Intravenous Fenoldopam Versus Sodium Nitroprusside in Patients With Severe Hypertension

Efrain Reisin, Mark M. Huth, Binh P. Nguyen, Sherrolyn G. Weed, and Francisco M. Gonzalez

In an open-label study, we compared the efficacy and safety of intravenous infusion of fenoldopam mesylate with that of sodium nitroprusside in patients with severe hypertension or in hypertensive crisis. Both antihypertensive medications were infused at a maximal dose increment of 0.2 \( \mu g/kg/min \) (fenoldopam) and 1 \( \mu g/kg/min \) (nitroprusside), with a maximal infusion rate of 1.5 \( \mu g/kg/min \) fenoldopam mesylate or 8 \( \mu g/kg/min \) sodium nitroprusside. Once the desired reduction in diastolic blood pressure was achieved (less than 110 mm Hg if initial diastolic blood pressure was 120-149 mm Hg, or by at least 40 mm Hg if initial diastolic blood pressure was 150-190 mm Hg), the maximal infusion rate used was maintained for at least 1 hour, and then, the infusion was slowed gradually over 2 hours. After the infusion treatment, patients remained in the hospital for 2 days of follow-up. Both antihypertensive agents successfully controlled the blood pressure in all the patients by the end of the maintenance periods. Between the baseline and the end of the maintenance period, analysis of variance showed that the changes in the variables induced by fenoldopam mesylate did not differ significantly from those induced by sodium nitroprusside. The incidence of side effects listed were similar in both groups of patients. The detection of toxic levels of thiocyanate in two patients treated with nitroprusside, however, shows that fenoldopam might be preferable for the control of a hypertensive crisis or severe hypertension in patients with decreased renal function. (Hypertension 1990;15(suppl 1):I-59–I-62)

A cute elevation of blood pressure is an emergency that necessitates prompt treatment to prevent target-organ complications or death. One of the most widely parenteral antihypertensive agents currently used for the treatment of such crises is sodium nitroprusside, a powerful vasoconstrictor that acts directly on the smooth muscle of blood vessels affecting both resistance and capacitance vessels, with a consequent decrease in arterial pressure, a decrease that is dose dependent.1

Fenoldopam is an agonist of peripheral postsynaptic dopamine (DA1) receptor,2 with weak \( \alpha_2 \)-antagonist properties.3 It has a vascular dilatation action that primarily affects the renal vasculature.4 Fenoldopam increases renal blood flow and controls arterial blood pressure by both oral and parenteral routes.5

In a randomized open-label study, we compared the efficacy and safety of intravenous infusion of fenoldopam mesylate with that of sodium nitroprusside in patients with severe hypertension or in hypertensive crisis.

Methods

Study Patients

Eighteen patients, 27-61 years old, with severe essential hypertension (diastolic blood pressure [DBP] greater than 120 mm Hg but lower than 171 mm Hg) entered the trial. Patients were recruited from the hospital emergency room or the special hypertension clinic at Charity Hospital of New Orleans and were randomly assigned to treatment with either sodium nitroprusside or fenoldopam mesylate. The study was approved by our institutional ethical committee and an informed written consent was obtained.

Eligibility for the study was determined by the following: complete medical history and physical examination and DBP higher than 120 mm Hg and lower than 170 mm Hg, confirmed by at least three
paired supine blood pressure measurements obtained at 5–10-minute intervals during the hour previous to initiation of the active treatment. Additionally, electrocardiogram (12-lead) with a 2-minute rhythm strip, routine hematology, blood chemistry, urinalysis, and chest x-ray tests were performed in all the patients. Patients were excluded because of the following: pregnancy or lactation, a known history of malignant ventricular arrhythmias, pheochromocytoma, hypothyroidism, need for hemodialysis or peritoneal dialysis, history of clinically significant liver disease, history of immunosuppressive therapy, or treatment with phenothiazines or dopamine antagonist within 1 year of presentation.

Methods

Paired blood pressures and heart rates were measured by an automated vital signs monitor (Critikon Dinamap model 845, Johnson and Johnson, Tampa, Florida) at 5 and 15 minutes after any dosing change and at least every 15 minutes during a 2-hour, constant-rate infusion. Antihypertensive medications were discontinued at initiation of the infusion and until the end of the maintenance phase. If necessary, however, oral antihypertensive medication was reinitiated during the down-titration phase. After the infusion, the patient remained in the hospital for 2 days' follow-up that included interim history, physical examination, electrocardiogram, and blood chemistry (complete blood cell count, blood urea nitrogen [BUN], and creatinine). Blood pressure measurements were obtained at the following intervals: every 15 minutes for the first 2 hours after the end of the infusion, hourly for the next 2 hours, and then, at a minimum of every 4 hours until the end of the second day after infusion. Serum electrolytes, BUN, and creatinine were measured by an automated vital signs monitor (Critikon Dinamap model 845, Johnson and Johnson, Tampa, Florida). Blood urea nitrogen and creatinine were measured at the time of infusion; urinalysis was obtained at 2, 24, and 48 hours after the end of the infusion; paired supine blood pressure measurements were obtained at the time of infusion. In patients who received sodium nitroprusside, a plasma thiocyanate level was obtained at the time the infusion was terminated.

