



A Phase III, Multicenter, Collaborative, Open-Label Clinical Trial of Sildenafil in Japanese Patients With Pulmonary Arterial Hypertension

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Background: There is evidence that phosphodiesterase type-5 is effective for the treatment of pulmonary arterial hypertension (PAH).

Methods and Results: A phase III, multicenter, open-label clinical trial of sildenafil 20 mg t.i.d. was conducted in 21 Japanese patients with PAH to examine its efficacy, safety, and pharmacokinetics. The present trial consisted of a screening period and 12-week treatment. Patients who were enrolled in the present trial increased their 6-min walking distance of administration increased at week 12 by 84.2 m from baseline. Hemodynamic parameters (eg, mean pulmonary artery pressure and pulmonary vascular resistance), Borg dyspnea scores, and plasma brain natriuretic peptide concentrations also improved compared to baseline. Most patients improved or sustained WHO functional class. Seven subjects, who were examined for the pharmacokinetics of sildenafil, showed relatively large interindividual variations in the C_{max} , AUC_{0-8} , $C_{ss,av}$, and C_{trough} of the drug. Any serious adverse events, severe adverse events, and deaths were not observed. Most of events of undeniable causality were mild or moderate in severity. Sildenafil was well tolerated by the subjects.

Conclusions: Sildenafil 20 mg t.i.d. was effective and safe for Japanese patients with PAH. (*Circ J* 2011; **75**: 677–682)

Key Words: Efficacy; Pharmacokinetics; Pulmonary arterial hypertension; Safety; Sildenafil

Pulmonary arterial hypertension (PAH) is a group of pathologies with a poor prognosis that are featured by progressive obliteration of the small pulmonary vascular bed and a progressive increase in pulmonary vascular resistance (PVR), eventually leading to refractory right heart failure and premature death.¹⁻³ A national prospective registry in the United States⁴ has reported that the estimated median survival of patients with primary pulmonary hypertension (PPH) who were untreated following a definite diagnosis was 2.8 years and that the estimated 5-year survival rate was 34%. PAH is diagnosed when a mean pulmonary artery pressure (mPAP) is greater than 25 mmHg at rest.⁵ The

disease is classified the following into several categories: PAH of unknown etiology (idiopathic or familial) and PAH associated with collagen vascular disease, congenital systemic-to-pulmonary shunts, portal hypertension, human immunodeficiency virus (HIV) infections, drugs/toxins, and others.⁶ PAH provokes exertional dyspnea, easy fatigability, palpitation, chest pain, syncope, cough, and/or other symptoms and considerably deteriorates quality of life of the patients.

In Japan, PPH is designated for listing in the Specified Disease Treatment Research Program, and in 2004 there were 758 patients with identifiable PPH.⁷ The number of patients with PAH, including patients with PAH associated with

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underlying disorders (eg, collagen vascular disease and congenital heart diseases), is estimated to be approximately 6,000 in Japan. Therapeutic drugs for PAH have been used in recent years in addition to treatment with conventional agents (anti-coagulants, diuretics, inotropic agents, supplemental oxygen, calcium-channel blockers, vasodilators, antiproliferative agents, and endothelin-receptor antagonists).⁸

New insights have been obtained on the pathogenesis of PAH through the action of various enzymes. For instance, Rho-kinase activation was recently found to be involved in the pathogenesis of PAH. The inhibition of Rho-kinase reduces monocrotaline-induced PAH, and the phosphorylation of RhoA and prevention of its translocation to the plasma membrane mediate hypoxia-induced PH. Furthermore, there is direct evidence for Rho-kinase activation in PAH patients.⁹⁻¹¹

Phosphodiesterase type-5 (PDE-5) is strongly expressed in the lung, and PDE-5 gene expression and activity are increased in chronic PH.¹²⁻¹⁴ Based on these findings, the inhibition of PDE-5 has been researched as a mechanism of a new approach to the treatment of PAH. Sildenafil (Viagra[®]), a potent and highly selective inhibitor of PDE-5 that metabolizes cGMP,¹⁵⁻¹⁸ was approved as a therapeutic drug for male erectile dysfunction. cGMP-specific PDE-5 is abundantly present in the pulmonary vasculature, and sildenafil leads to nitric oxide-mediated vasodilation and decreases PVR.^{19,20}

The present study was designed as a small-scale clinical trial to clarify the features of sildenafil as a therapeutic drug for PAH in Japan, and its objective was to examine the efficacy, safety, and pharmacokinetics of sildenafil administered orally to Japanese patients with PAH at the regimen of 20 mg t.i.d. for 12 weeks.

