Beneficial Effect of Oral Sildenafil Therapy on Childhood Pulmonary Arterial Hypertension
Twelve-Month Clinical Trial of a Single-Drug, Open-Label, Pilot Study

Tilman Humpl, MD; Janette T. Reyes, RN, MN (ACNP); Helen Holtby, MBBS;
Derek Stephens, MSc; Ian Adatia, MBChB

Background—Pulmonary arterial hypertension (PAH) is a progressive and fatal disease. Sildenafil is a type 5 phosphodiesterase inhibitor and pulmonary vasodilator. Therefore, we hypothesized that sildenafil would improve distance walked in 6 minutes and hemodynamics in children with PAH.

Methods and Results—After baseline assessment of hemodynamics by cardiac catheterization and distance walked in 6 minutes, we administered oral sildenafil at 0.25 to 1 mg/kg 4 times daily to 14 children (median age, 9.8 years; range, 5.3 to 18). Diagnoses were primary (n=4) and secondary (n=10) PAH. We repeated the 6-minute walk test at 6 weeks and at 3, 6, and 12 months (n=14) and cardiac catheterization (n=9) after a median follow-up of 10.8 months (range, 6 to 15.3). During sildenafil therapy, the mean distance walked in 6 minutes increased from 278 ± 114 to 443 ± 107 m over 6 months (P=0.02), and at 12 months, the distance walked was 432 ± 156 m (P=0.005). A plateau was reached between 6 and 12 months (P=0.48). Mean pulmonary artery pressure decreased from a median of 60 mm Hg (range, 50 to 105) to 50 mm Hg (range, 38 to 84) mm Hg (P=0.014). Median pulmonary vascular resistance decreased from 15 Wood units m^2 (range, 9 to 42) to 12 Wood Units m^2 (range, 5 to 29) (P=0.024).

Conclusions—Oral sildenafil has the potential to improve hemodynamics and exercise capacity for up to 12 months in children with PAH. Confirmation of these results in a randomized, controlled trial is essential. (***Circulation***. 2005;111: 3274-3280.)

Key Words: heart defects, congenital ∎ hypertension, pulmonary ∎ pediatrics ∎ pharmacology ∎ phosphodiesterase inhibitors

Pulmonary arterial hypertension (PAH) is an unremitting disease that progresses inexorably to right ventricular failure and death in adults and children. Until recently, there were few treatment options. Treatments included continuous intravenous prostacyclin infusion,[1] oral calcium channel blockers,[2] and anticoagulation.[3] Newer therapies are emerging, such as endothelin receptor blockers,[4–6] continuous inhalation of nitric oxide (NO),[7,8] and aerosolized prostacyclin and analogs.[9,10] There are serious disadvantages with some of these therapies that may be challenging to overcome in the treatment of children, including cost, systemic side effects, complications of prolonged intravenous access, and rebound pulmonary hypertension.[11]

Recently, pulmonary vasodilation with type 5 phosphodiesterase inhibitors has been demonstrated in animals with experimental pulmonary hypertension, humans with primary and secondary PAH, and healthy volunteers with hypoxic pulmonary vasoconstriction.[12–15] Type 5 phosphodiesterase is abundant in the pulmonary vascular bed and is upregulated in pulmonary hypertension.[12,16] Sildenafil is a highly selective and potent inhibitor of the cGMP-specific type 5 phosphodiesterase isoenzyme. At the cellular level, vasodilation involves alterations in calcium signaling in part by opening of BK_{ca} channels in humans with PAH.[15] Type 5 phosphodiesterase is highly expressed in the human pulmonary artery smooth muscle cell. Therefore, we hypothesized that oral sildenafil would ameliorate symptoms and improve pulmonary vascular hemodynamics selectively in children with chronic PAH. Therefore, the objectives of the present study were to evaluate the effects of prolonged oral sildenafil on distance walked in 6 minutes and hemodynamics in children with PAH.

Methods

Study Design
We performed a 12-month clinical trial of oral sildenafil in an open-label, single-drug, pilot study.

Protocol

The study protocol was approved by the research and ethics review board of the Hospital for Sick Children, Toronto, Canada, and informed, signed consent and assent were obtained from the study subjects and their parents.

