Effects of long-term therapy with oral ibopamine on resting hemodynamics and exercise capacity in patients with heart failure: relationship to the generation of N-methyldopamine and to plasma norepinephrine levels

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ABSTRACT N-Methyldopamine (epinine), one of the few modifications of the dopamine (DA) molecule that retains agonist activity at the DA₁ receptor, was administered orally as the diisobutyric ester, ibopamine (100, 200, and 300 mg), to 15 patients with congestive heart failure. An increase in cardiac index and decline in systemic vascular resistance was observed with each dose, and these hemodynamic effects persisted for 3 to 6 hr. Small transient increments in right atrial and pulmonary capillary wedge pressures occurred 0.5 hr after ingestion of 200 and 300 mg of ibopamine, but these pressures returned to baseline or lower levels within 30 min. Heart rate and mean arterial pressure were unchanged. Plasma concentrations of epinephine peaked 0.5 hr after administration of drug and then declined to minimal levels at 3 hr. Ten patients enrolled in a trial to evaluate the efficacy of long-term therapy with ibopamine; after 8 weeks of treatment, the initial hemodynamic responses to the drug were attenuated and no significant improvement in oxygen uptake at peak exercise was observed. A decline in plasma norepinephrine concentrations, which could be attributed to activation of α₂-adrenoceptors and/or DA₂ receptors on sympathetic nerves, was observed after initial administration of ibopamine and persisted after long-term drug ingestion; no long-term hemodynamic benefit could be ascribed to the reduction in sympathetic activity. Circulation 73, No. 4, 740–748, 1986.

THE ADMINISTRATION of dopamine to patients with congestive heart failure may effect an improvement in the performance of the impaired myocardium, and thus an oral formulation of this drug would be desirable. The beneficial actions of dopamine in patients with heart failure have been attributed not only to a positive inotropic effect that is mediated by activation of the β₁-adrenoceptor, but also to its agonist activity at the dopamine vascular (DA₁) receptor. Activation of the DA₁ receptor in the renal vascular bed appears primarily responsible for the marked natriuresis produced by this drug. N-Methyldopamine (epinephine) is one of the few modifications of the dopamine molecule that retains full agonist activity at the DA₁ receptor. Ibopamine is the diisobutyric ester of epinephine, and after ingestion, it is hydrolyzed by plasma esterases to yield epinephine. Initial studies have demonstrated beneficial short-term hemodynamic responses to ibopamine in patients with heart failure. This investigation was undertaken to evaluate the hemodynamic actions and bioavailability of ibopamine after short- and long-term administration to patients with chronic congestive heart failure, and to assess the role of the sympathetic nervous system in modulating the hemodynamic responses to the drug. An intravenous
infusion of dopamine was administered to each patient to allow comparison of the hemodynamic responses to this agent and to ibopamine.

Methods

Short-term hemodynamic evaluation

Patient population. The study group consisted of 11 men and four women with congestive heart failure of at least 3 months duration. They ranged in age from 34 to 72 years, with a mean (± SEM) age of 55 ± 3 years. Two patients were classified as meeting the criteria for New York Heart Association functional class IV, 12 were in class III, and one was in class II. Heart failure was due to ischemic heart disease in four patients, hypertensive heart disease in one patient, and idiopathic cardiomyopathy in 10 patients. No patient had experienced unstable angina pectoris or acute myocardial infarction within the preceding 12 weeks. Normal sinus rhythm was present in 14 patients and atrial fibrillation was present in one. All patients had echocardiographic or angiographic evidence of severe left ventricular dysfunction and cardiomegaly on the chest roentgenogram.

Hemodynamic measurements. The investigational protocol was approved by the University of Chicago Clinical Investigation Committee. After written informed consent was obtained, each patient underwent placement of a flow-directed, balloon-tipped, thermodilution catheter in the pulmonary artery so that balloon inflation allowed measurement of the pulmonary capillary wedge pressure. Systemic arterial pressure was measured through a cannula in the radial artery. Systemic arterial, pulmonary arterial, and right atrial pressures were monitored continuously with Hewlett-Packard 1250A quartz pressure transducers interfaced with Hewlett-Packard 7854A recording units. Mean pressures were obtained by electronic integration. The electrocardiogram was monitored continuously, and the heart rate was measured from the simultaneous electrocardiographic signal.

Cardiac output was determined by the thermodilution technique with an Edwards Laboratories' 9520A cardiac output computer and by averaging three replicate determinations that varied less than 10%.

