Chapter 2

Epoprostenol in pulmonary arterial hypertension

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Chapter 2

Abstract

Background
Pulmonary arterial hypertension (PAH) is a devastating disease leading to right heart failure and death in a relatively young patient population. In recent years novel PAH specific therapies have become available.

Objective
To determine the place of epoprostenol in current PAH treatment strategies.
Methods: An extensive medline search was performed to evaluate the use of epoprostenol in PAH. Data from both human and animal studies were reviewed.

Results/conclusion
Epoprostenol is an effective and potent treatment in pulmonary arterial hypertension and has greatly improved survival, exercise capacity, PAH symptoms, pulmonary haemodynamics and disease progression. A major disadvantage is that it can only be delivered through a continuous intravenous pump infusion.
Introduction

Pulmonary arterial hypertension (PAH) is a rare disease with a poor prognosis. It was first described in the late 19th century as a clinical-pathological syndrome characterised by obstruction of the small pulmonary arteries and right ventricular hypertrophy in patients presenting with severe dyspnea and cyanosis.\(^1\,^2\) Idiopathic pulmonary arterial hypertension (IPAH) has an estimated incidence of 1-2/million inhabitants/year in industrialized countries\(^3\,^5\). Reported prevalence of PAH in patients with connective tissue disease varies from 2-50%\(^6\,^16\). Furthermore PAH can be detected in 0.5% of HIV patients.\(^17\,^18\)

In the past 15 years 3 groups of PAH specific drug therapies have become available. They are the endothelin-receptor antagonists, phosphodiesterase type 5 inhibitors and prostanooids. These medications have a vasodilatory effect on the pulmonary vasculature and target 3 major pathways involved in abnormal contraction and proliferation of pulmonary artery smooth muscle cells in PAH.\(^19\) The first to be developed was the prostacyclin analogue epoprostenol.\(^20\) Current treatment guidelines recommend epoprostenol as preferred first line therapy in the most severe PAH patients, i.e. those in New York Heart Association (NYHA) functional class 4 and state that epoprostenol can be considered in more severe NYHA class 3 patients.\(^21\) Introduction of epoprostenol has significantly improved long-term survival in idiopathic PAH with a 3-year survival of 62.8% compared with 35.4% based on historical data.\(^22\,^23\)

However the high cost and the complex mode of delivery by continuous intravenous infusion and consequent risk of catheter related infections\(^24\) are a major burden. Several alternative prostacyclin derivatives have recently been developed or are investigated.\(^25\)

Chemistry and pharmacodynamics

Epoprostenol is a chemical analogue of prostacyclin (prostaglandin I2). Prostacyclin was discovered in 1976 by Moncada and Vane, while investigating how blood vessel walls make unstable prostanooids.\(^26\) It is the main product of arachidonic acid in all vascular tissues and is formed through the cyclooxygenase pathway.\(^27\) The ability of the vessel wall to synthesize prostacyclin is greatest at the intimal surface and progressively decreases towards the adventitia.\(^28\) Prostacyclin relaxes isolated vascular strips. It has a hypotensive effect through vasodilation of all vascular beds studied, including the pulmonary and cerebral circulations.\(^29\) In addition it is a potent inhibitor of platelet aggregation. For example prostacyclin inhibits thrombus formation in a constricted dog artery and an electrically damaged rabbit artery.\(^30\,^31\) Also the substance disperses existing thrombocyte aggregates in vitro\(^26\,^10\) and in vivo.\(^32\) This anti-thrombotic effect is short-lasting in vivo, disappearing within 30 minutes of cessation of administration. In addition to its vasodilator and anti-aggregating effect prostacyclin also exhibits a cytoprotective effect.\(^33\,^37\) For instance, in models of myocardial infarction prostacyclin reduces infarct size\(^38\,^40\), arrhythmias\(^41\), oxygen demand\(^40\), and enzyme release from the infarcted areas.\(^42\) Further investigations have demonstrated antiproliferative actions and the reduction of matrix secretion in smooth muscle cells, endothelial cells and fibroblasts, as well as an anti-inflammatory profile in leucocytes.\(^43\) In vitro inhibition
of vascular smooth muscle cell growth by prostacyclin analogues has been shown.\textsuperscript{44} Endothelial cells are the major source of endogenous prostacyclin. Its action is directed at both the local vascular wall and blood cells. In particular those blood cells that adhere to the endothelium. The main target of prostanoids is the IP receptor, which is abundantly expressed in blood vessels, leucocytes and thrombocytes and is rapidly activated by prostanoids. The IP receptor is coupled with Gs proteins and activates adenylate cyclase, leading to increased cyclic adenosine monophosphate levels in target cells, which explains most of the biological effects.\textsuperscript{45} However, prostacyclin is not highly specific to the IP receptor. It also activates prostaglandin E (EP) receptors\textsuperscript{46}, which are located on the cell surface as well as in the nucleus\textsuperscript{47,48}, and peroxisome proliferator activated receptor (PPAR)\textdelta, which is located in the nucleus.\textsuperscript{49} Both PPAR\textalpha and PPAR\textdelta may also be activated via IP receptor-dependent protein kinase (PK)\textalpha activation, but the intracellular prostaglandin (PG)I\textsubscript{2} from the endogenous PGI synthase seems to specifically activate the apoptosis pathway by activation of PPAR\textdelta.\textsuperscript{50-53}

