Case Report

Long-Term Vardenafil Therapy Improves Hemodynamics in Patients with Pulmonary Hypertension

Kazunori AIZAWA[1)], Takeshi HANAOKA[1)], Hiroki KASAI[1)], Kaoru KOGASHI[1)], Setsuo KUMAZAKI[1)], Jun KOYAMA[1)], Hiroshi TSUTSUI[1)], Yoshikazu YAZAKI[1)], Noboru WATANABE[1)], Osamu KINOSHITA[1)], and Uichi IKEDA[1)]

The phosphodiesterase-5 (PDE-5) inhibitor, sildenafil, has been reported to produce sustained pulmonary vasodilatation in patients with pulmonary hypertension (PH). Recently, vardenafil, a more potent and selective PDE-5 inhibitor than sildenafil, has been approved for the treatment of erectile dysfunction. However, the long-term effects of oral vardenafil in patients with PH are unknown. We studied five consecutive patients with PH; one with primary pulmonary hypertension, two with chronic pulmonary thromboembolism, one with Eisenmenger syndrome (ventricular septal defect) and one with secondary pulmonary hypertension after a ventricular septal defect closure operation. In an acute hemodynamic trial, vardenafil (5 mg) significantly decreased both the pulmonary vascular resistance (PVR) and systemic vascular resistance (SVR) with an increase in cardiac output. In a chronic hemodynamic trial, the maintenance dose of vardenafil (10 to 15 mg) for 3 months significantly decreased the PVR, but not the SVR, with a 20.7% reduction of the PVR/SVR ratio. Plasma brain natriuretic peptide (BNP) levels were also significantly decreased after 3 months. This pilot study demonstrates that long-term oral vardenafil therapy may be a safe and effective treatment for patients with PH. (*Hypertens Res* 2006; 29: 123–128)

***Key Words*: phosphodiesterase-5 inhibitor, vardenafil, pulmonary hypertension, vascular resistance, brain natriuretic peptide**

Introduction

The prognosis of patients with pulmonary hypertension (PH) is poor (*1*). The goals of long-term therapy for PH are to reduce pulmonary vasoconstriction, cause the regression of vascular remodeling and prevent thrombosis. Available therapies including calcium channel blockers, anticoagulants, bosentan, beraprost and epoprostenol, have limited efficacy or are associated with significant complications (*2*). Phosphodiesterases are a superfamily of enzymes that degrade cyclic guanosine monophosphate (cGMP), the second messengers of prostacyclin and nitric oxide, leading to the relaxation of smooth muscle (*3*). The phosphodiesterases have different tissue distributions and substrate affinities (*4*). Phosphodiesterase-5 (PDE-5) is abundantly expressed in the penis and lung (*5*). Because of PDE-5's tissue distribution (pulmonary>systemic vasculature), PDE-5 inhibitors are attractive candidates for pulmonary vasodilators that minimally decrease systemic blood pressure. When administered acutely in patients with PH, the PDE-5 inhibitor sildenafil achieves a marked improvement in the cardiopulmonary hemodynamics with significant reductions in the pulmonary vascular resistance (*6–12*). Chronic therapy with oral sildenafil has also

From the [1)]Division of Cardiovascular Medicine, Shinshu University School of Medicine, Matsumoto, Japan.

Address for Reprints: Kazunori Aizawa, M.D., Division of Cardiovascular Medicine, Shinshu University School of Medicine, 3–1–1 Asahi, Matsumoto 390–8621, Japan. E-mail: kaizawa@hsp.md.shinshu-u.ac.jp

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Table 1. Baseline Characteristics of the Study Population

Patient No.	Age/sex	NYHA class	Etiology	Vardenafil	Previous treatment		
					Epoprostenol	O_2	Beraprost
1	32/M	II	PPH	5 mg BID	–	+	+
2	71/F	II	CTEPH	5 mg TID	–	+	+
3	58/F	III	CTEPH	5 mg TID	–	+	+
4	27/M	III	Eisenmenger (VSD shunt +)	5 mg BID	–	+	+
5	60/F	III	Eisenmenger (VSD shunt –)	5 mg TID	–	+	+

NYHA, New York Heart Association; PPH, primary pulmonary hypertension; CTEPH, chronic thromboembolic pulmonary hypertension; VSD, ventricular septal defect; BID, twice daily; TID, three times daily.

