Combination Therapy With Oral Sildenafil and Beraprost for Pulmonary Arterial Hypertension Associated With CREST Syndrome

Kenji MIWA,1 MD, Takashi MATSUBARA,1 MD, Yoshihide UNO,1 MD, Toshihiko YASUDA,1 MD, Kenji SAKATA,1 MD, Toyonobu TSUDA,1 MD, and Honin KANAYA,1 MD

SUMMARY

Pulmonary arterial hypertension (PAH) is commonly associated with CREST (Calcinosis, Raynaud phenomenon, Esophageal motility disorders, Sclerodactyly, and Telangectasia) syndrome. Sildenafil, an oral phosphodiesterase type-5 inhibitor, may offer benefits in the pharmacological management of PAH. However, little is known about the long-term hemodynamic effects of sildenafil, and the potential role of sildenafil in long-term combination with beraprost, an oral prostacyclin analogue, remains unclear. We therefore examined the hemodynamic effect of oral sildenafil alone and when coadministered with beraprost in a patient with PAH associated with CREST syndrome.

Traces of the acute hemodynamic effects of beraprost (20 µg) disappeared after 2 hours. In contrast, the acute hemodynamic effects of sildenafil (50 mg) produced a greater reduction in PAP (31%) and PVR (40%), and these effects also disappeared after 5 hours.

After 1 month of combination therapy of sildenafil (25 mg) twice daily and beraprost (20 µg) 3 times daily, the fall in pulmonary artery pressure and pulmonary vascular resistance was sustained (31% in both). Furthermore, the patient had significantly improved her 3-minute walk test and NYHA function class without significant adverse effects at the reported doses.

The findings indicate that oral sildenafil is a potent pulmonary vasodilator that appears to act synergistically with oral beraprost to cause sustained pulmonary vasodilation in a patient with PAH associated with CREST syndrome. (Int Heart J 2007; 48: 417-422)

Key words: Pulmonary artery hypertension, CREST syndrome, Sildenafil, Beraprost

PULMONARY artery hypertension (PAH) is a life-threatening disease characterized by progressive pulmonary hypertension that leads to right ventricular failure and death.1) PAH comprises idiopathic PAH and PAH in the setting of collagen disease (eg, in localized cutaneous systemic sclerosis, also known as the
CREST syndrome), congenital systemic to pulmonary shunts, portal hypertension, and HIV infection. All these conditions exhibit virtually identical obstructive pathologic changes in the pulmonary microcirculation. Median survival is 2.8 years from the time of diagnosis. Therefore, a novel therapeutic strategy for PAH is desirable.

A number of vasodilating agents, including adenosine, nitroprusside, calcium antagonists, and prostacyclin have been tested as the basis for long-term therapy. Unfortunately, these vasodilator therapies have limited efficacy due to lack of selectivity for pulmonary vasculature.

Sildenafil\textsuperscript{3-5} is a specific inhibitor of phosphodiesterase isoform 5 (PDE5) and induces smooth-muscle relaxation via a nitric oxide (NO) dependent increase of cyclic guanosine 5-monophosphate. Lung PDE5 inhibition by sildenafil may thus reduce pulmonary vascular pressures along this pathway.

Uncontrolled clinical studies have examined the acute hemodynamic effects of sildenafil and its potential role in the long-term treatment of patients with PAH. However, little is known about the long-term hemodynamic effects of sildenafil, and its potential role in long-term combination therapy remains unclear.

On the other hand, prostacyclin produces strong vasodilatation and inhibition of platelet aggregation. Beraprost is the first chemically stable and orally active prostacyclin analogue,\textsuperscript{6} and is an approved therapy for PAH in Japan.

Considering that sildenafil and beraprost dilate pulmonary vessels through different mechanisms, combination therapy with both drugs may have additive or synergistic effects on pulmonary hemodynamics.

We report on a case that demonstrated an acute response to oral sildenafil alone, as well as a sustained response in combination with oral beraprost, which we believe to justify detailed long-term studies looking at symptomatic and prognostic benefit for patients with PAH.

**CASE**

A 63-year-old Japanese woman with a 30-year history of CREST syndrome was admitted to our hospital because of worsening dyspnea and palpitations upon exertion. Primary biliary cirrhosis and chronic thyroiditis had been diagnosed 13 years previously. Physical examination revealed mild facial and manual telangiectasias, prominent right ventricular impulse, increased P\textsubscript{2}, a holosystolic murmur at the left lower sternal border, trace ankle edema, and sclerodactyly. Oxygen saturation of hemoglobin with the patient at rest without oxygen supplementation was 95\%. Chest radiography revealed moderate cardiomegaly, and echocardiography showed a steady increase in pulmonary artery pressure with right ventricular enlargement. There was no evidence of pulmonary embolism according to
SILDENAFIL ACTS SYNERGISTICALLY WITH BERAPROST

Vol 48  
No 3

perfusion scinti-scanning of the lung.

At catheterization, the right jugular vein and radial artery were cannulated. Left-heart catheterization revealed normal coronary arteries and left ventricular function. Right-heart catheterization revealed an increased pulmonary artery pressure (PAP) of 59/24 mmHg (normal range, 15-30/4-12 mmHg), mean PAP of 35 mmHg (normal range, 9-19 mmHg), systemic arterial pressure (SAP) of 164/90 mmHg (normal value, < 140/ < 90 mmHg), mean SAP of 114 mmHg, cardiac index of 2.4 L/m² per minute (normal range, 2.5-4.2 L/m² per minute), systemic vascular resistance (SVR) of 2683 dyne·s/cm⁵ (normal range, 700-1600 dyne·s/cm⁵), and pulmonary vascular resistance (PVR) of 748 dyne·s/cm⁵ (normal range, 20-130 dyne·s/cm⁵).

