Long-term Treatment With Oral Sildenafil in Addition to Continuous IV Epoprostenol in Patients With Pulmonary Arterial Hypertension*

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Objectives: To evaluate the effect of long-term oral therapy with sildenafil in patients with pulmonary arterial hypertension receiving long-term IV epoprostenol.

Design: Open, uncontrolled trial.

Setting: University hospital.

Patients: Two patients with primary pulmonary hypertension and one patient with pulmonary arterial hypertension after surgical closure of an atrial septal defect. All patients were receiving continuous epoprostenol for 1.7 to 7.1 years; two patients also received inhaled iloprost for 1.8 years and 3.8 years, respectively.

Interventions: Addition of oral sildenafil, up to 200 mg/d, divided in four to six single doses, and hemodynamic measurements and the 6-min walking distance (6MWD) before and after 5 months of treatment with sildenafil.

Results: One patient was treated with sildenafil, 200 mg/d; two patients received 75 mg/d due to nausea and headache. Long-term treatment with sildenafil in the three patients reduced mean pulmonary artery pressure by 14%, 41%, and 22%, respectively; in two patients, pulmonary vascular resistance was decreased by 52% and 55%. The 6MWD increased by 34%, 6%, and 29%, respectively. No significant systemic hypotension or decrease of arterial oxygen saturation was seen.

Conclusion: Sildenafil therapy may be of benefit in patients with pulmonary arterial hypertension receiving long-term infusion of epoprostenol.

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Key words: epoprostenol; pulmonary hypertension; pulmonary hemodynamics; sildenafil; treatment

Abbreviations: 6MWT = 6-min walking test; PAP/m = mean pulmonary arterial pressure; PDE5 = phosphodiesterase isoform 5; PPH = primary pulmonary hypertension; PVR = pulmonary vascular resistance; \( \text{SaO}_2 \) = arterial oxygen saturation; \( \text{SvO}_2 \) = mixed venous oxygen saturation

Primary pulmonary hypertension (PPH) is a rapidly progressive disease of the pulmonary vasculature with consequent right-heart failure. Other illnesses such as congenital heart disease, collagen vascular disease, and HIV infection are frequently associated with pulmonary hypertension. Prognosis of pulmonary arterial hypertension without treatment is poor. Treatment of PPH with IV epoprostenol has been shown to prolong survival in patients unresponsive to conventional therapy, and to improve hemodynamics and quality of life in patients with pulmonary arterial hypertension in association with congenital heart disease. In spite of improved medical treatment, patients with pulmonary hypertension may progress and ultimately may require lung transplantation. Further progress in the medical treatment of pulmonary arterial hypertension could be expected by combination treatment modalities.

Sildenafil is a specific inhibitor of the phosphodiesterase isoform 5 (PDE5), and leads to smooth-muscle relaxation via a nitric oxide-dependent increase of cyclic guanosine 5-monophosphate. Lung PDE5 inhibition by sildenafil might reduce pulmonary vascular pressures by this pathway. PDE5 is more abundant in the lung than in other tissues, and therefore offers the possibility of relatively selective pulmonary vasodilation with little systemic hypotension. There are anecdotal reports of beneficial effects of sildenafil in childhood PPH, in a young man with PPH, and in HIV-related pulmonary hypertension. Given that PDE5 plays an important role in maintaining pulmonary arterial tone and that sildenafil is a pulmonary selective vasodilator, combining epoprostenol and sildenafil could be more effective than epoprostenol alone. We therefore administered sildenafil orally for 5 months in three patients with pulmonary arterial hypertension, in addition to long-term IV epoprostenol.

Materials and Methods

For measurements of hemodynamic and gas exchange parameters, a thermodilution pulmonary artery catheter was inserted before and after 5 months treatment with sildenafil. A 6-min
The walking test (6MWT) was performed before and after the sildenafil trial. The dose of epoprostenol and iloprost was not changed in the 3 months before and during the sildenafil trial. The 6MWT distance and the hemodynamic measurements were made before the administration of sildenafil and iloprost. The study was approved by the institutional ethics board, and written informed consent was given by each patient.

