Effect of Inhaled Iloprost Plus Oral Sildenafil in Patients With Primary Pulmonary Hypertension

Heinrike Wilkens, MD; Angelika Guth, MD; Jochem König, PhD; Nicole Forestier; Bodo Cremers, MD; Benno Hennen, MD; Michael Böhm, MD; Gerhard W. Sybrecht, MD

Background—The application of iloprost, a stable prostacyclin analogue, by inhalation has been shown to improve hemodynamic variables in patients with primary pulmonary hypertension. However, repetitive inhalations are required due to its short-term effects. One potential approach to prolong and increase the vasorelaxant effects of aerosolized iloprost might be to combine use with phosphodiesterase inhibitors.

Methods and Results—The short-term effects of 8.4 to 10.5 μg of aerosolized iloprost, the phosphodiesterase type 5 inhibitor sildenafil, and the combination thereof were compared in 5 patients with primary pulmonary hypertension. Aerosolized iloprost resulted in a more pronounced decrease in mean pulmonary arterial pressure (PAP) than sildenafil alone (9.4±1.3 versus 6.4±1.1 mm Hg; P<0.05). The reduction in mean PAP after sildenafil was maximal after the first dose (25 mg). The combination of sildenafil plus iloprost lowered mean PAP significantly more than iloprost alone (13.8±1.4 versus 9.4±1.3 mm Hg; P<0.009). No significant changes in heart rate or systemic arterial pressure were observed during any treatment. The treatments were well tolerated, without major adverse effects.

Conclusions—Sildenafil caused a long-lasting reduction in mean PAP and pulmonary vascular resistance, with a further additional improvement after iloprost inhalation. These data suggest that small doses of a phosphodiesterase type 5 inhibitor may be a useful adjunct to inhaled iloprost in the management of pulmonary hypertension. (Circulation. 2001;104:1218-1222.)

Key Words: hypertension, pulmonary ■ iloprost ■ sildenafil

Primary pulmonary hypertension (PPH) is a progressive disease with a median survival of 2.8 years from the time of diagnosis.1 Only the few patients responding to calcium antagonists2 or anticoagulation with coumadine3 may have a better prognosis. The continuous infusion of prostacyclin has been shown to reduce mortality rates from PPH markedly.4 The application of systemic prostacyclin is limited by catheter infection, systemic hypotension, tachyphylaxis, and a lack of selectivity for the pulmonary vasculature. The application of inhaled iloprost, a stable prostacyclin analogue, causes pulmonary vasodilatation matched to ventilation but avoids vasodilatation in nonventilated lung areas. This treatment has been shown to improve exercise capacity and hemodynamic variables in patients with PPH.5,6 However, repetitive inhalations are required for the use of inhaled prostanooids because the short-term effect levels off within 30 to 60 minutes after termination of nebulization. Treatment with infusion or inhalation of prostanooids is hampered by very high costs. One potential approach to prolong and to increase the vasorelaxant effects of iloprost, thereby reducing therapeutic doses and treatment costs, might be the concomitant use of inhibitors of phosphodiesterase (PDE) subtypes 3, 4 and 5.

Sildenafil is a selective vasodilator that enhances and prolongs the action of cyclic guanosine monophosphate (cGMP), a primary mediator of vasodilation, by selectively inhibiting the cGMP-specific PDE5 isozyme. Inhibition of cGMP breakdown might be particularly efficacious in achieving pulmonary vasodilatation, because cGMP formation and urinary excretion is increased in patients with PPH.7 In an animal model of acute pulmonary hypertension, sildenafil decreased pulmonary artery pressure (PAP) dose-dependently.8 There are anecdotal reports of beneficial effects of sildenafil in humans.9–11 Recently, Prasad et al12 observed a reduction of PAP and an improvement of exercise capacity in a young man with PPH who had received sildenafil for 3 months. In the present report, we describe the response to a combined treatment of sildenafil and nebulized iloprost in patients suffering from PPH.