PAH is associated with vasoconstriction, thrombosis and proliferation, and this may be partly due to a lack of endogenous prostacyclin\textsuperscript{43, 54, 55}, secondary to prostacyclin synthase downregulation.\textsuperscript{56} Vice versa overexpression of prostacyclin synthase protects against development of pulmonary hypertension in transgenic mice and rats.\textsuperscript{57,58} After intravenous infusion of prostacyclin there are beneficial haemodynamic effects in the vast majority of patients, with a significant decrease in pulmonary vascular resistance and a minor decrease in systemic pressure. However if the dose is rapidly increased, systemic vasodilation may cause intolerable symptoms and a systemic pressure drop. In chronic prostacyclin therapy excessive prostacyclin dosage can lead to a high cardiac output state. In this circumstance by reducing the dose, cardiac output normalizes without worsening the clinical state.\textsuperscript{59} If prostanoids are infused at a constant dose there may be IP receptor desensitisation with a complete loss of vasodilatory effect.\textsuperscript{60} In clinical practice there is no loss of pharmacological effect during constant infusion in the short-term, but epoprostenol doses have to be gradually increased to keep the same level of pulmonary vasodilation and systemic side effects (from 4 ng·kg\textsuperscript{-1}·min\textsuperscript{-1} as an average tolerated dose to ~20-60 ng·kg\textsuperscript{-1}·min\textsuperscript{-1} after 1 year).

In PAH there is increased \textsuperscript{18}F fluorodeoxyglucose accumulation in the right ventricle indicating increased glucose metabolism. This accumulation increases with PAH disease severity and treatment induced decreases after epoprostenol administration were shown.\textsuperscript{61} Chronic intravenous prostacyclin has been shown to reduce right ventricular (RV) size, septal displacement and tricuspid insufficiency, in pulmonary hypertension indicating an improvement in RV function due to decreased RV afterload.\textsuperscript{62,63} It has been hypothesized that prostacyclin therapy would also benefit PAH patients through positive inotropic effects.\textsuperscript{64} However in an animal model of acutely induced right heart failure and in an animal model of chronic PAH no positive inotropic effects of epoprostenol administration were found.\textsuperscript{63,65} In a pulmonary angiography study epoprostenol treatment led to so-called cotton grass-like regional stains of the capillary imaging phase. These angiographic changes were attributed to vasodilation and it was suggested that alternatively they may be induced by neovascularization.\textsuperscript{66}
Prostacyclin analogues have induced neovascularisation in a mouse model and in rats they enhanced neovascularisation in ischaemic myocardium by mobilizing bone marrow cells.

**Pharmacokinetics**

In biological fluids at physiologic pH values there is a rapid enzymatic degradation and spontaneous hydrolysis of epoprostenol. Plasma half-life is 2–3 minutes. All metabolites are inactive or less active. Metabolites are mostly excreted by urine. Because of the rapid biotransformation epoprostenol can only be used as continuous infusion through a central venous catheter. Delivery through peripheral veins leads to painful vein irritation after a short time. Epoprostenol is provided by the manufacturer as a stable freeze-dried preparation. It is supplied with an alkaline buffer, which allows it to remain stable in a dissolved form. After mixing the drug powder with the solvent, the solution can be used up to 12 hrs at room temperature. When cooled it can be used up to 48 hrs after reconstitution (SPC Flolan®).