Derived hemodynamic variables were calculated as follows: cardiac index (liters/min/m2) = cardiac output (liters/min)/body surface area (m2); stroke volume index (ml/beat/m2) = cardiac index/heart rate (beats/min); systemic vascular resistance (dyne · sec · cm−5) = (80 [mean systemic arterial pressure (mm Hg) − mean right atrial pressure (mm Hg)])/cardiac output.

Administration of drug. Patients were studied in the recumbent, postabsorptive state after diuretics had been withheld for at least 24 hr and vasodilators had been discontinued for at least 72 hr. Digitalis was administered daily at 6:00 p.m. throughout the investigation. The thermodilution catheter was placed 12 to 18 hr before the initial study period. Control hemodynamic measurements were performed each morning at 20 to 30 min intervals until stable values were obtained. Ibopamine was then administered orally and hemodynamic measurements were repeated 0.5, 1, 2, 3, 4, 6, and 8 hr after ingestion of drug. The hemodynamic responses to 100, 200, and 300 mg of ibopamine were determined on consecutive days. The 300 mg dose of ibopamine was omitted in five patients because after ingestion of 200 mg, substantial hemodynamic improvement was observed in three patients, an increase in uniform premature ventricular contractions was noted in one patient, and an increase in mean pulmonary capillary wedge pressure of 6 mm Hg was seen in the fifth patient.

A graded infusion of dopamine was administered 24 hr before the first dose of ibopamine in the initial five patients and 24 hr after the final dose of ibopamine in the latter 10 patients. Dopamine was infused initially at a rate of 1 μg/kg/min. The rate was subsequently increased at 20 to 30 min intervals to 2, 4, and 6 μg/kg/min, unless one of the following was observed: increase in heart rate of 15 beats/min, increase in mean arterial pressure of 15 mm Hg, or an adverse response. Hemodynamic measurements were obtained just before each increment in dosage and 20 min after the peak infusion rate was achieved. The infusion of dopamine was then discontinued.

Measurement of plasma concentrations of epinephrine and norepinephrine. Plasma concentrations of epinephrine and norepinephrine were determined during the study period immediately before and 0.5, 1, 2, 3, 4, and 8 hr after the oral administration of ibopamine. Blood samples for analysis were obtained from the right atrium and placed in chilled heparinized glass tubes containing sodium metabisulfite. The plasma was immediately separated and stored at −20°C until assay. Epinephrine and norepinephrine were extracted from 1 ml of plasma by a micromodificaiton of the aluminum oxide procedure of Anton and Stayre.10 They were separated by high-performance liquid chromatography on a C-18 reverse-phase column (Ultraspere-ODS, 5 μm, Altex) with a mobile phase consisting of 0.075M monochloroacetic acid, 2.0 mM disodium EDTA, 1.0 mM sodium octyl sulfate, and 12% methanol, pH 2.95, and a flow rate of 0.7 ml/min. Epinephrine and norepinephrine were detected electrochemically with a Bioanalytical Systems LC-4B detector at 0.7 V and with use of a glassy-carbon electrode.

Evaluation of long-term treatment

Hemodynamic evaluation. On completion of the short-term evaluation described above, the latter 10 patients (nine men and one woman) enrolled in a study to evaluate the efficacy of long-term therapy with ibopamine. Their ages averaged 55 ± 4 years (range 34 to 72). One patient was classified as meeting the criteria for New York Heart Association functional class IV, eight were in class III, and one was in class II. The causes of heart failure were ischemic heart disease in three patients, hypertensive heart disease in one patient, and idiopathic cardiomyopathy in six. Normal sinus rhythm was present in nine patients and one had atrial fibrillation.

Each patient resumed their prestudy dosages of diuretics after concluding the short-term hemodynamic study. Seventy-two hours later, placebo tablets were added to the drug regimen of each subject and ingested every 8 hr for 72 hr. (The initial two patients entered this phase of the study 15 and 24 weeks later, respectively, because of unanticipated delays; no change in clinical status occurred during this interval.) Ibopamine was then administered at a dose of 100 mg every 8 hr. The total daily dosage was increased 300 mg every 2 days up to the dose of ibopamine that elicited the greatest increase in cardiac index without the development of adverse effects (optimal dose). Five patients (including the initial two patients) were titrated to a dose of 300 mg every 8 hr and four patients to a dose of 200 mg; one patient received 100 mg every 8 hr. Patients were then discharged from the hospital, and their clinical status was evaluated weekly on an outpatient basis. Administration of ibopamine was discontinued 2 weeks later in one patient (receiving 600 mg/day) who exhibited ventricular arrhythmias and who was receiving procainamide for ventricular arrhythmias before enrollment in the protocol. The arrhythmias persisted despite withdrawal of ibopamine. Nine subjects were readmitted 8 weeks after completion of the initial study and the hemodynamic response to the optimal dose of ibopamine was evaluated. Diuretics were discontinued 24 hr before this study. The thermodilution catheter was placed 12 to 18 hr before the hemodynamic evaluation. Digitalis was withheld on the morning of the study. Ibopamine therapy was continued, and baseline hemodynamic measurements were obtained 8 to 9 hr after the previous dose of the drug. The same dose of ibopamine was administered and hemodynamic measurements were repeated as in the initial
The greatest increase in cardiac index was maximal with 300 mg 
min/m². The short-term studies were performed with the t test for 
paired samples. A p value less than .05 was considered 
elevated for 6 hr. After ingestion of the 200 and 100 mg doses, cardiac index increased significantly for 
and 3 hr, respectively.

