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Epoprostenol (Flolan®)

Summary

Indications: Epoprostenol is indicated for the long-term treatment of primary pulmonary hypertension and secondary pulmonary hypertension due to intrinsic precapillary pulmonary vascular disease. It is also indicated for patients with pulmonary hypertension associated with the scleroderma spectrum of disease in NYHA class II and class IV patients who do not respond to conventional therapy.

Dose: Epoprostenol is administered as a continuous infusion through a central venous catheter. The infusion should be started at 2 ng/kg/min and increased in increments of 2 ng/kg/min every 15 minutes or longer until dose-limiting effects occur. Dosing is uncertain due to tolerance development over long-term use, requiring monthly increases in dose as symptoms return. The average dose after 6 months of therapy ranges from 12 to 20 ng/kg/min.

Monitoring Parameters: Hemodynamic monitoring is essential for assessing drug efficacy and the need for dose adjustment. Catheter site infections, thrombosis, and pump malfunction are potentially fatal and should be closely monitored for. The most common adverse effects are flushing, jaw pain, headache, diarrhea, nausea and vomiting.

Pregnancy Category: B. Reproductive studies were performed on rats and rabbits at doses 2.5 to 4.8 times higher than the human dose without evidence of impaired fertility or harm to the fetus.

Breast-feeding: It is not known whether poprostenol is excreted in breast milk.

Pediatrics: Safety and efficacy have not been established in the pediatric population.

Geriatrics: Clinical studies included very few patients over the age of 65; therefore therapy initiation should be conservative for these patients.

Cost: Epoprostenol is available in 0.5 mg and 1.5 mg vials. The average wholesale prices are \$18.28 and \$36.55 per vial, respectively. Epoprostenol can only be reconstituted using the sterile diluent for poprostenol, which is \$10.98 per vial.

Storage: The vials of poprostenol should be stored at 15° to 25 °C (59° to 77°F) and need to be protected from light. The sterile diluent for poprostenol should be stored at room temperature and not frozen. Reconstituted solutions may be stored refrigerated at 2° to 8°C (36° to 46°F) for no longer than 48 hours. At room temperature, the solution should not be used after 8 hours.

Introduction

Pulmonary hypertension is defined as a mean pulmonary arterial pressure greater than 25 mm Hg at rest or 30 mm Hg during exercise, and a normal pulmonary artery wedge pressure.^{1, 2, 3} Pulmonary hypertension is classified as primary or secondary. A diagnosis of primary pulmonary hypertension (PPH) is made when all types of secondary hypertension have been excluded.^{1, 2} Secondary causes include lung diseases, congenital heart defects, thromboembolic disease, connective tissue disease, left-sided cardiac valvular disease, and liver disease associated with portal hypertension. The estimated annual incidence of PPH in European and US studies is 1-2 cases per million people per year in the general population.⁴ Autopsy studies have shown a prevalence as high as 1300 per million. The incidence of PPH in users of appetite suppressants may be upwards of 25-50 per million per year.¹ The mean age at diagnosis of PPH is 36 years. Females are at higher risk than males in both adult disease and childhood familial PPH. Familial PPH accounts for approximately 10% of cases.¹

The etiology of PPH is unknown.⁵ Recently, it was discovered that the genetic mutation associated with familial pulmonary hypertension resides on the long arm of chromosome 2 (q31-q32) locus.⁶ Toxins associated with pulmonary hypertension include appetite suppressants, monocrotaline, inhaled solvents, methamphetamine, cocaine, rapeseed oil, and L-tryptophan. Infections such as HIV-1, inflammatory disorders like autoimmune thyroid disease and diseases producing circulating antinuclear and anti-Ku antibodies have also been linked to pulmonary hypertension.¹ Raynaud's phenomenon is associated with a worse prognosis, and occurs in 10% of patients, mostly female. A positive antinuclear antibody test is found in 29% of patients, also mostly female.²

