Augmentation of renal blood flow and sodium excretion in hypertensive patients during blood pressure reduction by intravenous administration of the dopamine_{1} agonist fenoldopam

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ABSTRACT Activation of dopamine_{1} (DA_{1}) receptors relaxes vascular smooth muscle, especially in the renal vascular bed. Fenoldopam, the first selective DA_{1}-receptor agonist that can be administered to man, was infused intravenously in 17 patients with essential hypertension (mean blood pressure 152/101 mm Hg). It reduced blood pressure in a dose-dependent fashion at doses between 0.025 and 0.5 μg/kg/min and the antihypertensive effect was sustained during 2 hr infusions. In 10 patients studied during free-water diuresis, fenoldopam increased renal plasma flow by 42%, glomerular filtration rate by 6%, and sodium excretion by 202%, while lowering mean arterial pressure by 12% (all p < .05). Similar promotion of sodium excretion was observed during blood pressure reduction in six additional patients studied without water loading. Pronounced enhancement of renal function in spite of blood pressure reduction suggests that fenoldopam might have a special role in the treatment of patients with hypertension and renal impairment.


THE ACTIONS of dopamine (DA) in increasing renal plasma flow and sodium excretion have led to clinical applications in the treatment of shock, congestive heart failure, and oliguric states. These beneficial renal effects are due primarily to effects of the catecholamine on DA_{1} receptors. DA also acts on α_{1}- and α_{2}-adrenoceptors to cause vasoconstriction, which prevents its use in hypertensive patients. Indeed, McNay et al. observed that intravenous administration of DA increased blood pressure in severely hypertensive patients. However, when DA was infused after administration of the α_{1}-adrenoceptor antagonist phenoxybenzamine, DA_{1}-mediated vasodilating actions were unmasked and blood pressure was decreased with enhancement of renal blood flow and sodium excretion. These studies suggested that a selective DA_{1} agonist should have a role in the treatment of hypertension, especially in patients with impairment of renal function.

Fenoldopam mesylate, a benzazepine derivative, is a novel DA_{1}-receptor agonist that differs from DA in being devoid of α- and β-adrenoceptor and DA_{2}-receptor agonist activity at therapeutic concentrations. In initial studies in hypertensive patients, fenoldopam, in oral doses of 50 to 100 mg, decreased systolic and diastolic pressures about 10 to 15 mm Hg with a duration of action of 1 to 4 hr. Significant increments in renal plasma flow and sodium excretion were observed also, but there were marked variations in response, and a dose-response relationship was not observed. Orally administered fenoldopam undergoes extensive first-pass metabolism with inactivation by sulphate conjugation, which explains the high dose required for oral administration and the variability in patient response. Fenoldopam has recently become available for study in the intravenous form, making it possible to quantitatively examine its potency and efficacy, its dose-response characteristics, and its renal and hormonal effects in steady-state concentrations and with constant blood pressure. The present study, the first of
intravenously administered fenoldopam in hypertensive patients, suggests that this DA1 agonist may play a useful role in treating hypertension when parenteral therapy is required. It also may be a preferable alternative for some nonhypertensive patients when the use of DA might be limited by vasoconstriction or cardiac stimulation.

Methods

The study was divided into three components: (1) examination of the dose-response effects of fenoldopam on arterial blood pressure, heart rate, and norepinephrine secretion, (2) comparison of the effects of fenoldopam and placebo on arterial blood pressure, renal function, and plasma hormone levels during free-water diuresis in hypertensive patients, and (3) examination of effects of fenoldopam on blood pressure and sodium and potassium excretion in the absence of free-water diuresis.

Study 1: dose-response evaluation. Seventeen patients who were previously untreated or free of antihypertensive medications for at least 2 weeks volunteered for study. Supine diastolic blood pressure was greater than 94 and less than 115 mm Hg at three consecutive weekly clinic visits. The characteristics of these patients are listed in table 1. All were found to have uncomplicated hypertension on the basis of physical examination and routine investigations. Other than hypertension, findings for each patient on physical examination, chest x-ray, urinalysis, and blood count were normal. Serum levels of sodium, potassium, blood urea nitrogen, creatinine, transaminase, phosphate, urate, and calcium were within normal limits. The only abnormality seen on the electrocardiogram was left ventricular hypertrophy in some of the patients.

