Introduction and objectives. Pulmonary arterial hypertension carries a poor prognosis in both adult and pediatric patients. Current understanding of the mechanisms underlying pulmonary arterial hypertension has enabled the rapid development of appropriate drugs, such as endothelin receptor antagonists and 5-phosphodiesterase inhibitors, that can be administered orally and which are generally well tolerated. The aims of the present study were to evaluate functional class and exercise capacity following long-term treatment with sildenafil or bosentan in patients with idiopathic pulmonary arterial hypertension and Eisenmenger’s syndrome and to compare results in the 2 groups.

Methods. Seven patients were included in the pulmonary arterial hypertension study, and diagnoses of idiopathic pulmonary arterial hypertension were confirmed. Five patients were treated with sildenafil, while 2 received bosentan. The 5 patients with a non-restrictive ventricular septal defect and pulmonary arterial hypertension were treated with sildenafil. In 1 patient, bosentan was added to the sildenafil.

Results. Both sildenafil and bosentan significantly improved exercise capacity in patients with idiopathic pulmonary arterial hypertension. The treatment effect was less in those with Eisenmenger physiology. Although the improvement in World Health Organization functional class was greater in patients with idiopathic pulmonary arterial hypertension, it was significant in both groups.

Conclusions. Long-term treatment with sildenafil and bosentan improved both exercise capacity and functional class in patients with idiopathic pulmonary arterial hypertension and in those with hypertension due to congenital heart disease. The changes were more marked in patients with idiopathic pulmonary arterial hypertension.

Key words: Pulmonary arterial hypertension. Sildenafil. Bosentan. Eisenmenger’s syndrome.

Tratamiento con sildenafil y/o bosentán en niños y jóvenes con hipertensión arterial pulmonar idiopática y síndrome de Eisenmenger

Introducción y objetivos. La hipertensión arterial pulmonar tiene mal pronóstico en pacientes adultos y pediátricos. El conocimiento actual de los mecanismos que condicionan la hipertensión arterial pulmonar ha permitido descubrir medicamentos como los antagonistas de los receptores de la endotelina e inhibidores de la 5-fosfodiesterasa, administrables ambos por vía oral y generalmente bien tolerados. En este estudio se valora la capacidad funcional y la tolerancia al ejercicio en el tratamiento a largo plazo con sildenafil o bosentán en pacientes con hipertensión arterial pulmonar idiopática y síndrome de Eisenmenger, y se comparan los resultados en ambos grupos de pacientes.

Métodos. Siete pacientes fueron incluidos en el protocolo de estudio de la hipertensión arterial pulmonar, y en ellos se confirmó el diagnóstico de hipertensión arterial pulmonar idiopática. Se trató con sildenafil a 5 pacientes y con bosentán a 2. Cinco pacientes con comunicación interventricular no restrictiva e hipertensión arterial pulmonar fueron tratados con sildenafil. En uno de ellos se añadió bosentán al tratamiento con sildenafil.

Resultados. El sildenafil y el bosentán mejoraron significativamente la capacidad de ejercicio en pacientes con hipertensión arterial pulmonar idiopática. El efecto fue menor en los pacientes con fisiología de síndrome de Eisenmenger. La mejoría en la clase funcional de la Organización Mundial de la Salud fue mayor en los pacientes con hipertensión arterial pulmonar idiopática, aunque fue significativa en ambos grupos.

Conclusiones. El tratamiento a largo plazo con sildenafil y bosentán mejora la capacidad de ejercicio y la clase funcional en la hipertensión arterial pulmonar idiopática y debida a cardiopatías congénitas. Los cambios son más llamativos en los pacientes con hipertensión arterial pulmonar idiopática.
INTRODUCTION

Idiopathic pulmonary arterial hypertension (IPAH) and pulmonary arterial hypertension (PAH) associated with congenital heart disease, are anatomically similar despite the much more grave prognosis associated with the former. Their etiopathogenesis is unknown, as are the factors that lead to their appearance. It is clear, however, that both forms of this same disease are associated with lesions in the small pulmonary arteries, including endothelial abnormalities, a reduction in the size of the lumen, vasoconstriction, thrombosis, vascular proliferation, and remodeling of the different wall layers, all of which leads to an increase in pulmonary vascular resistance and the failure of the right ventricle.

