Hemodynamic and Hormonal Effects of Beraprost Sodium, an Orally Active Prostacyclin Analogue, in Patients With Secondary Precapillary Pulmonary Hypertension

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Earlier studies have shown that administration of beraprost sodium (BPS), an orally active prostacyclin analogue, improves hemodynamics in patients with primary pulmonary hypertension (PH), but it is not known whether BPS has beneficial effects in secondary precapillary PH. The present study investigated the hemodynamic and hormonal parameters of 18 patients with secondary precapillary PH (8 patients with chronic thromboembolic PH, 7 with collagen vascular disease, and 3 with residual PH after surgery for atrial septal defect). Hemodynamics were repeatedly measured by right heart catheterization. Treatment with BPS improved New York Heart Association (NYHA) functional class in 10 of the 18 patients and significantly decreased pulmonary vascular resistance by 17% (12.9±1.1 to 10.7±1.2 Wood units, p<0.01). Circulating brain natriuretic peptide and uric acid significantly decreased from 246±61 to 215±65 pg/ml and from 6.5±0.6 to 5.3±0.3 mg/dl, respectively. In summary, BPS therapy improved NYHA functional class, hemodynamics, and hormonal parameters in patients with secondary precapillary PH. Thus, oral administration of BPS may be a new therapeutic strategy for the treatment of secondary precapillary PH. (Circ J 2003; 67: 375-378)

Key Words: Collagen vascular disease; Prostacyclin; Pulmonary heart disease; Pulmonary hypertension
Table 1  Baseline Characteristics of the Study Patients With Secondary Precapillary Pulmonary Hypertension

<table>
<thead>
<tr>
<th>Variables</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>44±3</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>3 (17%)</td>
</tr>
<tr>
<td>Female</td>
<td>15 (83%)</td>
</tr>
<tr>
<td>NYHA class, n (%)</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>4 (22%)</td>
</tr>
<tr>
<td>III</td>
<td>14 (78%)</td>
</tr>
<tr>
<td>Hemodynamic measurements</td>
<td></td>
</tr>
<tr>
<td>Heart rate, beat/min</td>
<td>82±3</td>
</tr>
<tr>
<td>Mean systemic arterial pressure, mmHg</td>
<td>89±3</td>
</tr>
<tr>
<td>Mean pulmonary arterial pressure, mmHg</td>
<td>49±2</td>
</tr>
<tr>
<td>Right atrial pressure, mmHg</td>
<td>6±1</td>
</tr>
<tr>
<td>Pulmonary capillary wedge pressure, mmHg</td>
<td>7±1</td>
</tr>
<tr>
<td>Cardiac index, L·min⁻¹·m⁻²</td>
<td>2.4±0.2</td>
</tr>
<tr>
<td>Pulmonary vascular resistance, Wood units</td>
<td>13±1</td>
</tr>
<tr>
<td>Medications n (%)</td>
<td></td>
</tr>
<tr>
<td>Anticoagulants</td>
<td>17 (94%)</td>
</tr>
<tr>
<td>Calcium antagonists</td>
<td>1 (6%)</td>
</tr>
<tr>
<td>Digitalis</td>
<td>5 (28%)</td>
</tr>
<tr>
<td>Diuretics</td>
<td>8 (44%)</td>
</tr>
</tbody>
</table>

Variables of age and hemodynamics are expressed as mean±SEM. NYHA, New York Heart Association.

excluded from the study. Of the 18 patients, 14 were having home oxygen therapy.

Treatment With BPS

Oral administration of BPS was begun at a dose of 600 µg/day and increased incrementally of 600 µg/day over 1–2 weeks to the highest dose tolerated (mean=1433 µg/day, range=60–360 µg/day). All patients were treated with conventional therapy including anticoagulants, calcium antagonists, digitalis, and diuretics etc. by their attending physicians ad libitum before starting BPS.

Hemodynamic measurements together with hormonal measurements were repeated in all patients during the BPS therapy (av. duration = 2.3±0.5 months).

Assessment of NYHA Functional Class and Hemodynamic Variables

All patients were classified according to NYHA functional class at baseline and during BPS therapy. Baseline hemodynamics, including mPAP, mean right atrial pressure (mRAP) and PCWP, were measured by right heart catheterization. Cardiac output (CO) was estimated by Fick’s method.11 PVR was calculated by standard equation and stroke volume (SV) was calculated by dividing CO by heart rate (HR). Cardiac catheterization was repeated during BPS therapy to evaluate the chronic hemodynamic effects of oral BPS. This procedure was performed approximately 2 h after taking BPS.

Measurements of Hormonal Parameters

Measurement of the concentrations of plasma brain natriuretic peptide (BNP) and serum uric acid (UA) was repeated in all patients during BPS therapy. BNP was measured by immunoradiometric assay using a specific kit (Shiono RIA BNP assay kit, Shionogi Co, Ltd, Osaka, Japan)12 and serum UA was measured by commercially available kit.