After an overnight fast, each patient was admitted to the outpatient facility of the University of Chicago Clinical Research Center. Intravenous cannulas were placed in both antecubital fossae for drug administration and blood sampling. Diastolic and systolic blood pressure and heart rate were recorded by an automated oscillometric apparatus (Dinamap, Critikon, Inc., Tampa, FL). After a 20 min baseline infusion of 5% dextrose (by a Harvard peristaltic pump) fenoldopam mesylate diluted in 5% dextrose was infused at doses of 0.025, 0.05, 0.1, 0.25, 0.375, and 0.5 μg/kg/min to determine the dose that lowered diastolic blood pressure by more than 10 but less than 20 mm Hg. Each infusion rate was administered for 15 min and blood pressure and heart rate were recorded at 10 and 15 min. In 13 patients a blood sample for estimation of serum potassium and plasma norepinephrine was drawn at 14 min and a 12-lead electrocardiogram was recorded at the fifteenth minute of each infusion. An electrocardiogram and urinalysis were repeated 1 hr after termination of the infusion, and were repeated again along with a complete blood count and biochemical screen 24 hr and 1 week later.

Study 2: studies of renal function. Ten participants in study 1 received reinusions of fenoldopam at least 1 week later during water diuresis by standard renal clearance techniques.6 Six additional hypertensive patients underwent the same protocol with the substitution of 5% dextrose for fenoldopam. The characteristics of the 10 study patients and the six control subjects are listed in table 1. All fasted overnight and emptied their bladders on arrival at the Clinical Research Center. Each was given tap water, 20 ml/kg, to drink over 10 min, and urine was collected thereafter at 30 min intervals. Tap water in amounts equal in volume to the urine passed, and an additional 1 ml/min for insensible loss, was given every 30 min for the remainder of the experiment. To measure renal plasma flow a bolus intravenous injection of para-aminohippurate (PAH), 8 mg/kg, was given followed by a continuous infusion at 15 mg/min. To measure glomerular filtration rate (GFR), a priming dose of 50 mg/kg inulin was administered by bolus intravenous injection and an infusion continued at 35 mg/min.

When urine osmolality was less than 100 mOsm/liter and consecutive urine volumes were within 10% of each other, three baseline half-hour collections were made. Blood pressure and heart rate were obtained at the twenty-seventh minute of each study period. Blood samples were drawn just before the first baseline period and at the twenty-eighth minute of each period thereafter for measurement of electrolytes, urea, creatinine, urate, renin, aldosterone, norepinephrine, PAH, and inulin concentrations. Urine was collected at the thirteenth minute, the volume was recorded, and aliquots were saved for electrolyte, water, creatinine, PAH, and inulin measurements.

After the three baseline periods, fenoldopam was infused at the rate found in study 1 to lower blood pressure in each patient by about 20 mm Hg. Control subjects received 5% dextrose only. Fenoldopam (or 5% dextrose) infusion was terminated after 2 hr (four "experimental" periods) and measurements were continued for a further hour (two "recovery" periods). Care was taken to ensure that the rate of intravenous fluid administration remained constant throughout the study, which lasted 6½ to 8 hr. A 12-lead electrocardiogram was performed during the control period, after 1 hr of fenoldopam infusion, and 1 hr after termination of infusion. Clinical chemistry measurements were repeated 1 day and 1 week after study.

Study 3: studies of electrolyte excretion in the absence of water load. Because the natriuretic response to DA has been shown to be influenced by waterload10 and because fenoldopam would be used clinically in its absence, the effects of fenoldopam were studied in six subjects without water diuresis (characteristics in table 1). The patients fasted overnight and emptied their

