Clinical Efficacy of Sildenafil in Patients With Pulmonary Hypertension in Functional Class II or III

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OBJECTIVE: To assess the efficacy of treatment with sildenafil monotherapy in patients with pulmonary hypertension. PATIENTS AND METHODS: An observational study was undertaken in 11 patients with pulmonary hypertension in functional class II or III who received treatment with sildenafil (150 mg/day). Seven of the patients had inoperable chronic thromboembolic pulmonary hypertension and 4 had pulmonary arterial hypertension. To assess treatment response, the following parameters were assessed during follow-up at 3, 6, and 12 months: exercise tolerance in the 6-minute walk test, change in functional class, and systolic pulmonary arterial pressure measured by echocardiography.

RESULTS: We observed a significant improvement in exercise tolerance, as shown by increased 6-minute walk distance after 3, 6, and 12 months of treatment (increases of 20, 67, and 95 m, respectively). All patients showed an improvement in functional class. The results of echocardiography did not reveal statistically significant differences in systolic pulmonary arterial pressure between baseline and 6 or 12 months of treatment.

CONCLUSIONS: The results of this study confirm that sildenafil is an effective drug for the management of pulmonary arterial hypertension and inoperable chronic thromboembolic pulmonary hypertension both in the short term and medium to long term, and that the drug is well tolerated and shows few side effects.

Key words: Pulmonary hypertension. Inoperable chronic thromboembolic pulmonary hypertension. Sildenafil. Clinical efficacy.

Introduction

Pulmonary hypertension is defined as an increase in mean pulmonary arterial pressure (mPAP) to more than 25 mm Hg at rest or more than 30 mm Hg during exercise, in the absence of left heart disease. The World Health Organization applies a 5-category descriptive classification based on the underlying mechanism.

Group I—pulmonary arterial hypertension (PAH)—includes processes of differing etiology but that share common pathophysiologic changes. This group includes idiopathic and familial forms; pulmonary hypertension due to drugs or toxins or secondary to collagen vascular disease, human immunodeficiency virus (HIV) infection, glycogen storage disease, hemoglobinopathies, portal hypertension, congenital systemic-to-pulmonary shunts, pulmonary venoocclusive disease, or pulmonary capillary hemangiomatosis; and persistent pulmonary hypertension of the newborn. Group IV—chronic thromboembolic pulmonary hypertension (CTEPH)—includes cases due to thromboembolic conditions affecting either the proximal or distal pulmonary arteries.
A progressive increase in pulmonary vascular resistance has been observed in patients with disease of the peripheral branches, along with some pathology findings similar to those seen in idiopathic PAH. Thromboendarterectomy is not indicated in this patient group and treatment similar to that used in patients with PAH should be offered.\(^2\)

Irrespective of the cause of pulmonary hypertension, there is rapid proliferation of the vascular endothelium, leading to right ventricular failure and death.\(^3\)

The principal mechanism implicated in the pathogenesis of the disease is endothelial cell dysfunction, which leads to reduced production of endogenous vasodilators (prostacyclin and nitric oxide) and increased synthesis of vasoconstrictors such as endothelin-1 and thromboxane \(\text{A}_2\) (Figure 1). These findings have led to the development of drugs such as the prostacyclin analogs epoprostenol,\(^4\) iloprost,\(^5\) and treprostinol,\(^6\) which have potent vasodilatory and antiproliferative effects. More recently, selective and nonselective endothelin receptor antagonists such as bosentan\(^7\) and sitaxsentan\(^8\) have been introduced on the market. Although their introduction for use in the treatment of PAH has led to a substantial improvement in patients’ quality of life and survival, some of these drugs present administration difficulties and possible side effects, and they are generally expensive.

The therapeutic potential of the nitric oxide pathway has been less explored. Sildenafil, a drug with a potent pulmonary vasodilatory effect,\(^9\) acts through this pathway by inhibiting phosphodiesterase-5 and preventing breakdown of cyclic guanosine monophosphate, leading to an increase in the activity of endogenous nitric oxide. It is an easily administered drug that is well tolerated and displays a good relationship between cost and efficacy, which is beginning to be demonstrated in controlled trials.\(^10\)

The aim of this study was to describe the clinical and functional characteristics of patients treated in our hospital for PAH and CTPH in functional class II or III along with their response to sildenafil monotherapy. The patients were studied in a hospital-based pulmonary hypertension clinic and were therefore not affected by the bias or selection associated with enrollment in a clinical trial.\(^11\)

### Patients and Methods

Between January 2003 and September 2005, 30 patients with PH attended our clinic. Eleven consecutive patients in functional class II or III were selected for treatment with sildenafil. The drug was prescribed for compassionate use following approval by the Spanish Ministry of Health and Consumer Affairs. The study protocol encompassed clinical assessment and blood analysis, including hematocrit, serology, and analysis of autoimmunity and hypercoagulability. The imaging techniques used were chest radiography, ventilation-perfusion lung scintigraphy, high-resolution computed tomography, computed tomography angiography, magnetic resonance angiography of the chest, and, based on clinical need, pulmonary arteriography. A complete lung function study was also performed, including a 6-minute walk test. Cardiologic assessment included electrocardiography, transthoracic echocardiography, and cardiac catheterization in all cases.

