Efficacy and Limitations of Continuous Intravenous Epoprostenol Therapy for Idiopathic Pulmonary Arterial Hypertension in Japanese Children

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Background  There is little data on the long-term effects of continuous intravenous epoprostenol for children with idiopathic pulmonary arterial hypertension (IPAH) in Japan.

Methods and Results  Thirty-one IPAH patients younger than 18 years old who had begun epoprostenol therapy at Toho University Omori Medical Center between January 1999 and June 2004 were reviewed. During a mean follow up of 3.4 years, the rate of those who survived or did not undergo a lung transplantation among the 27 patients who received home infusion therapy of epoprostenol was 100% at 1 year, 96.3% at 2 years, and 79.4% at 3 years. In 82% of survivors, the World Health Organization functional class was changed from III or IV to II according to improvements in the plasma brain natriuretic peptide level and the distance walked in 6 min during the follow-up period. In most cases, mean pulmonary artery pressure and the ratio of pulmonary to systemic vascular resistance remained high, although the cardiac index had improved to within a normal range 1 year after the initiation of epoprostenol. Therefore, sildenafil was administered as an additional therapy to 16 patients who presented with sustained severe PAH.

Conclusions  Continuous IV epoprostenol certainly improves survival and exercise tolerance in childhood IPAH, although the improvement of pulmonary vascular resistance regardless of long-term epoprostenol therapy is insufficient. Therefore, the addition of a new drug, such as sildenafil, is recommended to be administered in conjunction with epoprostenol.  

Key Words:  Children; Epoprostenol; Long-term outcome; Pulmonary arterial hypertension (PAH)

Idiopathic pulmonary arterial hypertension (IPAH) is a disease with a poor prognosis that is characterized by progressive pulmonary vascular occlusion. Since the middle of the 1990s, continuous intravenous (IV) epoprostenol has been the gold standard for the treatment of severe IPAH, and several studies have shown that long-term results are mostly favorable. However, these previous reports pertained to adult patients in Western countries. Few studies have been carried out on children despite the fact that the clinical features and response to vasodilators in pediatric patients with IPAH differ from those of adult patients. We retrospectively investigated the records of Japanese children with IPAH for whom IV epoprostenol was initiated at the Toho University Omori Medical Center (Tokyo, Japan) and ascertained the long-term effects and limitations of this therapy.

Methods

Subjects  The records of 31 consecutive patients with IPAH younger than 18 years of age who began IV epoprostenol at Toho University Omori Medical Center from January 1999 to June 2004 were retrospectively examined. We excluded patients with persistent pulmonary hypertension of newborn or secondary PAH related to congenital heart defects. Subjects were divided into 2 groups according to the year during which epoprostenol treatment began—there were 17 patients in the early group (1999–2001) and 14 patients in the late group (2002–2004).

Therapeutic Strategy  IV epoprostenol was begun at a dosage of 0.5–2.0 ng·kg⁻¹·min⁻¹, and the dosage was increased by 0.5–1.0 ng·kg⁻¹·min⁻¹ every 2 to 4 weeks. During the chronic phase, once the cardiac index (CI) increased to 3.5 L·min⁻¹·m⁻² or the ratio of pulmonary to systemic vascular resistance (RP/Rs) dropped below 0.5, the dose of epoprostenol was no longer increased and a maintenance dose was then administered continuously. Catecholamines or phosphodiesterase-III inhibitors were administered to World Health Organization functional class IV patients, as an advanced therapy against cardiac failure. Other supportive therapies included home oxygen therapy, warfarin, diuretics, digoxin, and angiotensin-converting enzyme inhibitors. Beraprost sodium was discontinued when IV epoprostenol was started. This treatment policy changed in July 2003; that is, after approval from the ethical review board at the institution and obtaining written informed consent from all parents, we administered sildenafil as an additional therapy to 16 patients who had sustained high pulmonary arterial hypertension.
pressure (PAP).

