Successful Epoprostenol Withdrawal in Pulmonary Arterial Hypertension: Case Report and Literature Review

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Pulmonary arterial hypertension is a rare and devastating disease characterized by vascular proliferation and remodeling. Epoprostenol, the drug counterpart of the eicosanoid prostacyclin, produced by the vascular endothelial cells, is the drug of choice for this disease. Its capacity to act rapidly and to significantly improve survival prospects in severe pulmonary hypertension patients has been supported by a wealth of evidence. Intravenous epoprostenol was believed to require therapy of indefinite duration. Since 2001, oral drugs have been approved for specific treatment. The availability of newer and less invasive drug therapies for pulmonary arterial hypertension led physicians to withdraw epoprostenol in carefully selected patients. We report a case of successful intravenous epoprostenol interruption in a patient with idiopathic disease. A literature review on epoprostenol withdrawal in pulmonary hypertension in adult patients is also provided. *Key words: pulmonary hypertension; prostanoids.* [Respir Care 2013;58(2):e1–e5. © 2013 Daedalus Enterprises]

Introduction

Pulmonary arterial hypertension (PAH) is an uncommon disease characterized by increased pulmonary vascular resistance (PVR) leading to right ventricular failure. Epoprostenol is a synthetic prostacyclin, a member of the prostanoids group produced predominantly by endothelial cells, and first described in 1976. The role of epoprostenol in PAH as a potent vasodilator of the pulmonary vascular bed and inhibitor of platelet aggregation, in conjunction with its anti-proliferative effects, is very well documented. Representing the first PAH-target therapeutic agent, produced in 1995, it remains the gold standard for advanced idiopathic PAH treatment.

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Epoprostenol has a half-life of about 5 minutes and is available as a stable freeze-dried preparation that needs to be dissolved in alkaline buffer for intravenous infusion.[1] At room temperature it is stable for only 8 hours, permitting the administration only via a permanent tunneled-cuffed central venous catheter and an infusion pump. In effect, daily reconstitution and self-administration of medication, safe operation of a continuous infusion pump, and central venous access care are required. Implantation of a Hickman catheter is required, necessitating hospitalization for the implantation and epoprostenol initiation. Risks of epoprostenol treatment include life-threatening blood stream infections, rebound pulmonary vasoconstriction induced by sudden interruption of therapy, acute right ventricular failure, death, jaw pain, flushing, nausea, headache, and systemic hypotension.[2–4] Furthermore, the costs associated with epoprostenol therapy are substantial.[5,6] All the aforementioned facts reflect the complexity of epoprostenol therapy, yet this is the only drug leading to approved survival improvement in idiopathic PAH.[7]

The perception that "once on epoprostenol, forever on epoprostenol," clearly reflected the belief that, following initialization, epoprostenol treatment would entail indefinite therapy. However, since 2001 oral drugs have been approved as PAH-specific treatment, offering patients the hope that epoprostenol might not be a life-long therapy.

We report a case of a 53-year-old woman, suffering from idiopathic PAH, first diagnosed in 2002, treated with intravenous epoprostenol for 6 years, whose pulmonary hemodynamics almost normalized in the third year of treatment, effectively exhibiting clinical improvement. Successful epoprostenol withdrawal was achieved, and one year after epoprostenol discontinuation the patient remains asymptomatic, treated only with oral PAH-specific drugs. A literature review of cases reported with transition from intravenous to new oral or subcutaneous therapies is also described.

Case Report

A 53-year-old woman without history of cardiopulmonary disease presented in 2002, reporting breathlessness and weakness. The physical signs included accentuated pulmonary component of second heart sound and left parasternal lift. Chest radiography was abnormal, with central pulmonary artery dilatation and right ventricular enlargement. The electrocardiogram revealed right ventricular hypertrophy and right axis deviation. Echocardiographic study demonstrated a left ventricular cavity of 44 mm with dilated right ventricle and systolic pulmonary arterial pressure of 100 mm Hg.