Methods

Five patients with PPH were included and gave written, informed consent. All patients fulfilled the diagnostic criteria of the National Institutes of Health registry for PPH1 and suffered from severe pulmonary hypertension and had New York Heart Association stage III or IV disease. Patient characteristics are listed in Table 1.

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TABLE 1. Patient Characteristics

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age, y</th>
<th>Sex</th>
<th>Duration of PPH, y</th>
<th>Weight, kg</th>
<th>Height, cm</th>
<th>Mean PAP, mm Hg</th>
<th>PVR, Dyne · s · cm⁻²</th>
<th>CVP, mm Hg</th>
<th>NYHA Class</th>
<th>Treatment</th>
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<tr>
<td>1</td>
<td>59</td>
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<td>2.5</td>
<td>69</td>
<td>155</td>
<td>68</td>
<td>1447</td>
<td>20</td>
<td>IV</td>
<td>Inhaled iloprost, warfarin, furosemide, spironolactone, LTOT</td>
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<tr>
<td>2</td>
<td>60</td>
<td>Female</td>
<td>4</td>
<td>54</td>
<td>158</td>
<td>62</td>
<td>1982</td>
<td>12</td>
<td>IV</td>
<td>Inhaled iloprost, warfarin, furosemide, LTOT</td>
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<tr>
<td>3</td>
<td>52</td>
<td>Female</td>
<td>2</td>
<td>73</td>
<td>159</td>
<td>58</td>
<td>1338</td>
<td>8</td>
<td>III</td>
<td>Inhaled iloprost, warfarin, amiodipine, LTOT</td>
</tr>
<tr>
<td>4</td>
<td>49</td>
<td>Female</td>
<td>15</td>
<td>53</td>
<td>162</td>
<td>52</td>
<td>1526</td>
<td>13</td>
<td>IV</td>
<td>Inhaled iloprost, warfarin, furosemide, spironolactone, LTOT</td>
</tr>
<tr>
<td>5</td>
<td>62</td>
<td>Male</td>
<td>1.5</td>
<td>70</td>
<td>170</td>
<td>49</td>
<td>820</td>
<td>3</td>
<td>III</td>
<td>Warfarin</td>
</tr>
</tbody>
</table>

LTOT indicates long-term oxygen treatment.

Exclusion criteria included secondary pulmonary hypertension, pregnancy, hypotension (blood pressure 90/60 mm Hg), or other significant systemic disease. No patients were taking high-dose calcium channel blockers. Four patients were treated with aerosolized iloprost for 2 to 4 years.

Patients were admitted to the intensive care unit, and a fiberoptic Swan Ganz Catheter (Baxter) and an arterial catheter were inserted. Patients were recumbent during the measurements. After a 30-minute equilibration period, hemodynamic variables were recorded. After the baseline hemodynamic variables had been recorded, the short-term hemodynamic response to aerosolized iloprost was measured. For that purpose, 50 μg of iloprost (Ilomedin, Schering) was diluted in 4.5 mL of isotonic saline, aerosolized in a jet nebulizer (Ilo-Neb, Nebu-Tec), and administered over a period of 12 to 15 minutes, which resulted in a cumulative dose of nebulized iloprost between 8.4 and 10.5 μg.⁶

Immediately after inhalation and every 15 minutes thereafter for up to 2 hours, hemodynamic variables were measured to determine the maximal short-term effect of inhaled iloprost and the timing of the hemodynamic response. After hemodynamic parameters had returned to baseline, patients received 25 mg of sildenafil (Pfizer). A second dose of 25 mg of sildenafil was given 30 minutes later. If there was no significant change in systemic arterial pressure, patients received 50 mg of sildenafil after another 30 minutes. A second iloprost inhalation was administered 30 minutes later, and hemodynamic parameters were recorded every 15 minutes for at least 2 hours. Patients were asked about the presence of side effects throughout the investigation.

