

## Review Article

*Drug Therapy*ALASTAIR J.J. WOOD, M.D., *Editor***FENOLDOPAM — A SELECTIVE PERIPHERAL DOPAMINE-RECEPTOR AGONIST FOR THE TREATMENT OF SEVERE HYPERTENSION**MICHAEL B. MURPHY, M.D., CLARE MURRAY, M.B.,  
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**F**ENOLDOPAM mesylate, a benzazepine derivative, is the first selective dopamine-1-receptor agonist that has been approved for clinical use. Administered parenterally, it acts predominantly as a vasodilator in peripheral arteries and as a diuretic in the kidneys. It has been approved by the U.S. Food and Drug Administration for the in-hospital, short-term (up to 48 hours) management of severe hypertension, when rapid but quickly reversible reduction of blood pressure is required, including malignant hypertension with deteriorating end-organ function. In this review, we examine the development of fenoldopam, its pharmacologic characteristics, and its clinical efficacy.

Severe hypertension is common, although its prevalence varies according to demographic, ethnic, and economic factors. In a recent audit of medical emergency department visits at a Miami hospital, 4.9 percent of the patients had severe hypertension (systolic pressure of at least 220 mm Hg or diastolic pressure of at least 120 mm Hg).<sup>1</sup> The majority of patients with severe hypertension can be treated satisfactorily with drugs that are given orally, but in some patients the hypertension is life-threatening and requires immediate parenteral therapy. Hypertensive emergencies have been defined as elevations in blood pressure accompanied by such complications as encephalopathy, intracranial hemorrhage, pulmonary edema, dissecting aortic aneurysm, and acute myocardial infarction.<sup>2</sup> In 1992, there were 32,000 admissions to hospitals in the United States in which hypertensive emergency or crisis was the sole diagnosis.<sup>3</sup>

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The ideal treatment for a patient who has a hypertensive emergency is a parenteral drug that acts rapidly to reduce blood pressure in a predictable way, has a short half-life so that its action is short-lived if an excessive reduction in blood pressure occurs, and has few adverse effects. Although there are many antihypertensive drugs, few have all these properties. Sodium nitroprusside is one such drug, and newer drugs such as nicardipine and esmolol are useful in particular circumstances, but none have all the desired properties (Table 1). Given the limited therapeutic options, fenoldopam merits consideration for the treatment of hypertensive emergencies.

**FROM DOPAMINE TO AN ANTIHYPERTENSIVE DRUG**

Research on dopamine has long been conducted almost exclusively in the domain of neurobiology. However, dopamine was found to have vasoconstrictor and sympathomimetic effects soon after its synthesis in 1910.

Many years later, the dose-dependent actions of dopamine were recognized. At low doses, it lowers the diastolic blood pressure and increases renal perfusion; at intermediate doses, it increases the heart rate and cardiac contractility; and at higher doses, it causes vasoconstriction and hypertension.<sup>18</sup> The vasodilator and renal effects of dopamine proved to be mediated by the activation of a receptor that is specific to dopamine, now called the dopamine DA1 receptor.

These findings suggested that a drug acting only at the DA1 receptor would be a useful antihypertensive drug, since it could combine vasodilator and diuretic properties in a single molecule. The development of such a drug has taken 30 years.

**DOPAMINE RECEPTORS**

To understand the actions of fenoldopam, it is necessary to understand the diversity of the membrane receptors for dopamine. An endogenous catecholamine, dopamine binds to and activates  $\alpha$ - and  $\beta$ -adrenergic receptors. Through widely distributed specific receptors, dopamine modulates the transmembrane flux of several ions, the release of prolactin, and functions such as nerve conduction, behavior, and movement.<sup>19</sup> All the dopamine receptors are members of the superfamily of G-protein-coupled receptors.<sup>20</sup> Those in the central nervous system were originally classified as D1 and D2 receptors, defined by their ability to stimulate (D1) or inhibit (D2) adenylate cyclase.<sup>21</sup> Newer cloning techniques have been used to reclassify them into two superfamilies: a D1-like group that in-

