Drugs 2004; 64 (7): 763-773
0012-6667/04/0007-0763/$34.00/0

Inhaled Iloprost
In Primary Pulmonary Hypertension

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Abstract

▲ Iloprost is a stable prostacyclin analogue with a pharmacokinetic profile allowing nebulised administration in patients with primary pulmonary hypertension (PPH).

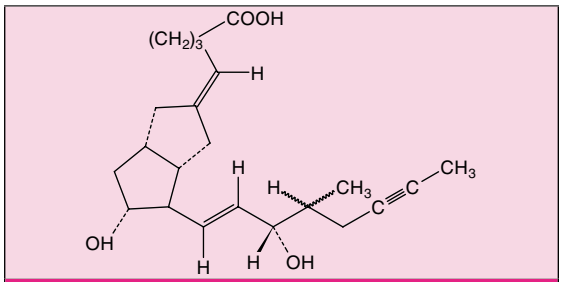
▲ Inhaled iloprost is a potent acute pulmonary vasodilator with a duration of action of about 60 minutes. It may exert additional long-term benefit through antiproliferative and antithrombotic effects.

▲ Inhaled iloprost 2.5 or 5μg six or nine times daily for 12 weeks (n = 101) significantly ($p < 0.01$) improved a combined clinical endpoint of a ≥10% increase in distance walked in 6 minutes and an improvement of ≥1 class in New York Heart Association functional class without clinical deterioration or death (16.8 versus 4.9% of placebo recipients, n = 102) in patients with severe PPH or selected forms of nonprimary pulmonary hypertension. Statistical analysis of the response for the PPH subgroup (20.8 versus 5.5% with placebo; n = 51 and 51) was not reported.

▲ Improvements from baseline in exercise capacity and haemodynamic/gas exchange variables have been reported in patients with PPH with continued use of inhaled iloprost. In addition, improvement in preinhalation vascular resistance occurred after 12 weeks of inhaled iloprost ($p < 0.01$ versus placebo) in a large randomised trial.

▲ Increased cough, headache, flushing and an influenza-like syndrome were the most common adverse events in the largest trial of patients receiving inhaled iloprost. Headache, flushing and jaw pain occurred significantly more frequently with inhaled iloprost than with placebo.

Features and properties of inhaled iloprost (Ventavis®)	
Indication	
To improve exercise capacity and symptoms in patients with New York Heart Association functional class III primary pulmonary hypertension	
Mechanism of action	
Pulmonary vasodilator	Prostacyclin analogue
Dosage and administration in a pivotal randomised, double-blind trial	
Route of administration	Nebulised (over ≈10 minutes)
Dose (at the mouthpiece)	2.5 or 5μg
Frequency of administration	Six or nine times daily
Pharmacokinetic profile (following 5μg inhaled dose in patients with pulmonary hypertension)	
Bioavailability	≈80%
Time to peak concentration in intravascular compartment	≈10–15 minutes
Peak serum concentration	≈160 pg/mL
Elimination half-life in plasma	6.5–9.4 minutes
Adverse effects	
Significantly more frequent than with placebo	Headache, flushing and jaw pain



Iloprost

Primary pulmonary hypertension (PPH) is characterised by raised (mean) pulmonary artery pressure (PAP) [>25mm Hg at rest or >30mm Hg during exercise] without an established secondary cause.[1] New cases occur in one to two people per million per year (European and US data),[2] with a natural history of death from progressive right heart failure after a median 2.8 years without treatment.[1,3] The pathology (including medial hypertrophy, remodelling and microthrombosis in precapillary pulmonary arteries), pathogenesis, clinical features and management of PPH have been reviewed in several recent articles.[1,3-5]

Treatment with epoprostenol (synthetic salt of prostacyclin) is considered to ameliorate the putative imbalance, as a result of pulmonary vascular endothelial injury, between endogenous vasodilators/antimitotics (e.g. prostacyclin and nitric oxide) and vasoconstrictors/mitogens (e.g. thromboxane A_2 and endothelin-1),[3,4] which results in chronic vasoconstriction. Administration of epoprostenol by continuous intravenous infusion, a practice introduced in the 1990s, has improved exercise capacity, haemodynamic status and overall survival in patients with severe PPH[6] but is associated with tolerance to the drug,[5] catheter complications and rebound pulmonary hypertension if the infusion is abruptly discontinued.[2]