<table>
<thead>
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<tr>
<td>Characteristics of patients</td>
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<table>
<thead>
<tr>
<th>Study 1</th>
<th>Fenoldopam</th>
<th>Control</th>
<th>Study 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>17</td>
<td>10</td>
<td>6</td>
</tr>
<tr>
<td>Age (years)</td>
<td>41 ± 2</td>
<td>39 ± 2</td>
<td>42 ± 2</td>
</tr>
<tr>
<td>Male/female</td>
<td>7/10</td>
<td>4/6</td>
<td>1/5</td>
</tr>
<tr>
<td>Black/white</td>
<td>14/3</td>
<td>9/1</td>
<td>6/0</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>82 ± 3</td>
<td>77 ± 3</td>
<td>88 ± 10</td>
</tr>
<tr>
<td>Blood pressure (mm Hg)</td>
<td>152 ± 2/101 ± 1</td>
<td>159 ± 4/103 ± 2</td>
<td>152 ± 3/102 ± 2</td>
</tr>
<tr>
<td>Heart rate</td>
<td>69 ± 3</td>
<td>66 ± 2</td>
<td>69 ± 1</td>
</tr>
</tbody>
</table>

Vol. 76, No. 6, December 1987 1313
bladders on arrival at the Clinical Research Center. Urine was collected over 2 hr and its sodium and potassium concentrations were measured. Thereafter, fenoldopam was infused for 2 hr at the dose that produced a reduction in pressure of approximately 20 mm Hg during dose ranging. Urine was collected throughout the infusion for measurement of sodium and potassium concentrations. Blood pressure and heart rate were recorded with the Dinamap.

**Analysis.** After the addition of sodium metabisulphite and storage at -20°C, plasma norepinephrine levels were measured within 1 month of sampling by high-performance liquid chromatography with electrochemical detection.11 Plasma and urine PAH and insulin levels were measured spectrophotometrically.12, 13 All samples from individual subject days were assayed in single batches to minimize variation. Plasma and urinary electrolytes and creatinine were measured by an AutoAnalyzer. Plasma renin14 and aldosterone15 levels were measured by radioimmunoassay.

Renal plasma flow was calculated as the clearance of PAH per minute and GFR as the clearance of insulin per minute with the use of standard formulas. Fractional excretion of solutes was ascertained by dividing solute clearance byulin clearance, and free-water clearance was deemed to be the difference between urine volume per minute and osmolar clearance per minute. Solute delivery out of the renal proximal tubules was estimated by the expression CCl + CHO. Renal vascular resistance was estimated by dividing mean arterial pressure by renal blood flow. All results are expressed as the mean ± SEM. Changes within groups were compared by paired t tests and those between groups by unpaired t tests, and differences were deemed significant at p < .05.

The protocol of the study was approved by the Clinical Investigation Committee of the University of Chicago, and all subjects gave written informed consent.

**Results**

**Study 1: dose ranging.** Fenoldopam reduced arterial blood pressure in a linear dose-related fashion in each of the 17 patients. The average results are shown in figure 1; the apparent plateau is due to the design of the study, which limited the hypotensive effect allowed. One of the patients attained the desired blood pressure reduction at an infusion rate of 0.1 μg/kg/min, five

![FIGURE 1](image1.png)

**FIGURE 1.** Decrease in systolic (●) and diastolic (□) blood pressures during infusion of fenoldopam. Numbers in brackets signify number of patients receiving each dose. *p < .05; **p < .01.

patients at 0.25 μg/kg/min, two patients at 0.375 μg/kg/min, and the remaining nine patients at 0.5 μg/kg/min. Heart rate increased in parallel with the reduction in blood pressure from a baseline of 69 ± 3 to a maximum of 82 ± 3 beats/min (p < .001). Plasma norepinephrine levels doubled from an average of 1.6 ± 0.15 to 3.37 ± 0.56 nmol/liter (p < .01). The latter value was obtained for each patient at the infusion rate with which the 20 mm reduction in blood pressure was obtained. There was no change in serum potassium concentration.

**Study 2: renal studies.** As can be seen in figures 2 and 3, steady-state conditions were achieved by the second experimental period. Consequently, to allow comparison of postdrug values with those at baseline and with the control group, data from the three baseline periods, experimental periods 2, 3, and 4, and the two recovery periods have been averaged to give the respective baseline, experimental, and recovery values. Average blood pressure was reduced from 159 ± 4/103 ± 2 to 144 ± 3/90 ± 2 mm Hg (p < .01) and the hypotensive effect was maintained throughout the infusion (figure 2). Heart rate increased by 16 ± 2 beats/min. These indexes returned to baseline within 1 hr of termination of infusion. In the control patients, on the other hand, blood pressure and heart rate did not change during the study (figure 2).