All patients with symptomatic PAH who were able to reliably perform a 6-minute walk test were eligible for inclusion. Patients with congenital heart disease were included if PAH persisted after cardiac repair or if they were considered inoperable. Patients with primary PAH were eligible only if they were nonresponders to inhaled NO, if they had unfavorable hemodynamics for calcium channel blockade, or who, despite meeting criteria for chronic intravenous prostacyclin, refused therapy after counseling by a member of the pulmonary hypertension clinic. We excluded patients with pulmonary hypertension secondary to chronic obstructive airway disease, pulmonary venous obstruction, and acute or chronic inflammatory lung disease. In addition, patients with hepatic or renal insufficiency and known retinal disease were excluded. The primary outcome measure was distance walked in 6 minutes. The secondary outcome measure was the pulmonary vascular resistance index (PVRI) at repeated cardiac catheterization.

We estimated that a sample size of ≈15 patients would be required to demonstrate an 85-m increase in distance walked in 6 minutes (comparable to the increase in the 6-minute walk distance reported after 6 weeks of intravenous prostacyclin[17]) with a significance level of 0.05 and 80% power to reject the null hypothesis.

All patients were evaluated in the pulmonary hypertension clinic according to the following protocol. Patients were assessed by history, physical examination, echocardiography, ECG, chest x-ray, nuclear ventilation-perfusion scan, high-resolution chest computed tomography scan, and baseline 6-minute walk test. All patients underwent diagnostic cardiac catheterization at either the referring hospital or our institution. We performed baseline and follow-up cardiac catheterizations in 9 patients at our institution according to the following protocol. Patients were studied under general anesthesia with mechanical ventilation with a baseline FiO_2 of 0.25. Anesthesia was induced with sevoflurane, midazolam, and remifentanil. Sevoflurane was discontinued after induction. Rocuronium was used for muscle relaxation. We recorded heart rate, systemic and pulmonary arterial pressures, left (or pulmonary capillary wedge) pressure, and right atrial pressure in the standard manner with fluid-filled catheters. Oxygen consumption was measured. Oxygen saturations were measured by co-oximetry after sampling in the superior vena cava, pulmonary vein, pulmonary artery, and systemic artery. We estimated systemic and pulmonary blood flows from the Fick equation. We calculated systemic and pulmonary vascular resistances from standard equations (mean arterial pressure − mean atrial pressure divided by flow). Blood flow and vascular resistances were indexed to body surface area. At the baseline cardiac catheterization, assessment of pulmonary vascular reactivity to inhaled NO at 40 ppm with an FiO_2 of 0.85 was undertaken. We defined pulmonary vascular reactivity as a ≥10% decrease in mean pulmonary artery pressure or a ≥20% decrease in PVR according to the criteria of Weir et al.[18] Follow-up cardiac catheterization did not include vasodilator testing and was limited to intravascular pressure and oxygen saturation measurements. A 6-minute walk test was performed at baseline and after 6 weeks and 3, 6, and 12 months. Additional assessments were made as required by clinical necessity. Evaluation included history and physical examination, complete blood count, urea, creatinine, liver function tests, and 6-minute walk test. Evaluation of visual acuity and color vision were undertaken at each assessment with standard charts and Hardy-Rand-Rittler pseudoisochromatic plates (third edition, Richmond Products).

The 6-minute walk test was performed according to a standardized protocol before the first sildenafil dose (baseline) and after 6 weeks, 12 weeks, 6 months, and 12 months. Subjects were asked to walk at their own pace but cover as much ground as possible in 6 minutes. They walked along an enclosed, level, measured corridor, and a technician escorted each patient. Noninvasive pulse oximetry was used to estimate systemic oxygen saturation during the walk. Sildenafil was prescribed orally at a starting dose of 0.25 mg/kg for

2 doses and increased to ≈0.5 mg/kg per dose administered 4 times daily. Doses were adjusted to be easily divisible fractions of the available tablets. If patients were receiving adjunctive therapies on enrolment to the study, these were continued. These included Coumadin in 9, aerosolized prostacyclin in 4, digoxin in 3, furosemide in 2, and L-arginine in 1 patient. We did not change the medications in any patient during 12 months of study observation.

