Oral Sildenafil Improves Primary Pulmonary Hypertension Refractory to Epoprostenol

Masaharu Kataoka, MD; Toru Satoh, MD; Tomohiro Manabe, MD; Toshihisa Anzai, MD; Tsutomu Yoshikawa, MD; Hideo Mitamura, MD; Satoshi Ogawa, MD

Background  Epoprostenol (prostaglandin I2) has become recognized as a therapeutic breakthrough that can improve hemodynamics and survival in patients with primary pulmonary hypertension (PPH). However, a significant number of patients have PPH that is refractory to epoprostenol, and lung transplantation has been the only remaining treatment option.

Methods and Results  The study subjects included 20 consecutive patients with PPH (mean pulmonary arterial pressure: 65±15 mmHg) who had received epoprostenol for more than 12 months. The patients were divided into 2 groups; responders and non-responders. In the non-responders, New York Heart Association (NYHA) functional class did not improve and mean right atrial pressure (mRA) increased to 8 mmHg or more, and additional sildenafil, a phosphodiesterase-5 inhibitor, was started. Six patients were included in the non-responders, whose mRA was 9±5 mmHg before and significantly increased to 13±3 mmHg after epoprostenol administration (p<0.05). One patient died and the other 5 patients received oral sildenafil. The mRA of 12±4 mmHg (value before sildenafil) improved to 8±5 mmHg after sildenafil administration. Three patients were classified in the NYHA functional class 4 and improved to class 3, and 2 patients were in class 3 and remained in the same class after the addition of sildenafil.

Conclusions  In patients with severe PPH refractory to epoprostenol treatment, additional oral sildenafil can improve pulmonary hemodynamics and symptoms. The combination therapy of epoprostenol and sildenafil is a new medical treatment to attempt before progressing to lung transplantation for patients with PPH refractory to epoprostenol.

Key Words: cAMP; cGMP; Epoprostenol; Primary pulmonary hypertension; Sildenafil

Continuous infusion of epoprostenol has increased the 5-year survival in primary pulmonary hypertension (PPH) from 34% to 60%, with improvement of exercise intolerance and quality of life.1,2 When epoprostenol is not sufficiently effective clinically, lung transplantation has been the remaining treatment option. However, there are few chances of lung transplantation because of the scarcity of donors.3 Thus, new medical treatment, that might be an actual alternative to lung transplantation, is needed.

Sildenafil, an inhibitor of phosphodiesterase (PDE)-5, was found to markedly dilate pulmonary arteries as well as the penile corpora cavernosa.4 Sildenafil ameliorates pulmonary hypertension at least in part through inhibition of the breakdown of cyclic guanosine 3',5'-monophosphate (cGMP) and an increment of nitric oxide (NO), leading to dilatation of pulmonary arteries.5-9

It has been demonstrated that both epoprostenol and sildenafil are effective for pulmonary arterial hypertension. However, it is not known whether additional sildenafil could achieve improvement if administered to patients who showed a poor response to epoprostenol.

The purpose of the present study was to investigate whether sildenafil has a synergistic effect with epoprostenol even in patients with PPH refractory to epoprostenol.