Fenoldopam increased urine flow from 13.8 ± 0.6 ml/min at baseline to 19.4 ± 1.41 ml/min (p < .05), while flow rate fell slightly in the control group from 13.6 ± 1.5 to 12.8 ± 1.7 ml/min (p < .05). During
Fnoldopam increased the clearance rates of PAH and inulin (figure 4). Renal plasma flow increased by 42 ± 7% from 509 ± 46 to 732 ± 83 ml/min (p < .001) in the face of a reduction in mean arterial pressure. Consequently, average renal vascular resistance decreased by 35 ± 4%. In contrast, in the control group renal plasma flow remained relatively stable (495 ± 31 baseline vs 459 ± 22 ml/min experimental, respectively, p = NS). While the hemodynamic effects of fnoldopam disappeared rapidly on terminating the infusion, it should be noted that renal plasma flow remained significantly elevated during the following hour: in the period 30 to 60 min after withdrawal of fnoldopam average renal plasma flow was 673 ± 99 ml/min, 30% higher than baseline. GFR increased by approximately 6% from 112 ± 10 to 118 ± 11 ml/min (p < .05) in the treated group, while it fell to a similar extent, from 120 ± 11 to 114 ± 13 ml/min, in the control group. Fractional excretion rates of sodium, calcium, magnesium, chloride, uric acid, and phosphate increased significantly, while in the control group the rates remained stable or, in the case of sodium and uric acid, fell slightly (table 2). CCl + C,H,O, an index of solute delivery out of the proximal tubule, increased during fnoldopam infusion from 0.12 ± 0.02 to 0.18 ± 0.03 (p < .05).

**TABLE 2**

Fractional excretion of solutes in 10 hypertensive patients treated with fnoldopam (Fen) and six hypertensive control subjects receiving 5% dextrose (C)

<table>
<thead>
<tr>
<th>Solute</th>
<th>Baseline</th>
<th>Experimental</th>
<th>Recovery</th>
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<tbody>
<tr>
<td>Sodium</td>
<td>1.65 ± 0.33</td>
<td>4.14 ± 0.83a</td>
<td>2.28 ± 0.40</td>
</tr>
<tr>
<td>C</td>
<td>1.61 ± 0.20</td>
<td>1.23 ± 0.16a</td>
<td>1.19 ± 0.09</td>
</tr>
<tr>
<td>Potassium</td>
<td>13.8 ± 3.8</td>
<td>14.0 ± 2.4</td>
<td>13.1 ± 2.3</td>
</tr>
<tr>
<td>Fen</td>
<td>11.2 ± 2.6</td>
<td>10.1 ± 1.7</td>
<td>11.1 ± 2.7</td>
</tr>
<tr>
<td>C</td>
<td>2.18 ± 0.30</td>
<td>2.91 ± 0.66a</td>
<td>1.84 ± 0.45</td>
</tr>
<tr>
<td>Calcium</td>
<td>2.05 ± 0.65</td>
<td>2.02 ± 0.58</td>
<td>2.66 ± 0.77</td>
</tr>
<tr>
<td>Magnesium</td>
<td>5.1 ± 1.1</td>
<td>9.5 ± 1.9c</td>
<td>6.4 ± 1.4</td>
</tr>
<tr>
<td>Fen</td>
<td>2.9 ± 0.5</td>
<td>3.2 ± 0.8</td>
<td>4.2 ± 1.1</td>
</tr>
<tr>
<td>Phosphate</td>
<td>14.9 ± 2.6</td>
<td>21.5 ± 3.4a</td>
<td>17.5 ± 2.3</td>
</tr>
<tr>
<td>C</td>
<td>18.1 ± 2.5</td>
<td>16.2 ± 1.9</td>
<td>17.5 ± 2.9</td>
</tr>
<tr>
<td>Urate</td>
<td>9.1 ± 1.3</td>
<td>12.9 ± 2.0a</td>
<td>10.4 ± 1.6</td>
</tr>
<tr>
<td>Fen</td>
<td>7.9 ± 1.0</td>
<td>6.9 ± 0.9a</td>
<td>7.8 ± 1.3</td>
</tr>
<tr>
<td>C</td>
<td>1.65 ± 0.38</td>
<td>4.57 ± 0.99a</td>
<td>2.47 ± 0.57</td>
</tr>
<tr>
<td>Chloride</td>
<td>1.42 ± 0.25</td>
<td>1.22 ± 0.20</td>
<td>1.14 ± 0.19</td>
</tr>
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</table>

<sup>a</sup>p < .05; <sup>b</sup>p < .01; <sup>c</sup>p < .001.