Statistical Analysis

Repeated ANCOVA was performed to assess whether there was a difference in the distance walked in 6 minutes over 12 months with adjustment for baseline. A covariance structure that adjusted for the unequal spacing of the data was used. An overall effect of time was first determined. Then we compared the difference in distance walked between baseline, 6 months, and 12 months. The probability values for multiple comparisons was adjusted by the Tukey-Kramer method. A check of the assumption of repeated-measures ANCOVA showed no evidence to reject the normality of the residuals, and a plot of the residuals against those predicted showed no evidence of a pattern, indicating that the assumption of homogeneity of variance was not violated. Hence, the model was accepted. The distance walked in 6 minutes is presented as mean±SD. A correlation between distance walked in 6 minutes and PVRI was sought by Pearson's test. We analyzed the hemodynamic and laboratory data with a Wilcoxon signed-rank test and presented these as median and range. Significance was set at the traditional 5% level.

Results

Between August 2001 and January 2003, 167 patients were evaluated in the pulmonary hypertension clinic. Sixty-three patients had symptomatic PAH. Forty-nine patients were excluded because they were too young to perform a 6-minute walk test (n=13), were suitable for therapy with or were already doing well on calcium channel blockers or intravenous prostacyclin (n=15), or after evaluation, were referred for closure of a vascular or intracardiac shunt (n=21). Fourteen patients (median age, 9.8 years; range, 5.3 to 18) with PAH fulfilled entry criteria and were enrolled in the study protocol. The clinical characteristics of the patients are outlined in Table 1. Diagnoses were primary PAH in 4 and secondary PAH in 10 patients (after repair of congenital heart disease in 7 or Eisenmenger syndrome in 3 patients). The median time from cardiac repair to the start of sildenafil therapy was 7 years (range, 0.8 to 15.5). The baseline systemic oxygen saturations of the patients with Eisenmenger syndrome (patients 5, 6, and 13 in Table 1) were 85%, 90%, and 73% and at 1 year of follow-up, respectively; the systemic oxygen saturations were 91%, 91%, and 92%, respectively. At diagnosis, 4 patients were assigned to New York Heart Association (NYHA) functional class II, 6 patients to class III, and 4 patients to class IV. At the end of the study period, 9 patients were assigned to NYHA functional class I, 2 patients to functional class II, and 3 patients to functional class III.

Six-Minute Walk Test

During sildenafil therapy, the mean distance walked at 6 weeks, 12 weeks, 6 months, and 1 year was 331 (±112), 355 (±91), 443 (±107), and 432 (±156) m, respectively (Figure). Improvement in distance walked in 6 minutes occurred between baseline and 6 months (P=0.02) without deterioration between 6 months and 12 months (P=0.9). Analysis without the 2 outliers in the Figure demonstrated improve-

TABLE 1.   Baseline Characteristics of Patients Treated With Sildenafil

| Pt	Sex	Diagnosis	Weight, kg	Height, cm	Age at Baseline, y	Other Medication	NYHA Class at Baseline	6-Minute Walk at Baseline, m
1	Female	Primary PAH	15	95	5	Coumadin	II	346
2	Male	Primary PAH	15	105	5	L-Arginine	II	268
3	Male	s/p VSD repair	11	98	6	None	III	345
4	Male	Primary PAH, PFO	15	109	7	Coumadin, inhaled prostacyclin	IV	58
5	Female	Unrepaired VSD	21	116	7	None	II	345
6	Female	Unrepaired AVSD Trisomy 21	19	113	9	Digoxin	III	192
7	Female	s/p VSD repair	29	133	9	Coumadin	III	461
8	Female	s/p VSD repair	42	145	10	Coumadin	II	422
9	Female	Primary PAH	37	147	12	Coumadin, inhaled prostacyclin	III	249
10	Male	s/p AVSD repair	47	144	12	Coumadin	III	288
11	Female	s/p AVSD repair Trisomy 21	26	125	13	Coumadin, inhaled prostacyclin, digoxin	III	288
12	Male	s/p AVSD repair Trisomy 21	43	149	16	Coumadin, inhaled prostacyclin, furosemide	IV	192
13	Male	Unrepaired VSD	62	170	18	Aspirin	IV	346
14	Female	Primary PAH	55	160	18	Coumadin, inhaled prostacyclin, digoxin, furosemide	IV	96

s/p indicates status post; VSD, ventricular septal defect; PFO, patent foramen ovale; and AVSD, atrioventricular septal defect.

