Expert Opinion

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Iloprost inhalation solution for the treatment of pulmonary arterial hypertension

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Pulmonary arterial hypertension (PAH) is a condition that is characterised by increased pulmonary arterial pressure and vascular resistance that can lead to right ventricular failure and death. A variety of disturbances in pulmonary vascular endothelial and smooth muscle function are present in PAH, including reduced production of vasodilator and antiproliferative substances, such as nitric oxide and prostacyclin, and an overproduction of mitogens, such as endothelin. As a result of these observations, therapies have been developed for PAH that specifically target these pathogenic processes, including prostacyclin analogues and endothelin receptor antagonists. This article reviews iloprost inhalation solution, the most recently approved form of prostacyclin therapy that is delivered directly to the lungs by inhalation.

Keywords: iloprost, prostacyclin analogues, pulmonary arterial hypertension

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1. Introduction

Pulmonary hypertension (PH) is a condition characterised by elevated pulmonary arterial pressure to > 25 mmHg at rest or > 30 mmHg with exercise [1]. The term pulmonary arterial hypertension (PAH) is used when the increased pressure and vascular resistance are the result of conditions that primarily affect the upstream (arterial) portion of the pulmonary circulation. Regardless of the aetiology, PAH is characterised by progressive deterioration in right ventricular function, producing impaired activity tolerance and, eventually, right ventricular failure and death.

The recently revised World Health Organization (WHO) classification of PH consists of five categories, separating 'pulmonary arterial hypertension' from 'pulmonary venous hypertension' and PH secondary to pulmonary and thromboembolic diseases, as well as from diseases indirectly affecting the pulmonary vessels [2]. This classification is of some therapeutic relevance, as PAH responds to the administration of prostanoids, but in pulmonary venous hypertension, prostanoids are generally contraindicated.

PAH occurs as an isolated acquired or inherited condition (idiopathic and familial PAH, respectively), or as a result of a variety of underlying conditions including connective tissue diseases, congenital heart disease, HIV infection or complicating chronic liver disease with portal hypertension.

Pathologically, PAH is characterised by intimal and smooth muscle proliferation of the small and medium-sized arteries and arterioles [3]. Although the precise mechanism responsible for the pathogenesis of PAH remains to be elucidated, a variety of abnormalities of endothelial and smooth muscle function are present in the pulmonary vessels of PAH, including reduced production of endothelial-derived vasodilator and antiproliferative substances, such as nitric oxide and prostacyclin, and enhanced production of endothelial-derived vasoconstrictors and mitogens, such as endothelin. It has been proposed that these abnormalities result from endothelial

injury and produce or contribute to the pathogenesis and progression of the pulmonary hypertensive state [4].

Although initial approaches to therapy for PAH were largely empiric and not highly effective, recent strategies have targeted these specific pathogenic processes with a greater degree of success. Indeed, the first regulatory approval for a treatment for PAH, continuous intravenous epoprostenol (prostacyclin), was granted 10 years ago, and four additional therapies have received regulatory approval within the last 3 years, including subcutaneous and intravenous treprostinil and inhaled iloprost (stable prostacyclin analogues with a longer duration of effect), oral bosentan (a dual endothelin receptor antagonist) and oral sildenafil (a phosphodiesterase type 5 [PDE-5] inhibitor); furthermore, several other novel therapies are in late-stage clinical trials, including selective endothelin type A (ET_A) receptor antagonists. The well-designed clinical trials with these agents have demonstrated that these therapies result in improved haemodynamics and exercise capacity in patients with PAH. This article reviews the rationale, mechanism of action and clinical experience with inhaled iloprost therapy for PAH.

2. Rationale for development

Prostacyclin (PGI_2), a product of arachidonic acid metabolism, is synthesised in the vascular endothelium and is involved in the maintenance of vascular integrity and blood flow through its effects on vascular endothelial and smooth muscle cells. In PH, the circulating levels of prostacyclin are diminished [4,5].

