1.0 μg/kg/min).

A summary of the urinary parameters observed in each of the 13 patients treated with fenoldopam is found in Table 2. As the fluid status of these patients varied on presentation, there was a large splay in urinary output; nonetheless, fenoldopam increased the mean urinary flow rate from 92±20 ml/hr to 168±28 ml/hr (p<0.003 by paired t test). Fenoldopam increased the mean urinary excretion of...
sodium from 227±73 μeq/min at baseline to 335±90 μeq/min during infusion (p<0.001). The mean urinary excretion of potassium was slightly increased (28.3±4.0 μeq/min before vs. 39.1±6.5 μeq/min during fenoldopam; p<0.04). The average creatinine clearance also increased from 70±11 ml/min to 93±13 ml/min (p<0.003). The two patients (second and fourth lines of Table 2) who did not demonstrate increases in creatinine clearance were clinically dehydrated at the beginning of the infusion: one from prolonged nausea and vomiting, and the other from diarrhea; these conditions could have limited their urinary flow. Repeated measurements of creatinine clearance in four patients who voided several times during the constant-dose infusion demonstrated excellent reproducibility and no evidence for tachyphylaxis to fenoldopam: six determinations in one patient averaged 86.4±1.2 ml/min over 4 hours; five determinations in another averaged 120.2±0.5 ml/min over 20 hours; four determinations in another averaged 25.8±2.0 ml/min over 6 hours; and three determinations in a fourth averaged 37.9±0.5 ml/min over 6 hours.

Six patients who produced less than 1.5 l urine during the infusion of fenoldopam were given furosemide as part of their oral antihypertensive regimen just before stopping the infusion of fenoldopam. In these patients, the effects of fenoldopam on urinary sodium excretion and urinary flow rate were compared with those of the combination of furosemide and fenoldopam. The average urinary flow rate increased from 146±38 ml/hr during fenoldopam to 398±70 ml/hr following administration of furosemide (p<0.02 by paired t test). The average urinary sodium excretion increased in parallel, from 381±148 μeq/min to 956±261 μeq/min (p<0.01). The average urinary potassium excretion increased from 39±11 μeq/min during fenoldopam to 79±11 μeq/min after the addition of furosemide (p<0.005), but there was no change in creatinine clearance.

### Table 2. Urinary Parameters Before and During Fenoldopam Therapy

<table>
<thead>
<tr>
<th>parameter</th>
<th>Before</th>
<th>During</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary flow rate (V, ml/hr)</td>
<td>58.9</td>
<td>71.1</td>
</tr>
<tr>
<td>Urinary sodium excretion (U_{Na}, μeq/min)</td>
<td>215</td>
<td>204</td>
</tr>
<tr>
<td>Urinary potassium excretion (U_{K}, μeq/min)</td>
<td>26.5</td>
<td>26.1</td>
</tr>
<tr>
<td>Creatinine clearance (CrCl, ml/min)</td>
<td>121.7</td>
<td>119.8</td>
</tr>
<tr>
<td>Averages</td>
<td>91.6</td>
<td>167.5†</td>
</tr>
<tr>
<td>SEM</td>
<td>20.9</td>
<td>36.6</td>
</tr>
</tbody>
</table>

Values are mean±SEM. V, flow rate; U_{Na}, urinary sodium; U_{K}, urinary potassium; CrCl, creatinine clearance.

* p<0.04; † p<0.003; ‡ p<0.001, by paired t test.
(101±12 ml/min for fenoldopam vs. 96±13 ml/min for furosemide and fenoldopam; p>0.80).

Table 3 shows the effects of nitroprusside on renal function. There were reductions in mean urinary flow rate, urinary sodium and potassium excretion, and creatinine clearance, but none of these decreases were statistically significant, compared with pretreatment. Table 3 also shows that there were no significant differences at baseline in any of the measured urinary parameters between the two treatment groups (p>0.67 for urinary flow rates, 0.66 for sodium excretion, 0.25 for potassium excretion, and 0.54 for creatinine clearance).

