Continuous Intravenous Epoprostenol in Pulmonary Hypertension: The Israel Experience

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Key words: primary pulmonary hypertension, epoprostenol, pulmonary arterial pressure

Abstract

Background: Primary idiopathic pulmonary hypertension is a rapidly progressive disease with a median survival of less than 3 years. Recently its prognosis was shown to dramatically improve with the use of epoprostenol, an arachidonic acid metabolite produced by the vascular endothelium, which increases the cardiac output and decreases the pulmonary vascular resistance and pulmonary arterial pressure. This drug enhances the quality of life, increases survival and delays or eliminates the need for transplantation.

Objective: To review the experience of Israel hospitals with the use of epoprostenol.

Methods: The study group comprised 13 patients, 5 men and 8 women, with an age range of 3–53 years. All patients suffered from arterial pulmonary hypertension. Epoprostenol was administered through a central line in an increased dose during the first 3 months, after which the dose was adjusted according to the clinical syndrome and the hemodynamic parameters.

Results: After 3 months the mean dose was 10 ng/kg/min and the pulmonary artery pressure decreased from 7 to 38%. After one year, the PAP decreased at a slower rate. Two cases required transplantation, three patients died, and seven continued taking the drug (one of whom discontinued). Four episodes of septicemia were observed. Today 10 patients are alive and well and 7 continue to take epoprostenol.

Conclusion: We found that epoprostenol improves survival, quality of life and hemodynamic parameters, with minimum side effects.

IMAJ 2002;4:255–258

Primary idiopathic pulmonary hypertension is a rare but rapidly progressive disease with a median survival of less than 3 years [1]. It is characterized by severe vasoconstriction, vessel wall remodeling and platelet aggregation. Vasodilators, anticoagulation, and as a last resort, lung or heart-lung transplantation constitute the common basis of treatment [2,3]. In recent years, the management of PPH has been revolutionized by the introduction of intravenous epoprostenol.

Epoprostenol (PGI2) is a metabolite of arachidonic acid produced by the vascular endothelium. It is a potent vasodilator that increases cardiac output, decreases pulmonary vascular resistance and inhibits platelet aggregation [4]. Over the last few years it has been shown to improve patients' quality of life, increase survival, and delay or eliminate the need for transplantation [5–8].

Four major medical centers in Israel – Rabin (Petah Tiqva), Sheba (Tel Hashomer), Hadassah (Jerusalem), and Rambam (Haifa) – use epoprostenol to treat pulmonary hypertension.

We present a review of epoprostenol treatment in these hospitals, with emphasis on the logistic problems, complications and outcome.

Patients and Methods

The study group comprised patients with pulmonary hypertension and symptoms corresponding to the New York Heart Association class 3 or 4. Between 1997 and 1999, 13 patients (5 men and 8 women) with an age range of 3–53 years were treated with epoprostenol. All patients suffered from severe pulmonary hypertension of the precapillary-arterial subtype (8 idiopathic, 4 scleroderma, 1 mixed connective disease). All patients received oral warfarin, and half were on calcium channel blockers. Dyspnea was the main symptom in all the patients, and recurrent syncope was the presenting symptom in two patients (Table 1).

Evaluation

The diagnosis of pulmonary hypertension was confirmed by right heart catheterization (pulmonary arterial pressure higher than 25 mmHg with normal pulmonary capillary wedge pressure) [9]. Other causes of pulmonary hypertension were excluded by lung perfusion scanning, pulmonary function tests and spiral computerized tomography. At the heart catheterization, hemodynamic parameters were measured and response to epoprostenol was tested at an initial rate of 2 ng/kg/min, increasing by 1 ng/kg/min every 10 minutes until adverse hemodynamic or toxic effects were observed. The challenge test was considered to be positive if there was a 20% decrease in pulmonary arterial pressure or pulmonary vascular resistance and an increase in cardiac output.

We followed the patients and PAP measurement by cardiac echography every 3 months. The dose of epoprostenol was adjusted according to the clinical symptoms. Initially, a small dose 2 ng/kg/min was administered and was increased rapidly during the first

PAP = pulmonary arterial pressure
PPH = primary idiopathic pulmonary hypertension

months until a dose of 10 ng/kg/min was reached. We then increased the dose gradually during the first year, about 1 ng/kg/min every month, according to the patients' symptoms and the hemodynamic parameters.