ment between baseline and 6 months ($P=0.006$) without deterioration between 6 and 12 months ($P=0.48$). The difference in the distance walked between baseline and 12 months remained significant with or without inclusion of the 2 outliers ($P=0.0005$ and 0.0006, respectively).

Hemodynamic Changes

Five patients (No. 1, 3, 12, 13, and 14 in Tables 1 and 3) did not undergo both a baseline and a follow-up cardiac catheterization before starting sildenafil. However, previous cardiac catheterization had been performed to establish the diagnosis. Therefore, in 9 patients, cardiac catheterization was performed at baseline and repeated after a median follow-up of 10.8 months (range, 6 to 15.3) (Tables 2 and 3).

At baseline cardiac catheterization, the median percentage decrease in PVRI in response to inhaled NO was 8% (range, +2% to −17%). At follow-up cardiac catheterization in response to sildenafil therapy, systolic pulmonary artery pressure decreased significantly from 86 mm Hg (range, 69 to 136) to 70 mm Hg (range, 54 to 120) ($P=0.014$), mean pulmonary artery pressure decreased significantly from 60 mm Hg (range, 50 to 105) to 50 mm Hg (range, 38 to 84) ($P=0.014$), and diastolic pulmonary artery pressure decreased significantly from 46 mm Hg (range, 30 to 81) to 30 mm Hg (range, 17 to 60) ($P=0.022$). PVR decreased from 15 Wood units m^2 (range, 9 to 42) to 12 Wood Units m^2 (range, 5 to 29) ($P=0.024$). Superior vena caval oxygen saturation increased from 66% (range, 57% to 74%) to 69%
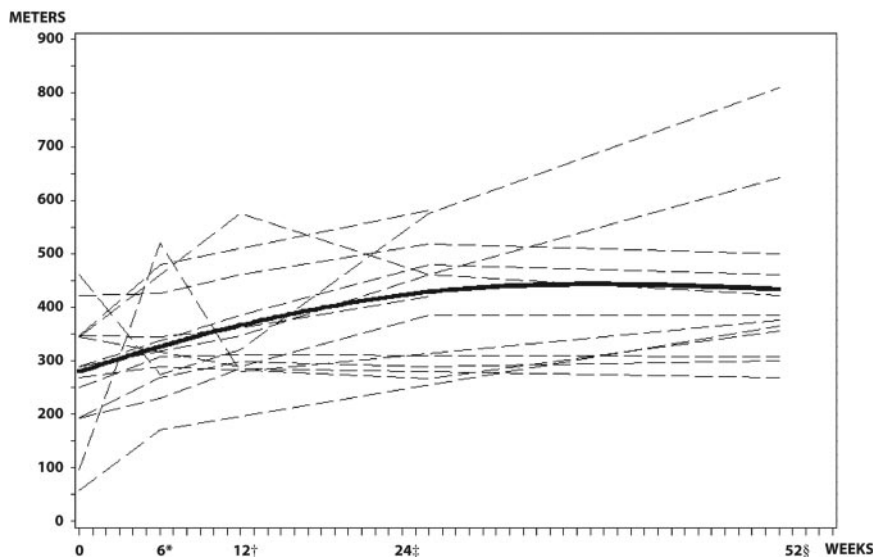
Graphic representation of distance walked in 6 minutes in all patients. Vertical axis represents distance in meters, and horizontal axis represents time in weeks. Dotted lines represent distance walked of individual patients. Bold line is locally weighted, smoothed estimator to show mean trend. Distance walked increased between baseline and 24 weeks, with sustained plateau between 24 and 52 weeks. *Baseline compared with 24 weeks, $P=0.02$; †Baseline compared with 52 weeks, $P=0.005$; ‡24 weeks compared with 52 weeks, $P=0.9$. Mean distance walked at 6 weeks, 12 weeks, 6 months, and 1 year was 331 (±112), 355 (±91), 443 (±107), and 432 (±156) m, respectively.