Cardiopulmonary hemodynamics were then monitored before and every 1 hour after administration of oral beraprost 20 µg. After 1 hour, mPAP and PVR were reduced by 9% and 10%, respectively. Her cardiac index improved 11%. This acute hemodynamic effect of beraprost disappeared after 2 hours. The next day after receiving written informed consent, sildenafil 50 mg was administered. After 3 hours, sildenafil reduced mPAP and PVR by a maximum of 30% and 40%, respectively. The cardiac index improved 7%. The acute hemodynamic effect of sildenafil disappeared after 5 hours (Figure 1).

![Figure 1. Acute response of mean pulmonary artery pressure (mPAP) and pulmonary vascular resistance (PVR) to beraprost (20 µg) and sildenafil (50 mg).]
After ingesting a 50 mg sildenafil tablet, the patient suffered a headache and refused another 50 mg dose. We therefore reduced treatment to a single dose of sildenafil. She was started on a combination therapy of sildenafil 25 mg twice daily and beraprost 20 µg three times daily. She experienced an improvement of dyspnea upon exertion 1 week after starting combination therapy, with further improvements over the following 1 month. Long-term hemodynamic effects were assessed by cardiac catheterization at 1 month (Figure 2). The last oral doses of sildenafil and beraprost were given 15 hours before the procedure. Interestingly, a sustained 31% decrease in both mPAP and PVR was seen, without affecting the cardiac index. In addition, sustained falls in mBP and SVR of 19% and 17%, respectively, were noted. It is clear that a combination therapy of sildenafil and beraprost possessed sustained efficacy with selectivity for the pulmonary vasculature over 1 month. Furthermore, after 1 month of combined therapy, the patient had significantly improved her 3-minute walk distance by 15% and her New York Heart Association (NYHA) heart function class returned to class II from class III. The plasma level of brain natriuretic peptide dropped from 126 pg/mL to 62 pg/mL. No significant decrease in arterial oxygen saturation and no adverse events except for transient flushing occurred during combination therapy.

Figure 2. Percent change in hemodynamic parameters from baseline at 1 month after combination therapy with sildenafil (25 mg) twice daily and beraprost (20 µg) three times daily. The last oral doses of sildenafil and beraprost were given 15 hours before the procedure. mPAP and PVR both showed sustained 31% drops, while mBP and SVR showed sustained drops of 19% and 17%, respectively. Combination therapy clearly exhibited sustained efficacy and selectivity for pulmonary vasculature.
DISCUSSION

We first examined the acute hemodynamic effects of sildenafil and beraprost separately for a patient with PAH. The acute hemodynamic effects of beraprost 20 µg alone were quite small and disappeared after 2 hours. In fact, in 2 randomized, double-blind, placebo-controlled trials (RCTs) which studied beraprost in PAH, no significant changes in cardiopulmonary hemodynamics and no difference in survival were observed between the 2 treatment arms. In contrast, the acute hemodynamic effects of sildenafil 50 mg alone produced a greater reduction in PAP (30%) and PVR (40%); however, these effects also disappeared after 5 hours. These results were compatible with the previously reported acute hemodynamic effects of sildenafil. In any event, the long-term hemodynamic effects of sildenafil remain controversial, and little is known about the potential role of sildenafil in long-term combination therapy.

We next examined the chronic hemodynamic effects of a combination therapy of sildenafil and beraprost. After 1 month, it was clear that this combination manifests sustained efficacy as well as pulmonary vasculature selectivity without significant adverse effect at the reported doses. In light of the short duration of these drugs when given alone, as well as the small amounts administered (sildenafil 25 mg twice daily, beraprost 20 µg three times daily), these chronic hemodynamic results may well be due to a synergistic effect of sildenafil and beraprost together.

As to a possible mechanism of synergy between these drugs, Niwano, et al have demonstrated that treatment of cultured human and bovine aortic endothelial cells with beraprost increased eNOS expression through the cAMP responsive elements, which indicates a close link between the PGI2 signal and NO pathways. The mechanism underlying the augmented response with sildenafil and prostanoids is incompletely understood, but these findings suggest significant cross talk between the cyclic nucleotides. Itoh, et al also demonstrated the additive effect of sildenafil and beraprost using an animal model of PAH.

Stiebellehner, et al treated 3 patients with PAH who were doing poorly despite long-term IV epoprostenol therapy, and reported hemodynamic and clinical improvements with the addition of sildenafil. However, continuous intravenous administration of epoprostenol is limited by serious infectious complications of the intravenous line, systemic side effects due to the nonselectivity of the vasodilator response, and extremely high costs incurred by tachyphyaxis with long-term administration. Thus, the potential utility of sildenafil and beraprost has particular appeal as a long-term treatment due to its ease of oral administration.

Recently, Ikeda, et al reported that the addition of oral sildenafil to bera-
prost for patients with pulmonary hypertension represents a safe and effective treatment in the acute phase. However, the effects of long-term use in chronic cases remain unclear. Our study leads us to believe that in combination with beraprost, sildenafil treatment may possess synergistic hemodynamic effects with no loss of selectivity for the pulmonary vasculature for a duration of at least 1 month. It should be noted that the severity of PAH was milder in our patient compared to other cases reporting the use of sildenafil. Combined sildenafil/beraprost therapy may thus prove more effective in patients with early stage PAH. In conclusion, appropriately designed RCTs are needed to compare the long-term efficacy of sildenafil with beraprost in patients with PAH.

REFERENCES