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Original Article

Low-dose oral sildenafil for patients with pulmonary hypertension: a cost-effective solution in countries with limited resources

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Abstract *Introduction:* Pulmonary arterial hypertension, both primary and secondary, continues to pose a therapeutic problem. In this study, we evaluate the efficacy and safety of a low-dose of oral sildenafil in 10 patients with pulmonary arterial hypertension. *Methods:* We administered a single daily dose of 0.5 milligrams per kilogram of sildenafil for 3 months to 10 patients with pulmonary arterial hypertension. Their average age was 26.8 years. Diagnoses were primary pulmonary arterial hypertension in 3 patients, and secondary pulmonary arterial hypertension due to congenital cardiac disease in the remaining 7 patients. Outcome measures included the clinical state, the mean pulmonary arterial pressure, and the indexed pulmonary vascular resistance; the latter two assessed at the beginning and at the end of the treatment period by cardiac catheterization. We also analysed the cost of the treatment. *Results:* Oral treatment was well tolerated, and resulted in an improvement of the functional capacity in 9 of the 10 patients. Pulmonary arterial pressure decreased from 70 to 60 millimetres of mercury (p equal to 0.05), and indexed pulmonary vascular resistance decreased from 21.8 to 15.8 Wood units per square metre (p equal to 0.006). The mean cost per patient for 3 months on oral treatment with sildenafil was 120.99 American dollars. *Conclusions:* A low dose of 0.5 milligrams per kilogram per day of oral sildenafil, instead of 1 to 4 milligrams per kilogram per day, provided early clinical and haemodynamic improvements, and proved less expensive. Additional experience is now required to define more reliably the true long-term benefits of this therapy.

Keywords: Open-label; pulmonary vascular disease; oral medication

PULMONARY ARTERIAL HYPERTENSION, BOTH primary and secondary, continues to pose a significant therapeutic problem.[1] Since established medical treatments with epoprostenol, nitric oxide, iloprost and bosentan, are not uniformly effective in all patients, and are expensive and therefore not affordable by many patients,[2–4] other agents have been investigated.[4–9] Sildenafil, an inhibitor of phosphodiesterase, has been recently proposed as a promising agent for management of pulmonary arterial hypertension in both children and adults.[4–10] According to currently available clinical trials,[5] oral sildenafil is well tolerated after 3 months of treatment, and seems to reduce mean pulmonary arterial pressure and pulmonary vascular resistance, leading to an early increased exercise tolerance. So far, only a limited number of patients have been evaluated, and the long-term effects on the human pulmonary vasculature remain unknown.[11–13] Furthermore, the lowest doses of oral sildenafil required to obtain optimal clinical results still need to be defined, which is of particular importance in low-income countries, where resources for health-care are limited, and inhaled nitric oxide and expensive intravenous drugs are not generally available.[14,15] In this study, therefore, we evaluated the efficacy and safety of oral sildenafil administered at low dosage over a period of 3 months to 10 patients with pulmonary arterial hypertension.

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Methods

Between August and December 2003, 24 patients with symptomatic pulmonary arterial hypertension were evaluated at the Pediatric Cardiac Surgery Unit of Guatemala. Patients included in the study had a mean pulmonary arterial pressure of 25 millimetres of mercury or more, and had pulmonary-capillary wedge pressure of 15 millimetres of mercury or less at rest before the commencement of oral therapy.[16] We included patients with both primary and secondary pulmonary arterial hypertension in the study. Patients with pulmonary arterial hypertension secondary to congenital cardiac disease were included if pulmonary arterial hypertension persisted after cardiac repair, or if they were considered inoperable. We excluded patients who were already being treated with medications that could have an influence on pulmonary arterial pressure, such as nitrates, calcium channel blockers and inhibitors of angiotensin converting enzyme.

The protocol was approved by the research and ethics committee of the Pediatric Cardiac Surgery Unit of Guatemala. Informed consent was obtained directly from patients, or from their legal caregivers if the patients were less than 18 years old.

Oral sildenafil was specially prepared by the pharmacy at out Institution in order to supply each patient with a daily single oral dose of 0.5 milligram per kilogram for 3 months.

Outcome measures included the clinical state of the patients, their standing within the categorization of the New York Heart Association, the pulmonary arterial pressure, and the indexed pulmonary vascular resistance. Regarding clinical state, during the period of the study, all patients were assessed every 15 days by history to confirm their compliance to treatment, and physical examination. Each patient was classified according to the system of the New York Heart Association at the beginning and at the end of the treatment with oral sildenafil, in accordance to his referred day-activities and tolerance to effort. Mean pulmonary arterial pressure, and indexed pulmonary vascular resistance, were assessed at our Institution by cardiac catheterization at baseline and at follow-up immediately after the 3 months of treatment. No drug was taken by any of the 10 patients on the day of the study prior to the final catheterization.