On a practical level, administration of prostacyclin is associated with a number of disadvantages, including a short half-life and poor stability that necessitates refrigeration. In addition, the need to administer prostacyclin continuously through an indwelling central venous catheter is associated with the risk of line infection and occlusion, necessitating great care in managing the catheter. Systemic administration of PGI_2 would not be expected to show any selectivity for the pulmonary vasculature and systemic side effects, such as hypotension and vasodilatation, may be dose-limiting [6]. In certain patients with underlying lung disease, hypoxia-induced vasoconstriction of the pulmonary vasculature may be antagonised by intravenous epoprostenol, leading to an increased ventilation-perfusion disturbance and to a worsening in arterial oxygenation [7].

These disadvantages are partly attributable to the properties of prostacyclin and partly to the mode of administration. Iloprost inhalation solution was developed to take advantage of the pharmacological profile of the prostanoids and to avoid the consequences of chemical instability and intravenous administration. The inhalation of aerosolised iloprost offers several advantages over the continuous intravenous infusion of a prostaglandin in terms of safety, efficacy, tolerability and patient compliance. Because iloprost is administered by inhalation, the drug is expected to preferentially reach well-ventilated parts of the lung, resulting in selective vasodilation in ventilated regions and minimising ventilation-perfusion mismatch. Inhalational delivery is non-invasive and avoids complications associated with permanent indwelling intravenous catheters.

3. Mechanisms of action

The vasodilatory effects of prostacyclin are mediated by binding to specific prostacyclin (IP) receptors, leading to stimulation of adenylyl cyclase and increasing cAMP concentrations in vascular smooth muscle [8,9]. Prostacyclins have been shown to have a number of effects that are potentially of benefit in PH, including relaxation of smooth muscle cells, inhibition of production and secretion of endothelin, inhibition of platelet aggregation and inhibition of cell migration and proliferation [10-14].

Iloprost is a synthetic analogue of prostacyclin with a pharmacological profile and potency comparable to PGI_2, but with greater stability and a longer half-life. In laboratory studies, a number of pharmacological effects contribute to its therapeutic effects in PAH by counteracting the three basic underlying causes of increased pulmonary vascular resistance: vasoconstriction, local inflammation and vascular wall remodelling, and thrombosis *in situ* [15-23]. Iloprost induces vasodilatation of arterioles in the circulation by a mechanism that is partly endothelium dependent. Iloprost inhibits vascular bed remodelling and smooth muscle cell proliferation *in vitro*. It has been shown to be protective of endothelial integrity and reduces endothelial permeability under hypoxic conditions or challenge with inflammatory mediators, such as 5-HT, bradykinin and histamine. Additional immunomodulatory effects include inhibition of leukocyte activation *in vitro* and adhesion of leukocytes *in vivo* [24-28]. Similar to prostacyclin, iloprost has antithrombotic effects, including inhibition of platelet activation [29-31].

The inhalational route of delivery of iloprost in PAH is a form of direct local administration of the drug, with the goal of selectively targeting the pulmonary vasculature with a higher concentration of drug, thereby improving the therapeutic index of efficacy in relation to systemic side effects. A possible explanation for the vasodilatory effect on the pulmonary vasculature of iloprost delivered via the alveolar route could be that the intra-acinar pulmonary arteries are closely associated with the distal bronchiolar and alveolar surfaces, so it is possible to preferentially vasodilate these vessels by means of alveolar deposition of such drugs. Precapillary sphincters and arteriolar smooth muscle cells will also receive a higher local concentration of iloprost from the abluminal (alveolar or interstitial) side before iloprost becomes diluted in the bloodstream.

4. Pharmacokinetics

When iloprost is administered via inhalation in patients with PAH (dose at the mouthpiece ~ 5 µg), peak serum levels of 100 – 200 pg/ml were observed at the end of an

inhalation session. These levels decline with half-lifes between ~ 5 and 25 min [32].

The bioavailability of inhaled iloprost has been estimated based on an indirect comparison of the inhaled and intravenous administration. With a mean AUC for inhaled iloprost 5 µg ranging from 48 to 54 pg × h/ml compared with the AUC of 119 pg × h/ml after a total intravenous dose of 9.4 µg (infusion of 3 ng/kg/min iloprost over 45 min) in healthy volunteers, the estimated absolute bioavailability of inhaled iloprost is ~ 80%. Total plasma protein binding of iloprost is ~ 60%, of which 75% is due to albumin binding. Iloprost is extensively metabolised principally via β-oxidation of the carboxyl side chain. No unchanged substance is eliminated. The main metabolite is tetranor-iloprost, which is found in the urine in free and conjugated forms in four diastereoisomers [33-35]. Tetranor-iloprost is pharmacologically inactive, as shown in animal experiments. *In vitro* studies suggest that metabolism of iloprost in the lungs is similar after intravenous administration or inhalation.