TABLE 1. INTRAVENOUS DRUGS USED IN THE TREATMENT OF SEVERE HYPERTENSION.\*

DRUG	HALF-LIFE DISTRIBUTION	ELIMINATION	DOSE	ONSET OF ACTION	DURATION OF EFFECT	CLINICAL ADVANTAGES	CLINICAL DISADVANTAGES
Esmolol ( $\beta$ -adrenergic antagonist)	2	9.2 <sup>4</sup> min	For immediate control, bolus of 1 mg/kg over a 30-sec period, then 150–300 $\mu$ g/kg/min <sup>4</sup>	2 min <sup>5</sup>	Complete cessa- tion of clinical effect in 18–30 min <sup>5</sup>	Rapid onset of action; short duration of action; decreases myocardial oxygen demand; useful if there is coexisting tachycardia	Must be used with caution in patients with a history of broncho- spasm, diabetes, or peripheral vascular disease; depresses myo- cardial contractility; contraindicated in patients with severe brad- ycardia or high-grade heart block; as an antihypertensive drug, approved only for perioperative use; caution required with the simultaneous use of morphine, digoxin, or warfarin <sup>5</sup> ; prolongs the action of suxamethonium and mivacurium <sup>5,6</sup>
Nicardipine (dihydropyridine calcium-channel antagonist)	2.7	60 <sup>7</sup>	5–15 mg/hr until target blood pressure achieved, then 3–5 mg/hr <sup>8</sup>	50% of maximal effect in 45 min <sup>8</sup>	50% decrease in effect on blood pressure at 30 min <sup>8</sup>	Intermediate rate of onset and duration of effect on blood pressure	Long elimination half-life precludes rapid titration; reflex tachy- cardia; potentiates neuromuscular blockade by vecuronium <sup>9</sup> ; interacts with inhalation anesthetic agents <sup>10</sup>
Nitroprusside (nitric oxide release)	0.89	14.3 <sup>11</sup>	0.5–8 $\mu$ g/kg/min <sup>12</sup>	Within seconds <sup>12</sup>	Cessation nearly complete in 3–4 min <sup>11,12</sup>	Immediate effect; very short duration of effect	Thiocyanate toxicity; photodegradation; reflex tachycardia; impairs cerebral autoregulation <sup>13</sup>
Fenoldopam (selective DA1 agonist)	NA	9.8 <sup>14</sup> or 4.6 <sup>15</sup>	0.1–1.6 $\mu$ g/kg/min <sup>16</sup>	50% of maximal effect within 15 min <sup>14</sup>	50% of effect lost within 15 min <sup>14</sup>	Preservation of renal function <sup>17</sup> ; interme- diate rate of onset and duration of effect on blood pressure	Tolerance after long-term (>48 hr) infusion <sup>15</sup> ; reflex tachycardia; contraindicated in patients with glaucoma

\*NA denotes not available.

cludes the D1 and D5 subtypes; and a D2-like group that includes the D2, D3, and D4 subtypes.<sup>22</sup>

Peripheral dopamine receptors have a different nomenclature — DA1 and DA2 — that is based on early experiments on vascular pharmacology in animals. The DA1 receptor was defined as the receptor that mediates renal arterial vasodilation and natriuresis during the intravenous or intraarterial administration of dopamine in anesthetized dogs.<sup>23</sup> Vascular DA1 receptors are located on the smooth muscle of most arterial beds, particularly in the renal and splanchnic arteries, with lesser density in the coronary and cerebral arteries.<sup>24</sup> The anatomical distribution of DA1 receptors is outlined in Table 2. These receptors have not been sequenced but are detectable by molecular probes derived from central nervous system receptors, and their pharmacologic characteristics resemble those of central D1-like receptors. Activation of DA1 receptors increases intracellular cyclic adenosine monophosphate (cAMP)-dependent protein kinase A activity, thus promoting the relaxation of smooth muscles.<sup>41</sup> Activation of DA1 receptors on renal tubular cells decreases sodium transport by cAMP-dependent and cAMP-independent mechanisms. Increasing cAMP production in the proximal tubular cells and the medullary part of the thick ascending limb of the loop of Henle inhibits the sodium-hydrogen exchanger<sup>42-44</sup> and the Na<sup>+</sup>/K<sup>+</sup>-ATPase pump.<sup>45</sup> The renal tubular actions of dopamine that cause natriuresis may be augmented by the increase in renal blood flow and the small increase in the glomerular filtration rate that follows its administration. The resulting increase in hydrostatic pressure in the peritubular capillaries and reduction in oncotic

pressure may contribute to diminished reabsorption of sodium by the proximal tubular cells.<sup>46</sup>

Vascular DA2 receptors, similar in many respects to the D2-like central nervous system receptors,<sup>47</sup> are located primarily on presynaptic adrenergic nerve terminals and on the sympathetic ganglia. Their distribution and actions are outlined in Table 2.

#### PHARMACOLOGY OF FENOLDOPAM

Fenoldopam is a benzazepine derivative that is a slightly more potent agonist than dopamine at DA1 receptors but does not act as an agonist at DA2 receptors or  $\alpha$ - and  $\beta$ -adrenergic receptors (Table 3).<sup>48</sup> Administered directly into the central nervous system, fenoldopam stimulates adenylate cyclase activity in the caudate nucleus, and it induces contralateral rotation in rats with lesions of the caudate nucleus — an effect that is consistent with the activation of D1-like receptors.<sup>48</sup> However, because it is poorly soluble in lipids, it does not penetrate the blood-brain barrier, and it has no central nervous system effects when administered intravenously.