Methods

Between April 2007 and February 2009, the phase III, multicenter, collaborative, open-label clinical trial of sildenafil 20 mg t.i.d. was conducted in 21 Japanese patients with PAH who met all inclusion criteria, who did not fall under any exclusion criterion, and who were enrolled at 8 medical institutions in Japan. The protocol of the present trial was approved by the institutional review board or ethical review board at each institution, and the trial was conducted in accordance with the protocol. All subjects provided written informed consent before their enrollment.

The present clinical trial consisted of the screening period and 12-week treatment period. Throughout the treatment period, one 20-mg tablet of sildenafil citrate was orally administered t.i.d. to each subject at intervals ≥ 6 h. Subjects visited the hospital 5 times (visit 1 at screening, visit 2 at the onset of administration, visit 3 at week 4 of administration, visit 4 at week 8 of administration, and visit 5 at week 12 of administration or at discontinuation), together with contact by phone at week 1 of administration.

The objectives of the present trial were as follows: 1) to verify the efficacy and safety of sildenafil 20 mg t.i.d. administered orally to Japanese patients with PAH for 12 weeks; and 2) to examine the steady-state pharmacokinetics of sildenafil and its metabolite under these conditions of administration.

The main inclusion criteria were as follows: the male or female patient should be aged ≥ 16 years, should be diagnosed with PAH, and should have a mean PAP > 25 mmHg and a pulmonary capillary wedge pressure (PCWP) < 15 mmHg in right heart catheterization at screening or baseline.

Assessment of Efficacy

The primary endpoints for efficacy were as follows: 1) change in 6-min walking distance at week 12 of administration from baseline; and 2) changes in baseline hemodynamic parameters [mean PAP, PVR, and cardiac output (CO)] at week 12 of administration from baseline.

The secondary endpoints for efficacy were as follows: 1) change in baseline 6-min walking distance at week 8 of administration from baseline; 2) changes in baseline WHO functional class at weeks 4, 8, and 12 of administration from baseline; 3) changes in baseline hemodynamic parameters [PAP (systolic and diastolic), systemic blood pressures (systolic, diastolic, and mean), PCWP, right atrial pressure, cardiac index, heart rate, PVR index, systemic vascular resistance, systemic vascular resistance index, arterial oxygen saturation, arterial oxygen tension, mixed venous oxygen saturation, and mixed venous oxygen tension] at week 12 of administration from baseline; 4) changes in baseline Borg dyspnea scores at weeks 8 and 12 of administration from baseline; and 5) changes in baseline plasma brain natriuretic peptide (BNP) concentration at weeks 4, 8, and 12 of administration from baseline.

Assessment of Pharmacokinetics

Subjects in the present trial were assessed for the plasma concentrations and pharmacokinetic parameters [time to reach maximum concentration (T_{max}), maximum concentration (C_{max}), and area under the curve (AUC_{0-8})] of sildenafil and its metabolite at steady state after sildenafil administration, and for the average plasma concentration at steady state ($C_{ss,av}$) and plasma trough concentration (C_{trough}) at the steady state of sildenafil.

Blood for the pharmacokinetic assessment was collected before administration and at 0.5, 1, 1.5, 2, 4, 6, and 8 h after administration on the specified visit days. The pretreated samples of the blood collected were used to measure the plasma concentrations of sildenafil and its metabolite at Covance (Indianapolis, IN, USA) according to the liquid chromatography–tandem mass spectrometry method. The lower limit of quantification was 1.00 ng/ml for both sildenafil and its metabolite.

Assessment of Safety

Subjects in the present trial were assessed for adverse events during history taking, physical examinations, laboratory tests [hematology: hemoglobin, hematocrit, red blood cell count, platelet count, white blood cell count, differential white blood count (neutrophils, eosinophils, basophils, lymphocytes, and monocytes), and prothrombin time; and blood chemistry (total bilirubin, direct bilirubin, AST, ALT, ALP, γ -GTP, albumin, total protein, BUN, creatinine, sodium, potassium, uric acid, and BNP)], vital signs (blood pressure, pulse rate, and body weight), 12-lead electrocardiography, and ophthalmology (examination, visual acuity, color sense, and funduscopy).

