PULMONARY HYPERTENSION

Epoprostenol treatment in children with severe pulmonary hypertension

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Introduction: Severe, sustained pulmonary arterial hypertension leads to a progressive reduction in exercise capacity, right heart failure and death. Use of intravenous epoprostenol has improved survival in adults, but data are limited in children.

Patients and methods: This study included all 39 children treated with continuous intravenous epoprostenol since November 1997 at Great Ormond Street Hospital for Children (London, UK). Patients were aged 4 months to 17 years (median 5.4 years) at the onset of therapy. The male:female ratio was 1:1.3. 25 patients had idiopathic pulmonary arterial hypertension and 14 had pulmonary arterial hypertension associated with congenital heart disease, connective tissue disease, chronic lung disease or HIV. All were in WHO functional class III and IV. Mean pulmonary arterial pressure (SD) was 59 (17) mmHg and mean pulmonary vascular resistance was 23.3 (11.6) units $\times$ m². Patients were assessed regularly (2–3 monthly intervals) by physical examination, electrocardiography, transthoracic echocardiography and a 6-min walk test, when practicable.

Results: The mean duration of follow-up was 27 (21) months. 7 patients died and 8 underwent transplantation. Cumulative survival at 1, 2 and 3 years was 94, 90 and 84%. The 6-min walking distance improved by a mean of 77 m ($p < 0.003$). WHO functional class improved during the first year ($p < 0.001$) and improvement was maintained for up to 3 years. Weight improved significantly from a baseline z score of -1.55 (1.74) to -1.16 (1.8) ($p < 0.03$). 28 children had additional oral specific therapy. Hickman line changes were 0.33/patient year.

Conclusions: Epoprostenol therapy improved survival, WHO functional class, exercise tolerance and ability to thrive in children with severe pulmonary arterial hypertension. Epoprostenol represents an effective and feasible therapy even in young children.

Severe, sustained pulmonary arterial hypertension (PH) leads to a progressive reduction in exercise capacity, right heart failure and death. Without treatment, the median survival time in adults with idiopathic pulmonary arterial hypertension (IPAH) is reported to be only 2.8 years and that in children only 10 months.^{1–3} The clinical picture has been transformed by the introduction of specific therapies including epoprostenol, the first effective treatment for severe, established disease. Efficacy was proven in adults with IPAH in a prospective 12-week, randomised trial published in 1996,³ which demonstrated improved quality of life, exercise tolerance, haemodynamic status and survival. A successful paediatric trial followed in 1999.² Conventionally, epoprostenol is given to adults with IPAH and with pulmonary arterial hypertension associated with connective tissue disease and to children with IPAH, all of whom are in WHO functional class III–IV and do not show a positive response to acute vasodilator testing at cardiac catheterisation. With experience, the indications in paediatric practice have widened beyond IPAH to include children with severe pulmonary arterial hypertension associated with connective tissue disease, congenital heart disease and other conditions.

Epoprostenol is the synthetic sodium salt of a naturally occurring metabolite of arachidonic acid (prostacyclin) produced by the endothelium, which has vasodilator, antiproliferative,⁴ platelet inhibitory⁵ and positive inotropic properties.⁶ A constant plasma concentration is reached after approximately 15 min. It has a short half-life of 2–3 min. Abrupt delivery failure or drug withdrawal may result in sudden “rebound pulmonary hypertension”, or even death.⁷ Side effects are not usually excessively troublesome. In both children and adults

these principally include diarrhoea, flushing, “light-headedness” and jaw pain.⁸

Epoprostenol is an expensive “high maintenance” therapy, which demands an ongoing commitment by the parents/carers and co-operation of the child. We reviewed our experience of this therapy in 39 children, most having been referred to the UK Pulmonary Hypertension Service after its establishment in 2002. This paper focuses on the indications to treat, efficacy, response to therapy and the morbidity associated with this treatment.

METHODS

Patient evaluation

Before and at regular intervals after initiation of epoprostenol treatment, all patients were assessed by physical examination, electrocardiography and transthoracic echocardiography, and their weight recorded. The functional status was assessed by WHO Functional Class. A 6-min walk test (6MWT) was performed in children old enough to do the test reliably. The test was performed in a standardised manner by an experienced investigator monitoring the distance walked and the transcutaneous systemic arterial oxygen saturation at baseline and on exertion.⁹ Cardiac catheterisation was performed under general anaesthesia before instituting treatment in all children. Accurate measurement of oxygen consumption was assessed in all but three patients.

