PULMONARY HYPERTENSION

Efficacy of Oral Sildenafil as Rescue Therapy in Patients With Severe Pulmonary Arterial Hypertension Chronically Treated With Prostacyclin. Long-Term Results

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Introduction and objective. Prostacyclin therapy is an effective treatment for severe pulmonary hypertension. Sildenafil, a selective phosphodiesterase type 5 inhibitor, induces selective vasodilatation of the pulmonary vessels. A synergistic effect has been described for these two drugs. The aim of this study was to evaluate the efficacy and safety of sildenafil as rescue therapy in patients with severe pulmonary hypertension on chronic treatment with prostacyclin whose clinical or functional course was unsatisfactory.

Patients and method. Observational study of 11 patients (7 men, 4 women, mean age 42 [8] years) diagnosed as having severe idiopathic pulmonary hypertension, who were receiving chronic prostacyclin therapy. Sildenafil was started after a worsening of their clinical or functional status. Baseline, 3-month and 12-month follow-up evaluations were based on functional status (NYHA functional class and 6-minute walking test), the presence of decompensated right heart failure and echocardiogram.

Results. Seven of the 11 patients showed significant improvements in exercise capacity (distance walked in 6 minutes) at 3 (+25 m) and 12 months' follow-up (+36 m). Improvements in functional class were seen, and heart failure disappeared. No significant adverse effects of sildenafil were detected. The echocardiographic parameters showed a significant reduction in right ventricular end-diastolic diameter and left ventricular diastolic eccentricity index. One patient died after 4 months of follow-up from sudden cardiac death.

Conclusions. The addition of oral sildenafil to chronic prostacyclin treatment in patients with severe pulmonary hypertension improved functional capacity and reduced episodes of decompensated right heart failure, with good tolerance and no significant adverse effects.

Key words: Pulmonary hypertension. Therapy. Sildenafil. Prostacyclin.

Eficacia del sildenafil por vía oral como terapia de rescate en pacientes con hipertensión arterial pulmonar severa en tratamiento crónico con prostaciclina. Resultados a largo plazo

Introducción y objetivo. La prostaciclina es un tratamiento eficaz en la hipertensión arterial pulmonar severa. El sildenafil, un inhibidor selectivo de la fosfodiesterasa (PDE) tipo 5, produce vasodilatación selectiva de los vasos pulmonares, y se ha descrito un efecto sinérgico con la prostaciclina. El objetivo es analizar la eficacia y seguridad del sildenafil como terapia de rescate en pacientes con hipertensión pulmonar (HTP) en tratamiento crónico con prostaciclina que presentan mala evolución clínica y funcional.

Pacientes y método. Estudio observacional de 11 pacientes (7 varones, edad 42 ± 8 años) con hipertensión pulmonar idiopática (HTPI) en tratamiento crónico con prostaciclina. Se asoció sildenafil oral cuando presentaban deterioro clínico o funcional. Basalmente, a los 3 y los 12 meses de tratamiento combinado, se evaluó la capacidad funcional (clase funcional [CF] de la New York Heart Association [NYHA] y prueba de los 6 min), la presencia de insuficiencia cardíaca derecha (ICD) descompensada y se realizó un ecocardiograma.

Resultados. Se produjo una mejoría significativa de la capacidad de esfuerzo, con incremento de la distancia recorrida en 6 min a los 3 y los 12 meses (+25 y +36 m, respectivamente), mejora de la CF y desaparición de la insuficiencia cardíaca en 7 de los 11 pacientes. No se observaron efectos adversos significativos. El ecocardiograma mostró una reducción significativa del diámetro diástolico del ventrículo derecho y del índice de excentricidad diástolico del ventrículo izquierdo. Un paciente falleció (muerte súbita) a los 4 meses.

Conclusiones. La adición de sildenafil al tratamiento crónico con prostaciclina en pacientes con HTP severa mejoró la capacidad funcional y disminuyó los episodios de ICD descompensada, con buena tolerancia al medicamento y sin efectos adversos graves.

