Oral Sildenafil as Long-Term Adjunct Therapy to Inhaled Iloprost in Severe Pulmonary Arterial Hypertension

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OBJECTIVES
We sought to investigate the impact of adjunct sildenafil on exercise capacity and hemodynamic parameters in patients with pulmonary arterial hypertension (PAH) who fulfilled predefined criteria of deterioration despite ongoing treatment with inhaled iloprost.

BACKGROUND
Inhaled iloprost is an effective therapy in PAH. The phosphodiesterase-5 inhibitor sildenafil exerts pulmonary vasodilation and may amplify prostanoid efficacy.

METHODS
Of 73 PAH patients receiving long-term inhaled iloprost treatment, 14 fulfilled criteria of deterioration unresponsive to conventional treatment. These patients received adjunct oral sildenafil over a period of nine to 12 months, leaving the inhalative iloprost regimen unchanged.

RESULTS
Before iloprost therapy, the baseline 6-min walking distance was 217 ± 31 m (mean ± SEM), with an improvement to 305 ± 28 m within the first three months of iloprost treatment and a subsequent decline to 256 ± 30 m after 18 ± 4 months. Adjunct therapy with sildenafil reversed the deterioration and increased the 6-min walk distance to 346 ± 26 m (p = 0.002, Wilcoxon test) at three months of combined therapy, with a sustained efficacy up to 12 months (349 ± 32 m, p = 0.002). The distribution of New York Heart Association functional classes (IV/III/II) improved from September 9, 2000, before sildenafil, to January 8, 2003, after nine to 12 months with sildenafil. All hemodynamic variables changed favorably: pulmonary vascular resistance decreased from 2,494 ± 256 before sildenafil to 1,950 ± 128 dynes·cm⁻²·m² after three months of adjunct sildenafil (p = 0.036). Two patients died of severe pneumonia during the period of combined therapy. No further serious adverse events occurred.

CONCLUSIONS
In patients with severe PAH deteriorating despite ongoing prostanoid treatment, long-term adjunct oral sildenafil improves exercise capacity and pulmonary hemodynamics. A combination of prostanoids and sildenafil is an appealing concept for future treatment of pulmonary hypertension. (J Am Coll Cardiol 2003;42:158–64) © 2003 by the American College of Cardiology Foundation

Continuous infusion of prostacyclin has been shown to be a life-saving therapy in severe primary pulmonary hypertension (PPH) (1) and to improve exercise capacity in collagen vascular disease–associated pulmonary hypertension (2). There are, however, serious drawbacks with this therapy, including substantial systemic side effects due to the lack of pulmonary selectivity of the prostanoid, the need for a progressive dosage increase, and septic complications of the intravenous line. To keep the advantageous effects of prostacyclin but leave behind several of these side effects, the concept of aerosolized iloprost for the treatment of pulmonary arterial hypertension (PAH) was developed (3,4). Iloprost is a chemically stable prostacyclin analogue (5) exerting strong pulmonary vasodilation upon inhalation as a nebulized agent (4,6–9). Several open-label, uncontrolled studies in severe pulmonary hypertension suggested that long-term use of aerosolized iloprost (6 to 9 inhalations per day) results in substantial clinical improvement (4,6,7,10–12). This notion was just recently corroborated by the results of a double-blinded, placebo-controlled, multicenter study: in patients with selected forms of PAH and chronic thromboembolic pulmonary hypertension, daily inhaled iloprost significantly improved exercise capacity, New York Heart Association (NYHA) functional class, dyspnea scoring, and event-free survival over a three-month observation period (13).

