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Sildenafil in the management of idiopathic pulmonary arterial hypertension in children and adolescents

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Abstract

Objective: This study aims to provide data on the use of oral sildenafil in patients in New York Heart Association functional class III or IV with severe idiopathic pulmonary arterial hypertension unresponsive to conventional therapy.

Method: In this series, six patients with idiopathic pulmonary arterial hypertension were prospectively treated with 2 to 8 mg of oral sildenafil in four to six doses a day. All patients were submitted to physical examination, electrocardiogram and echocardiogram, chest computed tomography, ventilation and pulmonary perfusion scintigraphy, coagulation studies, and tests for collagen vascular disease, acquired immune deficiency syndrome and schistosomiasis in order to rule out secondary causes of pulmonary arterial hypertension. All patients underwent cardiac catheterization for vasoreactivity tests using nitric oxide, O_2 at 100% and oral nifedipine, and a 6-minute walking test was performed in those patients who were considered able to exercise.

Results: All patients achieved a good therapeutic response, with improvement by at least one functional class, and presented an increase in systemic arterial oxygen saturation. Five patients showed a decrease in the pulmonary systolic pressure to systemic systolic pressure ratio and improvement in the 6-minute walking test. No major side effects were observed at 4 to 36 months of follow-up. One patient had sudden death after sildenafil had been withdrawn by mistake.

Conclusions: These data suggest that sildenafil may be useful in the management of idiopathic pulmonary arterial hypertension. Patients should be advised against the withdrawal of sidenafil without medical supervision.

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Introduction

Idiopathic pulmonary arterial hypertension (IPAH) is defined as a mean pulmonary artery pressure higher than 25 mmHg at rest or 30 mmHg on exercise, of unknown etiology, and with normal pulmonary capillary pressure.[1] It is a rare disease, with an incidence of one to two cases per one million inhabitants/year. IPAH may show familial predisposition in 10% of cases. Observations suggest that vasoconstriction plays a crucial role in the pathogenesis of this disease, which is characterized by pathological hypertrophy of the tunica media of pulmonary arterioles, reduction in the endothelial production of prostacyclin and nitric oxide, and increase in endothelin production.[2] Symptoms, such as fatigue, dizziness, chest pain, heart failure and hypoxemia often develop in the presence of severe hypertension. After its onset, the expectation is of 68, 48 and 34% in one, 3 and 5 years, respectively,[3] in the absence of treatment to reduce pulmonary pressure (PP). The disease is incurable, and patients need lifelong treatment. Reducing PP is the most effective way to alleviate heart failure symptoms, to increase survival, and to improve the quality of life of these patients. Unfortunately, there is no ideal drug for this purpose.

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Several drugs have been used in a continuous fashion, of which calcium antagonists, especially nifedipine, have been used for a longer time period. The pulmonary vasodilatory action of these antagonists is acknowledged, with reduction in PP and increase in the survival of IPAH patients.[4] The necessary doses for PP reduction are usually greater than those used to treat systemic hypertension. It is common knowledge that most patients do not respond to calcium antagonists and may have severe side effects, which shows the importance to perform acute reactivity tests in order to select those patients who would definitely benefit from their use. Pulmonary reactivity tests employ oxygen at 100% and short half-life drugs with pulmonary vasodilatory action, such as adenosine,[5] prostacyclin,[6] acetylcholine and mainly nitric oxide,[7] since it is a selective and short-acting pulmonary vasodilator.

Prostaglandins,[8] in aerosol or continuous infusion pump, are promising drugs, but they have some disadvantages, such as the necessity of many applications a day, risk of complications (infection and thrombosis) when used in continuous infusion, and their high cost. Endothelin inhibitors[9] have been investigated recently, but their cost is also high and they may cause severe side effects (e.g.: liver disorders). Other medication, such as home oxygen therapy and oral anticoagulants, are only palliative, and their impact on the improvement of survival of IPAH patients is still unclear. Atrial septostomy[10] and lung transplantation[11] are extreme forms of treating IPAH and have a poor result in the medium run.

