Inhaled Iloprost for Treatment of Pulmonary Arterial Hypertension

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Inhaled therapy for pulmonary hypertension is an interesting concept as it offers selectivity of hemodynamic effects for the lung vasculature, thus avoiding systemic side effects. Selective pulmonary vasodilatation has been described for inhaled nitric oxide (NO) but use of this agent has several drawbacks. Most importantly, there are no data demonstrating improved survival with long-term inhaled NO treatment, and there is evidence that this agent possesses less vasodilator potency than do the prostanoids in primary pulmonary hypertension (PPH) patients.[1,2] The intravenous prostacyclin epoprostenol (Flolan) has been shown to improve survival, exercise capacity, and hemodynamics in patients with severe PPH.[3-5] Epoprostenol has been approved for treatment of PPH in the United States and several European countries.

Iloprost, a Stable Prostacyclin Analog

Iloprost is a prostacyclin analog that has the same biologic profile as the natural substance with respect to prostaglandin receptor binding and cellular effects.[6] This explains why during continuous intravenous use its effects as well as its side effects are the same as those of epoprostenol.[7] In contrast, the chemical stability is considerably different. Epoprostenol has to be freshly dissolved, continuously cooled, and protected from light to provide full activity, while iloprost is stable at room temperature and normal light. Epoprostenol has a half-life in vivo of 3 to 5 minutes, while iloprost has a serum half-life of 20 to 25 minutes.[8]

For these reasons iloprost has practical advantages for daily use compared with epoprostenol, and it has been approved for treatment of pulmonary arterial hypertension (PAH) in New Zealand. While epoprostenol is available in the United States and Europe, iloprost is not approved for use in the United States.

The dosages used with continuous epoprostenol range between 10 and 50 ng/kg/min, while the dosages for continuous intravenous iloprost range between 1 and 5 and rarely up to 10 ng/kg/min. The reasons for this huge difference have not been not fully elucidated but probably result from a higher potency of iloprost (about 5:1) and the different delivery method, as well as from more aggressive dosing with intravenous epoprostenol in the United States compared with Europe.

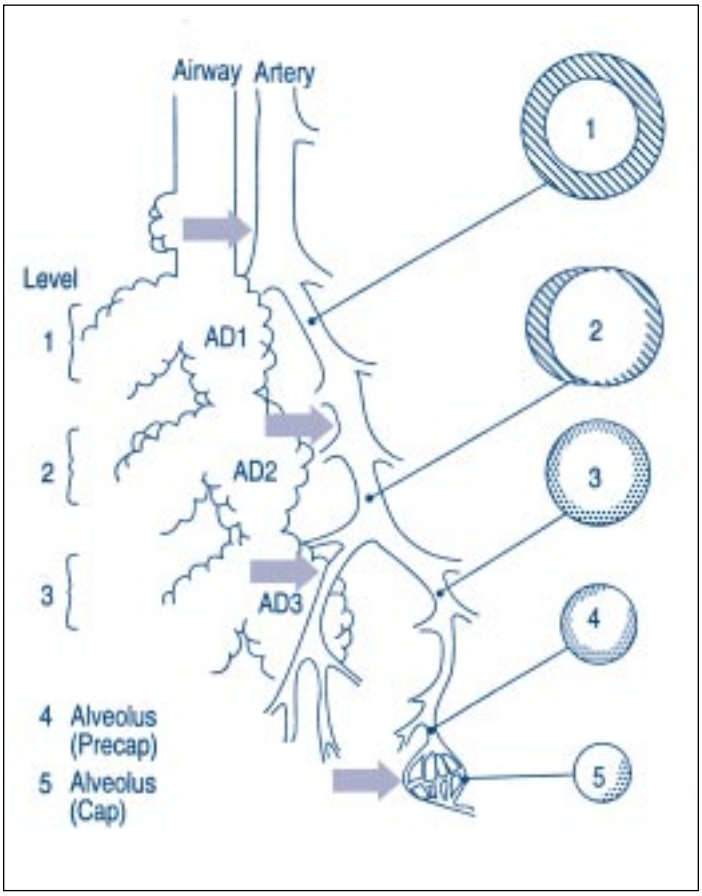

Fig. 1—Anatomy of precapillary pulmonary arteries. Note that at all levels the vessels are in close contact with alveolar surfaces and deposited drug can reach the vessel wall (arrows). Level 1, muscular arteries. Level 2, partly muscular arteries. Level 3, intermediate cells. Level 4, partly intermediate cells. Level 5, pericytes surround lung capillaries.[33]

