

First experience with an oral combination therapy using bosentan and sildenafil for pulmonary arterial hypertension

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Abstract

Background New oral substances such as beraprost, bosentan and sildenafil have proven effective in different forms of pulmonary arterial hypertension (PAH), both alone and in combination with standard treatment such as intravenous and inhaled prostacyclins. However, there are few reports so far on the effect of a combination of exclusively oral substances. In this paper, we present our initial findings of treatment using a combination of these oral substances in a heterogeneous group of patients with different forms of PAH.

Materials and methods Eleven patients with a median age of 12.9 years (5.5–54.7 years) with both idiopathic PAH and forms associated with congenital cardiac defects (PAH-CHD) with a mean pulmonary arterial pressure > 25 mmHg were enrolled in an observational, open-label, prospective, single-centre study. Either combination treatment with bosentan and sildenafil was started initially, or an existing bosentan treatment was complemented with sildenafil given as an add-on therapy. Mean doses given were 2.3 ± 0.6 mg kg⁻¹ for bosentan and 2.1 ± 0.9 mg kg⁻¹ for sildenafil. Clinical status, exercise capacity, and haemodynamics were assessed at baseline and at the end of the observation period after a mean follow-up time of 1.1 years (0.5–2.5 years).

Results No major side effects regarding liver function and blood pressure regulation were noted. One patient died of sudden death elsewhere. Most patients were in New York Heart Association (NYHA) functional class III. Clinical improvement was about one NYHA class (mean 2.8 ± 0.4 – 1.6 ± 0.8 , $P = 0.001$), which was associated with an increase of transcutaneous oxygen saturation (89.9 ± 9.9 – $92.3 \pm 7.1\%$; $P = 0.037$), maximum oxygen uptake (18.1 ± 6.8 – 22.8 ± 10.4 mL kg⁻¹ * min; $P = 0.043$), and 6-minute walking distance (351 ± 58 – 451 ± 119 m; $P = 0.039$). Mean pulmonary arterial pressure measured invasively decreased (62 ± 12 – 46 ± 18 mmHg; $P = 0.041$).

Conclusions In our patient group, a combination of oral bosentan and sildenafil proved to be safe and effective. Clearly, randomized, double-blind, placebo-controlled studies are warranted to define the role and type of combination therapies in PAH.

Keywords Bosentan, combination, endothelin receptor antagonists, phosphodiesterase inhibitors, pulmonary arterial hypertension, sildenafil, congenital heart disease, children, competence network.

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Introduction

Idiopathic pulmonary arterial hypertension (iPAH) is a devastating disease with a poor prognosis. Without appropriate therapy, median life expectancy at the time of diagnosis is only about 2.8 years and 3-year survival only 48% [1]. With maximal medical therapy of continuous intravenous administration of prostanoids, 3-year survival has been confirmed in several independent studies as no more than 63% [2,3]. Indication for lung transplantation or heart-lung transplantation is given in patients who are refractory to medical treatment. Transplantation poses severe restrictions to patients' quality of life. Three-year survival even after lung transplantation is only about 55% [4,5].

Current medical treatment following international guidelines [6,7] is based on oral anticoagulation, diuretics, calcium channel blockers, and supplemental oxygen, where applicable. Furthermore, it includes vasoactive agents from the prostaglandin, nitric oxide and endothelin pathways.

Synthetic prostacyclins are a substitute for the relative endogenous prostacyclin deficiency in iPAH patients. They can be administered intravenously (epoprostenol), subcutaneously (treprostinil), inhaled (iloprost) or orally (beraprost). Continuous intravenous therapy with prostanoids has beneficial effects on haemodynamics and exercise capacity and is the only treatment proven in controlled clinical trials to improve survival time in patients with iPAH [8,9]. However, it is expensive and may be complicated by line infections, tachyphylaxis, and systemic side effects due to lack of pulmonary selectivity. Patients suffering from complications due to intravenous application of prostanoids may be switched to continuous subcutaneous treprostinil; however, large trials have shown only a modest increase in exercise capacity and a high incidence of therapeutic limitations due to local pain at the site of infusion [10]. Inhalation therapy showed improvement of clinical and haemodynamic parameters [11], but the need for regular short-term repetitive inhalations represents a major inconvenience for patients. In addition, long-term therapy with iloprost has shown disappointing results [12]. Oral therapy is most practical but seems to lack an improvement beyond a time of 6 months [13,14].

