Aerosolized Iloprost Therapy Could Not Replace Long-term IV Epoprostenol (Prostacyclin) Administration in Severe Pulmonary Hypertension*

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Objectives: To switch patients with severe pulmonary hypertension and previous life-threatening catheter-related complications from long-term IV epoprostenol therapy to aerosolized iloprost therapy.

Design: Open, uncontrolled trial.

Setting: Medical ICU of a university hospital.

Patients: Two patients with primary pulmonary hypertension and one patient with pulmonary hypertension after surgical closure of atrial septal defect (mean pulmonary artery pressure ≥ 50 mm Hg). All were classified as New York Heart Association class II under treatment with continuous IV epoprostenol for 4 years.

Interventions: Stepwise reduction of IV epoprostenol (1 ng/kg/min steps every 3 to 10 h) during repeated inhalations of aerosolized iloprost (150 to 300 μg/d with 6 to 18 inhalations/d). Continuous pulmonary and systemic arterial monitoring were performed.

Results: Aerosolized iloprost reduced pulmonary artery pressure by 49%, 49%, and 45%, respectively, and increased cardiac output by 70%, 75%, and 41% in the three patients. The effect lasted for 20 min and was similar at different doses of IV epoprostenol. Persistent treatment change to inhaled iloprost could not be achieved because all patients developed signs of right heart failure. After termination of iloprost inhalations, return to standard epoprostenol therapy led to clinical and hemodynamic restoration.

Conclusions: Although aerosolized iloprost demonstrated short-term hemodynamic effects, it could not be utilized as alternative chronic vasodilator in patients with severe pulmonary hypertension.

(CHEST 2001; 119:296–300)

Key words: aerosolized iloprost; catheter-related complications; inhaled vasodilator therapy; pulmonary hypertension

Abbreviations: LDH = lactate dehydrogenase; PPH = primary pulmonary hypertension

Primary pulmonary hypertension (PPH) is a rare disease of unknown etiology with a progressive course, characterized by an elevated pulmonary artery pressure and pulmonary vascular resistance leading to right ventricular failure and death. Other forms of pulmonary hypertension may occur as a result of conditions such as collagen vascular disease, congenital systemic-to-pulmonary shunts, left-sided ventricular and valvular heart disease, respiratory disease, thromboembolic disease, portal hypertension, or HIV infection. The responsiveness of pulmonary hypertension to vasodilators has led to the speculation that vasoconstriction is an important pathophysiologic feature of this disease. Various vasodilators have been used for long-term treatment, such as oral diazoxide and oral calcium-channel blockers. IV epoprostenol (prostacyclin) is one of the most potent pulmonary vasodilators, but it requires continuous IV administration due to its half-life of 2 to 3 min and, like calcium antagonists, lacks pulmonary vascular selectivity. The major adverse effects of IV epoprostenol therapy are attributable to
the complex delivery system involved: pump malfunction, catheter-related infections, and thrombosis. Interruption of the infusion may lead to rebound pulmonary hypertension, which may be life threatening. Inhaled nitric oxide and aerosolized epoprostenol act as selective pulmonary vasodilators without causing systemic hypotension. Inhaled epoprostenol has been shown to effectively reduce pulmonary artery pressure and vascular resistance in experimental pulmonary hypertension, as well as in patients with PPH and secondary pulmonary hypertension. Based on these data, we attempted a switch from long-term IV epoprostenol to inhaled iloprost in three patients with severe pulmonary hypertension.

**Materials and Methods**

The three patients were women, 42, 30, and 49 years old; the first two patients had PPH and the third patient suffered from progressive pulmonary hypertension after occlusion of an atrial septal defect. All had been treated with continuous IV epoprostenol and warfarin for 4 years, which had improved their New York Heart Association functional class from III and IV to II. All three patients had experienced episodes of life-threatening sepsis caused by the catheter (Port-A-Cath; SIMS Deltec; St. Paul, MN) and had required catheter replacement. For measurement of hemodynamic and gas exchange parameters, a thermodilution pulmonary artery catheter and a radial artery catheter were inserted.