Prostanoid Inhalation

Patients receiving prostanoids are prone to side effects such as headache, jaw pain, leg pain, and diarrhea, and there may be complications with the delivery system. These findings are well documented for continuous intravenous epoprostenol therapy[3,9,10] and have also been reported with the subcutaneous delivery of the prostacyclin preparation treprostinil.[11]

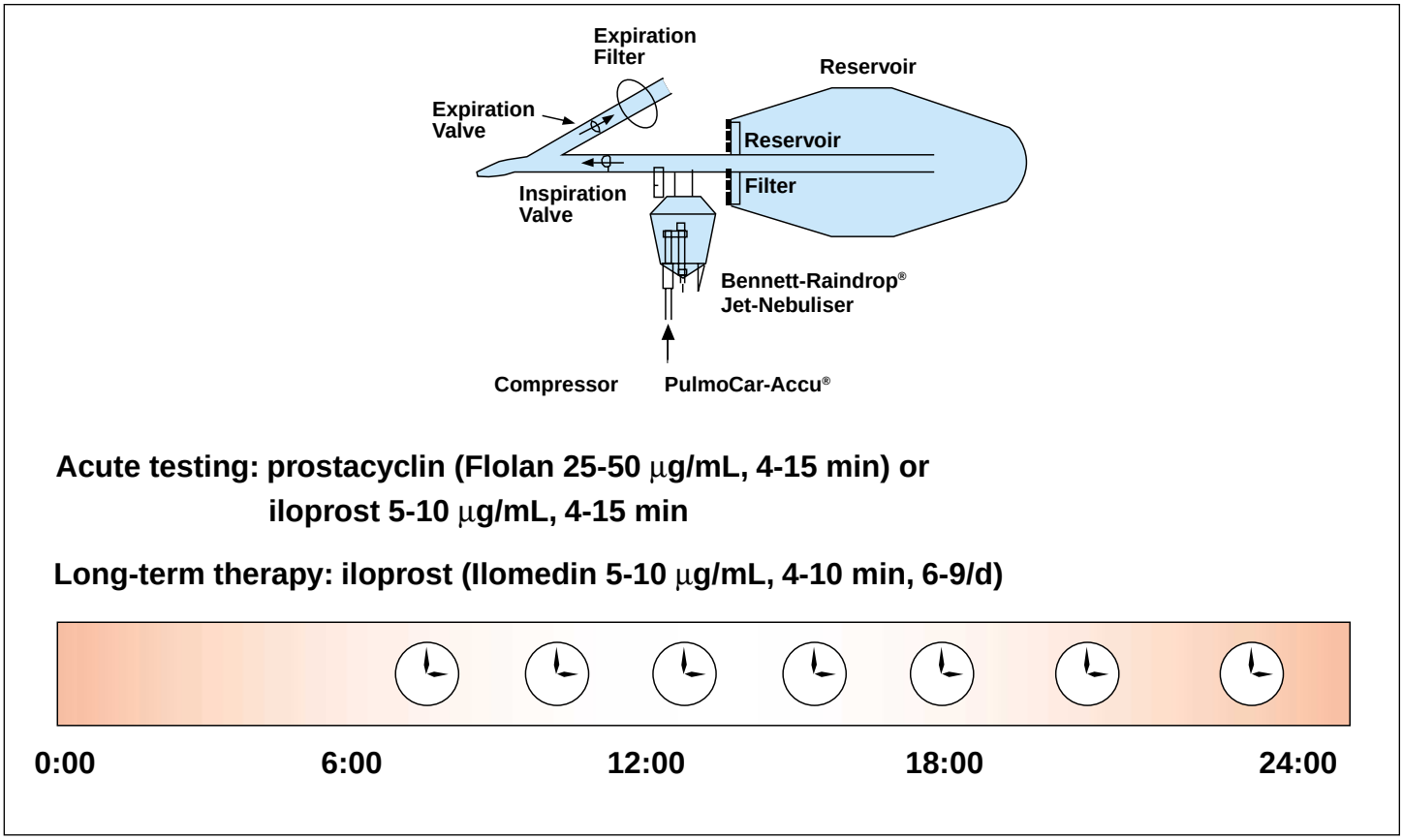

Fig. 2—Inhalation of prostanoids. A schematic of the IloNeb™ Device with Aerotrap™ Reservoir (NebuTec, Elsenfeld, Germany) is shown to demonstrate prostanoid aerosolization for testing and as therapy for pulmonary hypertension. Alternative devices allow inhalation times as short as 4 minutes. Inhalations are repeated six to nine times a day with an overnight pause.

Oral application of prostanoids (beraprost) may decrease delivery-associated risks, but this therapy has not yet proved effective in severe disease, although in moderately ill PPH patients there was a significant benefit in a controlled study.[12]

In order to selectively treat the pulmonary vessels in the ventilated areas of the lung, inhaled prostacyclin and iloprost were ultimately considered as treatment options. Due to the fact that the intraacinar pulmonary arteries are tightly surrounded by alveolar surfaces (**Figure 1**), it is possible to vasodilate these vessels via the alveolar deposition of a prostanoid. For acute vasodilator testing with inhaled prostacyclin or iloprost, a special inhalation device with a drug-saving reservoir for delivery of aerosols is utilized.

