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Original scientific paper

One Year Efficacy and Safety of Oral Sildenafil Treatment in Severe Pulmonary Hypertension

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A B S T R A C T

Severe pulmonary hypertension is a progressive disease which leads to limitations of functional status and poor survival. We evaluated efficacy and safety of a short (3 months) and a long term (12 months) sildenafil treatment in patients with severe pulmonary hypertension. We treated 12 patients with pulmonary hypertension with oral sildenafil. Patients were followed at three time points, at baseline, and after 3 and 12 months of treatment. Primary end point was improvement in functional exercise capacity assesed by 6-minute walk test, and secondary end points were changes in right ventricle hemodynamics. We found significant improvement in 6-minute walk test distance from 357±193 m at baseline to 431±179 m after three months and further improvement to 501±159 m after 12 months ($p<0.01$); decrease in right ventricule pressure from 107±42 mmHg at baseline to 87±32 mmHg after 12 months ($p<0.01$); and, decrease in right ventricule diameter from 3.2±1.1cm to 2.76±0.86 cm after twelve months ($p<0.01$). Drug-related adverse events were mild and transient in our group of patients. Long term (12 months) sildenafil treatment is effective and safe in our patients with idiopathic and chronic thrombo-embolic pulmonary hypertension.

Key words: *pulmonary hypertension, idiopathic, chronic thrombo-embolic, sildenafil, 6-minute walk test*

Introduction

Severe pulmonary hypertension is a disease which leads to severe limitations of functional status and poor survival. Clinical features include progressive dyspnea and exertion limitation. Pulmonary arterial hypertension is characterized by elevation of pulmonary vascular resistance and consequently elevation in pulmonary artery pressure. This can lead to the right heart failure and death[1]. Three factors contribute to increase in pulmonary vascular resistance: vasoconstriction, small pulmonary vessel remodeling and thrombosis in situ[2]. Abnormalities in mediator pathways contribute to pathogenesis of pulmonary arterial hypertension. These include insufficient production of vasodilators like nitric oxide (NO) and prostanoids, as well as increased production of vasoconstrictors like endothelin, thromboxanes and serotonin[3–8]. Advances in understanding molecular mechanisms suggest that endothelial dysfunction plays a key role in pathogenesis of pulmonary hypertension[2,3,6].

The current, most used conventional therapeutic modalities like diuretics, digoxin, oral anticoagulants and calcium channel blockers are limited and unsatisfactory[9–11]. Therefore, novel therapeutic agents like prostanoids (epoprostenol, beraprost, iloprost) and endtohelin-receptor antagonists (bosentan) are recently approved[12–18].

One of the new targeted molecules are phosphodiesterases. Phosphodiesterases (PDE) are superfamily of enzymes that inactivate cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP), the second messengers of prostacyclin and NO. The phophodiesterases have different tissue distribution and substrate affinities[19]. The major cGMP degrading phosphodiesterase, PDE-5, is abundantly expressed in lung tissue[20]. Inhibition of PDE-5 could augment and prolong prostanoid and NO related vasodilator effects[21–24]. The selective PDE-5 inhibitor sildenafil was approved for

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treatment of erectile disfunction. Sildenafil causes only minor systemic effects in healthy humans[25]. Data from experimental model of pulmonary hypertension showed that sildenafil is a potent pulmonary vasodilator[23]. First data of sildenafil efficacy in treatment of pulmonary hypertension were reported as case reports[26,27,28]. Since then, several reports on small number of patients suggest efficacy of sildenafil treatment in patients with pulmonary arterial hypertension, alone or in combination with prostanoids or NO[29–34]. Most of these reports showed a short term (3 months) sildenafil efficacy. Two reports showed a prolonged benefit of 5 and 6 months sildenafil treatment as adjunct therapy[32,34] and one small series in patients with non-operable chronic thromboembolic pulmonary hypertension showed efficacy of 12--months oral sildenafil treatment alone[36]. Only one, large, double-blind, placebo-controlled study showed prolonged sildenafil efficacy in patients with pulmonary hypertension[37]. Recent studies suggested that sildenafil may also have direct anti-hypertrophic effect in cardiac muscle[38,39].

In this study, we tried to estimate efficacy and safety of a short (3 months) and a long term (12 months) treatment with oral sildenafil in patients with severe pulmonary hypertension. Primary end point of the study was improvement in functional capacity measured with six--minute walking test, and secondary end points were decrease in right ventricle pressure and decrease in right ventricle diameter.

Methods

Selection of patients

Patients with pulmonary arterial hypertension (PAH) attending University Hospital for lung diseases »Jordanovac« during 2004 were considered for the study. Patients with idiopathic pulmonary hypertension, chronic thrombo-embolic pulmonary hypertension who are not suitable for surgical treatment and patients with pulmonary hypertension due to non – corrected congenital cardiac shunt were eligible for the study (40). The PAH diagnosis was based on right heart catheter mean pulmonary artery pressure at rest over 25 mmHg. All patients were symptomatic despite their conventional diuretic, digoxin and anticoagulant therapy. None of the patients received calcium-channel blockers. Eight patients showed irreversibility of pulmonary hypertension to prostanoids. Four patients who showed reversibility to prostanoids could not tolerate calcium-channel blockers. Study medication was added to patients' conventional therapy. Exclusion criteria included previous sildenafil treatment and six-minute walking distance at the inclusion less then 200 meters.

The study was done according to 1983 Declaration of Helsinki and according good clinical practice. This study was approved by the University Hospital for Lung Diseases »Jordanovac« Ethics Committee and all patients gave written informed consent before entering the study.