TABLE 2.   Hemodynamic Measurements/Calculations and Laboratory Values (Median and Range) During Cardiac Catheterization at Baseline and at Median Follow-Up of 10.8 Months

	Baseline		Follow-Up	
	Median	Range	Median	Range
Heart rate, bpm	75	55–94	70	55–105
Systemic arterial pressure, mm Hg				
Systolic	86	80–93	86	74–110
Diastolic	50	44–66	50	40–56
Mean	64	57–72	64	58–70
Pulmonary arterial pressure, mm Hg				
Systolic	86	69–136	70*	54–120
Diastolic	46	30–81	30†	17–60
Mean	60	50–105	50‡	38–84
Right atrial mean pressure, mm Hg	6	5–16	6	3–11
Left atrial mean pressure, mm Hg	6	5–16	6	3–16
Systemic O_2 saturation, %	95	87–98	97	90–99
Superior vena caval O_2 saturation, %	66	57–74	69	60–81
Pulmonary venous O_2 saturation, %	98	93–100	98	92–100
Pulmonary arterial O_2 saturation, %	73	57–84	72	67–88
Oxygen consumption, $mL \cdot m^{-2} \cdot min^{-1}$	167	102–262	148	100–204
Hemoglobin, g/L	151	117–175	138	125–156
Cardiac index, $L \cdot min^{-1} \cdot m^{-2}$	2.9	2.3–4.4	3.0	2.3–4.7
Pulmonary blood flow index, $L \cdot min^{-1} \cdot m^{-2}$	2.9	2.4–5.6	3.0	2.4–7.2
Systemic VRI, Wood U m^2	20	13–47	19	13–26
PVRI, Wood U m^2	15	9–42	12§	5–29
pH, U	7.41	7.37–7.48	7.44	7.37–7.5
$Paco_2$, mm Hg	33	32–39	36	30–41
Pao_2, mm Hg	75	62–104	91	52–126
Bicarbonate, mmol/L	22	19–24	23	21–25

*$P=0.014$, †$P=0.022$, ‡$P=0.014$, §$P=0.024$.

(range, 60% to 81%) ($P=0.033$). There were no significant changes in systemic blood pressure, systemic VRI, cardiac index, left and right atrial pressures, hemoglobin, oxygen consumption, or aortic oxygen saturation. Arterial blood gas analysis demonstrated no differences between cardiac catheterizations. There was no correlation between the change in PVRI or distance walked in 6 minutes at 6 weeks, 6 months, or 12 months.

Dose of Sildenafil

The median dose at the start of therapy was 0.5 mg/kg (range, 0.3 to 0.7), and at 12 months, the median was 0.5 mg (range, 0.3 to 1). We started at a dose of 0.25 mg/kg, and if this was well tolerated, it was increased to 0.5 mg/kg with the next dose. All patients received the first 4 doses in hospital.

Patient No. 12 had trisomy 21 and a repaired atrioventricular septal defect with multiple ventricular septal defects. The cardiac defect was repaired at age 11 months. At age 16 years, his physical condition deteriorated. He was referred to the pulmonary hypertension clinic with increasing cyanosis, decreased right ventricular function, suprasystemic right ventricular pressures, hepatomegaly, thrombocytopenia, chylous pleural effusion, and plastic bronchitis. His baseline 6-minute

walk distance was 192 m. He improved with oral sildenafil and a low-fat diet, and the plastic bronchitis resolved. The plastic bronchitis reappeared at 3 months and was abolished again with an increase in sildenafil dose, from 0.5 mg/kg 4 times daily to 1 mg/kg 4 times daily, as well as a short course of aerosolized tissue plasminogen activator. His 6-minute walk distance peaked at 285 m but decreased at 12 months to 269 m. He died after contracting a community-acquired respiratory infection after 22 months of therapy. There was no recurrence in the plastic bronchitis.