Figure 3 shows the changes in renal function in the two treatment groups, expressed as average percentage change from pretreatment. Not shown in the figure is the fact that there was a small difference between the two treatment groups in urinary potassium excretion, which achieved statistical significance when calculated in microequivalents per minute (fenoldopam: +10.8±4.7 μeq/min vs. nitroprusside: −5.1±3.6 μeq/min; p>0.01), but was less impressive when expressed as percentage change compared with pretreatment (fenoldopam: +47±27% vs. nitroprusside: −8±10%; p=0.054). There were, however, highly statistically significant differences between fenoldopam- and nitroprusside-treated patients in urinary flow rate (+76±20 vs. −16±15 ml/hr, fenoldopam versus nitroprusside, respectively; p<0.001), urinary sodium excretion (+109±28 vs. −39±28 μeq/min; p<0.001), and creatinine clearance (+23±6 vs. −11±7 ml/min; p<0.001). There were no statistically significant differences between the urine collection times, urinary creatinine, or electrolyte concentrations between the treatment groups that would otherwise explain these differences. Because the pretreatment volume, sodium, and renal function status of the patients varied widely in each group (but were not different between groups), it is perhaps preferable to compare the percentage change in each of these parameters between the two groups, as shown in Figure 3. In each case, there was an improvement in renal function with fenoldopam compared with nitroprusside: urinary flow rates (+110±35% vs. +5±18%, respectively; p<0.01), urinary sodium excretion (+133±57% vs. −1±22%;

![Figure 3](http://circ.ahajournals.org/)

**FIGURE 3.** Bar graphs of relative effects of infusion of either fenoldopam or nitroprusside on renal parameters, measured for each patient as the percent change from baseline (before infusion), and then averaged. Error bars represent standard errors; statistics were generated by nonpaired t test.
Discussion

This study, the first to directly compare the renal effects of fenoldopam with those of standard intravenous vasodilator therapy, demonstrates that fenoldopam, like nitroprusside, is an effective antihypertensive agent in severe, accelerated, and malignant hypertension. In the direct comparison with nitroprusside, however, fenoldopam significantly increased urinary flow, urinary sodium excretion, and creatinine clearance. Both drugs were well tolerated by these patients.

This study confirms and extends previous studies that have demonstrated the antihypertensive efficacy of fenoldopam, both after oral18–21 and, especially, intravenous administration. A dose-dependent relation between the decrease in blood pressure and the dose of administered fenoldopam has been shown in most of the intravenous studies,14,15,17 but the responses to orally administered fenoldopam19,21 are difficult to compare, probably because of limited bioavailability of the orally administered material. The average dose of intravenous fenoldopam used in the therapy of hypertension has been remarkably similar across these studies: 0.30±0.40 μg/kg/min in this series; 0.34±0.22 μg/kg/min17; 0.34±0.03 μg/kg/min14; 0.27±0.12 μg/kg/min23 and 0.32±0.08 μg/kg/min. Previous studies have shown that intravenous fenoldopam is effective in mild-to-moderate hypertension,14 refractory hypertension (i.e., patients with diastolic blood pressures >115 mm Hg on triple-drug therapy),23 and severe hypertension,17,24,25 but this is the first series to include a majority of patients with accelerated/malignant hypertension, which is presumably the population in which it will find the widest use. In addition, the present series includes a preponderance of black patients, who comprise a small minority of those previously treated with fenoldopam.27

Indeed, because of the greater frequency of severe hypertension and its complications (including accelerated/malignant hypertension) in blacks,26,27 fenoldopam may be especially useful in such patients, who more commonly have reduced salt and water excretion rates,28 independent of the degree of renal dysfunction.

