INHALED ILOPROST FOR SEVERE PULMONARY HYPERTENSION

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ABSTRACT

Background   Uncontrolled studies suggested that aerosolized iloprost, a stable analogue of prostacyclin, causes selective pulmonary vasodilatation and improves hemodynamics and exercise capacity in patients with pulmonary hypertension.

Methods   We compared repeated daily inhalations of 2.5 or 5.0 μg of iloprost (six or nine times per day; median inhaled dose, 30 μg per day) with inhalation of placebo. A total of 203 patients with selected forms of severe pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension (New York Heart Association [NYHA] functional class III or IV) were included. The primary end point was met if, after week 12, the NYHA class and distance walked in six minutes were improved by at least one class and at least 10 percent, respectively, in the absence of clinical deterioration according to predefined criteria and death.

Results   The combined clinical end point was met by 16.8 percent of the patients receiving iloprost, as compared with 4.9 percent of the patients receiving placebo (P=0.007). There were increases in the distance walked in six minutes of 36.4 m in the iloprost group as a whole (P=0.004) and of 58.8 m in the subgroup of patients with primary pulmonary hypertension. Overall, 4.0 percent of patients in the iloprost group (including one who died) and 13.7 percent of those in the placebo group (including four who died) did not complete the study (P=0.024); the most common reason for withdrawal was clinical deterioration. As compared with base-line values, hemodynamic values were significantly improved at 12 weeks when measured after iloprost inhalation (P<0.001), were largely unchanged when measured before iloprost inhalation, and were significantly worse in the placebo group. Further significant beneficial effects of iloprost treatment included an improvement in the NYHA class (P=0.03), dyspnea (P=0.015), and quality of life (P=0.026). Syncope occurred with similar frequency in the two groups but was more frequently rated as serious in the iloprost group, although this adverse effect was not associated with clinical deterioration.

Conclusions   Inhaled iloprost is an effective therapy for patients with severe pulmonary hypertension. (N Engl J Med 2002;347:322-9.)
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A CONTINUOUS infusion of prostacyclin was the first therapy shown to reduce mortality in a controlled study of patients with severe pulmonary hypertension.[1] However, its use is associated with a number of serious drawbacks. The lack of pulmonary selectivity results in systemic side effects, tolerance leads to progressive increases in the dose, and there may be recurrent infections of the intravenous catheter.[2] As an alternative, inhaled nitric oxide possesses pulmonary selectivity, but it is less potent than prostacyclin in the pulmonary vasculature.[3,4] Moreover, an interruption in the inhalation of continuous nitric oxide may cause rebound pulmonary hypertension.[5,6] Designed to combine the beneficial effects of prostacyclin with those of an inhalational application, aerosolized prostacyclin was found to be a potent pulmonary vasodilator in patients with acute respiratory failure, exerting preferential vasodilatation in well-ventilated lung regions.[7-10] Similar results were obtained in spontaneously breathing patients who had lung fibrosis and severe pulmonary hypertension.[11]

Iloprost is a stable analogue of prostacyclin that is associated with a longer duration of vasodilatation.[12] When administered during a short aerosolization ma-

neuver to patients with pulmonary hypertension, its pulmonary vasodilative potency was similar to that of prostacyclin, but its effects lasted for 30 to 90 minutes, as compared with 15 minutes.[4,11,13-15] Several open-label, uncontrolled studies of patients with severe pulmonary hypertension suggested that long-term use of aerosolized iloprost results in substantial clinical improvement.[11,13,16-20] Our objective in this trial was to evaluate the effects of inhaled iloprost using a rigorous end point of clinical efficacy.

METHODS

Selection of Patients

Patients with primary pulmonary hypertension and selected forms of nonprimary pulmonary hypertension were candidates for the study. The forms of nonprimary pulmonary hypertension included appetite-suppressant–associated and scleroderma-associated pulmonary hypertension as well as inoperable chronic thromboembolic pulmonary hypertension. The inclusion criteria were a mean pulmonary-artery pressure greater than 30 mm Hg, the ability to cover between 50 and 500 m without encouragement on a six-minute walk test,[21] and a New York Heart Association (NYHA) functional class of III or IV[22] despite the use of standard conventional therapy (anticoagulants, diuretics, digitalis, calcium-channel blockers, and supplemental oxygen). Patients who were taking investigational drugs, prostanoids, or beta-blockers were excluded. The doses of calcium-channel blockers had to be constant for more than six weeks before study entry. Exclusion criteria were a pulmonary-artery wedge pressure at rest of more than 15 mm Hg, a cardiac index at rest of less than 1.5 or more than 4 liters per minute per square meter of body-surface area, bleeding disorders, a bilirubin level of more than 3 mg per deciliter (51 μmol per liter), creatinine clearance below 30 ml per minute, a forced vital capacity below 50 percent, a forced expiratory volume in one second that was less than the mean normal value minus twice the standard deviation, and clinical instability.

