INTERNAL MEDICINE

□ CASE REPORT □

Marked Improvement with Sildenafil in a Patient with Idiopathic Pulmonary Arterial Hypertension Unresponsive to Beraprost and Sarpogrelate

Hiroaki Kawano, Hideyori Sengyoku, Osami Satoh,
Shigetoshi Urabe, Yuji Koide and Katsusuke Yano

Abstract

We report a 16-year-old man with severe heart failure due to idiopathic pulmonary arterial hypertension (IPAH). The patient was initially treated with a combination of beraprost, a prostacyclin analog, and sarpogrelate, a serotonin receptor inhibitor. However, he was unresponsive to the treatment. We then changed the treatment to sildenafil, and his condition dramatically improved. Sildenafil has an immediate pulmonary vasodilator effect in patients already receiving vasodilators for IPAH.

Key words: beraprost, saprogrelate, sildenafil, pulmonary hypertension, treatment

(DOI: 10.2169/internaimedicine.46.1848)

Introduction

Idiopathic pulmonary arterial hypertension (IPAH) is a rare but life-threatening disease, characterized by progressive pulmonary hypertension, that ultimately leads to right ventricular failure and death (1). Traditionally, treatment is based on the administration of vasodilators, particularly calcium channel blockers. However, calcium channel blockers are effective in only a limited number of patients (2).

Previous reports have shown that beraprost, a prostacyclin analog, reduces pulmonary vascular resistance and improves exercise capacity and ventilatory efficiency in patients with IPAH (3-6). Sarpogrelate, a serotonin receptor antagonist also attenuates the development of pulmonary artery hypertension in both clinical and experimental settings (7-10). However, there is no report on the combination therapy of beraprost and sarpogrelate for IPAH patients.

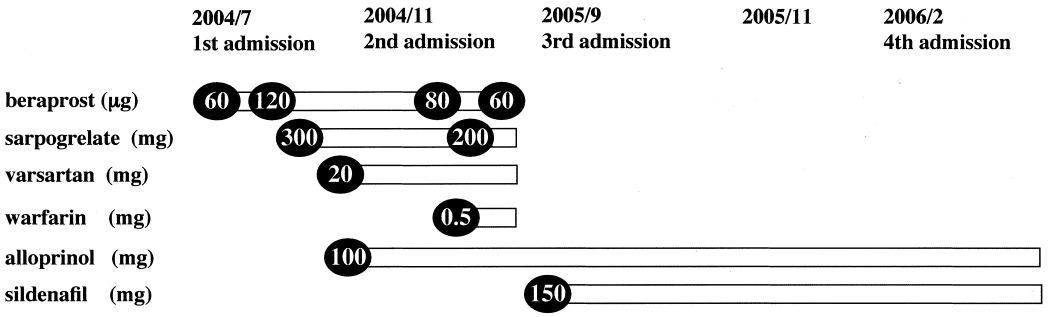
Recently, sildenafil, a phosphodiesterase inhibitor (PDE)-5 approved for the treatment of erectile dysfunction, has been investigated for the treatment of IPAH (11-13). We report here a patient with IPAH who improved with sildenafil but not with the combination therapy of beraprost and sarpogrelate.

Case Report

A 16-year-old man was admitted to our hospital in mid July 2004 because of dyspnea on exertion. His ECG on admission showed right ventricular hypertrophy. Right ventricular catheterization revealed pulmonary artery pressure (PAP) of 90/50 (mean 63) mmHg and a normal pulmonary capillary wedge pressure (PCWP) of 9 mmHg. Cardiac index (CI) was 1.57 l/min m^2 (Fig. 1). We also conducted examinations that included blood tests, pulmonary function tests, perfusion lung scintigraphy, echocardiography, magnetic resonance imaging, and computed tomography to rule out collagen vascular disease, pulmonary disease, pulmonary thromboembolism, congenital heart disease, and other systemic heart diseases that induce pulmonary hypertension. A diagnosis of IPAH was made and he was started on amlodipine 5 mg, a calcium channel blocker, once daily, but no improvement was noted. After the patient refused our recommendation of continuous intravenous (IV) infusion of epoprostenol, treatment with beraprost 20 μg tid (60 μg/day) was subsequently started and its dose was increased to 40 μg tid (120 μg/day). When we confirmed that he experienced no side effects with beraprost, sarpogrelate 100 mg

