EFFECTS OF CONTINUOUS INTRAVENOUS EPROSTENOL THERAPY ON ADVANCED PRIMARY PULMONARY HYPERTENSION IN TAIWANESE PATIENTS

Hsao-Hsun Hsu, Jin-Shing Chen, Sow-Hsong Kuo, Fu-Tien Chiang, Wen-Je Ko, Shuenn-Wen Kuo, Shu-Chien Huang, and Yung-Chie Lee

Abstract: Primary pulmonary hypertension (PPH) is a progressive disease for which there is no cure. Continuous intravenous infusion of epoprostenol in selected patients with advanced PPH improves symptoms and survival, but the long-term impact has not been reported in Taiwanese patients. Four patients with advanced PPH treated with epoprostenol therapy were enrolled in this study from July 2000 to September 2001. The basic hemodynamic status, cardiothoracic ratio, 6-minute-walk test results, maximum oxygen consumption, New York Heart Association functional class and survival were re-evaluated before and after 12 months of epoprostenol treatment. One of the patients died after 10 months of epoprostenol therapy due to heart failure, and the other 3 were still alive after a mean of 28 months. The surviving patients had pronounced symptomatic, hemodynamic, functional and survival benefit from epoprostenol therapy. Our results suggest that chronic infusion of epoprostenol can improve functional status and survival of Taiwanese patients with advanced PPH disease.

Key words: Epoprostenol; Pulmonary hypertension; Taiwan; Treatment outcome

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Primary pulmonary hypertension (PPH) is a rare disease of unknown origin that is characterized by medial hypertrophy and intimal proliferation of the pulmonary arterioles, leading to progressive elevation of pulmonary artery pressure and vascular resistance, right ventricular failure and death. The incidence has been estimated at approximately 1 to 2 cases per million. Without treatment, the median survival is very short from the time of diagnosis. Continuous intravenous infusion of epoprostenol has recently become a new modality in the management of advanced PPH, when conventional oral medical therapy fails. However, epoprostenol was not available in Taiwan for PPH until 2000, and its long-term effects and clinical response among Taiwanese are still unclear. This report describes the effects of continuous intravenous epoprostenol on basic hemodynamic status, exercise performance, New York Heart Association Functional Class (NYHA FC), and survival in Taiwanese patients with advanced PPH.

Clinical Summary

Four Taiwanese patients (mean age, 38 years; 1 man and 3 women) with advanced PPH were enrolled for this study between July 2000 and September 2001. One patient had NYHA FC III and the others had FC IV disease. The mean pulmonary artery pressure before epoprostenol infusion (Flolan; Glaxo-Wellcome, Research Triangle Park, NC, USA) was 55 mm Hg despite optimal medical therapy. Secondary causes of pulmonary hypertension were carefully excluded.

A Hickman catheter was placed into a subclavian or jugular vein for continuous infusion of epoprostenol with the use of a portable infusion pump. Epoprostenol therapy was initiated at 2 ng/kg/min and the dose was gradually increased to the maximum tolerated dose during the initial hospitalization. The
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Dose was additionally increased at the outpatient clinic, mainly depending on the symptoms of pulmonary hypertension and side effects of epoprostenol. Conventional therapies, including digitalis, diuretics, warfarin, and supplemental oxygen, were continued in all patients as indicated on the basis of clinical judgment. Patients who survived for more than 1 year underwent re-evaluation including the basic hemodynamic parameters, cardiothoracic ratio, functional status, including the distance of 6-minute-walk test, maximum oxygen consumption (MVO2) measured by bicycle ergometry, and NYHA FC. The patients were followed for up to 36 months.

Changes in basic hemodynamic parameters and cardiothoracic ratio in the 4 PPH patients are shown in Table 1. After 12 months of continuous epoprostenol therapy, the 3 surviving patients had stable hemodynamic status without any inotropic infusion or oxygen supplement. The cardiothoracic ratio after 1 year of treatment was also decreased compared with the value obtained just before initiation of epoprostenol in the 3 surviving patients.

The outcome of epoprostenol therapy in the 4 patients is shown in Table 2. Two of 3 surviving patients were bedridden before therapy and their exercise performance improved significantly. The average 6-minute-walk test in the 3 surviving patients after treatment was 489 m. The average MVO2 and NYHA FC was also improved in the surviving patients.