Hemodynamic Monitoring

Heart rate, pulmonary and systemic arterial pressure, right atrial pressure, and transcutaneous and pulmonary arterial oxygen saturation were monitored continuously. The pulmonary capillary wedge pressure was determined at the end of each evaluation period. Cardiac output was measured by the thermodilution method using the mean of triplicate measurements. A femoral artery catheter was used to measure systemic arterial pressure and systemic arterial oxygen saturation. The pulmonary vascular resistance (PVR) and the systemic vascular resistance were calculated using standard hemodynamic formulas.

Statistical Analysis

All values are presented as mean±SE. Two baselines were set, the first before iloprost inhalation and the second before sildenafil intake. Treatment periods were compared using Student’s 2 sided, paired t test. Within each treatment period, changes in hemodynamics (mean PAP, cardiac output, PVR, blood pressure, heart rate, right atrial pressure, and mixed venous oxygen saturation) after iloprost and sildenafil administration were tested using repeated measures ANOVA with Greenhouse Geisser correction. The first baseline was included for testing the effect of iloprost, the second baseline was included when testing the effects of sildenafil and combined treatment. Post hoc comparisons between baseline and each point in time were performed by Student’s 2-sided, paired t test followed by Bonferroni adjustment of all probability values on the basis of the number of comparisons made in each period. P<0.05 was considered statistically significant.

Results

Iloprost Inhalation

Mean PAP was decreased after iloprost inhalation (repeated-measures ANOVA P<0.0001). Patients displayed a reduction in mean PAP of 9.6±1.3 mm Hg (−16.3±2.2% of baseline; P=0.01) immediately after the inhalation of iloprost (Figure 1A and Table 2). The effect was maximal after 15 to 30 minutes (−17.1±2.9%; P<0.025), with a return to baseline levels after 120 minutes. PVR was markedly diminished after iloprost inhalation (repeated-measures ANOVA P<0.001) by 43.8±3.9% (P=0.002; Figure 2A), with a corresponding in-
crease in cardiac output (repeated-measures ANOVA \( P<0.05 \)) of 43.6\(\pm\)12.2\% (Figure 3A) and an increase in mixed venous oxygen saturation (Table 2). There was no complete return of PVR to baseline after 120 minutes (\(-13.1\pm6.4\% \) lower than baseline, \( P=0.45 \)).

**Sildenafil**

Patients received a cumulative dose of 100 mg of sildenafil. In one patient, only 50 mg of sildenafil was applied because of a decrease in mean systemic arterial pressure from 75 to 65 mm Hg. Oral administration of sildenafil caused a reduction in mean PAP (repeated-measures ANOVA \( P<0.01 \)) of 6.4\(\pm\)11 mm Hg (\(-12.6\pm9.9\% , \ P<0.005 \); Figure 1B). Interestingly, the effect was already maximal after the ingestion of the first dose (25 mg). Further dosing did not produce a cumulative reduction of PAP within our observation interval of 90 minutes. After the first dose of sildenafil, PVR was markedly lowered in all patients (mean decrease, 21.8\(\pm\)3.0\%; \( P<0.03 \)). However, there was no additional decrease in PVR, despite the additional doses of sildenafil (Figure 2B).

**Iloprost Plus Sildenafil**

After the second inhalation of iloprost, mean PAP was 14.1\(\pm\)1.4 mm Hg lower than the baseline values before sildenafil (\(-24.7\pm3\% ; \ P=0.02 , \) repeated-measures ANOVA \( P<0.009 \); Figure 1C). It remained lower than the baseline values before sildenafil in 4 patients after 120 minutes (mean difference, 11.3\(\pm\)4.4\%). PVR was diminished after the second iloprost inhalation (repeated-measures ANOVA \( P<0.002 \)) by \(-43\pm2.7\% (P<0.02 \); Figure 2C), and there was a heart rate–independent increase in cardiac output (repeated-measures ANOVA \( P<0.07 \)) of 22.5\(\pm\)5.1\% (\( P<0.03 \); Figure 3C). Mixed venous oxygen saturation also increased independent of heart rate (Table 2) compared with baseline values before sildenafil after 120 minutes. PVR still was lower than the baseline values before sildenafil in all patients (mean difference, 13.1\(\pm\)3.5\%; \( P=0.1 \)).

