Long-term Continuous Intravenous Infusion of Prostacyclin for Severe Primary Pulmonary Hypertension

Yoshiaki Okano *,†, Shoji Senju**, Yasuhiro Tsutsui***, Shingo Kyotani*, Masayoshi Ishibashi**, Minoru Yoshida** and Takeyoshi Kunieda*,††

A patient suffering from severe symptomatic primary pulmonary hypertension (PPH) underwent long-term intravenous prostacyclin therapy; the first time for such treatment in Japan. A 26-year-old male had experienced gradually progressive dyspnea for about one year. Despite conventional therapy he suffered repeated syncopal attacks. However, after receiving a permanent central venous access device and a portable infusion pump, he recovered fully and was discharged. This remedy seems to be promising for PPH as has already been proven in Europe and North America, although in Japan it is not as yet commercially available and some problems still need to be resolved. (Internal Medicine 36: 794-798, 1997)

Key words: pulmonary vascular disease, vasodilating therapy, ambulatory intravenous infusion, venous access device, portable pump

Introduction

Primary pulmonary hypertension (PPH) is a disease of unclear etiology and is characterized by an extreme elevation in pulmonary arterial pressure and pulmonary vascular resistance, ultimately resulting in right ventricular failure and death (1–3). The median survival of patients recorded in the National Institute of Health (NIH) Registry on PPH was 2.8 years after diagnosis (2). The effects of conventional vasodilating therapy on patients with PPH have either been inconclusive or mostly disappointing, thus a single lung or heart-lung transplantation (3) has been considered as the only way to improve patient survival. Recently, the clinical efficacy of PGI2 (epoprostenol) has been proven in some trials in Europe (4, 5) and the United States (6–8). They have shown that long-term intravenous administration produces marked improvements in both the quality (4-7) and duration of life (8) in patients with severe PPH. Here, we describe the first case in Japan of a patient with severe symptomatic PPH undergoing long-term intravenous PGI2 infusion via a permanent central venous access device and portable infusion pump. The patient was able to recover and leave the hospital.

Case Report

A 26-year-old man (height: 170 cm, weight: 73 kg) was referred to our hospital with a presumptive diagnosis of severe pulmonary hypertension of unknown etiology. He had experienced gradually progressive dyspnea on exertion and repeated syncopal attacks for about one year. He had never smoked and had no significant past or familial medical histories. On admission in June 1994, his blood pressure was 112/78 mmHg with a regular pulse rate of 84 bpm. Subsequent cardiac and pulmonary physical examinations revealed the following: a right ventricular heave was palpable, a pulmonic valve closure was accentuated, a S3/S4 summation gallop was detected, and grade II holosystolic murmurs from tricuspid regurgitation were audible along the left lower sternal border. Normal vesicular sounds were audible without rales nor pulmonary arterial (PA) flow murmurs in the precordium and back. There was a slight hepatomegaly located 0.5 cm below the right costal margin and a mild lower extremity edema. Laboratory blood tests results were all within normal limits, except for a slightly high level of total bilirubin (2.0 mg/dl) and γ-glutamyl transeptidase (γ-GTP) (66 U/l). No abnormality in coagulation or the autoimmune systems was found. Analysis of arterial blood gas in room air conditions showed pH 7.46, partial pressure of oxygen (PaO2)
87 Torr, partial pressure of carbon dioxide (PaCO₂) 30 Torr, and saturation of oxygen (SaO₂) 97%. Pulmonary function tests revealed no primary parenchymal disease. A chest X-ray film did show a mild cardiomegaly, and a prominent dilatation of the main PA with a tendency of abrupt and diffuse peripheral narrowing (Fig. 1, left panel). An electrocardiogram demonstrated normal sinus rhythm, pulmonary P waves, right axis deviation and a marked right ventricular hypertrophy with strain (Fig. 1, right panel). Pulmonary scintigraphic scans showed a mottled perfusion abnormality (Fig. 2, left panel). A marked right ventricular enlargement and left ventricular deformity were also noted on a transthoracic echocardiography (Fig. 2, right panel). Doppler studies did not show any intracardiac shunt, although they did confirm a moderate tricuspid regurgitant flow with an estimated pressure gradient of 84 mmHg across the cusp. Cardiac catheterization revealed a mean pulmonary capillary wedge pressure of 10 mmHg, PA pressure of 102/45 (mean 63) mmHg, right ventricular pressure of 100/-22 mmHg, and right atrial pressure of 15 mmHg. Cardiac output (CO) determined by the thermodilution method was recorded as 2.4 l/min (Table 1). An oximetric study also confirmed no intracardiac shunt. Coronary arteriography was found to be normal, but pulmonary angiography was not performed because of the considerable risk to the patient indicated by the hemodynamic data, and the absence of major thromboembolic disease as revealed by the perfusion scan described above. These results allowed us to make a final diagnosis of the PPH according to the criteria of the NIH registry on PPH (1).