During the follow-up period, local infection developed at the exit site of the catheter in 1 patient, which was successfully treated with a 5-day course of antibiotics. There was no episode of catheter-related complications such as sepsis or the necessity of catheter replacement during epoprostenol therapy.

Patient 4 died 10 months after starting epoprostenol therapy. She initially had NYHA FC IV PPH and was referred to our hospital for possible lung transplantation because she was refractory to conventional therapy. On admission, her mean pulmonary artery pressure was 66 mm Hg with right heart failure signs including bilateral lower leg edema, hepatomegaly and apparent cardiomegaly. Epoprostenol therapy was administered in an attempt to stabilize her disease but her clinical symptoms and signs of heart failure did not respond to the drug. Urgent lung transplantation was recommended. At the time of her death due to heart failure secondary to cor pulmonale, she was still awaiting transplantation.

### Comment

Continuous central venous infusion of epoprostenol sodium reduces symptoms of dyspnea, improves exercise capacity, and prolongs survival in selected patients with PPH. Epoprostenol is the first Food and Drug Administration (FDA)-approved treatment for

### Table 1. Comparison of basic hemodynamic parameters and cardiothoracic ratio in 4 patients with primary pulmonary hypertension before and after epoprostenol therapy.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Heart rate (beats/min)</th>
<th>SBP/DBP (mm Hg)</th>
<th>Sat (%)</th>
<th>Cardiothoracic ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
<td>Before</td>
<td>After</td>
</tr>
<tr>
<td>1*</td>
<td>97</td>
<td>96</td>
<td>165/112</td>
<td>128/78</td>
</tr>
<tr>
<td>2*</td>
<td>67</td>
<td>78</td>
<td>119/72</td>
<td>110/70</td>
</tr>
<tr>
<td>3*</td>
<td>100</td>
<td>79</td>
<td>115/76</td>
<td>98/62</td>
</tr>
<tr>
<td>4†</td>
<td>93</td>
<td>118</td>
<td>109/65</td>
<td>90/70</td>
</tr>
</tbody>
</table>

Measures:
- † Measured after 6 months of epoprostenol treatment.
- ‡ Measured during intravenous inotropic treatment.
- § Measured during oxygen supplementation.

SBP = systolic blood pressure; DBP = diastolic blood pressure; Sat = oxygen saturation.

### Table 2. Outcome of epoprostenol therapy in 4 patients with primary pulmonary hypertension patients.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Six-minute-walk distance (m)</th>
<th>MVO2 (mL/min/kg) [% predicted]</th>
<th>NYHA functional class</th>
<th>Survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before treatment</td>
<td>After treatment</td>
<td>Before treatment</td>
<td>After treatment</td>
</tr>
<tr>
<td>1*</td>
<td>Bedridden</td>
<td>604</td>
<td>Bedridden</td>
<td>12.88 (30.5)</td>
</tr>
<tr>
<td>2*</td>
<td>NA</td>
<td>478</td>
<td>NA</td>
<td>9.85 (38.22)</td>
</tr>
<tr>
<td>3*</td>
<td>Bedridden</td>
<td>384</td>
<td>Bedridden</td>
<td>13.02 (52.64)</td>
</tr>
<tr>
<td>4†</td>
<td>Bedridden</td>
<td>Bedridden</td>
<td>Bedridden</td>
<td>Bedridden</td>
</tr>
</tbody>
</table>

Measures:
- † Measured after 6 months of epoprostenol treatment.
- ‡ Died of heart failure secondary to cor pulmonale.

MVO2 = maximum oxygen consumption; NYHA = New York Heart Association; NA = not available.
advanced PPH. Before this drug was registered in Taiwan in 2000, lung or heart-lung transplantation was the only effective therapy for treatment of advanced PPH patients who were no longer improving or deteriorating while receiving conventional therapy. In July 2000, our institution first attempted to use intravenous epoprostenol to treat patients who were recommended to receive transplantation, according to previous therapeutic guidelines. To our knowledge, this is the first report on the long-term effects of continuous epoprostenol infusion on exercise performance, FC, and survival in Taiwanese patients with advanced PPH.

Although re-evaluation with right heart cardiac catheterization after epoprostenol therapy could accurately demonstrate the treatment benefit on hemodynamic status, 2 of our surviving patients declined requests to repeat this study on schedule. In the 3 surviving patients, the basic hemodynamic parameters, including heart rate, blood pressure and oxygen saturation, were clinically stable during 12 months’ follow-up without intravenous inotropic treatment or oxygen supplement. Their cardiothoracic ratios measured after therapy for 12 months were decreased compared with those obtained just before epoprostenol infusion. These data suggest that chronic infusion of epoprostenol not only effectively prevented the disease deterioration but also potentially improved the cardiac function in the 3 surviving patients.