Infusion-Titration Phase

Fenoldopam mesylate or sodium nitroprusside were infused after an open-label randomization. Both antihypertensive agents were diluted in 5% dextrose in water and administered by continuous intravenous infusion. Maximal dose increment was 0.2 μg/kg/min (fenoldopam) and 1 μg/kg/min (nitroprusside) with a maximal infusion rate of 1.5 μg/kg/min fenoldopam mesylate or 8 μg/kg/min sodium nitroprusside. The infusion rate was increased to the concentration needed to reduce DBP to less than 110 mm Hg if initial DBP was 120–149 mm Hg, or by at least 40 mm Hg if initial DBP was 150–170 mm Hg.

Infusion control rate. Once the protocol-specified reduction in DBP was achieved, the maximal infusion rate used was maintained for at least 2 hours.

Table 1. Initial Characteristics of All Patients

<table>
<thead>
<tr>
<th></th>
<th>Fenoldopam</th>
<th>Nitroprusside</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (n)</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>43±4</td>
<td>46±3</td>
</tr>
<tr>
<td>Race (black/white)</td>
<td>7/2</td>
<td>9/0</td>
</tr>
<tr>
<td>Sex (female/male)</td>
<td>2/7</td>
<td>1/8</td>
</tr>
<tr>
<td>Electrocardiographic changes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left ventricular hypertrophy</td>
<td>9/9</td>
<td>9/9</td>
</tr>
<tr>
<td>Left atrial hypertrophy</td>
<td>2/9</td>
<td>3/9</td>
</tr>
<tr>
<td>Nonspecific ST-T wave changes</td>
<td>5/9</td>
<td>6/9</td>
</tr>
<tr>
<td>BUN (mg/dl)</td>
<td>20±10</td>
<td>30±13</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td>2.0±0.4</td>
<td>2.0±0.2</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>200±5</td>
<td>194±4</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>137±4</td>
<td>132±3</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>86±4</td>
<td>89±7</td>
</tr>
</tbody>
</table>

Infusion down-titration. The infusion was slowed gradually over a period of 2 hours.

Analysis of Data

The data, evaluated by means of the Statistical Analysis Systems (SAS), were tested for statistical difference by analysis of variance (the general linear model in SAS). Results are reported as mean±1 SEM. A p value less than 0.05 was considered to be statistically significant.

Results

Table 1 shows the mean clinical characteristics, electrocardiographic changes, BUN, and creatinine levels of all the patients at the initiation of the infusion treatment. Treatment groups did not differ significantly for age, sex, race, electrocardiographic data, systolic blood pressure (SBP) or DBP, heart rate, BUN, or serum creatinine levels.

Figure 1 shows the changes in SBP, DBP, and heart rate in patients from both studied groups. Both antihypertensive agents successfully controlled the blood pressure in all the patients by the end of the maintenance periods; both produced an increased heart rate. In the three variables previously mentioned, all the changes induced by fenoldopam mesylate or sodium nitroprusside between the baseline and the end of the maintenance period were statistically nonsignificantly different by analysis of variance. The range of doses used were 0.5–3.5 μg/kg/min (nitroprusside) and 0.10–1.50 μg/kg/min (fenoldopam). During the down-titration phase, oral antihypertensive medication was initiated, and the measurements of blood pressure done at 24 and 48 hours after infusion reflect the effect of different oral antihypertensive agents.

The renal function determined by BUN and serum creatinine levels remained stable in both groups of patients. Nitroprusside-treated patients had an initial BUN of 28±13 mg/dl and an initial creatinine of 2.1±0.7 mg/dl, and 12 hours after the
TABLE 2. Side Effects Reported by the End of the Maintenance Phase

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Fenoldopam</th>
<th>Nitroprusside</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (n)</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>Dizziness</td>
<td>1/9</td>
<td>0/9</td>
</tr>
<tr>
<td>Nausea</td>
<td>2/9</td>
<td>2/9</td>
</tr>
<tr>
<td>Headache</td>
<td>1/9</td>
<td>3/9</td>
</tr>
<tr>
<td>Flushes</td>
<td>0/9</td>
<td>1/9</td>
</tr>
<tr>
<td>ST wave changes</td>
<td>3/9</td>
<td>2/9</td>
</tr>
</tbody>
</table>