To further improve the inhalative therapy while maintaining preferential vasodilation in the pulmonary circulation, strategies for combination with phosphodiesterase (PDE) inhibitors were developed. The PDEs represent a superfamily of enzymes, with PDE-1 through PDE-11 being currently known, that inactivate cyclic adenosine monophosphate and cyclic guanosine monophosphate (cGMP), the second messengers of prostacyclin and nitric
oxide, with different tissue distribution and substrate specificities (14). Due to stabilization of these second messengers, PDE inhibitors offer to augment and prolong prostanoid- and nitric oxide–related vascular effects, and the efficacy of this approach has been proven in several experimental studies (15–18). Interestingly, the major cGMP-degrading phosphodiesterase, PDE-5, is abundantly expressed in lung tissue (19). Three recent studies investigated the short-term effects of orally administered sildenafil, a selective PDE-5 inhibitor that has been approved for the treatment of erectile dysfunction in patients with severe pulmonary hypertension (20–22). Interestingly, this agent, per se, caused pulmonary vasodilation, with amplification of the pulmonary vasodilatory effect when combined with inhaled iloprost, while maintaining pulmonary selectivity.

In the present study, we extended this approach to long-term treatment with oral sildenafil combined with inhaled iloprost. Within a study entry period of one year, all PAH patients receiving long-term inhalative iloprost treatment were regularly surveyed, and those fulfilling predefined criteria of clinical deterioration were offered oral sildenafil as adjunct therapy while leaving the iloprost inhalation regimen unchanged. Most impressively, all 14 severely ill pulmonary hypertensive patients selected according to these criteria displayed marked improvement of their clinical state, exercise capacity, and hemodynamics over the subsequent nine- to 12-month observation period. This is the first trial demonstrating that a suitable combination of prostanoid and PDE inhibitor has beneficial long-term effects in patients with severe pulmonary hypertension.

METHODS

Patients. In 2001, a total number of 73 patients with PAH were treated with long-term inhaled iloprost in our pulmonary hypertension referral center on an outpatient basis. All patients had initially been admitted to our center for testing of pulmonary vasoreactivity and evaluation of therapeutic options for severe pulmonary hypertension. Diagnostic procedures that had been performed preceding iloprost treatment and that were repeated according to clinical necessities included immunologic laboratory analysis, chest X-ray, lung function testing, carbon dioxide diffusion testing, echocardiography, high-resolution computed tomography of the lung, lung perfusion scintigraphy, and a spiral computed tomographic scan and/or pulmonary angiography for exclusion of chronic thromboembolism as the underlying reason for pulmonary hypertension. All patients were offered outpatient visits every three months for control of therapy, performance of the unencouraged 6-min walk test, and assessment of NYHA functional class; more frequent visits occurred based on clinical necessity. Patients were suggested to enter the present study when at least two of the following criteria of deterioration were fulfilled over a three-month observation period: 1) subjective clinical worsening; 2) deterioration in 6-min walk distance of more than 20%; 3) signs of increased right heart load, despite adapted dose increases of the ongoing iloprost therapy and optimization of diuretics (e.g., edema refractory to diuretic therapy, ascites or pleural effusion refractory to diuretic therapy, increased liver enzymes attributable to venous congestion, central venous pressure 17 mm Hg or higher); and 4) syncope.

Within the study entry period in 2001, in total, 18 of the 73 PAH patients receiving long-term inhaled iloprost therapy fulfilled these criteria. Fourteen of these 18 patients agreed to enter the present study with oral sildenafil as adjunct therapy to inhaled iloprost. Nine of the 14 patients suffered from PPH, and five had PAH associated with collagen vascular disease. The mean age of these patients was 58 ± 3 years, and the average iloprost inhalation frequency was 9/day. For assessment of hemodynamics, a thermodilution pulmonary artery catheter was used to measure central venous pressure, pulmonary artery pressure, pulmonary artery wedge pressure, and cardiac output. Patients received nasal oxygen throughout the entire test procedure to achieve arterial oxygen saturation >88%. Measurements were performed after an overnight break of prostanoid inhalation (pre-iloprost) and 15 min after performing an iloprost inhalation maneuver (post-iloprost), as described previously (23). When assessing hemodynamics after the onset of long-term adjunct sildenafil treatment, the pre-iloprost values were measured ~10 h after the last oral intake of the routine sildenafil dose the night before (25 to 50 mg; see subsequent text).