Statistical Analysis

Data were expressed as mean±SEM. Changes in NYHA functional class and hemodynamics and hormonal parameters during BPS therapy were analyzed by paired Student t test. A p<0.05 was considered statistically significant.

Results

Adverse effects of BPS were observed in 4 patients within 1 week of beginning therapy: facial flushing in 2 patients, headache in 1, and epigastralgia in 1; however, no clinically significant hypotension was observed. The side effects were overcome either by reducing the dose of BPS or splitting the same daily dose. All patients tolerated at least 600 µg/day of BPS.

Following oral administration of BPS, NYHA functional class significantly improved in 10 patients (56%), worsened in 1 (6%) and was unchanged in 7 (38%) (Fig 1). BPS significantly lowered mPAP by 10% (49±2 to 44±2 mmHg, p<0.01) and increased CO by 11% (3.6±0.3 to 4.0±0.3 L/min, p<0.05, Fig 2). Consequently, PVR significantly decreased by 17% (12.9±1 to 10.7±1 Wood units, p<0.01). There was a significant decrease in HR by 7% (82±3 to 76±3 beats/min, p<0.05) and an increase in SV by 23% (44±4 to 54±5 ml, p<0.01). However, mean systemic arterial pressure (mSAP) did not reduce significantly (89±3 to 86±3 mmHg, p=NS).

Before starting BPS therapy, there was a significant positive correlation between plasma BNP concentration and PVR (r=0.72, p<0.05), but there was none between serum uric acid concentration and any hemodynamic parameter. The plasma BNP concentration significantly decreased from 246±61 to 215±65 pg/ml (p<0.01) during BPS therapy (Fig 3). In addition, the serum UA concentration decreased from 6.5±0.6 to 5.3±0.3 mg/dl (p<0.01). The decrease in plasma BNP was positively correlated with the decrease in PVR (r=0.88, p<0.01), but serum UA was not significantly correlated with PVR.

Arterial blood gas analysis was repeatedly performed in 9 of the 18 study patients at baseline and during BPS therapy. Arterial oxygen pressure did not change significantly (68±3 to 66±4 mmHg, p=NS). Arterial carbon dioxide pressure significantly increased from 31±1 to 35±1 mmHg (p<0.05).

Discussion

In the present study, we demonstrated (1) that oral administration of BPS improved NYHA functional class in patients with secondary precapillary PH, (2) that BPS therapy decreased mPAP and PVR and increased CO and
SV, and (3) that BPS decreased the concentrations of plasma BNP and serum UA, which are markers for disease severity.

Quality of life is impaired in patients with PH as indicated by a decrease in peak oxygen consumption and an increase in ventilatory response during cardiopulmonary exercise. The present study demonstrates that BPS therapy improved the impaired NYHA functional class in patients with secondary precapillary PH.

In the present study, BPS therapy caused beneficial hemodynamic effects in patients with secondary precapillary PH, similar to observations in patients with primary PH. The imbalance between prostacyclin and thromboxane A2 secretion in the pulmonary arteries has been proposed as a mechanism of primary or secondary PH. Oral administration of BPS supplies prostacyclin analogue to the pulmonary arteries and thereby may improve the imbalance of prostacyclin/thromboxane. Medial hypertrophy, intimal fibrosis and thrombotic lesions of pulmonary arteries are frequently observed in patients with secondary precapillary PH, especially when the etiology is collagen vascular disease, and BPS has been shown to produce strong vasodilation, and inhibition of platelet aggregation and vascular smooth muscle proliferation. Thus, it is interesting to speculate that oral BPS may improve these abnormalities of the pulmonary vasculature.

Finally, we analyzed the effects of BPS therapy on plasma BNP and serum UA concentrations, because these are markers of disease severity. BNP is mainly secreted from cardiac ventricles in proportion to ventricular overload and we recently demonstrated that plasma BNP increases in proportion to the extent of right ventricular dysfunction in PH. In fact, the baseline concentration of plasma BNP was markedly high in patients with secondary precapillary PH and as expected, it significantly decreased after BPS treatment, suggesting that BPS ameliorated right ventricular overload through its pulmonary vasodilatory effect.

The concentration of serum UA was also elevated in patients with secondary precapillary PH. Reduced CO causes tissue ischemia, which depletes ATP and activates the purine nucleotide degeneration pathway that leads to UA.

In patients with primary PH, an increased concentration of serum UA reflects hemodynamic and prognostic severity, and in the present study, BPS therapy significantly decreased the concentration of serum UA in patients with secondary precapillary PH, thus indicating a possible beneficial effect of oral BPS in this condition also.

Study Limitations

This preliminary study was not a placebo-controlled study, which may bias the results. Second, the number of patients was relatively small and large population studies are necessary to confirm the effects of BPS. Third, other medications, which included anticoagulants and calcium antagonists, were not controlled. Nevertheless, 17 patients (94%) were taking anticoagulant agents and only 1 was taking a calcium antagonist.

In summary, oral BPS improved functional class, hemodynamics, and hormonal parameters in patients with secondary precapillary PH and may be a new therapeutic strategy for this disease.
Acknowledgements
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References