For long-term therapy,

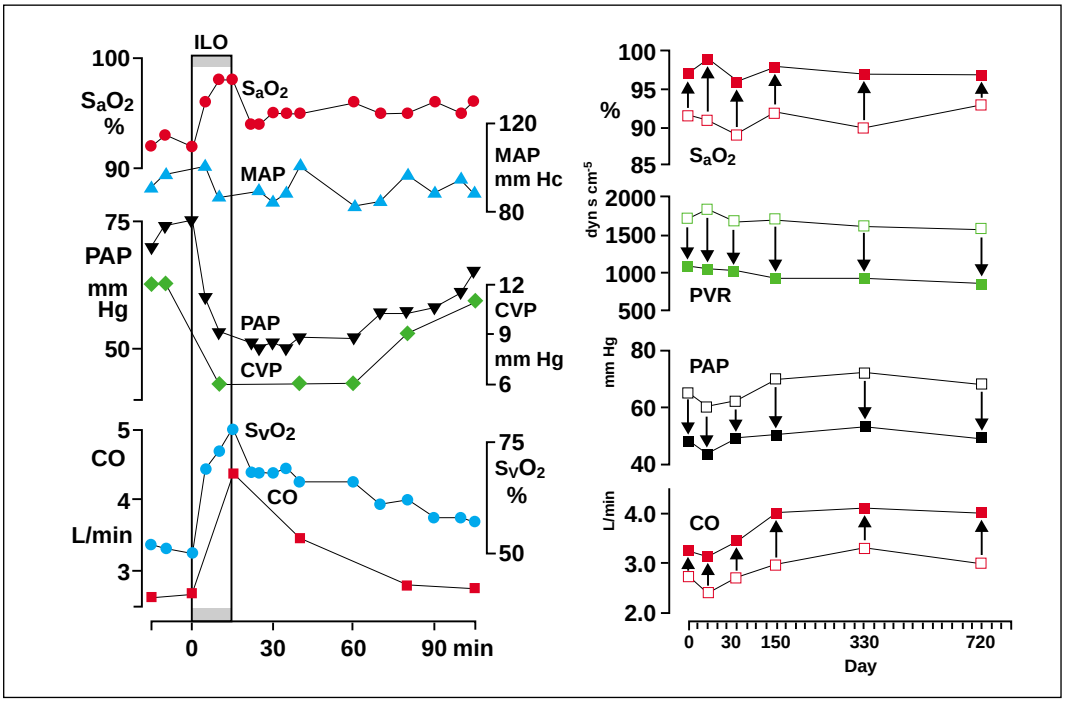

Fig. 3—Acute hemodynamic effects of iloprost inhalation. Left: Inhalation of 2.8 μg of iloprost during a 15-minute inhalation time (ILO). S_aO_2, systemic arterial O_2 saturation; MAP, mean systemic arterial pressure; PAP, mean pulmonary artery pressure; PVR, pulmonary vascular resistance; CVP, central venous pressure; S_vO_2, pulmonary artery O_2 saturation; CO, cardiac output. Note that inhalation decreases PAP but not MAP. Right: Results of repeat cardiac catheterization in the same patient. Arrows indicate acute changes induced by iloprost inhalation.[14]

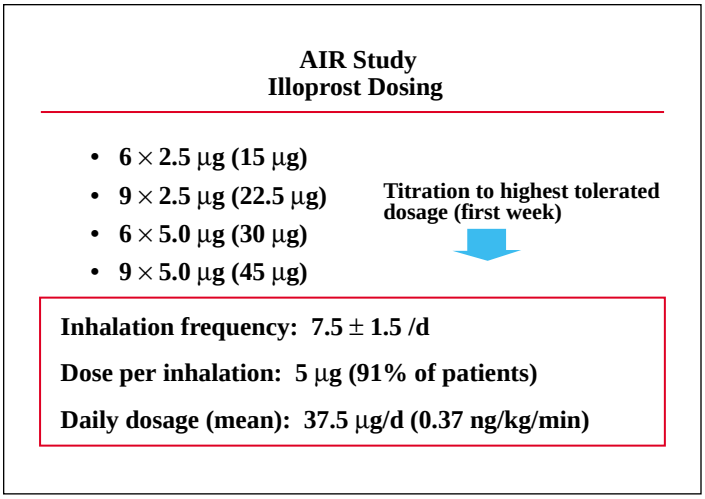

Fig. 4—Dose titration with inhaled iloprost in AIR study. During the first week of the study, the dose was increased until side effects appeared or a maximal