Methods  Epoprostenol Administration

We studied 20 consecutive patients with PPH who had received continuous infusion of epoprostenol for more than 12 months (age 36±16 years; 9 male/11 female; New York Heart Association (NYHA) class 3 or 4). Patients were diagnosed with PPH after ruling out collagen vascular disease, pulmonary disease, pulmonary thromboembolism, left heart abnormality and other systemic diseases by blood tests, pulmonary function tests, perfusion lung scintigraphy and echocardiography, respectively. Patients underwent right heart catheterization, including the measurement of pulmonary vascular resistance (PVR), mean pulmonary arterial pressure (mPA) and mean right atrial pressure (mRA). Patients whose functional class deteriorated were divided into 2 groups; responders and non-responders. In the non-responders, New York Heart Association (NYHA) class 3 or 4 in NYHA class 3 or 4). Patients were diagnosed with PPH after ruling out collagen vascular disease, pulmonary disease, pulmonary thromboembolism, left heart abnormality and other systemic diseases by blood tests, pulmonary function tests, perfusion lung scintigraphy and echocardiography, respectively. Patients underwent right heart catheterization, including the measurement of pulmonary vascular resistance (PVR), mean pulmonary arterial pressure (mPA) and mean right atrial pressure (mRA) before and after epoprostenol administration and after 3 months' sildenafil treatment. Epoprostenol was started at 1 ng/min per kg and increased every 4 days for 2 months, then increased weekly for another 2 months, and increased every 2 weeks for the next 2 months, leading to a dose of approximately 30 ng/min per kg at 6 months. We then investigated the clinical parameters and set the dose according to the improvement. We evaluated the hemodynamics and symptoms 20.5±7.5 months after the start of epoprostenol administration. Patients whose functional class deteriorated and mRA worsened to 8 mmHg or more, and who needed to be admitted for heart failure after
epoprostenol infusion, were defined as non-responders, and the other patients were defined as responders. In the non-responders, the dose of epoprostenol was fixed and additional administration of sildenafil was started. The mRA of the non-responders increased in spite of administration of a significant amount of diuretics.

**Sildenafil Administration**

Sildenafil was started at: (i) 3.125 mg tid if the patient had right heart failure and low blood pressure (systolic blood pressure <100 mmHg); (ii) 6.25 mg tid if the patient had no right heart failure but had low blood pressure; or (iii) 12.5 mg tid if the patient had neither right heart failure nor low blood pressure (systolic blood pressure >100 mmHg).

After that, the dose was increased every 1 to 2 weeks according to the schedule described above until the target dose of 25 mg tid. Right heart catheterization was then performed 3 months after the start of sildenafil administration. Sildenafil is not covered by health insurance. We received approval of the ethical committee of our hospital (No. 14–28) and obtained informed consent from the patients before starting sildenafil.

**Results**

**Overall Change**

In the 20 study patients, mPA was 65±15 mmHg (mean ± SD) at baseline and decreased to 50±13 mmHg (p<0.0001), PVR decreased from 28±12 to 15±8 wood units (p=0.0001), and mRA decreased from 11±6 to 8±5 mmHg (p=0.085) (Tables 1,2) after approximately 18 months of epoprostenol therapy.

**Different Changes in 2 Groups**

Six patients were included in the non-responders. The change in mRA is shown in Fig 1. In the non-responders, mRA was 9±5 mmHg at baseline and significantly increased to 13±3 mmHg after epoprostenol (p=0.045). The change in mPA is shown in Fig 2. It decreased in all of the responders. However, in the non-responders, mPA did not decrease in spite of epoprostenol infusion. The change in PVR is shown in Fig 3. Pulmonary vascular resistance decreased in both the responders and non-responders.

**Effect of Sildenafil in Non-Responders**

One patient died in the non-responder group before sildenafil was administrated, therefore additional oral sildenafil was started in the other 5 patients. Although NYHA classification was class 4 in 3 patients and class 3 in 2 patients before sildenafil therapy, the former all improved to class 3 and the latter remained in the same class after the addition of sildenafil. Right heart catheterization was conducted in 3 of these 5 patients. The mRA decreased in 2 patients, and rapid deterioration was halted and the condition stabilized in another patient (Fig 4a). The value before sildenafil was 12±4 mmHg, which improved to 8±5 mmHg.
Improvement of PPH by Sildenafil

**Fig 1.** Change in mean right atrial pressure (mRA) after epoprostenol infusion. (a) Responders (n=14), (b) non-responders (n=6). In the responders, a significant decrease in mRA is recognized (p=0.005). However, in the non-responders, a significant increase in mRA is shown (p=0.045). Data are mean±SD.