Abbreviations: IPAH, idiopathic pulmonary arterial hypertension; RVH, right ventricular hypertrophy; 6MWT, 6-minute walk test; CDC, Center for Disease Control; APH, associated pulmonary hypertension

The electrocardiograms were analysed specifically for evidence of right ventricular hypertrophy (RVH) and strain. RVH was assessed using voltage criteria (R wave amplitude in V1 plus the S wave amplitude in V5 or V6).^{10–11} Right ventricular strain was defined as a QRS-T angle $\geq 90^\circ$ in combination with a T axis between 0 and -90° . Possible strain was defined as a QRS-T angle >90 degrees and a T-axis between 0 and $+90$ degrees.¹¹ On transthoracic echocardiography, evidence of right ventricular dilatation, hypertrophy and function was assessed. Right ventricular function was described semi-quantitatively as being normal, mildly, moderately or severely impaired.^{12–13} Tricuspid and pulmonary valve regurgitation was described as trivial, mild, moderate or severe. In the presence of a complete velocity signal, the right ventricular systolic pressure was estimated using the modified Bernoulli equation.

Statistical analysis

Values are presented as median or mean (standard deviation (SD)). Comparisons between groups were made using the Student's *t* test, Mann–Whitney U test or χ^2 test as appropriate. Kaplan–Meier survival plots were constructed from the start of epoprostenol treatment. Weight was considered to be normally distributed. Z-scores of weight were calculated by $z = (\text{measured value} - \text{reference mean}) / \text{reference SD}$. Reference values were taken from CDC (Center of Disease Control) growth charts.¹⁴ For all analyses a *p* value of <0.05 was considered significant.

Characteristics of the patient population

In total, 39 children were treated with epoprostenol between 1997 and 2005 (table 1). Of these, 25 had IPAH. Associated pulmonary hypertension (APH) occurred in 14 children, who had postoperative congenital heart disease, cardiomyopathy, connective tissue disease, chronic lung disease or HIV (table 1). The male:female ratio was 1:1.8 for IPAH and 1.3:1 for APH. The median age at the onset of therapy was 5.4 years (range 4 months–7 years).

Indications to treat

Children were treated with epoprostenol when they had failed to improve or to sustain an initial improvement on an oral therapy for pulmonary arterial hypertension or had severe symptoms on presentation. In total, 24 children had previously been treated with bosentan, sildenafil or a calcium channel blocker.

Baseline status

All patients were severely symptomatic; 27 patients were in WHO functional class III and 12 were in class IV (fig 1). The median weight was 16.0 kg, mean (SD) 21.0 (15.3) kg. The children were underweight and had a mean z-score of -1.55 (1.74) (range -2.14 to -0.96). All had electrocardiographic evidence of RVH. The amplitude of the R wave in V1 plus the S wave in S5 or S6 was 43.5 (20.7) mV. Evidence of right ventricular strain was present in the electrocardiograms of 14 children and possible strain in another 13 cases.

Transthoracic echocardiography showed RVH in all children, with right ventricular dilatation in 33 children. Right ventricular systolic function was impaired in 32 children. None had a significant pericardial effusion. In total, 34 children had tricuspid regurgitation with a mean velocity of 4.6 m/s (mean right ventricular systolic pressure 84.4 mmHg plus right atrial pressure). Pulmonary regurgitation was present in 23 patients, but was not severe in any child. The mean end-diastolic velocity was 2.9 (0.6) m/s, indicating an end-diastolic right ventricular pressure of 33.6 mmHg (table 2).

At cardiac catheterisation, the mean pulmonary arterial pressure (PAP) was 59 (17) mmHg, and in 26 children the PAP equalled or exceeded the systemic arterial pressure (table 1). The mean pulmonary vascular resistance index (PVRI) was 23.3 (11.6) units $\times \text{m}^2$ in the 34 children in whom it was assessed. The lowest PVRI was seen in a child with cardiomyopathy. The child had an elevated PAP, was thought to be a high risk candidate for heart transplantation alone and, to try to avoid a heart–lung transplantation, was treated with epoprostenol for a month and then had a successful heart transplant. There was little change in PVRI in children who were tested either with inhaled nitric oxide ($n = 31$) or with an inspired oxygen concentration of 100% ($n = 18$) (table 1).

Treatment

A Hickman line was inserted under general anaesthesia and connected to a portable infusion pump (CADD legacy pump, Pharmacia Deltec, St Paul, Minnesota, USA).

In each patient the drug was titrated upwards according to the clinical response. The children were started on 2 ng/kg/min. The rate of increase depended on the severity of the disease, clinical response to therapy and the development of side effects. In this series, the mean dose of epoprostenol was 29.6 (15.2) ng/kg/min (range 6–63 ng/kg/min). The lowest dose was given to a child with cardiomyopathy who underwent heart transplant 1 month later. The mean dose given to children with IPAH was 32.5 (12) ng/kg/min (10–63 ng/kg/min).