Iloprost, a stable analogue of prostacyclin, has a longer elimination half-life[1,7] than epoprostenol, which facilitates administration by the inhaled route (Ventavis®)[1] several times a day. This review profiles the available pharmacological and clinical data on inhaled iloprost, focusing on the results of a recent large, placebo-controlled, randomised trial in patients with New York Heart Association (NYHA) functional class III or IV severe pulmonary hypertension (including PPH and selected forms of non-primary pulmonary hypertension [NPPH], i.e. pulmonary hypertension secondary to an established cause).[8]

1. Pharmacodynamic Profile

Epoprostenol administration produces acute vasodilation and may exert long-term benefits in patients with PPH (even in initial non-responders to acute vasoreactivity testing) by inhibiting platelet aggregation and by its antiproliferative effects.[6,7,9]

The cellular mechanisms behind the actions of epoprostenol are not clear, but most attention has focused on increased intracellular cyclic adenosine monophosphate (cAMP) concentrations produced by binding of epoprostenol to prostanoid cell surface receptors coupled to adenylate cyclase by the G-protein G_s.[9] Inhaled iloprost has also been associated with a rapid decrease in atrial natriuretic peptide and cyclic guanosine monophosphate levels[10] and an increase in pulmonary clearance of big endothelin-1 in patients with pulmonary hypertension.[11]

The general pharmacodynamic properties of iloprost, which has similar biological properties to those of epoprostenol, have been reviewed previously in *Drugs*;[7] this section focuses on the haemodynamic effects of inhaled iloprost in patients with PPH (duration of acute response about 60 minutes).[12-14]

1 The use of trade names is for product identification purposes only and does not imply endorsement.

Haemodynamic Effects

Compared with Placebo

Acute and delayed haemodynamic responses to iloprost inhalation (median dosage 30 μg/day) were assessed after 12 weeks in 203 patients with severe pulmonary hypertension in a randomised, double-blind, placebo-controlled trial (the Aerosolized Iloprost Randomized Study; AIRS).[8]

- Mean preinhalation (delayed) values of most parameters remained similar to baseline values in patients receiving iloprost after 12 weeks, but values of several parameters worsened significantly versus baseline in placebo recipients (figure 1).[8] There was a significant difference in preinhalation pulmonary vascular resistance (PVR) between the iloprost and placebo groups at 12 weeks (figure 1).
- Postinhalation (acute) values for PAP, PVR, cardiac output (CO) and arterial oxygen saturation (AOS) improved significantly from baseline in iloprost recipients after 12 weeks; however, there were no significant differences between groups in any postinhalation haemodynamic variables, as improvements were also seen in the placebo group (results not reported).[8] Pulmonary artery wedge pressure increased significantly from baseline in iloprost recipients both pre- and postinhalation; the preinhalation increase with placebo was not significant.

Noncomparative Trials

In general, several small, noncomparative trials have also demonstrated significant acute and delayed haemodynamic effects associated with inhaled iloprost in patients with PPH.[15-21]

Delayed effects from long-term treatment with inhaled iloprost have been assessed in five recent studies.[15-19]

- In 19 patients with progressive right heart failure (12 of whom had PPH) who were receiving maximal conventional therapy, treatment with inhaled iloprost (50–200 μg/day in 6–12 divided doses) for 3 months significantly improved several preinhalation haemodynamic variables compared with baseline (including PAP, cardiac index [CI] and PVR) [all $p < 0.05$].[15]
- Similarly, long-term inhaled iloprost therapy for 12 months significantly improved preinhalation haemodynamic status in 24 patients with PPH (NYHA functional class III or IV) that was refractory to conventional medical treatment in a prospective study.[16] Patients received iloprost at a nebulised dosage of 100 or 150 μg/day in six or eight divided

