Prolonged Fenoldopam Infusions in Patients With Mild to Moderate Hypertension
Pharmacodynamic and Pharmacokinetic Effects
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Thirty-three patients with mild-to-moderate essential hypertension received either placebo or fenoldopam, a selective dopamine-1 agonist, by intravenous infusion at a fixed infusion rate ranging from 0.1 to 0.8 μg/kg/min for 48 h during a double-blind, placebo-controlled, randomized inpatient clinical trial. Blood pressure and heart rate were measured every 15 min for 24 h before, during, and 24 h after the 48-h drug infusion. Plasma concentrations of racemic fenoldopam were measured at frequent intervals during and for 24 h after fenoldopam infusion.

In the 26 patients who received fenoldopam, there were dose-dependent reductions in systolic and diastolic blood pressure, which usually reached a nadir within 2 h of beginning infusion and were significant even at the lowest dose studied (−9 and −9 mm Hg for systolic and diastolic blood pressure, respectively, at 24 h for the dose of 0.04 μg/kg/min, \( P < .05 \)). There were associated increases in heart rate that were greater in the first than in the last 24 h of drug infusion. Compared to the average 24-h control blood pressure, maximum mean reductions in systolic and diastolic blood pressures of 33 and 21 mm Hg, respectively, were noted in patients receiving fenoldopam at 0.8 μg/kg/min and occurred 4 and 1 h, respectively, after beginning infusion. Tolerance to the blood pressure lowering effects of the drug developed slowly during the 48 h of drug infusion; the half-life for this effect was 60 h. No serious adverse clinical effects were noted in any patient.

These results demonstrate that fenoldopam is effective in reducing blood pressure of patients with mild-to-moderate hypertension at doses as low as 0.04 μg/kg/min, is well tolerated at doses up to 0.8 μg/kg/min, maintains most of its antihypertensive efficacy throughout 48 h of continuous, constant rate infusion, and produces neither prolonged pharmacodynamic effects nor rebound hypertension when discontinued. The pharmacodynamic effects of the drug are best predicted by pharmacokinetics of racemic and R-fenoldopam. Am J Hypertens 1999;12:906–914 © 1999 American Journal of Hypertension, Ltd.

KEY WORDS: Hypertension, fenoldopam, pharmacokinetics, pharmacodynamics.
Fenoldopam is a selective, dopamine-1 agonist that lowers blood pressure by peripheral vasodilatation without significant effects on α- or β-adrenergic or dopamine-2 receptors at therapeutic concentrations in humans. Fenoldopam effectively lowers blood pressure during infusions of 24 h or less in patients with severe or malignant hypertension with a rapid onset of action similar to that of sodium nitroprusside. Fenoldopam is at least as effective as either nifedipine or sodium nitroprusside in the control of postoperative hypertension in patients after coronary artery bypass grafting and improves hemodynamics in patients with congestive heart failure.

Pharmacokinetics of fenoldopam have been examined in healthy volunteers and in patients with hypertension during and after intravenous infusions of 4 h or less. The terminal phase half-life of plasma fenoldopam in these volunteers and patients was estimated to be 5 to 10 min. The pharmacodynamic and pharmacokinetic effects of fenoldopam, its enantiomers, and metabolites in patients with mild-to-moderate hypertension after more prolonged infusions have been assessed in only one previous study. The results of this single-blind pilot study in 8 hypertensive patients suggested that intravenous infusion of fenoldopam for 48 h at rates higher than 1 μg/kg/min may be associated with an increased incidence of adverse clinical and hemodynamic effects, such as headache, nausea, vomiting, diaphoresis, tachycardia, hypertension, and precipitous bradycardia, usually noted within 2 h of starting infusion.

The objectives of the present double-blind, randomized, placebo-controlled intravenous infusion study were 1) to define the pharmacodynamic responses to fenoldopam during 48-h constant rate, fixed-dose infusions in patients with mild-to-moderate hypertension; 2) to define the minimally effective dose of fenoldopam in lowering blood pressure; 3) to determine whether tolerance to the hemodynamic effects of fenoldopam occurred during continuous 48-h fixed-dose infusions of the drug; 4) to determine the rate of return of blood pressure and heart rate toward baseline (preinfusion) levels after discontinuation of the drug, 5) to determine whether the pharmacokinetics of racemic fenoldopam, its R- and S-enantiomers, or its 7- and 8-methoxy metabolites correlated with the pharmacodynamic effects of fenoldopam during its infusion and upon completion of infusion.