Department of Cardiovascular Medicine, Course of Medical and Dental Science, Graduate School of Biomedical Science, Nagasaki University, Nagasaki
Received for publication April 6, 2006; Accepted for publication February 26, 2007
Correspondence to Dr. Hiroaki Kawano, hkawano@net.nagasaki-u.ac.jp

DOI: 10.2169/internaimedicine.46.1848



NYHA	II	III	III	II	II
6min.walk dist. (m)	200	-	160	420	460
RAP mean (mmHg)	9	17	-	12	7
PA (mmHg)	90/50(63)	85/48(60)	-	87/43(60)	85/46(61)
PVR (wood unit)	12.9	14.7	-	10.5	12.1
C.O. (l/min)	3.17	3.06	-	4.28	4.21
C.I. ($l/min/m^2$)	1.57	1.55	-	2.08	2.00
UA (mg/dl)	10.3	9.9	12.1	7.1	8.3
BNP (pg/ml)	279	752	1030	284	224

Figure 1. **Clinical course of the patient. 6 min. walk dist., 6-minute walking distance; RAP, right atrial pressure; PAP, pulmonary arterial pressure; PVR, pulmonary vascular resistance; C.O., cardiac output; C.I., cardiac index; UA, uric acid; BNP, brain natriuretic peptide.**

tid (300 mg/day) was added to the regimen, as an antiplatelet antagonist for prevention of thrombus in pulmonary vessels although it is not indicated for treatment of IPAH, because brain natriuretic peptide (BNP) increased (410 pg/ml) after admission. Sildenafil is also a treatment option, but it is not readily given as it is also not indicated for treatment of IPAH in Japan. We then compared the acute lowering effects on the PAP of combined beraprost 40 μg and sarpogrelate 100 μg administration with that of sildenafil 50 μg alone. The patient was monitored for 3 hours post administration. We elected to continue with beraprost 120 μg/day and sarpogrelate 300 mg/day because there was no difference in the change in mean PAP and pulmonary vascular resistance (PVR) between the combined regimen with that of sildenafil alone (mean PAP, -7 mmHg vs -6 mmHg; PVR, -1.2 wood unit vs -1.3 wood unit). After discharge, symptoms persisted and valsartan (20 mg once a day) was added because BNP increased (752 pg/ml) and chest X-ray showed progression of cardiomegaly. We also added allopurinol because of continuous hyperuricemia.

After 3 months of beraprost and sarpogrelate treatment that began in late October 2004, the patient was re-admitted for evaluation. PAP was unchanged (85/48 (mean 60) mmHg), and there was no improvement in CI (1.55 l/min m^2) (Fig. 1). We again recommended epoprostenol treatment, but the patient refused the therapy. Warfarin (0.5 mg once a day) was added and he was subsequently discharged. However, his condition gradually deteriorated. In June 2005, the patient developed hemoptysis and warfarin was immediately discontinued. The doses of beraprost and sarpogrelate were gradually reduced because of nausea and headache. Finally, in late September 2005, he was admitted for the third time because of dyspnea due to an inability to take his medication.