Cardiac catheterization was undertaken under stable conditions in all patients and assessed the following parameters: systolic pulmonary artery pressure (sPAP), diastolic pulmonary arterial pressure (dPAP), mPAP, pulmonary capillary pressure, right atrial pressure, cardiac output, pulmonary vascular resistance, and systemic and pulmonary oxygen saturation.

Acute vasodilator challenge was performed with prostacyclin in all cases. Until July 2004, the results of the test were considered positive if a reduction of more than 20% in mPAP was observed,\(^12\) but from that date onwards, we followed international consensus\(^13\) that a positive response corresponded to a reduction of at least 10 mm Hg in mPAP, and that this pressure remained at 40 mm Hg or less, without deterioration of cardiac output. All patients received anticoagulation therapy with acenocoumarol. 4 received treatment with digitals, and 7 with furosemide. The patients with CTPH were not considered eligible for thromboendarterectomy because they did not present central thrombi. One patient with CTPH was prescribed continuous home oxygen therapy. Sildenafil was prescribed as monotherapy without addition of other vasodilators. Treatment was initiated during a brief period of hospital admission for blood pressure monitoring and pulse oximetry. Sildenafil was provided at an initial dose of 25 mg every 8 hours, which was increased to 50 mg every 8 hours in the following 48 to 72 hours. Clinical follow up, blood testing, and a 6-minute walk test were performed every 3 months, while echocardiography was performed every 6 months.

Statistical analysis of the data was carried out with Prism, version 3.0. Results are expressed as medians (interquartile range [IQR]). The Wilcoxon test was used to assess differences between data obtained before and after treatment. Differences were considered statistically significant when the value of \(P\) was less than 0.05.

### Results

#### Baseline Characteristics

Of the 11 patients who received treatment, 2 presented idiopathic PAH, 1 had PAH associated with mixed connective tissue disease, 1 PAH associated with HIV infection, and 7 CTPH with involvement of the peripheral
arteries that was not suitable for surgery. One patient with CTPH had a diagnosis of hereditary spherocytosis, for which splenectomy had been performed 35 years earlier. In the remaining patients, no other procoagulant factors were detected during assessment of hypercoagulability (table). The study group contained 5 women and 6 men. The median (IQR) age of the patients was 58 (41.5-70.5) years. The median age of the patients with PAH was 25.5 (12-47) years, lower than the median age of 64 (59-72) years in the group of patients with CTPH. Prior to initiating the treatment, 5 patients were in functional class II and 6 in class III. Exercise tolerance was assessed with the 6-minute walk test. Under baseline conditions, the patients walked a median distance of 390 (300-460) m.

The magnitude of hypertension calculated using transthoracic echocardiography was severe, with a median systolic pressure of 83 (71-114.5) mm Hg. Hemodynamic data were as follows: sPAP, 80 (45-89) mm Hg; mPAP, 47 (33-55) mm Hg; cardiac index, 3 (1.5-3.5) L/s/m²; pulmonary vascular resistance, 936 (480-1423) dyn·s/cm⁵. The results of acute vasodilator challenge were negative in all cases.

**Treatment Response**

Following diagnosis and prescription of sildenafil, follow-up was performed in the clinic for all 11 patients over a minimum of 3 months. In 9 patients, follow-up lasted more than 6 months and in 7 patients it was continued for 1 year. Two patients continued to receive treatment for more than 2 years.

**Functional class.** The 9 patients who received treatment for more than 6 months showed an improvement in functional class, and this improvement was maintained in the 7 patients who reached 1 year of treatment. Of the 2 patients who received 3 months of treatment, 1 improved from functional class III to class II and the other remained stable.

**Response to exercise.** A continuous improvement in exercise tolerance was observed over the entire follow-up period (Figure 2). At 3 months of treatment, the median distance walked was 410 (284-510) m, an increase of 20 m compared with baseline (P=0.0002). At 6 months the improvement was 67 m (P=0.007) and at 12 months it was 95 m (P=0.015) (Figure 2).

**Hemodynamic follow-up.** Echocardiography was performed at 6-month and 12-month follow-up (Figure 3). The median estimated sPAP was 80 (65-105) mm Hg at 6 months and 67.5 (53-102) mm Hg at 12 months; thus, there was a trend towards decreasing sPAP, but this trend did not achieve statistical significance (P=0.21 and P=0.06, respectively).

**Tolerance and undesirable effects.** None of the patients presented severe side effects. One patient reported nasal congestion, which disappeared within a few weeks of treatment. In another case the treatment was suspended after 4 months due to persistent headache. That patient, who was diagnosed with CTPH with an mPAP of 56 mm Hg, remained stable with no signs of clinical deterioration following suspension of sildenafil treatment.