In spite of limiting the patient to only mild daily activity and only then within his own room with the protection of an oxygen...
Table 1. Symptoms and Hemodynamics before and after Prostacyclin

<table>
<thead>
<tr>
<th></th>
<th>before treatment</th>
<th>acute phase</th>
<th>after treatment</th>
<th>chronic phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Functional Class</td>
<td>IV</td>
<td>IV</td>
<td>III</td>
<td>III</td>
</tr>
<tr>
<td>(NYHA)</td>
<td>1994.7.19</td>
<td>1994.10.27</td>
<td>1995.8.31</td>
<td></td>
</tr>
<tr>
<td>Hemodynamics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR</td>
<td>84</td>
<td>76</td>
<td>80</td>
<td>72</td>
</tr>
<tr>
<td>SA</td>
<td>98/69 (79)</td>
<td>90/62 (71)</td>
<td>110/80 (90)</td>
<td>108/70 (83)</td>
</tr>
<tr>
<td>PCW</td>
<td>(mmHg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PA</td>
<td>(mmHg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RV</td>
<td>(mmHg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RA</td>
<td>(mmHg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CO (l/min/m²)</td>
<td>2.4 (1.5)</td>
<td>3.0 (1.8)</td>
<td>3.7 (2.2)</td>
<td>4.9 (2.8)</td>
</tr>
<tr>
<td>TPR (units)</td>
<td>26.3</td>
<td>20.3</td>
<td>15.9</td>
<td>12.7</td>
</tr>
<tr>
<td>PVR (units)</td>
<td>22.1</td>
<td></td>
<td>14.6</td>
<td></td>
</tr>
<tr>
<td>Rp/Rs</td>
<td>0.80</td>
<td>0.86</td>
<td>0.66</td>
<td>0.75</td>
</tr>
<tr>
<td>dosage (ng/kg/min)</td>
<td>6</td>
<td>8</td>
<td>10</td>
<td></td>
</tr>
</tbody>
</table>


supply and anticoagulation, he continued to experience syncopal attacks. In response to this unstable and life-threatening condition, we decided to urgently administer aggressive vasodilating remedies. Although treatment using inhaled nitric oxide at levels up to 80 ppm was tried at first, no beneficial effects were gained. We subsequently initiated a continuous infusion of PGI2 via a peripheral vein after obtaining informed consent from the patient. PGI2 was infused at an initial rate of 2 ng/kg/min, with increments of 2 ng/kg/min every 15 minutes while monitoring PA and systemic arterial pressure according to standard techniques using a Swan-Ganz catheter and radial arterial canulation. Although CO increased by 25% compared with the baseline value at the dosage of 6 ng/kg/min (Table 1), the patient suffered another syncopal attack accompanied by rapid progressive hypotension just after the dosage was increased to 8 ng/kg/min. But shortly after decreasing the dosage to 4 ng/kg/min and administering dopamine (4 µg/kg/min) concomitant with isoproterenol at 0.02 µg/kg/min, he recovered completely. After catheterlamines were gradually tapered off, we increased the infusion rate of PGI2 again at increments of 2 ng/kg/min a week up to 8 ng/kg/min, while carefully monitoring changes in systemic arterial pressure and maintaining his general condition.

The patient's subjective symptoms significantly improved 2 weeks after the regimen, and he was able to walk at his own pace in the hospital without feeling dyspnea. His condition improved from grade IV to III in terms of his New York Heart Association (NYHA) functional class. Hemodynamic measurements obtained 3 months after the regimen showed a 34% decrease in pulmonary vascular resistance (PVR) and an 18% decrease in the ratio between pulmonary and systemic vascular resistance (Rp/Rs) (Table 1). However, while we were planning to taper off PGI2, he fainted again at rest and gradually deteriorated afterwards. Once again he completely recovered following a gradual increment of PGI2 dosage up to 10 ng/kg/min. Upon evaluation, we realized that the patient was still in serious condition and he would not survive longer without continuous PGI2 infusion.

After obtaining special approval from the Health and Welfare Ministry and the ethical committee of our hospital, and again with the patient's informed consent, in August 1995, we implanted a venous access device for stable and ambulatory PGI2 infusion (Hemed CVAC, Gish Biomedical, Inc., Irvine, California, USA) by inserting a permanent intravenous catheter into the right subclavian vein and then tunneling subcutaneously (Fig. 3). PGI2 was infused continuously by a portable pump (Ambulatory infusion pump CADD-plus, Smith Industries Medical Systems, USA, Fig. 4). Before discharge, the patient was thoroughly trained in the proper techniques of catheter care, asepsis, drug preparation and administration. Finally, in February 1996, he was discharged from our hospital and returned to his home town in Fukuoka prefecture.