On examination, the patient's height was 173 cm, and weight was 99.8 kg which had increased from 92 kg one years previously. Blood pressure was 100/54, pulse rate 98/min, and respiration rate was 24/min. The jugular vein was visible 7 cm above Louis' angle. There was splitting of the second heart sound (S2) with accentuated pulmonary component. The lungs were clear. The liver and spleen were not palpable. Edema was slightly present in both legs. His physical activity was NYHA III, and his 6-minute walking distance was 160 m. Laboratory examinations revealed a hematocrit of 58.3% and white blood cell count (WBC) of 7100/mm^3. Blood urea nitrogen was 11 mg/dl, serum creatinine 0.9 mg/dl, total protein 6.2 mg/dl, total bilirubin 2.3 mg/dl, aspartate aminotransferase 37 IU/l, alanine aminotransferase 34 IU/l, lactate dehydrogenase 319 IU/l, creatine kinase 92 IU/l, γ-glutamyltransferase 138 IU/l, glucose 93 mg/dl, total cholesterol 223 mg/dl, triglyceride 109 mg/dl, HDL-C 41 mg/dl, sodium 142 mEq/l, potassium 4.8 mEq/l, chloride 106 mEq/l, and C-reactive protein (CRP) 0.23 mg/dl. BNP was 1030 pg/ml. Arterial blood gas analysis showed pH 7.477, partial pressure of carbon dioxide (pCO_2) 29.9 Torr, partial pressure of oxygen (pO_2) 63.1 Torr, HCO_3 21.6 mmol/l, and base excess -0.4 mmol/l. The patient continued to refuse treatment with epoprostenol. We therefore decided to treat the patient with sildenafil, receiving approval from the Ethics Committee at our hospital and obtaining informed consent from the patient.