The children were kept in hospital until clinical improvement was evident, and then further increases in dose were carried out at home. Epoprostenol is an unstable compound and must be prepared every 24 h. The parents were trained to prepare and administer the drug, and those looking after the child in the community were trained to care for the drug delivery system. The child did not go home until the parents were proficient in administering the drug. Children were followed up in the outpatient clinic at 2–3 monthly intervals or more frequently if clinically indicated.

Response to treatment

Survival

The mean follow-up time was 27 (21) months (range 1–90 months). A Kaplan–Meier analysis showed that the cumulative survival of all patients who received epoprostenol at 1, 2 and 3 years was 94%, 90% and 84%, respectively. The cumulative survival in patients with IPAH at 1, 2 and 3 years was 96%, 91% and 83%, respectively (fig 2). Censoring events were transplantation and cessation of epoprostenol. In total, 32 patients survived, four having taken epoprostenol for more than 5 years. Seven patients died after receiving treatment for a median of 29 months (range 3–61 months): four patients with IPAH died from disease progression despite maximum therapy, one died from systemic sclerosis and two from corrected congenital heart disease.

When treatment with epoprostenol was started, nifedipine was withdrawn in the six patients taking the drug, because it may compromise right ventricular function.¹⁵ Sildenafil was withdrawn in four unstable, sick children so as not to risk compromising the systemic arterial pressure at initiation of epoprostenol treatment. Once established on epoprostenol, this drug alone was insufficient to maintain clinical improvement in all children, and additional therapies were added in 14 children: bosentan in 8, sildenafil in 5 and both in 1 child. Seventeen children with syncope or pre-syncope had an atrial septostomy.¹³

Table 1 Patient characteristics

Patients	n = 39
Male:female	17:22
Age (median)	5.4 years (4 months–7 years)
Weight	21.2 (15.3) kg (4.6–76.4 kg)
Aetiology of pulmonary arterial hypertension	
IPAH	n = 25
Pulmonary arterial hypertension associated with	
Congenital heart disease	n = 6
Cardiomyopathy	n = 3
Connective tissue disease	n = 2
Chronic/interstitial lung disease	n = 2
HIV	n = 1
WHO functional class I/II/III/IV	0/0/27/12
Drugs taken before epoprostenol treatment	
Bosentan	n = 8
Sildenafil	n = 6
Calcium channel blocker	n = 6
Bosentan and sildenafil	n = 2
Bosentan and Ca channel blocker	n = 2
Diuretics	n = 20
Digoxin	n = 24 (8 warfarin, 13 aspirin, 3 dipyridamol)
Anticoagulation/antiplatelet	n = 5
Haemodynamics at the onset of treatment	
Mean pulmonary arterial pressure	59 (17) mmHg (25–88)
Mean systemic arterial pressure	62 (14) mmHg (42–95)
Right atrial pressure	8.1 (5.2) mmHg (3–28)
Mean left atrial pressure/PCWP	9.4 (4.6) (3–23)
PVRi: baseline	23.3 (11.6) units $\times$ m ² (3.5–49.8)
PVRi: 100% FiO ₂	20.4 (10.8) units $\times$ m ² (8.7–44.0)
PVRi: 65%FiO ₂ /20 ppm NO	19.5 (11.1) units $\times$ m ² (2.5–39.0)
Pulmonary arterial saturation	65.9 (12.5%) (23–87)
Systemic saturation	96 (4.7%) (83–100)

HIV, human immunodeficiency virus infection; IPAH, idiopathic pulmonary arterial hypertension; NO, nitric oxide; PCWP, pulmonary capillary wedge pressure; Ca, calcium; ppm, parts per million; PVRi, pulmonary vascular resistance index; WHO, World Health Organization
Data are shown as mean (SD). In addition, the range is presented in brackets.

Discontinuation of epoprostenol

Epoprostenol was discontinued in 10 children, eight of whom received transplants. Six of the transplanted children had IPAH and two had cardiomyopathy. All are alive and well. Four children with IPAH had a double lung transplant and two had a heart and lung transplant. One child with cardiomyopathy had a heart and lung transplant and one a heart transplant. In these eight children, epoprostenol therapy was started at a median age of 4.8 years (range 1.2–16.8) and the mean duration of treatment before transplantation was 26.2 (16.4) months (range 1–51). For patients with IPAH it was 32 (13.9) months, and for those with cardiomyopathy 1 and 17.2 months.