Our present knowledge of these anatamopathological abnormalities, including the associated reduction in the production of endogenous vasodilators (such as prostacyclin and nitric oxide [NO]) and the increase in the synthesis of vasoconstrictors (such as endothelin 1 and thromboxane A2), permits the use of medications with potent vasodilatory and anti-proliferative effects, such as analogs of prostacyclin (epoprostenol, iloprost, treprostinil, beraprost), endothelin receptor antagonists (bosentan, ambrisentan, sitaxsentan), and 5-phosphodiesterase inhibitors (sildenafil). The use of these drugs has reduced the high mortality rate once seen in both adults and children, and has changed the natural progression of the disease, clearly improving patient prognosis.

In the present work, patients with IPAH (group A) and patients with PAH associated with congenital heart disease (group B) were treated with sildenafil or bosentan and their responses studied over a follow-up period of two years.

METHODS

This study was performed over the period January 2003 - January 2006. The study subjects were 12 patients who were divided into two groups: group A, composed of seven patients, six with IPAH and one with PAH plus a small, residual, restrictive ventricular septal defect (VSD) (five patients in functional class III, one in functional class II, and one in functional class IV according to WHO criteria), and group B, made up of five patients with Eisenmenger’s syndrome plus complex heart disease involving a non-restrictive VSD (all in functional class III) (Table 1).

The medical history of all patients was examined, and all were subjected to an electrocardiogram (ECG), a chest x-ray, transthoracic echocardiography, ventilation-perfusion pulmonary scintigraphy, computed tomography, magnetic resonance angiography (MRA), antinuclear antibody, tests for serological markers of hepatitis B and C and HIV, hypercoagulability studies, and liver and thyroid function tests. Children over 5 years of age were also subjected to a six-minute walk test (6MWT) and pulmonary function testing.

All patients in group A underwent a hemodynamic study at baseline and after acute vasodilation with NO. Oxygen pressure and saturation were determined both at baseline and after NO administration and the pulmonary and systemic resistances calculated along with the pulmonary and systemic cardiac output (Table 2). The acute vasodilation test was performed by administering 10-20 ppm NO with O2. A favorable acute response was defined by a fall in the mean pulmonary arterial blood pressure (mPAP) of at least 10 mm Hg and it was located below 40 mm Hg.

Of the five patients with Eisenmenger’s syndrome (group B), two were catheterized at another center and three at our own. All underwent the acute vasodilation test.

Five patients of group A received sildenafil 1 or 2 mg/kg divided into three doses. Two children with IPAH were administered bosentan; one received an initial dose of 31.25 mg twice per day for one month followed by a maintenance dose of 62.5 mg twice per day (the subject weighed <40 kg). The other received 62.5 mg twice per day for one month, and 125 mg twice per day as a maintenance dose (the subject weighed >40 kg).

The decision to begin treating the members of group B was taken due to a worsening of their symptoms, including dyspnea and/or repeated hemoptysis. All were treated with sildenafil 50 mg every 8 h. One patient also received bosentan in an attempt to optimize her clinical condition before surgery for scoliosis.

All the above medications were administered after receiving informed consent; sildenafil and bosentan were used as a compassionate treatment after approval by the Ministry of Health.

All patients were clinically evaluated once every three months for a minimum of two years; all were subjected to an ECG, echocardiography, the 6MWT, measurements of oxygen saturation before, during and after the 6MWT, the recording of their Borg dyspnea index, and the assessment of their WHO functional class. Liver enzyme levels were measured every two months in patients treated with bosentan.

The Wilcoxon test was used to compare paired means for pulmonary blood pressure before and after NO

ABBREVIATIONS

6MWT: 6-minute walk test
IPAH: idiopathic pulmonary arterial hypertension
PAH: pulmonary arterial hypertension
ASD: atrial septal defect
VSD: ventricular septal defect

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RESULTS

Table 1 shows the baseline conditions of all 12 patients. The group A subjects included two children with an intracardiac shunt: patient nº 1 with an atrial septal defect (ASD), and nº 7 with a residual restrictive VSD that had been surgically corrected 10 years earlier. The patients of group A were aged between 1 and 16 years (mean 9.57 years; median 11 years; boys n=4, girls n=3). Patient no. 1, who presented with a functional class of IV, was too young to undertake the 6MWT. The remainder, all with IPAH, covered 394 (55) m in this time (median 390 m). Patients 5 and 6 covered 450 m in the six minutes allowed despite their high baseline pulmonary pressure. After two years of treatment they were able to cover 600 m in the same time.

The five group B patients all suffered a large, non-restrictive shunt: four had a complete atrioventricular canal (one with a double outlet right ventricle), and one with a D-transposition of the great arteries plus a VSD. The age of these patients (two males, three females) varied from 12 to 31 years (mean 19.8 years; median 19 years). These patients covered 286 (117) m (median 240 m) at baseline in the 6MWT. The patient with D-transposition of the great arteries underwent a palliative arterial switch operation before starting treatment.