#### PHARMACOKINETICS

Less than 6 percent of an orally administered dose of fenoldopam is absorbed,<sup>49</sup> because of the extensive presystemic formation of sulfate, methyl, and glucuronide conjugates.<sup>50</sup> The mean elimination half-life of intravenously infused fenoldopam, estimated on the basis of the decline in the plasma concentration in hypertensive patients after the cessation of a 2-hour infusion, is 9.8 minutes.<sup>14</sup> During longer infusions (up to 48 hours), the elimination half-life may be short-

TABLE 2. EFFECTS MEDIATED THROUGH PERIPHERAL DOPAMINE RECEPTORS.

DA1	EFFECT	DA2	EFFECT
Vessels		Adrenergic nerve terminals on peripheral vasculature	Vasodilation (inhibition of norepinephrine release from sympathetic-nerve terminals) <sup>24</sup>
Renal		Sympathetic ganglia	Inhibition of transmission <sup>35</sup>
Artery	Vasodilation <sup>24</sup>	Pituitary gland	Inhibition (high concentration of DA2 agonist) or stimulation (low concentration of DA2 agonist) of prolactin release <sup>36</sup>
Afferent arteriole	Vasodilation <sup>25</sup>	Area postrema	Emesis <sup>37</sup>
Efferent arteriole	Vasodilation <sup>25</sup>	Kidney	Function unclear but simultaneous activation of DA1 and DA2 receptors required for inhibition of proximal tubular Na <sup>+</sup> /K <sup>+</sup> -ATPase activity <sup>38</sup>
Coronary arteries	Vasodilation <sup>24</sup>	Renal tubules	
Mesenteric arteries	Vasodilation <sup>24</sup>	Inner medullary collecting duct	Stimulation of prostaglandin E <sub>2</sub> production <sup>39</sup>
Cerebral arteries	Vasodilation <sup>24</sup>	Stomach	Increase in gastric secretion and acidity <sup>33</sup>
Venous capacitance vessels	Vasodilation <sup>26</sup>	Adrenal glands	Inhibition of aldosterone secretion <sup>40</sup>
Brain			
Kidney			
Renal tubules	Natriuresis, diuresis <sup>27,28</sup>		
Juxtaglomerular apparatus	Renin release <sup>29</sup>		
Mesangial cells	Possibly relaxation <sup>30,31</sup>		
Eye	Increase in intraocular pressure <sup>32</sup>		
Stomach	Decrease in gastric secretion and acidity <sup>33</sup>		
Adrenal glands	Inhibition of aldosterone secretion <sup>34</sup>		

**TABLE 3.** COMPARISON OF THE RECEPTOR ACTIVITIES OF FENOLDOPAM AND DOPAMINE.

RECEPTOR	LEVEL OF ACTION	
	DOPAMINE*	FENOLDOPAM
Dopaminergic		
DA1	Major	Major
DA2	Major	None
Adrenergic		
$\alpha_1$	Moderate	None
$\alpha_2$	Moderate	None
$\beta_1$	Major	None

\*The receptor-activation profile of dopamine varies according to the dosage. In the low-dose range (2 to 5  $\mu\text{g}$  per kilogram of body weight per minute), only the DA1 and DA2 receptors are activated. At doses of 5 to 10  $\mu\text{g}$  per kilogram per minute,  $\beta_1$ -adrenergic receptors are also activated. In the highest dose range (10 to 50  $\mu\text{g}$  per kilogram per minute) the  $\alpha$ -adrenergic receptors are also activated.

er.<sup>15,51</sup> After an infusion has begun, steady-state plasma concentrations are reached within 30 to 60 minutes.<sup>15</sup> The mean rate of clearance from the body has been estimated at 30.3 ml per kilogram of body weight per minute.<sup>14</sup> In plasma, 85 to 90 percent of fenoldopam is bound to proteins,<sup>52</sup> and its volume of distribution is approximately 600 ml per kilogram.<sup>14</sup> There is a predictable relation between the dose and the plasma concentration of fenoldopam, and there is a linear relation between the reduction in blood pressure and the rate of infusion of fenoldopam.<sup>14</sup>

#### ANTIHYPERTENSIVE ACTIONS OF FENOLDOPAM

Classification of the severity of hypertension by the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure has evolved during the past 10 years. Currently, three stages of severity of hypertension are recognized: stage 1, in which systolic blood pressure ranges from 140 mm Hg to 159 mm Hg or diastolic blood pressure ranges from 90 mm Hg to 99 mm Hg; stage 2, in which systolic blood pressure ranges from 160 mm Hg to 179 mm Hg or diastolic blood pressure ranges from 100 mm Hg to 109 mm Hg; and stage 3, in which systolic blood pressure exceeds 179 mm Hg or diastolic blood pressure exceeds 109 mm Hg.<sup>53</sup> The clinical trials of fenoldopam that have been conducted were designed at a time when an older classification, based exclusively on diastolic pressure, was in use; in this system, mild hypertension was defined as diastolic blood pressure ranging from 90 to 104 mm Hg, moderate hypertension as diastolic blood pressure ranging from 105 to 114 mm Hg, and severe hypertension as diastolic blood pressure greater than 114 mm Hg. Since it is not possible to apply the current classification ret-

respectively, we report the actual blood-pressure ranges studied in the various clinical trials.