Statistical Analysis

SAS software version 8.2 (SAS Institute Inc; Cary, NC, USA) was used to perform all statistical analyses according to Student's t-test. Full analysis set (FAS) was analyzed for efficacy, and FAS and per protocol set (PPS) were analyzed for primary endpoints. FAS consisted of subjects who received at least 1 dose of sildenafil and who were assessed for efficacy at baseline and after sildenafil administration. A P value of < 0.05 was considered statistically significant.

PPS consisted of subjects in FAS who met the following

Table 1. Subject Disposition and Analysis Sets	
	No. of subjects
Enrolled	21
Medicated	21
Completed	19
Discontinued	2
Analyzed for efficacy	
Full analysis set	20
Per protocol set	16
Assessed for pharmacokinetics	7
Assessed for safety	21
Adverse events	21
Laboratory tests	20

Table 2. Demographic Characteristics of Subjects and Their Features at Baseline	
Background factors	No. of subjects
Gender	
Male	4
Female	17
Age (years)	
<18	0
18–44	9
45–64	10
≥65	2
Mean ± SD	47.1±14.7
Minimum to maximum	19–68
Body weight (kg)	
Mean ± SD	58.5±10.6
Minimum to maximum	38.1–84.0
WHO functional class	
I	0
II	7
III	14
IV	0

Table 3. Types of PAH and Duration of Disease	
	No. of subjects
Idiopathic PAH	
No. of subjects	6
Duration of disease (years)	
Mean	1.46
Minimum to maximum	0.1–4.0
Familiar PAH	
No. of subjects	5
Duration of disease (years)	
Mean	1.15
Minimum to maximum	0.3–4.0
PAH associated with other disorders (eg, collagen vascular disease, congenital systemic to pulmonary shunts, portal hypertension, HIV infection, and drugs/toxins)	
No. of subjects	10
Duration of disease (years)	
Mean	3.33
Minimum to maximum	0.1–15.0

PAH, pulmonary arterial hypertension; HIV, human immunodeficiency virus.

Table 4. Combination Therapies (Therapeutic Drugs for PAH and Basic Therapeutic Drugs for PAH)	
	No. of subjects
No. of subjects	21
Therapeutic drugs for PAH	
Beraprost	9
Basic therapeutic drugs for PAH	
Warfarin	9
Cardiotonic drugs (eg, digoxin)	0
Calcium-channel antagonists	12
Diuretics	21
Oxygen therapy	14

PAH, pulmonary arterial hypertension.

Table 5. Six-minute Walking Distance at Baseline and at Weeks 8 and 12 of Administration, as Well as Its Changes From Baseline in Subjects		
Endpoint	Six-minute walking distance (m)	
	Actual value	Change from baseline
Subjects		
Baseline		
No. of assessed subjects	20	–
Mean ± SD (95%CI)	326.0±86.2 (285.7, 366.3)	–
Week 8 of administration		
No. of assessed subjects	19	19
Mean ± SD (95%CI)	410.2±72.9 (375.0, 445.3)	87.5±75.3* (51.2, 123.8)
Week 12 of administration or discontinuation (LOCF)		
No. of assessed subjects	20	20
Mean ± SD (95%CI)	410.2±66.6 (379.0, 441.3)	84.2±74.9* (49.1, 119.2)

CI, confidence interval; LOCF, last observation carried forward.

*P<0.0001.

Table 6. Changes in Hemodynamic Parameters at Baseline and at Week 12 of Administration in Subjects