Patients were studied under sedation with ketamine at 1 milligram per kilogram given intravenously, and midazolam at 0.1 milligram per kilogram, also given intravenously, and local anesthesia with 2% lidocaide. Heart rate, systemic and pulmonary arterial pressures, left atrial or pulmonary capillary wedge pressure, and right atrial pressure were recorded. Consumption of oxygen was derived from standard tables. Saturations of oxygen were determined by co-oxymetry after sampling within the superior caval vein, a pulmonary artery, a systemic artery, and the pulmonary veins. Pulmonary venous saturation of oxygen was assumed by sampling of the pulmonary arterial wedge in patients without an atrial septal communication. Systemic and pulmonary flows of blood were calculated based on the Fick principle, including also the dissolved oxygen when 100% inspired fraction of oxygen was used. Systemic and pulmonary resistances were calculated from standard equations. Flows of blood, and vascular resistances, were indexed to body surface area. At baseline and follow-up cardiac catheterization, pulmonary vascular reactivity was evaluated with a 100% inspired oxygen fraction.

The mean cost per patient for 3 months of treatment with oral sildenafil was calculated in American dollars, and compared to the estimated cost of the average dose for 3 months of treatment with other medication for pulmonary arterial hypertension, specifically bosentan at 125 milligrams orally twice a day, epoprostenol at 20 nanograms per kilogram per minute given intravenously, iloprost at 5 micrograms inhaled six times each day, nitric oxide inhaled at 20 parts per million, and treprostinil given intravenously at 10 nanograms per kilogram per minute.[17–23]

Results are presented as mean and standard deviations. Differences between interval measurements, before and after treatment with sildenafil, in the same individual were assessed by a paired t-test.[24] A p-value less than 0.05 was considered statistically significant.

Results

Population studied. We found that 10 patients with pulmonary arterial hypertension fulfilled all our criterions for inclusion, and they were enrolled for the study. Their demographic data is listed in Table 1. Diagnoses were primary pulmonary arterial hypertension in 3 patients, and secondary pulmonary arterial hypertension in the remaining 7 patients, occurring after repair of congenital cardiac disease in 2 patients, and because of Eisenmenger's syndrome in 5 patients. Their mean age was 26.8 years, with standard deviation of 15.12 years.

Oral sildenafil was well tolerated, and no patient withdrew from this study, albeit that 4 patients complained of mild headache that resolved with anti-inflammatory medications, and 2 patients reported dyspepsia during the first 15 days of treatment, which resolved spontaneously. There were no changes in visual acuity or colour vision during the period of study, and there were no deaths during the period of follow-up.

Table 1. Demographic data of patients and functional state before and after treatment with sildenafil.

Pts	Sex	Age (years)	Weight (kg)	Diagnosis	NYHA pre	NYHA post
1	M	8	19	Surgical closure VSD	II	I
2	M	10	32	Un-repaired VSD	II	I
3	M	18	49	Surgical closure VSD	III	II
4	F	20	46	Primary PAH	III	III
5	F	22	42	Un-repaired FSV-TGA	III	II
6	M	25	43	Un-repaired ASD	III	II
7	F	31	48	Un-repaired ASD	III	II
8	F	34	40	Un-repaired ASD	III	II
9	M	42	73	Primary PAH	III	II
10	M	58	50	Primary PAH	III	II

Abbreviations: ASD: atrial septal defect within the oval fossa; kg: kilograms; NYHA: New York Heart Association class; PAH: primary pulmonary hypertension; FSV-TGA: functionally single ventricle with transposed great arteries; VSD: ventricular septal defect

Table 2. Haemodynamic measurements/calculations during cardiac catheterization before and after treatment with sildenafil.