The mean stroke volume index peaked at 1 to 2 hr after administration of ibopamine. After administra-

Study. Plasma concentrations of epinephrine were determined at the times when hemodynamic measure-
ments were obtained.

Exercise protocol. Exercise capacity was assessed on each of the 3 days of placebo ingestion, and 1, 4, and 8 weeks after the administration of ibopamine. The exercise test on the third day of placebo ingestion was considered the baseline study. Exercise testing was performed 1 to 2 hr after the ingestion of placebo or ibopamine and subjects exercised in the upright position on an electronically braked cycle ergometer. According to a protocol described by Wasserman and Whipp, the workrate was increased 6 W each minute after 3 min of “unloaded” pedaling, and the patients exercised to exhaustion. Continuous measurements of breath-to-breath expired flow and expired oxygen and carbon dioxide partial pressures were obtained with a Medical Graphics System 2000 (Medical Graphics Corp., St. Paul, MN). The subjects breathed through a low-resistance valve, and expired gas flow was measured by a heated pneumotachograph attached to the expiratory port of the valve. Respired oxygen and carbon dioxide partial pressures were determined by fast-responding oxygen (zirconium cell) and carbon dioxide (infrared absorption) analyzers, respectively. The electrocardiogram was monitored continuously. The signals from these 
device underwent analog-to-digital conversion and were then processed by a Tektronix 4052 computer for on-line, breath-to-breath determination of minute ventilation, oxygen uptake, carbon dioxide output, and heart rate.

Data analysis. All values are expressed as mean ± SEM. Statistical analyses involving comparisons of control with post-
treatment data were performed with analysis of variance of repeated measures and Duncan’s multiple-comparisons procedure. Comparisons of baseline measurements obtained during the short- and long-term studies were performed with the t test for paired samples. A p value less than .05 was considered indicative of statistical significance.

Comparisons of data obtained before and after the administration of ibopamine were accomplished by use of the t test for 
paired samples and the Bonferroni correction for multiple comparisons. Since measurements obtained at four infusion rates of dopamine were compared with baseline values, a p value less than .0125 (.05/4) was considered indicative of statistical signif-

cance.

Results

Short-term effects of ibopamine

Hemodynamic responses. The short-term hemodynamic responses to ibopamine are depicted in figures 1 and 2. Cardiac index was significantly elevated at 30 min and peaked at 1 to 2 hr after administration of the drug. With the ingestion of 100 mg of ibopamine, cardiac index increased from a mean of 1.83 ± 0.12 liters/min/m² to a peak of 2.18 ± 0.16 liters/min/m² (p < .01), an increment of 19%. The administration of 200 mg of ibopamine was associated with a rise in cardiac index from a baseline of 1.91 ± 0.12 liters/min/m² to a maximal value of 2.22 ± 0.13 liters/min/m² (p < .01). The greatest increase in cardiac index was observed with the 300 mg dose; the peak value achieved, 2.37 ± 0.18 liters/min/m², represented a 25% increment (p < .01) above the control measurement of 1.90 ± 0.10 liters/min/m². The duration of effect of ibopamine was related to the dose; after administration of 300 mg of ibopamine, cardiac index remained significantly elevated for 6 hr. After ingestion of the 200 and 100 mg doses, cardiac index increased significantly for 4 and 3 hr, respectively.

The mean stroke volume index peaked at 1 to 2 hr after administration of ibopamine. After administra-

FIGURE 1. Time course of changes in cardiac index, stroke volume index, mean pulmonary capillary wedge pressure (PCWP), and mean right atrial pressure (RAP) after oral administration of 100, 200, and 300 mg of ibopamine to patients with congestive heart failure. Vertical bars denote SEM. *p < .05; †p < .01 vs control (time = 0).