Quite recently, sildenafil (Viagra®), used to treat erectile dysfunction and marketed with this purpose, has been used to treat IPAH. This drug is a selective and powerful phosphodiesterase 5 (PDE5) inhibitor specific to cyclic guanosine monophosphate (GMPc), abundant in the lungs. PDE5 inhibition prevents the degradation of GMPc, which is an intracellular messenger for nitric oxide, with consequent pulmonary vasodilation. The medical literature has shown more and more frequent reports on the use of sildenafil for the treatment of pulmonary hypertension (PH) of different etiologies.[12,13]

The present study describes the results of oral sildenafil therapy in six patients with IPAH in functional class III and IV, despite the use of conventional therapeutic measures.

Patients and methods

This is a prospective case series including six patients diagnosed with severe idiopathic pulmonary hypertension, who did not respond to conventional treatment. The diagnosis of PH was suspected due to the increase in the intensity of the pulmonary valve component of the second heart sound on auscultation and due to the signs of right ventricle (RD) enlargement, assessed by chest x-ray and electrocardiogram. Echocardiographic findings for the diagnosis of PH included an increase in PP, using the right ventricle-right atrium (RV-RA) gradient, estimated by tricuspid regurgitation, with addition of 10 mmHg, value assumed as right atrium (RA) pressure. Secondary causes of PH were ruled out by means of chest computed tomography, ventilation and pulmonary perfusion scintigraphy, coagulation studies, investigation for schistosomiasis and acquired immunodeficiency syndrome, echocardiogram, and cardiac catheterization. For cardiac catheterization, all patients were sedated with midazolam and fentanyl.

PP was monitored using a Swan-Ganz 7F catheter for adult patients and 5F for children, whereas arterial blood pressure was monitored with a 3F catheter inserted into the femoral artery. During catheterization, pressure measurements were performed in the pulmonary artery, aorta, pulmonary capillary bed and RA. Cardiac output and pulmonary and systemic vascular resistance were determined. This was carried out while patients breathed room air, after oxygen therapy at 100% for 15 minutes and use of nitric oxide in an initial concentration of 10 ppm; in the absence of response, the concentration was increased every 10 minutes, up to 80 ppm.[6] Oral nifedipine was initially given in the dose of 5 mg to patients weighing more than 30 kg and in the dose of 0.2 mg/kg to children, with a 50% increase in the dose every 6 hours in case of no response or of side effects. Pulmonary reactivity tests were defined as positive in the presence of a decrease greater than 20% in mean PP, without reduction of systemic output and with maintenance of the reduction in the pulmonary systolic pressure (PSP)/systolic arterial pressure (SAP) ratio greater than 20%. Decrease in systemic output, maintenance or increase in the PSP/SAP ratio, persistent tachycardia and reduction in systemic oxygen saturation were regarded as absence of response to the tests. The patients were observed at an ICU, with monitoring of PP and arterial blood pressure during 12 to 24 hours. The six-minute walking test was not performed in four patients, due to the fact that they were receiving vasoactive drugs at the ICU, with heart failure and severe hypoxemia, and/or because they were children. Ongoing medications were maintained. Oral sildenafil was initially used in the dose of 2 mg/kg/day, up to 100 mg/day given in four or six doses. The doses could be increased every 15 days up to 8 mg/kg/day, or until they reached 500 mg/day[14] in the absence of response or in case of side effects.

The study protocol was approved by the Research Ethics Committee of Hospital Vera Cruz, Belo Horizonte, and by the Research Ethics Committee of Universidade Federal de Minas Gerais (UFMG). An informed consent form was signed by the patients and/or their surrogates, wherein it was stated that sildenafil was being tested for the treatment of IPAH and that it was not primarily marketed for this purpose. The contact of patients and their families with the assistant physician was facilitated and so was the treatment of intercurrent events.