Phosphodiesterase-5 (PDE5) inhibitors enhance endogenous and exogenous effects of nitric oxide (NO) via inactivation of cyclic adenosine monophosphate and cyclic guanosine monophosphate, the NO second messengers. Evidence shows improvement in clinical and haemodynamic parameters for oral sildenafil [15,16]. It promotes pulmonary vasodilatation in children [17]. A recent controlled trial with sildenafil supported previous findings, showing improvement in the 6-minute walk test (6-MWT), NYHA functional class and decrease in pulmonary artery pressure [18]. Oral vardenafil and tadalafil have markedly different haemodynamic and oxygenation responses [19].

Endothelin receptor antagonists (ERAs) block one or both endothelin receptors, thus preventing them from exerting their vasoconstrictor and pro-inflammatory effects. Controlled trials in iPAH patients with the dual oral ERA bosentan demonstrated improvement in exercise capacity,

functional class, and time to clinical worsening [20] as well as haemodynamic and echocardiographic parameters [21]. The effects of bosentan are maintained in the long term [22], and patients' quality of life is improved [22–24]. The selective orally active ERAs sitaxsentan [25] and ambrisentan [26] have been evaluated in pilot studies and have shown dose-dependent improvements in exercise capacity, haemodynamics and clinical events.

It is clear that the combination of different drugs with different mechanisms of action and different ways of metabolism is an attractive therapeutic option with the hope of maximizing effectiveness and mode of drug delivery while minimizing side effects. Furthermore, the overall aim of any oral or inhaled therapy will strive to prevent patients from being submitted to a continuous intravenous administration of prostanoids or lung transplantation with its poor outcome and severe limitations for our patients' quality of life. In this study, we used a combination of oral substances in order to take advantage of the mode of application and present our findings on the combination treatment of bosentan and sildenafil in terms of clinical efficacy and safety.

Patients and methods

Patients

Pulmonary arterial hypertension was conventionally defined as a mean pulmonary arterial pressure greater than 25 mmHg. At the time of enrolment, all patients were in clinically stable conditions, according to New York Heart Association (NYHA) functional class II or III, with no new medication started within the previous 3 months. The study was conducted to the provisions of the Declaration of Helsinki of 1975, as revised in 1983, and in adherence to local guidelines for Good Clinical Practice. Informed consent was obtained from all patients.

Study design and treatment

This was an observational, open-label, prospective single-centre study. Baseline data were obtained including clinical examination, echocardiography, cardiopulmonary exercise testing on the treadmill, the 6-MWT, and echocardiography. Bosentan dosage was 0.75 mg kg⁻¹ twice daily for the first 4 weeks and then doubled, corresponding to the standard adult dose of 2 × 125 mg d⁻¹. Sildenafil dosage was 0.5 mg kg⁻¹ three to four times per day. Both drug regimens were to be individually adjusted if necessary to limit side effects such as impairment of liver function (bosentan) or vision disturbances (sildenafil), respectively.

Clinical assessment and laboratory values

Patients had an extensive diagnostic work-up to define the type and severity of PAH, including clinical examination

with NYHA classification, measurement of transcutaneous oxygen saturation and heart rate. All patients had standard laboratory tests on haematology, chemistry and liver enzymes before the start of combination therapy and then at monthly intervals.

Echocardiography

Right and left ventricular function was assessed by measuring the echocardiographic end-systolic and end-diastolic areas in the apical four-chamber view with calculation of ejection fraction. The maximal tricuspid and pulmonary regurgitant jet velocity was measured by determining the peak regurgitant velocity in the continuous-wave Doppler flow profile obtained from the cardiac apex and expressed as gradients in mmHg without correction for (unknown) central venous pressure.