Study Design

A total of 203 patients participated after giving written informed consent and after the study had been approved by the local ethics committees at 37 European specialist centers. Patients were randomly assigned to receive iloprost (Ilomedin, Schering) or placebo after stratification according to NYHA functional class (III or IV) and type of pulmonary hypertension (primary or nonprimary) by an independent committee whose members were unaware of patients' identities. A total of 101 patients were randomly assigned to the iloprost group, and 102 were assigned to the placebo group.

For inhalation, iloprost or placebo was diluted with saline to a concentration of 10 μg per milliliter, and 2 ml was added to a nebulizer (HaloLite, MedicAid). This device delivered short pulses of aerosolized particles (geometric median [$\pm$SD] aerodynamic diameter of particles, 4.3$\pm$0.05 μm)[23] during the first part of each inspiration until a predefined total inhaled dose of 2.5 μg had been dispensed. The inhalation was then stopped or repeated once, to achieve a total dose of 5.0 μg, depending on how well the patient tolerated the treatment. After each inhalation, the residual volume in the nebulizer was discarded. This maneuver was repeated six or nine times daily, with an overnight break. The frequency of inhalation and the dose were individually determined within the first eight days of therapy according to a predefined dosing algorithm.

Right-heart catheterization was performed in all patients at base line and after 12 weeks. The acute effects of inhaled iloprost were evaluated after 12 weeks in all patients, but not at base line, to avert unblinding. At base line and after 4, 8, and 12 weeks, patients completed a six-minute walk test, the Mahler Dyspnea Index ques-

tionnaire,[24] the EuroQol questionnaire,[25] and the 12-item Medical Outcomes Study Short-Form General Health Survey.[26]

Patients were removed from the study if they met two or more of the following predefined criteria for a deterioration in their condition: refractory systolic arterial hypotension (blood pressure, less than 85 mm Hg); worsening right ventricular failure (e.g., as indicated by the development of refractory edema or ascites); rapidly progressing cardiogenic, hepatic, or renal failure; a decrease of at least 30 percent in the distance walked in six minutes; and a decline in measures of hemodynamic function, such as central venous pressure and mixed venous oxygen saturation.

Outcome Measures

The primary end point of the study consisted of an increase of at least 10 percent in the distance walked in six minutes and an

TABLE 1. BASE-LINE CHARACTERISTICS OF THE PATIENTS.*

CHARACTERISTIC	ILOPROST GROUP (N=101)	PLACEBO GROUP (N=102)
Age — yr	51.2±13.2	52.8±12.0
Weight — kg	71.3±14.6	72.6±13.9
Sex — %		
Male	31.7	33.3
Female	68.3	66.7
Underlying disease — no. (%)		
Primary pulmonary hypertension	51 (50.5)	51 (50.0)
Nonprimary pulmonary hypertension	50 (49.5)	51 (50.0)
Appetite suppressants	4 (4.0)	5 (4.9)
Collagen vascular disease	13 (12.9)	22 (21.6)
Chronic thromboembolic pulmonary hypertension	33 (32.7)	24 (23.5)
Oral vasodilator therapy — no. (%)	52 (51.5)	58 (56.9)
NYHA functional class — no. (%)		
III	60 (59.4)	59 (57.8)
IV	41 (40.6)	43 (42.2)
Mahler Dyspnea Index†	4.14±1.8	4.27±1.8
6-Minute walk distance — m	332±93	315±96
Hemodynamic variables‡		
Pulmonary-artery pressure — mm Hg	52.8±11.5	53.8±14.1
Cardiac output — liters/min	3.8±1.1	3.8±0.9
Pulmonary vascular resistance — dyn·sec·cm⁻⁵	1029±390	1041±493
Systemic vascular resistance — dyn·sec·cm⁻⁵	1872±673	1827±503
Central venous pressure — mm Hg	9.2±5.3	8.2±5.0
Pulmonary-artery wedge pressure — mm Hg	7.5±3.3	7.6±3.9
Arterial oxygen saturation — %	92.6±4.4	92.2±5.0
Mixed venous oxygen saturation — %	60.4±7.5	60.5±8.2
Heart rate — beats/min	83.9±12.2	81.8±15.4