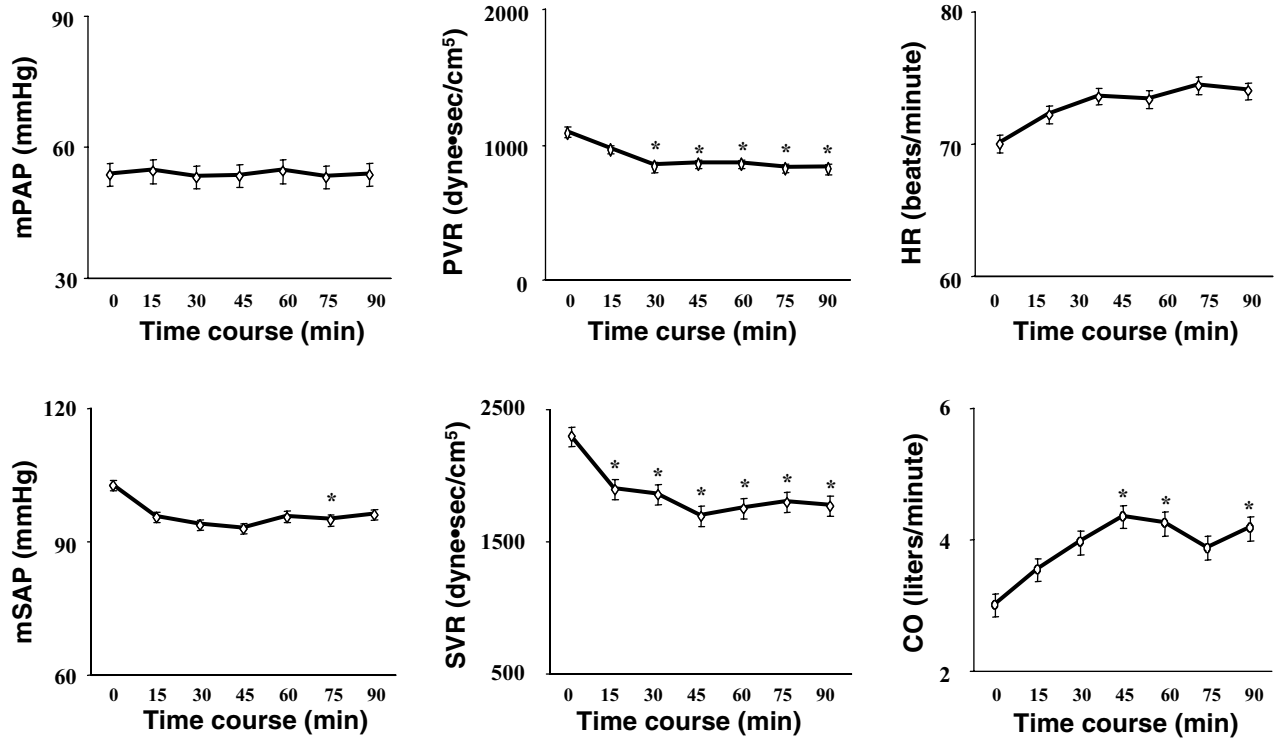

Fig. 1. *Time course of mean pulmonary artery pressure (mPAP; upper left), mean systemic artery pressure (mSAP; lower left), pulmonary vascular resistance (PVR; upper middle), systemic vascular resistance (SVR; lower middle), heart rate (HR; upper right), and cardiac output (CO; lower right) after vardenafil 5 mg administration in 5 patients with pulmonary hypertension.* *$p < 0.05$ vs. *baseline (*$n = 5$*).*

been reported to improve the cardiopulmonary hemodynamics and clinical symptoms (*13*, *14*).