Exercise tolerance

In the adult patients, exercise capacity was evaluated with the unencouraged 6-MWT. In those patients older than 6 years, complementary cardiopulmonary exercise testing was performed and consisted of a bicycle or treadmill ramp protocol with a resting period, an exercise load which was increased by 15 Watt min^{-1} , and was continued until exhaustion in both surgically corrected and Eisenmenger patients, tolerating marked transcutaneously measured desaturations in the latter group. For monitoring, cardiopulmonary measurements were continued during recovery and until return of all parameters to baseline. Maximum exercise parameters were determined as the last 15-second average, and submaximum exercise parameters (slope of min ventilation (V_E ; L min^{-1}) versus carbon dioxide production (V_{CO_2} ; L min^{-1}) were calculated by using the entire data set during exercise.

Cardiac catheterization

Haemodynamic assessment of pulmonary vascular pressures was performed either as an initial diagnostic procedure or in patients where the risk of cardiac catheterization deemed acceptable; it was done by right heart catheterization including pharmacological testing for pulmonary vascular responder status using inhaled oxygen together with inhaled NO and nebulized iloprost. In patients with corrected heart disease, cardiac output was measured using conventional thermodilution, and pulmonary vascular resistance was calculated using standard formulas. In patients with the Eisenmenger syndrome, pulmonary vascular resistance was either expressed as a relation to systemic vascular resistance ($R_p : R_s$), or it was calculated on the basis of the Fick principle using measured resting oxygen consumption. Invasive follow-up was not performed in patients with post-operative persisting PAH when a clear tricuspid regurgitation jet allowed for satisfactory

echocardiographic measurements, or in Eisenmenger patients with unrestricted transmission of systemic pressures to the pulmonary circulation.

Statistical analysis

Data compared consisted of those obtained before bosentan treatment (baseline), and those obtained after at least six months of treatment (end of observation). All values are presented as mean $\pm$ standard deviation. The effect of the bosentan treatment was evaluated using only pairs of values in each patient (baseline value, end of observation value) for the two-tailed, paired *t*-test. A *P*-value < 0.05 was considered to be statistically significant.

Results

Patients and length of follow-up

Eleven consecutive patients were enrolled. Patient median age was 12.9 years (range 5.5–54.7 years). Origin of PAH was: idiopathic ($n = 4$), secondary to congenital heart disease (ventricular septal defect, $n = 2$; complete endocardial cushion defect, $n = 1$; aortopulmonary window, $n = 1$), chronic pulmonary thromboembolism (CTEPH; $n = 1$), and radiotherapy ($n = 1$). Mean doses given were $2.30 \pm 0.6 \text{ mg kg}^{-1}$ for bosentan and $2.1 \pm 0.9 \text{ mg kg}^{-1}$ for sildenafil. Concomitant medication included phenprocoumon, amlodipine, acetyl salicylic acid, captopril, spironolactone, furosemide, digoxin, clopidogrel, hydrochlorothiazide/triamteren, and hydroxyurea. Mean follow-up time was 1.1 years (range 0.5–2.5 years). No major side effects were noted. Specifically, liver function tests and blood pressure remained within normal limits. One patient died of sudden death elsewhere (Table 1, Pat. 3).

Clinical status, exercise tolerance and haemodynamic parameters

Most patients were in NYHA functional class III. Clinical improvement was about one NYHA class (mean 2.8 ± 0.4 – 1.6 ± 0.8 , $P = 0.001$), which was associated with an increase of transcutaneous oxygen saturation (89.9 ± 9.9 – $92.3 \pm 7.1\%$; $P = 0.037$), maximum oxygen uptake (18.1 ± 6.8 – $22.8 \pm 10.4 \text{ mL kg}^{-1} \cdot \text{min}$; $P = 0.043$), and 6-minute walking distance (351 ± 58 – $451 \pm 119 \text{ m}$; $P = 0.039$). Mean pulmonary arterial pressure measured invasively decreased (62 ± 12 – $46 \pm 18 \text{ mmHg}$; $P = 0.041$), and resting heart rate normalized from a mean of 94.7 ± 14.4 – 84.5 ± 12 beats per min ($P = 0.034$). Right ventricular systolic pressure tended to decline under treatment both measured by echocardiography (from 86 ± 31.4 to $71 \pm 32.0 \text{ mmHg}$; $P = 0.054$) and measured invasively by cardiac catheterization (101 ± 17.2 – $80 \pm 19.9 \text{ mmHg}$; $P = 0.088$).