The diagnostic process for pulmonary hypertension classification began with the exclusion of the more common clinical groups. Left heart disease (systolic and diastolic dysfunction and valvular disease) and congenital heart disease were not identified in transthoracic echocardiography. Coronary angiography was unremarkable. Lung disease was excluded. Pulmonary function tests identified only a decreased lung diffusion capacity for carbon monoxide (60% of predicted). High-resolution computed tomography did not reveal interstitial lung disease, emphysema, or characteristic changes of pulmonary veno-occlusive disease and pulmonary capillary hemangiomatosis, conditions excluded in combination with physical examination. Overnight oximetry screening excluded obstructive sleep apnea or hypopnea. Ventilation-perfusion lung scan showed small peripheral unmatched and non-segmental patchy perfusion defects, so the possibility of chronic thromboembolic pulmonary hypertension diagnosis was less likely. Absence of hematological, systemic, or metabolic disorders excluded group-5 pulmonary hypertension form. Thus, PAH diagnosis was established. Immunologic and serologic testing did not detect underlying congenital tissue disorder or human immunodeficiency virus. Liver cirrhosis and portal hypertension were not identified with the use of abdominal ultrasound. The patient did not report drug or toxin use. Idiopathic PAH diagnosis was established, and she was classified as functional class II, according to the World Health Organization classification.

The parameters provided by right heart catheterization were as follows: mean pulmonary arterial pressure 53 mm Hg, pulmonary capillary wedge pressure 11 mm Hg, PVR 13.2 Wood units, and a significantly low cardiac index of 1.62 L/min/m^2. A vasoreactivity test with the use of epoprostenol was performed, but the patient was not positively vasoreactive.

PAH-specific drug therapy with endothelin receptor antagonist (bosentan) was started, with titration at the indicated dose of 125 mg twice a day, in conjunction with anticoagulation therapy with acenocumarol. The patient continued treatment with bosentan but was not followed up medically for a year. In 2004 she experienced progressive clinical decline and syncopal episodes. She was admitted to hospital and severe progression of PAH was documented. The patient underwent right heart catheterization that revealed the following hemodynamic parameters: mean pulmonary arterial pressure 80 mm Hg, pulmonary capillary wedge pressure 12 mm Hg, PVR 30.2 Wood units, and cardiac index 1.2 L/min/m^2. A vasoreactivity test with epoprostenol was performed, but she did not demonstrate acute vasoreactivity, as the mean pulmonary arterial pressure and cardiac index were only reduced to 74 mm Hg and 1.1 L/min/m^2, respectively. The clinical findings and the echocardiographic parameters (Table 1) were compatible with clinical deterioration. Prostanoid therapy was initiated.

The patient was immediately treated with intravenous epoprostenol via a central vein, with a dose of 2 ng/kg/min, rapidly titrated to 10 ng/kg/min, and she subsequently demonstrated pronounced hemodynamic improvement, as she did not experience any more syncope. A Hickman catheter (central venous catheter) was implanted for the continuous intravenous epoprostenol administration, and the patient was discharged. The dose titration took place uneventfully, and the final dose of 40 ng/kg/min was achieved a month later. In 2007 the patient was nearly asymptomatic, and since 2008 the N-terminal brain natriuretic peptide (NT-proBNP) values have been normal, while the 6-min walk test (6MWT) distance has remained above 500 m. The hemodynamic parameters provided by right heart catheterization were almost normalized. Clinical improvement remained stable over 3 years (see Table 1) and the hemodynamic stability was verified on an annual basis by right heart catheterization (Table 2).

The clinical status, as illustrated by the echocardiographic and the hemodynamic parameters, during the 8-year follow up (since 2002, when the diagnosis was made) are presented in Table 1. During this time, the patient experienced 2 episodes of central-venous-catheter-related bloodstream infection, consequently necessitating replacement of the Hickman catheter twice.

Having maintained World Health Organization functional class I status for 3 consecutive years while presenting concomitantly normal NT-proBNP values, the patient's stabilized and satisfactory clinical profile was verified with good hemodynamic values provided by right

Table 1. Hemodynamic, Echocardiographic, and Clinical Data

	2002	2004	2005	2008	2010	2010	2011
Right Heart Catheter Data							
Mean pulmonary arterial pressure, mm Hg	53	80	50	30	28	30	28
Pulmonary capillary wedge pressure, mm Hg	11	12	10	9	10	11	7
Cardiac index, L/min/m^2	1.62	1.2	2.39	2.6	3.0	3.05	3.2
Pulmonary vascular resistance, Wood units	13.2	30.2	10.4	3.4	3.6	3.4	3.4
Echocardiographic Data							
Systolic pulmonary arterial pressure, mm Hg	100	110	80	40	40	45	35
Left ventricular diameter in diastole/systole, mm	40/29	35/23	47/33	49/34	50/35	50/35	49/34
Right ventricle condition	Dilated	Dilated	Normal	Normal	Normal	Normal	Normal
World Health Organization clinical classification	II	IV	III	II	I	I	I
6-min walk distance, m	340	210	350	435	547	550	553
NT-proBNP, pg/mL (normal upper level 125 pg/mL)	540	2,460	1,500	537	56	22	16
Epoprostenol, ng/kg/min	0	40	40	40	40	2	0