A variety of defects have been linked with PPH, including vascular smooth muscle abnormalities, increased concentrations of endothelin 1, a potent pulmonary vasoconstrictor, and decreased levels of pulmonary enzymes responsible for the production of the potent vasodilators, nitric oxide and prostacyclin.^{4, 6, 7} Another common finding is increased plasma serotonin.⁷ Appetite suppressant like fenfluramine (Pondimin®) and dexfenfluramine (Redux®) inhibit serotonin reuptake, in-

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creasing the local concentration of platelet-derived serotonin, which is a pulmonary vasoconstrictor. This may, in part, explain the connection between appetite suppressants and PPH.

Primary pulmonary hypertension is a progressive disease, ultimately resulting in right heart failure and death. Current treatment options include vasodilators, anticoagulants, and lung or heart-lung transplant. Diuretics are used for edema and systemic vascular congestion associated with advanced right heart failure. None of these options have been shown to improve survival.² Epoprostenol (Flolan[®], Glaxo Wellcome), an injectable prostaglandin, may be of benefit in selected patients with secondary pulmonary hypertension.⁵ Epoprostenol has been shown to improve hemodynamics, improve exercise tolerance and prolong survival in patients with PPH. Although once utilized as a bridge to transplantation, epoprostenol is now emerging as an alternative to transplantation.¹ As more patients are maintained on long-term epoprostenol therapy, pharmacists in a variety of practice settings, not just those associated with transplant centers, will be required to be familiar with the drug.

Pharmacology/Pharmacokinetics

Epoprostenol, also known as prostacyclin or PGI₂, is the principle product of arachidonic acid in all vascular tissue. This naturally occurring prostaglandin has both vasodilatory action and inhibitory activity on platelet aggregation. PGI₂ exerts its effect by 2 major actions. The first is direct vasodilation of pulmonary and systemic arterial vascular beds. The second action is inhibition of platelet aggregation. The vasodilatory effects decrease right and left ventricular afterload, resulting in increased cardiac output and stroke volume. In animal studies, low doses of epoprostenol had a vagally mediated bradycardic effect, while higher doses caused reflex tachycardia in response to vasodilation and hypotension. Other effects observed in animals included bronchodilation, inhibition of gastric acid secretion and decreased gastric emptying.⁸

Epoprostenol has a limited volume of distribution, approximately 357 mL/kg, and the clearance is high at 93 mL/min/kg. Epoprostenol is rapidly hydrolyzed and enzymatically degraded at the neutral pH of blood.⁸ Steady-state plasma levels are achieved within 15 minutes and are proportional to the rate of infusion. The elimination half-life is 3 to 5 minutes. Epoprostenol has two major metabolites: 6-keto-PGF₁α (formed by spontaneous degradation) and 6,15-diketo-13, 14-dihydro-PGF₁α (formed enzymatically). Neither metabolite has the same degree of activity as the parent compound. Epoprostenol is extensively metabolized; 82% of a radio-labeled dose is recovered in the urine following intravenous administration.

