Transition From Intravenous to Subcutaneous Prostacyclin in Pulmonary Hypertension

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Treatment of arterial pulmonary hypertension with epoprostenol (intravenous prostacyclin) improves survival and quality of life, but the need for an implanted central venous catheter is associated with frequent complications, that often (as in the case of infection or dislodgment) are serious and require catheter replacement. Treprostinil is a prostacyclin analogue suitable for continuous subcutaneous administration. We report the successful transition from intravenous epoprostenol to subcutaneuos treprostinil in four patients with severe pulmonary hypertension who suffered from serious complications associated with the epoprostenol infusion system.

Key words: *Pulmonary hypertension. Prostacyclin. Treprostinil.*

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Transición de prostaciclina intravenosa a subcutánea en la hipertensión pulmonar

El tratamiento de la hipertensión arterial pulmonar con epoprostenol (prostaciclina intravenosa) mejora la supervivencia y la calidad de vida de los pacientes. Sin embargo, la necesidad de implantar un catéter intravenoso central implica frecuentes complicaciones que en algunos casos (infecciones, desplazamientos) son graves y requieren su reemplazo. Treprostinil es un análogo de la prostaciclina que puede administrarse en infusión continua por vía subcutánea. Describimos la transición de tratamiento con epeprostenol intravenoso a treprostinil subcutáneo en 4 pacientes con hipertensión pulmonar severa que presentaron complicaciones graves asociadas al sistema de infusión de epoprostenol.

Palabras clave: *Hipertensión pulmonar. Prostaciclina. Treprostinil.*

INTRODUCTION

Intravenous prostacyclin (epoprostenol) is effective treatment for pulmonary arterial hypertension (PAH), demonstrating clinical and hemodynamic improvement and increased survival.[1-4] Because of its short half-life (2-5 min), however, it must be administered by continuous infusion through a central venous catheter connected to a perfusion pump. Serious complications related to the infusion system frequently occur, requiring the system to be changed and increasing the morbidity and mortality of the patients.[5]

Treprostinil, a stable prostacyclin analogue with a longer half-life (3-4 h), can be administered by continuous subcutaneous infusion. In a recent study, treprostinil showed short-term clinical efficacy (12 weeks) for the treatment of severe pulmonary hypertension without serious complications related to the infusion system.[6] Based on these results, we contemplated a transition to subcutaneous treatment in clinically stable patients receiving intravenous treatment and presenting complications associated with the infusion system, as an alternative to replacement. We report the cases of four patients under epoprostenol treatment who presented infectious complications and were transitioned to subcutaneous treprostinil.

PATIENTS AND METHODS

Between November 2001 and April 2002, four women with severe pulmonary hypertension, one with primary pulmonary hypertension, two associated with lupus erythematosus and the other with scleroderma, presented serious infectious complications. In three

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patients the infection was associated with the central venous catheter and made withdrawal of the catheter necessary, and in the fourth it was related with multiple soft tissue abscesses, making catheter insertion unadvisable. Prior treatment time with epoprostenol ranged from 2 to 128 months. All patients were informed orally and in writing, and gave written consent. The medication was requested under compassionate use and the proposal was approved by the appropriate health authorities.

Treprostinil was infused using a continuous delivery pump (MiniMed 407) through a needle implanted in subcutaneous abdominal tissue. All patients learned to handle the delivery system during hospitalization. The initial infusion rate of treprostinil was 2.5-3.75 ng/kg/min and the same peripheral dose of epoprostenol was maintained for the first 12 h. The infusion dose of epoprostenol was then gradually decreased and the dose of treprostinil was increased every 12 h until complete withdrawal of epoprostenol. The transition was carried out in a conventional hospital ward, monitoring the vital signs and watching for the development of the signs or symptoms of prostacyclin excess (erythema, headache, diarrhea or arterial hypotension) or insufficiency (increased symptoms of pulmonary hypertension, or the appearance of right-sided heart failure).

The functional class and exercise capacity were initially assessed by the New York Heart Association (NYHA) criteria and the six-minute walking distance, respectively, then measured every three months after the transition.

RESULTS

The baseline characteristics of each patient are described in Table 1. In three patients (patients 1, 2 and 3) epoprostenol dosage had not been changed in the previous 3 months. Two experienced infection of the Hickman catheter caused by *Staphylococcus aureus* and *Pseudomonas aeruginosa*, respectively, presenting fever, reddening of the surrounding skin tissue and purulent drainage through the catheter orifice, making it necessary to withdraw the catheter. The third was wearing a Port-A-Cath® system, which was withdrawn because of pneumococcal sepsis. Epoprostenol was then administered through a peripheral line at the same doses.