**Clinical efficacy**

The first patient treated by epoprostenol was a 27 year old woman, who suffered from progressive dyspnea for over 6 years. A diagnosis of primary pulmonary hypertension was made. She was cyanotic, bed bound due to severe dyspnea and suffered from an intractable unproductive cough. Mild exertion such as standing and walking resulted in syncope. Peripheral oedema had occurred due to right-sided heart failure. After treatment with epoprostenol pulmonary vascular resistance decreased and exercise capacity improved. No further syncopal attacks occurred and peripheral oedema was eliminated. The patient learnt how to prepare and store the epoprostenol solution and was discharged home. She was treated with epoprostenol for more than a year at time of publication. In 1987 Jones et al. reported 10 IPAH patients with subjective and clinical improvements and improved exercise capacity after 1-25 months of epoprostenol treatment. Rubin et al. reported improved hemodynamics after epoprostenol treatment in several reports. Improved cardiac output and decreased pulmonary vascular resistance at 12 months and sustained improvement in exercise capacity at follow-up up till 18 months after initiation of prostanoids were shown in an open-label uncontrolled trial. Subsequently a pivotal trial involving 81 IPAH was performed, after which the FDA and European health authorites approved epoprostenol for IPAH treatment. Patients were randomised to epoprostenol in addition to conventional therapy or conventional therapy alone. Conventional therapy consisted of warfarin, digoxin, oxygen and oral vasodilators. Patients were followed for 12 weeks. Subjects on active therapy had a mean 32m improvement in 6-min walk distance compared with a 15m decrease in the conventional group (p<0.01). Pulmonary artery pressure decreased by 8% in the epoprostenol group, as opposed to a 9% increase in the conventional group (p<0.001). Cardiac index increased by 0.3 l/min/m² in the epoprostenol group versus a 0.2 l/min/m² decrease. All deaths (n=8) were in the placebo group (p<0.01). Since then observational cohort
studies demonstrated long-term beneficial effects of epoprostenol. McLaughlin reported clinical and haemodynamic improvements in 162 NYHA III and IV IPAH patients. Patients had improved survival in comparison with expected survival based on historical data. The 1, 2 and 3 year survival rates of 87.8, 76.3 and 62.8% were significantly better than the expected survival rates of 58.9, 46.3 and 35.4%. Sitbon et al. evaluated a cohort of 178 IPAH and reported similar results. Compared with a historical cohort survival rates improved from 58, 43, 33 and 28% to respectively 85, 70, 63 and 55% at 1, 2, 3 and 5 years. Use of epoprostenol can delay or avoid lung transplantation in PAH.

Additional evidence has emerged supporting epoprostenol use in PAH from associated causes. In a randomized 12-week trial scleroderma patients treated with epoprostenol experienced a 46m improvement in 6-minute walk distance compared to a 48m decrease in the conventional arm. The median difference in distance walked at 12 weeks between both groups was 108m (p<0.001). A number of uncontrolled studies also suggest improvements in patients with connective tissue disease associated PAH, congenital left-to-right cardiac shunts and HIV related PAH. Results are ambiguous in portopulmonary hypertension.

Safety and tolerability

Treatment with epoprostenol has limitations based on its pharmacology. It requires initiation by experienced physicians in designated centres. Long-term epoprostenol infusion is costly and requires a permanent central venous catheter and a portable infusion pump. Medication needs to be prepared every other day when kept cold or twice daily when used at room temperature. Patients need education in sterile technique, operation of the pump and care of the catheter. Serious complications include infection and thrombosis of the catheter and temporary interruption of the infusion due to pump malfunction or line disconnection. Because of the short half-life of epoprostenol, interruption of infusion can be life-threatening. In a multicenter study the incidence of catheter related infections was 0.43/1000 intravenous infusion days for epoprostenol versus 1.11/1000 infusion days for i.v. treprostinil. Epoprostenol side effects are predominantly related to its vasodilatory effects. Side-effects are usually well tolerated, may be dose-related and vary in intensity between individuals. The most common side-effects include flushing (42%), headache (83%), nausea (67%), loose stool (37%), jaw discomfort (54%) and musculoskeletal pain (35%). Hyperthyroidism has rarely been reported (<1%).