**Table 1—Hemodynamics and Gas Exchange During the Weaning Trial From Long-term IV Epoprostenol to Aerosolized Iloprost**

<table>
<thead>
<tr>
<th>Time, h</th>
<th>IV PGI2, ng/kg/min</th>
<th>PAPm, mm Hg</th>
<th>CO, L/min</th>
<th>PVR, dyn·s·cm⁻⁵</th>
<th>CVP, mm Hg</th>
<th>ABPm, mm Hg</th>
<th>SVR, dyn·s·cm⁻⁵</th>
<th>HR, beats/min</th>
<th>Art.Sat, %</th>
<th>Mv.Sat, %</th>
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<td>5.3</td>
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<td>75</td>
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<td>69</td>
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<td>73</td>
<td>1,478</td>
<td>85</td>
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<td>44</td>
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<td>480</td>
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<td>75</td>
<td>882</td>
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<td>1,092</td>
<td>79</td>
<td>93.5</td>
<td>67.2</td>
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<td>60</td>
<td>5.2</td>
<td>800</td>
<td>5</td>
<td>76</td>
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<td>79</td>
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*PGI2 = epoprostenol; PAPm = mean pulmonary artery pressure; CO = cardiac output; PVR = pulmonary vascular resistance; CVP = central venous pressure; ABPm = mean arterial pressure; SVR = systemic vascular resistance; HR = heart rate; Art.Sat = arterial oxygen saturation; Mv.Sat = mixed venous oxygen saturation.*

Case 1

Baseline measurement under 13 ng/kg/min IV epoprostenol is shown in Table 1. Iloprost was diluted in normal saline solution, 12.5 µg/mL, and delivered by a jet nebulizer with room air (Promenade MB2 Portable Aerosol Equipment; Mefar; Bovezzo, Italy) at a pressure of 2 bar (fluid flux, 0.23 mL/min; aerodynamic diameter of particles, 0.5 to 6 µm). The patient inhaled iloprost, 25 µg, for 15 min every 4 h; concerning the dosage and treatment intervals, we were guided by the study of Olschewski et al. Inhalation of iloprost caused an immediate drop of pulmonary artery pressure, no change of systemic artery pressure, and a slight reduction of heart rate. The trough pulmonary artery pressure occurred a few minutes after starting iloprost inhalation, as shown in on-line recordings (Fig 1). After stopping iloprost inhalation, pulmonary artery pressure gradually increased over the next minutes and reached the preinhalation level after 20 min. IV epoprostenol was slowly reduced within the next 3 days in a stepwise fashion (1 ng/kg/min each step) every 3 to
10 h. During reduction of epoprostenol, pulmonary artery pressure between iloprost inhalations gradually increased. This was accompanied by a decrease in cardiac output and an increase in pulmonary vascular resistance (Table 1). Reduction to 6 ng/kg/min epoprostenol caused a further increase in pulmonary artery pressure to suprasystemic value, associated with a further drop in cardiac output. The magnitude of lowering pulmonary artery pressure by iloprost inhalations was the same at each dose of IV epoprostenol (only the effect at 6 ng/kg/min is shown). Iloprost decreased mean pulmonary artery pressure from 87 to 44 mm Hg (49%), increased cardiac output from 3.7 to 6.3 L/min (70%), and decreased pulmonary vascular resistance from 1,717 to 486 dyne · s · cm⁻² (72%). The tremendous reduction of right ventricular afterload caused an impressive, but short-acting improvement of right ventricular function, as measured by the pulmonary artery catheter (increase of right ventricular ejection fraction from 13 to 22%). The dosage of 6 ng/kg/min epoprostenol could not be further reduced because the patient became dyspneic and hypoxemic; serum bilirubin and lactate dehydrogenase (LDH) rose threefold; transesophageal echocardiography revealed increased size and impaired function of the right ventricle. Doubling the dosage of iloprost (50 μg at each inhalation) could not persistently lower pulmonary artery pressure and improve right heart function. Therefore, the trial of treatment change had to be stopped and the previous epoprostenol dosage was reinstalled; the patient's symptoms and hypoxemia disappeared, pulmonary artery pressure decreased to baseline values, laboratory parameters normalized within 12 h, and echocardiography showed improvement of right ventricular size and function.

