Effects of Beraprost Sodium, an Oral Prostacyclin Analogue, in Patients With Pulmonary Arterial Hypertension: A Randomized, Double-Blind, Placebo-Controlled Trial

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OBJECTIVES
The purpose of this study was to assess the efficacy and safety of beraprost sodium, an orally active prostacyclin analogue, in New York Heart Association (NYHA) functional class II and III patients with pulmonary arterial hypertension (PAH).

BACKGROUND
Pulmonary arterial hypertension is a life-threatening disease for which continuous intravenous infusion of prostacyclin has been proven effective. However, this treatment is associated with serious complications arising from the complex delivery system.

METHODS
In this double-blind, placebo-controlled study, 130 patients with PAH were randomized to the maximal tolerated dose of beraprost (median dose 80 μg four times a day) or to placebo for 12 weeks. The primary end point was the change in exercise capacity assessed by the 6-min walk test. Secondary end points included changes in Borg dyspnea index, cardipulmonary hemodynamics and NYHA functional class.

RESULTS
Patients treated with beraprost improved exercise capacity and symptoms. The difference between treatment groups in the mean change of 6-min walking distance at week 12 was 25.1 m (95% confidence interval [CI]: 1.8 to 48.3, p = 0.036). The difference in the mean change of Borg dyspnea index was −0.94 (95% CI: −1.63 to −0.24, p = 0.009). In the sub-group of patients with primary pulmonary hypertension, the difference in the mean change of 6-min walking distance was 46.1 m (95% CI: 3.0 to 89.3, p = 0.035). Cardipulmonary hemodynamics and NYHA functional class had no statistically significant changes. Drug-related adverse events were common in the titration phase and decreased in the maintenance period.

CONCLUSIONS
Beraprost improves exercise capacity and symptoms in NYHA functional class II and III patients with PAH and, in particular, in those with primary pulmonary hypertension. (J Am Coll Cardiol 2002;39:1496–502) © 2002 by the American College of Cardiology Foundation

Pulmonary arterial hypertension (PAH) is defined, according to the 1998 World Health Organization classification (1), as a group of diseases characterized by a progressive increase of pulmonary vascular resistance leading to right ventricular failure and death (2,3). Pulmonary arterial hypertension includes primary pulmonary hypertension (2,4) and pulmonary hypertension associated with various conditions such as collagen vascular diseases (5), congenital systemic-to-pulmonary shunts (6), portal hypertension (7) and human immunodeficiency virus (HIV) infection (8). All these conditions share virtually identical obstructive pathologic changes of the pulmonary microcirculation (9). Prostacyclin is an endogenous substance produced by vascular endothelium that has vasodilating, antiplatelet aggregation and antiproliferative effects (10–12). A dysregulation of prostacyclin metabolic pathways has been demonstrated in patients with PAH (13) and in experimental models of pulmonary hypertension (14,15). Recently, therapy with continuous intravenous prostacyclin (epoprostienol) has been shown to improve symptoms and prognosis in New York Heart Association (NYHA) functional class III and IV patients with different types of PAH (16–20). However, epoprostenol requires permanent intravenous catheters and
portable pumps and is associated with several side effects and potentially serious complications. For these reasons, alternatives to intravenous prostacyclin have been sought, and this has led to analogues, which can be administered subcutaneously (treprostinil), by inhalation (iloprost) or orally (beraprost sodium) (21).

Beraprost sodium is the first chemically stable and orally active prostacyclin analogue (22). In experimental studies, beraprost sodium has been shown to exert a protective effect on the development of monocrotaline-induced pulmonary hypertension (23). Uncontrolled and retrospective experiences in patients with primary pulmonary hypertension have preliminarily shown that long-term oral treatment with beraprost sodium improves hemodynamics (24) and prognosis (25).

We report on the results of a randomized, double-blind, placebo-controlled, multicenter study designed to determine the effects of 12-week oral administration of beraprost sodium on exercise capacity, symptoms and cardiopulmonary hemodynamics in NYHA class II and III patients with PAH.