After starting sildenafil treatment, the patient's condition

DOI: 10.2169/internaimedicine.46.1848

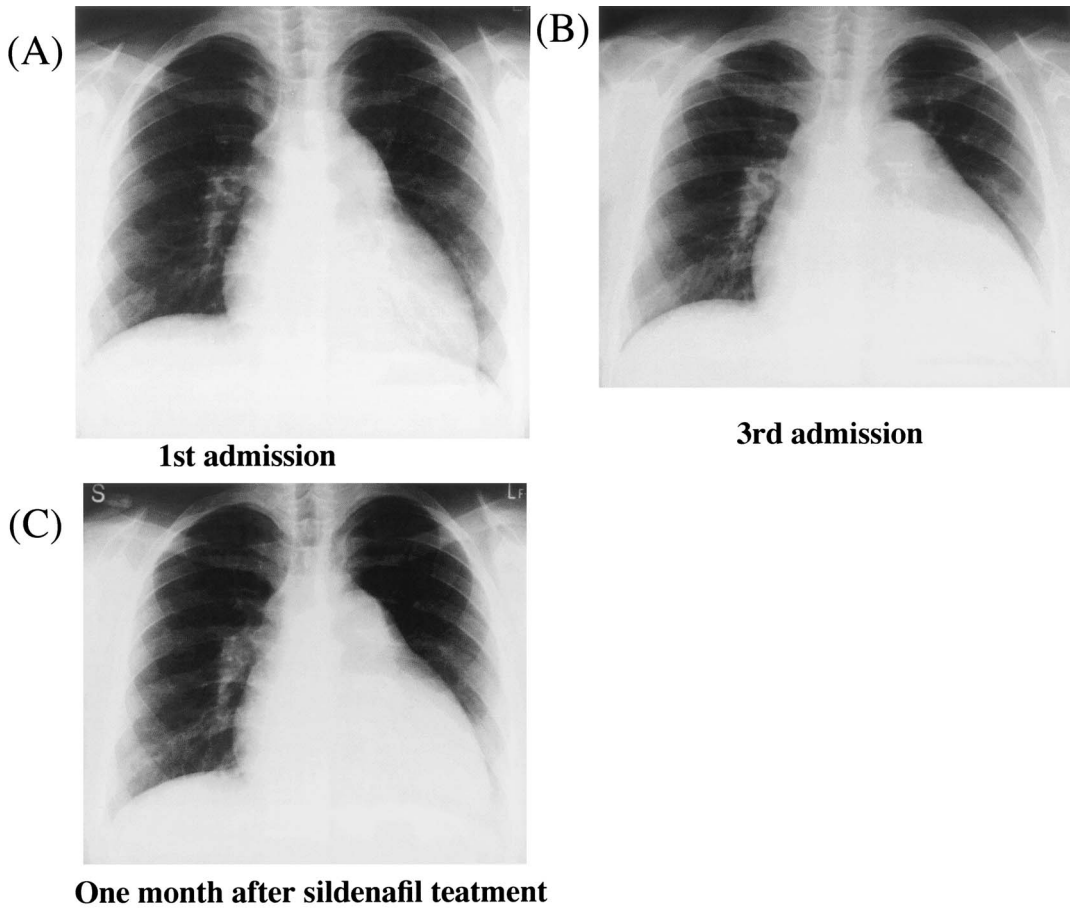


Figure 2. **Chest roentgenographic changes. The cardio-thoracic ratio (CTR) increased 3 months after the combination therapy of beraprost and saproglerate (B) compared to that on the first administration (A), but decreased after changing to sildenafil (C).**

dramatically improved, and he had no side effect from sildenafil. After 1 month of treatment, his 6-minute walking distance increased from 160 m to 420 m and his NYHA classification changed from III to II (Fig. 1). PVR, mean right atrial pressure, uric acid, and BNP were all decreased; CI also improved 1 month after switching to sildenafil, and these parameters did not change at 3 months after starting sildenafil (Fig. 1). Chest X-ray showed marked cardiomegaly and decreased CTR (Fig. 2). ECG showed right ventricular (RV) hypertrophy and decreased right axis deviation (Fig. 3). Echocardiography showed decreased RV pressure overload and decrease of mild pericardial effusion (Fig. 4).

Discussion

In the present case, we initially treated the patient with a combination of two different kinds of drugs, i.e., beraprost, a prostacyclin analog, and sarpogrelate, a serotonin receptor inhibitor. However, he was unresponsive to the treatment. After we changed the treatment to sildenafil, his condition dramatically improved.

For patients unresponsive to an acute challenge with oral calcium channel blocker, epoprostenol, a form of intravenous prostacyclin (prostaglandin I_2), is considered the next therapeutic approach because it is currently the most effective treatment for IPAH. Continuous IV infusion of prostacyclin has proven beneficial effects on hemodynamics, exercise capacity, and survival in patients with IPAH (14-17).

However, continuous IV prostacyclin therapy is hampered by infections, tachyphylaxis, and systemic side effects due to the lack of pulmonary selectivity. Furthermore, the patient may also be reticent to undergo this invasive treatment. In Japan, aerosolized iloprost is not available for patients with IPAH. Thus, we selected oral medications for treatment in the present case.

Unlike epoprostenol, beraprost has a prolonged effect and can be taken orally. It produces potent vasodilatation and inhibits platelet aggregation similar to epoprostenol (18). Previous reports have shown that beraprost reduces PVR and improves exercise capacity and ventilatory efficiency in patients with IPAH (3-6). Beraprost alone was not sufficient to improve the present patient's condition. Bosentan, an endothelin 1-receptor antagonist, is available for treatment of IPAH in patients with symptoms of WHO class III or IV heart failure (19, 20). However, bosentan was not used in our hospital at that time. Sildenafil has been shown to have beneficial effects in patients with IPAH (11-13). However, it is not indicated for the treatment of IPAH in Japan. Serotonin (5-HT) released from blood platelets accelerates plate-