FIGURE 2. Time course of changes in systemic vascular resistance, mean arterial pressure, and heart rate in patients with congestive heart failure after ingestion of 100, 200, and 300 mg of ibopamine. Vertical bars denote SEM. *p < .05; †p .01 vs control (time = 0).
tion of 100 mg of ibopamine the reduced stroke volume index of 21.2 ± 1.3 ml/beat/m² increased to a maximum of 24.6 ± 1.7 (p < .01) ml/beat/m², an improvement of 16%. Peak increments in stroke volume index after ingestion of 200 and 300 mg were 11% and 19%, respectively. Significant improvement in stroke volume index was observed for 4 hr after administration of 300 mg of ibopamine and for 3 hr after the 200 and 100 mg doses of the drug.

The improvements in cardiac index and stroke volume index were accompanied by a reduction in systemic vascular resistance, which was apparent at 0.5 to 1.0 hr and reached a nadir at 1 to 2 hr after administration of drug. The maximal fall in systemic vascular resistance after ingestion of 100, 200, and 300 mg of the drug averaged 14%, 12%, and 14%, respectively. The mean arterial pressure and heart rate were not altered appreciably after ingestion of ibopamine at any dose.

The mean pulmonary capillary wedge pressure tended to rise transiently 30 min after ingestion of 200 and 300 mg of ibopamine, reaching a statistically significant value (26 ± 2 mm Hg, p < .05) only after the 200 mg dose (control of 24 ± 2 mm Hg). A sustained fall in the pulmonary capillary wedge pressure was then observed, which achieved statistical significance (p < .05) 3 hr after administration of 200 mg of ibopamine (21 ± 2 mm Hg) and 2 hr after ingestion of 300 mg (20 ± 2 mm Hg; control of 22 ± 2 mm Hg).

Mean right atrial pressure fell to a value of 7 ± 2 mm Hg (p < .05) 1 hr after the administration of 100 mg of ibopamine and remained significantly reduced at 4 hr (7 ± 2 mm Hg, p < .05). The ingestion of the 200 mg dose was associated with a transient rise in right atrial pressure from a baseline of 9 ± 2 to 12 ± 2 mm Hg (p < .05) 0.5 hr later. At 2 hr it declined to 8 ± 2 mm Hg and remained at this level for the ensuing 6 hr. The response to 300 mg of ibopamine paralleled that observed after 200 mg.

**Hemodynamic responses to dopamine.** All patients received dopamine at infusion rates of 1 and 2 μg/kg/min. Three patients did not receive dopamine at a rate of 4 μg/kg/min because an increase in uniform, premature ventricular contractions occurred with the infusion rate of 2 μg/kg/min. When dopamine was administered at a rate of 4 μg/kg/min, four subjects developed an increase in heart rate greater than 15 beats/min or an elevation in mean arterial pressure larger than 15 mm Hg; therefore, dopamine was not infused at a higher rate in these patients. In one of these four subjects mean pulmonary capillary wedge pressure increased 9 mm Hg (from 23 to 32 mm Hg) and in another it increased 10 mm Hg (from 20 to 30 mm Hg). No subject reported adverse symptoms during the infusion of dopamine.

The hemodynamic responses to dopamine are presented in table 1. The maximal changes in cardiac index, stroke volume index, and systemic vascular resistance seen with ibopamine were similar in magnitude to those produced by dopamine at infusion rates of 1 to 2 μg/kg/min. Increases in mean pulmonary capillary wedge pressure and right atrial pressure, as observed 30 min after the ingestion of ibopamine, did not occur with dopamine at these infusion rates. No significant changes in mean arterial pressure and heart rate were seen with dopamine at infusion rates of 1 to 2 μg/kg/min.

**Plasma concentrations of epinephrine.** Serial determinations

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**TABLE 1**

<table>
<thead>
<tr>
<th>Hemodynamic responses to dopamine in patients with heart failure</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dopamine infusion</strong></td>
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<tr>
<td>Control (n = 15)</td>
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<td>------------------</td>
</tr>
<tr>
<td>Cardiac index (liters/min/m²)</td>
</tr>
<tr>
<td>Stroke volume index (ml/beat/m²)</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
</tr>
<tr>
<td>Systemic vascular resistance (dyne·sec·cm⁻²)</td>
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<tr>
<td>Left ventricular filling pressure (mm Hg)</td>
</tr>
<tr>
<td>Mean right atrial pressure (mm Hg)</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
</tr>
</tbody>
</table>

Values are mean ± SEM.
*Ap < .01 for the difference from control values; *p < .001 for the difference from control values.
of plasma epinephrine levels revealed that maximal concentrations occurred 0.5 hr after administration of ibopamine at each of the doses studied (figure 3). After the ingestion of 300 mg of ibopamine, the plasma concentration of epinephrine rose to 26.1 ± 5.1 ng/ml at 0.5 hr and then declined progressively, reaching 2.4 ± 0.9 ng/ml by 3 hr. Minimal levels of epinephrine were detected 4 through 8 hr after administration of ibopamine. A similar pattern was seen after ingestion of 200 and 100 mg of ibopamine. The peak plasma concentrations of epinephrine measured after the 200 and 100 mg doses were 20.5 ± 5.9 and 15.0 ± 3.9 ng/ml, respectively.