**Case 2**

Baseline hemodynamics under 10 ng/kg/min IV epoprostenol are shown in Table 1. Because of the experiences with patient 1, iloprost was aerosolized at a higher dosage from the beginning (50 μg at each inhalation at intervals of 4 h [300 μg/d]) with the Promenade jet nebulizer and the dose of epoprostenol was gradually reduced over the next 36 h. Iloprost had similar effects on pulmonary circulation...
as in patient 1. The epoprostenol infusion could be stopped after 42 h; however, hemodynamic parameters worsened with an increase in pulmonary artery pressure and a dramatic deterioration of cardiac output and mixed venous oxygen saturation within the following 2 h. Laboratory parameters (increase in serum bilirubin, LDH, alanine aminotransferase, and aspartate aminotransferase to 1.9 mg/dL, 327 U/L, 75 U/L, and 51 U/L, respectively) and echocardiographic findings indicated right heart failure. Consequently, the trial of treatment change had to be stopped and continuous IV epoprostenol therapy was reinstalled. Hemodynamic parameters rapidly improved and laboratory parameters normalized thereafter.

Case 3

Baseline measurements at 16 ng/kg/min IV epoprostenol are shown in the Table 1. Due to the experiences with patients 1 and 2, the scheme for iloprost inhalations was changed: the intervals between iloprost inhalations were shortened to 1 h (6 μg at each inhalation) during daytime and maintained at 4 h during nighttime (25 μg at each inhalation; 24-h cumulative dose, 150 μg); the regimen for reduction of IV epoprostenol was prolonged. In addition, a new, specially designed nebulizer for iloprost inhalation was used (Ilo-Neb; Nebu-Tec GmbH; Elenfeld, Germany), aerosolizing iloprost with room air at a pressure of 0.8 bar (third flux, 0.08 mL/min; mass median aerodynamic diameter of particles, 3.5 μm; SD, 0.2) and delivering it to a spacer connected to the afferent limb of a y-valve mouthpiece. Inhaled iloprost decreased mean pulmonary artery pressure by 45% and pulmonary vascular resistance by 73%, and also improved cardiac output by 56%. However, as in patients 1 and 2, this effect was short lasting and preinhalation values were reached after 20 min. The dosage of IV epoprostenol was slowly reduced (1 ng/kg/min each step) over a period of 6 days, and finally the patient could be successfully weaned from epoprostenol. After weaning from epoprostenol, hemodynamic measurement showed a further decrease of cardiac output with no change in pulmonary artery pressure. The patient was discharged from the hospital with the prescription of aerosolized iloprost inhalations every 2 h during daytime and every 4 h during the night (cumulative, 150 μg/d). Two weeks later, the patient complained about deterioration in liver size; laboratory parameters revealed elevated serum bilirubin and LDH. Repeated catheterization demonstrated an increase of pulmonary artery pressure to systemic values and a critically low cardiac output (Table 1). Thus, a new Port-A-Cath catheter had to be inserted and treatment with continuous IV epoprostenol had to be reestablished, leading to gradual improvement of the patient’s clinical situation, hemodynamic and laboratory parameters.

Discussion

Weaning from long-term treatment with continuous IV epoprostenol under repeated inhalations of aerosolized iloprost was not successful in the three patients with severe pulmonary hypertension. In patient 1, IV epoprostenol could only be reduced from 13 to 6 ng/kg/min, because at this dosage the patient developed acute right heart failure. In patient 2, termination of epoprostenol was immediately followed by right heart failure. In patient 3, weaning from epoprostenol seemed to be successful; however, after 2 weeks, the patient presented with signs of right heart failure.

Prostacyclin is one of the most potent pulmonary vasodilators available for long-term treatment of patients with pulmonary hypertension, and results in symptomatic and hemodynamic improvement as well as increased survival. However, it is well known today that catheter infection, pump malfunction, and subclavian vein thrombosis are potentially life threatening in these patients. Theoretically, the administration of aerosolized epoprostenol and iloprost could overcome all these problems.