**Fig 2.** Change in mean pulmonary arterial pressure (mPA) after epoprostenol infusion. (a) Responders (n=14), (b) non-responders (n=6). In the responders, a significant decrease in mPA is recognized (p<0.0001). However, in the non-responders, the change in mPA is not significant (NS). Data are mean±SD.

**Fig 3.** Change in pulmonary vascular resistance (PVR) after epoprostenol infusion. (a) Responders (n=14), (b) non-responders (n=6). In the responders, a significant decrease in PVR is recognized (p<0.0001). However, in the non-responders, the change in PVR is not significant (NS). Data are mean±SD.
of 8 mmHg or more as survival factors. Some researchers adopted the NYHA functional class and right atrial pressure unresponsiveness is defined is a difficult problem. We prostenol, although many obtain great improvement. How sion. However, some patients are unresponsive to epoprostenol, but rather worsened. After additional sildenafil, mRA decreased in 2 patients, and its rapid increase was halted and the condition stabilized in 1 patient. Mean pulmonary arterial pressure and PVR decreased in all patients after additional sildenafil. In 1 patient, mPA increased with epoprostenol but greatly decreased after addition of sildenafil. Pulmonary vascular resistance decreased further after the addition of sildenafil. Patients who died.

Discussion

The present report demonstrates that among 20 consecutive PPH patients who received epoprostenol for more than 18 months, 6 patients were unresponsive to long-term intravenous epoprostenol infusion, but showed an improvement in their clinical symptoms and hemodynamics with oral sildenafil for 3 months.

Even most of the non-responders to epoprostenol showed a reduction of PVR or mPA and improvement of pulmonary hypertension. However, they had to be admitted to hospital for treatment of heart failure with worsening of symptoms and an increase in right atrial pressure, in spite of administration of significant doses of diuretics. After the addition of sildenafil, their symptoms markedly improved, with a decrease in right atrial pressure. We consider that sildenafil is a promising drug for PPH patients whose condition is not improved by epoprostenol.

Poor Response to Epoprostenol

Presently, the most powerful and effective treatment is continuous infusion of epoprostenol (prostaglandin I2). It has been shown to prolong survival in patients unresponsive to conventional therapy and to improve hemodynamics and quality of life in patients with pulmonary arterial hypertension. However, some patients are unresponsive to epoprostenol, although many obtain great improvement. How unresponsiveness is defined is a difficult problem. We adopted the NYHA functional class and right atrial pressure of 8 mmHg or more as survival factors. Some researchers have put emphasis on exercise tolerance, functional class and right atrial pressure, while others adopted a history of right-sided heart failure, functional class and a fall in total pulmonary resistance of less than 30% as predictors of poor survival during epoprostenol therapy, suggesting that our criteria for unresponsiveness are reasonable.

One of our criteria for deterioration, mRA of 8 mmHg or more, was defined based on the following. Before this study, epoprostenol was introduced in 35 patients with pulmonary hypertension at our hospital. We evaluated the difference in hemodynamics between patients who died and those who survived. There were 9 deaths. Seven out of the 8 patients who died, excluding one with sudden death, had mRA of 8 mmHg or more. However, among the 26 patients who survived, 4 had mRA of 8 mmHg or more, and they were administered sildenafil with a subsequent improvement.

McLaughlin et al reported that the 2-year survival of PPH patients with epoprostenol was 76%. Sitbon et al reported that the 2-year survival was 70%. In the present study, epoprostenol was not effective in 30% of patients when the survival was determined at 21 months on average after the start of epoprostenol, showing almost the same ratio of ineffectiveness. Epoprostenol can dilate pulmonary arteries and reduce pulmonary arterial resistance, but if pulmonary arterial pressure is not sufficiently reduced, right ventricular afterload is not lessened, resulting in right heart failure.