Hemodynamic parameter	Baseline (n=20)			12 week of administration (LOCF) (n=20)			Changes from baseline		
	Actual value			Actual value			Mean ± SD		
	Mean ± SD	95%CI		Mean ± SD	95%CI		Mean ± SD	95%CI	
Systolic pulmonary artery pressure (mmHg)	75.3±18.5	66.6, 84.0		72.0±20.9	62.2, 81.7		-3.4±13.4	-9.6, 2.9	
Diastolic pulmonary artery pressure (mmHg)	30.1±12.4	24.2, 35.9		26.9±11.9	21.3, 32.5		-3.2±8.3	-7.0, 0.7	
Systolic systemic arterial pressure (mmHg)	115.4±17.5	107.2, 123.5		116.1±16.1	108.5, 123.6		0.7±16.5	-7.0, 8.4	
Diastolic systemic arterial pressure (mmHg)	68.3±14.8	61.3, 75.2		65.2±14.7	58.3, 72.1		-3.1±9.0	-7.3, 1.2	
Mean systemic arterial pressure (mmHg)	88.5±19.0	79.6, 97.4		87.7±18.7	78.9, 96.4		-0.9±12.9	-6.9, 5.2	
Pulmonary capillary wedge pressure (mmHg)	8.48±2.48	7.31, 9.64		9.15±3.15	7.68, 10.62		0.68±3.14	-0.79, 2.14	
Right atrial pressure (mmHg)	6.6±3.4	5.0, 8.2		6.4±3.6	4.6, 8.1		-0.3±4.4	-2.3, 1.8	
Cardiac index (L · min ⁻¹ · m ⁻²)	2.35±0.78	1.98, 2.71		2.67±0.99	2.20, 3.13		0.32±0.62	0.03, 0.61	
Heart rate (beats/min)	73.59±15.05	66.54, 80.63		69.45±15.98	61.97, 76.93		-4.14±7.45	-7.62, -0.65	
Pulmonary resistance index (dyne · s/cm ⁵ /m ²)	1,581.31±791.94	1,210.67, 1,951.95		1,199.31±660.73	890.09, 1,508.54		-382.00±491.80	-612.17, -151.83	
Systemic vascular resistance (dyne · s/cm ⁵)	1954.86±945.04	1,512.57, 2,397.16		1,689.09±606.04	1,405.45, 1,972.73		-265.77±785.52	-633.41, 101.86	
Systemic vascular resistance index (dyne · s/cm ⁵ /m ²)	3,127.11±1,564.66	2,394.82, 3,859.39		2,717.22±1,027.45	2,236.35, 3,198.08		-409.89±1271.30	-1,004.88, 185.09	
Mixed blood oxygen saturation index (%)	65.37±9.74	60.81, 69.93		68.28±5.82	65.56, 71.00		2.91±9.05	-1.33, 7.15	
Atrial blood oxygen saturation (%)	92.930±6.877	89.711, 96.149		93.370±3.799	91.592, 95.148		0.440±5.437	-2.104, 2.984	
Atrial oxygen tension (mmHg)	74.36±15.63	67.05, 81.67		72.35±12.09	66.69, 78.00		-2.02±11.17	-7.24, 3.21	
Mixed venous oxygen tension (mmHg)	36.55±4.33	34.46, 38.64		37.12±2.67*	35.83, 38.40*		0.57±4.35*	-1.53, 2.66*	

*n=19.

n, no. of evaluated patients; LOCF, last observation carried forward; SD, standard deviation; CI, confidence interval.

criteria; primary endpoints are assessed; there is no violation of the inclusion and exclusion criteria that could possibly affect primary endpoints; any combination-prohibited drug with possible effects on primary endpoints is not used during the study period; and the medication adherence 80–100%. Summary statistics and 95% confidence intervals for the means were calculated with respect to the actual values of the 6-min walking distance, hemodynamic parameters, Borg dyspnea score, and plasma BNP concentration and to their changes from baseline.

The WinNonlin software version 4.1 (Pharsight Corp.; Mountain View, CA, USA) was used to determine pharmacokinetic parameters of sildenafil and its metabolite according to the noncompartment model method in subjects who did not receive any other therapeutic drug for PAH, who met all inclusion criteria for pharmacokinetic assessment and who did not fall under any exclusion criteria for the assessment. All subjects who received at least 1 dose of sildenafil were assessed for safety.

Results

Subject disposition and analysis sets are shown in **Table 1**. Twenty-one subjects were enrolled, 2 of whom discontinued the trial. Therefore, 19 subjects completed the trial. Of those who discontinued, 1 showed insufficient efficacy and 1 had an adverse event.

Among 21 subjects who were enrolled, 1 and 5 were excluded from FAS and PPS, respectively. The former patient was excluded due to no postdose measurement of all endpoints for efficacy. The latter patients were excluded from PPS because of the following reasons: 2 subjects violated the inclusion/exclusion criteria; 1 subject was excluded from FAS; 1 subject was not evaluated for primary endpoints; and 1 subject ingested a combination-prohibited drug.

The demographic characteristics of subjects and their features at baseline are shown in **Table 2**. The percentages of males and females were as follows: 19.0% (4 males) and 81.0% (17 females). Subjects had different baseline WHO functional classes: 7 with class II and 14 with class III.

The types of PAH and duration of disease are shown in **Table 3**. Among the subjects, 6, 5, 10 were diagnosed with idiopathic PAH, familiar PAH, and PAH associated with underlying disorders, respectively.