METHODS

Patient Selection This multiple site, randomized, placebo-controlled, double-blind, 4-day inpatient study enrolled hypertensive patients 18 to 65 years of age without a previous clinical history of other serious clinical conditions and without significant laboratory abnormalities. Patients were screened during an initial 10- to 30-day outpatient phase. The study was approved by the Institutional Review Boards for Human Research of the three participating centers and all patients gave written informed consent before their enrollment in the study. Antihypertensive medications were discontinued at the time of initial evaluation. During the outpatient phase, patients were required to have a supine diastolic blood pressure (average of three values taken at 1-min intervals) between 95 and 119 mm Hg on at least two occasions 3 days apart with the difference between the two average values being no more than 7 mm Hg to qualify for the inpatient phase.

Inpatient Study Design The study design for the 4-day inpatient phase of the study is shown in Table 1. Supine systolic (SBP) and diastolic (DBP) pressures were recorded from the nondominant arm by a calibrated oscillometric blood pressure recording device (Dinamap Model 9710, Critikon, Tampa, FL) at least every 15 min during the 4 days of hospitalization. Heart rate (HR) was recorded from a continuously monitored Dinamap lead II electrocardiographic signal. Patients remained supine for at least 5 min before each blood pressure recording. On the morning of day 1, an indwelling catheter was inserted into a forearm vein and a solution of 5% dextrose in water was infused at a rate of 0.5 mL/min. During the last hour of the first 24 h infusion, supine DBP on three consecutive measurements had to average 90 to 119 mm Hg for the patient to receive fenoldopam intravenously. Fenoldopam was diluted with 5% dextrose in water by an unblinded research pharmacist to achieve a final concentration sufficient to deliver the drug at a predetermined rate (0.04 to 0.8 μg/kg/min) in a volume of 0.5 mL/min. Supine SBP and DBP and HR were monitored every 5 min for the first hour of infusion, then every 15 min thereafter. Blood was obtained from an indwelling intravenous catheter in the contralateral arm for fenoldopam pharmacokinetic measurements at 5, 10, 15, 30, 45, and 60 min after beginning fenoldopam infusion, then every hour for an additional 5 h, then every 6 h. After 48 h of infusion, hemodynamic and pharmacokinetic measurements were repeated with the same sampling schedule as that during the first 24 h of fenoldopam infusion. Blood for routine serum chemistries and complete blood count was obtained on the morning of initiation of fenoldopam infusion and again 24 h after discontinuing the fenoldopam infusion.

Analytic Methods Concentrations of racemic fenoldopam in plasma were measured by coulometric electrochemical detection after separation by HPLC using the method of Boppana et al. The analytical method for 7- and 8-methoxyfenoldopam was similar, with identical extraction methodology but with a mobile phase of acetonitrile/methanol/monochloroac-
etate buffer pH 3.2 (18/4/78 vol/vol). R- and S-fenoldopam enantiomers were measured in the plasma of patients who received fenoldopam at a dose of either 0.4 or 0.8 mg/kg/min by a modification16 of the method of Bopanna and coworkers.17

Statistical Determinations All statistical calculations were performed using the SigmaStat Statistical Software Program by Jandel Scientific Software, San Rafael, CA. Comparisons of hemodynamic data before, during, and after fenoldopam infusion were made in each patient by linear regression analysis. Pharmacokinetic and pharmacodynamic variables were modeled using the NONMEM software (NONMEM Project Group, UCSF, San Francisco, CA).

RESULTS

Patient Characteristics Characteristics of the 33 patients randomized in this trial are summarized in Table 2 by fenoldopam infusion rate. One patient received fenoldopam at a dose of 0.01 rather than 0.1 µg/kg/min due to a medication preparation error. That patient’s data are included in the demographic tables but are not included in the pharmacokinetic or pharmacodynamic data or in the statistical calculations. At the time of screening, 19 of 33 patients were taking antihypertensive medications and 12 of 19 patients were taking more than one medication. The three drug classes most commonly included in the antihypertensive regimens of these patients were calcium channel blockers (39%), diuretics (27%), and angiotensin converting enzyme inhibitors (24%).