Clinical Trials

In a study conducted by McLaughlin et al, 38 consecutive patients with PPH were followed for 12 to 24 months to investigate the effects of long-term epoprostenol.⁹ The patients had New York heart association (NYHA) class III or IV heart failure despite optimal medical therapy. Epoprostenol was started at 2 ng per kilogram per minute and increased to the maximum tolerated dose within 7 days. Concurrent medications used include digoxin (93%), diuretics (85%), warfarin (100%), and calcium-channel blockers (41%). Patients were stable on these medications prior to enrollment. Of the 38 patients treated, 27 patients had a follow-up evaluation, including 19 women and 8 men. The majority, 63%, was in NYHA class III, while 37% were in class IV. The mean duration of treatment was 16.7 ± 5.2 months (range, 12 to 24). The mean dose at follow-up was 40 ± 15 ng per kg per minute, or a mean increase of 2.4 ng/kg/min each month. At follow-up, all patients had improvements in their symptoms and classification, as 22% were NYHA class I, 74% in class II, and 4% were in Class III (*p*<0.001). The duration of exercise on the treadmill increased by 142% from 261±175 seconds at baseline to 631±283 seconds (*p*<0.001). The mean pulmonary arterial pressure was 22% lower than baseline levels, 52±12 vs 67±10 mm Hg (*p*<0.001). Cardiac output increased by 67% (range – 15 to 155%) from 3.76±1.19 L/min to 6.29±1.97 L/min. Pulmonary vascular resistance (PVR) improved in 26 of the 27 patients (mean reduction: 27%, range 0 to 56; *p*<0.001). The most common side effects included diarrhea, jaw pain, headaches, and flushing, experienced by all patients. There were a total of 17 local infections of the Hickman catheter in 10 patients. Three of the 10 patients progressed to sepsis requiring intravenous antibiotics. There were no reported pump failures or thrombosis.

A 12-week prospective, unblinded, randomized multi-center open trial conducted by Barst and colleagues compared the effects of continuous epoprostenol infusion with concurrent conventional therapy to conventional therapy alone.¹⁰ Conventional therapy for PPH included anticoagulants, oral vasodilators, diuretics, cardiac glycosides, and supplemental oxygen. A total of 81 patients with severe PPH with NYHA class III and IV were enrolled; 41 patients received epoprostenol with conventional therapy, and 40 continued their prior therapy. Objectives included exercise capacity, quality of life, hemodynamics, and survival. Baseline hemodynamics were established by right-heart catheterization and re-evaluated at the end of the study. The initial dose in patients with long-term infusion was 5.3 ± 0.5 (4 ng/kg/min less than the maximal tolerated dose). The dose increased to 9.2 ± 0.8 ng/kg/min by the end of the study. Patients receiving epoprostenol had significant improvements in exercise capacity and cardiopulmonary hemodynamics, while patients receiving conventional

therapy deteriorated. Exercise capacity measured by the change in distance walked increased 31 meters from baseline in the epoprostenol group and decreased 29 m in the conventional therapy group ($p < 0.002$). Quality of life was assessed at baseline, 6 and 12 weeks with the Chronic Heart Failure Questionnaire, the Nottingham Health Profile, and the Dyspnea-Fatigue Rating. The quality of life for patients receiving epoprostenol increased significantly in all parts of all three questionnaires ($p < 0.01$). Mean pulmonary artery pressure changes for the epoprostenol and control group were -8% and $+3\%$, respectively ($p < 0.002$). An improvement in afterload was seen, as measured by a mean change in pulmonary vascular resistance of -21% and $+9\%$, respectively ($p < 0.001$). Eight patients in the control group died during the 12 week study ($p = 0.003$). Two control group patients and one epoprostenol patients underwent lung transplant. Complications related to epoprostenol were similar to those seen in other studies, including jaw pain, diarrhea, flushing, headaches, nausea, and vomiting. Four episodes of non-fatal catheter-related sepsis and one thrombotic event occurred. There were 26 episodes of interruption in the drug-delivery system, including occlusions, perforations, catheter dislocation and pump malfunction.

A randomized, multi-center trial with 8-week treatment periods and nonrandomized treatment for up to 18 months was conducted by Rubin et al to evaluate treatment of PPH with continuous intravenous epoprostenol.¹¹ A sequential sample of 24 patients with PPH were enrolled. Nineteen patients completed the study. Four patients died and one dropped out due to pulmonary edema. All patients had been on stable doses of their medications for at least 2 weeks prior to treatment. Six of 10 epoprostenol-treated patients had a greater than 10 mm Hg decrease in mean pulmonary artery pressure, compared with one person in the control group ($p = 0.057$). Total PVR decreased from 21.6 Wood's units at baseline to 13.7 Wood's units in the prostacyclin group ($p = 0.022$). There was no change in the conventional treatment group. Exercise tolerance determined by the 6-minute walk improved by 54% and 36% in each group, respectively. All patients in the epoprostenol group and two in the control group improved by at least one NYHA functional class during the 2-month period. There were no significant differences from baseline in the hemodynamic variables in either group. Four patients, 3 in the control group and 1 in the epoprostenol arm, died during the 8 week trial. Adverse effects were similar to other reports, including diarrhea, jaw pain, and photosensitivity seen in 100%, 57%, and 36% of patients, respectively. Pump malfunction occurred on 5 different occasions and 4 patients required catheter replacement.