5. Clinical efficacy

The development of inhaled iloprost for PAH followed a number of investigator-initiated pilot studies that provided initial data suggesting that inhalational therapy with iloprost was safe and effective [7,36-39]. These results led to a randomised, double-blind, multi-centre, placebo-controlled trial in 203 adult patients with New York Heart Association (NYHA) Class III or IV PAH who received inhaled iloprost (n = 101) or inhaled placebo (n = 102) being conducted [40]. In this Phase III study, 53% of patients had idiopathic PAH (primary PH) and 19% had PAH associated with connective tissue disease, including calcinosis cutis, Raynaud's phenomenon, oesophageal dysfunction, sclerodactyly and telangiectasia (CREST) syndrome and scleroderma (17%), or associated with anorexigen use (2%). An additional 28% had PH related to chronic thromboembolic disease (CTEPH). Inhaled iloprost or placebo were added to patients' current therapy, which could have included anticoagulants, calcium channel blockers, diuretics, oxygen and digitalis, but not prostacyclin or its analogues, or endothelin receptor antagonists. Patients received iloprost 2.5 or 5.0 µg by multiple inhalations of a minimum of six repititions, up to a maximum of nine times/day during waking hours. The randomised treatment period was 12 weeks, after which patients rolled over into open-label therapy with inhaled iloprost.

The mean age of the entire study population was 52 years and 68% of the patients were female. In total, 59% were NYHA Class III, and 41% were NYHA Class IV. The baseline 6-min walk test values reflected a moderate exercise limitation (the mean was 332 and 315 m for the iloprost and placebo groups, respectively). In the iloprost group, the median daily-inhaled dose was 30 µg (range of 12.5 – 45 µg/day). The mean number of inhalations per day was 7.3. In the iloprost group, 91% of patients never inhaled study medication during the night time.

The primary efficacy end point was clinical response at 12 weeks, a composite end point was defined by:

- Improvement in exercise capacity (6-min walk test) by ≥ 10% versus baseline evaluated 30 min after dosing
- Improvement by at least one NYHA class versus baseline
- No death or deterioration of PH

Deterioration required two or more of the following criteria:

- Refractory systolic blood pressure < 85 mmHg
- Worsening of right heart failure despite adequate background therapy
- Rapidly progressive cardiogenic hepatic failure
- Rapidly progressive cardiogenic renal failure
- Decrease in 6-min walking distance by ≥ 30% of baseline value
- New long-term need for intravenous catecholamines or diuretics
- Deterioration in haemodynamics (cardiac index ≥ 1.3 l/min/m^2, right atrial pressure ≥ 22 mmHg despite adequate diuretic therapy, and mixed venous oxygen saturation < 45%, despite supplemental O_2 therapy)

Additional efficacy measures included the change at the end of the study period in 6-min walk distance and haemodynamic measures obtained via right heart catheterisation.

The response rate for the primary efficacy end point among iloprost patients was 17%, compared with 5% in the placebo patients (p = 0.007). All three components of the composite end point favoured iloprost. Although effectiveness was observed in the full study population (which included PAH and CTEPH), a subgroup analysis based upon the small subset of patients with CTEPH indicated that this subpopulation had a poorer overall response. Considering PAH patients alone, the response rate for the primary efficacy end point was 19% for the iloprost group, compared with 4% for the placebo group (p = 0.0033) (**Figure 1**).

A greater proportion of patients receiving iloprost had an increase of ≥ 10% in 6-min walk (43% iloprost versus 26% placebo), as well as an improvement in NYHA class (25% iloprost versus 8% placebo). Fewer iloprost patients died or had clinical worsening of disease (4% iloprost versus 13% placebo).

The absolute mean change in 6-min walk distance (**Figure 2**) measured after inhalation among patients with PAH was greater in the iloprost group compared with the placebo group at all time points. At week 12, the placebo-corrected difference was 40 m (p < 0.01). When walk distance was measured immediately prior to inhalation, the improvement compared with placebo was ~ 60% of the effect seen at 30 min after inhalation.