The fourth patient was diagnosed of pulmonary hypertension following hospitalization for severe right-sided heart failure and required treatment with epoprostenol, dobutamine and diuretics. Following stabilization, she presented multiple subcutaneous abscesses caused by *Staphylococcus aureus*, a situation in which insertion of a central venous catheter is unadvisable.

The changes in the epoprostenol and treprostinil infusion rate during transition are described in Table 2. Epoprostenol was withdrawn between the fourth and sixth day. The baseline epoprostenol dose was 10 to 13 ng/kg/min and the dose of treprostinil after transition was 12.5 to 15 ng/kg/min, i.e., 15%-20% greater. The transition was well tolerated, and there were no signs or symptoms of prostacyclin excess or insufficiency, or significant changes in blood pressure or heart rate.

The functional class and exercise capacity of each patient as measured by NYHA and the six-minute walking distance, respectively, before and after the treatment change are listed in Table 1. In the medium-term follow-up (3 to 8 months), no patient experienced clinical deterioration and the clinical parameters remained similar. In two patients (Patients 1 and 2), the values were similar. Patient 3 showed a decrease in the distance walked and a worsening of NYHA functional class, mainly attributed to severe pain at the subcutaneous infusion site, since no other functional deterioration was observed. Patient 4 was NYHA Class IV and did not perform the baseline six-minute test. However, the treatment change was carried out after clinical stabilization and at the sixth month of follow-up, her functional class and exercise capacity had improved.

TABLE 1. **Baseline characteristics of the patients**

Patients	Age (years)	Sex	PH Type	Diagnosis time[a]	Treatment time[b]	NYHA Pre	NYHA Post	6 min Pre	6 min Post	sPAPe	Associated complication
1	46	F	Scleroderma	143	128	II	II	492	500	72	Pneumococcal sepsis
2	28	F	Lupus erythematosus	18	12	III	II	408	425	59	Localized staphylococcal infection
3	29	F	Primary	61	37	I	II	570	480	89	Localized Pseudomonas infection
4	38	F	Lupus erythematosus	4	2	IV	II	–	434	45	Multiple soft tissue abscesses

[a]Diagnosis time: time between diagnosis and transition (months). [b]Treatment time: treatment time with epoprostenol until time of transition (months). PH indicates pulmonary hypertension; NYHA, New York Heart Association class; 6 min, walking distance during the 6-minute test; pre, corresponds to values before treatment change (meters); post, corresponds to values after change (third month, except for Patient 4, sixth month; sPAPe, systolic pulmonary artery pressure estimated by echocardiography in the pre-transition visit (89 mm Hg); F, female

TABLE 2. **Prostacyclin dose during transition**

	Baseline (Day 0)		Day 1		Day 2		Day 3		Day 4		Day 5	
Case	Ep	Tep	Ep	Tep	Ep	Tep	Ep	Tep	Ep	Tep	Ep	Tep
1	13	2.5	9	5	4	10	0	16				
2	10	3.75	8.5	6.25	4	10	0	12.5				
3	12	2.5	10	5	7	7.5	5	10	2	12.5	0	15
4	11	3.75	8	6.25	5	8.75	3	11.25	0	15		

Ep indicates intravenous epoprostenol dosage (ng/kg/min); Tep, subcutaneous treprostinil dosage (ng/kg/min).

Infusion site pain was the most important adverse effect observed. One of the patients required a slower dosage increase, and three required specific analgesic treatment, one with local measures (cold and topical anti-inflammatory agents), and two with oral drugs (gabapentin).

DISCUSSION

The clinical progress of our patients demonstrates that transition from intravenous to subcutaneous prostacyclin can be safely performed in stable patients and can achieve good medium-term clinical progress.

Although pulmonary arterial hypertension continues to be an incurable condition, treatment with intravenous prostacyclin has led to a significant change in the disease in terms of clinical improvement and survival.[1-4] Nevertheless, the use of continuous intravenous perfusion is associated with potentially serious complications requiring catheter replacement, and the outcome is sometimes fatal. The incidence of catheter infection is estimated at 0.22-0.68 per patient-year, with that of sepsis estimated at 0-0.39 per patient-year.[5] Other frequent complications are catheter dislodgement, thrombosis and paradoxical embolism in patients with intracardiac shunts. Furthermore, because of the short half-life of epoprostenol (3-5 min), any interruption in treatment can result in sudden worsening of pulmonary hypertension, leading to syncope and a life-threatening condition.