INTRODUCTION

Idiopathic pulmonary arterial hypertension is an infrequent disease characterized by an increase in pulmonary artery pressure. If left untreated, there is rapid disease progression, which leads to refractory right heart failure and death.1 It has been shown that continuous intravenous infusion of prostacyclin increases long-term survival, and improves quality of life, exercise capacity and hemodynamic parameters.2-4 Treatment with treprostinil and iloprost, stable prostacyclin analogues that are administered subcutaneously or by inhalation, respectively, has resulted in significant improvements in both functional capacity and quality of life.5-6 Nevertheless, no long-term studies of their effect on survival have been carried out.

Phosphodiesterases (PDEs) form a superfamily of enzymes that inactivate cyclic adenosine monophosphate (cAMP) and guanosine 5’-cyclic monophosphate (cGMP), compounds which are intracellular second messengers for prostacyclin and nitric oxide. Sildenafil is a selective phosphodiesterase type-5 (PDE-5) inhibitor that exerts a vasodilatory effect via the nitric oxide pathway, in a manner dependent on an increase in the intracellular cGMP concentration. High levels of PDE-5 are found in pulmonary muscular arteries and in the corpus cavernosum penis. PDE-5 inhibition results in selective pulmonary artery vasodilation, which has little impact on systemic vascular resistance. Prostacyclin’s vasodilatory effect is mediated by the intracellular second messenger cAMP, which is, in turn, inactivated by PDE-3. It is known that an increase in the intracellular cGMP concentration exerts an inhibitory effect on PDE-3. Sildenafil probably acts in a similar indirect way, thereby functioning synergistically to augment the vasodilatory effect of prostacyclin.7

Experience with the long-term use of sildenafil, whether administered as monotherapy or in association with prostacyclin, for treatment of idiopathic pulmonary arterial hypertension is very limited. There are only few reports on its use in a small number of patients.8-12 The aim of the present study was to investigate the benefits of long-term sildenafil treatment in patients with pulmonary hypertension in whom treatment with prostacyclin, administered as monotherapy through different routes, was insufficient to stabilize patients in New York Heart Association (NYHA) functional class II without signs of right heart failure.

PATIENTS AND METHOD

An observational study was carried out in patients with severe pulmonary hypertension that was either idiopathic or associated with toxic oil syndrome.11 Pulmonary hypertension was diagnosed in all patients before the initiation of prostacyclin treatment using criteria from the United States National Institutes of Health’s patient registry for the characterization of pulmonary hypertension.1 All patients had been receiving continuous treatment with prostacyclin or one of its analogues (i.e., intravenous epoprostenol, subcutaneous treprostinil, or iloprost inhalation) for at least 6 months. Long-term oral treatment with sildenafil was added when patients presented at least 2 of the following clinical criteria: a) they were classified as being in NYHA functional class III or IV; b) there were signs of decompensated right heart failure that did not respond to optimized diuretic therapy; c) syncope; and d) a >20% reduction in the distance walked in the 6-min walk test. Decompensated right heart failure was defined as the presence of signs of systemic venous congestion (i.e., hepatomegaly, ascites, or edema) that did not respond to treatment with diuretics. The absence of symptoms and signs of right heart failure was considered as an indication of effective control.

Patients with systemic arterial hypotension (i.e., a systolic arterial pressure <85 mm Hg) or with altered levels of enzymes associated with hepatic cytolysis (i.e., when aspartate aminotransferase and alanine aminotransferase levels were more than three times the normal reference levels) were excluded. The initial sildenafil dose used in all patients was 25 mg per 12 hours. This was increased progressively to a target dosage of 150 mg/day, taken in 3 doses. The prostacyclin dose remained the same during the first 3 months of follow-up; it was later adjusted individually according to the patients’ clinical evolution. Patients were informed in advance, both verbally and in writing, of the clinical characteristics of the medicine being administered. Patients gave written agreement (accepting their inclusion in the study and consenting to use of information obtained) and a request was made for com-
passionate use the medication, which was accepted by the relevant health authorities. In the study, a serious adverse event was defined as any event that was life-threatening, or that resulted in death, permanent incapacity, or the need for hospitalization or prolongation of hospital stay. The medication was regarded as being well tolerated if there were no adverse events and it was possible to increase the dose to the target level.