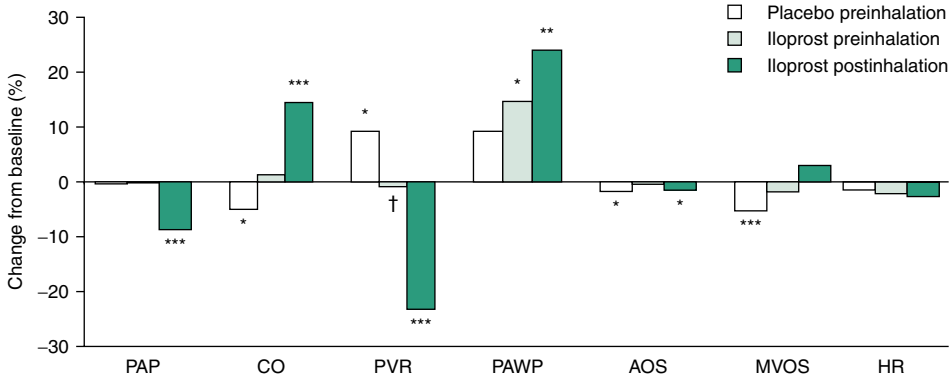


Fig. 1. Effect of inhaled iloprost on haemodynamic variables. Patients with severe primary pulmonary hypertension (PPH) or nonprimary pulmonary hypertension (NPPH) were randomised to receive inhaled iloprost 2.5 or 5μg six or nine times daily (median dosage 30 μg/day; n = 51 with PPH and 50 with NPPH) or placebo (n = 51 and 51) for 12 weeks.[8] Mean percentage changes from baseline after 12 weeks are shown for pulmonary artery pressure (PAP), cardiac output (CO), pulmonary vascular resistance (PVR), pulmonary artery wedge pressure (PAWP), arterial oxygen saturation (AOS), mixed venous oxygen saturation (MVOS) and heart rate (HR). * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ vs baseline; † $p < 0.01$ vs preinhalation placebo.

doses. Mean values for PAP and PVR had decreased significantly from baseline at 12 months (by 12 and 23%, both $p < 0.01$). Mean CO had increased significantly ($p < 0.05$) from baseline at 12 months but was the only haemodynamic variable measured (except heart rate) that had not improved significantly from baseline after 3 months. Systemic vascular resistance (SVR) continued to decrease and stroke volume (SV) continued to increase significantly between 3 and 12 months (both $p < 0.05$) with continued treatment.

- However, in an observational study (reported in a letter),[17] 15 patients with PPH who were more severely haemodynamically compromised than in the 12-month study reported by Hoeper et al.,[16] but using the same dosage range, showed no significant changes in preinhalation haemodynamic variable measurements after 12 months' inhaled iloprost treatment. Results after 12 months from another study (reported as an abstract)[18] in 12 patients receiving inhaled iloprost (17μg six times daily) also showed no significant change in preinhalation measurements.

- Finally, 2 years' treatment with inhaled iloprost (median daily dosage of 100μg in six divided doses) significantly ($p = 0.047$) improved preinhalation PVR in 24 patients with PPH; however, no significant changes occurred in PAP and CO (study reported as an abstract).[19]

The acute (postinhalation) effects of inhaled iloprost have been assessed at rest,[12,20] during exercise[21] and following treatment with the drug for up to 2 years.[15,18,19]

- A single dose of inhaled iloprost 17μg produced acute vasodilation, as measured by significant improvements in several haemodynamic variables, in 11 patients with pulmonary arterial hypertension (ten of whom had PPH) and NYHA functional class III.[20] Compared with preinhalation values, PAP, PVR and right atrial pressure (RAP) decreased significantly and CO increased significantly (all $p < 0.05$). The increased CO was associated with improved exercise capacity.

- In 16 patients with pulmonary hypertension (eight of whom had PPH), PAP, PVR, CO, SV and mixed-venous oxygen saturation (MVOS) measurements were significantly improved (all $p < 0.05$) during exercise following administration of single-dose inhaled iloprost 14–28μg, even in those patients who did not experience an acute vasodilatory response to the drug at rest.[21] There was no significant decrease in the systemic arterial blood pressure (SAP).

- After 3 months, the acute haemodynamic response to iloprost inhalation was maintained, compared with baseline, in a fully published study in 19 patients with severe pulmonary hypertension.[15] In two further studies (n = 12[18] and 24[19] with PPH) [presented as abstracts], postinhalation haemodynamic responses were maintained[18] or improved (no p-value or quantitative data reported)[19] with inhaled iloprost therapy for up to 2 years.