When fulfilling the study entry criteria, oral treatment with sildenafil was commenced, while leaving the iloprost inhalation regimen unchanged during the period of combination therapy. The sildenafil dosage was slowly increased over three to four days, allowing final target doses between 25 mg three times per day (9 of 14 patients) and 50 mg three times per day (5 of 14 patients). Outpatient visits were then performed every four weeks for control of therapy. After three months, complete clinical evaluation and catheter testing were again performed, and clinical evaluation was repeated after six months and after nine to 12 months.

The study protocol was approved by the Ethics Committee of the Justus-Liebig-University Giessen, and each patient gave written, informed consent. Data were evaluated before initiation of adjunct sildenafil therapy (pre-sildenafil) and up to 12 months of combined therapy. Moreover, for the 14 patients entering the study, data were compared with the initial baseline clinical and catheter evaluation before starting iloprost therapy and with the data obtained after the
first three months of iloprost treatment. The mean interval between the onset of long-term iloprost inhalation therapy and the onset of adjunct sildenafil therapy due to clinical deterioration was 18 ± 4 months.

**Statistics.** All baseline data are given as the means and SEM. The Wilcoxon signed rank test was used to display significant differences (with two-sided p value) in the 6-min walk distance and pulmonary vascular resistance index in response to prostanoid inhalation. Hodges-Lehman point estimates of median differences and exact 95% confidence intervals are presented for the response of each parameter to the intervention (pre- and post-intervention values) (StatExact-4 version 4.0.1, Cytel Software Corp., Cambridge, Massachusetts).

**RESULTS**

**Baseline exercise capacity and hemodynamics before starting iloprost therapy.** The initial 6-min walk distance of the patients entering the study was 217 ± 31 m (mean ± SEM) (Fig. 1). According to a standardized clinical evaluation protocol, five patients were classified in NYHA class III and nine patients in class IV (Fig. 2). Detailed baseline hemodynamics for all patients are given in Table 1. The severity of the disease was reflected by a mean pulmonary artery pressure of 58.4 ± 2.4 mm Hg, a cardiac index of 2.0 ± 0.2 l/min⁻¹m⁻², a pulmonary vascular resistance index of 2,312 ± 271 dynes·s·cm⁻⁵·m², and a central venous pressure of 8.3 ± 1.5 mm Hg.

**Exercise capacity and hemodynamics after the initial three-month period of iloprost therapy.** Over this period, the 6-min walk distance increased to 305 ± 28 m (Fig. 1). The majority of patients were then in NYHA functional class III (Fig. 2). Pre-inhalation hemodynamics, assessed in the morning after an overnight break of iloprost inhalation, were largely unchanged but markedly improved in response to prostanoid inhalation (Table 1, Fig. 3). This improvement included a decrease in pulmonary artery pressure, pulmonary vascular resistance, and central venous pressure and an increase in the cardiac index. Heart rate and systemic arterial pressure were virtually unchanged in response to iloprost inhalation.
Exercise capacity and hemodynamics before initiation of adjunct sildenafil therapy. After a mean treatment period of 18 ± 4 months, worsening was apparent from a substantial loss of the initial increment in the 6-min walk distance (256 ± 30 m) (Fig. 1). The majority of patients had again switched to NYHA class IV (Fig. 2). At this time point, the pre-inhalation pulmonary vascular resistance was increased and the cardiac index was decreased compared with the initial baseline values, with a clear beneficial response to the iloprost inhalation (Table 1, Fig. 3).

**Figure 2.** Distribution of patients (n = 14) in New York Heart Association (NYHA) functional classes. The numbers of patients classified in class II (open bars), III (bars with diagonal lines), or IV (solid bars) are given for the initial pre-intervention baseline, for three months of inhaled iloprost therapy (Ilo 3 months), for a mean interval of 18 ± 4 months when clinical deterioration was noted (Pre-Sil), and for 3, 6, and 9–12 months of adjunct sildenafil therapy while leaving the iloprost regimen unchanged (Sil-Ilo). Note that one patient died between three and six months and one died at eight months of adjunct sildenafil therapy (n = 13 penultimate and n = 12 ultimate column).