Table 1 Patient data and medication

Patient	Cause of PAH	age/years	kg	treatment/years	Sildenafil/kg	Bosentan/kg
1	CHD1	5.5	18.4	1.5	1.6	1.6
2	CHD2	6.0	18.0	1.5	4.2	2.2
3	idiopathic	6.0	20.7	0.4	1.8	3
4	idiopathic	6.4	27.0	0.5	2.8	2.3
5	CHD3	7.1	22.4	2.5	1.8	2.8
6	CHD3	12.9	30.0	1.0	2.5	3.1
7	post-radiogenic	14.1	27.1	0.5	2.8	2.3
8	CHD4	17.5	47.5	0.4	0.9	1.3
9	CTEPH	24.0	110.7	1.8	2.5	2.3
10	idiopathic	44.3	78.0	1.4	1.6	1.6
11	idiopathic	54.7	80.0	0.5	0.9	3.1
Mean		18.1	43.6	1.1	2.1	2.3
Median		12.9	27.1	1.0	1.8	2.3

Diagnoses, body weight and doses given for 11 patients. Values are presented as means $\pm$ SD, medians and ranges. CHD1–4 = multiple VSD, atrioventricular septal defect, single VSD, and aortopulmonary window, respectively; CTEPH, chronic thromboembolic arterial hypertension; Concomitant medication included digoxine (Pat. 1), acetyl salicylic acid (Pat. 2,8), captopril, spironolactone, furosemide (Pat. 2), amlodipine (Pat. 4), phenprocoumon (Pat. 7,9), clopidogrel, hydrochlorothiazide/triamteren (Pat. 10) and hydroxyurea (Pat. 11). PAH, pulmonary arterial hypertension; BW, body weight.

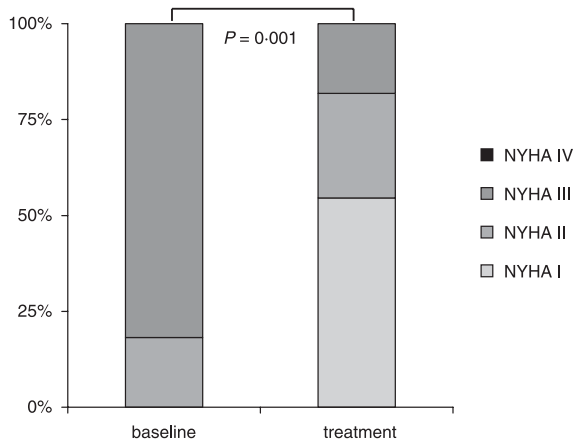


Figure 1 Improvement of clinical status (New York Heart Association class) in 11 patients in response to combination therapy. Values are given as per cent of total patient number, and the different grey shades refer to the different NYHA classes.

Discussion

In a cohort of 11 children and adults with pulmonary arterial hypertension of different origins, we observed an improvement in clinical status, exercise capacity, and haemodynamics in response to a combination treatment of oral bosentan and sildenafil. These findings suggest that this combination therapy is safe and may be effective in different forms of PAH.