**Case Report 1**

In this 61-year-old female patient, the diagnosis of PPH was established 3.5 years ago. She was first started on iloprost inhalation, but 1 year later epoprostenol IV was added due to clinical deterioration (the dosage of epoprostenol was 20 ng/kg/min at the time when sildenafil was added). Baseline measurement before sildenafil treatment is shown in Table 1. A 50-mg oral dose of sildenafil was tolerated without any side effects, and the patient continued to receive 50 mg qid. She reported an improvement in dyspnea on exertion as early as 2 weeks after beginning with sildenafil, with a gradual, further improvement in the next weeks. After 5 months, her mean pulmonary arterial pressure (PAPm) was reduced by 14%, cardiac output improved (67% at baseline vs. 97% at 6 months), and arterial oxygen saturation (SaO2) increased by 48%, and pulmonary vascular resistance (PVR) was reduced by 52% (Table 1). Arterial oxygen saturation (SaO2) and mixed venous oxygen saturation (SvO2) levels remained stable. The 6MWT distance increased by 34%.

**Case Report 2**

A 33-year-old female patient received a diagnosis of PPH 5 years before this trial. She received long-term IV epoprostenol since diagnosis of PPH (the dosage was 30 ng/kg/min throughout the sildenafil trial). Iloprost inhalations were added 2 years ago due to a steady clinical deterioration. Also at that time, she started to have some hemoptysis. One massive episode of hemoptysis 1.5 years ago required intubation. No obvious reason for the hemoptysis was found in the following workup. Because of the hemoptysis, anticoagulation was changed from warfarin to a low-molecular-weight heparin. Baseline measurements before sildenafil treatment are also given in Table 1. After ingesting a 50-mg sildenafil tablet, the patient had nausea and headache, and refused another 50-mg dose. We therefore reduced the single sildenafil dose; the patient started with 12.5 mg (1/4 tablet) qid for the first week, and then increased the dose to 12.5 mg six times daily. Any attempt to increase the single dose or the daily dose was followed by nausea and headache. She had an improvement of dyspnea on exertion 4 weeks after starting with sildenafil with further improvement in the next months. After 5 months of treatment with additional sildenafil, hemodynamics were measured, demonstrating a reduction of the PAPm by 41%. Unfortunately, the correctly placed catheter (documented by pressure tracings and chest radiography) dislocated before cardiac output was measured. In order to avoid catheter-associated complications, the study was finished after several unsuccessful relocation attempts without measuring cardiac output. No significant change in SvO2 was found. The 6MWT distance increased by 6%.

**Case Report 3**

A 51-year-old female patient had a surgical occlusion of an atrial septal defect when she was 26 years old. Ten years later, pulmonary hypertension was diagnosed and treatment with diltiazem was initiated. IV epoprostenol was started 7 years ago (dosage was 23 ng/kg/min at beginning of the sildenafil trial), and diltiazem was discontinued. A progression of her disease was observed 1 year ago, and any attempts to increase the epoprostenol dose were unsuccessful due to systemic hypotension. Hemodynamic measurements before receiving sildenafil showed advanced pulmonary hypertension with right-heart failure, with a low cardiac output of 2.2 L/min and an SvO2 of 52%. She reported also nausea and headache after receiving 50 mg of sildenafil. Like patient 2, she started with about 12.5 mg of sildenafil qid for 2 weeks, and increased the daily dose by receiving 12.5 mg six times daily. Four weeks after starting sildenafil, she reported less dyspnea on exertion. After 5 months of additional oral sildenafil therapy, her PAPm was reduced by 22%, her cardiac output increased by 59%, resulting in a decrease in PVR of 55% (Table 1). Her SvO2 improved from 52 to 57%. Corresponding with her clinical improvement, the 6MWT distance improved by 29%.