An open, multicenter, uncontrolled trial was conducted by Barst and colleagues to evaluate the effects of long-term intravenous epoprostenol infusion on exercise tolerance, he-

modynamic variables, and survival in 18 patients with NYHA class III or IV despite conventional treatment.¹² The mean initial dose was 6.9 ± 3.0 ng/kg/min (range 2 to 8 ng/kg/min). The mean dose at one year was 17.6 ± 11.2 ng/kg/min, 36.7 ± 21.2 ng/kg/min at 2 years, and 52.9 ± 30.2 ng/kg/min after 3 years. After 6 months of epoprostenol, exercise capacity increased from 264 ± 160 m at baseline to 370 ± 199 m ($p < 0.001$). The mean cardiac index increased from baseline by 18% (95% CI, 0.1% to 36.7%; $p = 0.02$). Mean pulmonary artery pressure and total PVR decreased 9% (CI, 1.4% to 15.7%; $p = 0.03$) and 26% (CI, 6.1% to 46.3%; $p = 0.02$), respectively. These improvements were sustained after 12 months. Survival improved compared with historical controls on conventional therapy in the National Institutes of Health Primary Pulmonary Hypertension Registry. The Kaplan-Meier estimated survival rates after 1, 2, and 3 years were 86.9%, 72.4%, and 63.3% compared with 77.4%, 51.6%, and 40.6% for the historical control group. ($p = 0.045$). Minor complications were similar to previously reported, including diarrhea, jaw pain, flushing, photosensitivity, and headaches. Five patients had 9 thrombotic episodes. Three patients had non-fatal episodes of sepsis, while 1 patient died as a result. Another patient died due to an interruption of the infusion. Five other patients had non-fatal temporary interruptions of the infusion as a result of mechanical problems.

Right heart failure is the ultimate cause of death in two thirds of patients with primary pulmonary hypertension.¹³ Abnormalities resulting in heart failure include ventricular hypertrophy, low cardiac output, elevated pulmonary arterial and right atrial pressures, tricuspid regurgitation, and pericardial effusion. A total of 81 patients in NYHA class III or class IV participated in a multicenter, open-label trial conducted by Hinderliter et al. Patients were randomized to treatment with a long-term epoprostenol plus conventional therapy ($n = 41$) or conventional therapy alone ($n = 40$) for 12 weeks. There were no significant differences between the two groups in baseline demographic characteristics, baseline hemodynamic values or 6-minute walk results. Compared with normal control subjects, patients with PPH had severely depressed right ventricular contractile function, marked septal displacement in both systole and diastole, marked right ventricular dilatation, and increased chance of having a pericardial effusion. All but 2 patients had tricuspid regurgitation detected by Doppler in the apical four-chamber view. After the 12-week epoprostenol infusion, benefits were seen in the right ventricle size, curvature of the interventricular septum and the tricuspid regurgitation. Eight patients in the conventional treatment group died during the study, while there were no deaths in the patients treated with prostacyclin.