Discussion

Since the description of the characteristic clinical abnormalities over 40 years ago (9), PPH has been regarded as a progressive, fatal disease that is usually refractory to treatment.
Intravenous Prostacyclin for PPH

Figure 3. A venous access device (Hemed CVAC, Gish Biomedical, Inc., Irvine, California, USA). This was inserted into the right subclavian vein by making a venipuncture from a skin incision (see, white arrow) and tunneled subcutaneously down to the right anterior chest wall. The catheter became fixed by firm tissue ingrowth within the cuff (see, black arrow) 2 to 3 weeks after insertion.

Figure 4. A portable pump.

The median survival period of patients with mild to moderate severity is 6 years compared with 2.5 years for class III patients, and only 6 months for class IV patients who were prospectively entered into the NIH Registry on PPH (2). The present patient was seriously ill before PGI2 therapy in terms of functional class and hemodynamic status, and the probability of his survival for one year was estimated as less than 50% based on the NIH Registry data (2).

PPH is also pathologically characterized by an extensive remodeling of the pulmonary vasculature, with proliferative changes such as intimal fibrosis, medial hypertrophy, and plexiform lesion (10). Some coagulopathy (11) and functional vasoconstriction (12) also contribute to the progress of this disease. PGI2, as originally discovered by Moncada et al in 1976 (13), is a potent short-acting vasodilator and inhibitor of the platelet aggregation produced by the vascular endothelium. Its pharmacodynamic properties are able to influence all of the above pathologic features and inhibit the progression of the disease (14). Rubin et al were the first to report that at the end of an 8-week randomized study of PPH, patients treated with PGI2 had gained an increase in exercise capacity and improved hemodynamics compared with those who only received conventional therapy (6). Ever since, continuous intravenous infusion of PGI2 has been utilized in PPH as a bridge to transplantation for patients enrolled in such programs, and its efficacy is manifested by successful stabilization of patient conditions. The short-term beneficial response to PGI2, characterized by a reduction in pulmonary arterial pressure and increase in cardiac output, also helped to identify those patients with a better prognosis (15), although it is not clear if the long-term beneficial effects of the compound are due to its hemodynamic, antiproliferative, or antithrombotic activity. Since PGI2 is,
however, chemically unstable and has a very short half-life within the blood circulation (16), it cannot be given orally but has to be administered by continuous intravenous infusion. Therefore, as in the present case, a permanent central venous catheter and a delivery system must be semipermanently used to ambulatorily continue the therapy. However, the quality of life for patients obviously suffers to some degree. Furthermore, reports indicate that there are substantial risks of serious complications, including catheter-related infections, thromboembolic events and temporary interruption to the infusion due to pump malfunction, all of which are potentially life-threatening (17, 18). But as for alternatives, the effects of long-term oral vasodilating therapy on PPH patients have so far been inconclusive, except for high-dose calcium channel blockers (19) and beraprost sodium (20), an orally active PGI2 derivative developed in Japan for patients with relatively mild symptoms. In addition, transplantation is not yet approved in Japan. Therefore under such circumstances, at present the continuous intravenous PGI2 therapy seems to be the most promising therapy for severe symptomatic PPH patients in Japan as well as for those in European and North American countries, although the major problems as described above remain to be resolved. To date, unfortunately, intravenous PGI2 is still not commercially available in Japan, even though its short-term beneficial effects and safety have been shown in a multicenter clinical trial (21) and in our own experience (22). Swift approval for its appropriate application in patients with severe PPH is an urgent need.

Acknowledgements: The authors are grateful to Tim W. Higenbottam MD and Yazdani A. Butt MD (Papworth Hospital, Cambridge, UK) for providing the benefit of their clinical experience and encouragement. We also gratefully acknowledge the contributions of the following physicians and nurses who participated in the medical care of the patient described in this report: National Cardiovascular Center; Toru Sato MD, Takao Yoshioka MD, Hiroshi Nonogi MD, Tatsuro Itoh MD, Mamori Toyofuku MD, Yoshiiro Yanagitani MD, Noritoshi Nagaya MD, Yukiko Satoh MN, Akiko Sakurai MN, Sachiko Takada MN, Yuki Yamada MN, Ayumi Watanabe MN; Fukuoka University; Kentaro Watanabe MD, Hideo Toyoshima MD, Hisako Terada MN, Shigeko Matsuda MN, Akiko Mizokami MN.

References