DOI: 10.2169/internaimedicine.46.1848

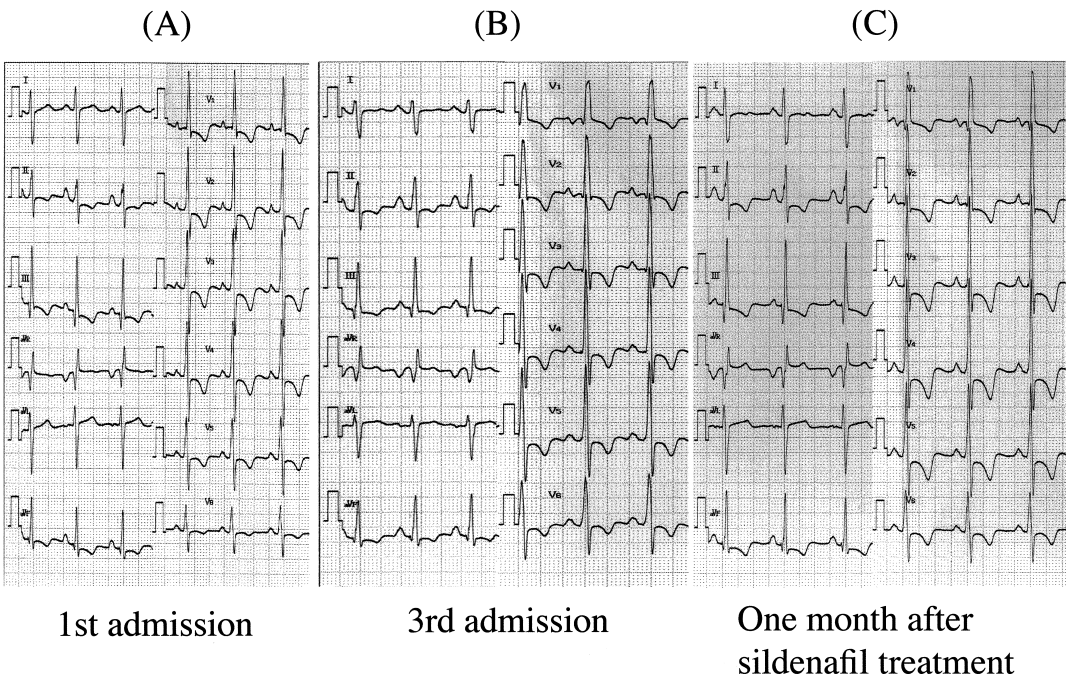


Figure 3. **Electrocardiographic changes. Right axis deviation progressed on the third admission (B) compared to the first admission (A); after 1-month of sildenafil administration, it decreased (C).**