**DISCUSSION**

Addition of sildenafil to the long-term therapy with IV epoprostenol improved pulmonary arterial pressures and the 6MWT distance in all three patients without significant adverse effects at the reported doses. IV epoprostenol is now established as a treatment to be considered for all patients with PPH, and hundreds of patients worldwide experienced the beneficial effect of this treatment. Introduced initially as a bridge to transplantation, it is now considered superior to lung transplantation in improving the quality of life and survival in such patients. However, the adverse effects of IV epoprostenol treatment led to studies of alternative treatment modalities to reduce the side effects. One of these adverse effects is tachyphylaxis, necessitating the replacement of IV epoprostenol with oral sildenafil. In this case report, we present three patients with idiopathic pulmonary arterial hypertension treated with sildenafil. All patients showed a good response to oral sildenafil with a clear clinical improvement and a reduction of the PAPm by 40-60%. The 6MWT distance increased by 34%, and arterial oxygen saturation (SaO2) increased by 48%. Pulmonary vascular resistance (PVR) was reduced by 52% (Table 1).

**Table 1—Hemodynamics, Oxygen Saturation, and 6MWT Distance Before and After 5 Months of Additional Sildenafil Treatment**

<table>
<thead>
<tr>
<th>Variables</th>
<th>PAPm, mm Hg</th>
<th>Cardiac Output, L/min</th>
<th>PVR, dyne·s·cm⁻⁵</th>
<th>Mean Arterial BP, mm Hg</th>
<th>SaO₂, %</th>
<th>SvO₂, %</th>
<th>6MWT Distance, m</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient 1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>49</td>
<td>4.8</td>
<td>536</td>
<td>73</td>
<td>89</td>
<td>75</td>
<td>305</td>
</tr>
<tr>
<td>Treatment</td>
<td>42</td>
<td>7.1</td>
<td>280</td>
<td>68</td>
<td>90</td>
<td>73</td>
<td>410</td>
</tr>
<tr>
<td><strong>Patient 2</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Baseline</td>
<td>70</td>
<td>4.8</td>
<td>1,128</td>
<td>76</td>
<td>93</td>
<td>60</td>
<td>550</td>
</tr>
<tr>
<td>Treatment</td>
<td>41</td>
<td>Not done</td>
<td>Not done</td>
<td>72</td>
<td>95</td>
<td>59</td>
<td>585</td>
</tr>
<tr>
<td><strong>Patient 3</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>55</td>
<td>2.2</td>
<td>1,464</td>
<td>75</td>
<td>91</td>
<td>52</td>
<td>245</td>
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<tr>
<td>Treatment</td>
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<td>3.5</td>
<td>664</td>
<td>72</td>
<td>94</td>
<td>57</td>
<td>315</td>
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</table>
regular dose escalations. Ultimately, patients having a treatment failure to IV epoprostenol need to be considered for lung transplantation; however, if another effective drug could be added to the long-term IV epoprostenol therapy safely, probably the time period receiving medical therapy with improved quality of life could be further expanded. Sildenafil is a reasonable candidate for this aim, because sildenafil is easy to administer, seems to vasodilate preferentially the pulmonary circulation, and is registered in most countries for the use in erectile dysfunction, making it available on a compassionate-use basis. Furthermore, if tachyphylaxis of epoprostenol could be reduced by adding sildenafil, the overall costs of therapy could be reduced.