The benefits of inhaled iloprost were seen across a range of patient subsets (**Table 1**). Clinical efficacy was seen for patients in NYHA Class III and IV disease, in both males and females, and was irrespective of age.

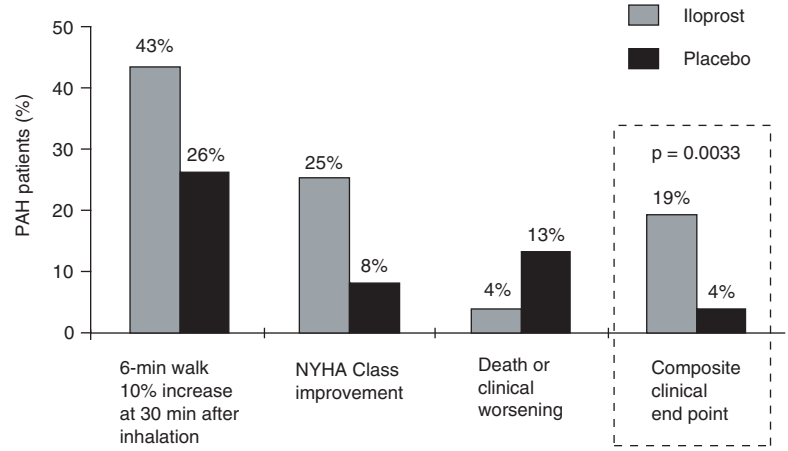

Figure 1. Composite primary end point for PAH patients (World Health Organization Group I).
NYHA: New York Heart Association; PAH: Pulmonary arterial hypertension.
Data from [40].

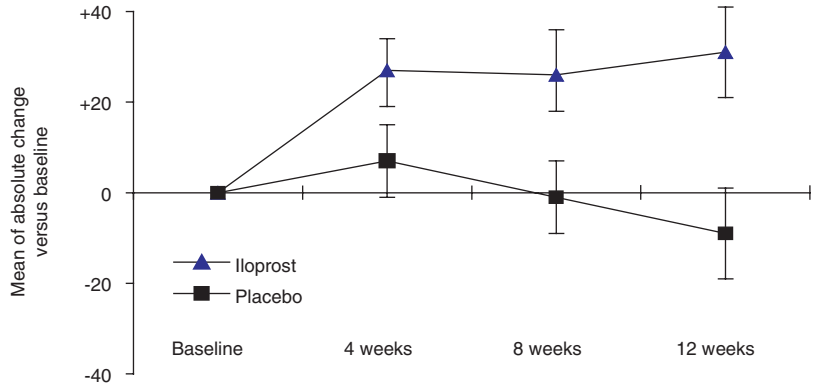

Figure 2. Change (mean ± SEM) in 6-min walk distance 30 min post-inhalation in PAH patients (World Health Organization Group I).
PAH: Pulmonary arterial hypertension; SEM: Standard error of mean.
Data from [40].

In addition to statistically significant improvements in mean walking distance and NYHA class compared with placebo, significant improvements compared with placebo were seen in the Mahler transitional dyspnoea index ($p = 0.015$) and the EuroQOL visual analogue score ($p = 0.016$); other secondary quality of life measures showed trends in favour of iloprost.

Patients receiving inhaled iloprost also showed beneficial haemodynamic changes when measured after inhalation. Compared with placebo, significant improvements were seen in pulmonary vascular resistance (PVR), mean pulmonary artery pressure (mPAP), cardiac output (CO) and mixed venous oxygen saturation (SVO_2) measured at week 12 after inhalation (**Table 2**). Consistent with the known pharmacodynamic and pharmacokinetic effects of inhaled iloprost, haemodynamic values obtained before inhalation at week 12 did not show significant changes from placebo. Although the clinical significance of a waxing and waning pharmacodynamic effect on pulmonary haemodynamics associated with intermittent iloprost administration is not completely understood, the demonstrated beneficial effects on exercise capacity when measured before inhalation, the improvement in NYHA Class and the strong trend towards fewer patients with clinical deterioration, suggests that the overall positive clinical outcomes with iloprost inhalation do not require uniform and constant reduction in pulmonary pressure or resistance.