Recently, a new PDE-5 inhibitor, vardenafil, was approved for the treatment of erectile dysfunction. Vardenafil has a more than 20-fold greater potency than sildenafil for inhibiting purified PDE-5 (*15*), which may result in more favorable clinical and side-effect profiles. However, Ghofrani *et al*. reported that short-term vardenafil therapy lacked selectivity for the pulmonary circulation (*16*). No data exist addressing the efficacy and safety of chronic vardenafil therapy for PH. The purpose of the present study was to investigate whether long-term treatment with oral vardenafil would be safe and would improve the hemodynamics and functional capacity in patients with PH.

Methods

Study Patients

We studied five consecutive patients with PH; one had primary PH (PPH), two had chronic pulmonary thromboembolism (CPTE), one had Eisenmenger syndrome (ventricular septal defect), and one had secondary PH after a ventricular septal defect closure operation. Pulmonary hypertension was

defined as a mean pulmonary arterial pressure >25 mmHg at right heart catheterization. Primary PH was diagnosed by exclusion, requiring the demonstration of the absence of a variety of cardiopulmonary and systemic diseases, and fulfilled the diagnostic criteria of the National Institutes of Health registry for PPH.

Patient characteristics are listed in Table 1. The mean age was 49.6±19.1 years. The New York Heart Association (NYHA) class was II or III. The patient's baseline therapy included the use of home-oxygen-therapy, beraprost and warfarin in all patients, and diuretics in three patients. All patients had been stable for >3 months, and their standard therapy was not altered during the present study.

Treatment and Follow-Up

We evaluated right cardiac catheterization, plasma brain natriuretic peptide (BNP) level, and 6-min walk distance both in acute and chronic hemodynamic trials. In the acute hemodynamic trial, the patients fasted for at least 6 h and were studied while in a supine position. After lines were placed, patients were allowed to rest for 10 min, and then the following hemodynamic measurements were recorded and defined as the baseline measurements: systemic arterial pressure, pulmonary arterial pressure, atrial pressure, pulmonary wedge pressure and heart rate. All measurements were performed during end expiration, and the mean pressures were electronically calculated over at least 10 beats. Cardiac output was measured with the thermodilution method using the mean of triplicate measurements. Pulmonary vascular resistance (PVR) and systemic vascular resistance (SVR) were calculated using the standard formulas. After baseline measurements were obtained, vardenafil 5 mg was administered orally, and hemodynamics were assessed over a subsequent 90-min observation period.

After the acute hemodynamic trial, the chronic trial followed. Oral vardenafil was started at 5 mg bid, and if vardenafil was well tolerated at 1 month, the dose was raised to 5 mg tid and continued till the end of the 3-month study period. The maintenance dose of vardenafil was based on each cardiologist's preference.

The protocol was approved by the Research Ethics Committee of Shinshu University School of Medicine. Written informed consent was obtained from all participants before starting vardenafil.

Data Analysis

All variables are expressed as the mean values±SEM. Repeated measures of analysis of variance (ANOVA) were used to look for differences in the measurements of the acute phase. If differences were found, then the Dunnett multiple comparisons procedure was used to determine where differences existed. Comparisons of the baseline values with the post-long term vardenafil values were performed with a 2-sided, paired *t*-test. The reduction in classification (NYHA classification) was compared using Wilcoxon's signed-rank test. *p* values less than 0.05 were considered statistically significant. The statistical calculations were performed with SPSS version 11.0 software (SPSS, Chicago, USA).

Results

Acute Hemodynamic Effects of Vardenafil

As shown in Fig. 1, vardenafil significantly decreased the mean systemic arterial pressure (before: 102.6±7.2 mmHg; after: 94.8±7.0 mmHg; $p<0.05$), while no significant reduction of the mean pulmonary arterial pressure was observed (before: 53.6±8.6 mmHg; after: 53.0±9.3 mmHg).