Acenocumarol was provided to all group A patients; no anticoagulants were given to group B patients. The average pulmonary systolic blood pressure of the group A patients was 90.4 (27.5) mm Hg (median 85 mm Hg), the average pulmonary diastolic pressure was 46.8 (17.3) mm Hg (median 43), and the average pulmonary mean blood pressure was 61.5 (20.5) mm Hg (median 55 mm Hg). The mean pulmonary arteriolar
resistance was 14.7 (7.7) UW/m² (median 12.2 UW/m²). The mean \(O_2\) saturation was 94.2 (2%) (median 95%).

The mean pulmonary systolic blood pressure in the group B patients was 97.8 (16.4) mm Hg (median 100 mm Hg), the average pulmonary diastolic pressure was 58.8 (8.5) mm Hg (median 57 mm Hg) and the average pulmonary mean blood pressure was 73.6 (13.5) mm Hg (median 71 mm Hg). The mean pulmonary arteriolar resistance was 15 (3.4) UW/m² (median 15 UW/m²). The mean \(O_2\) saturation was 89 (1.6%) (median 89%) (Tables 1 and 2).

The acute vasodilation test with NO returned negative results for all patients (Figure 1).

The response to exercise improved significantly in both groups, but more so in the group A patients. The latter covered a mean 394.2 (55.2) m (median 390 m) at baseline, 464.2 (38.3) m (median 470 m) at six months, and 526.7 (44.6) m (median 510 m) at two years (Figure 2). The group B patients covered a mean of 286 (117) m (median 240 m) at baseline, 321 (109) m (median 260 m) at six months, and 393 (124) m (median 340 m) at two years (Figure 3).

The functional class of group A patients had improved notably and significantly at two years; no group A patient fell into functional class III or IV at this time (Figure 4). The improvement experienced by the group B patients was less notable although still significant. Three patients with an atrioventricular canal improved from functional class III to functional class II. One patient failed to change functional class, and another did so only after one year of treatment (Figure 5).

Echocardiographic monitoring (tricuspid regurgitation, left ventricular eccentricity index, Tei index, and the right atrial area index) was performed periodically; no statistically significant variations were detected. The mean baseline pulmonary blood pressure, measured by echo-Doppler, was 91.2 (20.3) mm Hg (median 92 mm Hg); at two years this was 86.2 (19) mm Hg (median 86 mm Hg) (Figure 6). One year after beginning treatment, three patients of group A were subjected to a hemodynamic study. No significant changes were detected.

<table>
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<th>Patient</th>
<th>PAR, UW/m²</th>
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<th>PCI, L/min/m²</th>
<th>S/D/M, UW/m²</th>
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<th>SCI, L/min/m²</th>
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*PCI indicates pulmonary cardiac index; SCI, systemic cardiac index; PAP, pulmonary arterial pressure; SAP, systemic arterial pressure; PAR, pulmonary arteriolar resistances; SR, systemic resistances; S/D/M, systolic pressure, diastolic pressure, mean pressure.

![Figure 1](http://www.revespcardiol.org)  
**Figure 1.** Mean baseline pulmonary arterial blood pressure and the same after the vasodilation test with inhaled NO.

![Figure 2](http://www.revespcardiol.org)  
**Figure 2.** Change in six-minute walk results in patients with idiopathic pulmonary hypertension. 6MWT indicates six-minute walk test. IPAH, idiopathic pulmonary hypertension.

**TABLE 2. Baseline Hemodynamic Values***

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Since magnetic resonance was introduced for the study of PAH by Wilkins et al. in 2005 (examining the reduction of right ventricular myocardial mass in patients treated with sildenafil) we have been reviewing our initial patient data. Sildenafil or bosentan treatment was maintained for a minimum of two years. As well as receiving vasodilatory treatment, all group A patients received acenocumarol; two also received digoxin and diuretics. The group B patients did not receive acenocumarol and all received digoxin and diuretics (Table 1).

No patient suffered important side effects. Before starting treatment, two group B subjects suffered hemoptysis, and three experienced increased dyspnea. The former patients did not experience further hemoptysis during the two years of treatment, and the dyspnea suffered by the latter three diminished. One 11 year-old and one 12 year-old girl in group A experienced menorrhagia after one year of treatment. Symptoms diminished after treating their anemia and regulating their menstruation. None of the patients who received bosentan suffered modifications of their liver enzyme levels.