METHODS

Patients selection. Patients eligible for this study were males or females over 8 years of age with PAH (1) in NYHA functional classes II and III, including primary pulmonary hypertension, pulmonary hypertension associated with collagen vascular disease, congenital systemic-to-pulmonary shunts, portal hypertension and HIV infection. A baseline 6-min walking distance between 50 and 500 m, a mean pulmonary artery pressure >25 mm Hg and a pulmonary capillary wedge pressure <15 mm Hg were required for inclusion. Patients were excluded if they had received long-term treatment with other prostacyclin analogues within one month of enrolment. The study was conducted in accordance with good clinical practices, the current version of the declaration of Helsinki and with local regulations. The local ethics review committee approved the protocol, and written informed consent was obtained from all patients.

Study design. This study was designed as a prospective, double-blind, randomized, placebo-controlled, 12-week trial conducted in 13 centers in Europe. The first six weeks of the study were considered as a titration period in which the dose of beraprost sodium was increased weekly until the maximal tolerated dose was achieved. Patients received one tablet (20 μg) of beraprost sodium or matching placebo four times a day for the first week, and the dose was increased by 20 μg or matching placebo four times a day each week. In case of intolerable side effects, the dose was reduced to that of the previous week, and this was considered as the maximal tolerated dose. Therefore, the up-titration was based on side effects and not on clinical efficacy, in order to administer the highest tolerated dose. The maximal dose allowed in the study was 120 μg four times a day at week 6. The maximal tolerated dose was kept constant during the maintenance period between week 7 and week 12. Side effects limiting dose increase were moderate to severe flushing, headache and diarrhea and usually occurred 1 to 2 h after single-dose intake. All patients were enrolled in an open-label study with beraprost sodium after the completion of the randomized study.

Outcome measures. Patients were evaluated at baseline, week 6 and week 12. The primary efficacy parameter was exercise capacity measured by the distance a patient could walk in 6 min (6-min walk test) at week 12. The 6-min walk test was performed after standardized procedures (26) 2 to 4 h after drug intake.

Secondary measures of efficacy included the Borg dyspnea index (27) assessed immediately after completion of the 6-min walk test and cardiopulmonary hemodynamics measured by right heart catheterization at baseline and week 12. Cardiac index (l/min/m²) was computed as cardiac output divided by body surface area; pulmonary vascular resistance index (U/m²) was calculated using standard formula: mean pulmonary artery pressure—pulmonary capillary wedge pressure/cardiac index. Secondary measures of efficacy also included the NYHA functional class and the reduction in all-cause mortality or hospitalization for worsening of symptoms related to pulmonary hypertension. Safety was assessed by adverse event recording and laboratory assessment.

Statistical analysis. The sample size was estimated under the assumptions of a two-sided alpha probability of 0.05, an 80%-power, an expected treatment difference for the change from baseline in 6-min walk test of 40 m and an SD of 70 m. Under these conditions, the study’s 1:1 randomization required a sample size of at least 50 evaluable patients in each group. Assuming a 10% drop-out rate, planned recruitment was for a total of 110 patients (55 per group).

Analysis were performed in the intent-to-treat population that included all patients who were randomized, received at least one dose of study treatment and who also had a valid assessment of the primary end point (change from baseline in exercise capacity after 12 weeks of treatment) after applying the imputation rules for missing data.

In the event that no data were available at week 12 for the primary or secondary efficacy variable, the week 6 values or, if lacking, the baseline values were carried forward and used as values at week 12 (last observation carried forward). Two additional methods for missing data imputation were prospectively planned for the primary efficacy variable to ensure robustness of the results: the “left censored data” and “worst quartile” methods.
The significant levels of the difference between treatment groups for the 6-min walk test were evaluated with analysis of covariance (ANCOVA) (i.e., analysis of variance adjusted by baseline values, using the change from baseline to week 12 for each patient [SAS, version 8, Cary, North Carolina]). This test was performed at 5% two-tail level. The changes from baseline to week 12 of Borg dyspnea index and hemodynamic parameters were compared between treatment groups with ANCOVA. Changes from baseline to week 12 in NYHA classification (ordinal scale) were analyzed using Mantel-Haenszel method. Values with a ± symbol are the mean ± SD. All the reported p values were two-tailed.

**RESULTS**

One hundred thirty patients were included in the study (65 beraprost/65 placebo). At the end of 12 weeks, mean dose of drug was 80 ± 35 μg four times a day (median = 80 μg four times a day) in the beraprost sodium group, and the hypothetical dose in the placebo group was 111 ± 22 μg four times a day.