	Pre mean value (SD)	Post mean value (SD)	p
Heart rate, bpm	72.3 (9.4)	72.2 (12.1)	0.95
SAP, mmHg			
Systolic	108.5 (9.54)	103.5 (7)	0.31
Diastolic	67.7 (9)	64.7 (6.81)	0.42
Mean	81.7 (8)	77.8 (6.8)	0.18
PAP, mmHg			
Systolic	109 (25.35)	105.5 (24.51)	0.09
Diastolic	47.1 (16.01)	36.8 (15.63)	0.05
Mean	70.6 (15.49)	60.1 (17.79)	0.05
RAP, mmHg	6.2 (3.42)	6.5 (3.1)	0.78
LAP, mmHg	6 (1.76)	7.6 (2.87)	0.15
Systemic O_2 saturation, %	92.3 (4.27)	94.5 (3.24)	0.08
Pulmonary venous O_2 saturation, %	91.7 (5.33)	94.1 (4.58)	0.93
Pulmonary arterial O_2 saturation, %	65.64 (10.56)	69.11 (10.93)	0.05
SCV saturation O_2 saturation, %	64.7 (8.27)	65.8 (12.66)	0.73
Haemoglobin, g/l	15.1 (2.81)	15.69 (2)	0.13
Cardiac index, l/min/m^2	3.19 (1)	3.29 (1.49)	0.74
Pulmonary blood flow index, l/min/m^2	2.97 (0.85)	3.24 (1.26)	0.22
SVRI, Wood units/m^2	24.1 (3.21)	21.9 (1.45)	0.1
PVRI, Wood units/m^2	21.81 (10.32)	15.78 (8.46)	0.006
PVRI/SVRI, Wood units/m^2	0.95 (0.4)	0.74 (0.34)	0.01

Abbreviations: g: grams; l: liters; LAP: left atrial pressure; mmHg: millimetres of mercury; min: minutes; m^2: square metres; O_2: oxygen; PAP: pulmonary artery pressure; PVRI: pulmonary vascular resistance index; RAP: right atrial pressure; SAP: systemic arterial blood pressure; SD: standard deviation; SCV: superior caval vein; SVRI: systemic vascular resistance index

Clinical state. At the beginning of the study, 2 patients were in New York Heart Association functional class II, and 8 patients were in class III. At the end of the treatment with sildenafil, 7 patients who had been in New York Heart Association functional class III improved to class II. Only one patient remained in class III. Two patients who had been in New York Heart Association class II improved to class I (Table 1).

Haemodynamic changes. At follow-up cardiac catheterization, systolic pulmonary arterial pressure decreased from 109 millimetres of mercury, with standard deviation of 25, to 105.5 millimetres of mercury, with deviation of 24 (−3.3%, p equal to 0.09). The mean pulmonary arterial pressure decreased from 70 millimetres of mercury, with standard deviation of 15, to 60 millimetres of mercury, the standard deviation being 17 (−14.3%, p equal to 0.05). Diastolic pulmonary arterial pressure decreased from 47 millimetres of mercury with deviation of 16, to 36 millimetres of mercury and standard deviation of 15 (−23.5%, p equal to 0.05). Indexed pulmonary vascular resistance decreased from 21.8 Wood units per square metre, standard deviation of 15.3, to 15.8 Wood units per square metre, standard deviation of 8.5 (−27.6%, p equal to 0.006). The ratio of indexed pulmonary to systemic vascular resistance decreased from 0.95, with standard deviation of 0.4, to 0.74, with standard deviation of 0.34 (p equal to 0.01) (Tables 2 and 3).

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Table 3. Individual haemodynamic data* before and after treatment with sildenafil.

Pts	Cardiac catheterization	MPAP (mmHg)	Change (%)	PVRI (Wood units/m^2)	Change (%)
1	Pre	56	−5	17	−8
	Post	53		15.7	
2	Pre	75	−3	27.7	−24
	Post	73		21	
3	Pre	83	−54	31	−52
	Post	38		14.7	
4	Pre	65	−2	28.9	−18
	Post	64		23.4	
5	Pre	70	+9	9.1	−34
	Post	77		6	
6	Pre	93	−10	16.2	−16
	Post	84		13.6	
7	Pre	86	−7	41.9	−18
	Post	80		34.5	
8	Pre	69	−26	20.8	−67
	Post	51		6.8	
9	Pre	70	−5	14.2	−23
	Post	44		10.9	
10	Pre	39	−5	11.3	−4
	Post	37		10.8	

*: with 21% inspired fraction of oxygen
Abbreviations: MPAP: mean pulmonary arterial pressure; PVRI: pulmonary vascular resistance index; SD: standard deviation

Table 4. Haemodynamic measurements during cardiac catheterization before and after treatment with sildenafil.

	FiO_2	Pre mean value (SD)	Post mean value (SD)	p
MPAP, mmHg	21%	70.6 (15.49)	60.1 (17.79)	0.05
	100%	66.9 (16.13)	56.8 (5.55)	0.02
	p	0.03	0.0001	
PVRI, Wood units/m^2	21%	21.81 (10.32)	15.78 (8.46)	0.006
	100%	11.96 (5.25)	9.34 (6.81)	0.03
	p	0.005	0.003	

Abbreviations: FiO_2: inspired oxygen fraction; MPAP: mean pulmonary arterial pressure; PVRI: pulmonary vascular resistance index; SD: standard deviation

Pulmonary vascular reactivity expressed as a decrease in mean pulmonary arterial pressure and indexed pulmonary vascular resistance with 100% inspired fraction of oxygen was similar between the pre and post catheterization data. Values for mean pulmonary arterial pressure and indexed pulmonary vascular resistance with 100% of inspired fraction of oxygen are significantly lower at follow-up (Table 4).