**Plasma concentrations of norepinephrine.** The mean baseline plasma norepinephrine concentration was elevated at 929 ± 114 pg/ml. No significant correlation between baseline plasma levels of norepinephrine and hemodynamic measurements was observed. Administration of the 300 mg dose of ibopamine was associated with a progressive fall in plasma norepinephrine concentration (figure 4); a significant reduction was measured 2 through 8 hr after dosing, with a nadir of 392 ± 113 pg/ml (p < .01 vs control) recorded at 8 hr. Similar trends were observed after ingestion of 100 and 200 mg of ibopamine, but the decline in norepinephrine levels did not achieve statistical significance.

**Clinical observations.** The short-term oral administration of ibopamine resulted in no untoward symptoms in any of the patients. In one patient, however, an increase in mean pulmonary capillary wedge pressure of 6 mm Hg (from 25 to 31 mm Hg) was observed 0.5 hr after administration of 200 mg of ibopamine and persisted for an additional 45 min. An asymptomatic increase in the frequency of uniform, single premature ventricular contractions occurred in another patient 0.5 hr after he ingested 200 mg of ibopamine and persisted for 30 min. (An increase in premature ventricular contractions was also seen after the administration of dopamine to this patient.) No electrocardiographic or clinical evidence of myocardial ischemia was observed during the investigation.

**Effects of long-term treatment with ibopamine**

**Hemodynamic studies.** The short-term hemodynamic responses to the optimal dose of ibopamine in the 10 patients enrolled in the long-term study are depicted in table 2. The cardiac index increased from 1.88 ± 0.10 liters/min/m² to a peak of 2.24 ± 0.16 liters/min/m² (p < .01) at 1 hr after ingestion of ibopamine and remained significantly elevated for 4 hr. Similarly, the stroke volume index rose from a baseline value of 23.6 ml/beat/m² to a maximum of 27.5 ± 2.3 at 1 hr (p < .01); significant improvement in the stroke volume index persisted for 4 hr. The systemic vascular resistance declined from 1728 ± 133 dyne·sec·cm⁻² to a nadir of 1429 ± 99 dyne·sec·cm⁻² at 2 hr after administration of ibopamine and remained significantly reduced for 4 hr. The mean arterial pressure and heart rate were not altered appreciably.

Significant changes from the baseline mean pulmonary capillary wedge pressure of 22 ± 2 mm Hg were observed 2 and 3 hr after ingestion of ibopamine when measurements of 19 ± 2 mm Hg (p < .05) and 18 ± 2 mm Hg (p < .01), respectively, were obtained. The only significant change in mean right atrial pressure occurred 4 hr after administration of drug, when the pressure decreased from 9 ± 2 to 6 ± 2 mm Hg (p < .05).

After the optimal dose of ibopamine, the plasma concentration of epinephrine rose to a maximum of 24.7 ± 6.5 ng/ml at 0.5 hr and then declined progressively to 1.0 ± 0.2 ng/ml at 3 hr (table 2). Plasma norepinephrine concentrations were significantly reduced from a baseline value of 915 ± 116 pg/ml at 0.5 hr (686 ± 136 pg/ml, p < .05) after the administration of the optimal dose of ibopamine and continued to decline to a nadir of 450 ± 65 pg/ml (p < .01) at 3 hr. Plasma levels of norepinephrine were still substantially depressed 8 hr after ingestion of drug (471 ± 93 pg/ml, p < .01).
TABLE 2

Hemodynamic measurements, plasma epine and plasma norepinephrine levels obtained before and after ingestion of ibopamine (optimal dose)