Epoprostenol therapy was discontinued in two patients who were successfully transitioned onto either bosentan or nifedipine. One child with IPAH had presented with cardiac arrest and had been treated with epoprostenol before endothelin antagonists were available. The other child was electively treated with epoprostenol after a late surgical closure of atrial and ventricular septal defects. She had had severe postoperative pulmonary hypertensive crises. A cardiac catheterisation study 7 months after surgery showed a normal PAP and PVR. The child was transitioned to nifedipine.

Follow-up assessment

The mean WHO functional class improved significantly during the first year of therapy, from 3.6 to 2.6 ($p < 0.001$), and remained stable up to and during the third year of treatment at 2.6 (fig 1). During the first year, an improvement in functional class was observed in 30 children; another 4 were stable, 3 deteriorated and 2 died.

Figure 1 Percentage of children in each WHO functional class at the start of the treatment with epoprostenol and after 1, 2 and 3 years. During the first year, no child died and one had a transplant, three children died during the second year, and three died and two had a transplant during the third year.

The children's appetite improved and they gained weight. The mean z score for weight improved significantly from -1.55 (1.74) (range -2.14 to -0.96) to -1.16 (1.8) ($p < 0.03$) during follow-up.

A 6MWT was undertaken in patients old enough to perform the test reliably. Twelve children performed the test before receiving epoprostenol and 16 performed their first test on treatment. For these 28 children the mean (SD) initial distance was 250 (93) m. After a follow-up of 11.4 (7.1) months, the distance walked increased to 327 (105) m ($p < 0.003$).

Electrocardiography showed no significant reduction in RVH (39.7 (21.2) vs 43.5 (20.7) mV, $p = 0.07$) or right ventricular strain.

During the first year of treatment, right ventricular function assessed by echocardiography improved in 12, was unchanged in 19 and deteriorated in 8 patients (table 2). The tricuspid regurgitant jet velocity was 4.6 (0.9) m/s at baseline and 4.2 (0.8) m/s on treatment, a non-significant reduction in the systolic right ventricular pressure ($p = 0.08$). There was little change in frequency or severity of pulmonary regurgitation on epoprostenol treatment. In all, 24 patients had regurgitation before and 21 on treatment. None had severe regurgitation. The mean end-diastolic velocities before and after treatment were 2.9 (0.6) m/s and 2.8 (0.5) m/s, respectively (table 2).

Complications and morbidity

Administration of epoprostenol was trouble-free in 24 patients. There were 0.33 Hickman line changes per patient year on treatment. The line needed replacing in 15 patients. The problems were infection on 20 occasions, a leaking line in 5 and the catheter fell out on 4 occasions. Antibiotics were required on 43 occasions, primarily for local site infections. Blood cultures were positive on six occasions in four patients (*Pseudomonas* $n = 1$, methicillin-resistant *Staphylococcus aureus* $n = 1$, *Staphylococcus aureus* $n = 3$, *Staphylococcus aureus* and *Candida* $n = 1$).

DISCUSSION

Epoprostenol improved survival in our patients with severe pulmonary hypertension who were all in WHO functional class III and IV. Survival in our patients with IPAH was 96%, 91% and 83% at 1, 2 and 3 years, respectively. Data on these patients compare favourably with those in other series. In one study on adults survival rates were 87.8%, 76.3% and 62.8% at 1, 2 and 3 years, respectively,⁷ and in a more recent study the survival rates were 91%, 84% and 75% at 1, 2 and 3 years, respectively.¹⁶ A study which included 35 children treated with epoprostenol

Figure 2 Kaplan-Meier cumulative survival plots with 95% CIs of (A) all children treated with epoprostenol and (B) those diagnosed as having IPAH. Children were censored at the time of transplant and when epoprostenol treatment ceased.

gave survival figures of 94%, 81% and 61% at 1, 5 and 10 years, respectively.¹⁷

In 36% of our children the pulmonary hypertension was not idiopathic, and these children also responded well to epoprostenol. Several of them had postoperative congenital heart disease. The closure of a cardiac defect in the presence of an elevated pulmonary vascular resistance is known to hasten the development of severe pulmonary vascular obstructive disease,^{18–19} and treatment of a child having severe symptoms with epoprostenol is logical. In adult practice, epoprostenol has been used successfully in patients with pulmonary hypertension associated with connective tissue disease and HIV,^{20–22} and the children in this series also benefited.

