diopathic pulmonary arterial hypertension (IPAH) is characterized by progressive elevation of pulmonary artery pressure (PAP) and pulmonary vascular resistance (PVR), which leads to right heart failure and death. Increased PVR is caused by pulmonary vasoconstriction, vascular remodeling, and thrombosis. A substantial number of molecules and cellular substrates have been implicated in the pathogenesis of IPAH, but impaired production of prostacyclin plays an important role in the mechanism underlying the onset of IPAH.

In 1995, intravenous epoprostenol (prostaglandin I2 or prostacyclin) was introduced as a treatment for IPAH. The median survival period was only 2.8 years, with a survival rate of 34% at 5 years before the availability of epoprostenol, and epoprostenol therapy has been shown to improve hemodynamics, exercise capacity, and long-term survival in patients with IPAH. The 5-year survival rate of patients receiving long-term epoprostenol therapy has been reported as 55%. Furthermore, long-term epoprostenol therapy (in the dose range of 21–40 ng·kg⁻¹·min⁻¹) reduced the mean PAP (mPAP) by 12% to 22% and reduced PVR by 32% to 53% compared with baseline values.

The dosage of epoprostenol is adjusted upward on the basis of symptoms of IPAH and side-effects of the drug. Because chronic overdose of epoprostenol could lead to a state of...
high cardiac output (CO). The appropriate dose range is thought to be 25–40 ng·kg⁻¹·min⁻¹ based on the results of previous study. However, the efficacy of treatment with epoprostenol doses greater than 40 ng·kg⁻¹·min⁻¹ has not been determined. Furthermore, treatment with epoprostenol doses less than 40 ng·kg⁻¹·min⁻¹ sometimes can not improve the hemodynamics in patients with severe IPAH. We have treated 14 patients with severe IPAH with high-dose epoprostenol monotherapy (>40 ng·kg⁻¹·min⁻¹) and in the present study, we evaluated the hemodynamic changes induced by this treatment.

Methods

Patient Selection
The patient population studied comprised 16 consecutive patients (5 men, 11 women; mean age, 29±10 years) admitted to National Hospital Organization Okayama Medical Center and Okayama University Hospital, Okayama, Japan between May 1999 and January 2010. We treated them with high-dose epoprostenol monotherapy (>40 ng·kg⁻¹·min⁻¹), without an endothelin receptor antagonist (bosentan) or phosphodiesterase type V inhibitor (sildenafil). None of the patients died, but 2 dropped out because we could not titrate up as needed to the highest effective dosage of epoprostenol as these patients had mental health issues. Therefore, we assessed 14 IPAH patients treated with high-dose epoprostenol monotherapy (5 men, 9 women; mean age, 28±10 years). The diagnosis of PAH was established by standard diagnostic criteria.

Informed consent was given by all patients and this observational study was approved by the institutional Review Board.

Protocol of Epoprostenol Therapy
We started epoprostenol monotherapy at a low dose (0.25–2.0 ng·kg⁻¹·min⁻¹) and increased it daily by 0.25–1.0 ng·kg⁻¹·min⁻¹. When the dose exceeded 5–10 ng·kg⁻¹·min⁻¹, we increased it weekly. Thereafter, we gradually increased the dose either weekly or monthly to the maximal tolerated dose based on clinical symptoms and side-effects in each case.

When the patient developed right heart failure, we increased the incremental pace of epoprostenol dosing together with treatment of right heart failure with cardiotonic drugs (dobutamine and dopamine). When the mixed venous oxygen saturation (SvO₂) was <60%, we started dobutamine infusion by 3 γ and if the right heart failure did not improve, we increased the dose of dobutamine up to 5 γ. When the SvO₂ was >60% and right heart failure had improved, we started to decrease the dobutamine infusion. When the systolic blood pressure (SBP) was <90 mmHg, we started to use a dopamine infusion by 3 γ. If the SBP could not be kept above 90 mmHg, we increased the dose of dopamine. When the SBP was >90 mmHg and right heart failure had improved, we started to decrease the dopamine infusion. We adjusted the dose to changes in body weight.