**Baseline Characteristics of Patients Treated With Sildenafil**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age, y</th>
<th>Diagnosis</th>
<th>sPAP (mm Hg)</th>
<th>dPAP (mm Hg)</th>
<th>dPAP echo (mm Hg)</th>
<th>NYHA</th>
<th>6MWD, m</th>
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<td>15</td>
<td>IPAH</td>
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<td>12</td>
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<td>55</td>
<td>75</td>
<td>82</td>
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<td>380</td>
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<tr>
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<td>PH-HIV</td>
<td>55</td>
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<td>440</td>
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<tr>
<td>4</td>
<td>Male</td>
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<td>CTPH</td>
<td>56</td>
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<td>115</td>
<td>II</td>
<td>480</td>
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<tr>
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<td>Female</td>
<td>55</td>
<td>CTPH</td>
<td>48</td>
<td>115</td>
<td>129</td>
<td>III</td>
<td>300</td>
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<tr>
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<td>CTPH</td>
<td>47</td>
<td>80</td>
<td>83</td>
<td>III</td>
<td>432</td>
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<tr>
<td>7</td>
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<td>47</td>
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<td>CTPH</td>
<td>70</td>
<td>106</td>
<td>136</td>
<td>II</td>
<td>410</td>
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</tbody>
</table>

*nPAP indicates mean pulmonary arterial pressure; dPAP, pulmonary arterial diastolic pressure measured by right heart catheterization; dPAP echo, pulmonary arterial diastolic pressure measured by transthoracic echocardiography; NYHA, New York Heart Association functional class; 6MWD, 6-minute walk distance; IPAH, idiopathic pulmonary arterial hypertension; PH-HIV, pulmonary hypertension associated with HIV infection; CTPH, chronic thromboembolic pulmonary hypertension; PH-MCTD, pulmonary hypertension associated with mixed connective tissue disease.
In recent years, extensive experience has been obtained with drug formulations that allow simple administration of vasodilators such as nebulized iloprost or oral bosentan. Sildenafil is a new drug with an efficacy similar to that of bosentan, as shown by Wilkins et al. in the only study published to date in which the 2 drugs were compared in the treatment of PAH. These findings, combined with the ease of administration, the limited side effects, and the low cost of the drug, contributed to our election of this treatment option. The efficacy of sildenafil in the treatment of PAH in functional classes II and III has been demonstrated in a large number of studies, in which the drug has been shown to improve hemodynamic variables, exercise tolerance, and quality of life. However, as is the case with other drugs, data are currently unavailable regarding its impact on survival. We observed a significant clinical improvement in exercise tolerance in the short-term and medium-term following initiation of sildenafil treatment. Thus, our results confirm the findings of clinical trials but in patients from day-to-day clinical practice, who are not subject to the selection requirements associated with large multinational trials. Clearly, we do not have a control group, for ethical reasons and because the focus was on the practical management of the patients, who acted as their own controls.

Treatment with vasodilators has recently been incorporated into the therapeutic options for CTPH involving the peripheral branches, either as a pretreatment prior to surgery or as a chronic treatment in nonsurgical cases. Treatment with bosentan and sildenafil leads to marked clinical improvement, with an increase in exercise tolerance and without negative repercussions on gas exchange. This was confirmed in patients who showed sustained improvements of this type.

Evaluation over the follow-up period involved assessment of improvement in functional class, exercise tolerance in the 6-minute walk test, and sPAP measured by transthoracic echocardiography. Although we demonstrated a significant and sustained improvement in exercise tolerance, we only observed a nonsignificant tendency towards reduction in the hemodynamic changes assessed by serial echocardiography, as has been reported by other authors. The 6-minute walk test is reproducible, safe, and easy to perform, and also acts as an independent prognostic factor, and therefore complements the results of echocardiography and allows more invasive methods such as right heart catheterization to be avoided. We did not perform right heart catheterization because we do not believe it should be used as a method for follow-up outside of the context of a clinical trial, instead, it should be reserved for specific situations such as changes in treatment due to clinical deterioration or inclusion on the transplant list. In terms of other parameters, classification on the basis of functional class appears not to be very objective and is subject to the interpretations of the patient and observer.

Cardiovascular magnetic resonance imaging has also been proposed for use during follow-up, although as yet with limited experience, since it provides information on the arteries and allows measurement of right ventricular...
mass. However, we envisage difficulties in incorporating this technique into health care practice. We should also mention the potential role of biological markers such as brain natriuretic peptide, which, given its usefulness, should be immediately incorporated into routine follow-up.17

In terms of the dosage of sildenafil, we administered 150 mg/d in all cases, according to proposals based on reliable experience.11,13,15-17 Nevertheless, in light of the results of the SUPER trial,12 there is reason to wonder whether a lower dose (60 mg/d) could be equally effective in patients with less severe disease. Although tolerance of the drug at a dose of 150 mg/d was good and in only 1 case was treatment suspended due to persistent headache, the use of a lower dose would lead to improved tolerance and reduction of treatment costs.

In summary, although the number of patients treated was very limited, the results of this study support sildenafil as an effective drug for the management of PAH and CTPH, both in the short-term and medium to long-term, with good tolerance and few side effects. It remains to be seen what impact these new drugs might have on survival or what advantages might be offered by combination therapy, particularly in patients with an inadequate response to the drug as monotherapy.

REFERENCES