**Baseline characteristics.** Baseline demographic, clinical and hemodynamic characteristics of the two groups are shown in Table 1. The groups did not differ significantly in etiology of PAH, in NYHA functional class, in distance walked at the 6-min walk test or in severity of pulmonary hemodynamics. In the beraprost sodium group, there was a nonsignificant trend toward a higher prevalence of patients with primary pulmonary hypertension as well as a trend toward a lower mean distance walked at baseline.

**Exercise capacity.** The distance walked in 6 min improved in the beraprost sodium group from 362 ± 94 m to 377 ± 106 m at week 6 and to 377 ± 113 m at week 12. The distance walked increased in the placebo group from 383 ± 93 m to 388 ± 111 m at week 6 and decreased to 374 ± 121 m at week 12. The difference in mean distance walked (beraprost sodium group – placebo group) at week 12 adjusted by baseline values was 25.1 m (95% confidence interval [CI]: 1.8 to 48.3) in favor of beraprost sodium (p = 0.036) (Fig. 1). The significance of the improvement in exercise capacity with beraprost sodium was confirmed if the missing walking distance was replaced utilizing left censored data (p = 0.048) and worst quartile (p = 0.046) methods. The significance was confirmed also in the per-protocol (standard) population (p = 0.041).

Because the clinical hypothesis of an interaction between treatment effect and the two sub-groups of patients with primary pulmonary hypertension and associated forms of pulmonary hypertension was suggested by an interaction test (p = 0.073 last observation carried forward, p = 0.036 left-censored, p = 0.044 worst quartile methods), a subgroup analysis was performed (post-hoc analysis). In the sub-group of patients with primary pulmonary hypertension, the distance walked in 6 min improved at week 12 in the beraprost sodium group from 357 ± 95 m to 380 ± 117 m and decreased in the placebo group from 406 ± 79 m to 383 ± 125 m. The difference in mean distance walked adjusted by baseline values (Fig. 2) was 46.1 m (95% CI: 3.0 to 89.3) in favor of beraprost sodium (p = 0.035). In the sub-group of patients with associated forms of pulmonary hypertension, the distance walked in 6 min increased at week 12 in the beraprost sodium group from 367 ± 94 m to 373 ± 110 m and was unchanged in the placebo group from

**Table 1.** Demographic and Hemodynamic Characteristics at Baseline, According to Treatment Group

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Beraprost (n = 65)</th>
<th>Placebo (n = 65)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs</td>
<td>45.8 ± 16.3</td>
<td>45.1 ± 14.4</td>
</tr>
<tr>
<td>Gender, no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>23 (35.4)</td>
<td>27 (41.5)</td>
</tr>
<tr>
<td>Female</td>
<td>42 (64.6)</td>
<td>38 (58.5)</td>
</tr>
<tr>
<td>Etiology, no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary pulmonary hypertension</td>
<td>35 (53.9)</td>
<td>28 (43.1)</td>
</tr>
<tr>
<td>Pulmonary hypertension associated with:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Congenital cardiac shunt</td>
<td>9 (13.8)</td>
<td>15 (23.1)</td>
</tr>
<tr>
<td>Portal hypertension</td>
<td>12 (18.5)</td>
<td>9 (13.8)</td>
</tr>
<tr>
<td>Collagen vascular diseases</td>
<td>5 (7.7)</td>
<td>8 (12.3)</td>
</tr>
<tr>
<td>HIV infection</td>
<td>4 (6.2)</td>
<td>5 (7.7)</td>
</tr>
<tr>
<td>NYHA functional class, no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>31 (47.7)</td>
<td>33 (50.8)</td>
</tr>
<tr>
<td>III</td>
<td>34 (52.3)</td>
<td>32 (49.2)</td>
</tr>
<tr>
<td>6-min walk distance, m</td>
<td>362 ± 94</td>
<td>383 ± 93</td>
</tr>
<tr>
<td>Borg dyspnea score, Borg scale</td>
<td>3.6 ± 2.4</td>
<td>3.5 ± 2.4</td>
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<tr>
<td>Hemodynamic parameters</td>
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<td></td>
</tr>
<tr>
<td>Right atrial pressure, mm Hg</td>
<td>8 ± 5</td>
<td>9 ± 6</td>
</tr>
<tr>
<td>Mean pulmonary artery pressure, mm Hg</td>
<td>58 ± 21</td>
<td>61 ± 15</td>
</tr>
<tr>
<td>Cardiac index, l/min/m²</td>
<td>2.4 ± 0.7</td>
<td>2.4 ± 0.7</td>
</tr>
<tr>
<td>Pulmonary vascular resistance index, U/m²</td>
<td>22.7 ± 12.8</td>
<td>23.9 ± 10.8</td>
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<tr>
<td>Treatment at inclusion, no. (%)</td>
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<tr>
<td>Anticoagulants</td>
<td>49 (75.4)</td>
<td>46 (70.8)</td>
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<td>Diuretics</td>
<td>33 (50.8)</td>
<td>36 (55.4)</td>
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<tr>
<td>Calcium channel blockers</td>
<td>17 (26.2)</td>
<td>11 (16.9)</td>
</tr>
<tr>
<td>Digoxin</td>
<td>12 (18.5)</td>
<td>13 (20.0)</td>
</tr>
</tbody>
</table>