**Table 1.** Hemodynamics at Baseline and in Response to Iloprost and Sildenafil Treatment

<table>
<thead>
<tr>
<th></th>
<th>HR (beats/min)</th>
<th>mSAP (mm Hg)</th>
<th>mPAP (mm Hg)</th>
<th>CVP (mm Hg)</th>
<th>CI (l/min per m²)</th>
<th>PVRI (dynes·s·cm⁻⁵·m²)</th>
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<tbody>
<tr>
<td>Baseline</td>
<td>80.3 ± 2.5</td>
<td>92.8 ± 3.5</td>
<td>58.4 ± 2.4</td>
<td>8.3 ± 1.5</td>
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<td>2,312 ± 271</td>
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<td>Iloprost at 3 months</td>
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<td>Pre-ilo</td>
<td>81.5 ± 2.2</td>
<td>96.3 ± 3.7</td>
<td>58.3 ± 2.4</td>
<td>7.7 ± 1.6</td>
<td>2.0 ± 0.2</td>
<td>2,266 ± 212</td>
</tr>
<tr>
<td>Post-ilo</td>
<td>83.5 ± 2.3</td>
<td>89.7 ± 4.0</td>
<td>49.5 ± 3.1</td>
<td>5.5 ± 1.0</td>
<td>2.5 ± 0.2</td>
<td>1,549 ± 214</td>
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<td>Pre-sildenafil</td>
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<tr>
<td>Pre-ilo</td>
<td>82.4 ± 2.8</td>
<td>92.5 ± 3.1</td>
<td>58.6 ± 2.1</td>
<td>10.1 ± 1.3</td>
<td>1.8 ± 0.1</td>
<td>2,494 ± 256</td>
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<td>Post-ilo</td>
<td>81.1 ± 2.2</td>
<td>89.0 ± 3.3</td>
<td>50.7 ± 3.2</td>
<td>5.7 ± 1.0</td>
<td>2.3 ± 0.1</td>
<td>1,640 ± 212</td>
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<td>Sildenafil + iloprost at 3 months</td>
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<tr>
<td>Pre-ilo</td>
<td>80.4 ± 2.5</td>
<td>88.4 ± 3.0</td>
<td>58.6 ± 2.6</td>
<td>5.3 ± 1.2</td>
<td>2.2 ± 0.2</td>
<td>1,950 ± 128</td>
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<tr>
<td>Post-ilo</td>
<td>78.6 ± 2.3</td>
<td>80.6 ± 2.5</td>
<td>47.8 ± 3.2</td>
<td>3.9 ± 1.3</td>
<td>2.6 ± 0.2</td>
<td>1,309 ± 114</td>
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Absolute values (mean ± SEM) of hemodynamic parameters are given: 1) for the initial pre-intervention baseline; and 2) for later time points, when measurements were undertaken in the morning after an overnight break of iloprost inhalation (pre-ilo) and subsequent to iloprost inhalation (post-ilo). The latter data pairs were obtained after 3 months of inhaled iloprost therapy (iloprost at 3 months), after a mean interval of 18 ± 4 months on clinical deterioration (pre-sildenafil), and after 3 months of adjunct sildenafil therapy while leaving the iloprost regimen unchanged (sildenafil + iloprost).

CI = cardiac index; CVP = central venous pressure; HR = heart rate; mPAP = mean pulmonary artery pressure; mSAP = mean systemic arterial pressure; PVRI = pulmonary vascular resistance index.
Exercise capacity and hemodynamics after 3, 6, and 9 to 12 months of adjunct sildenafl therapy. In each single patient, the 6-min walk distance increased upon the onset of combined therapy. The walking distance increased to 346 ± 1100 m (p < 0.002 vs. pre-sildenafl [Wilcoxon test]), 338 ± 32 m (p = 0.014), and 349 ± 32 m (p = 0.002) after 3, 6 and 9 to 12 months of adjunct sildenafl (Fig. 1). The Hodges-Lehmann point estimates of median differences between pre- and post-sildenafl values and exact 95% confidence intervals (CI) were 86 m (CI 30 to 144), 69 m (CI 21 to 135), and 87 (CI 22 to 152). Clinical improvement was also reflected by a favorable change in NYHA class distribution: 2 patients after 3 months (3 patients after 6 months and 3 patients after 9 to 12 months) were classified in class II; after 3 months 9 patients were classified in class III (8 patients after 6 months, and 8 patients after 9 to 12 months), and after 3 months 9 patients were classified in class IV (2 patients after 6 months, and 1 patient after 9 to 12 months) (Fig. 2). Moreover, the pulmonary vascular resistance index was significantly decreased compared with the pre-sildenafl values, though being assessed at the nadir of sildenafl medication (~10 h after last intake) (Fig. 3). A further reduction on inhalation of iloprost was still noted. In line with these observations, higher pre- and post-iloprost values of the cardiac index and lower values of central venous pressure were observed (Table 1).