A study conducted by Higenbottam et al was done to determine whether epoprostenol or heart-lung transplantation

or both would improve survival in patients with severe pulmonary hypertension compared to patients on conventional therapy.¹⁴ Over a period of six years, 44 patients were enrolled. Due to the expense of the drug, only 25 patients could be treated long-term. Anticoagulant and other vasodilator therapy were stopped and only diuretics continued during the study. The mean initial dose of epoprostenol was 0.5 ng/kg/min and increased to a maximum dose of 4.5 ng/kg/min at death or transplant surgery. Treatment efficacy was assessed by progressive exercise tests and 12-minute walk test every 3 months. Epoprostenol reduced mortality risk by 66% per month, compared to 18% reduction by heart-lung transplantation. Epoprostenol doubled the time on the transplant waiting list or the time until death from 8 to 17 months.

In an open-label study, Badesch et al evaluated the effect of epoprostenol on pulmonary hypertension secondary to the scleroderma spectrum of disease in 111 patients with moderate to severe pulmonary hypertension.¹⁵ Patients were randomized to receive epoprostenol along with conventional therapy or conventional therapy for 12 weeks. In the epoprostenol arm, exercise capacity improved from 270 meters at baseline to 316 m, while it decreased in the conventional therapy group from 240 m at baseline to 192 m (95% CI, 55.2m to 180.0 m; $p < 0.001$). The NYHA classification improved in 21 epoprostenol-treated patients compared to no patients in the conventional therapy group. Mean pulmonary artery pressure decreased by 5.03 ± 1.09 mm Hg from baseline in the epoprostenol and compared to 0.94 ± 1.10 mm Hg in the conventional therapy group. The mean changes in PVR were -4.6 and 0.9 mm Hg/L/min (difference, -5.5 mm Hg/L/min [95% CI, -7.3 to -3.7 mm Hg/min]). The cardiac index improved from baseline by 0.5 L/min/m² in the epoprostenol group, while it decreased by 0.1 in the conventional group. Right atrial pressure decreased by 1.26 in the epoprostenol group, but increased by 1.2 in the conventional group. Reported side effects included anorexia, nausea, diarrhea, and jaw pain.

Adverse Effects

The most common adverse reactions reported with epoprostenol include flushing (58%), headache (49%), nausea/vomiting (32%), hypotension (16%), anxiety/nervousness/agitation (11%), chest pain (11%), and dizziness (8%).⁸ In clinical trials, the adverse effects occurring at least 10% more frequently in the epoprostenol population than those treated with conventional therapy included dizziness (83% vs 70%, epoprostenol vs conventional therapy), headache (83% vs 33%), nausea/vomiting (67% vs 48%), jaw pain (54% vs 0%), myalgia (44% vs 31%), flushing (42% vs 2%), diarrhea (37% vs 6%), tachycardia (35% vs 24%), musculoskeletal pain (35% vs 15%), chills/fever/sepsis/flu-like symptoms (25% vs 11%), anxiety / nervousness / tremor (21% vs 9%), and

hypesthesia/hyperesthesia/paresthesia (12% vs 2%).

Cost, Dose, and How Supplied

Epoprostenol is administered as a continuous infusion through a central venous catheter using an ambulatory infusion pump. During initiation of epoprostenol, a peripheral line may be used. The infusion should be started at 2 ng/kg/min and increased in increments of 2 ng/kg/minute every 15 minutes or longer until dose-limiting effects occur. Concentrations of 3,000 ng/mL and 10,000 ng/mL are generally enough to deliver between 2 to 16 ng/kg/min in adult patients. The reconstituted solution has a pH of 10.2 to 10.8 and is unstable at a lower pH.

Epoprostenol must be reconstituted using only the sterile diluent for Flolan®.⁸ Once reconstituted, epoprostenol may be not be diluted with other solutions or medications. The reconstituted solution expires after 8 hours at room temperature and 48 hours under refrigeration (2° to 8°C). If two frozen 6-oz gel packs are used, a single the reservoir of epoprostenol may be used for up to 24 hours. The gel packs should be changed every 12 hours.