#### Oral Fenoldopam in Mild-to-Moderate Hypertension

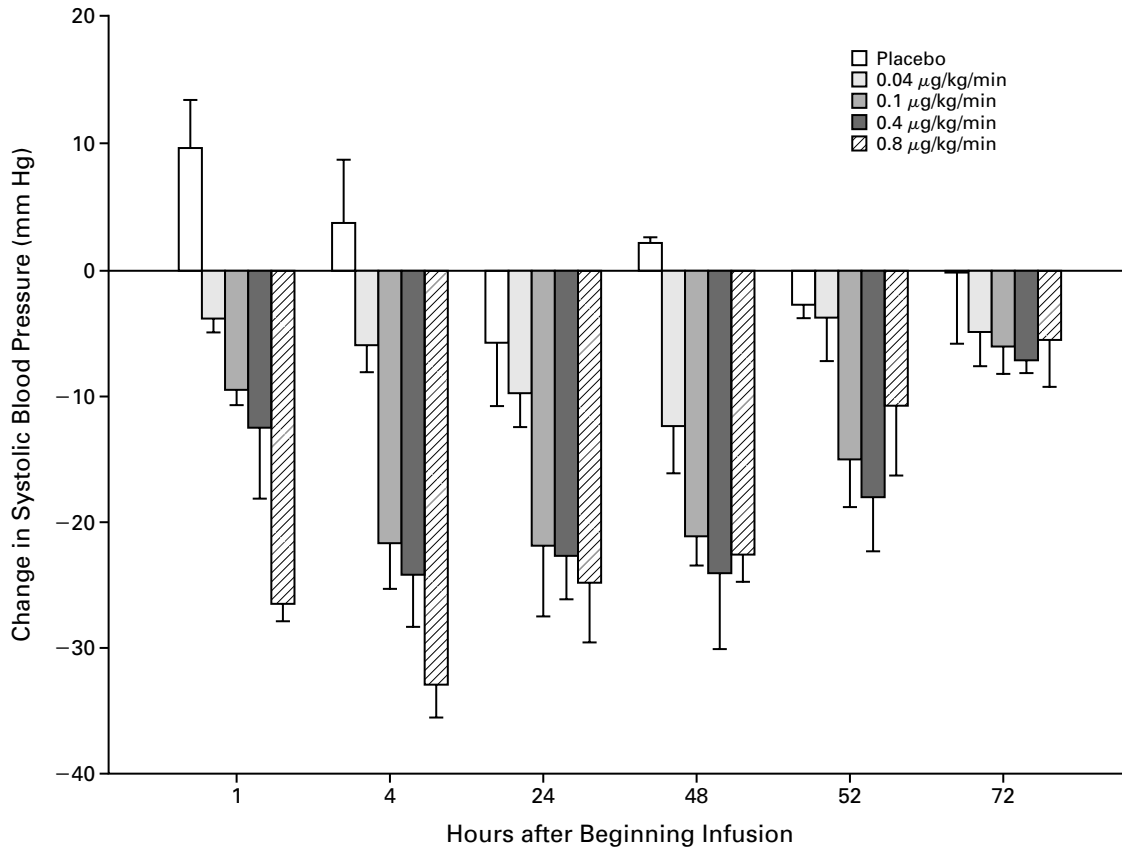
The earliest clinical trials focused on fenoldopam as a potential treatment for patients with mild-to-moderate hypertension, with diastolic blood pressure ranging from 90 to 114 mm Hg. In several small studies, oral doses of fenoldopam ranging from 25 to 100 mg resulted in variable and short-lived reductions in blood pressure,<sup>54-57</sup> concomitant increases in heart rate,<sup>54-57</sup> and in some studies, increases in plasma renin activity,<sup>55-57</sup> serum aldosterone concentrations,<sup>56,57</sup> and urinary flow.<sup>55,56</sup> However, after the poor and variable oral bioavailability of the drug had been recognized, the focus of clinical research changed to the evaluation of its efficacy after parenteral administration.

#### Intravenous Fenoldopam in Mild-to-Moderate Hypertension

The first study of intravenous fenoldopam was conducted in 17 patients with mild hypertension (mean blood pressure, 152/101 mm Hg).<sup>58</sup> The infusion of increasing doses, from 0.025 to 0.5  $\mu\text{g}$  per kilogram per minute, each administered over a 15-minute period, resulted in a dose-dependent decrease in blood pressure, an increase in heart rate, and an increase in plasma catecholamine concentrations. The tachycardia was later found to be preventable by  $\beta$ -adrenergic-receptor blockade, indicating that it was probably caused by the activation of the baroreflex.