Vardenafil also caused a significant reduction of PVR (before: 1,090.6±256.7 dyn·s/cm^5; after: 836.0±192.2 dyn·s/cm^5; $p<0.05$) and SVR (before: 2,142.1±441.3 dyn·s/cm^5; after: 1,549.9±316.6 dyn·s/cm^5; $p<0.05$). A significant increase of cardiac output was also observed (before: 3.5±0.2 l/min; after: 4.2±0.3 l/min; $p<0.05$) with no changes in heart rate.

In this acute trial, a minor complication (flashing) occurred in one patient. No other clinically significant adverse effects, including hypotension accompanying any symptom or heart failure, were observed.

Long-Term Outcome with Vardenafil Therapy

Patient No. 4 dropped out of the chronic trial due to paroxysmal atrial flutter, which occurred 6 days after starting the vardenafil. The hemodynamic measurements and functional capacity of the remaining four patients are shown in Table 2 and Fig. 2.

Chronic vardenafil therapy significantly decreased the mean pulmonary arterial pressure and PVR. Contrary to the short-term response to vardenafil observed in the acute hemodynamic trial, the mean systemic arterial pressure was not significantly reduced, and SVR was not changed. There were also no significant changes in heart rate, cardiac output, mean right atrial pressure or pulmonary capillary wedge pressure.

Baseline plasma BNP levels were elevated in all patients (reference range: 59.8–413.8 pg/ml), and the vardenafil therapy significantly decreased BNP levels after 3 months (Fig. 3).

Two patients (No. 3 and No. 5) classified in NYHA function class III were improved to class II, and two patients (No. 1 and No. 2) in class II were improved to class I after 3 months of vardenafil treatment. There were no changes in the 6-min walk distance.

No adverse events (such as flushing and light headache) were observed during long-term vardenafil therapy, while liver enzymes were slightly increased in patient No. 1 during the first 2 weeks, but recovered spontaneously. In this case, oral vardenafil was continued at 5 mg bid till the end of the 3-month study period.

Table 2. Hemodynamic Measurements and Functional Capacity

Parameter	Baseline	3 months after	*p* value
HR (bpm)	67.5±7.0	72.0±5.4	NS
mPAP (mmHg)	46.0±2.0	37.3±2.1	<0.05
mSAP (mmHg)	98.0±7.1	86.5±3.6	NS
PCWP (mmHg)	9.0±1.2	13.0±1.5	NS
mRA (mmHg)	7.5±0.6	7.3±2.9	NS
CO (l/min)	3.6±0.3	4.4±0.4	NS
PVR (dyn·s/cm^5)	838.2±89.0	500.6±35.0	<0.05
SVR(dyn·s/cm^5)	2,081.4±308.9	1,568.3±79.4	NS
BNP (pg/ml)	177.3±166.0	129.5±146.0	<0.05
6 min walk distance (m)	411.3±31.8	431.0±33.4	NS
NYHA class	2.5±0.3	1.5±0.3	<0.05

All values are means±SEM ($n=3$). HR, heart rate; mSAP, mean systemic arterial pressure; mPAP, mean pulmonary arterial pressure; mRA, mean right atrial pressure; PCWP, pulmonary capillary wedge pressure; CO, cardiac output; PVR, pulmonary vascular resistance; SVR, systemic vascular resistance; NYHA, New York Heart Association.