In the present series, long-term treatment with epoprostenol was successful although the children had no positive response to vasodilator testing at cardiac catheterisation, as has also been reported by other investigators.^{23–24} During the first year of epoprostenol therapy the WHO functional class improved significantly and was maintained. The 6MWT also improved significantly, reflecting an increase in exercise tolerance. The clinical condition of the children generally improved soon after starting treatment. In adults with IPAH, the benefit of epoprostenol treatment is most apparent soon after starting

therapy (17 (15) months), with little additional improvement thereafter.⁷ Early improvement might be due to the positive inotropic effect of epoprostenol.⁶ An early increase in cardiac output is well documented in patients with IPAH receiving epoprostenol.^{3–7, 25} High-output cardiac failure as reported in some adults was not seen in our patients.⁶ We found that clinical improvement was accompanied by favourable changes in right ventricular function assessed by echocardiography. The function either improved or did not deteriorate in 31 of the 39 children. Electrocardiographic measures of RVH and strain did not deteriorate. Achieving stability in a disease with a poor prognosis, such as pulmonary vascular disease, can be considered a therapeutic success.

Fourteen children remained on bosentan or sildenafil at the start of epoprostenol therapy, and another 14 children were given a second specific therapy when their clinical condition deteriorated. Whether they would have fared better had they been given a combination therapy when they first presented is uncertain, but the fact that they improved when either epoprostenol or bosentan was added to their existing treatment regimen suggests that they would have benefited from being given dual therapy from the outset.²⁶ Pulmonary vascular obstructive disease can develop rapidly in children, and maximum early intervention is desirable. Established pulmonary vascular disease is incurable, and therefore the aim is to improve the quality of life, prolong life and hopefully offer transplantation when medical treatment fails. In young children, prolonging life means that they should survive to reach an age when lung or heart and lung transplant becomes feasible and suitable organs are more likely to become available.

Embarking on any invasive therapy needs careful consideration of the cost-benefit ratio. World-wide experience with epoprostenol has shown that this is the most effective treatment in patients with IPAH with severe symptoms. It is used as a rescue therapy in patients failing to respond to oral therapies such as bosentan and sildenafil. In the present study, children were selected for treatment with epoprostenol because they were ill and deteriorating, were in WHO functional class III or IV, and had either failed to respond to monotherapy or were considered to be too ill and unlikely to respond quickly to oral therapy. These conditions comply with the management guidelines for IPAH prepared by the European Society of Cardiology²⁷ and the American Heart Association.^{28–29} Unfortunately, less invasive therapies that are effective in adults with IPAH are not suitable for small children. Subcutaneous treprostinil, an analogue of epoprostenol, is often extremely painful and difficult to tolerate.³⁰ Inhaled iloprost must be used every 2–3 h to be effective, takes 20 min or so to administer, and is tiring for a sick child to use. In the

Table 2 Echocardiographic parameters at baseline and during epoprostenol treatment

	Baseline, n (SD)	Epoprostenol therapy, n (SD)
Right ventricular function		
Normal	7	11
Mildly impaired	17	13
Moderately impaired	13	12
Severely impaired	2	3
Tricuspid regurgitation		
None	2	0
Trivial	3	9
Mild	30	18
Moderate	3	11
Severe	1	1
V _{max} tricuspid valve, m/s (complete envelope)	4.6 (0.9)	4.2 (0.8)
Pulmonary regurgitation		
None	16	18
Trivial	7	6
Mild	13	14
Moderate	3	1
Severe	0	0
End diastolic PR velocity, m/s (complete envelope)	2.9 (0.6)	2.8 (0.5)
	16	12

n, number of patients; PR, pulmonary valve regurgitation; V_{max}, maximal velocity.

present study, there was no mortality associated with the invasive therapy itself. Morbidity was due primarily to infections, as anticipated, and these were generally limited to site infections.

The patients in this study were not routinely recatheterised in order to monitor disease progression because of the risks involved in doing so. For the future, one of the major challenges in managing children with pulmonary hypertension is the non-invasive assessment of right and left ventricular performance and the estimation of pulmonary arterial pressure and resistance. Improved echocardiographic assessment and magnetic resonance imaging to monitor changes in ventricular mass and blood flow probably offer the greatest promise.

In conclusion, the findings in this study indicate that epoprostenol therapy can improve survival and slow the progression of pulmonary vascular disease both in children with IPAH and in those with APH. Epoprostenol therapy improved survival, WHO functional class, exercise tolerance and ability to thrive in children with severe pulmonary arterial hypertension, resulting in a better quality of life. It is thought that epoprostenol can either slow down or stabilise the pulmonary vascular disease process. The particularly rapid course of the disease in childhood suggests that children should be treated promptly and effectively as soon as they present to the physician. Epoprostenol represents an effective, feasible therapy with an acceptable morbidity even in young children with severe pulmonary hypertension.

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