*Plus–minus values are means ±SD. NYHA denotes New York Heart Association. There were no significant differences between the iloprost and the placebo groups. Data on all variables were available for all patients except in the following categories: pulmonary-artery pressure, 1 patient in each group; cardiac output, 1 patient in the iloprost group and 6 in the placebo group; pulmonary vascular resistance, 10 and 6, respectively; systemic vascular resistance, 11 and 14; central venous pressure, 5 and 7; pulmonary-artery wedge pressure, 8 and 3; arterial oxygen saturation, 35 and 31; mixed venous oxygen saturation, 16 and 18; and heart rate, 2 and 3.

†On this 12-point scale, higher scores indicate less dyspnea.

‡Patients who were receiving long-term oxygen therapy received nasal oxygen during the measurement of base-line hemodynamic variables.

improvement in the NYHA functional class in the absence of a deterioration in the clinical condition or death during the 12 weeks of the study. Secondary efficacy variables were changes in the values for the six-minute walk test, the NYHA class, Mahler Dyspnea Index scores, hemodynamic variables, and the quality of life; clinical deterioration; death; and the need for transplantation.

Statistical Analysis

The primary evaluation of efficacy included all randomized patients. Data are presented as means ±SD, unless otherwise stated. We included data on patients who prematurely discontinued the study using a last-observation-carried-forward analysis for the six-minute walk test. Patients who died were assigned a value of 0 m. All statistical tests for efficacy variables were two-tailed, with an alpha level of 0.05.

To analyze the primary efficacy end point and the improvement criteria, we used the Mantel–Haenszel test,[27] stratified according to the type of pulmonary hypertension (primary or nonprimary) and NYHA class (III or IV). Patients with missing data on the primary end point at week 12 were considered not to have had a response.

Changes in the results of the six-minute walk were evaluated with use of nonparametric analysis of covariance stratified according to the type of pulmonary hypertension (primary or nonprimary) and the NYHA class (III or IV), with use of the base-line value as the covariate (analysis of covariance), and the Wilcoxon signed-rank test.

Changes from base line in hemodynamic values were analyzed with t-statistics. The investigators had full access to the data and performed the analyses independently of the sponsor.

RESULTS

Base-line demographic and hemodynamic data are given in Table 1. The mean frequency of inhalation was 7.5 times per day. Ninety-one percent of patients received 5.0 μg per inhalation, and 9 percent received 2.5 μg, corresponding to a median inhaled dose of 30 μg per day.

Primary Efficacy End Point

For the primary end point, we found a significant effect of treatment in favor of iloprost (P=0.007) (Fig. 1). The estimated odds of an effect in the iloprost group, as compared with the placebo group, were 3.97 (95 percent confidence interval, 1.47 to 10.75, by the Mantel–Haenszel test), with no significant heterogeneity among the four subgroups categorized according to type of pulmonary hypertension and NYHA class at base line (P=0.79 by the Breslow–Day test). The secondary analysis of the primary end point was a logistic-regression model that included treatment assignment, demographic data, and base-line characteristics. Only treatment assignment (P=0.01) contributed significantly to the probability of a response.

Secondary End Points

Six-Minute Walk Test

The percentage of patients who had an increase of at least 10 percent in the distance walked in six minutes at week 12 was slightly, but not significantly, higher in the iloprost group than in the placebo group (P=0.06) (Table 2). The type of pulmonary hypertension had no significant effect on the outcome in either group (P=0.90). A higher percentage of patients in the placebo group than in the iloprost group had a decrease in the distance walked of at least 10 percent or did not complete the study (Table 2).

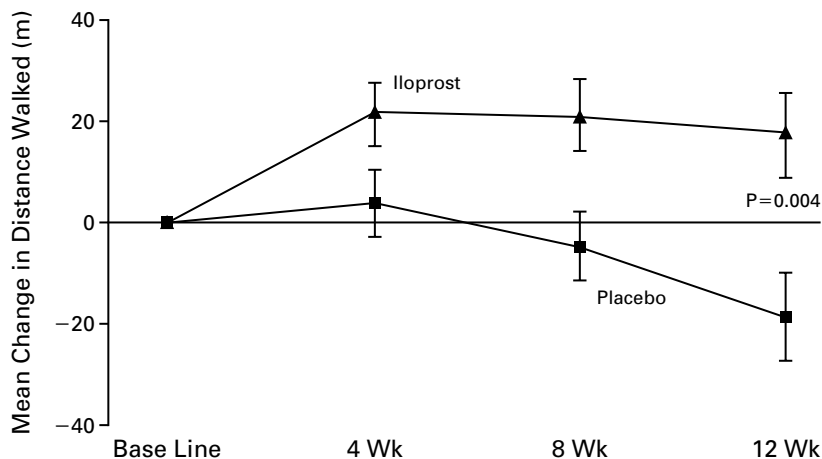The absolute change in the distance walked in six minutes was significantly larger (by 36.4 m) in the