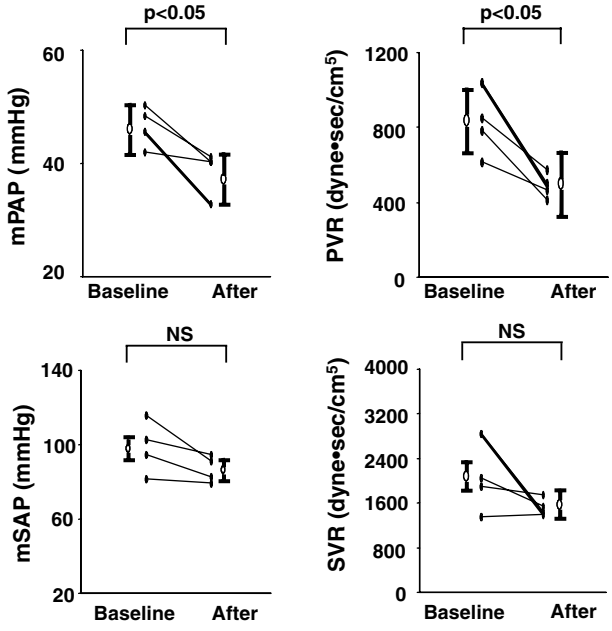

Fig. 2. *The effect of vardenafil therapy for 3 months on mean pulmonary arterial pressure (mPAP; upper left), pulmonary vascular resistance (PVR; upper right), mean systemic artery pressure (mSAP; lower left), and systemic vascular resistance (SVR; lower right) in patients with pulmonary hypertension (*n*=4).*

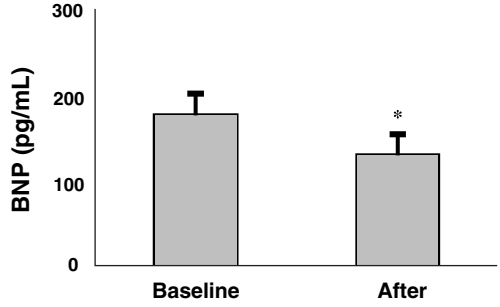

Fig. 3. *The effect of vardenafil therapy for 3 months on plasma BNP levels in patients with pulmonary hypertension.* *p*< 0.05* vs. *baseline (*n*=4).*

Discussion

Vardenafil is a new PDE-5 inhibitor that shows more potent and selective inhibition of PDE-5 than sildenafil (*17*). This study showed for the first time that long-term treatment with oral vardenafil produces significant clinical improvement in patients with PH with no significant side effects.

Several previous studies have demonstrated that short-term treatment with sildenafil significantly reduces pulmonary artery pressure and PVR (*6–10*, *18, 19*). Ghofrani *et al*. (*16*) compared the short-tem effect of three different PDE-5 inhibitors on the pulmonary and systemic hemodynamics in patients with PH. In their study, sildenafil and tadalafil caused a significant reduction in the PVR/SVR ratio, while vardenafil caused an almost equipotent reduction of PVR and SVR, suggesting that vardenafil lacks selectivity for the pulmonary circulation even at high doses. Also in our study, there was no selectivity for the pulmonary vasculature of the acute effects of vardenafil, as reflected by a change of the PVR/SVR ratio of +4% after the administration.

Several papers have also reported the long-term hemodynamic effects of sildenafil in patients with PH (*11*, *13*, *14*). Watanabe *et al*. (*14*) studied the effects of oral sildenafil in one subject with PPH and one subject with secondary PH (both with NYHA class III). Right heart catheterization was performed after oral sildenafil was administered for 3 months.

Follow-up right heart catheterization showed that there was no effect on aortic pressure, the decrease in pulmonary artery pressure, the increase in cardiac index or the overall decrease in PVR. The present study demonstrates for the first time the chronic effects of vardenafil: Like sildenafil, long-term treatment with vardenafil significantly decreased the PVR, but not the SVR, as reflected by the change of the PVR/SVR ratio of 20.7%, which is compatible with a relatively selective pulmonary vasodilatory effect. Therefore, the chronic effects of vardenafil may be significantly more efficacious than the short-term effects, such as has been observed with epoprostenol.

Apart from pulmonary vasodilatation, other factors, such as anti-proliferative effects of the PDE-5 inhibitor on pulmonary artery cells, may be related to the long-term effect of vardenafil (*20*). Heinrike *et al*. reported that small doses of a PDE-5 inhibitor may be a useful adjunct to iloprost, a stable prostacyclin analogue, in the management of PH (*21*). Kataoka *et al*. also demonstrated that additional oral sildenafil was effective in patients with PPH refractory to continuous infusion of epoprostenol (*11*). Though our study does not address the role of vardenafil as an adjunct to beraprost, the chronic effects of vardenafil may be attained through the inter-relationship between the 2 drugs.