Pharmacodynamic Effects of Fenoldopam Changes in supine SBP and DBP and HR after 1, 4, 24, and 48 h of constant rate, fixed-dose fenoldopam infusion compared to the 24-h average for these parameters during vehicle infusion are summarized in Figures 1 to 3, respectively. Values at 52 and 72 h are those obtained 4 and 24 h after discontinuing fenoldopam infusion. When analyzed by linear regression analysis, a significant dose-dependent reduction in both supine SBP and DBP was observed for all four fenoldopam doses. The supine DBP reduction was maximum at 1 to 4 h and tended to decline slightly at 24 h and more so after 48 h of infusion. Among patients receiving fenoldopam at 0.1 to 0.8 µg/kg/min, the average supine DBP 24 h after stopping infusion was persistently lower compared to the day 1 average DBP (Figure 2), although these differences did not reach statistical sig-

### TABLE 1. STUDY FLOW DIAGRAM FOR THE INPATIENT PHASE OF THE STUDY

<table>
<thead>
<tr>
<th>Day 0</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Admission H &amp; P Entry DBP 95–119 mm Hg</td>
<td>Vehicle infusion†</td>
<td>Placebo or fenoldopam infusion*</td>
<td>Placebo or fenoldopam infusion</td>
<td>Vehicle infusion Safety lab</td>
</tr>
<tr>
<td>Safety lab</td>
<td>Qual. DBP ≥95–119 mm Hg</td>
<td>BP and HR every ≤15 min</td>
<td>BP and HR every ≤15 min</td>
<td></td>
</tr>
<tr>
<td>BP and HR every ≤15 min</td>
<td>Fenoldopam PK</td>
<td>Fenoldopam PK</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Patients were randomized to receive fenoldopam at fixed, constant rate of 0.04, 0.1, 0.4, and 0.8 µg/kg/min for 48 h starting on day 2 of admission.
† Blood was obtained at 0, 5, 10, 20, 30, 45, 60, 120, 180, 240, 300, and 360 min and then every 6 h after initiation of infusion for determination of plasma fenoldopam, its R- and S-enantiomers, and 7- and 8-methoxy metabolites.

† Vehicle is 5% dextrose in water.

### TABLE 2. PATIENT DEMOGRAPHICS BY DOSE GROUP

<table>
<thead>
<tr>
<th>Dose (µg/kg/min)</th>
<th>N</th>
<th>Age</th>
<th>Black Race (%)</th>
<th>White Race (%)</th>
<th>Gender M/F (%)</th>
<th>SuSBP† (mm Hg)</th>
<th>SuDBP† (mm Hg)</th>
<th>Weight (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0</td>
<td>7</td>
<td>49</td>
<td>28.6</td>
<td>57.1</td>
<td>43/57</td>
<td>163.5</td>
<td>99.6</td>
<td>93.3</td>
</tr>
<tr>
<td>0.04</td>
<td>7</td>
<td>54</td>
<td>28.6</td>
<td>71.4</td>
<td>86/14</td>
<td>148.4</td>
<td>95.3</td>
<td>106.8</td>
</tr>
<tr>
<td>0.1</td>
<td>7</td>
<td>49</td>
<td>0*</td>
<td>85.7*</td>
<td>100/0</td>
<td>151.6</td>
<td>99.2</td>
<td>102.0</td>
</tr>
<tr>
<td>0.4</td>
<td>5</td>
<td>47</td>
<td>40.0</td>
<td>60.0</td>
<td>80/20</td>
<td>150.5</td>
<td>97.5</td>
<td>88.1</td>
</tr>
<tr>
<td>0.8</td>
<td>6</td>
<td>54</td>
<td>66.7</td>
<td>16.7*</td>
<td>100/0</td>
<td>148.8</td>
<td>99.7</td>
<td>86.4</td>
</tr>
<tr>
<td>Totals</td>
<td>32</td>
<td>50</td>
<td>33.0</td>
<td>57.5</td>
<td>82/18</td>
<td>154.3</td>
<td>98.2</td>
<td>94.9</td>
</tr>
</tbody>
</table>