None of our patients was in a NYHA class IV or requiring intravenous prostanoids or a more intensive treatment. However, while in our adult patients, the combination of

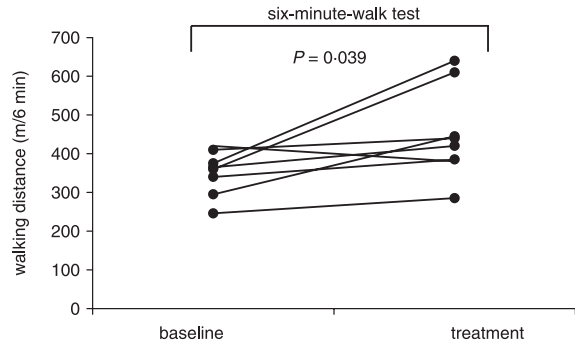


Figure 2 Improvement of six-minute walking distance at the beginning and at the end of the observation period with bosentan/sildenafil combination treatment in eight patients.

agents had the aim to provide a most effective treatment for NYHA class III symptoms, in the children with milder symptoms, the intention was more focused on the prevention of further progression of the disease. So, at the time when our patients presented, bosentan was the only oral treatment approved for pulmonary arterial hypertension, which includes, by definition, idiopathic PAH together with PAH due to congenital heart disease. Recently, we have shown that bosentan is safe and is of clinical benefit in both children and adult patients with congenital heart disease. Sildenafil was chosen as the other oral drug because of its proven efficacy profile in different types of PAH – post-operative in children, chronic idiopathic and congenital heart disease related in children and adults – which has actually led to its recent approval for the treatment of PAH as well. Furthermore, there are also the practical advantages of oral drugs: they avoid the danger of line infections and

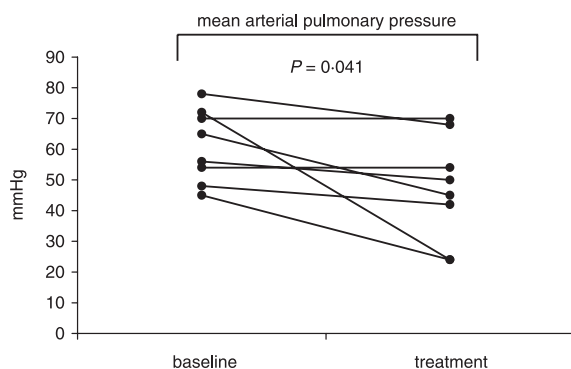


Figure 3 Improvement of mean arterial pulmonary pressure at the beginning and at the end of the observation period with bosentan/sildenafil combination treatment in nine patients.

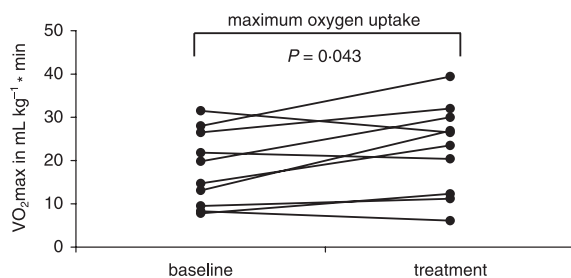


Figure 4 Improvement of maximal oxygen uptake at the beginning and at the end of the observation period with bosentan/sildenafil combination treatment in 10 patients.

rebound PAH associated with the intravenous continuous administration of prostanoids as well as the aversion or depression with which some patients react to the more impractical repeated inhalations of iloprost. These considerations appear to be especially valid in paediatric patients. Finally, the economical aspects are not without impact and have been highlighted before [27]. Depending on the exact doses applied and its effect, oral combination treatment costs approximately 75% of a treatment with inhaled iloprost and 33–20% of a treatment with intravenous prostanoids, respectively.

Our considerations for combination treatment were different from the recently reported concept of step-by-step, goal-oriented therapy described by Hoeper [28]. In that paper, a therapeutic goal (6-MWT > 380 m, VO_2max > $10.4 \text{ mL kg}^{-1} \cdot \text{min}$, and maximum systolic pressure during exercise > 120 mmHg) was set to be achieved by a stepwise crescendo of new therapeutic options (bosentan, sildenafil, inhaled and intravenous iloprost). This crescendo-like therapeutic approach is based on the same logic as the treatment of systemic arterial hypertension with a pre-defined systemic blood pressure level being the therapeutic goal. However, although an improved survival was demonstrated for patients compared with 'historical' patients treated without this approach and the new agents, this study