Compared with Intravenous or Inhaled Epoprostenol

Two small, nonblind, crossover, single-dose studies[22,23] and a small nonrandomised, nonblind 3-month study[24] have investigated the comparative haemodynamic effects of inhaled iloprost and either inhaled or intravenous epoprostenol.

- Effects on haemodynamic and gas exchange profiles were similar with inhaled iloprost 9–21μg and inhaled epoprostenol 52–112μg in six patients with severe pulmonary hypertension (four of whom had PPH).[23]

- Significant improvements from baseline were seen in PAP, AOS and PVR/SVR with inhaled iloprost (17μg) but not with intravenous iloprost (1.2 ng/kg/min) or intravenous epoprostenol (7.2 ng/kg/min) in 21 patients with severe PPH.[22] However, the only statistically significant differences between inhaled iloprost and intravenous epoprostenol were a greater decrease in RAP with inhaled iloprost (26 versus 16%, $p < 0.05$), and greater improvements in CO, pulmonary and systemic blood flow, and SVR with intravenous epoprostenol (32–40% versus 9–20%, $p < 0.05$). Significant

changes from baseline in CI were seen with all three treatments.

- Improvements in PAP, CI and PVR from baseline were also similar in 14 patients with severe pulmonary hypertension (ten of whom had PPH) receiving inhaled iloprost or continuous epoprostenol infusion (dosages not reported) for 3 months.[24]

Compared with Inhaled Nitric Oxide

- Inhaled iloprost was a more effective pulmonary vasodilator than inhaled nitric oxide in 35 patients with PPH (the majority in NYHA functional class III or IV) who received the drugs sequentially.[13] Inhaled iloprost 14–17μg, compared with inhaled nitric oxide 40 parts per million, produced significantly greater decreases in mean PAP (13 versus 7%), SAP (3 versus 1%), SVR (21 versus 5%) and PVR (33 versus 14%) and greater increases in CO (34 versus 9%), CI (20 versus 5%), SV (21 versus 9%), systemic arterial oxygen pressure (SAOP) [11 versus 3%] and MVOS (12 versus 3%) from baseline (all $p < 0.05$). A small crossover study in six patients with severe pulmonary hypertension showed numerically greater haemodynamic and gas exchange improvements with inhaled iloprost than with inhaled nitric oxide.[23]

In Combination with Other Vasodilators

- Additional inhaled iloprost (30μg over 15 minutes) improved the acute haemodynamic profile in eight patients with PPH, initially nonresponsive to nitric oxide but subsequently stabilised on submaximal (due to adverse effects) dosages of continuous intravenous epoprostenol (mean 20 ng/min/kg for 18 months).[25] Mean PAP and PVR decreased significantly (by 22 and 40%, both $p < 0.01$ versus epoprostenol alone) without inducing systemic hypotension. Other significant improvements occurred in MVOS, SAOP and CI (all $p < 0.05$).

- Small doses of the phosphodiesterase (PDE) tolafentrine[26] and the PDE type 5 inhibitor sildenafil[27,28] appeared to both enhance and prolong the acute vasodilatory effect of inhaled iloprost in patients with severe pulmonary hypertension, including those with PPH. In five patients with PPH (NYHA functional class III or IV), inhaled iloprost (8.4–10.5μg) 30 minutes after the administration of oral sildenafil (cumulative dosage of 50–100mg given over 1 hour) resulted in an additional 32% reduction in mean PAP compared with inhaled iloprost alone ($p < 0.01$).[28] Mean PAP with the combination remained below the nadir caused by inhaled iloprost alone (which occurred between 15 and 30 minutes) for 2 hours in four patients.

- Coadministration of iloprost with oxygen resulted in additional acute improvement in mean PAP, MVOS and AOS in six patients with severe pulmonary hypertension on long-term oxygen therapy.[29]

Effects on Platelet Aggregation

- Inhaled iloprost caused mild but sustained inhibition of platelet function and was associated with raised plasma cAMP levels in healthy volunteers.[30] In six subjects receiving a single dose of inhaled iloprost 15μg, platelet aggregation (maximal percentage at 5 minutes) was significantly inhibited ($p < 0.05$) when challenged with adenosine diphosphate, epinephrine or collagen (but not arachidonic acid) after 30 minutes and again after 4 hours (except with collagen) and had normalised by 6 hours (bleeding time unaltered). Similarly, plasma cAMP levels were increased (by 17%) from baseline after 30 minutes and at 4 hours ($p < 0.05$) and had normalised at 6 hours. No changes in platelet function or cAMP levels were recorded in the four volunteers receiving placebo.