**Comparison of Treatments**

A comparison of the 3 treatments showed that iloprost inhalation resulted in a more pronounced decrease in mean PAP than sildenafil alone (9.4\(\pm\)1.3 versus 6.4\(\pm\)1.1 mm Hg; \( P<0.05 \); Figure 4). The combination of sildenafil plus iloprost lowered the mean PAP significantly more than iloprost alone (13.8\(\pm\)1.4 versus 9.4\(\pm\)1.3 mm Hg; \( P<0.009 \)), but there was no significant difference in PVR. The duration of treatment effect was significantly longer after sildenafil than after iloprost inhalation. After iloprost inhalation, baseline values were reached after 60 to 120 minutes; after sildenafil, there was still a treatment effect at the end of study, which was 210 minutes after intake of the first dose. Hemodynamic data in one patient were measured for 5 hours after the first

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**TABLE 2. Hemodynamic Variables in 5 Patients With PPH Before and After Iloprost Inhalation, Sildenafil, and Iloprost Plus Sildenafil**

<table>
<thead>
<tr>
<th></th>
<th>Iloprost Before</th>
<th>Iloprost After</th>
<th>Sildenafil Before</th>
<th>Sildenafil After</th>
<th>Sildenafil + Iloprost Before</th>
<th>Sildenafil + Iloprost After</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate, beats/min</td>
<td>70(\pm)4</td>
<td>72(\pm)4</td>
<td>70(\pm)3</td>
<td>69(\pm)3</td>
<td>70(\pm)3</td>
<td>73(\pm)5</td>
</tr>
<tr>
<td>Mean systemic arterial pressure, mm Hg</td>
<td>83(\pm)3</td>
<td>80(\pm)4</td>
<td>84(\pm)3</td>
<td>77(\pm)5</td>
<td>84(\pm)3</td>
<td>75(\pm)5</td>
</tr>
<tr>
<td>Mean PAP, mm Hg</td>
<td>58(\pm)3</td>
<td>48(\pm)3*</td>
<td>57(\pm)3</td>
<td>50(\pm)3*</td>
<td>57(\pm)3</td>
<td>43(\pm)4†</td>
</tr>
<tr>
<td>Mean right atrial pressure, mm Hg</td>
<td>11(\pm)3</td>
<td>10(\pm)3</td>
<td>11(\pm)3</td>
<td>11(\pm)4</td>
<td>11(\pm)3</td>
<td>9(\pm)4</td>
</tr>
<tr>
<td>Cardiac output, L/min</td>
<td>2.9(\pm)0.3</td>
<td>4.1(\pm)0.4*</td>
<td>3.2(\pm)0.3</td>
<td>3.5(±)0.3</td>
<td>3.2(±)0.3</td>
<td>4.1(±)0.3</td>
</tr>
<tr>
<td>PVR, dynes (\cdot) s (\cdot) cm(^{-5})</td>
<td>1464(±)201</td>
<td>775(±)63*</td>
<td>1256(±)143</td>
<td>953(±)135</td>
<td>1256(±)143</td>
<td>680(±)54*</td>
</tr>
<tr>
<td>Systemic vascular resistance, dynes (\cdot) s (\cdot) cm(^{-5})</td>
<td>2025(±)239</td>
<td>1426(±)155</td>
<td>1832(±)172</td>
<td>1507(±)263</td>
<td>1832(±)172</td>
<td>1174(±)193</td>
</tr>
<tr>
<td>Mixed venous oxygen saturation, %</td>
<td>62(±)2</td>
<td>71(±)3*</td>
<td>63(±)2</td>
<td>71(±)2</td>
<td>63(±)2</td>
<td>72(±)4*</td>
</tr>
</tbody>
</table>

Values are mean\(\pm\)SE.