So far, there are only two case reports about long-term treatment with sildenafil in adults published in the literature. The doses used in these reports were 200 mg/d and 500 mg/d, respectively. No other treatment than warfarin for anticoagulation was used. In order to avoid systemic hypotension and/or worsening of ventilation/perfusion mismatch by the combination of two systemic-acting vasodilators, we set the upper limit of the daily sildenafil dose at 200 mg/d. Surprisingly, two patients tolerated only a maximum daily dose of 75 mg, due to nausea and/or headache. Although the first dose in both patients was a 50-mg tablet, none of the two patients had a clinically significant drop in mean systemic arterial pressure. No adverse effects during the whole treatment period of 5 months were observed, suggesting that this dose can be administered safely in patients receiving long-term IV epoprostenol. It is noteworthy that this was also the case in patient 3, whose hemodynamics (cardiac output of 2.2 L/min) demonstrate an advanced stage of pulmonary hypertension. She did not tolerate an increase in the epoprostenol dose due to systemic hypotension, but she improved dramatically when sildenafil was added. In addition to the reduction in PAPm, the improvement in cardiac output in this patient likely contributed to the clinical improvement in this patient.

Although sildenafil was administered systemically, none of the patients had a drop in the SaO2, implying that no worsening of ventilation-perfusion mismatch occurred (Table 1). Two patients also inhaled iloprost six times daily, known to improve the ventilation/perfusion mismatch by the combination of two systemic-acting vasodilators, we set the upper limit of the daily sildenafil dose at 200 mg/d. Surprisingly, two patients tolerated only a maximum daily dose of 75 mg, due to nausea and/or headache. Although the first dose in both patients was a 50-mg tablet, none of the two patients had a clinically significant drop in mean systemic arterial pressure. No adverse effects during the whole treatment period of 5 months were observed, suggesting that this dose can be administered safely in patients receiving long-term IV epoprostenol. It is noteworthy that this was also the case in patient 3, whose hemodynamics (cardiac output of 2.2 L/min) demonstrate an advanced stage of pulmonary hypertension. She did not tolerate an increase in the epoprostenol dose due to systemic hypotension, but she improved dramatically when sildenafil was added. In addition to the reduction in PAPm, the improvement in cardiac output in this patient likely contributed to the clinical improvement in this patient.

Although sildenafil was administered systemically, none of the patients had a drop in the SaO2, implying that no worsening of ventilation-perfusion mismatch occurred (Table 1). Two patients also inhaled iloprost six times daily, known to improve the ventilation/perfusion mismatch by causing pulmonary vasodilation matched to ventilation. We therefore cannot rule out the possibility that that this prevented a sildenafil-induced ventilation/perfusion mismatch by causing pulmonary vasodilation matched to ventilation. We therefore cannot rule out the possibility that that this prevented a sildenafil-induced ventilation/perfusion mismatch; however, patient 3 did not inhale iloprost, and she showed a clear improvement of SaO2. A sildenafil-induced worsening of the ventilation-perfusion mismatch was probably prevented by the low single and daily doses of sildenafil.

In a recent report, Ghofrani et al. demonstrated that the short-term administration of oral sildenafil and inhaled iloprost produced a much greater vasodilatory response in patients with pulmonary arterial hypertension and in patients with chronic thromboembolic pulmonary hypertension than did each single agent alone. Because untretable right-heart failure after discontinuation of IV epoprostenol has been described, we did not study the patients receiving sildenafil alone. We therefore cannot answer the question if the combination of epoprostenol and sildenafil in the reported patients would produce a higher vasodilatory response than each single agent alone. Further studies are needed to confirm the results reported here and to compare the short-term and long-term effects of IV epoprostenol or inhaled iloprost, each in combination with oral sildenafil.

When this report was submitted, all three patients were still receiving the same daily dose of sildenafil for another 3 months, and the epoprostenol rate had not been increased. All three patients still feel clinically improved. Long-term treatment with IV epoprostenol is considered to be the most potent medical therapy for pulmonary arterial hypertension available today, and patients with treatment failures should be referred for lung transplantation. In the three patients reported here, we found a marked clinical and hemodynamic improvement after 5 months of therapy with oral sildenafil in addition to IV epoprostenol. Our data suggest that sildenafil might serve as an additional beneficial treatment for patients with pulmonary arterial hypertension receiving continuous IV epoprostenol therapy.

References


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