*Values with a ± symbol are the mean ± SD.

HIV = human immunodeficiency virus; NYHA = New York Heart Association.

![Figure 1. Change in 6-min walking distance from baseline to week 6 and week 12 in the beraprost and placebo groups. Values are expressed as mean ± standard error. p = 0.036 for no difference between treatment groups with analysis of covariance at week 12.](image-url)
366 ± 100 m to 366 ± 120 m. The difference in mean distance walked adjusted by baseline values (Fig. 2) was 5.1 m (95% CI: −19.5 to 29.6) in favor of beraprost sodium (p = 0.676).

**Signs and symptoms.** Borg dyspnea index improved (decreased) at week 12 in the beraprost sodium group from 3.6 ± 2.4 m to 3.0 ± 2.4 m and worsened (increased) in the placebo group from 3.5 ± 2.5 m to 3.9 ± 2.8 m. The difference in mean Borg dyspnea index adjusted by baseline values (Fig. 3) was −0.94 (95% CI: −1.63 to −0.24) in favor of beraprost sodium (p = 0.009). In the primary pulmonary hypertension sub-group, the difference in mean Borg dyspnea index was −1.46 (95% CI: −2.63 to −0.28) in favor of beraprost sodium (p = 0.013) and in the associated forms of pulmonary hypertension sub-group was −0.45 (95% CI: −1.31 to 0.40) in favor of beraprost sodium (p = 0.283).

At the end of 12 weeks, 16 patients (25%) treated with beraprost sodium and 10 patients (15%) of the placebo group showed improved NYHA functional class (p = 0.190).

During the 12-week study period, four patients (6%) in the beraprost sodium group and three (5%) patients in the placebo group either died or were hospitalized for worsening...
of symptoms related to pulmonary hypertension. Two patients died, one in the beraprost sodium group due to progressive right heart failure and one in the placebo group due to septic shock.

**Cardiopulmonary hemodynamics.** The changes in hemodynamic measures from baseline to week 12 are shown in Table 2. The beraprost and placebo treated patients had small variations of hemodynamic parameters, and no statistically significant changes were detected.

**Safety and tolerability.** Selected adverse events attributed to the underlying disease or to the treatment are shown in Table 3. Disease-related events had similar incidence in patients receiving beraprost and in those receiving placebo. Drug-related adverse events like headache, flushing, jaw pain and diarrhea were more common in patients treated with beraprost sodium and occurred mostly during the six-week titration period. The incidence was markedly reduced in the maintenance period.

Six patients (9%) in the beraprost sodium group and two patients (3%) in the placebo group withdrew prematurely from the study because of adverse events. No clinically adverse changes in hematologic or biochemical variables were seen in the beraprost sodium group. Liver transaminases increased by more than 0.6 times the upper normal limits in four (6%) patients in the placebo group as compared with none in the beraprost sodium group.

**DISCUSSION**

**Exercise capacity.** This double-blind, placebo-controlled, 12-week study demonstrated that the oral prostacyclin analogue beraprost sodium improves exercise capacity and symptoms in patients with PAH. As in other trials performed in this patient population, the primary end point of this study was the 6-min walking distance that has been shown to be an independent predictor of mortality (16,28). In our study the robustness of the 6-min walk test results were confirmed by different statistical analysis. So far, therapeutic trials in PAH have included more severely compromised subjects in NYHA functional class III or IV (16,18). For the first time, our study has included a larger proportion (49% of overall population) of less severe patients in NYHA functional class II (Table 1). Interestingly, no significant interaction was observed between NYHA functional class and treatment effect, suggesting that the favorable effects of beraprost sodium were similar in both NYHA functional class II and III patients.