In a second study, after water loading to permit studies of renal function, 10 patients received a two-hour infusion of fenoldopam; their blood pressure was reduced from a mean of 159/103 mm Hg to a mean of 144/90 mm Hg with no evidence of tachyphylaxis.<sup>58</sup> The maximal steady-state hypotensive effect was evident within 20 to 30 minutes (Fig. 1). Urinary flow increased by 50 percent and urinary sodium excretion increased by 300 percent, but there was no increase in urinary potassium excretion. Plasma renin activity increased by 50 percent. Renal blood flow increased by 42 percent, and the glomerular filtration rate, as measured by inulin clearance, increased by 6 percent. The results were similar in a further study involving the same patients, even in the absence of previous water loading.<sup>58</sup>

In a randomized, placebo-controlled study involving 33 patients with mild-to-moderate hypertension, the infusion of fenoldopam, in doses of 0.04 to 0.8  $\mu\text{g}$  per kilogram per minute, resulted in a significant dose-dependent reduction in blood pressure (Fig. 2).<sup>15</sup> The maximal decrease in blood pressure was achieved in 1 to 4 hours and was maintained for 24 hours but waned thereafter. Rebound hypertension did not occur when the infusion of the drug was discontinued. No patient had a serious adverse effect. In a pilot study, the infusion of doses of more than 0.8  $\mu\text{g}$  per



**Figure 1.** Mean ( $\pm$ SE) Change from Base Line in the Systolic Blood Pressure of Hypertensive Patients 4, 24, and 48 Hours after Beginning Infusion of Either Placebo or Fenoldopam (at 0.04 to 0.8  $\mu$ g per Kilogram per Minute).

The values at 52 and 72 hours are those obtained 4 and 24 hours after the cessation of the infusion. Reprinted from Taylor et al.<sup>15</sup> with the permission of the publisher.

kilogram per minute was associated with a high frequency of adverse effects (headache, nausea, vomiting, hypotension, diaphoresis, tachycardia, or precipitous bradycardia).<sup>51</sup>

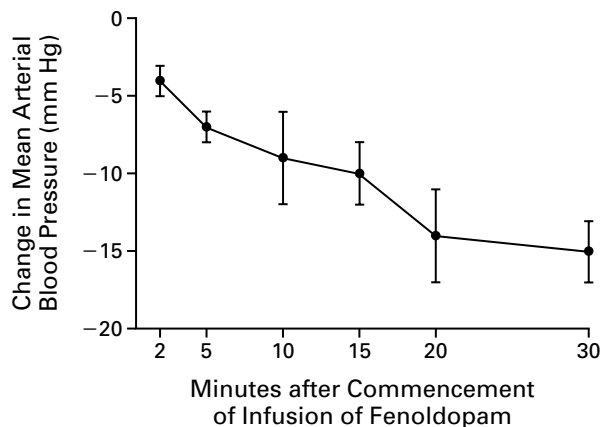
#### Intravenous Fenoldopam in Severe Hypertension

A prospective, randomized, multicenter trial comparing intravenous fenoldopam with sodium nitroprusside in 153 patients with acute severe hypertension was conducted at 24 centers.<sup>59</sup> All the patients had a diastolic blood pressure exceeding 120 mm Hg at entry, and the majority had accelerated or malignant hypertension. They ranged in age from 20 to 80 years, the majority (63 percent) were black, and men and women were equally represented. The study was open-label and used predefined dose-titration steps, with each dose being administered for at least 10 minutes. The dose was increased until a diastolic blood pressure of less than 110 mm Hg had been achieved or until the diastolic blood pressure had been reduced by more than 40 mm Hg if it had exceeded 150 mm Hg be-

fore treatment. A maintenance infusion lasting at least 6 hours but no more than 24 hours was given, and drug therapy was added at the discretion of the investigating physician, usually after the maintenance infusion. The rate of infusion of fenoldopam was then reduced in decrements ranging from 12 percent every 30 minutes to 50 percent every hour. Consequently, in the absence of a standardized approach to the transition to oral drug therapy, and in the absence of studies combining fenoldopam with existing antihypertensive drugs, the optimal approach to weaning patients from fenoldopam remains undefined.

Drug doses ranged from 0.1 to 1.5  $\mu$ g per kilogram per minute for fenoldopam and from 0.5 to 3.5  $\mu$ g per kilogram per minute for nitroprusside. The increments in fenoldopam dosing ranged from 0.05 to 0.1  $\mu$ g per kilogram per minute, and the increments in nitroprusside dosing were 0.25 or 0.5  $\mu$ g per kilogram per minute, at the discretion of the investigator.

Overall, the efficacy of fenoldopam in lowering blood pressure was similar to that of nitroprusside.