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>0.5</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>6</th>
<th>8</th>
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<tbody>
<tr>
<td>Cardiac index (l/min/m²)</td>
<td>1.88±0.10</td>
<td>2.10±0.13</td>
<td>2.24±0.16</td>
<td>2.24±0.12</td>
<td>2.19±0.10</td>
<td>2.11±0.10</td>
<td>2.00±0.10</td>
<td>2.01±0.10</td>
</tr>
<tr>
<td>Stroke volume index (ml/beat/m²)</td>
<td>23.6±1.4</td>
<td>26.0±1.8</td>
<td>27.5±2.3</td>
<td>27.2±1.7</td>
<td>26.6±1.5</td>
<td>26.1±1.9</td>
<td>25.2±1.7</td>
<td>24.7±1.5</td>
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<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>83±4</td>
<td>86±3</td>
<td>85±4</td>
<td>82±3</td>
<td>81±4</td>
<td>81±4</td>
<td>82±3</td>
<td>82±4</td>
</tr>
<tr>
<td>SVR (dyne · sec · cm⁻³)</td>
<td>1728±133</td>
<td>1559±103</td>
<td>1514±121</td>
<td>1429±99</td>
<td>1476±108</td>
<td>1560±114</td>
<td>1654±125</td>
<td>1618±109</td>
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<tr>
<td>PCWP (mm Hg)</td>
<td>22±2</td>
<td>23±2</td>
<td>20±2</td>
<td>19±2</td>
<td>18±2</td>
<td>19±2</td>
<td>19±2</td>
<td>20±2</td>
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<tr>
<td>RAP (mm Hg)</td>
<td>9±2</td>
<td>10±3</td>
<td>8±3</td>
<td>8±2</td>
<td>7±2</td>
<td>6±2</td>
<td>7±2</td>
<td>7±1</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>80±2</td>
<td>82±3</td>
<td>83±3</td>
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<td>80±2</td>
<td>82±2</td>
</tr>
<tr>
<td>Plasma epine (ng/ml)</td>
<td>0</td>
<td>24.7±6.5</td>
<td>18.3±5.5</td>
<td>8.0±3.9</td>
<td>1.0±0.2</td>
<td>0.7±0.3</td>
<td>0.3±0.2</td>
<td>0.10±0.04</td>
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<tr>
<td>Plasma norepinephrine (pg/ml)</td>
<td>915±116</td>
<td>686±136</td>
<td>646±138</td>
<td>523±97</td>
<td>450±65</td>
<td>534±77</td>
<td>521±81</td>
<td>471±93</td>
</tr>
</tbody>
</table>

Values are mean ± SEM.

PCWP = mean pulmonary capillary wedge pressure; RAP = mean right atrial pressure; SVR = systemic vascular resistance.

*p < .05 for the difference from the baseline value; **p < .01 for the difference from the baseline value.

Nine patients were reevaluated after receiving ibopamine for 8 weeks. Hemodynamic responses measured 1 hr (time of peak effect on cardiac index) after the ingestion of ibopamine are presented in table 3. (Values for mean pulmonary capillary wedge pressure and right atrial pressure are those measured 0.5 hr after administration of drug.) The baseline hemodynamic measurements obtained after 8 weeks of therapy with ibopamine were similar to those observed over the short term, except for the significant increase in mean pulmonary capillary wedge pressure from 21 ± 2 to 24 ± 2 mm Hg (p < .05) after long-term treatment. A further increase in the pulmonary capillary wedge pressure from 24 ± 2 to 27 ± 2 mm Hg (p < .05) occurred 0.5 hr after drug ingestion and then returned to baseline. A similar pattern was noted for the mean right atrial pressure, but no statistically significant changes were recorded. The increment in cardiac index and stroke volume index and the decline in systemic vascular resistance documented during the initial study were attenuated after long-term therapy. No substantial changes in heart rate and mean arterial pressure were documented after long-term ibopamine. Similar baseline and peak hemodynamic values were observed with the exclusion of the initial two patients whose entry into the long-term phase of the protocol was delayed.

The peak plasma concentration of epine achieved after long-term therapy was 24.8 ± 5.4 ng/ml; this value was similar to the average peak concentration of

TABLE 3

Hemodynamic responses to short- and long-term administration of ibopamine in nine patients with congestive heart failure

<table>
<thead>
<tr>
<th></th>
<th>Initial study</th>
<th>Long-term study</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>After treatment</td>
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<tr>
<td>Cardiac index (l/min/m²)</td>
<td>1.90±0.10</td>
<td>2.30±0.17</td>
</tr>
<tr>
<td>Stroke volume index (ml/beat/m²)</td>
<td>23.8±1.5</td>
<td>28.0±2.5</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>82±4</td>
<td>84±4</td>
</tr>
<tr>
<td>Systemic vascular resistance (dyne · sec · cm⁻³)</td>
<td>1727±149</td>
<td>1494±133</td>
</tr>
<tr>
<td>Mean pulmonary capillary wedge pressure (mm Hg)</td>
<td>21±2</td>
<td>22±2</td>
</tr>
<tr>
<td>Mean right atrial pressure (mm Hg)</td>
<td>8±2</td>
<td>9±3</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>80±2</td>
<td>84±3</td>
</tr>
</tbody>
</table>

Values are mean ± SEM.