* Missing percent due to race = Asian and Hispanic.
† SuSBP, supine systolic blood pressure; SuDBP, supine diastolic blood pressure.
nificance. There was much greater variability among groups in the magnitude and duration of the SBP response (Figure 1). Increases in HR reciprocal to the decrement in supine DBP were noted among all infusion groups; again, these increases tended to be greatest at 1 and 4 h and were substantially less by 48 h of infusion. Except for an unexpected reduction in heart rate 24 h after infusion in the group of patients receiving 0.4 \( \mu g/kg/min \), mild reflex tachycardia persisted in treated but not placebo groups, which mirrored the persistent reductions in supine DBP (Figure 3).

Adverse Events  No serious adverse clinical events occurred during the 48 h infusion or in the 24 h after discontinuation of intravenously administered fenoldopam. The most common clinical symptom was headache, which was reported by 12 patients one or more times. Headaches tended to be reported with
greater frequency and to be more persistent in patients receiving 0.4 and 0.8 \( \mu g/kg/min \) fenoldopam than those on lower doses or placebo. Nonspecific ST-segment changes on electrocardiograms, previously reported to be associated with fenoldopam infusion and not thought to represent myocardial ischemia, were noted in 3 patients. The second most commonly reported clinical symptom was dizziness in 3 patients, a symptom related to the known pharmacologic effect of the drug. No clinically or statistically significant changes were noted in any of the routine laboratory chemistry tests when day 1 results were compared with those obtained at the end of the study.

**Pharmacokinetics of Fenoldopam** The pharmacokinetic parameters, terminal phase plasma elimination half-life, and total body clearance for racemic fenoldopam, R- and S-fenoldopam, and for 7- and 8-methoxyfenoldopam in these hypertensive patients are summarized in Table 3. The mean half-life for racemic fenoldopam in this study (4.6 min) and that of a pilot study of mild-to-moderate hypertensive patients also infused for 48 h (6.1 min)\(^{14}\) was slightly less than that reported after 2-h infusions (9.8 min) in another group of mild-to-moderate hypertensives\(^{13}\) and in normotensive volunteers\(^{12}\).

Mean (±SEM) plasma concentrations of racemic fenoldopam for patients in each of the four drug treatment groups are summarized in Figure 4. Average plasma concentration for each infusion group was proportional to the infusion rate. For example, the mean steady-state plasma concentration for patients receiving fenoldopam at a rate of 0.8 \( \mu g/kg/min \) was approximately 28 ng/mL, twice that of the 14 ng/mL mean value for patients receiving 0.4 \( \mu g/kg/min \). Plasma concentrations reached steady state 30 to 60 min after beginning infusion and remained relatively constant for the remainder of the 48-h infusion. Upon discontinuation of fenoldopam infusion, there was a prompt reduction of the plasma concentration. There was no obvious prolonged residual elimination phase for racemic fenoldopam and pharmacokinetic modeling did not detect any hemodynamic effects after cessation of infusion that were unaccounted for by the rate of elimination of racemic fenoldopam.

**Pharmacokinetic and Pharmacodynamic Interactions** Measured plasma concentrations of racemic fenoldopam, its enantiomers (R, S), and two metabolites (7- and 8-methoxyfenoldopam) are summarized in Table 3. The significant increase in plasma concentration with increasing infusion rate observed for fenoldopam was not apparent for the two metabolites, indicating a lower rate of elimination of these metabolites.

### Table 3. Total Body Clearance and Plasma Elimination Half-Life (T\(_{1/2}\)) of Fenoldopam, Its Enantiomers, and Two Major Metabolites

<table>
<thead>
<tr>
<th>Drug or Metabolite</th>
<th>Clearance (L/min)</th>
<th>Plasma t(_{1/2}) (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Racemic fenoldopam*</td>
<td>2.6</td>
<td>4.6</td>
</tr>
<tr>
<td>R-Fenoldopam†</td>
<td>3.4</td>
<td>6.3</td>
</tr>
<tr>
<td>S-Fenoldopam†</td>
<td>1.9</td>
<td>6.1</td>
</tr>
<tr>
<td>7-Methoxyfenoldopam†</td>
<td>1.3</td>
<td>13.2</td>
</tr>
<tr>
<td>8-Methoxyfenoldopam†</td>
<td>1.1</td>
<td>12.5</td>
</tr>
</tbody>
</table>