**Figure 2.** Reduction in Mean Arterial Blood Pressure in 10 Hypertensive Patients after the Commencement of Infusion of Fenoldopam.

The infusion rate was  $0.25 \mu\text{g}$  per kilogram of body weight per minute in four patients,  $0.375 \mu\text{g}$  per kilogram per minute in five patients, and  $0.5 \mu\text{g}$  per kilogram per minute in one patient. The I bars indicate the SD. Derived from Murphy et al.<sup>58</sup>

There was no difference in mean base-line blood pressure between the two groups (212/135 mm Hg in the fenoldopam group and 210/133 mm Hg in the nitroprusside group). After six hours of infusion, the average decrease in systolic blood pressure was 39 mm Hg in the fenoldopam group and 44 mm Hg in the nitroprusside group, and the average reductions in diastolic blood pressure were 29 mm Hg and 33 mm Hg, respectively. When the doses had been increased to achieve the target blood pressure, the average maintenance infusion rate of fenoldopam was  $0.41 \mu\text{g}$  per kilogram per minute (range, 0.1 to 1.62), and the average maintenance infusion rate of nitroprusside was  $1.67 \mu\text{g}$  per kilogram per minute (range, 0.3 to 8.0). The time required to reach the maintenance infusion rate was also similar in the two groups (85 minutes for patients who received fenoldopam and 94 minutes for those who received nitroprusside).

At one of the participating centers, the investigators collected urine samples from 28 patients at prespecified times before and during the drug infusions.<sup>17</sup> Creatinine clearance was less than 100 ml per minute in 10 of the 13 patients randomly assigned to receive fenoldopam and in 9 of the 15 patients randomly assigned to receive nitroprusside. The patients who were treated with fenoldopam had significant increases in urinary output (from 92 ml per hour to 168 ml per hour), sodium excretion (from  $227 \mu\text{mol}$  per minute to  $335 \mu\text{mol}$  per minute), and creatinine clearance (from 70 ml per minute to 93 ml per minute), whereas all these rates decreased slightly in the patients who were given nitroprusside. Although an increase in renal blood flow or other effects of fenoldopam on the kid-

ney might result in a reduced need for dialysis (a recognized complication of the short-term treatment of malignant hypertension<sup>60,61</sup>), there are, at present, no data from prospective clinical trials to support the existence of such a benefit.

Both drugs were equally well tolerated. There were no instances of thiocyanate toxicity, which is a matter of concern with nitroprusside. In the single study in which plasma thiocyanate was measured, two of nine patients treated with nitroprusside had high concentrations (more than 10 mg per liter) but no symptoms or signs of toxicity.<sup>62</sup>

#### Intravenous Fenoldopam in Hypertensive Emergencies

The effect of fenoldopam in patients with hypertensive emergencies was evaluated in 107 patients with a diastolic blood pressure of more than 120 mm Hg and clinical evidence of acute vasculopathy.<sup>63</sup> Half the patients had at least two of the criteria that define hypertensive emergency; these include encephalopathy, heart failure, acute myocardial ischemia, and hematuria. The majority of the patients were black, and 60 percent were men. The patients were randomly assigned to receive fixed-rate infusions of fenoldopam at 0.01, 0.03, 0.1, or  $0.3 \mu\text{g}$  per kilogram per minute for 24 hours. At 4 hours, there was a dose-dependent reduction in blood pressure; the time required to reduce the diastolic blood pressure by 20 mm Hg ranged from an average of 55 minutes among the patients given the highest dose to 133 minutes among those given the lowest dose. Within this range of doses, fenoldopam was safe. The overall results confirmed the need for a flexible dose-titration regimen when the blood pressure must be reduced rapidly.

#### Fenoldopam for Hypertension during the Perioperative Period

Antihypertensive drugs must be given parenterally to patients who are unable to take drugs orally — for example, after injury, loss of consciousness, or during the perioperative period. Preoperative hypertension is associated with an increased risk of myocardial ischemia during anesthesia, and this risk is reduced by antihypertensive-drug treatment.<sup>64</sup> Postoperative hypertension may be associated with complications such as bleeding, cerebrovascular accident, and myocardial infarction. Rapid establishment of blood-pressure control may reduce the frequency of these complications.