Vol. 76, No. 6, December 1987
Reflecting the preponderance of black subjects in the study groups, initial plasma renin levels were low (table 3). Fenoldopam increased plasma renin by 50% (p < .05), but plasma aldosterone levels did not change. Plasma renin concentrations did not change in the control subjects while there was a small but statistically significant reduction in aldosterone levels. In contrast, plasma norepinephrine levels increased in both groups, but the response in the treated patients was much greater (table 3).

Study 3: 2 hr infusion without water diuresis. Average blood pressure was reduced from 146 ± 3/98 ± 1 to 132 ± 4/75 ± 6 mm Hg (p < .001) within 15 min of commencing fenoldopam, and the hypotensive effect was maintained throughout the infusion. Heart rate increased from 62 ± 3 to 73 ± 3 beats/min and plasma norepinephrine levels doubled. These indexes returned to baseline within 1 hr of termination of infusion. The effects of fenoldopam on urine output are listed in table 4. The average urine flow rate increased by 50%, although two of the six patients experienced a small reduction in flow. Both sodium and potassium excretion increased in each of the six subjects.

Adverse reactions. Two of the 17 subjects reported flushing and mild headache during fenoldopam infusion. There were no changes in the hematologic or biochemical screening tests after drug administration. The electrocardiogram of most patients demonstrated flattening of the T wave, particularly in the anterior and lateral leads, but this usually disappeared within 1 hr of termination of the infusion. In four patients T wave inversion occurred; this was asymptomatic and cardiac enzymes measured in two of these patients did not change. The inverted T waves returned to normal within 1 hr in three patients and within 24 hr in the fourth patient.

Table 3

Table 4: Effects of fenoldopam on urinary volume and electrolyte excretion in six non–water loaded, hypertensive patients

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Fenoldopam</th>
<th>p value</th>
</tr>
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<tbody>
<tr>
<td>Urine volume (ml/min)</td>
<td>3.5 ± 1.0</td>
<td>5.2 ± 0.5</td>
<td>= .16</td>
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<tr>
<td>Urine sodium (μeq/min)</td>
<td>221.7 ± 23.1</td>
<td>571.5 ± 67.3</td>
<td>&lt; .003</td>
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<tr>
<td>Urine potassium (μeq/min)</td>
<td>48.8 ± 12.8</td>
<td>69.8 ± 16.6</td>
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Discussion

The results of this study demonstrate that the selective DA1 agonist fenoldopam is an effective antihypertensive agent when administered intravenously. Infusions of only 0.1 to 0.5 μg/kg/min decreased diastolic blood pressure approximately 20 mm Hg in each of the 17 hypertensive patients studied. Of more importance, fenoldopam markedly increased renal blood flow and sodium excretion, despite the reduction in renal perfusion pressure.

Reduction in blood pressure by fenoldopam appears to be due primarily to reduced peripheral vascular resistance. In addition to causing renal vasodilation, it also dilates the splanchnic arteries, and since DA1 receptors have been demonstrated in cerebral and coronary arteries, it is likely that these vascular beds are also diluted. Recently, Hughes et al. used fenoldopam to demonstrate DA1 receptors in the human forearm vasculature, suggesting that skeletal muscle vasodilation may also contribute to the hypertensive effect. Flushing, which was reported by two of our patients and has also been observed after oral administration of fenoldopam, suggests some cutaneous vasodilation in addition.