* \( n = 32 \) patients.
† \( n = 13 \) patients who received fenoldopam at infusion rates of 0.4 and 0.8 \( \mu g/kg/min \).
and 8-methoxyfenoldopam) (Figure 5), as well as the recorded supine SBP and DBP and HR, were used in the pharmacokinetic/pharmacodynamic models to examine dose–concentration and concentration–effect relationships. A one-compartment model best fits the kinetics of racemic fenoldopam, with an average clearance and plasma elimination half-life of 2.6 L/min and 4.6 min, respectively. None of the measured pharmacodynamic effects were delayed compared to the increase in plasma concentrations of racemic fenoldopam or R-fenoldopam. The development of partial pharmacologic tolerance to the effects of racemic fenoldopam could not be detected in the pharmacokinetic/pharmacodynamic models using racemic fenoldopam (ΔSBP, ΔHR), or R-fenoldopam (ΔSBP, ΔDBP, ΔHR). Only in the pharmacokinetic/pharmacodynamic model of ΔDBP and racemic fenoldopam did the potency decline, with a half-life of about 60 h.

**DISCUSSION**

The design of this randomized, double-blind, placebo-controlled study of the pharmacodynamics and pharmacokinetics of 48-h fixed-dose intravenous fenoldopam in patients with mild-to-moderate hypertension is different from those of previous studies in some important aspects. Most previous studies, especially those in which patients with severe hypertension were enrolled, used a titration-to-effect design.\(^3\)–\(^7\),\(^13\) Thus, the extent of blood pressure reduction and HR increase produced by fenoldopam in these studies cannot be strictly compared with the quantitative hypertensive and tachycardic effects of the drug when it is given at a predefined fixed dose, especially as initial doses higher than 0.3 \(\mu g/\text{kg/min}\) were not used in these previous trials.\(^18\) Furthermore, a substantial proportion of the patients in these titration-to-effect trials had not only significantly higher initial values for blood pressure than those in this study, but also had evidence of target organ damage. Because patients with accelerated or malignant hypertension may have blunted autonomic baroreceptor reflexes,\(^19\),\(^20\) their response to arterial vasodilators like fenoldopam may involve blunting of the tachycardia mediated by autonomic activation as blood pressure is decreased. Finally, patients enrolled in previous titration-to-effect trials were predominantly African-American, whereas a majority of patients in this study were white. Despite these differences, comparable doses of fenoldopam produced similar proportional decreases in blood pressure in this compared to other studies.\(^21\),\(^22\) In one of these trials,\(^27\) a fenoldopam dose of 0.1 \(\mu g/\text{kg/min}\) produced no significant tachycardia when administered for 4 h to patients with accelerated hypertension, whereas the same dose in the patients with mild-to-moderate hypertension produced about a 10 beat/min increase in HR at both 1 and 4 h (Figure 3). The comparability of blood pressure reduction with similar doses in patient populations that not only differ in objective evidence for target organ involvement but are also ethnically different suggests that there is not likely to be a racial difference in the hemodynamic response to this dopamine agonist.

Significant dose-dependent and comparable reductions in supine SBP and DBP were noted 1 h after
starting fenoldopam infusion and persisted or increased slightly at 4 h (Figures 1 and 2). Dose-proportional heart rate increments were also comparable at 1 and 4 h (Figure 3). There was a gradual decline in the average blood pressure, proportionally greater for diastolic than systolic, which was apparent after 24 h of infusion and even more noticeable after 48 h. The heart rate, on the other hand, returned toward baseline values more quickly than did the blood pressure, such that by 48 h the average HR was significantly greater than baseline for only those patients receiving 0.4 and 0.8 \( \mu g/kg/min \). This partial tolerance to the hemodynamic effects of fenoldopam is not explained by alterations in drug plasma concentrations or metabolism (Figures 4 and 5) and is most likely attributable to either dopamine-1 receptor downregulation or to autonomic neuronal or neuroendocrine adaptation to the persistent reduction of blood pressure, or both.