Esmolol has proved particularly useful in lowering blood pressure in patients undergoing coronary-artery bypass grafting,<sup>65</sup> but it is contraindicated in patients with bradyarrhythmias or heart failure and must be given cautiously in those with obstructive airway disease. Nicardipine has also proved effective in patients undergoing bypass surgery.<sup>66</sup> The efficacy of fenoldopam in similar patients has been examined in several small studies. In a phase 2 trial involving 16 patients with postoperative hypertension, defined as

a systolic or diastolic blood pressure while supine that is 20 percent higher than the preoperative base-line value, 8 patients were given fenoldopam starting at a dose of 0.1  $\mu\text{g}$  per kilogram per minute with increases as needed to reduce blood pressure to less than 10 percent above the preoperative level, and 8 patients were given placebo.<sup>67</sup> All eight patients who were given fenoldopam had the desired reduction in blood pressure at infusion rates of less than 1.5  $\mu\text{g}$  per kilogram per minute. Four patients given placebo had similar reductions in blood pressure, but the effect was not sustained. In another study in which the effects of fenoldopam were compared with those of nitroprusside in 20 patients whose systolic blood pressure exceeded 130 mm Hg after coronary-artery bypass grafting, both drugs lowered the blood pressure rapidly and the reduction was sustained during two hours of therapy.<sup>68</sup>

In a third study, the antihypertensive effects of intravenous fenoldopam and intravenous nifedipine were compared in 62 patients with a mean diastolic blood pressure greater than 105 mm Hg within 24 hours after coronary-artery bypass grafting.<sup>69</sup> The goal of therapy was the attainment and maintenance of a mean diastolic blood pressure between 80 and 95 mm Hg. The initial infusion rate of fenoldopam was 0.8  $\mu\text{g}$  per kilogram per minute (with incremental increases of 0.2  $\mu\text{g}$  per kilogram per minute), and the initial infusion rate for nifedipine was 0.3  $\mu\text{g}$  per kilogram per minute (with incremental increases of 0.03  $\mu\text{g}$  per kilogram per minute). The mean blood pressure was reduced to a similar extent by both drugs, but the fenoldopam took effect more rapidly.

In summary, the available data indicate that fenoldopam may be considered for the short-term control of perioperative hypertension. However, drugs such as nitroprusside, with a shorter elimination time, more rapid onset of action, and shorter duration of effect, would be expected to confer better minute-to-minute blood-pressure control during surgery.

#### ADVERSE EFFECTS

The majority of adverse effects attributed to fenoldopam are related to the vasodilator action of the drug. These include headache, flushing, dizziness, and tachycardia or bradycardia. Most adverse effects are mild, occur within the first 24 hours of treatment, and diminish thereafter.<sup>70</sup> In the trial comparing fenoldopam with nitroprusside in patients with severe hypertension, the incidence of these adverse effects was similar with the two drugs.<sup>59</sup> Two particular adverse effects were noted during the trials — electrocardiographic changes and an increase in intraocular pressure.

An unanticipated finding in the first study of intravenous fenoldopam was that most patients had a flattening of the T waves in the anterior and lateral leads of the electrocardiogram, and 4 of the 17 pa-

tients had T-wave inversion.<sup>58</sup> Although similar electrocardiographic changes had been reported during the short-term administration of hydralazine,<sup>71</sup> minoxidil,<sup>72</sup> and verapamil,<sup>73</sup> the high frequency of the changes in the fenoldopam-treated patients led to a formal study of the phenomenon in the later randomized trial in which fenoldopam was compared with nitroprusside.<sup>74</sup> A detailed analysis of digitized electrocardiographic recordings revealed that both drugs decreased T-wave amplitude in all leads except aVR, but there was no other evidence of myocardial ischemia. The authors speculated that acute changes in left ventricular geometry, after an acute reduction in blood pressure, might explain the changes in the T waves, since the height and duration of the T wave depend on the thickness of the ventricular wall and the transmural conduction velocity.

Fenoldopam increases intraocular pressure. In one study of eight normal subjects, fenoldopam, infused intravenously at a rate of 0.5  $\mu\text{g}$  per kilogram per minute, increased the mean intraocular pressure from 14.6 mm Hg to 17.6 mm Hg ( $P < 0.05$ ), whereas a saline infusion had no effect.<sup>32</sup> In subsequent studies in patients with accelerated or malignant hypertension, those who were given an intravenous infusion of fenoldopam had an increase in intraocular pressure, whereas there was no change in the intraocular pressure in the patients given nitroprusside who had similar reductions in blood pressure.<sup>75</sup> The increase in intraocular pressure induced by fenoldopam has been attributed, at least in part, to diminished drainage of aqueous humor.<sup>76</sup> Fenoldopam also increases the intraocular pressure in patients with ocular hypertension, and the increase may be more marked than in patients with normal intraocular pressure.<sup>77</sup> Fenoldopam should therefore be given cautiously, if at all, in patients with glaucoma or high intraocular pressure.

#### DRUG-DRUG INTERACTIONS

The concomitant oral administration of fenoldopam and acetaminophen in 12 normal subjects resulted in a 32 percent increase in the peak plasma fenoldopam concentration.<sup>78</sup> The mechanism of this increase is thought to be competition for the inorganic sulfate to which both are conjugated. In 10 patients with congestive heart failure who were taking digoxin, oral fenoldopam did not alter the plasma digoxin concentration.<sup>79</sup> The poor oral bioavailability of fenoldopam, however, detracts from the conclusiveness of this study.