Indeed, in contrast to the need for dose increases generally required during long-term treatment with continuous systemic prostanoids, tachyphylaxis (tolerance) has not been seen with iloprost. In the Phase III study, no increases in mean delivered dose were observed over the course of 12 weeks. In addition, the beneficial haemodynamic changes seen after 12 weeks of therapy following inhalation were comparable with changes seen following the initial dose of iloprost, indicating persistence of treatment effects.

Table 1. Treatment effects by subgroup among pulmonary arterial hypertension patients.

	Composite clinical end point				6-min walk*			
	N	Iloprost	N	Placebo	N	Iloprost (mean ± SD)	N	Placebo (mean ± SD)
All subjects with PAH	68	13 (19%)	78	3 (4%)	64	31 ± 76	65	-9 ± 79
NYHA Class III	40	7 (18%)	47	2 (4%)	39	24 ± 72	43	-16 ± 86
NYHA Class IV	28	6 (21%)	31	1 (3%)	25	43 ± 82	22	6 ± 63
Male	23	5 (22%)	24	0 (0%)	21	37 ± 81	21	-22 ± 77
Female	45	8 (18%)	54	3 (6%)	43	29 ± 74	44	-2 ± 81
Age ≤ 55	41	6 (15%)	40	2 (5%)	39	24 ± 79	32	-5 ± 78
Age > 55	27	7 (26%)	38	1 (3%)	25	42 ± 71	33	-13 ± 81

*Change from baseline to 12 weeks with measurement 30 min after dosing, based on all available data.
N: Number of patients; NYHA: New York Heart Association; PAH: Pulmonary arterial hypertension; SD: Standard deviation.
Data from [40].

Table 2. Change from baseline to week 12: haemodynamic parameters before and after iloprost inhalation (all available patient data).

	Baseline		Week 12 absolute change (mean ± SD)		
Parameter	Iloprost	Placebo	Iloprost		Placebo
			Before inhalation	After inhalation	
PVR (dyn•s•cm^{-5})	1029 ± 390	1041 ± 493	-9.2 ± 275 (n = 76)	-238.7* ± 278.6 (n = 70)	+96 ± 323 (n = 77)
mPAP (mmHg)	53 ± 12	54 ± 14.1	-0.2 ± 7.3 (n = 93)	-4.6* ± 9.3 (n = 90)	-0.1 ± 6.9 (n = 82)
CO (l/min)	3.8 ± 1.1	3.8 ± 0.9	+0.1 ± 0.9 (n = 91)	+0.5* ± 1.1 (n = 89)	-0.2 ± 0.8 (n = 80)
SVO_2 (%)	60 ± 7.5	60 ± 8.2	-1.1 ± 7.6 (n = 72)	+1.8* ± 8.3 (n = 70)	-3.2 ± 6.7 (n = 63)

*Significantly different versus placebo at $p < 0.01$.
CO: Cardiac output; mPAP: Mean pulmonary artery pressure; N: Number of patients; PVR: Pulmonary vascular resistance; SVO_2: Mixed venous oxygen saturation.
Data from [40].

In addition, rebound effects after overnight rest or following temporary interruption of dosing with inhaled iloprost have not been onbserved. Based upon the occurrence of desensitisation of the human prostacyclin receptor following constant long-term exposure to prostacyclin, the absence of tachyphylaxis and rebound may be due to the intermittent administration of inhaled iloprost with overnight breaks.

In summary, the efficacy of inhaled iloprost in PAH was demonstrated by improved exercise tolerance and NYHA functional class, prevention of clinical deterioration and improved indices of dyspnoea and quality of life. The advantage of inhaled iloprost over placebo was evident in the robust combined efficacy end point result, consisting of the proportion of patients with ≥ 10% improvement in walk distance, improvement in NYHA class and absence of mortality or clinical deterioration. The absolute change in the 6-min walk distance was also significantly greater for iloprost compared with placebo. Improvement by at least one NYHA class was consistently more frequent in the iloprost group than in the placebo or control groups. These clinical effects are consistent with the haemodynamic improvements that were observed following iloprost inhalation.