Results

The clinical characteristics of the six patients are shown in Table 1. All of them were categorized into functional class III or IV even if they were receiving medication for heart failure, including dopamine in two patients. Tables 2 and 3 show the results of the complementary exams. The data

shown in these tables reveal that all patients had normal pulmonary capillary wedge pressure. Five of six patients had suprasystemic pulmonary pressure and the other patient had systemic pressure. Systemic oxygen saturation was less than 90% in four of them and no patient showed response to the pulmonary reactivity tests. Table 4 describes the results and the clinical outcome after oral administration of sildenafil. In the follow-up period, there was improvement by at least one functional class in all patients, improvement in systemic oxygen saturation and increase in the distance achieved within six minutes in those patients submitted to the walking test. Five of 6 patients demonstrated a decrease in the PSP/SAP ratio, which characterizes an effective decrease in PP.

Discussion

The six patients included in this study showed clinical improvement after oral administration of sildenafil, characterized by the reduction in at least one NYHA (New York Heart Association) functional class, decrease in the PSP/SAP ratio, improvement in systemic saturation, and increase in the distance achieved on the 6-minute walking test. Pulmonary systolic pressure is usually assessed by echocardiogram, and this is why the pulmonary systolic/systemic systolic pressure ratio was used for the comparison. Nevertheless, a 19-year-old female patient (case 4), in functional class IV, with an 88% systemic saturation, and severe heart failure, died after showing clinical improvement and increase in systemic saturation. The patient had sudden death 24 hours after abrupt withdrawal of the medication she had been receiving while in hospital. Therefore, all patients and the medical staff should be warned against the abrupt withdrawal of the medication. In the other patients, the use of sildenafil was safe, with no side effects, despite the high doses. Remarkable systemic unsaturation (< 90%) was detected in four patients, which is not common in IPAH. However, pulmonary arterial blood pressure levels were greater than the systemic pressure, and unsaturation may be explained by RA shunt to the left atrium through the patent foramen ovale, observed on the echocardiogram and cardiac catheterization.

The medical literature has described a growing number of case reports on the use of oral sildenafil in the treatment of PH of different etiologies. Such reports indicate that this

Table 1 - Clinical characteristics of six patients with idiopathic pulmonary arterial hypertension

Patient	Age (years)	Sex	FC (NYHA)	↑B_2	TI	HM	Medication					ICC	WAR	OC
							Dig	Warf	Diur	O_2	Dob			
1	4.5	F	IV	+	+	+	+	+	+	+	+	+	–	–
2	11	F	III	+	+	–	–	+	–	–	–	–	–	+
3	3	F	IV	+	+	+	+	+	+	+	+	+	–	–
4	19	F	IV	+	+	+	+	+	+	+	–	–	+	–
5	19	F	III	+	+	–	+	+	–	–	–	–	–	+
6	4	M	IV	+	+	+	+	+	+	+	–	–	+	–

FC = functional class; NYHA = New York Heart Association; ↑ B_2= hyperphonesis of B_2; TI = tricuspid insuficiency; HM = hepatomegaly; Dig = Digital; Warf = Warfarin; Diur = Diuretics; O_2 = oxigen therapy; Dob = Dobutamine; ICC = intensive care center; WAR = ward; OC = outpatient clinic; (+) = present; (-) = absent.

Table 2 - Results of the complementary exams of six patients with idiopatic pulmonary arterial hypertension

Patient	ECG	Cardiac area (chest x-ray)	ECG Ventricular function (↓; N)		PASP* (mmHg)	SAP (mmHg)	PSP/SAP	SpO_2 (%)
			RV	LV				
1	SVD	↑	↓	N	105	80/60	1.31	90
2	SVD	N	N	N	90	100/70	0.90	98
3	SVD	↑	↓	N	110	90	1.22	85
4	SVD	↑	↓	N	110	95	1.16	88
5	SVD	↑	N	N	120	100/60	1.20	86
6	SVD	↑	↓	N	105	90/70	1.17	74

ECG = echocardiogram; RV = right ventricule; LV = left ventricule; PASP* = pulmonary artery systolic pressure with echocardiogram; SAP = systolic arterial pressure on auscultation; PSP = pulmonary systolic pressure with echocardiogram; SpO_2 = hemoglobin oxygen saturation; RVO = right ventricle overload; N = normal; ↑ = increased; ↓ = decreased.