Alternative prostaclin therapies

Several alternative prostaclin analogues have recently been developed for intravenous (treprostinil, iloprost), subcutaneous (treprostinil) and inhaled (iloprost) administration and others are investigated for inhaled (treprostinil) or oral (beraprost, treprostinil) routes. These therapies have similar pharmacodynamic, but different pharmacokinetic properties. On a nanomolar basis drug efficacy amongst these different compounds is not equal. Practical advantage of these medications are that they do not need cooling. Also the longer half-lives of these drugs make patients less
prone to cardiovascular collapse in case of interrupted administration. Oral beraprost improved exercise capacity after 3 and 6 months. However improvements were non-sustained at 9 and 12 months follow-up. Beraprost is currently not approved in Europe and the USA. But it is an approved therapy in Japan. Treprostinil has the advantage of less invasive subcutaneous administration. Treprostinil half-life is about 80 minutes when administered subcutaneously and risks associated with treatment interruption are reduced. In a multicenter randomized placebo controlled trial involving 470 patients a 16m significant increase in 6-,minute walk distance occurred in the treprostinil group. Sustained improvement in exercise capacity was reported in an open label study with a mean 26 months follow-up. In a long-term observational study of 860 patients (811 PAH of which 412 IPAH, and 49 thromboembolic pulmonary hypertension) the effects of subcutaneous treprostinil, followed by addition of other PAH therapies if needed, were followed for up to 4 years. During follow-up 196/860(23%) discontinued the drug due to treprostinil infusion site pain and 3 due to other adverse event. During follow-up 136(16%) died, 117 (14%) discontinued owing to deterioration, 29(3%) withdrew consent and 11(1%) underwent lung transplantation. In total 97 patients (11%) switched to an alternative prostacyclin analogue, bosentan was added in 105 patients (12%) and sildenafil in 25(3%). Survival rates for the whole cohort were 87% at 1 year and 68% at 4 years. Survival in the IPAH subgroup was 72% at 4 years compared to 38% from historical data. Alternatively treprostinil can be administered intravenously or orally. A randomized placebo-controlled trial is ongoing to determine efficacy of oral treprostinil.

Inhalation of prostanoids is possible for iloprost or treprostinil. Inhaled iloprost needs administration by nebulizer 6-9 timed daily. Iloprost as well as treprostinil have also been used as i.v. infusion. It is difficult to directly compare the clinical effects and side-effects of different prostanoids and different administration routes. This is due to differences in enrolled patient populations, the mode of application and dosing and trial design in the different randomised controlled trials that have been performed. No trials have compared efficacy of different prostanoids head on.

**Combination therapy**

Epoprostenol therapy is neither curative nor does it normalise pulmonary artery pressure in the majority of cases. Investigators have examined the effects of targeting multiple pathways and combined prostanoids with endothelin antagonists and phosphodiesterase type 5 inhibitors. In the Bosentan Randomized Trial of Endothelin Antagonist Therapy (BREATHE)-2 study 33 PAH patients were started on epoprostenol and randomised in a 2:1 ratio for addition of bosentan or placebo for a total duration of 16 weeks. In this small study no significant benefit in clinical or haemodynamic measurements could be observed from the addition of bosentan. A study by Simmoneau et al. reported the results of a 16-week multinational, double-blind, placebo-controlled trial assessing safety and efficacy of sildenafil added to epoprostenol. Patients had improvements in exercise capacity with a 26 m increase in 6-minute walk distance (p<0.001), improved pulmonary haemodynamics (mean
pulmonary artery pressure –3,8mm Hg; p<0.0001) and improved time to clinical worsening (p=0.012). This benefit was maintained at 1 year in the subsequent long-term open-label extension study.101

Costs and regulatory affairs
The cost of epoprostenol is approximately $100,000 per year in the U.S.A., but may be higher depending on patient dose. Most USA based insurance companies, as well as Medicaid and Medicare, will pay for epoprostenol. (Medicaid is the United States health program for selected low income groups and Medicare the federal health insurance plan for senior citizens > 65 years). Cost varies considerably between countries. For instance treatment cost is currently around $115,000 per year in the Netherlands, whilst treatment cost can rise in excess of $300,000 in other countries if list prices are not discounted.