regimen of 5 μg delivered nine times was achieved. The majority of patients tolerated 5 μg per inhalation. About 50% of patients inhaled six times per day and 50% inhaled nine times daily.

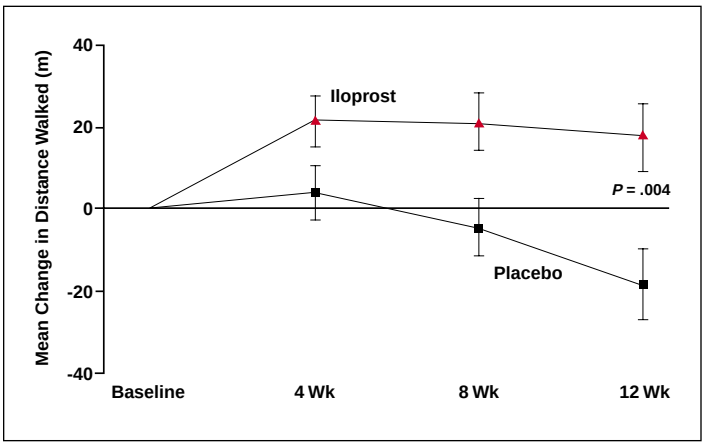

Fig. 5—Change in 6-minute walk test in AIR study. There was a significant improvement in distance walked in favor of the iloprost-treated group. The difference between groups was 36.4 meters. For the subgroup of PPH patients the difference was 59 meters, for the other patients 12 meters.[26]

repetitive inhalations with iloprost, six to nine times per day are required (**Figure 2**). Each inhalation takes approximately 10 to 15 minutes. With newer devices, it is possible to reduce the inhalation time to about 4 minutes[13] and to avoid noisy delivery by using ultrasound energy for nebulization.