Between December 2001 and December 2002, 11 out of 45 (24%) patients with idiopathic pulmonary arterial hypertension who had received continuous treatment with prostacyclin for at least 6 months fulfilled criteria for inclusion in the study. These patients underwent clinical follow-up, complete laboratory analysis, evaluation of functional capacity using the standardized 6-min walk test (quantified as meters walked), and echocardiography, at baseline and 3 and 12 months after the initiation of sildenafil treatment.

Transthoracic echocardiography was carried out according to an agreed protocol by a single experienced individual using an Acuson Sequoya echocardiographic scanner. All echocardiographic investigations were recorded in both digital and video formats. Quantitative analysis of variables was performed offline, with values being derived as the mean of 3 measurements. The variables recorded were:

- Geometric parameters that characterize right ventricular function: systolic and diastolic eccentricity indices, which were calculated according to Ryan’s method; fractional area shortening (percentage shortening \(=100\times[\text{end-diastolic area–end-systolic area/}\text{end-diastolic area}]\); diastolic minor diameter, and right atrial area.

- Non-geometric parameters that characterize right ventricular function: myocardial performance index or Tei index.

- Maximum tricuspid regurgitant jet velocity, which can be used to give an estimate of the pressure gradient between the right ventricle and right atrium by using Bernoulli’s equation \((p=4v^2)\).

Statistical Analysis

The SPSS 10.0 statistical program was used. All continuous quantitative variables are expressed as a mean ± standard deviation. The differences between the means of the different quantitative variables measured before and after sildenafil treatment were analyzed using a non-parametric Wilcoxon test. A difference was considered to be statistically significant if the \(P\) value was <.05.

RESULTS

Of the 11 patients studied, 7 were men and 4 were women. Their mean age was 42±8 years. Eight patients presented with idiopathic pulmonary arterial hypertension and 3 had pulmonary arterial hypertension associated with toxic oil syndrome. Prostacyclin administration was being carried out as follows: 6 patients were receiving treprostinil subcutaneously; 3 were receiving iloprost by inhalation, and 2 were receiving epoprostenol intravenously. The form of prostacyclin administration remained unchanged throughout follow-up. Ten of the 11 patients were followed up for 12 months.

The patients started receiving prostacyclin as monotherapy for a mean of 21 months (range: 6–34 months) before study entry. Initial responses in the first 6 months were favorable (i.e., there was an increase of 29 m in the distance walked in the 6-min walk test, and NYHA functional class improved in 6 of the 11 patients). Subsequently, the patients’ conditions deteriorated markedly and could not be controlled by optimizing their current treatment. For this reason, it was decided to add sildenafil to the existing treatment regimens.

Patients’ Clinical Status and Functional Capacity Before Combination Treatment With Sildenafil (Baseline)

All patients were in NYHA functional class III, with the exception of 1 patient who was in NYHA functional class II and who experienced dyspnea and syncope during exertion. Seven of the 11 patients had decompensated right heart failure that did not respond to diuretic treatment. Two patients had syncope, which occurred on minimum exertion in one. The mean distance walked in the 6-min walk test prior to sildenafil administration was 374±63 m. The mean prostacyclin dose before the start of sildenafil therapy was 23±6 ng/kg per min for intravenous epoprostenol, 31±6 ng/kg per min for treprostinil, and 150 µg/day for the 3 patients on iloprost.