**Sub-group analysis.** Sub-group analysis has shown that the improvement in the 6-min walk test was achieved only in patients with primary pulmonary hypertension, while no statistically significant changes were observed in the associated forms group (Fig. 2). The treatment effect observed in NYHA class II and III patients with primary pulmonary hypertension was 45 m. In a previous study with intravenous epoprostenol, carried out in a more severe patient population (NYHA functional class III and IV), the treatment effect was 47 m (16).

The absence of significant improvement of exercise capacity in associated forms of pulmonary hypertension could be attributed to different causes. Firstly, in this trial the group of associated forms was heterogeneous including 36% of patients with congenital systemic-to-pulmonary shunts, 32% with portal hypertension, 19% with collagen vascular disease and 13% with HIV infection. Analysis of the effects on each individual sub-group is prevented by the small sample size. So far, a single controlled clinical study has demonstrated a positive effect of epoprostenol on exercise capacity in patients with pulmonary hypertension associated...
with scleroderma (18). Treatment with prostanoids of all the other forms of associated pulmonary hypertension have been evaluated in uncontrolled studies (17), and the favorable effects require further confirmations. Secondly, the doses of beraprost sodium were substantially lower in patients with associated forms of pulmonary hypertension than in patients with primary pulmonary hypertension (62 ± 36 μg four times a day vs. 96 ± 35 μg four times a day, respectively). Dose increase was usually limited by symptoms like headache, flushing and diarrhea, and it is possible that patients with associated conditions are more predisposed to these side effects. In fact, patients with portal hypertension, HIV infection and collagen vascular disease have a multi-organ involvement that could interfere with beraprost sodium tolerability. It is unclear from our data if the higher dose of beraprost sodium tolerated by patients with primary pulmonary hypertension may explain the better results obtained on 6-min walking distance. Finally, a 12-week study may be too short to demonstrate a beneficial effect of prostanoid therapy in the associated forms group. In fact, patients with pulmonary hypertension associated with systemic-to-pulmonary shunt or to portal hypertension (67% of associated forms in this trial) may show a slower rate of clinical deterioration (29) and a longer preservation of the cardiac output. This evidence is supported in our study by the absence of a reduction of the 6-min walking distance in placebo-treated patients with the associated forms, whereas the placebo-treated patients with primary pulmonary hypertension showed a significant decrease of exercise capacity (Fig. 2).

Symptoms and outcome. In the overall population, the improvement in the 6-min walking distance was associated with a concomitant significant improvement in the perception of dyspnea, as assessed by the reduction of Borg dyspnea score (Fig. 3). On the other hand, we observed no statistically significant improvement of NYHA functional class in patients treated with beraprost, as compared with placebo. In addition, the rate of the combined end point of death or hospitalization was low and similar in both beraprost sodium and placebo groups (6% vs. 5%, respectively). Possible explanations for these findings include the high proportion of NYHA functional class II patients at baseline and the short duration of the study that was not specifically designed to detect a difference in these secondary end points.

Cardiopulmonary hemodynamics. Unlike the previous studies with epoprostenol (18), we did not find statistically significant improvements in resting hemodynamic variables even if small favorable trends in the beraprost sodium group were observed. Possible reasons for explaining these differences include the greater severity of baseline hemodynamic changes in earlier epoprostenol trials and the small deterioration we observed in the placebo group.

Safety and tolerability. Despite the high doses of beraprost sodium used in this study, the safety profile of the drug was excellent with neither systemic hypotension nor hepatic, renal or hematologic side effects. Adverse events commonly observed with all prostacyclin analogues (headache, flushing, jaw pain, diarrhea and nausea) were frequent during the titration period when the highest possible doses were tested, while the tolerability of the drug was much better in the maintenance phase.

Conclusions. Oral beraprost sodium therapy is effective in improving functional capacity and symptoms in NYHA functional class II and III patients with PAH and, in particular, in those with primary pulmonary hypertension. The benefit/risk ratio of beraprost sodium appears to be satisfactory. However, further studies are needed to define the long-term effect of this treatment on morbidity and mortality of patients with PAH.

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