Clinical Follow-up

Clinical assessment was based on WHO functional class, plasma brain natriuretic peptide (BNP), echocardiography, and the distance walked in 6 min (6MWD). In addition, hemodynamic parameters, including PAP, CI, and the pulmonary vascular resistance index (Rp) were evaluated by cardiac catheterization after 3 months and after every year of epoprostenol therapy. All data obtained immediately before treatment with oral sildenafil was used for clinical data concerning epoprostenol.

Statistical Analysis

All data are expressed as the mean±SD. Analysis of variance was used to compare each parameter after the start of continuous IV epoprostenol, and Scheffe’s F-test was used as a multiple comparison test. Furthermore, multiple analysis of variance was used to compare the difference in epoprostenol dosage between the early and the late groups. The Kaplan–Meier method was used to calculate survival rates, and the Log-rank test was performed to compare survival rates between the 2 groups. A value of p<0.05 was considered statistically significant.

Results

Background Characteristics

As displayed in Table 1, 4 patients were infants, 18 were elementary school students, and 9 were attending junior high school or high school. The mean length of time from diagnosis of IPAH to initiation of continuous IV epoprostenol was 1.4±2.0 years. Beraprost sodium was given to 22 patients (71%) until IV epoprostenol was begun. One 3-year-old boy had been taking sildenafil for 4 months before beginning IV epoprostenol. According to the WHO functional classification, 28 cases (91%) were classified as either class III or IV, and 3 cases (9%) were classified as class II. Two of these 3 patients had a history of sibling death, and the third had repeated syncope on exertion despite the long-term administration of medication, including the maximum dose of beraprost sodium. Sildenafil treatment was started in 16 patients (age range 1.0–4.4 years) at an average of 2.7±1.2 years after beginning IV epoprostenol, comprising 9 patients in the early group and 7 patients in the late group.

Outcome After Epoprostenol Therapy

Four patients died soon after starting treatment with IV epoprostenol (range 3–12 days after beginning therapy). Causes of death included a pulmonary hypertension crisis triggered by menstruation, anesthesia during insertion of a central venous catheter, and influenza infection. The remaining 27 patients were discharged from 8 to 198 days (median 39 days) after starting IV epoprostenol therapy. The average length of follow-up observation after the start of IV epoprostenol was 3.4 years (range 1.2–6.1 years), and 4 patients died as a result of heart failure or rapid exacerbation after developing hemoptysis at an average of 760±214 days. One patient underwent a living donor lobar lung transplantation on day 737. Of the remaining 22 patients, 18 improved to functional class II, and 4 remained in functional class III. Among the 27 patients who were discharged from hospital after commencing IV epoprostenol therapy, the event-free rate from death or lung transplantation after 1 year, 2 years and 3 years was 100%, 96.3%, and 79.4%, respectively, from the start of IV epoprostenol therapy (Fig 1).
Dosage of Epoprostenol

The average dose of epoprostenol at 3 months, 1 year, 2 years, and 3 years after the start of IV epoprostenol therapy was 5.8±0.9, 15.7±3.1, 22.0±9.0 and 24.7±6.7 ng·kg⁻¹·min⁻¹, respectively. Hence, on average, the dose of epoprostenol was kept constant from 2.0 years after the start of treatment. The epoprostenol dosage in the late group, to which sildenafil was added earlier, tended to be lower than that of the early group (Fig 2).

Plasma BNP Levels

Plasma BNP at 3 months, 1 year, and 2 years after the start of IV epoprostenol therapy was 187.0±221.4, 86.6±133.9 and 85.3±206.1 pg/ml, respectively. Plasma BNP normalized (ie, <20 pg/ml) in 12 of 23 patients (52%) who were followed for at least 2 years (Fig 3). Three of 4 patients who showed markedly elevated plasma BNP levels (ie, >1,000 pg/ml) died within 2 weeks after the start of IV epoprostenol therapy. With a cut-off level of 400 pg/ml
BNP at the start of IV epoprostenol therapy, the survival rate for patients with levels above this cut-off was significantly lower than that of patients with levels below the cut-off (0.48±0.15 vs 0.83±0.10, respectively, p<0.05) (Fig 4). Moreover, 3 of 5 patients in whom levels of BNP remained high or increased died during the chronic phase.