Clinical Follow-up After 3 and 12 Months of Combination Treatment With Prostacyclin and Sildenafil

The distance walked in the 6-min walk test increased in all patients, by a mean of 25 m at 3 months and 36 m at 12 months (Figure 1). At 3 month follow-up, 5 patients exhibited an improvement in NYHA functional class (Figure 2). Syncope, which was present in 2 patients, disappeared within the first 3 weeks of treatment. The symptoms and signs of right heart failure, which were observed in 7 patients before initiation of sildenafil treatment, had already disappeared within the first 3 months of combination treatment in 5 patients, and disappeared within the following months in a sixth patient. One patient continued to have decompensated heart failure, though symptoms of con-
gestion were better controlled, and died suddenly in the fourth month of follow-up.

The mean sildenafil doses achieved at 3 and 12 months were 146±44 mg/day and 152±34 mg/day, respectively. No patient withdrew from treatment because of poor tolerance, hypotension, or altered biochemical liver test results. Two patients experienced headache and 2 had dyspepsia, which meant that the increase in sildenafil dosage in these patients had to be implemented more slowly. Only 1 patient could not be given the target daily sildenafil dosage of 150 mg, because of headache.

Table. Change in Echocardiographic Parameters

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>Prostacyclin + Sildenafil at 3 Months</th>
<th>Prostacyclin + Sildenafil at 12 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Means±SD</td>
<td>Means±SD</td>
<td>Means±SD</td>
</tr>
<tr>
<td>RVDD, mm</td>
<td>47.9±10</td>
<td>43.3±8</td>
<td>41.5±11</td>
</tr>
<tr>
<td>Percentage variation in RV area</td>
<td>19.2±11</td>
<td>19.7±6</td>
<td>24.5±7</td>
</tr>
<tr>
<td>LV diastolic eccentricity index</td>
<td>1.6±0.25</td>
<td>1.5±0.29</td>
<td>1.3±0.22</td>
</tr>
<tr>
<td>LV systolic eccentricity index</td>
<td>2.4±0.7</td>
<td>2.2±0.64</td>
<td>2.2±0.75</td>
</tr>
<tr>
<td>Tei index</td>
<td>0.6±0.2</td>
<td>0.6±0.2</td>
<td>0.5±0.1</td>
</tr>
<tr>
<td>RA area, cm²</td>
<td>20.6±8.0</td>
<td>17.9±6.3</td>
<td>18.7±5.9</td>
</tr>
<tr>
<td>RV-RA pressure gradient, mm Hg</td>
<td>84±15</td>
<td>82.6±17</td>
<td>81±12</td>
</tr>
</tbody>
</table>

*LV indicates left ventricle; RA, right atrium; RV, right ventricle; RVDD, right ventricular diastolic diameter; SD, standard deviation.
Echocardiographic Follow-up of Combination Treatment With Prostacyclin and Sildenafil

Geometric parameters of right ventricular function had improved by the third month of combination treatment and remained unchanged after twelve months. Changes from baseline in the right ventricular minor diastolic diameter and in the diastolic eccentricity index reached statistical significance. There was also an improvement in myocardial performance index, though it did not reach statistical significance. However, the right ventricle-atrium pressure gradient did not change during follow-up (Table).

DISCUSSION

In our study group, which comprised patients with severe pulmonary hypertension in a poor functional state and with a limited therapeutic response margin, long-term treatment with prostacyclin and sildenafil not only stabilized clinical status, but also lead to significant and sustained improvements in exercise capacity (as measured by the 6-min walk test), the level of dyspnea (i.e., in NYHA functional class), and the prevalence of decompensated right heart failure. Similarly, there was also a trend towards beneficial remodeling of the right ventricle, which was demonstrated by improved ventricular function and reduced ventricular dilatation.

After the initiation of prostacyclin monotherapy, our patients followed a favorable clinical course. There was an improvement in NYHA functional class and an increase in the distance walked in the 6-min walk test, as has been described in the medical literature in other patients treated with prostanooids.