Adverse events. No sildenafl-related serious adverse events were reported during the six-month observation period, including headache, dyspepsia, or unwanted erections. Ophthalmologic examinations did not reveal abnormal vision. A slight decrease in systemic arterial pressure was noted (Table 1), but there was no syncope in any patient during sildenafl treatment, and the patients did not complain of dizziness. One patient, the eldest one included in the study (73 years old), acquired severe pneumonia after four months of combined therapy, required mechanical ventilation, and died of pneumonia-associated septic multi-organ failure. Another patient with pulmonary hypertension
associated with CREST (calcinosasis cutis, Raynaud’s phenomenon, esophageal dysfunction, sclerodactyly, and telangiectasia) syndrome died after eight months of combination therapy, also due to severe pneumonia and secondary organ failure in a peripheral hospital. No other deaths occurred, and no patient had to be hospitalized due to clinical deterioration.

**DISCUSSION**

The patients entering this study had severe PAH, as obvious from the predominance of NYHA functional class IV, the low 6-min walk distance, and the high pulmonary vascular resistance, along with low cardiac indexes before starting iloprost treatment. Compared with the available multicenter trials in this field, each of these variables reflected a more serious state of disease; the baseline mean 6-min walk distances were 315, 326, 362, 330, and 332 m in the intravenous prostacyclin (1), subcutaneous teproprostinil (24), oral beraprost (25), oral bosentan (26), and inhaled iloprost (13) studies, compared with 217 m in the present investigation. Impressive improvement of exercise capacity and NYHA class was noted at the onset of inhaled iloprost treatment. Compared with the available multicenter trials in this study population of severely impaired patients, the primary objective was to maximize the therapeutic effect.

Although a high inhalation frequency might be cumbersome, the vast majority of patients currently treated with this approach are not significantly impaired by this procedure. The duration of each inhalation could be reduced to 4 min, due to improvements of nebulizer techniques. Still, one advantage of the combination therapy could be to reduce the frequency of inhalations by prolonging the duration of the vasodilation subsequent to each inhalation. However, in this particular study population of severely impaired patients, the primary objective was to maximize the therapeutic effect.

According to the concept of selective vasodilation, only a minor decrease in systemic blood pressure was noted in response to the combined therapy in PAH patients. Moreover, there were no serious adverse events under this regimen, including ophthalmologic controls undertaken in view of a putative retinal effect of the PDE-5 inhibitor. In view of the severity of disease of the group of patients included, the present death rate was impressively low (32). The two deaths were both associated with severe pneumonia, without preceding right heart failure. Pneumonia in this severely compromised patient collective is often observed to be life-threatening. Moreover, there was no evidence of an increased incidence of respiratory tract infections associated with the treatment in the recent randomized, controlled trial with inhaled iloprost (13).

**Conclusions.** The present study provides strong evidence that patients who are failing while receiving inhaled iloprost may be rescued by adjunct treatment with oral sildenafil. This is most remarkable as pulmonary hypertensive patients deteriorating despite long-term prostanoid therapy are commonly regarded as urgent candidates for lung transplantation. This is the first report of successful use of combined vasodilator therapy in a series of pulmonary hypertensive patients. Despite the limitations of a non-controlled study, the present investigation, due to the profound and lasting improvements observed, strongly suggests that co-administration of prostanoid and PDE-5 inhibitor opens a new perspective for the treatment of pulmonary hypertension and warrants controlled clinical trials for definite proof.

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