In addition to the Phase III clinical study, there have been a large number of publications from investigator-led studies of the safety and efficacy of iloprost in PH [41-54]. These studies have generally supported and extended the observation of beneficial treatment effects seen in the Phase III study. Some investigators have described their experience with long-term (> 1 year) treatment using inhaled iloprost. Hoeper *et al.* [55] treated 24 patients with primary PH with inhaled iloprost for ≥ 1 year and found sustained effects on exercise capacity and pulmonary haemodynamics as measured by improvements in 6-min walk distance, reductions in pulmonary artery pressure and resistance, and increases in cardiac output. Olschewski *et al.* [56] presented data on the long-term (2-year) outcome of therapy with inhaled iloprost in 52 patients with NYHA Class II – IV PH. In 31 patients for whom 6-min walk distance results were available at baseline and the end of 2 years, walking distance increased by 89 m (95% confidence interval [CI], 51 – 125 m). Heart failure due to progression of PH was

Table 3. Adverse events in a Phase III clinical trial.

Adverse event	Iloprost N = 101	Placebo N = 102	Placebo subtracted %
Vasodilation (flushing)	27	9	18
Cough increased	39	26	13
Headache	30	20	10
Trismus	12	3	9
Insomnia	8	2	6
Nausea	13	8	5
Hypotension	11	6	5
Vomiting	7	2	5
Alk phos increased	6	1	5
Flu syndrome	14	10	4
Back pain	7	3	4
Abnormal lab test	7	3	4
Tongue pain	4	0	4
Palpitations	7	4	3
Syncope	8	5	3
GGT increased	6	3	3
Muscle cramps	6	3	3
Haemoptysis	5	2	3
Pneumonia	4	1	3

Alk phos: Alkaline phosphatase; GGT: γ-Glutamyl transferase; N: Number of patients.
Data from [40].

the most common serious adverse event. The treatment effects were maintained with minor increases in iloprost dosing (17% over 2 years). The investigators concluded that inhaled iloprost was effective for the long-term treatment of PH with 2-year data, suggesting sustained clinical benefit. Opitz *et al.* [57] also described their experience with using inhaled iloprost as first-line therapy in IPAH in 76 patients in Germany. They found that only a minority of patients could be stabilised with inhaled iloprost monotherapy during a follow-up period of ≤ 5 years. However, as this study was conducted prior to the availability of approved PAH-specific therapy, the mean time from diagnosis to start of iloprost therapy was 1.5 years and the low cardiac index at baseline (mean CI: 1.8 l/min/m^2) suggested that many patients had right heart decompensation. Nevertheless, survival at 3 years was 59%, which was higher than the 46% predicted by the NIH formula [58]. Overall, chronic therapy with inhaled iloprost was well tolerated.

6. Safety and tolerability

Iloprost has been studied in over 160 clinical trials spanning two decades and involving more than 12,000 subjects in whom the drug was administered via the intravenous, oral or inhaled routes. Early clinical studies in the 1980s focused on the intravenous route of delivery in patients with peripheral arterial occlusive disease, which was followed by approval in Europe in 1990. The safety of parenteral iloprost in this patient population has been confirmed in over a decade of commercial use, during which no significant postmarketing safety issues have emerged. More recently, studies with an oral extended release formulation of iloprost, iloprost clathrate, have also been conducted in > 3000 subjects, in whom > 2000 received iloprost. Overall, the pooled safety database comprises > 4500 patients in randomised controlled studies, of whom > 3000 patients have received iloprost.

The main adverse effects seen following iloprost inhalation treatment in PAH patients include those commonly known to occur with the administration of prostanoid agents. Common adverse events reported by > 10% of iloprost patients include vasodilatation, headache, trismus, nausea and diarrhoea. Side effects likely to be due to inhalational delivery include cough and chest discomfort or pain. Less common adverse events include rash, hypotension, syncope, palpitation, insomnia, vomiting and tongue pain. Rash is likely to be a result of drug-induced cutaneous vasodilation. In most cases, these side effects are mild-to-moderate in severity and generally have not required discontinuation of therapy.

Adverse events reported by at least four iloprost patients and reported ≥ 3% more frequently for iloprost patients than placebo patients in the Phase III clinical trial are shown in **Table 3**. Serious adverse events reported with the use of inhaled iloprost, and not shown in **Table 3**, include congestive heart failure, chest pain, supraventricular tachycardia, dyspnoea, peripheral oedema and kidney failure.