However, after 20 months of follow-up and without any concurrent precipitating cause, the patients exhibited a marked functional deterioration, which did not respond to an increase in prostacyclin dose. A particularly important feature was the appearance of right heart failure in more than half the patients. This occurrence was similar to observations reported by Ghofrani et al. in patients treated with prostacyclin, who responded favorably in the beginning, but who later exhibited a slow and progressive deterioration in hemodynamic parameters and functional capacity after 18 months of treatment.

There are few reports in the literature on combination treatment with prostacyclin and sildenafil. Those that do exist involve, as does this study, only a small number of patients. Our findings are consistent with those reported by Ghofrani et al. in a study of 14 patients. They demonstrated that there was no change in pulmonary artery systolic pressure but confirmed, nevertheless, that there were positive changes in the cardiac index and in the vascular resistance index, both of which are more closely related to right ventricular function.

In our experience, sildenafil was found to be a safe drug. No serious secondary adverse effects, such as systemic hypotension, were observed, probably because the drug’s vasodilatory action selectively affects pulmonary vessels.

Patients receiving long-term treatment with prostacyclin who start to exhibit heart failure or functional deterioration in the absence of precipitating factors (e.g., pneumonia or anemia) have a very poor short-term prog-
nosis and need to undergo urgent transplantation. In this situation, the favorable responses obtained in our group of patients who were receiving long-term prosta-
cyclin treatment and who exhibited evidence of progressive heart disease are especially relevant.

One death occurred in our series, in a patient who was receiving an epoprostenol infusion. The patient re-
mained in state of severe right heart failure, despite bet-
ter control of congestive symptoms following the addi-
tion of sildenafil, and died suddenly at home during the fourth month of follow-up. It is remarkable that only one death was observed in our patients considering their dis-
ease severity and the long duration of the follow-up peri-

Although this study was open, uncontrolled and involved only a small number of patients, the low prevalence of the illness and the need to try all of the few therapeu-
tical alternatives available for these patients, whose clinical condition is so dismal, means that these findings are encouraging and of great interest. Moreover, they are in accordance with the results obtained by Ghofrani et al.

CONCLUSIONS

The administration of sildenafil to patients with severe pulmonary hypertension who exhibit clinical and func-
tional deterioration despite long-term treatment with prostacyclin or one of its analogues resulted in improved NYHA functional class and exercise capacity and re-
duced signs of decompensated right heart failure. These gains were maintained over time, during a mean follow-
up period of 12 months. The combination of treatments that act via different cellular mechanisms could provide a starting point for more effective therapies, which could perhaps be administered at lower doses and which may result in fewer side effects. Moreover, whether sildenafil is used as monotherapy or in combination, its impact on survival is still unknown. Further clinical trials are need-
ed to provide answers to these questions.

REFERENCES

5. Olschewski H, Simonneau G, Galie N, Higenbottam T, Naeije R, Rubini L, et al. Inhaled iloprost is an effective treatment for severe pulmo-
nuous subcutaneous infusion of treprostinil, a prostacyclin analogue, in pa-
tients with pulmonary arterial hypertension: a double blind, randomized, pla-
11. Ichelakis ED, Tymchak W, Noga M, Webster L, Wu XC, Lien D, et al. Long term treatment with oral sildenafil is safe and improves functio-
nal capacity and hemodynamics in patients with pulmonary arterial hy-
13. Ich S, editor. Executive summary from the World Symposium on Pri-
17. Berger M, Hamwowitz A, van Tosh A, Berdof RL, Goldberg E. Quan-
titative assessment of pulmonary hypertension in patients with tricus-
18. Gómez Sánchez MA, Sáenz de la Calzada C, Gómez Pajuelo C, Martí-
nez Tello PJ, Mestre de Juan MJ, James TN. Clinical and pathologic-
hic measures of right ventricular structure and function in primary pul-
23. Rich S, Brundage BH. High dose calcium channel-blocker therapy for primary pulmonary hypertension: evidence of long term reduction in pulmonary arterial pressure and regression of right ventricular hy-