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Effects of chronic sildenafil in patients with Eisenmenger syndrome versus idiopathic pulmonary arterial hypertension

Elaine M.C. Chau*, Katherine Y.Y. Fan, W.H. Chow

Department of Cardiology, Grantham Hospital, 125 Wong Chuk Hang Road, Hong Kong

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Abstract

Background: To test the hypothesis that chronic sildenafil treatment has similar functional and hemodynamic effects in patients with severe pulmonary arterial hypertension due to Eisenmenger syndrome as those due to idiopathic pulmonary arterial hypertension without intracardiac shunts.
Methods: A prospective open-label study was carried out to compare the effects of sildenafil on the pulmonary hemodynamics between two groups of patients with severe pulmonary hypertension and similar baseline functional capacity — Eisenmenger syndrome (ES group) ($n=7$) versus idiopathic pulmonary arterial hypertension (IPAH group) ($n=6$).
Results: After 6 months of sildenafil, there was a significant improvement in the functional capacity, the arterial saturation and the pulmonary hemodynamics in the ES group, as shown by significant reduction in the systolic and mean pulmonary artery pressures and the pulmonary vascular resistance.
Conclusion: Sildenafil increases pulmonary blood flow and improves cyanosis in patients with Eisenmenger syndrome. Efficacy of sildenafil as treatment for idiopathic pulmonary arterial hypertension may be extended to patients with Eisenmenger syndrome.

Keywords: Sildenafil; Pulmonary arterial hypertension; Eisenmenger syndrome; Idiopathic pulmonary arterial hypertension

1. Introduction

Sildenafil, a phosphodiesterase type 5 inhibitor, has been shown to be beneficial in patients with pulmonary arterial hypertension, either idiopathic or associated with connective tissue disease or with repaired congenital systemic-to-pulmonary shunts [1,2]. Patients with either idiopathic pulmonary arterial hypertension (IPAH) or previously repaired congenital heart disease were considered to carry a worse prognosis than those with Eisenmenger syndrome [3]. Therefore many studies involving novel treatments for pulmonary arterial hypertension have concentrated on the IPAH patients. However, the functional capacity of some Eisenmenger patients may be as limited as the IPAH patients. A more recent study showed that Eisenmenger syndrome without diagnosis until adulthood in fact had a poor prognosis with the mean survival time from diagnostic catheterization to death being 5.4 years [4]. The definitive treatment of lung transplantation with intracardiac repair or heart–lung transplantation is limited by the scarcity of donors and the many complications associated with graft rejection and infection due to immunosuppression after transplantation. However, efficacy of sildenafil in patients with Eisenmenger syndrome (pulmonary hypertension associated with unrestrictive shunting) has not yet been established. It has been suggested that sildenafil may be detrimental to patients with Eisenmenger syndrome because it may potentially cause a reduction in pulmonary blood flow and an increase in cyanosis [5]. Therefore it was interesting to see if this drug may benefit patients with Eisenmenger syndrome, both hemodynamically and functionally.

2. Methods

From June 2003 to May 2005, patients with significant symptoms attributable to severe pulmonary arterial

* Corresponding author. Tel.: +852 25182612; fax: +852 25188558.
E-mail address: echau@hkucc.hku.hk (E.M.C. Chau).

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hypertension either idiopathic or secondary to Eisenmenger syndrome were recruited into the study. Pulmonary arterial hypertension was defined as systolic pulmonary arterial pressure >35 mmHg or mean pulmonary arterial pressure >25 mmHg [6]. Eisenmenger syndrome was defined as congenital systemic-to-pulmonary arterial shunts leading to pulmonary hypertension and resulting in a right-to-left or bidirectional shunt [7]. Each patient underwent thorough baseline assessment, including evaluation of the New York Heart Association (NYHA) functional class, echocardiogram, 6-minute walk, left and right heart catheterization with acute vasodilator study. Only those with severe and fixed pulmonary arterial hypertension were recruited. Subjects were continued on same doses of their usual therapy, including diuretics, calcium channel blockers, anticoagulation, digoxin and home oxygen therapy. After informed consent was obtained, each patient was given oral sildenafil, starting at 25 mg 12 hourly and increasing to 25 mg to 50 mg 8 hourly as tolerated. They were followed up closely for possible side-effects of the drug. Follow-up assessment of functional capacity was done by repeating 6-minute walk and evaluation of the NYHA functional class at 1 month and 6 months after therapy. Pulmonary hemodynamics was reassessed using left and right heart catheterization after 6 months of sildenafil. Calculation of the pulmonary and systemic blood flow, pulmonary and systemic vascular resistance was performed using the Fick equation and assumed values of oxygen consumption according to the age and gender of the patient.