In our study, inhaled iloprost was very effective in all three patients: it reduced pulmonary artery pressure by 49%, 49%, and 45%, respectively, and increased cardiac output to normal values. However, the main limitation in our study is the short duration of hemodynamic effects. Twenty minutes after stopping inhaled iloprost treatment, hemodynamic variables had returned to the preinhaled time levels. This finding is discordant with the study by Olschewski and coworkers, who reported that inhaled iloprost was effective for 60 to 120 min. The reason for this difference is unknown; it might be the preexisting vasodilator therapy in our patients. However, Groves et al reported hemodynamic effects lasting 10 to 15 min for IV iloprost in 26 PPH patients, which was similar to previous findings in patients with peripheral vascular disease. In our patients, worsening of hemodynamics and subsequent acute right heart failure could not be prevented by increasing the iloprost dose or using a special nebulizer. According to our observations, intervals between iloprost inhalations should be shortened to approximately 45 min, an impracticable recommendation for the patient. Epoprostenol weaning over a period of several days or weeks with very slow reduction of the IV drug may be a potentially successful experiment to undertake in the future.

A promising approach to prolong and increase the vasorelaxant properties of inhaled prostanooids may be the concomitant use of phosphodiesterase inhibitors, which increase the content of cyclic adenosine monophosphate, the second messenger of iloprost, in vascular smooth muscle cells. In experimental pulmonary hypertension in rabbits, coapplication of IV phosphodiesterase inhibitors resulted in augmented and prolonged pulmonary vasodilating effects of aerosolized prostacyclin.

Although our patients received IV epoprostenol continuously, simultaneous administration of aerosolized iloprost showed tremendous hemodynamic efficacy. This implies that additional therapy with inhaled iloprost could be beneficial to patients receiving long-term IV epoprostenol. In addition, it shows the enormous potential for further development of inhaled vasodilator therapies, given that longer-acting prostacyclin analogs will be available in the future.

References

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A 20-year-old female Ethiopian refugee presented with progressive left shoulder tip pain. After extensive investigation, which failed to demonstrate a cause, she proceeded to thoracotomy, where a 25-cm length of tubing was found that had perforated the left hemidiaphragm and had extended into the apex of the left lung. This appeared to have arisen as a complication of a termination of pregnancy performed years previously. This represents the first reported case of significant pulmonary trauma arising as a complication of a termination of pregnancy.

(CHEST 2001; 119:300–302)

Key words: cavitative; obstetric tubing; termination of pregnancy; thoracotomy; transdiaphragmatic migration

Abbreviations: LUL = left upper lobe; TOP = termination of pregnancy

Termination of pregnancy (TOP) is the most widely performed surgical procedure in the world, with an annual incidence of up to 53 million. While complications are infrequent, sepsis, hemorrhage, and uterine perforation with trauma to adjacent organs have been reported.

In this report, we describe an Ethiopian refugee who presented with progressive cavitatory lung disease. After extensive investigation and treatment, at thoracotomy she was found to have a 25-cm length of obstetric tubing perforating the diaphragm and extending into the left upper lobe (LUL). This appeared to have arisen as a complication of a TOP performed years previously in Ethiopia.

We believe there are two unique features of this report. To our knowledge, this is the only recorded description of pulmonary trauma arising from a TOP, and it is the first reported case of the migration of a foreign body from the abdomen or pelvis to the lung that has not occurred via the blood stream.

Case Report

A 20-year-old female Ethiopian refugee presented with a 6-month history of left shoulder pain, productive cough, and minor hemoptysis. Prior to emigration, screening undertaken in Khartoum, Sudan, demonstrated no evidence of active tuberculosis. The initial chest radiograph demonstrated a left basal infiltrate with associated pleural change (Fig 1).

In Australia, ongoing symptoms necessitated further evaluation. CT scan of the thorax showed additional changes of cavitation and consolidation in the LUL (Fig 2). No endobronchial abnormality was evident at fiberoptic bronchoscopy, and bronchial washings were negative for tuberculosis. CT-guided biopsy showed changes of fibrosis. Given a high clinical and radiologic suspicion of tuberculosis, empiric quadruple antituberculosis therapy with isoniazid, rifampicin, ethambutol, and pyrazinamide was commenced. Due to ongoing symptoms and progressive LUL cavitation, she proceeded to thoracotomy. A 25-cm stiff plastic tube was found to perforate the left hemidiaphragm.