Table 2 Results of bosentan/sildenafil combination treatment

	<i>n</i>	Before treatment	End of observation	<i>P</i> -value
Clinical status				
SatO ₂ in percentage	11	89.9 ± 9.9	92.3 ± 7.1	0.037
HR per min	11	94.7 ± 14.4	84.5 ± 12.0	0.034
NYHA class	11	2.8 ± 0.4	1.6 ± 0.8	0.001
Exercise capacity				
VO ₂ max in mL/kg * min	10	18.1 ± 6.8	22.8 ± 10.4	0.043
6-MWT in m	8	351 ± 58	451 ± 119	0.039
Echo				
RVSP in mmHg	9	86 ± 31	71 ± 32	0.054
Invasive testing				
RVSP in mmHg	9	101 ± 17	80 ± 20	0.088
mPAP in mmHg	9	62 ± 12	46 ± 18	0.041

Clinical status, exercise capacity, and haemodynamic values before the start of the treatment and at the end of the combination period, during which therapy with bosentan and sildenafil was given as indicated in Table 1. Values are presented as means ± SD. SatO₂, transcutaneous oxygen saturation; HR, heart rate; NYHA-class, clinical state according to the classification of the New York Heart Association; VO₂max, maximum oxygen uptake; 6-MWT, 6-minute walking test; RVSP, right ventricular systolic pressure; mPAP, mean pulmonary arterial pressure.

does not provide an insight as to which of the new drugs is more effective and whether any combination is more effective than any one drug alone.

However, there is multiple evidence that there is a justified 'rescue' role for a combination therapy in PAH: patients with iPAH who were on bosentan treatment with insufficient clinical results experienced a marked and sustained improvement when sildenafil was added to the treatment [27]. The same benefit from additional sildenafil was shown acutely and chronically in patients who were on chronic iloprost inhalation [29–31], and seems to be valid also for the combination with other prostanoids (intravenous epoprostenol [32–35], oral beraprost [36]).

In our study, we combined these two oral agents, bosentan and sildenafil, aiming at a targeted treatment effect on PAH while minimizing the side effects by using different intracellular modes of action. Sildenafil inhibits CYP3A4 activity and thus leads to an increased bosentan plasma concentration [37]. It is unknown whether this additionally increases the potential of bosentan to cause liver damage. We did not observe increased transaminases levels in our patients. This corresponds to the findings of an extensive bosentan post-marketing surveillance in about 5000 patients, in which the rate and pattern of potential safety signals, specifically aminotransferase elevations in a combination therapy bosentan and sildenafil (*n* = 213) was not substantially different from patients on bosentan who were not taking sildenafil [38]. On the other hand, sildenafil peak plasma level and area under the curve after the administration of a single dose of 100 mg oral sildenafil is reduced to a third in the presence of chronic bosentan treatment and subsequent activation of the hepatic CYP3A4 [37], so that a three-fold

sildenafil dose might be justified in chronic bosentan patients. Conversely, in another study in healthy volunteers, sildenafil three times daily increased bosentan plasma levels by 50% [39]. Clearly, more data are needed in this area to provide safe evidence for future treatment strategies.

Limitations

Given the small sample size in our cohort, we were not able yet to determine any treatment advantage according to diagnosis. Also, the study was not designed to show the superiority of the combination treatment versus a monotherapy. Clearly, larger studies are needed to show the incidence of possible unfavourable interactions of sildenafil and bosentan, as well as its effectiveness in terms of reverse remodelling of the pulmonary vascular bed, especially in children. Finally, part of the response to the combination might be an increased pulmonary arterial blood flow due to right ventricular recompensation which leads to almost unchanged pulmonary arterial pressure; however, flow was not assessed during cardiac catheterization in our patients. This issue remains an important consideration and will be the focus of further studies in this area.

Conclusion

Our initial experience with a combination of oral bosentan and sildenafil in a group of patients with different forms of PAH suggests that this treatment strategy is efficient and safe. Further trials with larger patient numbers are necessary to provide evidence for clinical and therapeutic decisions in the diverse forms of PAH.

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