In patients with severe PAH, we have demonstrated that inhalation of aerosolized iloprost results in a substantial decrease in pulmonary artery pressure and pulmonary vascular resistance. This decrease is concomitant with an increase in cardiac output, in the absence of a significant decrease in mean arterial pressure (**Figure 3**) or worsening ventilation-perfusion mismatch.[14,15]

In a statistical comparison of the effects of intravenous epoprostenol and inhaled iloprost, the mean acute effect on pulmonary vascular resistance was equal. However, during treatment with inhaled iloprost, pulmonary artery pressure decreased significantly and systemic artery pressure remained stable, whereas during treatment with intravenous

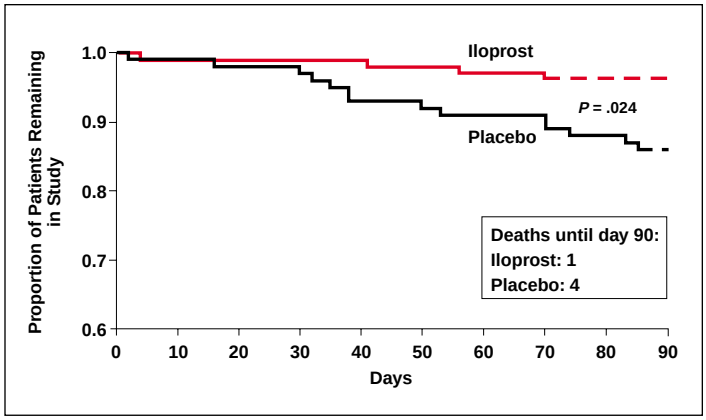

Fig. 6—Likelihood of completing 12-week AIR study. Kaplan-Meier survival estimates are shown for patients receiving iloprost vs placebo. Reasons for not completing included death, discontinuation of study medication, and withdrawal of consent, usually because of clinical deterioration.[26]

epoprostenol, systemic pressure decreased significantly and pulmonary artery pressure was minimally changed.[14] These observations were consistent with preceding findings in mechanically ventilated patients with acute respiratory failure.[16-22] In uncontrolled studies, inhaled iloprost was effective in decompensated right heart failure[23] and led to favorable long-term hemodynamic improvement.[24]

AIR Study

A large randomized double-blind placebo-controlled multicenter study in Europe with inhaled iloprost has been performed (Aerosolized Iloprost Randomized, AIR).[25] A total of 203 patients with PPH or other forms of PAH were enrolled. These included New York Heart Association (NYHA) Functional Class III or IV patients with PAH due to appetite suppressants or collagen vascular diseases and those with associated or non-operable thromboembolic pulmonary hypertension. In the iloprost and placebo groups, about 50% had PPH and 50% had PAH of other causes. About 60% were in NYHA Functional Class III and 40% in Functional Class IV.

The primary end point of the study, defined as an improvement in NYHA Functional Class combined with at least 10% improvement in the 6-minute walk test and no prior deterioration or death (combined clinical end point), was reached by 3.4 times more patients in the iloprost group compared with the placebo group (16.8% vs 4.9%; $P = .007$). Treatment effects did not differ between subgroups. This effect was achieved with a mean inhaled iloprost dosage of 0.37 ng/kg/min (**Figure 4**).

In the 6-minute walk test the treatment effect was 36.4 meters in favor of iloprost ($P < .004$, **Figure 5**). There was a treatment effect with iloprost on NYHA Functional Class ($P < .05$), quality of life assessments by means of the EuroQoL visual analogue scale ($P < .05$), and on the Mahler Dyspnea Transition Index ($P < .05$). Hemodynamics significantly deteriorated in the placebo group, whereas in the iloprost group, although preinhalation values were unchanged compared with baseline, postinhalation values were significantly improved. Importantly, the number of patients remaining on study medication was significantly higher in the ilo-

prost than in the placebo group (**Figure 6**).

Over 3 months of therapy, there was no indication of tachyphylaxis. In the iloprost group, 1 patient (1.0%) died during the double-blind study period vs 4 patients (4.0%) in the placebo group. Overall, iloprost therapy was well tolerated. Cough, headache, and flushing occurred more commonly in the iloprost group. These adverse events were mild and mostly transient. Syncope occurring in the iloprost group was more often rated as serious, compared with the placebo group, but was commonly not associated with clinical deterioration. It can be concluded from this study that inhalation of iloprost is an effective and safe therapy for patients with severe (NYHA Functional Class III and IV) PPH and for patients with the other causes of PAH that were studied.