The renal effects of fenoldopam demonstrated in this study are similar to those first reported with low-dose dopamine by McDonald et al.29 That these renal effects are due to activation of the dopamine-1 receptor by dopamine was later shown during concomitant therapy with phenoxybenzamine;30 such additional therapy is not necessary with the specific dopamine-1 agonist fenoldopam. In addition to recent studies demonstrating improved renal function with intravenous fenoldopam in normal subjects,31 or patients with heart failure,21 there are now several studies in patients with various degrees of hypertension that also have improved renal function during dopamine-1 receptor activation. The most similar results to those reported here are those of White and Halley,24 who compared the effects of fenoldopam in six patients with those of nitroprusside given to five others. Although significant increases in urinary parameters (relative to preinfusion) were seen only with fenoldopam, direct comparisons of the effects of the two drugs were not carried out, presumably because the number of patients in each group was insufficient. In contrast to the current series, their patients were water loaded before drug administration, and had a high prevalence of renal arterial disease and a low prevalence of acute target organ damage. Ruilope et al25 also have found significant improvements in renal parameters in water-loaded patients known to be severely hypertensive when withdrawn for 1 day from triple-drug therapy, but no comparison to a similar group of nitroprusside-treated patients was done in this series. Previous studies have also shown improvements in renal parameters in less severely hypertensive patients given intravenous14,22 or oral18–20 fenoldopam.

Because of the severity of illness and the necessity for timely blood pressure reduction in most of the patients, there are several limitations to our findings. It is generally agreed that in vivo studies of renal function are best carried out in catheterized patients after water loading to ensure complete collection of urine without limitations of urinary flow. Because such interventions are of no intrinsic benefit to the individual patient,32 and indeed may cause frank volume overload in patients with cardiac dysfunction due to severe hypertension, we could not ethically justify the insertion of Foley or Swan-Ganz catheters (for measurement of pressures and cardiac output) or the administration of either intravenous23 or oral24 water. This, of course, restricted the collection of urine to a schedule dictated by the bladder capacity of each patient, and did not allow timed urine collections, as would have been desirable in patients who were less ill.23,24 The fact that we have demonstrated a significant increase in urinary flow rate and other renal parameters in non-water-loaded patients is therefore all the more remarkable. For ethical reasons, we had no control over the fluid and sodium status of the patients before therapy, as all patients presented acutely and were treated promptly for their hypertensive urgency or emergency. Nonetheless, there were no significant differences before therapy between the mean urinary flow rates, sodium excretion rates, or creatinine clearances between the fenoldopam- and nitroprusside-treated groups. The rates of fluid administration (i.e., the solution containing the hypotensive drug) during the maintenance phase were not significantly different between groups, and were small compared with the rate of urine flow (21±6 ml/hr for fenoldopam; 24±10 ml/hr for nitroprusside). Inulin clearances are, in general, preferable to intrinsic creatinine clearances, but require a bolus and constant rate infusion, which we could again not ethically justify in our patients. The fact that the repeated measurements of creatinine clearance (cited
urea nitrogen/creatinine from 58/8.9 to 56/8.6 mg/dl and was dialedyzed electively for diabetic renal failure when his blood urea nitrogen/creatinine rose to 113/11.6 mg/dl after 6 days of oral antihypertensive medication. Replication of this dramatic difference between fenoldopam and nitroprusside regarding preservation of renal function (and avoiding or delaying the need for dialysis) remains to be demonstrated in a larger series (e.g., 38).

In summary, the data presented demonstrate that fenoldopam, a specific dopamine-1 agonist, reduces blood pressure reliably and safely in severely hypertensive patients with acute target organ damage, and causes increases in urinary flow rate, sodium excretion, and creatinine clearance. These salutary renal effects were not seen in similar patients treated with nitroprusside, the standard parenteral agent for hypertensive emergencies. Thus, fenoldopam may be preferable when preservation of renal function is important.

References


32. Declaration of Helsinki: Recommendations guiding physicians in biomedical research involving human subjects. 35th World Medical Assembly, October 1983; Section I, subsections 4, 5, and 7


**KEY WORDS** • fenoldopam • nitroprusside • hypertension • renal function
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