Antiproliferative Effects

- There have been no studies assessing the antiproliferative effects of inhaled iloprost. However, iloprost solution (30 nmol/L) inhibited fetal bovine serum-induced proliferation of cultured human pulmonary artery smooth muscle cells for 48 hours with minimal desensitisation (the cell count was 28% of that which occurred in the presence of fetal bovine

serum alone).[9] Similarly, DNA synthesis, as measured by [^{3}H] thymidine incorporation after 30 hours was reduced. Intracellular cAMP was probably the cellular mediator of this effect, as levels were raised 9-fold, although iloprost was the weakest of a series of epoprostenol analogues (treprostinil, cicaprost and beraprost) on this measure.

2. Pharmacokinetic Profile

Pharmacokinetic data on inhaled iloprost are restricted to one study using isolated perfused rabbit lungs[31] and one further study comparing nebuliser devices in patients with pulmonary hypertension.[12] Additional data on the pharmacokinetic profile of iloprost, following intravenous and oral administration are summarised here where relevant.

Absorption and Distribution

- Following intravenous infusion, steady-state iloprost concentrations in plasma are dose dependent.[7] Nebulised iloprost also rapidly entered the intravascular compartment of isolated perfused rabbit lungs.[31] Iloprost levels were detected within 5 minutes of commencing the 10-minute nebulisation and maximal concentrations were achieved 30 minutes after commencing.
- In 12 patients with pulmonary hypertension, the maximum serum concentration following administration of iloprost 5μg jet-nebulised over about 10 minutes was about 160 pg/mL with serum concentrations peaking at the end of inhalation or within the following 5 minutes.[12]
- Appreciable initial retention of iloprost in the bronchoalveolar space and/or lung tissue after inhalation and more rapid metabolism of inhaled drug by β-oxidation before reaching the intravascular space are considered to underlie the differences in iloprost bioavailability between inhalation and infusion methods of administration.[31] In patients, the bioavailability (proportion of intact drug reaching the pulmonary intravascular compartment compared with the amount of nebulised iloprost deposited in the lung) was calculated to be about 80%.[12] Total plasma protein binding of iloprost is about 60%.[32]
- The degree of systemic absorption or distribution into other tissues following inhaled administration is not known.

Metabolism and Elimination

- Iloprost is completely metabolised by β-oxidation to the inactive tetranor derivative and its conjugates.[7] Less than 20% of intact iloprost reaches the systemic circulation following oral administration because of metabolism in the gut wall and liver.[7] The liver is considered to be the dominant site of metabolism following intravenous administration in humans.[31]
- Some metabolism also occurs in the lung following inhaled iloprost administration in isolated perfused rabbit lungs.[31] Within 5 minutes of commencing nebulisation about 20% of iloprost was metabolised to dinoriloprost or tetranoriloprost, whereas no metabolites were detected within this period following intravenous infusion. Cells between the alveolar surface and the intravascular space capable of β-oxidation include epithelial, smooth muscle, endothelial and macrophage cells. Following entry of the drug into the intravascular space, metabolism rates were similar for the inhalation or infusion routes.
- Iloprost elimination is biphasic, with an initial distribution half-life of about 4 minutes and a terminal half-life ($t_{1/2}\beta$) in plasma of about 20–30 minutes after intravenous administration,[7] whereas that of intravenous epoprostenol is estimated to be about 3–5 minutes.[1,14] The $t_{1/2}\beta$ of inhaled iloprost was 170 minutes, compared with 220 minutes following intravenous infusion, in isolated perfused rabbit lungs.[31] Following inhalation in patients with severe pulmonary hypertension (n = 12), the $t_{1/2}\beta$ of iloprost once having entered the blood system was 6.5–9.4 minutes, which is shorter than the half-life of the pharmacodynamic effect (about 20 minutes).[12]

● About 70% of metabolites are excreted renally and an additional 12–17% are excreted by the faecal route.[7] Total body clearance following intravenous administration is decreased 2- to 3-fold in patients with severe hepatic or renal disease.