*p < .05 for the difference from the baseline value for the long-term study; **p < .05 for the difference between baseline values for the initial and long-term studies; **p < .01 for the difference from the baseline value for the initial study.
27.0 ± 6.7 ng/ml observed after short-term therapy. The plasma concentration of norepinephrine measured during the baseline period of the long-term study averaged 446 ± 69 pg/ml and was substantially less than that documented during the control period of the initial study (823 ± 79 pg/ml, p < .01). (With the exclusion of the initial two patients, these values were essentially unchanged; the control value during the short-term study was 870 ± 91 pg/ml, which was substantially greater than the baseline measurement of 410 ± 56 pg/ml [p < .01] obtained during the long-term study.) No further change in plasma norepinephrine levels was observed after drug ingestion.

Exercise studies. The oxygen uptake at peak exercise averaged 1020 ± 73 ml/min (14.5 ± 1.1 ml/kg/min) at baseline. After 1 week of therapy with ibopamine, this value rose insignificantly to a mean value of 1184 ± 78 ml/min and varied little for the duration of the investigation (1179 ± 85 ml/min at 4 weeks; 1220 ± 104 ml/min at 8 weeks).

Clinical observations. All nine patients reported symptomatic improvement on completion of the protocol. One patient developed tremulousness that abated on reducing the dose of ibopamine from 300 to 200 mg. The patients’ weights remained stable. No significant change in use of diuretics occurred. The cardiothoracic ratio measured from the chest roentgenogram was unchanged after 8 weeks of therapy with ibopamine.

Discussion

Short-term hemodynamic study. The short-term oral administration of ibopamine, the diisobutyric ester of epinine (N-methyl dopamine), to patients with chronic congestive heart failure resulted in significant hemodynamic changes that persisted for 3 to 6 hr. An improvement in cardiac index and stroke volume index was accompanied by a decline in systemic vascular resistance. Small transient increases in mean pulmonary capillary wedge pressure and right atrial pressure were observed 0.5 hr after ingestion of 200 and 300 mg of ibopamine, but these values then declined to baseline or lower levels for the duration of the study period. The short-term hemodynamic effects of single doses of ibopamine (100 and 150 mg) have been reported by other investigators. The magnitude of the responses was similar to that observed in our investigation, and the duration of action of the drug ranged from 2 to 5 hr. Ren et al., in a multiple-dose trial similar to ours, did note comparable hemodynamic changes at doses of 200 and 300 mg.

Appreciable plasma levels of epinine were achieved with the oral administration of ibopamine to our pa-

patients. Furthermore, the plasma concentrations of epinine tended to increase as the dose of ibopamine was augmented. The plasma levels of epinine and the hemodynamic responses to ibopamine exhibited a similar pattern of change, although the alteration in epinine levels preceded the hemodynamic changes. These observations suggest that epinine generated from orally administered ibopamine may elicit significant hemodynamic responses in patients with congestive heart failure.

Hemodynamic effects produced by epinine probably represent an amalgamation of the responses to its complex pharmacologic actions. The β1-adrenoceptor activity of epinine can elicit an increase in cardiac output that is accompanied by a reduction in systemic vascular resistance; the latter is attributed to a reflex withdrawal of the elevated vascular tone characteristic of patients with heart failure. In addition, activation of β2-adrenoceptors and DA receptors by epinine may induce a decline in peripheral vascular resistance. Stimulation of vascular β2-adrenoceptors leads to generalized vasodilation, while DA receptors subserve arterial dilation in the renal, mesenteric, coronary, and cerebral vascular beds. The decline in left ventricular afterload may result in an improvement in cardiac performance. Ren et al., using systolic time intervals, noted minimal positive inotropic effects when ibopamine (100, 200, and 300 mg) was administered to patients with heart failure.

The elevated systemic vascular resistance characteristic of chronic congestive heart failure has been attributed in part to augmented sympathetic neuronal activity. Increased levels of plasma norepinephrine have been documented repeatedly in patients with heart failure, and a substantial elevation was measured in our patients. The reduction in plasma norepinephrine concentrations associated with the ingestion of ibopamine did not parallel the hemodynamic changes. Although an improvement in cardiac function in patients with heart failure may be accompanied by a decline in plasma norepinephrine levels due to reflex withdrawal of sympathetic neuronal activity, activation of presynaptic DA1 receptors and/or α2-adrenoceptors by epinine may also induce a reduction in plasma norepinephrine concentrations. Activation of these receptors, which are located on postganglionic sympathetic nerves, has been shown to result in decreased release of norepinephrine from the nerve endings. Longhini et al. demonstrated a decrease in peripheral vascular resistance and increased venous capacity in the upper extremities of patients with heart failure at 2 to 6 hr after administration of ibopamine. These effects were
inhibited by sulpiride, which possesses antagonist activity at DA1 and DA2 receptors. On the other hand, the ability of epinephrine to activate presynaptic α2-adrenoceptors has not been established to date. We recently reported that epinephrine activates postsynaptic α1-adrenoceptors located on vascular smooth muscle; therefore, it is likely that this agent also stimulates presynaptic α2-adrenoceptors. A decline in plasma norepinephrine levels has also been observed after administration of the selective DA2 agonist bromocriptine to patients with heart failure.