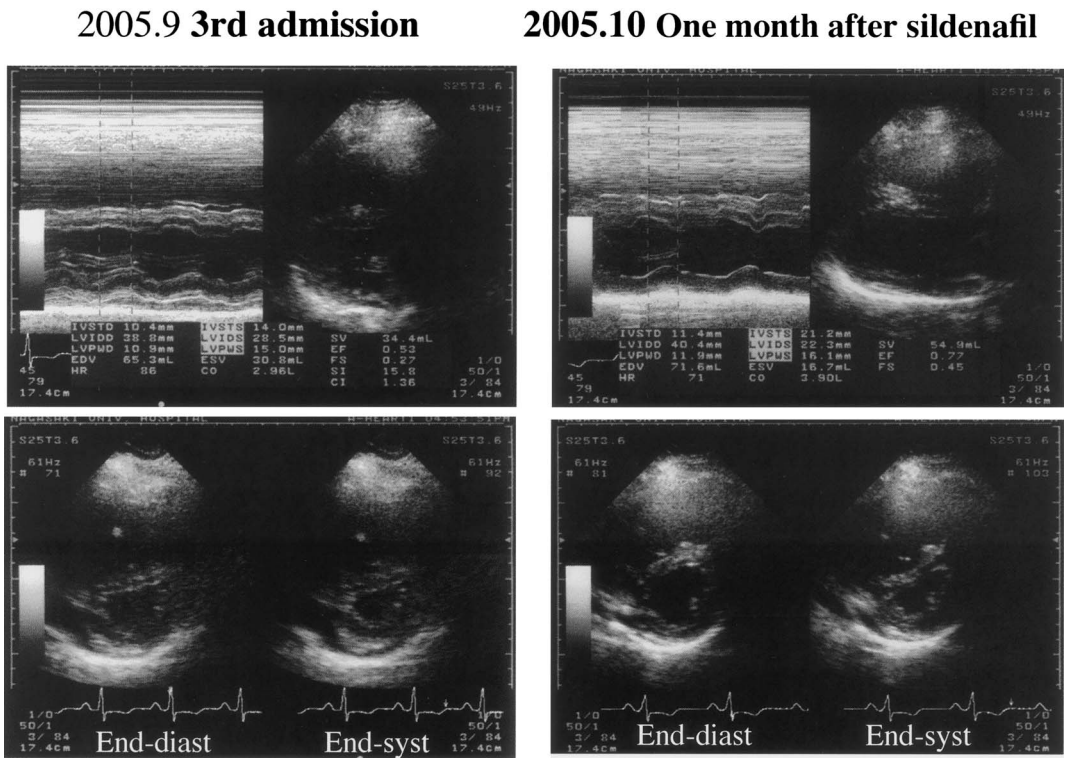


Figure 4. **Echocardiographic changes. Before sildenafil administration, the interventricular septum (IVS) was flattened and mil pericardial effusion was seen at the end-diastolic and the end-systolic phases (A). At 1 month after the treatment, pericardial effusion disappeared and the flattening of IVS also disappeared at the end-diastolic phase (B). End-diast, end-diastolic phase; End-syst, end-systolic phase.**

let coagulation and is one of the most potent vasoconstrictors of pulmonary arteries (21), and Kato et al (7) reported that 5-HT2 receptor antagonist attenuated the development of PAH. In the present case, we compared the acute lowering effects on the PAP of a combined beraprost and sarpogrelate regimen with that of sildenafil alone. Because there was no difference between these two treatments, we decided to start combination therapy with beraprost and sar-

pogrelate. However, the combination of these drugs was not effective for the long-term treatment of the present patient, and finally he was not able to continue to have these drugs because of the side effects, i.e., nausea and headache. However, sildenafil improved his condition in 1 month and continued this effect for 3 months. We have no data to explain this result, but the chronic effect of sildenafil may be significantly more efficacious than the combination of beraprost and sarpogrelate. Apart from pulmonary vasodilatation, other factors, such as anti-proliferative effects of sildenafil on pulmonary arterial cells, may be related to the chronic effect of sildenafil (22). Another possible explanation is that the poor compliance of the combination of beraprost and sarpogrelate because of the side effect may cause the unresponsiveness to the treatment.

Sildenafil is an effective and well-tolerated agent for management of IPAH. However, there are some controversial issues, such as maintenance dose, monotherapy, or in combination with other vasodilator agents. In the present case, sildenafil was started at 50 mg bid (100 mg/day) and increased to 50 mg tid (150 mg/day) because the patient's body weight was 100 kg. In previous studies, sildenafil was administered orally at a dose ranging from 75 mg to 300 mg (23). Recently, Galie et al (24) demonstrated that sildenafil 20, 40, or 80 mg tid improves exercise capacity, WHO functional class, and hemodynamics in patients with PAH, and that there was no evidence of a dose-response relationship associated with exercise capacity. However, in their study, mean body weight was 71 kg. Thus, the optimal dose of sildenafil for IPAH, especially in obese patients is unknown.

At present, it has not been determined whether treatment with sildenafil or bosentan is superior. To date, only one study has compared the effects of sildenafil and bosentan, demonstrating a superior quality of life score and 6-minute walking test improvement with sildenafil, although there was no difference in improved cardiac function (25).

Previous studies have also discussed combination therapy for IPAH. Combination therapy with sildenafil and beraprost showed additive effects to increase plasma cAMP and cGMP levels in rats (26). Sildenafil therapy may be beneficial to patients with PAH receiving long-term infusion of epoprostenol (27). In Japan, Kataoka et al (28, 29) reported that additional sildenafil improves IPAH in patients who showed a poor response to epoprostenol. They also suggested that physicians consider combination therapy of epoprostenol and sildenafil as a new medical treatment before recommending possible lung transplantation for patients with IPAH refractory to epoprostenol (29). Moreover, Hoeper et al (30) suggested that combining bosentan and sildenafil might be safe and effective in patients with IPAH.

In conclusion, sildenafil has an immediate pulmonary vasodilator effect in patients already receiving vasodilators for IPAH. Further studies are required to establish long-term safety, efficacy, and optimal maintenance dose of sildenafil for Japanese patients.

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