Future Perspectives

In addition to treatment of PPH, the pulmonary selectivity of inhaled iloprost provides the chance to safely apply prostanoids in patients who are prone to systemic hypotension, such as patients with portopulmonary hypertension, and in emergency situations. The intrapulmonary selectivity allows prostanoid application in patients who are prone to intrapulmonary right-to-left shunt, such as patients with pulmonary fibrosis.[15] The inhaled application may be combined with other effective treatments for PAH, although this has not yet been studied in a controlled fashion.

A more specific positive interaction is the use of inhaled iloprost in combination with phosphodiesterase (PDE) inhibitors. The specific pulmonary vasodilating effects of iloprost that may be mediated by an intracellular increase of cAMP can be increased by blocking the breakdown of this second messenger by means of PDE inhibition.[26-31] We noticed excellent clinical results with the combination of inhaled iloprost and sildenafil, a specific PDE 5 inhibitor[32] and have been successfully using this combination for more than a year in a considerable number of patients. At present sildenafil is not approved for use as therapy for PAH, but clinical studies are under way. Inhalation intervals could be lengthened and pulmonary selectivity could still potentially be achieved with the concominant use of PDE inhibitors. This approach could also lead to simpler delivery methods, such as via metered dose inhaler, for treatment of PAH.

Conclusions

Inhaled iloprost has been shown to be effective for the treatment of PAH and may provide an alternative to the use of intravenous epoprostenol. When the clinical effects of inhaled iloprost and intravenous epoprostenol are compared, iloprost inhalation has clear advantages but also certain drawbacks. Most importantly, inhalation provides potent pulmonary vasodilatation with minimal systemic side effects and no risk of catheter-related complications. Additionally, iloprost could be considered as therapy in patients with pre-existent ventilation-perfusion mismatch and in those who are prone to develop such a mismatch during systemic prostanoid application. The most important disadvantage is the fact that the hemodynamic effects of inhaled iloprost last only 30 to 90 minutes, and that six to nine inhalations are needed to achieve good clinical results. In addition, sustained hemodynamic improvement and long-term survival with long-term use of inhaled iloprost have yet to be demonstrated in more than a small number of patients.

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(Sir John Vane, continued from page 3)

the mode of action of aspirin, for example. As a pharmaceutical consultant, Dr Vane initiated the program in inhibiting angiotensin-converting enzyme (ACE) that led to the development of the ACE inhibitor captopril (Capozide). He also oversaw the development of atracurium (Tracrium), acyclovir (Zovirax), and lamotrigine (Lamictal). After achieving knighthood, Dr Vane founded the William Harvey Research Institute in 1986 and has built the Institute to more than 100 members. In 1971 Dr Vane and his associates discovered that aspirin and similar drugs produced their effects because they inhibit the biosynthesis of prostaglandins. This paved the way for further discovery implicating the cyclooxygenases as being responsible for producing prostaglandins. This, in turn, has led the way for additional research into the COX-2 inhibitor used to treat such inflammatory diseases as rheumatoid arthritis.

Dr Vane has also explored other avenues of research into the mechanisms of prostaglandin, including its cytoprotective effects. "In models of myocardial infarction, it will reduce the infarct size. It will reduce oxygen demand and enzyme release from the infarcted areas. Other prostaglandins also share similar cytoprotective activity, distinct from the activity on platelet aggregation or vasodilatation."

One of the intriguing questions still unresolved is the possibly synergistic relationship between prostacyclin—essentially a cyclic AMP agonist—and the phosphodiesterase inhibitor sildenafil (Viagra). Dr Vane suggested that the synergism could be related to the fact that sildenafil inhibits consumption of both cyclic GMP and cyclic AMP. This could enhance the effect of prostacyclin in pulmonary hypertension.

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