Table 3 - Measures taken during cardiac catheterization in six patients with idiopatic pulmonary arterial hypertension

Patient	RAP (mmHg)	PCP (mmHg)	PASP (mmHg)	MPAP (mmHg)	MAP (mmHg)	IRP (dyn.s.cm^{-5})	SRI (dyn.s.cm^{-5})	Pulmonary reactivity		
								NO	FiO_2=1.0	Nifedipine
1	13	12	105	75	70	2800	2560	–	–	–
2	08	10	90	70	80	1289	2320	–	–	–
3	12	14	110	85	68	2800	2240	–	–	–
4	15	09	110	73	72	2640	2080	–	–	–
5	14	13	116	77	75	2080	2000	–	–	–
6	13	10	105	80	66	3200	2320	–	–	–

RAP = right atrium pressure (N = 1-5); PCP = pulmonary capillary pressure (N = 2-12); PASP = pulmonary artery systolic pressure (N =30-35); MPAP = mean pulmonary artery pressure (N = 25); MAP = mean aortic pressure; PRI = pulmonary resistance index (N = 80-240); SRI = systemic resistance index (N = 1600-2400); NO = nitric oxid; (–) = nonresponsive.

Table 4 - Results and clinical progress after sildenafil administration in patients with idiopatic pulmonary arterial hypertension

Patient	Functional class		SpO_2		Walking test 6′ (m)		PASP/SAP			SE	Follow-up period (months)
	Before	After	Before	After	Before	After	Before	After	%		
1	IV	II	90	90	NR	NR	1.31	0.90	32	–	9
2	III	II	98	98	260	420	0.90	0.70	23	–	18
3	IV	II	85	90	NR	NR	1.22	0.90	27	–	36
4*	IV	II	88	94	NR	NR	1.16	1.16**	0	–	0.3
5	III	II	86	92	220	380	1.20	1.05	13	–	7
6	IV	III	74	88	NR	NR	1.17	0.95	19	–	4

SpO_2 = systemic oxygen saturation; PASP* = pulmonary artery systolic pressure with echocardiogram; SAP = systolic arterial pressure on auscultation; SE = side effects; NI = non-indicated; (–) = absent. % = reduction percentage.
* Sudden death 24 hours after abrupt withdrawal of sildenafil by mistake.
** Measured 5 days after medication intake.

drug brings benefits to the patients, as it potentiates or allows for the withdrawal of nitric oxide in cases of PH crises.[15] When combined with other drugs, sildenafil can increase the efficiency of each one of them, allowing their doses to be reduced or the dose intervals to be improved.[16] Sildenafil has proved equally efficient in the treatment of PH secondary to collagen diseases,[14] of chronic pulmonary thromboembolism without surgical management[15] and mainly of IPAH.[13,17]

Despite the clearer understanding about its pathophysiology and about the new treatment options, IPAH is still a serious disease, without any cure, and with no ideal drug therapy. All the available therapies have restrictions and risks of complications and also have a very high cost. IPAH patients in functional class IV are a special group, since they are often young and have a life expectancy shorter than 1 year. In this study, despite the low number of patients, there was some improvement in the functional class, in the tolerance of exertion (assessed by the increase in the walking distance in the two patients who were able to exercise) and by the improvement in the quality of life, with social reinsertion and absence of hospital admissions during the follow-up period. These findings suggest that sildenafil may be an alternative to this special group of patients. However, studies with a larger patient population and longer follow-up are necessary so that long-term results can be assessed and the ideal doses and ideal interval between them can be established.

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