*\( P<0.05 \), †\( P<0.002 \) for before vs after dose variables.
sildenafil dose. He reached the pre-sildenafil baseline mean PAP values after 4.5 hours, and there was still an effect on PVR. No significant changes in heart rate, pulmonary capillary wedge pressure, right atrial pressure, or systemic arterial pressure were observed during any treatment.

Side Effects

No major side effects were observed. Two patients reported mild coughing during the first iloprost inhalation. Two patients reported mild headache after the second dose of sildenafil. One patient had moderate headache and transient nausea after the second iloprost inhalation; this resolved within 30 minutes without intervention. One patient experienced a drop in mean systemic arterial pressure after a cumulative dose of 50 mg of sildenafil without subjective side effects.

Discussion

PPH is characterized by extensive remodeling of the pulmonary vasculature, with consequent deleterious hypertrophic changes in the right ventricle. During the last 10 years, some advances in the medical management of this debilitating disorder have been achieved. However, the available therapies are limited by poor efficacy or very high costs. There is a need for a treatment achieving a sustained reduction in mean PAP and PVR without these shortcomings.

The aim of the present study was to compare the efficacy of the short-term administration of inhaled iloprost, which has documented beneficial short- and long-term effects, and the oral intake of sildenafil, which has been proposed to be beneficial in case reports in patients with pulmonary hypertension. Furthermore, a cumulative dose-response curve to sildenafil was integrated into the protocol.

The inhalation of iloprost caused a transient decline of mean PAP with a reduction in PVR. Similar data were obtained in previous results. Sildenafil caused a smaller decrease in mean PAP with a much longer lasting duration of action. The effect of iloprost inhalation in addition to oral sildenafil resulted in a further decrease of PAP and an increase in cardiac output without significantly influencing systemic blood pressure or heart rate. The increase in cardiac output without an increase in heart rate provides evidence that the mechanism is an unloading of the right ventricle rather than an increase of sympathetic tone, as was reported recently for sildenafil in healthy volunteers. In a recent experimental study in rabbits with acute pulmonary hypertension induced by treatment with a thromboxane mimetic, the combined effects of inhaled prostacyclin and PDE inhibitors was investigated. Low systemic doses of PDE 3, 4, and 5 inhibitors, which did not affect pulmonary hemodynamics alone, caused significant amplifications of the pulmonary vasodilatory response to inhaled prostacyclin.

Because the second iloprost inhalation was given 30 minutes after the last dose of sildenafil, the ongoing sildenafil absorption might have influenced the response to the iloprost inhalation in our patients. Oral sildenafil application produces peak serum concentrations 0.8 to 0.9 hours after a 100-mg oral dose. The initial hemodynamic effect of 25 mg of sildenafil occurred within 15 minutes of administration. We observed the maximal effect of sildenafil after the 25 mg dose, with no further improvement with the following doses. In contrast, sildenafil caused a dose-dependent decrease in PAP in an animal model of acute pulmonary hypertension induced by the administration of the stable thromboxane analog U46619. Additional dosing with sildenafil decreased PAP further, with no apparent saturation of the effect. This points toward a fundamental hemodynamic difference between experimentally induced pulmonary hypertension and chronic pulmonary hypertension in humans.
In conclusion, the inhalation of iloprost produced a marked reduction of PAP and PVR with a return of PAP to baseline values within 2 hours. The selective PDE5 inhibitor sildenafil caused a long-lasting reduction in mean PAP and PVR, with a further additional improvement after iloprost inhalation. The data suggest that small doses of sildenafil may be a useful adjunct to inhaled iloprost in the management of pulmonary hypertension. These data provide the basis for larger clinical trials in PPH patients for the effects of prostacyclin and sildenafil on outcome in this disabling condition.

References
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