Study Assessments
Right-heart catheterization was performed before and during epoprostenol monotherapy. The mean duration of high-dose epoprostenol monotherapy was 1,355±627 days (range, 582–2,410 days). Hemodynamics were assessed before the start of epoprostenol monotherapy and at either the completion of the treatment (patient no. 1–12, Table) or at the time of the most recent follow-up catheterization (patient no. 13 and 14, Table). Cardiopulmonary hemodynamic parameters (mPAP, mean right atrial pressure (mRAP), SvO₂, PVR, CO, cardiac index (CI), non-invasive SBP (NISBP), and heart rate) were measured in all patients. CO was measured by Fick. The WHO functional class, 6-min walking test and B-type natriuretic peptide (BNP) were assessed at the time of catheterization.

Statistical Analysis
All statistical analyses were performed with SPSS software version 11.0 (SPSS Inc, Chicago, IL, USA). Differences within groups before and after high-dose epoprostenol therapy were analyzed using a paired t-test. A value of P<0.05 was considered statistically significant.
Baseline Characteristics

The clinical characteristics of the patients before the start of epoprostenol therapy are shown in Table. All patients were diagnosed with IPAH: 8 patients were classified as being in WHO functional class III and 6 were in class IV. The mean serum BNP level was 278±205 pg/ml and the mean distance achieved in the 6-min walking test was 176±166 m. Baseline hemodynamics were mPAP of 66±16 mmHg (Figure 1A), PVR of 21.6±8.3 Wood units (Figure 1B), and CI of 1.9±0.5 L·min⁻¹·m⁻² (Figure 1C).

Dosing of Epoprostenol

We evaluated hemodynamics in the 14 IPAH patients who received high-dose epoprostenol monotherapy according to our protocol. The dosing of epoprostenol in all patients is shown in Figure 2. The minimal initial dosage of epoprostenol was 0.25 ng·kg⁻¹·min⁻¹ (patient no. 8) and the maximal initial dosage was 2.0 ng·kg⁻¹·min⁻¹ (patient no. 1). The mean dosages of epoprostenol were 15±9 ng·kg⁻¹·min⁻¹ at discharge and 107±40 ng·kg⁻¹·min⁻¹ at final evaluation (range, 54–190 ng·kg⁻¹·min⁻¹) (Table). We stopped increasing the dosage of epoprostenol in 2 patients (patient no. 2 and 3) because sufficient reductions of mPAP and PVR were achieved.

The patients’ characteristics at final evaluation are shown in Table. High-dose epoprostenol monotherapy was terminated because of the addition of bosentan (8 patients), addition of sildenafil (3 patients), transition from epoprostenol to treprostinil (1 patient) and cadaveric lung transplantation (1 patient). Treatment with high-dose epoprostenol monotherapy has been continued in 1 patient (patient no. 14). The WHO functional class at final evaluation improved compared with that before the start of epoprostenol therapy. The serum BNP levels were significantly decreased (Figure 3A) and the distance attained in the 6-min walking test was significantly increased with the increased epoprostenol dose (Figure 3B).

Hemodynamic Measurements

The hemodynamic measurements are showed in Figure 1. Significant decreases from baseline values were seen in mPAP (from 66±16 to 47±12 mmHg, P<0.001, Figure 1A) and PVR (from 21.6±8.3 to 6.9±2.9 Wood units, P<0.001, Figure 1B). Significant increases from baseline values were seen in CO (from 2.9±0.7 to 5.3±1.6 L/min, P<0.001), CI (from 1.9±0.5 to 3.6±0.8 L·min⁻¹·m⁻², P<0.001, Figure 1C) and SvO₂ (from 64.3±10.4 to 76.6±4.6%, P<0.05, Figure 1D). Compared with the baseline state, the patients had reductions in mPAP of 30% and PVR of 68%, and a significant increase in CI of 89%. The of mRAP value was not significantly different from that before the start of epoprostenol therapy (from 6.6±5.9 to 7.7±3.5 mmHg).