The increases in mean pulmonary capillary wedge pressure and mean right atrial pressure observed 0.5 hr after administration of ibopamine are of concern. The increase in pressures occurred concomitantly with a reduction in systemic vascular resistance, suggesting differential influences of epinephrine on arterial and venous beds. We and others have demonstrated a greater density of postsynaptic α1-adrenoceptors in several venous beds when compared with arterial tissue. The postsynaptic α1-adrenoceptor, which subserves vasoconstriction, may be activated at the peak plasma epinephrine concentrations achieved with the higher doses of ibopamine. Venoconstriction may then occur and result in augmented venous return to the heart, which may accompany the reduction in arteriolar tone observed with ibopamine (see below). Thus, it would appear inadvisable to administer larger doses of ibopamine to patients with heart failure as suggested by Ren et al.

The hemodynamic effects observed after the administration of ibopamine were comparable to those elicited at low infusion rates of dopamine, with the exception of the transient elevation in mean right atrial and mean pulmonary capillary wedge pressures measured 30 min after the ingestion of ibopamine. These responses are consistent with the known pharmacologic actions of dopamine and epinephrine. At low infusion rates, dopamine demonstrates significant activity at DA1 and DA2 receptors and the β1-adrenoceptor; minimal activation of the α-adrenoceptor occurs at these infusion rates. Epinephrine is a more potent agonist than dopamine at the α-adrenoceptor and displays greater activity at the α2-adrenoceptor subtype. The latter action may lead to a reduction in venous capacitance; therefore, higher mean right atrial and mean pulmonary capillary wedge pressures may be observed with epinephrine than with dopamine.

**Long-term effects of ibopamine.** Attenuation of the initial hemodynamic responses to ibopamine was observed after long-term administration of the drug. Measurements of plasma epinephrine levels suggest that the bioavailability of ibopamine was not altered during the 8 week period of the study. Decreased efficacy of β-adrenoceptor agonists during long-term administration has been reported previously, perhaps due to down-regulation of β-adrenoceptors. However, development of tolerance to the hemodynamic effects of the oral dopamine prodrug levodopa did not occur during long-term administration to patients with congestive heart failure. We are unable to provide a definitive explanation for these observations. It is conceivable that the sustained decline in sympathetic neural activity that accompanied the ingestion of ibopamine might lead to an up-regulation of β1- and α-adrenoceptors (receptors activated by the neurotransmitter), the densities of which have been reported to be reduced in patients with heart failure. Increased responsiveness to the postsynaptic, α-adrenoceptor activity of epinephrine could then occur and counterbalance the vasodilating and positive inotropic actions of the drug. The greater rise in pulmonary capillary wedge pressure after long-term therapy with ibopamine provides further support for this concept. With respect to the β1-adrenoceptor, our data are consistent with either desensitization of additional β1-adrenoceptors during long-term exposure to epinephrine or lack of significant activation of this receptor at the concentrations of epinephrine observed in our patients. The report of Ren et al., who noted minimal positive inotropic effects with similar doses of ibopamine, supports the latter possibility.

Cohn et al. reported recently that in patients with heart failure the plasma concentration of norepinephrine was a more sensitive predictor of subsequent mortality than measurements of resting left ventricular performance. The authors suggested that sympathetic nervous system activity may be a more accurate measure of the severity of heart failure than hemodynamic measurements, or that excessive sympathetic activity may itself be a risk factor for death in patients with heart failure. Elevated sympathetic neuronal activity has been implicated in the precipitation of lethal arrhythmias and in the production of myocardial tissue necrosis. The substantial decline in plasma norepinephrine levels that accompanied the long-term administration of ibopamine to our patients was not associated with an improvement in their hemodynamic status or a significant increase in maximal aerobic capacity. The administration of ibopamine to a larger group of patients for a longer period of time may shed light on whether the sustained decline in sympathetic activity induced by ibopamine will alter the course of patients with severe heart failure.
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