Abid et al. calculated the cost needed to prevent 1 death per year in different diseases and with different therapies. In the treatment of PAH epoprostenol cost was estimated at $968,000 per life saved per year. This compared to $406,000 per life saved for bosentan, $873,000 per life saved for inhaled iloprost and $1,715,000 per life saved for subcutaneous treprostinil. This compared to $315,000 per life saved for an automatic cardiac defibrillator, $654,968 per life saved for a left ventricular assist devices, $1,080,000 per life saved for the treatment of follicular non-Hodgkin’s lymphoma with Cyclophosphamide, Adriamycin, Vincristine, Prednisone and Rituximab, $1,795,846 per life saved for pacemakers for atrial fibrillation, and $16,065,000 per life saved for treatment of lupus nephritis with Mycophenolate mofetil. It was concluded that the costs of epoprostenol and other PAH treatments are at an acceptable cost effectiveness range compared to other pharmacotherapeutic and biotechnological interventions in other diseases.102 In a cost-minimization analysis two theoretical U.S.A. cohorts of 270 patients were treated with subcutaneous treprostinil and intravenous epoprostenol, and were evaluated over 3 years. Probabilistic sensitivity analyses resulted in average 3-year cost-savings of 41,051 US dollars per patient in favour of treprostinil. The greatest savings came from reduced or minimal hospitalizations attributed to the dose titration and treatment of adverse events, such as sepsis, associated with epoprostenol and its delivery system.103 This was confirmed by a canadian cost-minimization analysis evaluating two cohorts of 60 patients, treated with treprostinil or epoprostenol. The Canadian evaluation included both the provincial ministries of health and societal perspectives: on a per-patient level, treatment with treprostinil resulted in an average annual savings of 14,504 US dollars and 15,452 US dollars, respectively.104

The financial aspect of chronic epoprostenol treatment for PAH and comparing costs are a complicated issue. Due to tachyphylaxia epoprostenol doses can increase from an initial 500-1000 micrograms per day to more than 6000 micrograms per day over a period of several years. In some countries epoprostenol is provided by hospital pharmacies only. In other countries epoprostenol is delivered by community pharmacists when the patient is at home. Reimbursement systems differ between countries, with or without separated financial systems for hospital use and use in
the community-setting. The costs per saved life year, whether or not adjusted for the quality of life, are under debate. Controlling epoprostenol treatment cost is of some concern. As an alternative, treatment may be offered for a fixed price, irrespective of the dose. Discussions between providers and payers should contribute to mutual agreement on acceptable cost for life saving treatments like epoprostenol in a rare disease such as PAH. The recent approval of 2 generic forms of epoprostenol in the U.S.A. will likely contribute to cost reduction.

**Conclusion and expert opinion**

Epoprostenol was the first PAH specific therapy developed and leads to improved exercise capacity, improved haemodynamic parameters, decreased PAH symptoms and decreased mortality. Improvements persist at long-term follow-up. Many clinicians view epoprostenol as the gold standard treatment to which other treatments should be compared. Its introduction has lead to great improvements in outcome in mostly young patients suffering from a devastating disease with a poor prognosis. For some patients PAH specific therapies have turned their disease chronic. The introduction of oral treatment alternatives from different drug classes and the development of inhaled and subcutaneously administered prostanoids have limited the use of epoprostenol. However, considering its potency epoprostenol remains first choice therapy for severe patients in NYHA class IV. In NYHA II and III patients the orally administered endothelin receptor antagonists and phosphodiesterase type 5 inhibitors are preferred first-line therapy. Combining oral therapies is effective and can delay clinical deterioration and the need for additional epoprostenol [105,106]. Clinical efficacy of epoprostenol remains excellent when used as second line therapy. Whether upon deterioration on oral therapy epoprostenol should substitute oral therapy or be used as add on therapy is unknown. No data are available comparing the different prostanoid compounds. In NYHA III patients not improving on oral therapy the choice of prostanoid is currently determined by clinical experience, patient preference, drug availability and costs. It is unknown whether patients started on first-line i.v. epoprostenol have improved long-term outcomes compared to patients started on less invasive therapies. Epoprostenol treatment is expensive and invasive. PAH symptoms may remain despite epoprostenol treatment. Long-term survival remains unsatisfactory. Further research is warranted.
References


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