Figure 1. Effect of Inhaled Iloprost and Placebo on the Mean (±SE) Change from Base Line in the Distance Walked in Six Minutes, According to an Intention-to-Treat Analysis.
The P value was obtained with Wilcoxon's test for two independent samples.

iloprost group than in the placebo group (P=0.004) (Fig. 1): 58.8 m among those with primary pulmonary hypertension and 12 m among those with non-primary pulmonary hypertension. A parametric analysis of covariance, which included the absolute value on the six-minute walk test at week 12 as a dependent variable and the treatment assignment (P=0.02), type of pulmonary hypertension (P=0.06), and distance walked at base line (P<0.001) did not show a statistically significant interaction between treatment and type of pulmonary hypertension (P=0.09).

NYHA Class

More patients in the iloprost group than in the placebo group had an improvement in the severity of heart failure, as assessed by the NYHA class (P=0.03) (Table 2). The type of pulmonary hypertension had no effect on the outcome in either group (P=0.39). The percentage of patients with a deterioration in NYHA class did not differ significantly between the groups, but the analysis did not include patients who left the study early owing to death or other reasons. A larger proportion of patients in the placebo group than in the iloprost group did not complete the study (Table 2 and Fig. 2). Reasons included death, discontinuation of study medication, and withdrawal of consent, mostly owing to clinical deterioration, insufficient clinical benefit, or both.

Hemodynamics and Gas Exchange

In the placebo group, cardiac output, systemic arterial oxygen saturation, and mixed venous oxygen saturation decreased significantly after 12 weeks and pulmonary vascular resistance and right atrial pressure increased significantly (Table 3). In the iloprost group, values assessed at 12 weeks, before the first morning dose of inhaled iloprost, were largely unchanged from base line, whereas values assessed after inhalation were significantly decreased (in the case of pulmonary-artery pressure, pulmonary vascular resistance, systemic arterial pressure, and systemic arterial oxygen saturation) or increased (in the case of carbon monoxide and pulmonary-artery wedge pressure). At the completion of the 12-week study, acute hemodynamic responsiveness to inhaled iloprost was equivalent in the placebo group and the iloprost group, though the latter group had been exposed to daily iloprost inhalation for three months (data not shown).

Mahler Dyspnea Index

The mean Mahler Dyspnea Index transition score was significantly better at week 12 in the iloprost

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TABLE 2. EFFECTS OF 12 WEEKS OF THERAPY WITH INHALED ILOPROST OR PLACEBO ON THE NEW YORK HEART ASSOCIATION (NYHA) CLASS AND THE SIX-MINUTE WALK TEST.

VARIABLE	ILOPROST GROUP			PLACEBO GROUP		
	ALL PATIENTS	PATIENTS WITH PRIMARY PULMONARY HYPERTENSION	PATIENTS WITH NONPRIMARY PULMONARY HYPERTENSION	ALL PATIENTS	PATIENTS WITH PRIMARY PULMONARY HYPERTENSION	PATIENTS WITH NONPRIMARY PULMONARY HYPERTENSION
			percentage of patients			
Change in NYHA class						
Improved by 2 classes	1.0*	1.9	0.0	0.0	0.0	0.0
Improved by 1 class	23.8*	22.6	25.0	12.7	7.3	19.1
Unchanged	64.4	66.0	62.5	65.7	69.1	61.7
Worsened	5.9	3.8	8.3	7.8	10.9	4.3
Data missing	1.0	1.9	0.0	0.0	0.0	0.0
Noncompletion of study	4.0	3.8	4.2	13.7	12.7	14.9
Death	1.0	1.9	0.0	3.9	3.6	4.3
Other	3.0†	1.9	4.2	9.8‡	9.1	10.6
Change in 6-minute walk distance						
≥10% increase	37.6§	49.1	25.0	25.5	30.9	19.1
<10% increase to <10% decrease	42.6§	37.7	47.9	32.4	20.0	46.8
≥10% decrease	13.9	5.7	22.9	25.5	32.7	17.0
Data missing	5.9	7.5	4.2	16.7	16.4	17.0
Combined end point	16.8¶	20.8	12.5	4.9	5.5	4.3

*P=0.03 for the comparison of rates of improvement (by one or two classes) with the placebo group.