Safety and Tolerability

Sildenafil was well tolerated, and no patient withdrew. There was no change in creatinine, urea, liver function tests, or platelet count. The medians and ranges at baseline and at 1 year, respectively, were 46 μmol/L (28 to 126) versus 53 μmol/L (30 to 102) for serum creatinine, 5.6 μmol/L (3 to 11.1) versus 4.4 μmol/L (2.3 to 10.5) for blood urea nitrogen, 74 g/L (69 to 85) versus 75 g/L (71 to 85) for total protein, 40 g/L (38 to 54) versus 42 g/L (40 to 46) for albumin, 191 U/L (75 to 508) versus 194 U/L (17 to 425) for alkaline phosphatase, 5 μmol/L (2 to 13) versus 5 μmol/L (2 to 23) for unconjugated bilirubin, 781 U/L (729 to 968) versus 627 U/L

TABLE 3. Individual Hemodynamic Data Before and After Treatment With Oral Sildenafil

Pt/Time of Evaluation	SABP, mm Hg	PAP, mm Hg	RAP, mm Hg	LAP, mm Hg	SVRI, Wood U m²	PVRI, Wood U m²	PVR Change, %
2							
Baseline	80/44 (57)	120/80 (105)	6	6	15	42	
Follow-up	93/48 (68)	116/60 (84)	6	6	23	29	−31
4							
Baseline	86/60 (68)	100/81 (82)	4	5	14	17	
Follow-up	90/56 (70)	80/50 (64)	4	4	14	13	−24
5							
Baseline	82/50 (65)	86/34 (60)	5	6	26	21	
Follow-up	80/50 (64)	80/30 (58)	3	3	26	23	+9
6							
Baseline	93/46 (64)	69/46 (58)	6	6	21	9	
Follow-up	74/40 (58)	60/40 (50)	11	11	18	5	−44
7							
Baseline	80/66 (64)	80/40 (60)	7	9	20	11	
Follow-up	82/50 (64)	54/17 (38)	3	5	21	10	−10
8							
Baseline	90/50 (63)	70/30 (52)	8	10	19	15	
Follow-up	86/56 (64)	60/30 (42)	6	10	18	10	−33
9							
Baseline	90/60 (72)	136/80 (100)	6	6	47	38	
Follow-up	92/53 (66)	120/40 (70)	6	6	20	21	−18
10							
Baseline	90/60 (70)	70/30 (50)	12	16	22	13	
Follow-up	110/51 (63)	70/30 (50)	10	16	19	12	−8
11							
Baseline	80 48 (58)	90/46 (62)	9	10	13	14	
Follow-up	80/45 (60)	64/24 (42)	8	12	13	8	−43

SABP indicates systemic arterial blood pressure, systolic/diastolic (mean); PAP, pulmonary artery pressure, systolic/diastolic (mean); RAP, right atrial pressure; LAP, left atrial pressure; and SVRI, systemic vascular resistance index.

(499 to 1015) for lactate dehydrogenase, 17 U/L (13 to 24) versus 14 U/L (4 to 32) for alanine aminotransferase, 30 U/L (21 to 52) versus 37 U/L (23 to 48) for aspartate aminotransferase, 24 U/L (19 to 83) versus 22 U/L (14 to 88) for γ-glutamic transpeptidase, and 202 10^9/L (91 to 291) versus 185 10^9/L (73 to 341) for platelet count. Two patients suffered heavy menstrual losses with the menarche, which responded to progesterone therapy. Two patients reported self-limiting nosebleeds. There were no changes in visual acuity or color vision during the study period. One patient noted earlier did not tolerate a dose of 1 mg/kg, but symptoms (facial flushing, headache, and dizziness on standing) disappeared with a reduction in dose to 0.5 mg/kg.

There were no deaths during the 12-month follow-up. However, 5 patients died after a median follow-up of 20.2 months (range, 12 to 30). All of the patients who died demonstrated an improvement during the first year by distance walked in 6 minutes.

Discussion

We found in a 12-month clinical trial of oral sildenafil in an open-label, single-drug, pilot study that sildenafil may im-prove both exercise tolerance as well as pulmonary vascular hemodynamics in children and adolescents with PAH. The distance walked in 6 minutes increased during the first 6 months of therapy and was maintained for 12 months. In addition, long-term therapy was not associated with any major adverse sequelae attributable to sildenafil.