**6MW Test**

Seven patients could not perform the 6-min walk test at the initiation of IV epoprostenol therapy because they were either infants (n=2) or critically ill (n=5). Shortness of breath during walking tended to improve after 1 or 2 weeks of treatment, and the 6MWD continued to increase at 3 months, 1 year and 2 years (387.7±105.2 m, 418±80.3 m and 445.1±109.1 m, respectively). Compared to baseline, the 6MWD improved significantly to 524.3±85.7 m at 3 years and 530.0±70.8 m at 4 years (Fig 5).

**Hemodynamic Parameters**

Fig 6 shows changes in each hemodynamic parameter after initiation of IV epoprostenol therapy. Although the mean PAP (mPAP) tended to decrease after IV epoprostenol therapy, it remained markedly elevated (>60 mmHg) even after 2 years of treatment in 13 (72%) of the 18 patients. The mPAP was lowest at 3 years (53.1±10.0 mmHg) after beginning IV epoprostenol therapy, and the magnitude of improvement was 37%. The CI increased significantly after 3 months and improved to a maximum of 58% in the fourth year. In 13 of the 23 patients, the CI improved to >3.0 L·min⁻¹·m⁻² in the first year and remained favorable from the second year. Rp, as well as the CI, decreased significantly 3 months after the start of IV epoprostenol therapy, reaching a maximum increase of 57% in the third year. These findings suggest that decreases in Rp were affected more by increases in the CI than by decreases in the mPAP. Two years after the start of IV epoprostenol therapy, the Rp/Rs ratio remained high at 0.94±0.32 and this ratio decreased to <0.6 in only 1 of 10 patients.

**Discussion**

**Initiation of Continuous IV Epoprostenol**

In general, epoprostenol is given to patients with severe IPAH who do not respond to conventional therapy and who are classed as either III or IV according to the WHO functional classification; most of our patients fit these criteria. At some institutions, IV epoprostenol is administered to children with IPAH who respond poorly to an acute vasodilator test. When taking into account the invasiveness of continuous infusion and the labor involved, it appears reasonable to use epoprostenol in patients classed as having class III disease or higher. However, it may be necessary in children to start epoprostenol earlier because the disorder can progress more rapidly than in adults. We obtained favorable results by starting epoprostenol early in familial cases and in patients with recurrent syncope, even if they were in functional class II, but long-term observation is needed to ascertain the validity of this approach. One study has reported that about one-third of patients who started IV epoprostenol died within 3 years, and prognosis was poor for patients who had a past history of right heart failure or...
who were older than 44 years. Nagaya and colleagues have reported that plasma BNP level is an independent prognostic indicator of survival in adult IPAH, and that the survival rate of patients with >180 pg/ml of plasma BNP was significantly lower. Our results in the present study confirmed that prognosis is extremely poor in patients with a BNP level over 400 pg/ml and in those who are classified as functional class IV. These findings suggest that plasma BNP reflects disease severity in IPAH, and that it might be useful in identifying patients who might benefit from IV epoprostenol. However, the extent to which plasma BNP level reflects the severity of IPAH in children may differ from that in adults because it has been reported that the normal range for plasma BNP in healthy children is higher than that of adults.

**Optimal Epoprostenol Dose**

In Western countries, epoprostenol therapy was first given in the early 1990s. The dose is increased incrementally to the maximum allowable dose to counter drug resistance. In adults, the dose is increased to 43 ng·kg⁻¹·min⁻¹ after 1 year and to 57 ng·kg⁻¹·min⁻¹ after 2 years; and in children, to 78 ng·kg⁻¹·min⁻¹ after 1 year and 116 ng·kg⁻¹·min⁻¹ after 2 years. Rich and McLaughlin have reported that the CI normalized without any further increase in mPAP by reducing the epoprostenol dose by an average of 38% in 12 patients who had high output cardiac failure due to high-dose epoprostenol. Based on this evidence, the epoprostenol dosage has not been increased markedly at other institutions since 1998. In more recent studies, it has been shown that the effect of a 22 ng·kg⁻¹·min⁻¹ dosage at the first year and a 27 ng·kg⁻¹·min⁻¹ dosage at the second year was equivalent to previous results. Furthermore, sildenafil and prostacyclin have been shown to exhibit synergistic effects, and the present study supports the possibility that the additional therapy of sildenafil with epoprostenol could reduce the maintenance dose of epoprostenol. Because left ventricular dysfunction owing to marked enlargement of the right ventricle is often complicated in severe cases of IPAH, low-dose epoprostenol was introduced with concomitant use of catecholamines, and increases in dosage were made under careful observation.