Side-Effects of High-Dose Epoprostenol Monotherapy

There were no deaths during the treatment of high-dose epoprostenol. All patients experienced jaw pain, leg pain, headache, flushing, skin eruptions, nausea, and diarrhea after the start of epoprostenol therapy, but they were able to tolerate these with supportive care. We used an analgesic drug for the jaw pain, leg pain and headache, an anti-diarrheal, and an antiemetic, plus topical cream for the eruptions. Just after epoprostenol therapy was started, the NISBP was decreased compared with the baseline value (from 112±18.3 to 91±18.3 mmHg, P<0.05), but it increased from 91±18.3 to 99±9.3 mmHg at hospital discharge (P<0.05). NISBP in the final evaluation was not significantly different from that before the start of epoprostenol therapy (from 112±18.3 to 101±11.4 mmHg). During the high-dose epoprostenol treatment, none of the patients had hepatic or renal dysfunction caused by epoprostenol itself. The platelet count fell significantly at

Results

Baseline Characteristics
High-Dose PGI2 Therapy in IPAH

the final evaluation compared with the start of epoprostenol therapy (from 18.8±4.4×10^4 to 11.7±5.8×10^4/μl, P<0.05) (Figure 3C). Of the 14 patients, 12 had thrombocytopenia (<15.0×10^4/μl). The platelet count fell below 5.0×10^4/μl in 2 patients (patient no. 9 and 10), who both had alveolar hemorrhage at the time. We did not decrease the dosage of epoprostenol. One patient was cured by platelet transfusion and the other by hemostatic agent. Although most of the patients experienced catheter-related infections, the catheter-related infection rate decreased after the introduction of a closed hub system.

Discussion

The results of the present study provide new insights into the effectiveness of epoprostenol therapy as a treatment strategy for IPAH. High-dose epoprostenol therapy resulted in marked reductions in mPAP and PVR in this group of patients with IPAH.

Epoprostenol has several pharmacologic properties. Firstly, it is a potent, short-acting vasodilator of pulmonary arteries, but it was shown to improve the hemodynamics and long-term survival of PAH patients, without a vasodilatory response to acute infusion.17,18 These findings indicated that epoprostenol therapy had effects other than pulmonary artery vasodilatation. In previous studies, long-term epoprostenol therapy reduced mPAP by 12% to 22% and reduced PVR by 32% to 53% compared with baseline values.7,9 In the present study, those reductions were greater: 30% and 68%, respectively, compared with baseline values. The mean dosage of epoprostenol in the present study (107±40 ng·kg\(^{-1}\)·min\(^{-1}\)) was higher than that in the previous studies (in the range of 21–40 ng·kg\(^{-1}\)·min\(^{-1}\)). High-dose epoprostenol therapy dramatically reduced mPAP and PVR values.

Sakuma et al reported that a cotton-grass-like stain appeared on the pulmonary angiograms of patients with IPAH whose PVR was reduced by chronic epoprostenol therapy.19 This angiographic change indicates that epoprostenol can alter the properties of pulmonary arteries. Wharton et al reported that prostacyclin analogs inhibit proliferation of human pulmonary artery smooth muscle cells.20 Therefore, high-dose epoprostenol therapy can reverse pulmonary artery remodeling.