†Treatment was discontinued in all three patients.

‡Treatment was discontinued in seven patients, and three patients withdrew their consent.

§P=0.06 for the comparison with the placebo group.

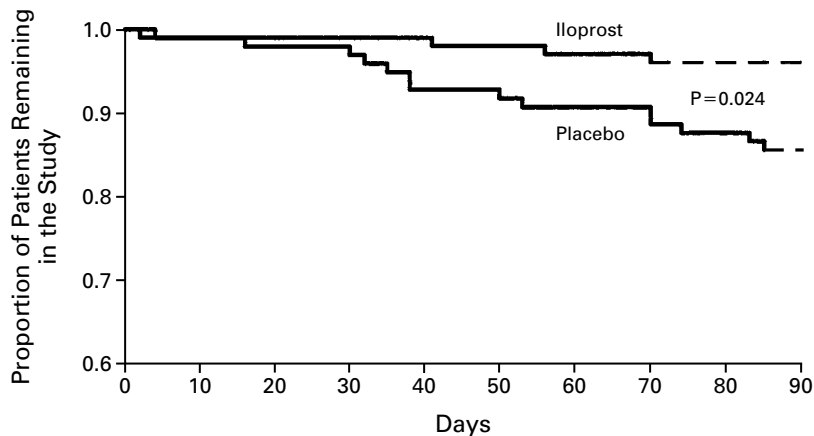¶P=0.007 for the comparison with the placebo group.

Figure 2. Kaplan–Meier Estimates of the Likelihood of Completing the 12-Week Study.
Reasons for not completing the study included death, discontinuation of study medication, and withdrawal of consent (see Table 2).

TABLE 3. MEAN (±SD) CHANGE FROM BASE LINE IN HEMODYNAMIC VALUES DURING 12 WEEKS OF THERAPY WITH INHALED ILOPROST OR PLACEBO.*

VARIABLE	PLACEBO GROUP	ILOPROST GROUP	
		BEFORE INHALATION	AFTER INHALATION
		mean ±SD	
Pulmonary-artery pressure (mm Hg)	−0.2±6.9	−0.1±7.3	−4.6±9.3†
Cardiac output (liters/min)	−0.19±0.81‡	+0.05±0.86	+0.55±1.1†
Pulmonary vascular resistance (dyn·sec·cm⁻⁵)	+96±322‡	−9±275§	−239±279†
Systemic arterial pressure (mm Hg)	−0.2±12.4	−1.7±12.8	−4.3±13.6¶
Right arterial pressure (mm Hg)	+1.4±4.8‡	+0.5±4.6	−0.8±4.6
Pulmonary-artery wedge pressure (mm Hg)	+0.7±3.6	+1.1±4.7‡	+1.8±5.3¶
Arterial oxygen saturation (%)	−1.6±4.4‡	−0.4±3.7	−1.4±3.7‡
Mixed venous oxygen saturation (%)	−3.2±6.7†	−1.1±7.6	+1.8±8.3
Heart rate (beats/min)	−1.2±9.5	−1.8±12.4	−2.25±12.6

*For the iloprost group, both preinhalation and postinhalation values after 12 weeks are compared with the base-line values at study entry.

†$P<0.001$ for the difference from base-line values.

‡$P<0.05$ for the difference from base-line values.

§$P<0.01$ for the comparison with the placebo group.

¶$P<0.01$ for the difference from base-line values.

group than in the placebo group (change, +1.42± 2.59 vs. +0.30±2.45; P=0.015). The type of pulmonary hypertension had no effect on this outcome.

Quality of Life

Mean scores on the EuroQol visual-analogue scale improved significantly (from 46.9±15.9 to 52.8±19.1) in the iloprost group but were virtually unchanged in the placebo group (dropping from 48.6±16.9 to 47.4±21.1, P=0.026 by analysis of covariance). The EuroQol health-state score improved from 0.49±0.28 to 0.58±0.27 in the iloprost group and was unchanged in the placebo group (0.56±0.29 to 0.56± 0.31, P=0.11 by analysis of covariance). None of the other measures of the quality of life were significantly different between the groups.

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