Several mechanisms may be responsible for the natriuretic and diuretic actions of DA1 agonists. First, they could be due entirely to renal vasodilation. Increased renal blood flow, coupled with a reduction in filtration fraction, could decrease proximal tubular sodium reabsorption by altering peritubular capillary hydrostatic and oncotic pressures. Furthermore, diversion of blood flow to the medullary and deep nephrons resulting in “washout” of the renal medulla also could enhance sodium excretion. An increase in the solute load entering the proximal tubule from a slight increase in GFR could explain the natriuresis. Fourth, and most controversial, it is possible that fenoldopam exerts a direct effect on the renal tubules to prevent reabsorption of sodium. Microperfusion studies have shown that DA inhibits sodium transport in the pars recta of the rabbit proximal tubule, and evidence has been presented to suggest that DA1 receptors are

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</tbody>
</table>

*p < .05; **p < .01.
located on proximal tubular cells.\textsuperscript{22} This study does not allow us to distinguish between these possible mechanisms; however, the increase in $C_{\text{Cl}} + C_{\text{H}_{2}\text{O}}$ index suggests that fenoldopam causes a substantial reduction in the reabsorption of sodium in the proximal tubule. Changes in activity of the renin-angiotensin-aldosterone system cannot be implicated. The small increase in plasma renin activity probably was mediated through enhanced sympathetic activity due to baroreflex activation, but it was not accompanied by an increase in plasma aldosterone levels. Blunting of the plasma aldosterone response to increased renin activity by DA agonists has been reported previously by Sowers et al.\textsuperscript{24} and Malchoff et al.\textsuperscript{25}; the present data suggest that this inhibition of aldosterone release may be mediated by the DA$_{1}$ receptor.

The study suggests that intravenous administration of fenoldopam should have a role in the treatment of severe and malignant hypertension. Like nitroprusside, presently the most widely used parenteral agent, its relatively rapid onset and short duration of action make it possible to easily adjust the dose required for the desired hypotensive effect. In contrast to nitroprusside, it does not require protection from light and does not produce potentially toxic metabolites. Furthermore, the renal vasodilating and diuretic effects of fenoldopam merit further evaluation in patients with severe hypertension who commonly exhibit renal dysfunction and in whom acute reduction in blood pressure with existing drugs often leads, in the short-term, to further impairment of renal function and sodium excretion.\textsuperscript{26, 27}

In addition to the treatment of hypertension, intravenous administration of fenoldopam may be a potential alternative to DA in patients in whom peripheral vasoconstriction and cardiac stimulation produced by DA are undesirable. It may be used to enhance renal perfusion and to promote diuresis in oliguric patients whose conditions are refractory to diuretics\textsuperscript{26–30} and may be added to therapy with drugs such as dobutamine, which stimulate the heart but are not potent renal vasodilators.\textsuperscript{31} Finally, intravenous fenoldopam may have a role in the short-term treatment of congestive heart failure by decreasing peripheral resistance and improving renal blood flow. In this regard, Young et al.\textsuperscript{16} have shown that oral administration of single doses produced beneficial hemodynamic effects in patients with severe congestive heart failure. On the other hand, reduction in blood pressure may limit its utility in some clinical situations. Nevertheless, it should be possible to increase renal blood flow with doses that do not alter systemic blood pressure, since it is likely that the plasma concentration required to enhance renal blood flow is less than that required to lower systemic blood pressure. The persistent enhancement of renal blood flow when blood pressure had returned toward baseline in the present study and previous studies of the oral formulation demonstrating pronounced increments in renal blood flow and sodium excretion with minimal changes in blood pressure support this possibility.\textsuperscript{7, 9, 32}

Fenoldopam appears to be well tolerated, the only side effects being occasional headache or flushing. The flattening or inversion of the T wave in the present study also occurred in studies of the oral formulation. That it might be mediated by changes in serum potassium due to increased sympathetic activity during baroreflex activation\textsuperscript{33} was excluded by the finding of unchanged serum potassium concentrations during fenoldopam dose ranging. Similar electrocardiographic changes have been reported occasionally after short-term administration of hydralazine,\textsuperscript{34} minoxidil,\textsuperscript{35} or verapamil.\textsuperscript{36} None of the patients complained of chest pain, and cardiac enzyme levels, when measured, were not changed.

In summary, fenoldopam fulfills the criteria for a useful parenteral antihypertensive drug. While the results of the present study confirm its efficacy in patients with mild-to-moderate hypertension, its major role may be in the treatment of more serious levels of high blood pressure\textsuperscript{37} and in the preservation of renal function when perfusion is jeopardized.

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Augmentation of renal blood flow and sodium excretion in hypertensive patients during blood pressure reduction by intravenous administration of the dopamine1 agonist fenoldopam.

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_Circulation_. 1987;76:1312-1318
doi: 10.1161/01.CIR.76.6.1312

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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