FIGURE 1. Graphs showing changes in systolic (SBP) and diastolic (DBP) blood pressure and heart rate in both groups of patients. All values are mean±SEM. Between baseline and end of maintenance period, analysis of variance showed that changes in variables induced by fenoldopam mesylate did not differ significantly from those induced by sodium nitroprusside.

end of the intravenous infusion, BUN and creatinine levels were 28±13 mg/dl and 2.0±0.7 mg/dl, respectively. Fenoldopam-treated patients had an initial BUN of 20±10 mg/dl and an initial creatinine of 1.1±1.2 mg/dl, and 12 hours after the intravenous infusion, BUN and creatinine levels were 34±17 mg/dl and 2.4±1.1 mg/dl, respectively.

Table 2 summarizes all the side effects reported during the intravenous antihypertensive treatment with fenoldopam or sodium nitroprusside. The incidence of side effects was similar in both groups of patients. Of the nine patients treated with nitroprusside, two had toxic levels of thiocyanate (>10 mg/l); however, these patients did not report toxic symptoms generally attributed to thiocyanate (i.e., weakness, vomiting, diarrhea, skin eruptions, arthralgia, palpitations, precordial pain, muscle cramps, blurred vision, funduscopic changes, tinnitus, hallucinations, delirium, and changes in hematocrit or hemoglobin).6-8 One of these patients showed an increase in serum creatinine levels (from 2.2 to 3.1 mg/dl) and BUN (from 54 to 60 mg/dl); these are changes, however, that can also be attributed to the severe initial hypertension (SBP/DBP, 201/131 mm Hg).

Discussion

The present data show that fenoldopam induces control of severe hypertension by effectively decreasing SBP and DBP when compared with sodium nitroprusside in a group of predominantly black males. The number of dose changes necessary to attain desirable control of DBP was not significantly different between the two antihypertensive medications. (Fenoldopam was seven dose changes, and sodium nitroprusside was four dose changes.)

No major side effects were reported with fenoldopam mesylate or nitroprusside treatments. In two patients treated with nitroprusside, however, thiocyanate was detected at toxic levels. The increase in heart rate was similar in both groups of patients.

Sodium nitroprusside is a potent antihypertensive widely used in the treatment of hypertensive crisis. One of the characteristics of nitroprusside is an instantaneous onset that allows a controlled titration of blood pressure because its action is by reaction with cysteine to form nitrosocysteine, a potent activator of guanylate cyclase that stimulates a cyclic guanosine monophosphate accumulation, which in turn relaxes vascular smooth muscle and causes hypotension.9 Nitroprusside decreases preload and afterload, causing decreased myocardial O2 demand.10 The reflex tachycardia induced by sodium nitroprusside is caused by a baroreceptor mechanism.11 With the use of sodium nitroprusside, especially in patients with decreased renal function, one of the concerns is that nitroprusside is metabolized to intermediate cyanide and then converted...
to thiocyanate that is excreted by the kidneys. Patients with hepatic disease or extremely poor tissue perfusion because of congestive heart failure can build cyanide to a toxic concentration, and the toxicity of thiocyanate induces the symptoms previously described.6–8

Intravenous administration of fenoldopam produces dose-related increases in renal blood flow and decreases in renal and systemic vascular resistance with a consequent decrease in arterial pressure and increase in urinary sodium excretion.12 The relatively rapid onset and short duration of action make possible an easy adjustment of the doses required to reduce blood pressure desirable levels.12 When compared with nitroprusside, fenoldopam is easily handled because it does not require protection from light and does not produce potentially toxic metabolites. Fenoldopam is apparently well tolerated. Some of the side effects reported are headache,12 flushing,12 and flattening or inversion of the T wave on the electrocardiogram.12 The incidence of these side effects, however, was not high in the group of patients treated with fenoldopam when compared with those who had received nitroprusside. Thus, in two groups of severe hypertensive patients in which the initial clinical and laboratory characteristics were similar, both intravenous antihypertensive medications, fenoldopam mesylate and sodium nitroprusside, reduced SBPs and DBPs to desirable levels. The detection of toxic levels of thiocyanate in two patients treated with nitroprusside, however, proves that fenoldopam might be preferable for the control of hypertensive crisis or severe hypertension in patients with decreased renal function.

References

KEY WORDS • severe hypertension • dopamine-receptor agonists • nitroprusside • thiocyanate toxicity • fenoldopam
Intravenous fenoldopam versus sodium nitroprusside in patients with severe hypertension.
E Reisin, M M Huth, B P Nguyen, S G Weed and F M Gonzalez

Hypertension. 1990;15:159
doi: 10.1161/01.HYP.15.2_Suppl.159

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1990 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/15/2_Suppl/159

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at:
http://hyper.ahajournals.org//subscriptions/