**DISCUSSION**

With the appearance of epoprostenol (an analog of prostacyclin that can only be administered intravenously) for the treatment of IPAH, the quality of life, survival and prognosis of patients with this disease have improved. Iloprost and treprostinil, both of which can be administered subcutaneously or by inhalation, also improve the capacity to undertake exercise and quality of life. However,
all of these administration routes have been associated with secondary effects, sometimes serious.

The year 2002 saw the advent of bosentan\textsuperscript{11-14} and sildenafil\textsuperscript{15-19} administration in Europe; these agents have the great advantage that they can be given orally. Bosentan is a non-selective antagonist of endothelin receptors, which are present in large numbers in patients with PAH. Its use in such patients was found to improve their functional class\textsuperscript{11,20}; some authors have used it to treat patients with Eisenmenger's syndrome, achieving an improvement in functional class with no secondary effects.\textsuperscript{21} The Breathe-5 study is the most important in this area published to date.\textsuperscript{22}

Sildenafil inhibits 5-phosphodiesterase in the lung, and impedes the degradation of cyclic guanosine monophosphate (cGMP), thus increasing the activity of endogenous NO. It has a potent vasodilatory action at the lung.\textsuperscript{23} Many authors have described its use in patients with IPAH and in others with PAH plus congenital heart problems.\textsuperscript{15,18,23-25} The largest randomized study was that of Galié et al.\textsuperscript{26}

Before the start of the present study, two patients with IPAH aged 12.5 years and with a functional class of IV were administered iloprost. Unfortunately, both died, the first one month after undergoing lung transplantation at our center, and the other while awaiting transplantation at another center.

Patient no. 1 (group A), an infant who fell into functional class IV, was administered sildenafil, and the in-hospital improvement observed was so remarkable that this treatment was maintained after discharge. However, the results may not have been so spectacular had no ASD existed.

Sildenafil was used more often than bosentan given the possibility of using small doses for suckling babies, its availability in solution, the possibility of its intravenous administration,\textsuperscript{16} and its lower cost.\textsuperscript{18,27} In two boys aged nine and 12 years, bosentan was used to avoid the possible secondary effects of sildenafil. The results achieved with both agents after six months of treatment were spectacular, their benefit becoming greater with usage (Figure 2). The patient with D-transposition of the large arteries plus a VSD who underwent palliative arterial switch was administered bosentan plus sildenafil given the poor response observed when the latter was given alone; a synergistic effect was hoped for. The patients of group B suffered complex heart disease and had large, non-restrictive VSD, and their response to treatment was similar. Patient no. 7, however, a girl with PAH and a residual restrictive VSD, showed a much stronger response. Her PAH appeared several years after corrective surgery. These factors led to her inclusion in group A.

The echocardiographic assessments undertaken at the three-monthly appointments involved the determination of tricuspid regurgitation, the left ventricular eccentricity index, the right atrial area index, and the Tei index.\textsuperscript{28} In agreement with other authors,\textsuperscript{12} no uniform nor statistically significant effect was seen over the two years of treatment (Figure 6).

One year after starting treatment, three group A patients were catheterized; no significant improvements were seen in the hemodynamic variables measured. We no longer catheterize the right ventricle to evaluate response to treatment; this invasive technique is only indicated in the case of clinical deterioration and/or when a change in treatment is being considered.

 Able to predict morbidity/mortality, the 6MWT is the most important of all tests for arriving at a prognosis for a patient with PAH.\textsuperscript{29} The members of both groups of present patients showed improvements in their 6MWT results, although those shown by the members of group A were larger. Improvements in functional class also were evident in all patients, although more-so in members of group A.

CONCLUSIONS

In our experience (which agrees with that of other authors), patients with IPAH or PAH associated with congenital heart problems show improvements with the new pulmonary vasodilatory agents available. Patients with IPAH falling into functional class III, with hemodynamic parameters suggestive of severe PAH and with a negative acute vasodilation test, require early treatment if the chances of survival are to be improved. In contrast, in patients with Eisenmenger’s syndrome, treatment is indicated when undesirable clinical signs are noticed or the disease progresses. In both types of patient, sildenafil and bosentan improve the capacity to undertake exercise and quality of life (although the response is more spectacular in patients with IPAH).

Clearly, this kind of quasi-experimental study, with values recorded before and after treatment, can be affected by factors that could modify the course of events independent of the treatment. However, the present evidence indicates that the patients with IPAH (at least) may well have died without treatment with these pulmonary vasodilators, and that the treatment was likely responsible for the improvements seen. Further work with larger number of patients is needed to confirm the present results.

REFERENCES

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