Drug Interactions

● Iloprost appeared to be associated with increased tissue-type plasminogen activator (t-PA) degradation in the canine liver,[33] although the pharmacokinetics of t-PA were not affected in patients with acute myocardial infarction who also received intravenous iloprost.[34] No clinically significant pharmacokinetic interactions were detected between iloprost and digoxin in patients with severe peripheral vascular disease.[35]

3. Therapeutic Efficacy

The efficacy of inhaled iloprost 15–45 μg/day in patients with severe pulmonary hypertension, including PPH, has been investigated in a randomised, double-blind, 3-month study (AIRS).[8] Several small, open-label or noncomparative studies have also reported the efficacy of inhaled iloprost (50–200 μg/day for 3–12 months) in improving exercise capacity.[15,16,24,36]

In the large multicentre phase III AIRS trial,[8] 203 adult patients with severe pulmonary hypertension were randomised in a double-blind manner to receive inhaled iloprost (10 μg/mL solution via nebuliser) [n = 101] or placebo (n = 102) for 12 weeks. Entry into the study required a mean PAP of >30mm Hg, a diagnosis of PPH (50.2% of patients) or a selected form of NPPH (appetite-suppressant-associated 4.4%, scleroderma-associated 17.2% or inoperable chronic thromboembolic pulmonary hypertension 28.1%) and an NYHA functional class of III (59%) or IV (41%). Patients in the study had a mean age of about 52 years and the majority were female (≈67%).

The iloprost dosage was 2.5 (9%) or 5μg (91%) six or nine times daily (median dosage 30 μg/day; mean frequency 7.5 times daily; inhalation duration about 10 minutes) depending on tolerability.

The primary endpoint, measured after 12 weeks, encompassed the percentage of patients achieving a combination of a ≥10% increase in the distance walked in 6 minutes, an improvement in NYHA functional class by ≥1 class and an absence, at any stage, of predefined clinical deterioration or death. Secondary endpoints included change in values from baseline for the 6-minute walk test, NYHA functional class, Mahler Dyspnea Index questionnaire, haemodynamic variables and quality-of-life measures. Some results were also reported (without statistical comparisons between iloprost treatment and placebo) for the PPH and NPPH subgroups.

Combined Primary Endpoint Versus Placebo

● Inhaled iloprost, in the overall AIRS population, significantly improved the distance walked in 6 minutes and NYHA functional class, without worsening clinical condition.[8] After 12 weeks, the combined endpoint was met by 16.8 and 4.9% of patients receiving inhaled iloprost and placebo, respectively ($p < 0.01$; figure 2). The estimated odds ratio was 3.97 (95% CI 1.47, 10.75). There was no significant heterogeneity in response among the four subgroups defined by type of pulmonary hypertension and NYHA functional class.

Effect on Exercise Capacity

● After 12 weeks, 38% of iloprost recipients in AIRS demonstrated a ≥10% increase from baseline in the distance walked in 6 minutes versus 26% of those receiving placebo, although differences were not statistically significant (figure 2).[8] Nearly 50% of patients with PPH who received active treatment achieved this outcome, although the type of pulmonary hypertension in the overall population did not contribute to treatment outcome in a statistically significant manner.

● Similarly, 13.9% of all patients (5.7% of PPH recipients) receiving iloprost showed a ≥10% de-