New forms of treatment for pulmonary hypertension have been developed in recent years. Subcutaneous (treprostinil)[6] and inhaled (iloprost)[7] prostacyclin have proven to be effective in pulmonary arterial hypertension (in particular, in its primary and collagen-disease related forms), in terms of clinical and functional class improvement, as observed in short-term follow-up (12 weeks).

The advantages of treprostinil over epoprostenol are its longer half-life (3-4 h) and subcutaneous delivery system, which is free of serious complications and more convenient to administer; no deaths directly attributable to complications derived from the infusion system have been reported. The impact on the natural course of the disease is unknown, however, although indirect data suggest that it can increase survival.[8] As reported recently by Vachiéry et al,[9] patients under epoprostenol treatment can be safely transitioned to subcutaneous treprostinil treatment at the physician's discretion. In that study, 8 patients with pulmonary arterial hypertension receiving various doses of epoprostenol (3.5-75 ng/kg/min) were changed to subcutaneous treprostinil (3-65 ng/kg/min) over a varying time period (1-4 days).

In our patients, the transition was completed between the fourth and the sixth day, with changes in the infusion rate every 12 h. The final treprostinil dosage was somewhat higher (between 15% and 20%) than the previous epoprostenol dosage. In the medium-term follow-up (3 to 8 months), no clinical deterioration was observed and the four patients were stable at the time of writing. The adverse effects reported most frequently with treprostinil are local pain and inflammation (over 80%).[6] The pain is generally well controlled with topical measures such as cold and local antiinflammatory drugs, or oral treatment with paracetamol, anti-inflammatories, gabapentin or short courses of steroids. Three patients in our series required analgesia, two of them with oral gabapentin. In one of them transition was slower due to local pain, although it was completed successfully.

In summary, subcutaneous treprostinil is an option for patients with pulmonary hypertension who are currently under intravenous epoprostenol treatment and who experience complications associated with the infusion system. The transition from one treatment to the other is safe, provided the patient´s underlying disease is stable.

REFERENCES

1. Barst RJ, Rubin LJ, Long WA, McGoon MD, Rich S, Badesch DB, et al. A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension. Primary Pulmonary Hypertension Study Group. N Engl J Med 1996;334:296-302.

2. McLaughlin V, Shillington A, Rich S. Survival in primary pulmonary hypertension. The impact of epoprostenol therapy. Circulation 2002;106:1477-82.
3. Badesch BD, Tapson VF, McGoon MD, Brundage BH, Rubin LJ, Wigley FM, et al. Continuous intravenous epoprostenol for pulmonary hypertension due to the scleroderma spectrum disease. A randomized, controlled trial. Ann Intern Med 2000;132: 425-34.
4. Rosenzweig EB, Kernstein D, Barst JR. Long-term prostacyclin for pulmonary hypertension with associated congenital defects. Circulation 1999;99:1858-65.
5. Rich S, editor. Executive Summary from the World Symposium on Primary Pulmonary Hypertension 1998. Evian, France. September 6-10, 1998. Co-sponsored by the World Health Organization. Disponible en: www.who.int/ncd/cvd/pph.htm
6. Simonneau G, Barst R, Galie N, Naeije R, Rich S, Bourge R, et al. Continuous subcutaneous infusion of treprostinil, a prostacyclin analogue, in patients with pulmonary arterial hypertension. Am J Respir Crit Care Med 2002;165:800-4.
7. Olschewski H, Simmoneau G, Galié N, Higenbottam T, Naejie R, Rubin LJ, et al. Inhaled iloprost for severe pulmonary hypertension. N Engl J Med 2002;347:322-9.
8. Escribano P, Lázaro M, Tello R, Delgado JF, Cea-Calvo L, Velázquez T, et al. Dos años de experiencia con treprostinil (análogo estable de la prostaciclina) en infusión subcutánea continua en el tratamiento de la hipertensión pulmonar severa [abstract]. Rev Esp Cardiol 2002;55(Supl 2):22.
9. Vachiéry JL, Hill N, Zwicke D, Barst R, Blackburn S, Naejie R. Transitioning from IV epoprostenol to subcutaneous treprostinil in pulmonary arterial hypertension. Chest 2002; 121:1561-5.