NT-proBNP = N-terminal brain natriuretic peptide

Table 2. Literature Review on Transition From Parenteral Prostanoids to Pulmonary Arterial Hypertension-Specific Oral Drugs

First Author	Year	*n*	Epoprostenol Group Total/ Treprostinil Group Total (no.)	Prostanoids Withdrawal Success (all or epoprostenol/ treprostinil groups) (no.)	Mean Pulmonary Arterial Pressure at Weaning, Success/Failure (mm Hg)	Mean Prostanoids Duration, Success/Failure (months)	Prostanoids Maximum Dose, Success/Failure (ng/kg/min)	Mean Follow-up Time (months)	Study Details
Diaz Guzman[8]	2008	21	17/4	15	38.2/42.8	26/16	18/14.5	27.3	1 death in failure group
Keogh[9]	2007	14	0/14*	0/10	No data available	20.2	10.4	3	2/3 failures had pulmonary artery systolic pressure > 100 mm Hg
Johnson[10]	2007	15	15/0	10	35.8	41/36	23.2	29.9	2 late failures. No deaths
Steiner[11]	2006	22	17/5	8/2	38/56	36	25.5/37.7	17.7	4 deaths: 2 in success group
Suleman[12]	2004	23	17/6	11	65.8/84.1	35.2/38.4	25.9/40.1	9.6	2 late failures, in 8 weeks
Kim[13]	2003	4	4/0	4	21	68.4	40.5	11	Normalization of pulmonary arterial pressure prior to withdrawal

* Subcutaneous treprostinil.

heart catheterization performed in 2010. The mean pulmonary arterial pressure was 28 mm Hg, the PVR was 3.6 Wood units, and the cardiac index was 3.0 L/min/m^2 (see Table 1). Thus, epoprostenol withdrawal was suggested.

Sildenafil was added to her regimen in January 2010, in combination with bosentan and acenocumarol, with the intent of facilitating the transition before beginning weaning of epoprostenol. The initial dose was at 20 mg, 3 times a day. One month later, epoprostenol began to be weaned at a rate of 2 ng/kg/min per week. Frequent telephone follow-up, every 15 days, was maintained during this period. A physical examination in an out-patient clinic, in combination with an echocardiographic study, 6MWT, and NT-proBNP estimation was performed every month. When the dose of epoprostenol had been decreased to 2 ng/kg/min (the dose at which she initiated the therapy), a repeat right heart catheterization was performed and the parameters were as follows: right atrial pressure 9 mm Hg, pulmonary artery systolic pressure 41 mm Hg, mean pulmonary arterial pressure 30 mm Hg, pulmonary capillary wedge pressure 11 mm Hg, PVR 3.4 Wood units, and cardiac index 3.05 L/min/m^2. An acute vasoreactivity test was performed, and no changes in hemodynamic measurements were observed. Epoprostenol was then discontinued (July 2010). The patient was monitored for the following 48 hours and then discharged.

Following discontinuation, the Hickman catheter was left in place for a month, to ensure efficient access in the event that epoprostenol needed to be restarted. In August 2010 the catheter was removed and the patient returned to the out-patient clinic one month later, complaining of dyspnea on exertion. The 6MWT did not demonstrate a clin-

ical deterioration, and the NT-proBNP value was normal. Moreover, an echocardiographic study revealed normal left and right ventricular function with pulmonary artery systolic pressure measured at 35 mm Hg. Despite the suspicion of atypical symptoms, a sildenafil dose increase was performed, at 40 mg 3 times a day.[14]

One month later the patient was stable, and returned to the clinic every 3 months thereafter. Repeat 6MWT and determination of functional class were performed at regular intervals, and right heart catheterization was performed 15 months after the discontinuation of epoprostenol, with parameters almost resembling those documented before discontinuation. The values were: right arterial pressure 8 mm Hg, mean pulmonary arterial pressure 28 mm Hg, pulmonary capillary wedge pressure 7 mm Hg, PVR 3.4 Wood units, and cardiac index 3,2 L/min/m^2 (see Table 1). A successful epoprostenol withdrawal was identified and the patient is now being treated with bosentan, sildenafil, and anticoagulation therapy with acenocumarol; she is evaluated every 3–6 months in the outpatient clinic.