Exercise testing has been used as a measure of functional capacity in patients with PPH, and previous studies have shown that performance on exercise tests has prognostic significance and may be used to evaluate treatment efficacy. Barst et al reported that exercise capacity, measured during the 6-minute-walk test, was an independent predictor of survival and could be also useful in determining whether alternative treatment options, such as lung transplantation, should be considered during epoprostenol therapy. Sun et al and Wensel et al demonstrated that measurement of aerobic capacity (MVO₂) in PPH was useful in quantitating PPH disease severity and predicting survival in PPH. The present study suggests that continuous infusion of epoprostenol has beneficial effects on exercise function of Taiwanese patients with advanced PPH, including improvements in both the distance walked in the 6-minute-walk test and MVO₂ measured by bicycle ergometry. On initial admission before starting epoprostenol therapy, 2 of the surviving patients were bedridden with intravenous inotropic treatment and needed oxygen supplementation. Because they were too weak to undergo bicycle ergometry or to perform the 6-minute-walk test, there was not enough data to make meaningful comparisons of exercise capacity prior to starting epoprostenol and after 12 months of epoprostenol treatment. Nonetheless, the dramatic increase in exercise performance and great enhancement in daily activities with long-term epoprostenol therapy was very satisfying for the 3 surviving patients.

Functional classification correlates with disease severity and outcome in patients with PPH. While simple in concept, demonstration of improvement in FC can be very effective in proving the clinical relevance of epoprostenol therapy. FC greatly improved in our 3 surviving patients after 12 months of epoprostenol treatment. They were able to return to work and were still alive at an average of 28 months of follow-up. At the time of the last follow-up evaluation, 1 of the 3 surviving patients was still receiving epoprostenol and was on the active transplantation list, while the other 2 patients had been removed from the active transplantation list because of clinical improvements.

One of the major limitations of chronic intravenous epoprostenol therapy is the morbidity associated with both a chronic indwelling Hickman catheter and a complex delivery system of constant intravenous infusion. Over our observation period of 36 months, 1 patient developed local infection at the exit site and was successfully treated with antibiotics. There was no episode of catheter-related tunnel infection, sepsis, or need for catheter replacement during the following period. Although previous reports mention that the epoprostenol delivery system has a number of inherent potential complications, our experience with these 4 patients suggests that long-term intravenous infusion of epoprostenol is clinically feasible where there is knowledge of the PPH disease process, experience with the drug and the delivery system, and cooperative participation of the patients, physician specialists, and home health care providers.

For patients with severe PPH who present with right heart failure, lung or heart-lung transplantation is the final therapeutic option if they are refractory to epoprostenol therapy or sudden deterioration occurs during therapy. Because the current waiting time for transplantations in our hospital is very long, it is often too late to rescue these patients from reversible hemodynamic crises. In addition to progressive deterioration of underlying disease, the long waiting time for transplantation also contributes to the high mortality rate of patients with severe PPH who are already on the active transplantation list.

The principal limitation of this study was the small number of Taiwanese patients with advanced PPH on long-term intravenous epoprostenol infusion therapy. The relative rarity of PPH incidence, few diagnosed patients in our institution, and administration of
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intravenous epoprostenol being restricted to PPH patients categorized as NYHA FC III/IV all contributed to this major limitation. Multicenter, controlled clinical trial with a large group of patients with advanced PPH is needed to determine the therapeutic efficacy of epoprostenol among Taiwanese patients.

In conclusion, exercise performance, as measured by the distance walked in 6 minutes and the MVO₂, improved in our patients who were treated for 12 months with continuous intravenous epoprostenol. Our findings are in agreement with data on the natural history of PPH from the NIH registry concerning the long-term effect of epoprostenol on improving basic hemodynamic status, NYHA FC and survival associated with advanced PPH. The major morbidities and possible mortalities associated with a complex drug-delivery system can be avoided and reduced in institutions with considerable infrastructure, including experienced nurses and physicians. For patients with severe PPH no longer responsive to epoprostenol, urgent lung or heart-lung transplantation is the only effective treatment to preserve life.

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References