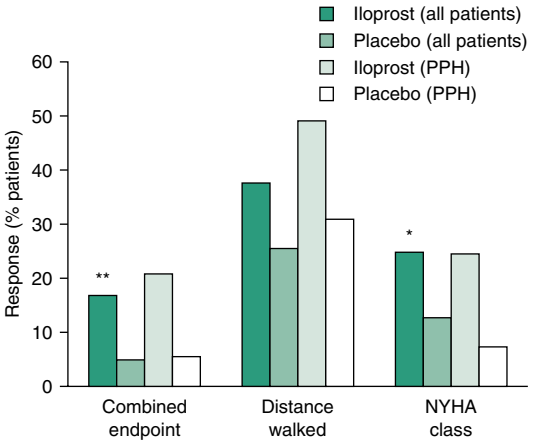


Fig. 2. Efficacy of inhaled iloprost in severe pulmonary hypertension. Patients with primary pulmonary hypertension (PPH) or selected forms (see text for details) of nonprimary pulmonary hypertension (NPPH) in New York Heart Association (NYHA) functional class III or IV were randomised to receive inhaled iloprost 2.5 or 5μg six or nine times daily (median dosage 30 μg/day; n = 51 and 50 with PPH and NPPH) or placebo (n = 51 and 51) for 12 weeks.[8] Bars show the percentage of patients after 12 weeks in the overall population and in the subgroup with PPH meeting a combined primary endpoint of a ≥10% increase in the distance walked in 6 minutes and an improvement in NYHA functional class by ≥1 class and who did not deteriorate clinically (or die) at any stage (all randomised patients); showing a ≥10% increase in the distance walked in 6 minutes (last-observation-carried-forward analysis); and showing an improvement in NYHA functional class by ≥1 class. Statistical analysis of the response in the PPH subgroup was not reported. * $p < 0.05$, ** $p < 0.01$ vs placebo.

crease in distance walked in 6 minutes (versus 25.5 and 32.7% of placebo recipients).[8] The mean distance walked by the total cohort increased by ≈18m (estimated from a graph) from 332m in iloprost recipients and decreased by a similar amount from 315m in placebo recipients, with an absolute treatment effect of 36.4m ($p < 0.005$) after 12 weeks. The difference between treatments was 58.8m in the PPH subgroup and 12m in the NPPH group.

- Inhaled iloprost also significantly ($p < 0.05$) increased the distance walked in 6 minutes in three small noncomparative trials of 3–12 months' duration (n = 13,[15] 28[36] and 24[16]). In one study, the mean 6-minute distance walked increased by 27% after 3 months' treatment (100 or 150 μg/day), and by 31% after 12 months (both $p < 0.05$ versus baseline).[16] There were no significant differences in improvements in exercise capacity between inhaled iloprost (n = 7; 12-minute distance walked increased by 40%) and epoprostenol infusion (n = 7; distance increased by 72%) [dosages not reported, 3 months' administration] in patients with severe pulmonary hypertension (ten of whom had PPH) in a small nonrandomised, open-label trial reported as an abstract.[24]

Effect on NYHA Functional Class

- The percentage of patients in the overall AIRS population receiving iloprost who experienced an improvement in NYHA functional class of one class was nearly twice that demonstrated in placebo recipients (24 versus 13%; $p = 0.03$).[8] One patient (from the PPH group) improved by two classes. The overall response to iloprost in the PPH group was similar to that in the total cohort (figure 2). The proportions of patients in the overall population who worsened according to this measure were similar in iloprost and placebo recipients (5.9 versus 7.8%).

Other Effects

- Inhaled iloprost significantly improved scores on the Mahler Dyspnea Index questionnaire, compared with placebo ($p = 0.015$) in AIRS; the type of pulmonary hypertension had no effect.[8] Quality of life was significantly improved in iloprost recipients compared with those receiving placebo ($p = 0.026$) in AIRS using the EuroQol visual analogue scale but not when the EuroQol health-state score or the 12-item Medical Outcomes Study Short-Form General Health Survey were used. No patients required lung transplantation during the study.[8]

4. Tolerability

- Treatment with inhaled iloprost for 12 weeks appeared to be generally well tolerated in the randomised, placebo-controlled trial (AIRS).[8] Significantly fewer patients receiving iloprost failed to complete the study (4 versus 13.7% of placebo recipients, $p = 0.024$); the most common reason for

premature discontinuation was clinical deterioration. There was one death in the group receiving iloprost and four deaths among those receiving placebo.

- The most common treatment-emergent adverse events in patients receiving iloprost were increased cough, headache, flushing and influenza-like syndrome (figure 3).[8] Headache, flushing and jaw pain occurred significantly more frequently in iloprost recipients than in those receiving placebo (figure 3) but were mostly mild and transient.

- Serious adverse events occurred at a similar rate in patients receiving iloprost (27.7%) or placebo (24.5%). The most common serious adverse event in iloprost recipients was syncope, which occurred in 5% of patients, in each case 2–9 hours after the last inhalation; syncope was not associated with clinical deterioration or withdrawal of any patient from the study. No episodes of syncope occurred in patients receiving placebo ($p = 0.03$ versus iloprost). Serious right ventricular failure plus oedema occurred in 4 and 9.8% of patients receiving iloprost and placebo.

