Bosentan Improves Exercise Tolerance and Tei Index in Patients With Pulmonary Hypertension and Prostanoid Therapy*

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Study objective: **Pulmonary arterial hypertension (PAH) is a progressive disease with a bad prognosis. Prostanoids are well established in the medical treatment of this disease. Treatment of patients with progressive disease despite prostanoids remains a therapeutic challenge. In this study, we examined the effect of adding bosentan, an endothelin antagonist, to existing prostanoid therapy on exercise capacity (6-min walking distance [6MWD]) and right ventricular (RV) function (Tei index) in patients with progressive pulmonary hypertension.**
Design: **Prospective, nonrandomized, open-label study.**
Setting: **University hospital.**
Patients: **Sixteen patients with pulmonary hypertension (PAH, n = 10; pulmonary hypertension due to other cause, n = 6) with progressive disease receiving either beraprost (n = 3), inhaled iloprost (n = 10), or iloprost IV (n = 3).**
Interventions: **Combination therapy with bosentan (final dosage, 125 mg bid) was initiated following an interval of 3-months minimum of unchanged prostanoid therapy.**
Measurements and results: **Tei index, 6MWD, and New York Heart Association (NYHA) functional class were assessed prior to the initiation of combination therapy (baseline), at 6 months after initiation of combination therapy, and every 3 months thereafter. Two patients were followed up for 6 months only; all remaining patients reached a mean follow-up period (± SD) of 13.5 ± 5.0 months (range, 9 to 22 months). 6MWD increased by 42.5 ± 66 m at 6 months and 44.6 ± 66 m at the last follow-up (both time points vs baseline, $p < 0.001$), and Tei index improved by − 0.13 ± 0.08 at 6 months and − 0.13 ± 0.11 at the last follow-up (both time points vs baseline, $p < 0.001$). All patients reported subjective improvements. Nine of 16 patients exhibited improvement in NYHA functional class at 6 months. No side effects occurred that required dose adjustment or discontinuation of the study medication.**
Conclusion: **Bosentan administered to patients with progressive pulmonary hypertension receiving prostanoids resulted in an increased exercise capacity and an improved RV function. Bosentan therefore appears to be well suited for combination therapy with prostanoids in selected patients pending results of ongoing randomized trials.** ***(CHEST 2005; 128:709–713)***

Key words: beraprost; bosentan; combination; drug therapy; iloprost; pulmonary hypertension

Abbreviations: 6MWD = 6-min walking distance; NYHA = New York Heart Association; PAH = pulmonary arterial hypertension; PPH = primary pulmonary hypertension; RV = right ventricular

Pulmonary arterial hypertension (PAH) is a rare, progressive disease with a bad prognosis. Without adequate therapy, the mean survival of patients with primary pulmonary hypertension (PPH) is < 3 years.[1] The use of prostanoids has become an effective therapy lately. Continuous IV administration of epoprostenol resulted in improved exercise capacity, quality of life, hemodynamics, and prognosis.[2–4] IV[5] as well as inhaled iloprost[6–8] has been shown to evoke similar effects. This has been demonstrated in patients with primary and in patients with various other types of pulmonary hypertension.[5,9,10] Oral beraprost[11] has also been demonstrated to be effective in a 12-week trial, but failed to cause significant effects at 6 months and 12 months.[12] The development of tachyphylaxis seems to be a feature common

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Manuscript received January 29, 2004; revision accepted January 4, 2005.

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to all modes of prostanoid therapy.[13] Prostanoid dosage is however often limited due to systemic side effects.[6]

The use of bosentan, an orally administered, dual endothelin receptor antagonist, offers a novel therapeutic strategy. This strategy has been shown to improve exercise capacity in patients with PPH and with PAH associated with systemic sclerosis.[14,15] Bosentan also led to improvements in right ventricular (RV) function.[14] This compound induced hemodynamic effects and exercise capacity improvements that were stable at 12 months of follow-up.[16]

An experimental study[17] as well as a clinical trial[18] demonstrated an additive effect of the combination of prostanoid treatment with oral bosentan. Bosentan, 125 mg bid, in combination with beraprost or inhaled iloprost improved 6-min walking distance (6MWD), and parameters of cardiopulmonary exercise testing (oxygen consumption as well as anaerobic threshold) in patients with PPH during a 12-week trial.[18]

The Tei index is a practical echocardiographic index that combines information on systolic and diastolic RV function. This noninvasive parameter is correlated well with prognosis in patients with chronic pulmonary heart disease due to PPH.[19] We hypothesized that adding bosentan may improve Tei index and 6MWD in patients with progressive pulmonary hypertension receiving prostanoid therapy.