Syncope, which is known to occur in patients with PAH, occurred somewhat more often among patients who received inhaled iloprost compared with placebo. In almost all cases, the clinical descriptions of the syncopal events noted other factors that could account for its occurrence, including drug effects (diuresis or tranquilisers), volume depletion (diarrhoea), arrhythmias (atrio-ventricular block), vasovagal effects and underlying disease. Importantly, all patients who had syncope continued inhaled iloprost therapy.

Prostacyclins, including iloprost, are known to inhibit platelet aggregation. However, there was no evidence in clinical trials to suggest that iloprost therapy increases the risk of severe or serious bleeding.

There were no clinically significant alterations in blood chemistry or haematology associated with iloprost inhalation seen in clinical studies. There is no evidence that inhaled iloprost affects the QT interval as measured by serial electrocardiograms.

A syndrome described as rebound has been noted to occur upon abrupt cessation of continuous systemic prostacyclin infusion or nitric oxide inhalation in patients with PAH, leading to acute dyspnoea, pallor, weakness, dizziness and, rarely, death [59-61]. This syndrome may be a result of desensitised or downregulated receptors suddenly left with small amounts

of the endogenous mediator, or it may be due to abrupt withdrawal of needed continuous therapy. No evidence of a rebound-like haemodynamic effect has been observed with iloprost inhalation. This may be due to the mode of administration, in which inhalations are taken at intervals with an overnight rest.

7. Dosing and administration

Iloprost for inhalation, prepared as a solution for use in a special nebuliser, is currently approved in the US, EU and Australia. In the US, it is indicated for the treatment of PAH (WHO Group I) in patients with NYHA Class III and IV symptoms. Iloprost is provided in glass ampules containing iloprost 10 μg/ml in 2 ml total volume.

Because it has a narrow therapeutic index, and commonly available nebulisers in general use may not provide consistent, reliable, reproducible and accurate delivery of aerosolised drug, iloprost was developed in conjunction with a new pulmonary drug delivery device that is capable of providing reliable and accurate drug dosing deep into the airways. For narrow therapeutic index drugs, patients may not experience clinical benefit if insufficient drug is delivered to the pulmonary vasculature, whereas too much drug can increase the risk for adverse effects. A nebuliser must generate aerosol droplets of a diameter of 2 – 5 μm that remains constant throughout the time of inhalation. Larger droplets would be caught in the upper airways, whereas smaller droplets would leave the respiratory system during exhalation.

Although other nebulisation devices were used to deliver iloprost early during testing and development, the Prodose™ Adaptive Aerosol Delivery (AAD®) system is the drug delivery system approved for administration of inhaled iloprost in the US. The AAD system was developed to address variations in the breathing patterns of different patients that might result in variations in the amount of drug delivered, as well as to minimise wastage due to aerosol dispersal into the environment, and enhance patient adherence to inhaled drug therapy [59-65]. The Prodose delivers a precise and reproducible dose of aerosolised drug regardless of a patient's age, size or breathing pattern. In Europe, some investigators have studied and successfully used a variety of other inhalation delivery devices [32].

The AAD system delivers a pulse of aerosolised drug during the first phase of inhalation, then continuously adapts to the patient's breathing pattern, eliminating the largest source of variability in drug delivery by conventional nebuliser devices. When administration of the specified dose is complete, the system turns off automatically and alerts the patient. Separate control discs for the 2.5 and 5.0 μg dose are provided with the device and can be changed by the patient if their healthcare practitioner so advises.

The first inhaled dose should be 2.5 μg (as delivered at the mouthpiece). If this dose is well tolerated, dosing should be increased to 5.0 μg and maintained at that dose. If not, the dose should be maintained at 2.5 μg. Each inhalation treatment requires one single-use ampule. Each single-use ampule delivers 20 μg/2 ml to the medication chamber of the Prodose AAD system, and delivers a nominal dose of either 2.5 μg or 5.0 μg to the mouthpiece. Iloprost should be taken no less than six times/day and up to a maximum of nine times/day (no more than every 2 h) during waking hours, according to individual need and tolerability. The maximum daily dose evaluated in clinical studies was 45 μg (5.0 μg nine times/day). The majority of patients (> 90%) studied in clinical trials did not require nocturnal dosing.

