Ibopamine in Very Severe Congestive Heart Failure: Pilot Haemodynamic Invasive Assessment

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Summary. The acute effects of ibopamine, a new, orally active dopaminergic agent, were assessed invasively in 8 patients with congestive heart failure (NYHA Class IV). The cardiac Index increased (P < 0.01) and preload and afterload decreased (P < 0.05) after a single mean dose of ibopamine 1.4 mg/kg. The peak effect occurred after 1 to 3 h and activity was still demonstrable after 4 to 6 h. There was no change in blood pressure, heart rate or rhythm. No clinical evidence of cardiac toxicity or side effects was noted. Oral ibopamine shows promise in the treatment of congestive heart failure, but more extensive studies after chronic treatment are desirable.

Key words: ibopamine, congestive heart failure, inotropic activity; dopaminergic agent, haemodynamic effects

Digitalis has been the keystone in the management of chronic congestive heart failure. However, it possesses a relatively low therapeutic ratio and, following the introduction of vasodilators and diuretics, the indication for digitalis is now virtually limited to the combination of congestive heart failure and atrial fibrillation. There is no published evidence showing the benefit of digitalis in very severe congestive heart failure (Class IV).

In contrast, the inotropic catecholamine-like agents, dopamine and dobutamine, can be useful in short-term therapy. However, as they only act intravenously, an orally effective dopamine-like agent would be useful [1].

Ibopamine (SB 7505)* is an orally active dopamine derivative, which increases cardiac contractility, renal blood flow and urine output in dogs and rats [2, 3], and reduces systolic times (PEP and EMS) in human subjects, without affecting heart rate or blood pressure [4, 5, 6]. Ibopamine also increases diuresis, Na+ excretion and renal clearance in humans [7, 8, 9].

The aim of the present trial was to study the acute effects of oral ibopamine administration in patients with severe congestive heart failure by an invasive technique.

Materials and Methods

Eight in-patients with severe congestive heart failure (Table 1) ranging in age from 50 to 75 years, NYHA functional Class IV, were treated orally with a single dose of ibopamine after their informed consent had been given. The mean dose of ibopamine was 1.4 mg/kg, range 1.2 to 1.6 mg/kg.

Patients entered the experiment after a stay of at least 3 days in the Coronary Care Unit.

Before the study, patients had been maintained on a no added-salt diet. Their regimen of digitalis and vasodilators was not changed during the trial (Table 1).

A Swan-Ganz catheter was inserted percutaneously via a subclavian or internal jugular vein, under pressure monitoring, as far as the pulmonary artery to monitor pulmonary and capillary pressure. Cardiac output was measured by the thermodilution technique, according to the method previously described [10].

Blood pressure was measured with a catheter in the radial artery. Measurements were made before treatment and 1, 2, 3, 4, 5 and 6 h thereafter. They are reported here as Heart Rate (HR), Mean Arterial Pressure (MAP), Pulmonary Capillary Wedge Pressure (PCWP), and Central Venous Pressure (CVP).
Table 1. Clinical details and dose of ibopamine in 8 patients with congestive heart failure (CHF) of NYHA Class IV

<table>
<thead>
<tr>
<th>Patients No.</th>
<th>Age [years]</th>
<th>Origin of CHF</th>
<th>Body weight [kg]</th>
<th>Dose of Ibopamine [mg/kg]</th>
<th>Associated therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>66</td>
<td>Cardiomyopathy</td>
<td>64</td>
<td>1.76</td>
<td>Nitroprusside</td>
</tr>
<tr>
<td>2</td>
<td>75</td>
<td>Hypertensive and ischaemic cardiomyopathy</td>
<td>65</td>
<td>1.78</td>
<td>100</td>
</tr>
<tr>
<td>3</td>
<td>60</td>
<td>Ischaemic cardiomyopathy</td>
<td>79</td>
<td>1.94</td>
<td>100</td>
</tr>
<tr>
<td>4</td>
<td>60</td>
<td>Ischaemic cardiomyopathy</td>
<td>79</td>
<td>1.94</td>
<td>100</td>
</tr>
<tr>
<td>5</td>
<td>75</td>
<td>Cardiomyopathy</td>
<td>108</td>
<td>2.15</td>
<td>Nitroprusside</td>
</tr>
<tr>
<td>6</td>
<td>71</td>
<td>Cardiomyopathy</td>
<td>74</td>
<td>1.82</td>
<td>Nitroprusside Digoxin</td>
</tr>
<tr>
<td>7</td>
<td>71</td>
<td>Ischaemic cardiomyopathy</td>
<td>82</td>
<td>1.96</td>
<td>100</td>
</tr>
<tr>
<td>8</td>
<td>50</td>
<td>Ischaemic cardiomyopathy</td>
<td>79</td>
<td>1.94</td>
<td>100</td>
</tr>
</tbody>
</table>

sure (PWP), Systemic Vascular Resistance (SVR), Total Pulmonary Resistance (TPR) and Cardiac Index (CI). An electrocardiographic lead was monitored continuously throughout the investigation, as well as MAP.

**Statistical Evaluation**

a) **Time-Course of the Parameters.** Each parameter was processed in order to calculate its mean value ± SE, and a randomized block analysis of variance was done. When the F obtained reached a degree of significance, Dunnett's "t" test was performed to ascertain the times at which the parameter differed from the baseline values [11].

b) **Analysis at Peak Values.** The individual peak value of each parameter was compared to the baseline value by Student's "t" test for paired samples.

**Results**

The mean control values of CI and PWP were 2.5 l·min⁻¹·m² and 32 mmHg. The maximum hemodynamic effects of ibopamine after oral administration are reported in Table 2.

Cardiac index increased by about 20% and PWP decreased by about 19%; TPR and SVR also decreased by about 18%. HR and MAP did not change significantly. The maximum effect was achieved between 1 and 4 h after oral administration.

The time course of the haemodynamic response to Ibopamine is shown in Fig.1. The trend of the curves was entirely consistent with the expected time-course of action of the drug. No toxic side effects were observed.

**Discussion**

The medical treatment of severe congestive heart failure calls simultaneously for salt and water retention to be controlled, workload to be reduced and pumping performance to be improved. The importance of only one of these factors may be variable but the prime requirement in most cases is to improve cardiac contractility. Cardiac glycosides have been widely used for this purpose. There is, however, no evidence that they are of any significant benefit in very severe congestive heart failure, a condition in which the therapeutic ratio of digitalis is very low. By contrast, dopamine has been shown to be beneficial in increasing cardiac output and renal sodium excretion [12]. Its action on β-adrenergic receptors in the myocardium stimulates cardiac contractility, and is inhibited by propranolol [13]. However, there is evidence to support the concept that the vasodilatation induced by dopamine is mediated through specific dopaminergic receptors (D₁, D₂) in the renal, mesenteric, coronary and cerebral vascular beds, which are not blocked by propranolol [13].

This action seems particularly valuable in congestive heart failure to improve blood flow in these territories and, in consequence, an orally active dopamine-like compound would certainly be useful. A single oral dose of ibopamine increased CI and decreased PWP and SVR. These effects were accompanied by a significant decrease in TPR. Ibopamine should be beneficial, therefore, in the management