In rats, the natriuretic effects of fenoldopam are markedly potentiated by the angiotensin-converting-enzyme inhibitors captopril<sup>80</sup> and enalaprilat,<sup>81</sup> as well as by the angiotensin II-receptor antagonist losartan.<sup>81</sup> This effect can be attributed to blockade of the intrarenal production or action of angiotensin II.<sup>81</sup> A more marked diuresis might be anticipated in patients treated with fenoldopam and one of these drugs, but this has not been documented.

## FENOLDOPAM AS A RENAL PROTECTIVE DRUG

After the discovery of the renal actions of dopamine, its use as a renal protective agent in clinical situations known to lead to impaired renal function, such as vascular surgery or shock, became nearly standard practice in spite of the virtual absence of definitive supportive evidence.<sup>82-84</sup> Fenoldopam may in time be given for the same reason. Evidence of its benefit in animals with renal damage is accumulating, but data regarding its clinical efficacy are sparse.

In rats with acute nephrotoxicity induced by antibiotics (such as cyclosporine<sup>85</sup> and amphotericin B<sup>86,87</sup>), the administration of fenoldopam (or the oral pro-drug form<sup>86</sup>) has beneficial effects on renal hemodynamics,<sup>85</sup> function,<sup>85,87</sup> and histology.<sup>86</sup> Intravenous fenoldopam attenuated the reduction in the glomerular filtration rate (assessed on the basis of the creatinine clearance) but not the renal vasoconstriction caused by amphotericin B in anesthetized dogs.<sup>87</sup> This seemingly perfusion-independent effect on the glomerular filtration rate may have been mediated by the activation of DA1 receptors on mesangial cells, which are known to contract in response to amphotericin B.<sup>88</sup> The effect of intravenous fenoldopam (infused at a rate of 0.5  $\mu\text{g}$  per kilogram per minute continuously for eight days) on the subacute toxicity of amphotericin B (given every other day for eight days) was limited.<sup>87</sup>

In dogs, fenoldopam also protects against the acute renal vasoconstriction that may be induced by radio-contrast medium.<sup>89</sup> Whether this translates into the preservation of renal function has not been determined.

In mildly hypertensive recipients of kidney transplants who were receiving cyclosporine, the administration of oral fenoldopam for three weeks resulted in a significant increase in renal plasma flow.<sup>90</sup>

In another study in 12 patients with hypoxemia due to multiple trauma or visceral surgery who required intermittent positive-pressure ventilation with positive end-expiratory pressure, intravenous fenoldopam (0.2  $\mu\text{g}$  per kilogram per minute) increased renal perfusion, urine flow, and the excretion of both sodium and potassium.<sup>91</sup> Beneficial renal effects have been demonstrated at infusion rates as low as 0.03  $\mu\text{g}$  per kilogram per minute — well below those usually required to lower the systemic blood pressure.<sup>92</sup>

In a recent study of 58 patients undergoing repair of a thoracoabdominal aortic aneurysm who were randomly assigned to receive fenoldopam or placebo, the survival rate was 93 percent in the fenoldopam group, as compared with 80 percent in the placebo group.<sup>93</sup>

### INDICATIONS FOR FENOLDOPAM THERAPY

Fenoldopam is indicated for in-hospital, short-term treatment (up to 48 hours) of patients with severe hypertension in whom a rapid reduction of blood pressure is clinically indicated. This group includes patients

with malignant hypertension and deteriorating organ function and patients with severe perioperative hypertension. The initial infusion rate should be 0.1  $\mu\text{g}$  per kilogram per minute to ensure a meaningful reduction in blood pressure within 15 minutes.<sup>16</sup> The recommended increments for titration are 0.05 to 0.1  $\mu\text{g}$  per kilogram per minute, at intervals of 15 to 20 minutes, up to a maximal dose of 1.6  $\mu\text{g}$  per kilogram per minute.<sup>16</sup> Bolus doses should not be given. The blood pressure and the heart rate should be measured frequently (at least every 10 minutes); monitoring of the intraarterial blood pressure is not required. Intravenous fenoldopam has been administered for up to 48 hours in patients in clinical trials. Transition to oral therapy with another drug can begin at any time after the blood pressure has been stabilized; the rate of fenoldopam infusion should be reduced gradually as the oral therapy becomes effective.

### CONCLUSIONS

Fenoldopam is a useful drug for patients with severe hypertension in whom the therapeutic options are limited. It is as effective as nitroprusside, the current standard therapy for these patients. The two drugs have a similar symptomatic side-effect profile, but fenoldopam is not associated with thiocyanate toxicity and is not degraded by light. Nitroprusside remains the drug of choice for patients in whom a rapid onset of action and a short duration of effect are desirable, as is the case during the perioperative period. The effects of fenoldopam on renal hemodynamics and renal tubular cells suggest that it has the potential to preserve kidney function; however, the ultimate clinical importance of these effects remains to be determined.

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