Pulmonary arterial saturations of oxygen increased at follow-up from 65, with standard deviation of 10%, to 69, with standard deviation of 11% (p equal to 0.05) (Table 2).

There were no significant changes in systemic blood pressure, systemic vascular resistance, cardiac index, left and right atrial pressures, haemoglobin, or aortic saturations of oxygen between baseline and follow-up (Table 2).

Cost calculation. In Guatemala, the mean cost per patient for 3 months on oral sildenafil at the dose of 0.5 milligrams per kilograms per day was 120.99 American dollars, with standard deviation of 37.37 dollars. The estimated cost for 3 months of treatment with other medications for pulmonary arterial hypertension was 82.6% to 744% higher than oral sildenafil at the dosage given, being 10,000 American dollars for bosentan, 15,000 American dollars for epoprostenol and iloprost, and 100,000 American dollars for nitric oxide and treprostinil.[16,22]

Discussion

A single-daily dose of 0.5 milligrams per kilogram of oral sildenafil given over a period of 3 months was well tolerated by our patients, and lead to subjective improvement of the functional capabilities in 9 of the 10 with significant pulmonary arterial hypertension. The improvement was noted as early as 15 days after the beginning of the treatment.

Regarding the haemodynamic data, a significant reduction of the mean pulmonary arterial pressure was achieved at the end of the study in 9 of 10 patients, and a reduction of indexed pulmonary vascular resistance in all patients when compared with baseline data before the initiation of the therapy. This improvement of pulmonary haemodynamics, led to significant increases in mean pulmonary arterial saturations of oxygen and indexed pulmonary flow, factors which could be responsible for the improvement in functional capacity.

Oral treatment with sildenafil has been recently proposed as promising for management of pulmonary arterial hypertension in both children and adults.[5–10] According to currently available clinical trials,[5] sildenafil is well tolerated when given orally, seems to reduce pulmonary arterial pressure and indexed pulmonary vascular resistance, and leads to an increase in exercise tolerance in most of the patients with pulmonary arterial hypertension.[5,10,16,25,26] In addition it has been demonstrated that clinical and haemodynamic results of the treatment with sildenafil were comparable to that of nitric oxide, and at least as effective as iloprost or epoprostenol in terms of pulmonary vasoreactivity.[13–15,26] Furthermore, the cost of sildenafil is low if compared to other medications for pulmonary arterial hypertension.[12,13]

According to these data, oral sildenafil could represent a reliable and cost-effective treatment for pulmonary arterial hypertension, especially in low-income

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countries where inhaled and intravenous medications are rarely available, and are also very expensive.[14,15] The appropriate dose of sildenafil to achieve optimal clinical results, however, still needs to be defined, as well as its long term effects upon human pulmonary vasculature.

In our study, we found clinical and haemodynamic improvements that were comparable to those reported previously,[16,26–32] despite using a mean single daily dose of oral sildenafil of 0.5 milligrams per kilogram per day, which is lower than the recommended minimal dose of 60 milligrams per day in three divided doses.[16] Our patients had a 40% to 50% decrease in indexed pulmonary vascular resistance with 100% inspired fraction of oxygen before treatment with sildenafil, demonstrating that their pulmonary vascular resistance was reactive even if it was elevated. The preserved pulmonary vascular reactivity could also explain the beneficial effect of a low single dose of sildenafil.

Our study, nonetheless, presents several limitations. First, the study included only 10 heterogeneous patients. Second, in this open-label study, we do not have a comparison limb with higher and more frequent dosing, nor did we include a control group to exclude a possible "placebo effect" of the drug. Third, we have used assumed and not calculated consumption of oxygen to determine systemic and pulmonary blood flows with the Fick principle. Fourth, although there was a statistically significant decrease in mean pulmonary arterial pressure and indexed pulmonary vascular resistance, the achieved values after treatment continued to remain within very abnormal ranges. Finally we have also a reported subjective functional improvement without any objective measure of improvement in exercise.

In conclusion, a single low dose of oral sildenafil, instead of giving the drug in three daily doses,[5,14,16,31,32] seems to provide an early subjective and objective improvement, and was less expensive than more established treatments. Although the patients experienced both early clinical and haemodynamic improvements after the treatment, it remains to be seen if and how this improvement will affect the progression of the pathologic vascular process, or prolong survival. More experience with a larger group of patients, giving multiple doses versus a single dose of medication, and using a control group and a longer period of follow-up, are required to define more reliably if there is a true long-term benefit of this therapy.

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