Oral Sildenafil

Sildenafil, a recently developed vasodilator, is a specific inhibitor of PDE-5, which specifically inactivates cGMP, leading to relaxation of smooth muscle in pulmonary arteries. Sildenafil is best known for its use in the treatment of male erectile dysfunction. In addition to its high concentration in the corpora cavernosa, PDE-5 is abundant in vascular, tracheal, and visceral smooth muscle and in platelets. Sildenafil has been studied in patients with pulmonary hypertension. Prasad et al observed a reduction of pulmonary arterial pressure and improvement of exercise capacity in a young man with PPH who had received sildenafil for 3 months. Long-term treatment with oral sildenafil improved exercise capacity and quality of life in patients with severe pulmonary hypertension.

Combination Therapy

Ghofrani et al demonstrated that short-term administration of oral sildenafil and inhaled iloprost, a stable prostacyclin analogue, produced a much greater vasodilator response in patients with pulmonary arterial hypertension and
in patients with chronic thromboembolic pulmonary hyperten-
sion than did each single agent alone.\textsuperscript{20,21} Stiebellehner et al reported 1 female patient who underwent surgical occlusion of an atrial septal defect and was diagnosed as having pulmonary hypertension 10 years later. She had shown resistance to 7 years' continuous infusion of epoprostenol, but 5 months' additional oral sildenafil produced a marked vasodilator response.\textsuperscript{22} Differing from the increase in cGMP by sildenafil, epoprostenol has a relaxant effect on pulmonary arteries by increasing cAMP. Successful treat-
ment of patients with PPH refractory to epoprostenol may be attained through not only addition of sildenafil with a different vasodilatory mechanism, but also the inter-relation-
ship between the 2 drugs. The interaction of cGMP inhibits PDE-3, increasing the cAMP level. Therefore, sildenafil further increases the cAMP level, which is already increased by epoprostenol.\textsuperscript{23} Moreover, Koide et al showed that an elevation of intracellular cAMP positively regulates NO production, resulting in increased cGMP.\textsuperscript{24} Niwano et al showed that expression of the endothelial NO synthase gene is increased by beraprost, an orally active prostacyclin analogue\textsuperscript{25} in vascular endothelial cells, leading to increased cGMP.\textsuperscript{26} Combination therapy with sildenafil and beraprost shows additive effects to increase plasma cAMP and cGMP levels.\textsuperscript{27} The detailed mechanism, however, is still uncertain and further study is needed.

Study Limitations

There are some limitations of the present study: (i) patients who received additional sildenafil were followed up for only 3 months, and thus the long-term effects are not known; and (ii) the number of patients with PPH refractory to epoprostenol was relatively small. A study with a greater number of patients is needed in the future.

Conclusions

Additional oral sildenafil was effective in patients with PPH refractory to continuous infusion of epoprostenol. These patients have a grave prognosis at the present time, and the only remaining therapy has been considered to be lung transplantation. The present study suggests that sildenafil has a synergistic effect with epoprostenol even in patients with PPH refractory to epoprostenol, and that there is a possibility for these patients to obtain prolonged survival by additional therapy with sildenafil.

References

cyclin) with conventional therapy for primary pulmonary hyperten-
8. Shekerdemian LS, Ravin HB, Penny DJ. Intraoperative sildenafil lowers pulmonary vascular resistance in a model of neonatal pulmonary hyperten-
sion. \textit{Am J Respir Crit Care Med} 2002; 165: 1088 – 1102.
11. McLaughlin VV, Genther DE, Panella MM, Rich S. Reduction in pulmonary vascular resistance with long-term epoprostenol (prosta-
13. McLaughlin VV, Shillington A, Rich S. Survival in primary pulmo-
17. Prasad S, Wilkinson J, Gatouil MA. Sildenafil in primary pulmo-
18. Abrams D, Schulze-Neick I, Magee AG. Sildenafil as a selective pul-
tinuous IV epoprostenol in patients with pulmonary arterial hyperten-
25. Ono F, Nagaya N, Kyotani S, Oya H, Nakanishi N, Miyatake M. Hemodynamic and hormonal effects of beraprost sodium, an orally active prostacyclin analogue, in patients with secondary precapillary pulmonary hyperten-