Discussion

Idiopathic PAH is a disorder characterized by a poor prognosis, especially in patients classified in accordance with World Health Organization III or IV functional status standards.[15–17] In the national North American registry of 194 patients treated without PAH-specific drug therapy (endothelin receptor antagonists, phosphodiesterase inhibitors, or prostanoids) the median survival was 2.8 years.[16] Currently, the evolution in PAH treatment has led to improvement in patients' symptoms and to a slower rate of clinical deterioration, but poor survival is of major concern. A meta-analysis on 23 randomized controlled trials in PAH patients[18] demonstrated a 43% decrease in mortality, compared to patients randomized to placebo, yet PAH cannot be considered a curable condition. Prostanoids are the PAH-specific therapy cornerstone with approved benefits in advanced functional status, and intravenous epoprostenol was the first FDA-approved therapy for idiopathic PAH.

Long-term continuous intravenous infusion of PGI2 (Flolan, GlaxoSmithKline) has been shown to improve exercise capacity and to ameliorate the hemodynamic parameters and the quality of life,[19–22] while improving survival prospects in PAH.[19,21–23] Factors predicting a good response after epoprostenol treatment are not well established. It was shown that survival prospects in World Health Organization III and IV patients treated with epoprostenol are mainly related to pre-therapeutic clinical variables such as clinical status and distance achieved in the 6MWT. Both clinical and hemodynamic responses to epoprostenol therapy, such as a decline in PVR in the first 3 months, appeared to be major predictors of survival.[22] It was also demonstrated that, in good responders to epoprostenol therapy, pulmonary selectivity to epoprostenol is high, resulting in an increase in blood returning to the left side of the heart via the pulmonary circulation.[24]

Intravenous epoprostenol therapy is believed to require an indefinite period of time.[25] The availability of newer and less invasive treatments for PAH makes replacement of epoprostenol tempting for both physician and patient. We decided to try to withdraw epoprostenol treatment in our patient, based on the fact that a protracted, stable clinical condition had been achieved, combined with almost normal hemodynamic parameters. The weaning protocol was based on an arbitrary protocol, mostly used in series in the literature, in which successful conversion from intravenous epoprostenol to oral therapy was achieved.

In the literature a few case series of prostanoids withdrawal in adult PAH patients are reported (see Table 2). Generally, patients with normal or near-normal hemodynamics before initiation of the weaning process have the best long-term survival prospects. Among the reported series, the longest follow-up is a recently published 5-year follow-up after transition from intravenous epoprostenol to oral bosentan,[26] including 23 patients.[12] In effect, among the 11 patients initially transitioned successfully to oral bosentan, 7 (64%) exhibited clinical deterioration, thus having to resume prostanoid administration. This study demonstrated that, after transition, patients frequently required prostanoid resumption (7 patients because of clinical deterioration), but, for some carefully selected patients, transition to oral therapy offered prolonged, stable functional class status and 6MWT distance.

In the literature, transition, in adult patients, to subcutaneous prostanoid drugs.[27–29] and to intravenous treprostinil (a longer-acting prostacyclin analog) is also reported.[30,31] A review on all pediatric patients with idiopathic PAH, treated at Columbia University (1987–2008) and transitioned to oral or inhaled PAH drugs, is described by Melnick et al.[32] They reported successful withdrawal in 13 among 14 patients, suggesting that transition is safe and efficacious when performed with close follow-up in a pulmonary hypertension specialty center.

The reported studies and the well recognized improved outcome in patients treated with epoprostenol point to an association between the drug and a reverse remodeling in PAH treated patients. Thus, the reverse pathogenic process in selected patients with PAH may allow a transition to less complex and less invasive treatment modalities.[10,13,33] The cost benefit, the improved quality of life, and the reduction in the burden of adverse events during epoprostenol discontinuation are tempting in suitable patients.

It is important to emphasize that epoprostenol withdrawal in a patient with PAH is a complex process, requiring close monitoring. Such endeavors should take place only in experienced centers, not only because there is no consensus about

patient selection, but also because previous studies have reported declining clinical status and even mortality in patients who failed to achieve successful transition.[10,11]

In conclusion, we may argue that the notion "once on epoprostenol, forever on epoprostenol" is not mandatory for carefully selected PAH patients who have marked clinical and hemodynamic improvement on epoprostenol therapy. These patients may be successfully weaned off epoprostenol, provided that transition is conducted with close follow-up to ensure sustained improvement.

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