Table 1. Patients' characteristics

Patient no.	Age/ Gender	NYHA	Disease	PAP Syst/Diast (mean) mmHg	PVR (units)	SVO_2 (%)	CO (L/min)	Vaso-reactivity
1	50/M	3	Idiopathic	70/44 (57)	22	51	3.9	Yes
2	13/M	3	Idiopathic	135/80 (100)	36	50	3.2	No
3	35/M	3	Idiopathic	100/60 (80)	20	50	2.8	No
4	3/M	3	Idiopathic	115/75 (95)	28	52	3.0	Yes
5	49/F	3	Scleroderma	65/25 (45)	10	51	4.0	No
6	36/F	3	Scleroderma	100/40 (70)	18	60	3.9	Yes
7	26/F	3	Idiopathic	80/60 (70)	11	50	4.6	No
8	54/F	3	Idiopathic	110/60 (85)	11	53	3.2	No
9	30/F	3	Scleroderma	65/35 (50)	13	60	2.8	Yes
10	25/F	3	MCT	90	ND	ND	ND	ND
11	3/M	3	Idiopathic	65/35 (50)	15	60	3.6	No
12	45/F	3	Scleroderma	80/50 (65)	ND	ND	ND	ND
13	54/F	3	Idiopathic	100/40(70)	12	66	4.5	No

SVO_2 = venous oxygenation saturation, ND = no data, MCT = mixed connective disease

Treatment

Epoprostenol has a half-life of 5 minutes, which enables the patient to have a continuous, uninterrupted infusion. Patient cooperation is essential since an abrupt interruption of the drug can result in a life-threatening reemergence of symptoms. We use a central intravenous line (Hickman catheter) and an infusion pump CADD (SIMS Deltec, USA) that delivers the medication for 24 hours around the clock. Educating the patient is of major importance: the patient must learn how to prepare the medication by him or herself in sterile conditions, how to store it, how to take care of the permanent central line, and must understand how the pump functions. A skilled nursing staff as well as a physician on call 24 hours a day are necessary to immediately resolve any problem arising with the drug-delivery system.

Results

At baseline, the systolic PAP ranged between 65 and 135 mmHg, pulmonary vascular resistance 11–36 U, venous oxygen saturation 50–66%, and carbon monoxide 2.8–4.5 L/min. Only three patients had a positive challenge test to prostacyclin [Table 1].

After 3 months the patients received about 10 ng/kg/min with a significant drop of the peak pulmonary pressure, ranging from 7 to 38% from the baseline levels [Table 2]. After 1–2 years of treatment, the PAP continued to decrease but at a slower rate [Figure 1]. The maximum dose of epoprostenol was 43 ng/kg/min but most patients received between 10 and 18 ng/kg/min [Figure 2].

After 12 months and 18 months, two patients (nos. 1 and 2) deteriorated clinically with a rise in PAP despite increased dosage of epoprostenol. Both patients underwent successful heart-lung transplantation. Three patients died: two at the beginning of the treatment from severe right heart failure, and one from sudden death after 1 year of treatment.

Table 2. Hemodynamic and clinical follow-up

Patient no.	Baseline PAP Syst/Diast	3 months peak PAP	% Decrease	Follow-up (mo)
1	70/44	64	8%	HLT* (12 mo)
2	135/80	85	37%	HLT* (18 mo)
3	100/60	ND	ND	Death (1 mo)
4	115/75	80	30%	Continue (24 mo)
5	65/25	60	7%	Continue (18 mo)
6	100/40	80	20%	Continue (18 mo)
7	80/60	68	15%	Continue (16 mo)
8	110/60	100	9%	Continue (12 mo)
9	65/35	80	No decrease	Death (4 mo)
10	90	ND	ND	Discontinue (2 mo)
11	65/35	40	38%	Death (12 mo)
12	80/50	70	12%	Continue (12 mo)
13	100/40	68	32%	Continue (6 mo)

* Heart-lung transplantation

There were four episodes of septicemia necessitating hospitalization, antibiotic treatment, and a change of the central line position. One patient who had severe recurrent septic episodes changed the mode of therapy to inhalation.

Among the three children (under 16 years old) who received epoprostenol, one died suddenly while on prostacyclin treatment, one had a successful heart-lung transplantation after a progressive deterioration, and one is continuing to receive the epoprostenol without complication for 2.5 years now.