Bone marrow-derived endothelial progenitor cells (EPCs) originate from hematopoietic stem cells in bone marrow and migrate into the peripheral circulation to promote endothelial repair and neovascularization (*22*). Foresta *et al*. reported a significant increase in the number of circulating EPCs in humans after vardenafil administration (*23*). This phenomenon may be related to the chronic effects of vardenafil.

As compared with sildenafil, vardenafil has different selectivities for PDE subgroups. Further studies are needed to address the question of whether this different profile is due to the differences in the PDE inhibition pattern or to PDE's unrelated, currently unknown modes of actions (*16*).

Pulmonary hypertension characterized by extensive remodeling of the pulmonary vasculature induces right ventricular afterload. The baseline plasma level of BNP, which is a prognostic indicator in patients with PH (*24*), was significantly increased in our patients. The long-term treatment with vardenafil caused a significant reduction of the BNP level, suggesting that the decrease in pulmonary artery pressure ameliorated increased wall stress (*25*, *26*) in the right ventricle and impaired left ventricle diastolic function (*27–29*) due to the enlarged right ventricle of those patients.

One patient (No. 4), who had Eisenmenger syndrome with a ventricular septal defect, dropped out of the chronic study due to paroxysmal atrial flutter. Eric *et al*. described that sildenafil in patients with Eisenmenger syndrome may potentially cause a reduction in pulmonary blood flow as a result of even mild systemic vasodilation and consequent increased right-to-left shunting (*30*). In our study, although we did not examine the pulmonary shunting (Q_p/Q_s), the changes in right-to-left shunting at the defect level due to the increase of the PVR/SVR ratio (before: 0.42; after: 0.47) may have been related to the pathogenetic mechanisms.

The accuracy of cardiac output measurement by the thermodilution technique in patients with low cardiac output or severe tricuspid regurgitation has been questioned. On the other hand, Marius *et al*. reported that thermodilution was equally accurate over a broad spectrum of cardiac output values ranging from as low as 1.7 l/min to as high as 7.8 l/min, and the agreement between the thermodilution and the metabolic (Fick) method was not affected by the severity of tricuspid regurgitation in patients with PH (*31*). In our study, the cardiac output ranged from 3.0 to 5.0 l/min in all patients, so we measured cardiac output by thermodilution.

There are some limitations in the present study: 1) The patients who received vardenafil were followed up for only 3 months. 2) The response to higher doses of vardenafil beyond 15 mg daily has not been tested and the ideal maintenance dose is not yet known. 3) The study was a nonrandomized small pilot study, because the disease is relatively rare. The efficacy, simplicity, and potential cost savings of the oral PDE-5 inhibitor regimen support the need for larger prospective, double-blind, randomized, placebo-controlled trials.

For patients with certain forms of PH, epoprostenol can be administered by continuous intravenous infusion, owing to its short half-life in the circulation (*i.e.*, 3 min) and its inactivation at low pH. Although continuous infusion epoprostenol was the first therapy shown to improve exercise capacity, functional class, and survival in patients with severe PH, therapy with this agent is limited by its side effect profile and its complex delivery system, which can lead to serious complications. In the present study, we demonstrate that vardenafil, a new PDE-5 inhibitor, can produce sustained pulmonary vasodilatation in patients with PH. Because it is widely available and relatively inexpensive and has practically no significant side effects, vardenafil may qualify as a first-line treatment for PH, as an alternative to the intravenous infusion of epoprostenol.

In conclusion, long-term treatment with oral vardenafil is well tolerated in patients with PH and significantly improves the hemodynamics and symptoms. We propose that oral vardenafil may be beneficial as a selective pulmonary vasodilator in patients with PH.

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