Steady-state plasma concentrations of racemic fenoldopam during continuous intravenous infusion were proportional to dose (Figure 4) in this study, were achieved within 30 to 60 min after initiation of drug infusion, and tended to remain constant throughout the 48 h of infusion. The time required to achieve steady state increased slightly at progressively higher fenoldopam doses but this effect was not statistically significant. The average steady-state values for fenoldopam in these patients were similar to steady-state values reported for comparable doses in both healthy volunteers\(^1\) and patients with essential hypertension.\(^2\) Plasma concentrations of R-fenoldopam, the enantiomer responsible for most or all of the pharmacologic activity,\(^1\) also were dose-proportional and tended to remain relatively stable throughout the 48 h of infusion, once steady state had been achieved. R-fenoldopam rapidly disappeared from the plasma after drug infusion was discontinued and, thus, is unlikely to have contributed to the residual modest persistent reduction in blood pressure compared to baseline values observed both 4 and 24 h after drug infusion had been stopped. Similarly, the hemodynamic responses to fenoldopam in these patients are not explained by the pharmacokinetic profile of either the 7- or 8-methoxyfenoldopam metabolites (Figure 5), both of which tended to reach steady-state concentrations in plasma only after 24 h of racemic fenoldopam infusion and contribute little, if any, to the antihypertensive action of fenoldopam.\(^2\)

The modestly lower blood pressures observed in this study 24 h after discontinuation of fenoldopam

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**FIGURE 5.** Average plasma concentration of R-fenoldopam (A), and for the 7- and 8-methoxy metabolites of fenoldopam (B and C) in patients receiving fenoldopam at 0.4 or 0.8 \( \mu g/kg/min \) during 48 h of infusion and in the 24 h after discontinuation of drug infusion.

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infusion contrasts with the rapid return of blood pressure to preinfusion values reported in previous studies of hypertensive patients with mild-to-moderate blood pressure elevations. This difference may be due to either the more prolonged duration of blood pressure reduction produced by fenoldopam in this study compared to much shorter times in previous studies or to the tendency of blood pressure to decline during prolonged hospitalization. The findings that the SBP and DBP values in the placebo-treated patients 24 h after infusion had returned to preinfusion baseline values is not consistent with the latter interpretation.

Although the number of patients exposed to fenoldopam in this study is too small to make broad generalization about the safety of fenoldopam, the most common clinical complaints, namely headache (33%), dizziness (9%), and asthenia (6%), are consistent with known pharmacologic consequences of vasodilators. These symptoms occurred more frequently in patients treated with fenoldopam than in the placebo-treated group. As in previous studies of arterial vasodilators including fenoldopam and sodium nitroprusside, electrocardiographic nonspecific ST-segment abnormalities were noted in 9% of patients. These changes were not associated with clinical symptoms during infusion and tended to resolve when drug infusion was discontinued. The 1 patient who reported angina did so 5 days after completing the 48 h of fenoldopam infusion and was not among the patients in whom electrocardiographic ST-segment changes were observed.

In summary, this randomized, double-blind, placebo-controlled study of the pharmacodynamics and pharmacokinetics of fixed-dose, constant rate, continuous intravenous infusion of fenoldopam confirms the previously reported short half-life of the drug, which we calculated to be approximately 5 min. In addition, this study clearly demonstrates that steady-state plasma concentrations of fenoldopam are achieved within 30 to 60 min, and that plasma concentrations of the drug are proportional to the dose infused. The findings do not suggest any alteration in the pharmacokinetics of fenoldopam during a prolonged infusion of 48 h. Fenoldopam is predictably and rapidly eliminated from the plasma upon discontinuation of the infusion. The pharmacodynamic effects of fenoldopam are also predictable with regard to dose-dependent SBP and DBP reductions and HR increases. The data suggest a gradual offset of action during the 48 h of infusion. Finally, no significant hemodynamic rebound phenomena were observed after the abrupt discontinuation of fixed-dose, 48-h infusions of fenoldopam. In this study population of patients with mild-to-moderate hypertension, fixed-dose infusions of the drug at rates as high as 0.8 μg/kg/min were tolerated with minimal symptoms and no serious adverse effects.

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REFERENCES