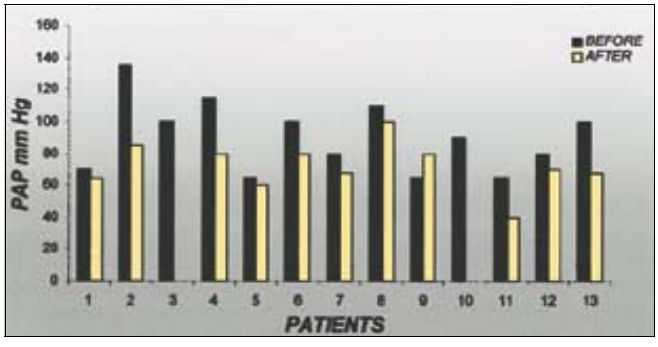

Figure 1. PAP before and after epoprostenol

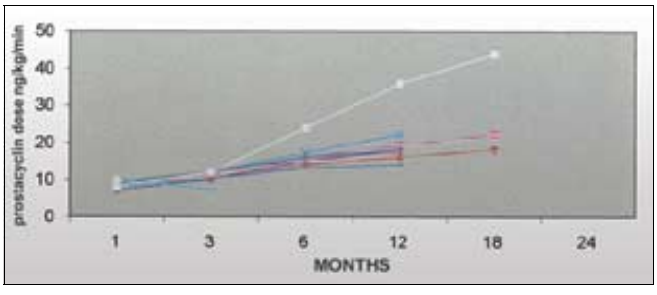

Figure 2. Epoprostenol dose

Discussion

Primary idiopathic pulmonary hypertension is a rare disease with an incidence of 1–2 per million each year [9]. Recently, a new classification of the disease was adopted, based on the anatomic localization of the disease (precapillary-arterial; postcapillary: venous and capillary) instead of its etiology (primary or secondary) [10]. Within this classification, prostacyclin has a predominant role in the arterial form. In this form, the pathologic process is localized in the pulmonary artery. It is associated with the idiopathic form (primary pulmonary hypertension), collagen vascular disease, human immunodeficiency virus infection, congenital heart disease (Eisenmenger syndrome), as well as the familial form and anorectic agents. Although the precapillary form of pulmonary hypertension is severe, it may respond to vasodilator treatment (epoprostenol, calcium blockers) [11]. In the postcapillary form, the lesions are localized in the pulmonary vein. It is associated with veno-occlusive disease and left-side heart disease (e.g., mitral stenosis). This form is severe and unresponsive to therapy. Moreover, vasodilator treatment is contraindicated because it may provoke a life-threatening pulmonary edema [12].

The other forms of pulmonary hypertension are secondary to thromboembolic disease or are associated with hypoxia (high altitude) and ventilatory disorders. Their treatments are based on the correction of the underlying disease. The prognosis of precapillary arterial pulmonary hypertension improves greatly with the use of vasodilators, specially epoprostenol [5,6,11]. Long-term therapy is highly effective in adults and in children in terms of hemodynamic parameters, clinical symptoms and increased survival [5–8,13]. The choice of vasodilators is determined by the vasoreactivity test and by the clinical staging of the patient [2,14–17]. The initial response to vasodilator challenge predicts who is likely to respond to oral calcium-blocker agents. The most commonly used drugs are nifedipine and diltiazem. In patients who did not respond to the challenge test or did not improve with oral calcium blockers, long-term therapy with epoprostenol provokes a sustained hemodynamic response, improves exercise capacity and survival and delays the need for transplantation [4–7,17–19].

Prostacyclin was first introduced by Higenbottan in a successful trial of a young woman [20]. Later on, other studies confirmed the effectiveness of the drug [5,6,18,21,22]. Since there is no set dose for epoprostenol, the drug is titrated to provide maximum relief of symptoms but it has to be increased over time because of tolerance to the drug. The major side effects are related to the delivery system: pump malfunction and infections. Properties of the drug that contribute to the long-term beneficial effect other than its vasodilator activity include platelet aggregation inhibition and effect on the vascular wall remodeling. Epoprostenol, however, is expensive and unstable in light: the cost of a day of therapy in Israel may reach US$ 300 and the annual cost is around US$ 100,000. Other studies with an analogue of PGI2 (iloprost) have show that iloprost is also effective in chronic therapy, and is stable in light, in isotonic solution and at room temperature [11,23]. In scleroderma, intermittent iloprost infusion is successful in decreasing the pulmonary arterial pressure. This analogue of prostacyclin can also be inhaled to produce pulmonary vasodilatation and offers an alternative to the intravenous route of administration [24]. It is easy to use but requires repeated administration every 2–3 hours. Other means of prostacyclin administration, e.g., beraprost (oral administration) or UT15 (subcutaneous administration), are still under investigation.

Inhaled nitric oxide is under study. The rationale behind it is that exhaled nitric oxide is low in patients with primary pulmonary hypertension. Although there is considerable experience in the use of nitric oxide as a short treatment for pulmonary hypertension in a variety of clinical situations, its role as a chronic therapy has yet to be proven.

Balloon atrial septostomy is another technique selected for patients with severe pulmonary hypertension. It increases cardiac output, and decreases the right ventricular load by creating an orifice in the atrial septum that is progressively dilated until the optimum cardiac output is obtained. Improved survival has been reported with this form of therapy [25].

As a last resort, lung and heart lung transplantations are performed for PPH and have a survival rate of 60% after 2 years [3,7,23]. Long-term survival is limited by the development of bronchiolitis obliterans. Selection of patients with pulmonary hypertension is limited today to those in whom prostacyclin fails to control symptoms. The timing of transplantation is also a difficult issue. The common approach is to initiate prostacyclin therapy and to place the patients on a transplantation list. We defer transplantation for those whose condition shows improvement with prostacyclin.

Viewed originally as a bridge to transplantation, epoprostenol is currently considered as the treatment of choice for pulmonary hypertension, thus transplantation may not be necessary for patients who improve on the drug. The experience in Israeli hospitals involved 13 patients for a period of 2 years. At this time, nine are alive, two are after heart-lung transplantation, and seven still continue to receive epoprostenol successfully. Although, the number of patients in our study is small, our data are compatible with worldwide experience using intravenous epoprostenol. Our findings demonstrate that this drug improves the patient's clinical status and quality of life, and increases longevity in those with precapillary pulmonary hypertension.

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