Epoprostenol is supplied as a sterile freeze-dried powder in 2 strengths, 0.5 mg (500,000 ng) and 1.5 mg (1,500,000 ng). The sterile diluent is supplied in 50 mL glass vials and is available in trays of four vials. The average wholesale prices for epoprostenol 0.5 mg, 1.5 mg, and diluent are \$18.28, \$36.55, and \$10.98, respectively. The estimated monthly cost for a 70-kg patient on a relatively low dose of 10 ng/kg/min is \$958.20 for the drug and diluent alone. A literature report found the cost at an unspecified university-based tertiary care PPH referral center located in the midwest to be approximately \$5000.¹⁶

Conclusion

Options for treating pulmonary hypertension are limited. Non-pharmacologic interventions include limitation of physical activity, avoidance of vasoactive decongestants, cardiodepressant antihypertensive drugs, such as beta-blockers, and oral contraceptives. Pharmacologic therapy is inadequate at this time. Vasodilator therapy with calcium channel blockers (CCB), most commonly nifedipine and diltiazem, offer little hope, as only 20% to 25% of patients will respond to therapy. Abrupt discontinuation of treatment with CCB can lead to fatal rebound pulmonary hypertension.¹ Therapy can also lead to severe and refractory systemic hypotension.

Other therapies are more invasive and associated with their own risks and complications. Surgical therapy, including heart-lung transplants for patients with left heart disease or congenital structural abnormalities, or single and bilateral lung transplant have questionable efficacy. Survival is limited by infections associated with immunosuppression, small airway

inflammation (bronchiolitis obliterans), and accelerated graft coronary artery disease. Survival rates are estimated at 37% to 44% after 5 years, provided the patient can receive an organ. Approximately 1300 patients in the United States are on the lung or heart and lung transplantation list. The estimated waiting time for a lung transplant is 1 year, but for heart and lung transplantation, the wait is over 18 months. An estimated 30% to 40% of patients with PPH die while waiting for a suitable donor.⁴ Pulmonary endarterectomy can be performed in patients with PPH due to chronic thromboembolic disease with 6-year survival rates approaching 75%. However, persistent PH and recurrent pulmonary emboli remain leading causes of death post hospital discharge. Balloon atrial septostomy increases cardiac output by creating a right-to-left shunt between the atria to improve blood flow to the left side of the heart. Although providing a less expensive alternative to intravenous prostaglandin or transplantation, it is associated with decreased arterial oxygenation.⁵ Further investigation and long-term studies are needed to better understand their role in treating pulmonary hypertension.

Left untreated, the prognosis of pulmonary hypertension is poor. The median survival of patients involved in the National Institutes of Health Registry was 2.8 years after diagnosis. Epoprostenol is the only Food and Drug Administration approved treatment for PPH. Epoprostenol is well tolerated and has been shown to offer a survival advantage over conventional therapy. The primary limitations on its use are the lack of an oral dosing form, the short half-life resulting in the need for continuous infusion via through a permanent indwelling central venous catheter via a small, portable infusion pump, the limited stability in solution necessitating the use of ice packs or frequent reservoir changes, and the high cost. Alternative prostacyclin analogues are slowly being developed and becoming available. Uniprost (UT-15), which features a longer half-life, is administered subcutaneously through an ambulatory insulin pump delivery system. Hemodynamic properties have been similar to epoprostenol in preliminary trials. Complications such as pain, induration, and erythema at the local injection site may prevent patients from receiving adequate doses. Beraprost is an oral prostacyclin. Although the bioavailability is reasonable, a short half-life still requires frequent dosing. Cicaprost, another oral prostacyclin, is available in Japan, but long-term efficacy remains in question.¹ Preliminary studies show favorable effects on hemodynamics and exercise tolerance. Iloprost is an inhaled prostacyclin currently in a multicenter trial. Non-selective ET-A and ET-B receptor antagonists have been developed and are undergoing trials.^{7,4} For the time being, epoprostenol provides an option for the 75% to 80% of patients who do not respond to conventional therapy. ■

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