Therapeutic drugs for PAH and basic therapeutic drugs for PAH, which were administered in combination with sildenafil during the study period, are shown in **Table 4**. The major therapeutic drug for PAH, which was used in combination therapies during the study period, was beraprost, and the major basic therapeutic drugs for PAH were diuretics and oxygen therapy. Among the subjects, 9 received beraprost in combination with sildenafil; 12 received sildenafil alone.

Efficacy

The actual values of 6-min walking distance at baseline and at weeks 8 and 12 of administration, as well as changes in 6-min walking distance from baseline are shown in **Table 5**. At week 8 of administration, 6-min walking distance improved statistically significantly ($P<0.0001$) by 87.5 m from baseline. Therefore, the distance was shown to have improved as much at week 8 of administration as at week 12 of administration. At week 12 of administration, the 6-min walking distance had also improved statistically significantly ($P<0.0001$) by 84.2 m from baseline.

The actual values of hemodynamic parameters (mean PAP,

PVR, and CO) at baseline and week 12 of administration are shown in **Table 6**. The mean PAP and PVR at week 12 of administration decreased as compared with baseline, and CO increased as compared with baseline. The mean PAP and PVR decreased as compared with baseline, and CO increased as compared with baseline.

Among the subjects, only 1 subject showed deterioration in WHO functional class from class II at baseline to class III at week 12 of administration; 6 subjects improved (5 from class III to class II and 1 from class III to class I). Other 13 subjects sustained their class at baseline.

Hemodynamic parameters other than mPAP, PVR, and CO were also assessed. In the subjects, consequently, the change (mean \pm SD) in PVR index in last observation carried forward (LOCF) at week 12 of administration from baseline was -382.00 ± 491.80 dyne \cdot s/cm⁵/m²; therefore, PVR decreased. Furthermore, the actual value (mean \pm SD) of PVR index in the LOCF at week 12 of administration was $1,199.31\pm 660.73$ dyne \cdot s/cm⁵/m².

The changes (mean \pm SD) in Borg's dyspnea score in the LOCF at weeks 8 and 12 of administration from baseline were -0.84 ± 1.89 and -0.95 ± 1.94 , respectively. Therefore, the scores decreased as compared with the baseline value (mean \pm SD: 3.10 ± 1.45).

Plasma BNP concentrations showed an average decrease of 78.00 pg/ml at week 4 of administration as compared with the baseline value (mean \pm SD: 216.52 ± 204.70 pg/ml) and also sustained decreases also at weeks 8 and 12 of administration.

Pharmacokinetics

The pharmacokinetics of sildenafil and its metabolite at steady state in the repeated oral administration of 20 mg t.i.d. was examined in 7 subjects. Consequently, the mean T_{max} of sildenafil was approximately 1.1 h after administration. The mean values (coefficients of variation) of C_{max} , AUC_{0-8} , $C_{ss,av}$, and C_{trough} of sildenafil at steady state were 164.88 ng/ml (45.4%), 545.14 ng \cdot h/ml (54.1%), 68.14 ng/ml (54.1%), and 19.608 ng/ml (63.4%), respectively. Therefore, relatively large interindividual variations were observed. Furthermore, sildenafil underwent the first-pass effect and rapidly produced its metabolite, and the mean T_{max} value was approximately 1.6 h after administration. The mean values (coefficients of variation) for C_{max} and AUC_{0-8} of the metabolite were 87.27 ng/ml (35.1%) and 365.85 ng \cdot h/ml (51.0%), respectively.

Safety

There were 36 episodes of undeniable causality in 16 cases (76.2%) among 21 subjects. There were no cases of serious and severe adverse events of undeniable causality. However, 2 subjects temporarily reduced the dose of the drug or discontinued its administration because of adverse events of undeniable causality. The major adverse events of undeniable causality were headache (10 cases, 22.7%) and flushing (8 cases, 18.2%); all the events were mild or moderate.

Therefore, there were no safety concerns about laboratory values, vital signs, and electrocardiographic findings.

Discussion

In the present multicenter, collaborative, open-label trial, PAH patients taking sildenafil showed sustained improvement in the 6-min walking distance at weeks 8 and 12 of administration without any serious adverse events causally related to sildenafil administration.