5. Dosage and Administration

- Iloprost is available for use in patients with PPH in NYHA functional class III as a 10 μg/mL nebuliser solution (Ventavis®).[32] The recommended dosage is 2.5 or 5μg (as delivered at the mouthpiece of the nebuliser) six to nine times daily according to individual need and tolerability.[32] Patients in the randomised, placebo-controlled trial (AIRS) received a median dosage of 30 μg/day, corresponding to a mean 0.37 ng/kg/min,[8] which is lower than the effective intravenous dose (1.2–2 ng/kg/min).[22,37]

- The estimated inhalation time using the HaloLite or Prodose compressed air nebuliser systems (the only systems established as suitable for the administration of Ventavis®) is 4–5 minutes for the 2.5μg dosage and 8–10 minutes for the 5μg dosage.[32] These systems provide a mass mean aerodynamic

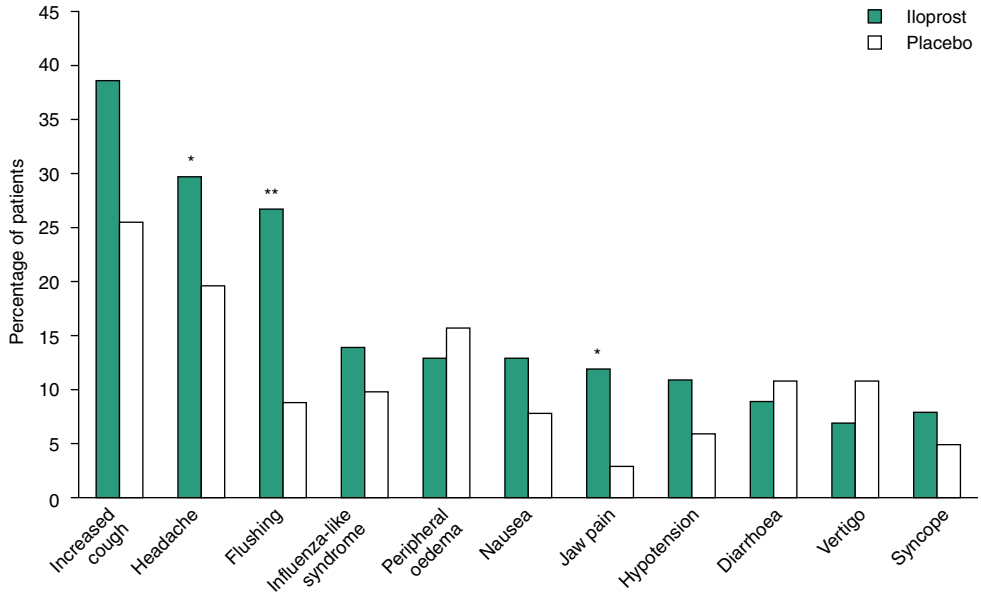


Fig. 3. Tolerability profile of inhaled iloprost. Patients with severe pulmonary hypertension receiving inhaled iloprost 2.5 or 5μg six or nine times daily (median 30 μg/day) [n = 101] or placebo (n = 102) for 12 weeks in a randomised, multicentre trial.[8] Patients had primary pulmonary hypertension (n = 102) or selected forms (see text for details) of nonprimary pulmonary hypertension (n = 101). Bars show the percentage of patients experiencing the most common treatment-emergent adverse events. * $p \leq 0.05$, ** $p = 0.001$ vs placebo.

diameter of the aerosol droplet with iloprost of between 2.6 and 2.7μm.[32]

6. Inhaled Iloprost: Current Status

Inhaled iloprost, a selective pulmonary vasodilator, is approved in Europe for the treatment of patients with PPH, classified as NYHA functional class III, to improve exercise capacity and symptoms.[32] Nebulised iloprost 2.5 or 5μg six or nine times daily was generally well tolerated and produced clinically significant improvements compared with placebo in distance walked in 6 minutes and NYHA functional class after 12 weeks in patients with severe PPH and selected forms of NPPH.

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