Materials and Methods

Patients

Sixteen consecutive patients treated with prostanoids for a minimum of 12 months (Table 1) were included in this prospective, nonrandomized, open-label study. Patients were included when progressive pulmonary hypertension was noted despite prostanoid treatment. Progression of disease was defined as follows: (1) a decline of $> 15\%$ in 6MWD compared with the individual best value, (2) a decline in cardiac index to < 2 L/min/m^2, and/or (3) a failure to increase in cardiac index to > 2 L/min/m^2 despite prostanoid treatment. Patients with contraindications for bosentan, especially severe liver dysfunction (Child/Pugh B or C liver cirrhosis), were excluded from the study.

All patients were receiving long-term oxygen, diuretics, and phenprocoumon; two patients additionally received oral nitrates; and three patients received oral trapidil (a nonspecific phosphodiesterase inhibitor). Prostanoids were administered in the maximum dosage tolerated and were not changed for a minimum period of 3 months before addition of bosentan. All other medications, except diuretics, were also kept constant.

Bosentan was administered starting at an initial dose of 62.5 mg bid. This dose was doubled after 4 weeks unless elevated liver enzymes were observed. Liver enzymes, serum bilirubin, international normalized ratio, and hemoglobin were monitored monthly. The study was approved by the local ethical review board of our institution. Informed consent was obtained from all patients.

Table 1—*Characteristics of the Included Patients

Characteristics	Data
Cause of pulmonary hypertension	
PAH	
Idiopathic PAH	9
Accompanying liver cirrhosis (Child/Pugh A)	1
Thromboembolic	5
Interstitial lung disease	1
Gender	
Female	15
Male	1
Age (range) yr	51.3 (25–71)
NYHA functional class	
II	6
III	8
IV	2
Patients receiving prostanoid	
Beraprost, 100 to 600 μg/d	3
Iloprost IV, 150 to 250 μg/d	3
Iloprost inhaled, 25 to 52.5 μg/d†	8
Iloprost inhaled, 60 to 120 μg/d‡	2
Time receiving prostanoids, mo	22.7 ± 12
Time since diagnosis, mo	35.3 ± 26
Hemodynamic	
Pulmonary arterial pressure, mm Hg	55 ± 11
Cardiac index, L/min/m^2	2.1 ± 1.0
Pulmonary vascular resistance, dyne · s · cm^5	1,371 ± 504

*Data are presented as No. or mean ± SD.
†Opti-Neb (Nebutec; Elsenfeld, Germany).
‡Ilo-Neb (Nebutec).

Methods

Doppler echocardiography and 6MWD were determined within 3 days before and again at 6 months after initiation of combination therapy. Fourteen patients were followed up for > 6 months. Mean follow-up period was 13.5 ± 5.0 months (range, 9 to 22 months).

6MWD before and after initiation of the combination treatment was determined with supplemental (nasal) oxygen with the flow set to 4 L/min. The walking course was marked on the floor and remained the same throughout the study period.

RV function was characterized by Tei index, the sum of isovolumetric contraction time and isovolumetric relaxation time divided by ejection time.[20] The tricuspid inflow velocity was recorded in the four-chamber view using pulsed-wave Doppler echocardiography (Ultramark 7; ATL; Bothell, WA). The sample volume was positioned at the tips of the tricuspid leaflets. Isovolumetric contraction time and isovolumetric relaxation time were obtained from the registration of the tricuspid inflow velocity pattern. The RV tract outflow velocity was recorded from the parasternal short-axis view with the pulsed-wave Doppler sample volume positioned just proximal to the pulmonary valve. Ejection time was measured using the RV outflow velocity pattern. Sweep speed used in all Doppler recordings was 100 mm/s. Five consecutive beats were measured and averaged for each measurement. One of the authors performed the echocardiography. To minimize bias, this investigator did not know the results of the 6MWD test.

Statistics

Data are presented as mean ± SD. The two-tailed Student *t* test for paired samples was performed for the comparison