Distance walked in 6 minutes has been reported to corre-late well with prognosis in patients with PAH[17,19] and has been used to gauge the success of other therapies for pulmonary hypertension in both adults and children.[4,5,6,17,20] Indeed, the improvement of 154 m over 12 months compares favorably with the increases of 44 and 70 m reported with bosentan (45 m) and prostacyclin[6] (47 m). The differences may be due to the younger age, smaller patient numbers, and the preponderance of secondary pulmonary hypertension in our study. However, the improvement in distance walked was comparable to the 128-m increase in adults with PAH treated with sildenafil for 3 months, as reported by Michelakis et al.[15] Furthermore, all of the patients included were nonresponders to acute vasodilator testing, as defined by Weir et al,[18] suggesting the presence of advanced disease,[21,22] which,

despite the difference in etiology, has histological features indistinguishable from those of primary PAH.[23,24]

The present study was not randomized and had no placebo or control group for comparison. However, historically similar patients with pulmonary hypertension reported from our institution did poorly, nonresponders did not survive 1 year, and survival of all patients was only 37% at 1 year.[22] In contrast, we demonstrated not only 100% survival at 1 year but also improved exercise capacity in patients treated with sildenafil. Nevertheless, randomized, placebo-controlled trials are required to elucidate the place of sildenafil in the treatment of childhood and adolescent PAH. However, late attrition occurred after a median 20 months in 5 patients, despite early improvement. Further study is required to evaluate the reasons for this. It is possible that the sildenafil doses need to be increased with time and that in certain patients, combination therapy may be advantageous, as reported with NO and sildenafil, and aerosolized iloprost and sildenafil.[13,25–27] In this regard, it is noteworthy that our patient who was receiving L-arginine therapy has done particularly well.

In 9 patients, pulmonary hemodynamics improved selectively at follow-up despite the absence of an acute response to inhaled NO. We did not measure an increase in cardiac output, as reported by others,[15] suggesting that in our patients at rest and under general anesthesia, cardiac output was not limited by PVR. We can only speculate whether the primary effect of sildenafil is due to vasodilation, vascular remodeling, or a combination. The improvement in PVR without an initial acute vasodilator response to inhaled NO suggests that vascular remodeling may have occurred. We speculate further that the mechanism for vascular remodeling may be cGMP-mediated suppression of extracellular signal–regulated kinase phosphorylation and decreased AML1B transcription factor, resulting in decreased smooth muscle cell production of endogenous serine vascular elastase.[28] The hemodynamic improvements with sildenafil in this report compare favorably with those reported by Barst et al[20] in children with primary and secondary PAH treated with bosentan for 12 weeks.

The resolution of plastic bronchitis in one of our patients is interesting and noteworthy. Plastic bronchitis is a rare complication of cyanotic heart disease, with elevated systemic venous pressures and damaged pleural lymphatics, resulting in the endobronchial leakage of lymph and subsequent cast formation.[29] It is often fatal, and we speculate that a decrease in systemic venous pressure due to a decrease in PVR decreased the endobronchial lymph leakage in our patient. Consideration of a trial of sildenafil may be justified in cases of plastic bronchitis, given the paucity of medical therapies and the safety of sildenafil.

Limitations of this report can be attributed to the small number of patients, the absence of randomization, and the lack of a contemporary control group. Confirmation of these promising findings in a randomized, controlled clinical trial is essential to verify efficacy, tolerance, and safety.

In summary, we report the results of a 12-month clinical trial of oral sildenafil in an open-label, single-drug, pilot study. We suggest that oral sildenafil may have the potential to improve distance walked in 6 minutes and pulmonary hemodynamics in children and adolescents with primary and secondary PAH. Furthermore, improvement may be sustained for 1 year with a reduction in mortality, compared with historical controls. Oral sildenafil was tolerated well by our patients, and there were no obvious effects on visual acuity and color vision. Confirmation of these results in a randomized, controlled clinical trial is essential.

Acknowledgment

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