Comparison of the baseline characteristics of the two groups was performed using *T*-test. Comparison of the parameters before and after chronic sildenafil treatment was performed using the paired *T*-test (2-sided). $p<0.05$ was considered significant. The NYHA functional class was regarded and assessed as a continuous variable for the scope of this study.

3. Results

Thirteen patients were recruited into the study. The etiologies of the pulmonary arterial hypertension were secondary to Eisenmenger syndrome (ES) in 7 cases and idiopathic (IPAH) in 6 cases. In the ES group, five patients had single or multiple atrial septal defects (size ranging from 1 cm to >3 cm) and two patients had ventricular septal defects (size 1.8 cm and 2.2 cm). Side-effects were reported by three patients and include facial flushing, warm sensation in the extremities and a dose-related idiosyncratic skin rash, respectively. None of the side-effects were severe enough for the patient to withdraw from the treatment. All thirteen patients survived during the study period.

Table 1
Baseline characteristics of the 2 groups of patients

Parameter	ES	IPAH	*p*-value
Male:female ratio	0:7	1:5	–
Etiologies	Atrial septal defect=5, ventricular septal defect=2	Idiopathic	–
Age	37+/−11 years	41+/−7 years	0.53
Hemoglobin	17.1+/−3.6 g/dl	14.6+/−1.9	0.16
SpO2 at baseline	78%+/−11%	95%+/−3%	0.003*
NYHA functional class	3.3+/−0.7	3.0+/−0.6	0.48
6-minute walk distance	297+/−133 m	289+/−156 m	0.91

* $p<0.05$.

Table 2
Functional class, oxygen saturation and 6-minute walk in both groups at baseline, 1 month and 6 months

Time		NYHA functional class	O2 Saturation	6-minute walk
Baseline	ES	3.3±0.7	0.78±0.11	297±133
	IPAH	3.0±0.6	0.95±0.03	289±156
At 1 month	ES	2.6±0.5	0.78±0.11	331±91
	IPAH	2.5±0.6	0.96±0.02	311±171
At 6 months	ES	2.1±0.4*	0.88±0.08*	325±100
	IPAH	2.2±0.4*	0.96±0.02	411±73

* Significant change compared with baseline ($p<0.05$).

3.1. Baseline characteristics

All patients except one were female. At baseline, there was no significant difference in the age, NYHA functional class and 6-minute walk distance between the two groups (Table 1). As expected, the ES group had secondary polycythemia with a higher hemoglobin level (17.1+/−3.6 g/dl) and cyanosis (arterial oxygen saturation 78%+/−11%).

3.2. Effect of chronic sildenafil on NYHA functional class, oxygen saturation and 6-minute walk

Results of the functional class, oxygen saturation and 6-minute walk in both groups at baseline, 1 month and 6 months are shown in Table 2. After 6 months of sildenafil therapy, there was a significant improvement in the oxygen saturation (from 78%+/−11% to 88%+/−8%, $p=0.02$) in the ES group. Functional capacity, as determined by the NYHA functional class, also improved significantly in both groups of patients — from 3.3+/−0.8 to 2.1+/−0.4 ($p=0.02$) in the ES group and from 3.0+/−0.6 to 2.2+/−0.4 ($p=0.04$) in the IPAH group (Fig. 1). There was a trend of improvement in the 6-minute walk distance in both groups but it did not reach statistical significance.

3.3. Comparison of efficacy of sildenafil in patients with Eisenmenger syndrome versus idiopathic pulmonary arterial hypertension

The results of the baseline and the 6-month post-sildenafil hemodynamic data in the two groups of patients are shown in Table 3. At baseline, ES patients had higher systolic and mean pulmonary pressure than those with IPAH. In both