8. Conclusion and expert opinion

The inhalational route of delivery of iloprost results in a prostanoid delivery profile that is distinct from that seen with continuous systemic infusion and offers some potentially significant benefits. Inhalation of iloprost provides clinical efficacy while minimising the systemic side effects of prostacyclin therapy. Because iloprost is inhaled, it is likely to be delivered preferentially to the well-ventilated areas of the lung, offering an advantage over systemic therapy with respect to the consequences of ventilation/perfusion mismatch. This treatment advantage has been documented clinically and is supported by an absence of hypoxaemia in the Phase III study. Inhaled therapy would be a viable treatment alternative as it will reduce pulmonary vascular resistance while preserving the level of oxygenation.

Although the intermittent administration of iloprost results in fluctuations in serum levels of the drug, intermittent inhalation of iloprost rather than constant infusion allows patients to tailor therapy in relation to activity, such that treatments are taken during the day when activity is greater, allowing for a rest period at night when activity is minimal. This may be an important reason why tolerance and tachyphylaxis have not been noted with inhaled iloprost. Despite intermittent administration, the improvement in outcomes as measured by the composite clinical end point and its components indicates that clinical benefits are seen not only immediately following inhalation, but also over the entire study period integrated over time. However, follow-up studies are needed to confirm that these short-term effects are sustained with long-term treatment.

The inhaled route of delivery also avoids the significant morbidity associated with subcutaneous and central venous catheters. Pain, thrombosis, infection and sepsis are all complications that can result in the need for concomitant analgesic therapy or lead to hospitalisation and possibly death. Patients with PAH who are unable or unwilling to tolerate indwelling catheters could benefit from inhaled iloprost.

The safety database for iloprost is broad because the drug has been extensively studied in diseases that are more common than PAH, with > 3000 patients having received iloprost in randomised controlled clinical studies. The overall clinical experience for inhaled iloprost supports a high degree of patient tolerability.

Rebound has not been an issue with inhaled iloprost, given its distinct delivery profile following inhalation compared with continuous infusion. This is in contrast with the need to avoid abrupt discontinuation or withdrawal of systemically administered prostacyclin therapy.

Given the ease of use and favourable tolerability profile, inhaled iloprost is likely to be considered as an alternative to continuous intravenous or subcutaneous prostanoid infusion for some patients with PAH. Iloprost may also be prescribed for patients who cannot tolerate continuous prostacyclin infusion or therapy with bosentan. In addition, because of the different mechanisms of action of prostacyclin and endothelin-1 inhibitors, inhaled iloprost may be used by physicians as combination therapy to enhance treatment response.

With the availability of a number of medications targeting different pathobiological pathways, physicians are increasingly using combinations of therapies to manage their patients with PH. Data from small uncontrolled studies suggest that the combination of an oral agent, such as the endothelin receptor antagonist bosentan or the phosphodiesterase inhibitor sildenafil, with inhaled iloprost provides additional clinical benefit beyond that seen with monotherapy. In particular, Hoeper *et al.* [66] found that bosentan as an add-on therapy in PPH patients receiving nonparenteral prostanoids (inhaled iloprost or beraprost) resulted in further improvements in 6-min walk distance, as well as benefical effects seen on cardiopulmonary exercise testing. These encouraging pilot data provided the impetus for the conduct of a multi-centre randomised study of inhaled iloprost versus placebo as add-on therapy in patients with PAH receiving bosentan, the results of which should provide additional valuable information on this emerging treatment approach. Similar promising pilot data have been generated for the combination of sildenafil and inhaled iloprost [67]. In view of the complementary mechanisms of action of sildenafil and iloprost, sildenafil may improve efficacy and prolong the duration of action of iloprost, thereby allowing for a decrease in the dosing frequency of iloprost.

In summary, inhaled iloprost is a novel, effective and safe treatment for PAH that is distinct from currently available therapies. The inhaled route of delivery of iloprost offers patients with PAH an important therapeutic option for the treatment of this devastating disease. In the future, refinements in the delivery device to make it more user-friendly (battery-operated, portable, quiet) and demonstration of safety and efficacy when used in specific drug combinations will help patients and physicians in their decision-making on optimal therapy.

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