**Long-Term Effects and Problems**

In adult IPAH patients, the survival rate at 1, 2 and 3 years after the start of IV epoprostenol therapy was 85–87%, 70–76% and 63%, respectively, and improvements in motor function and hemodynamics are seen in the first 12–18 months. The 3-year survival rate in the present study of pediatric cases was approximately 80%, and all school-aged children were able to return to school. The outcomes for chronic-phase childhood IPAH were comparable with those of adults, thus supporting the validity of the basic therapeutic approach at our institution. However, it has been reported that after 5 years of commencing epoprostenol therapy, the number of death and lung transplantations following epoprostenol therapy increased. One of the problems concerning epoprostenol therapy during the chronic phase is that the decrease in PAP is not proportional to the increase in the CI. In the present study, the epoprostenol dose was adjusted based on changes in the CI and Rp/Rs ratio during the chronic phase, and it was noted that even when the CI reached the target value, it was extremely rare for the Rp/Rs ratio to drop below 0.5. We hypothesize that because Rp does not substantially decrease then PAP does not decrease. It is possible that any decrease in Rp is counterbalanced by normalizing the CI due to the epoprostenol therapy. When the epoprostenol dosage was increased, the increase in pulmonary flow did not match the level of pulmonary arterial dilatation. Hence, it is difficult to know if pulmonary vessels were specifically targeted during the chronic phase. Because excessive doses of epoprostenol lead to high cardiac output, palpitations, malaise and tachycardia, once the CI normalizes, it is recommended that the epoprostenol dose be decreased or kept constant. However, disease progression and exacerbation cannot be ignored. In recent years, new drugs, such as sildenafil and bosentan (an endothelin receptor antagonist), whose mechanisms of action differ from those of epoprostenol, have been used clinically, and several studies have reported that concomitant administration of such drugs allowed the dosage of epoprostenol to be reduced or discontinued in selected patients.

We hesitated to increase the dosage of epoprostenol as a therapeutic strategy in patients who did not experience enough of a decrease in PAP even if the CI reached 3.5 L·min⁻¹·m⁻². Instead, we added sildenafil to obviate the need for an increase in epoprostenol dosage. It is believed that the prognosis for severe cases of IPAH that do not respond to available medical treatments is extremely poor, and that lung transplantation is an only therapeutic option. However, the system for pediatric transplantation in Japan lags behind that in Western countries and, although patients can be placed on a waiting list, organ donation by brain-dead patients younger than 15 years of age is prohibited by law. As a result, living donor lobar lung transplantation is one of the few therapeutic options available. One study has reported a relationship between prognosis and response at 3 months after commencement of IV epoprostenol therapy, and it is therefore necessary to obtain informed consent early to determine whether the ABO blood type of the child matches that of the parents.

**Study Limitations**

The present study was conducted to retrospectively review the results of IV epoprostenol treatment in children with IPAH at one Japanese hospital. Although some patients were diagnosed with IPAH at our institution and then monitored, most patients were referred to our institution to undergo continuous IV epoprostenol therapy. Therefore, there may have been some bias in subject selection. Furthermore, although our results show that favorable outcomes can be obtained with low doses of epoprostenol, the optimal dose of epoprostenol must be ascertained by a prospective study.

**Conclusions**

Continuous IV epoprostenol certainly improves survival and exercise tolerance in childhood IPAH. However, from our experience, we insist that the concomitant use of new drugs such as sildenafil might be superior to epoprostenol alone because the improvement in pulmonary hemodynamics during the remote phase is insufficient regardless of long-term epoprostenol treatment.

**References**