In the present study, high-dose epoprostenol monotherapy proved to be effective in patients with IPAH. However, we ceased high-dose epoprostenol monotherapy by adding bosentan or sildenafil for some patients in order to evaluate the synergistic effects of their medications and to suppress side-effects, such as flushing and leg pain. We previously reported that the addition of bosentan to the treatment of patients whose hemodynamics had been markedly improved by high-dose epoprostenol therapy can generate synergistic effects.21 We changed epoprostenol to treprostinil in 1 patient (patient no. 12) because of the marked improvements in hemodynamics (mPAP: from 68 to 35 mmHg, PVR: 29.7 to 4.7 Wood units) achieved with an intermediate dosage of epoprostenol (54 ng·kg\(^{-1}\)·min\(^{-1}\)). One patient hoped to receive a cadaveric lung transplantation even though remarkable improvements in the hemodynamics (mPAP: from 68 to 35 mmHg, PVR: 29.7 to 4.7 Wood units) had been achieved.

Two patients dropped out of the study because we could not titrate up as needed to the highest effective dosage of epoprostenol. In 1 of them, we were able to gradually increase the dosage of epoprostenol up to 59.6 ng·kg\(^{-1}\)·min\(^{-1}\) over a period of 2 years. Although a higher dosage of epoprostenol

Figure 2. Epoprostenol dosing history of all patients.
Figure 3. Relationship between epoprostenol dose and (A) B-type natriuretic peptide, (B) 6-min walking distance, and (C) platelet count.
was required, we had to use a fixed dosage because the patient refused dose titration. For the other patient, we were able to gradually increase the dosage of epoprostenol up to 92.9 ng kg$^{-1}$ min$^{-1}$ over a period of 2 years, but we had to decrease the dosage because the patient developed panic disorder. As a result, we added bosentan to the treatment regimen of these patients because of progression of PAH. The success of high-dose epoprostenol therapy requires the understanding and agreement of the patient of the protocol of high-dose epoprostenol therapy.

High-dose epoprostenol therapy was attempted in patients with IPAH in a previous study. Those patients were treated with 98±61 ng kg$^{-1}$ min$^{-1}$ and showed reduction in mPAP by 25% and PVR by 71% compared with baseline. However, dose reduction of epoprostenol was required because of the occurrence of high CO (from 4.4±0.3 to 10.1±2.3 L/min). None of the present patients developed high CO, although it was elevated from 2.9±0.7 to 5.3±1.6 L/min. The mean incremental duration of epoprostenol in the present study (45±21 months) was longer than in the previous study (39±20 months). Furthermore, we followed all patients every month in the outpatient clinic and adjusted the dosage of epoprostenol carefully in individual cases. When CO was elevated, we slowed down the incremental pace of epoprostenol dosage. We increased the dosage of epoprostenol gradually by careful titration over a long period. This strategy might have prevented the occurrence of an undesirable state of high CO, which can lead to dose reduction or termination of therapy.

Epoprostenol is an expensive drug, so high-dose epoprostenol therapy costs a lot. Although the addition of bosentan can decrease the dosage of epoprostenol, the dosage of epoprostenol was still over 40 ng kg$^{-1}$ min$^{-1}$. We consider that treatment with epoprostenol >40 ng kg$^{-1}$ min$^{-1}$ is required for improvement of PAH. Systemic administration requires high dosage of epoprostenol for the improvement of PAH. In the future, local delivery of epoprostenol might reduce both the dosage of epoprostenol and its cost.

Study Limitations

The patient population was relatively small and almost all patients had been treated with bosentan or sildenafil at first. Since those drugs became available, we have been treating IPAH patients with a combination of epoprostenol and bosentan or sildenafil from the initial period because the combination therapy can generate synergistic effects. Therefore, we could not increase the number of patients treated with epoprostenol monotherapy. We have treated patients with IPAH by the strategy of sufficient reduction in PVR in individual cases. High dosage of epoprostenol is required to achieve sufficient reduction of PVR. Therefore, we could not have a control group of low-dose or recommended-dose epoprostenol therapy. However, the marked hemodynamic improvements observed in the study would indicate the effectiveness of high-dose epoprostenol therapy.

Conclusion

We demonstrated that high-dose epoprostenol therapy caused marked hemodynamic improvements in patients with IPAH. High-dose epoprostenol therapy could be a novel treatment strategy.