PAH is considered to be caused by pulmonary endothelial

dysfunction, by the imbalance between vasoconstrictive factors such as endothelin and thromboxane, and vasorelaxant factors such as prostacyclin and nitric oxide, followed by pulmonary arterial vasoconstriction, and by the proliferation of the vascular wall including endothelium, smooth muscle and adventitia, resulting in increased resistance of pulmonary blood flow through pulmonary arterioles.¹⁸⁻²⁰ At present, there are 3 categories of effective drugs for PH which present one of the following pharmacological mechanisms. Endothelin receptor antagonists (eg, bosentan) suppress vasoconstriction induced by a vasoconstrictive factor endothelin, dilate pulmonary arteries, and regresses the proliferation of vascular wall cells.²¹ Prostacyclin and nitric oxide—which are secreted from the pulmonary artery endothelium, relax smooth muscle cells, and inhibit the proliferation and promote apoptosis of vascular walls—are depleted in PAH patients. Cyclic adenosine monophosphate stimulated by prostacyclin in smooth muscle cells has a potent vasodilating and antiproliferative ability, and a synthetic prostacyclin, epoprostenol, is the first effective drug in the treatment of PH. Nitric oxide stimulates cGMP, which in turn produces cGMP with potent vasodilating and antiproliferative ability. cGMP is degraded by PDE-5 which has been reported to be increased in PAH.²² Sildenafil inhibits PDE-5 and increases guanosine monophosphate, and alleviates PH.

Six-minute walking distance is a reliable index of functional capacity in patients with PAH and has been widely used as the primary endpoint in most clinical trials designed for patients with PAH.²³⁻²⁵ In the present subjects, the 6-min walking distance increased by 87.5 m and 84.2 m at weeks 8 and 12 of administration, respectively; these values were greater than those reported with other therapeutic drugs for PAH [eg, epoprostenol (47 m),²³ bosentan (44 m),²⁴ and beraprost (63 m)²⁵].

The efficacy and safety of sildenafil for PAH patients have been demonstrated in uncontrolled¹⁸⁻²⁰ and controlled^{8,16} clinical trials. The controlled clinical trial with the largest number of patients was the Sildenafil Use in Pulmonary Arterial Hypertension (SUPER) study, in which 278 patients were enrolled; the mean 6-min walk distance and mean PVR significantly increased by 45 m and decreased by 122 dyne \cdot s/cm⁵, respectively, as compared with the placebo group.⁹ Our study afforded comparable results in efficacy. Safety profiles also were almost equivalent between the SUPER study and ours. Namely, any laboratory changes of clinical concern were not observed in these studies. One patient each in the placebo group and the sildenafil 20 mg group died from right heart failure and from acute embolism and urosepsis, respectively, in the SUPER study in contrast to the present trial in which no deaths occurred. The SUPER study reported 1 serious adverse event of undeniable causality in one patient receiving 20 mg of sildenafil in contrast to none in the present trial. The incidences of headache in the SUPER study and ours were 46.0% and 22.7%, respectively.

Changes in hemodynamic parameters (mean PAP, PVR, and CO) at week 12 of administration improved as compared with baseline and indicated a decrease in the mean PAP and an increase in CO. However, no statistically significant changes were found in systemic arterial pressure and heart rate. Therefore, improvement in CO did not involve increases in systemic artery pressure and heart rate. The improvement in CO was also corroborated by an increase in mixed venous oxygen saturation. Decreases in right atrial pressure, systolic pulmonary arterial pressure, and diastolic pulmonary arterial pressure suggested the overall improvement in right heart

function by the administration of sildenafil. The secondary endpoints—changes in other hemodynamic parameters, changes in Borg dyspnea scores, and changes in plasma BNP concentrations—also improved. These results indicated the efficacy of sildenafil which was orally administered to PAH patients at a regimen of 20 mg t.i.d. for 12 weeks.

Study Limitations

The principal limitation of the present trial is the fact that it was not a double-blind, controlled study, because of ethical considerations. Therefore, the possibility of investigator or selection bias cannot be excluded completely with regard to the endpoints examined, especially functional capacity. Another limitation of the present trial was that it did not enroll any PAH patients with WHO class IV. This has possibly favored the clinical outcomes of enrolled subjects with respect to their background at baseline. Although the number of enrolled subjects was as low as at 21, the present study is the first systematically designed study that provides clinical evidence for the efficacy, safety, and pharmacokinetic profile of sildenafil in Japanese patients with PAH.

Conclusions

Sildenafil 20 mg t.i.d. was effective for patients with PAH through improvements in the 6-min walking distance, hemodynamic parameters, Borg dyspnea scores, and plasma BNP concentration after 12-week oral administration. Furthermore, sildenafil showed relatively large interindividual variations in pharmacokinetic parameters, was well tolerated by the patients, and did not elicit any concerns about safety based on the results from laboratory tests, vital signs, and electrocardiography.

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