Study design

The study was non-sponsored, open-labeled and uncontrolled. All patients received during the first week 12.5 mg of oral sildenafil three times a day. Dose was then up-titrated to 50 mg of sildenafil three times a day if no systemic hypotension or other side-effects occurred. Patients were followed in three time points: at baseline, after three months and after 12 months of therapy. Sildenafil treatment efficacy was estimated after first three months of treatment and patients with improvement in functional capacity were eligible for continuation of sildenafil treatment.

Outcome measures

Before entering the study in all patients was performed: the right heart catheterization, perfusion and ventilation lung scan and pulmonary angiography. During the right heart catheterization the right heart and pulmonary artery pressure were measured, pulmonary vascular resistance and cardiac index were calculated, and reversibility test was performed. Reversibility of pulmonary hypertension was tested with iloprost. If there was decrease in systolic pulmonary artery pressure for more than 25% or pulmonary vascular resistance for 30% or increase in systemic arterial oxygen saturation, pulmonary hypertension was declared reversible.

The following parameters were analyzed at baseline and at each time point: NYHA functional class, Borg scale at rest and after 6-minute walk test (41), 6-minute walking distance (42,43), right ventricle pressure (RVP) and right ventricle diameter (RVD) estimated by transthoracic echocardiography, blood gas analysis at rest and after walking test, lung function and carbon dioxide diffusion.

Statistical analysis

All variables were tested for normal distribution with Kolmogorov-Smironov's test. For variables with normal distribution ANOVA for repeated measurement test was performed, and a value of $p<0.05$ was considered significant. For variables which showed a significant improvement between baseline and at the end of follow-up period, Scheffe's post hoc test was performed. P value less than 0.05 was found statistically significant.

Results

We included 12 patients in the study. Base-line patients' characteristics are shown in Table 1. Five patients with idiopathic pulmonary hypertension (IPH) (4 females, 1 male, average age 36.8 years, range from 22–52); five patients with chronic thrombo-embolic pulmonary hypertension (CTEPH) (3 females, 2 males, average age 46; range from 36–57) and two males with Eisenmenger' syndrome (average age 39 years; range 30–48). All patients had severe pulmonary hypertension. Mean pulmonary artery pressure measured during right heart catheterization was 53±15 mmHg (range from 37 to 68 mmHg).

TABLE 1
PATIENT CHARACTERISTICS

Demographic characteristics	
Female: male	7:5
Age in years, mean (range)	40.7 (22–57)
Cause of pulmonary hypertension	
Idiopathic	5
CTEPH	5
Cardiac shunt	2
Functional status	
6-min walk distance, m	357 ± 153
Dyspnea score (Borg index)	3.9 ± 1.6
Hemodynamic variables	
RA pressure, mmHg	8.9 ± 4
PAP	
systolic, mmHg	86 ± 36
diastolic, mmHg	31 ± 24
mPAP, mmHg	53 ± 15
PVR, din sec cm^{-5}	718.4 ± 275.6
Cardiac index, L min^{-1} m^{-2}	2.41 ± 0.43
RV pressure, mmHg	107 ± 42
RV diameter, cm	3.2 ± 1.1
Reversibility to prostanoids Yes/No	4:8

CTEPH = chronic thrombo – embolic pulmonary hypertension; PAP = pulmonary artery pressure; RA = right atrium; mPAP = mean pulmonary artery pressure; PVR = pulmonary vascular resistance; RV = right ventricule.
RA, PAP, mPAP, CI and PVR were estimated during right heart catheterization. RV pressure and RV diameter were estimated by echocardiography.

At the time of the inclusion patients were NYHA class III and IV, most of them NYHA III. All patients were successfully titrated to dose of 50 mg three times a day during first two weeks of treatment.

At the first time point, after three months, in two patients with Eisenmenger' syndrome there was a decrease in 6-minute walk test distance from 200±20 m to 165±45 m. We also noticed in these two patients increase in Borg dyspnea score for average 1.5 units, NYHA class remained the same, as well as right ventricle pressure. These two patients were excluded after three months.

Functional capacity

The mean 6-minute walk distance increased for 74 m after three months (from 357±193 m at baseline to 431±179 m after three months, $p<0.01$, and further increased by 70 m (to 501±159 m after 12 months of sildenafil treatment, $p<0.01$). Overall improvement was 144 m after twelve months ($p<0.01$) (Figure 1). Borg dyspnea scores at rest and after exertion improved for an average one point. This improvement was not statistically significant. Patients NYHA functional status improved for one class in average.

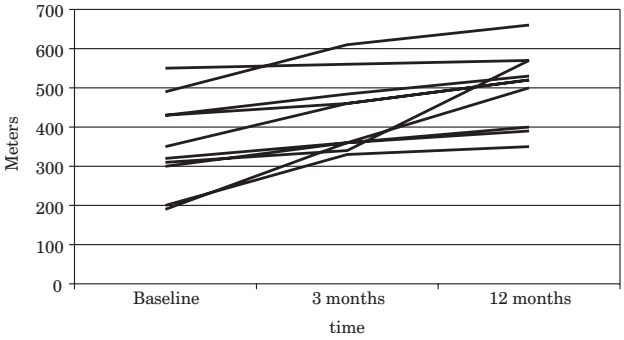

Fig. 1. Change in 6 – minute walk test distance from baseline to three and twelve months of sildenafil treatment (each line represent one patient).

Right ventricle pressure

Right ventricle pressure (RVP) decreased by 12 mmHg after three months (from 107±42 to 95±40 mmHg; $p<0.01$) and further decreased for 8 mmHg after twelve months of treatment (to 87±32 mmHg; $p<0.01$). In total, after twelve months of treatment we noticed decrease for 20 mmHg ($p<0.01$) (Figure 2).

Right ventricle diameter

After three months of treatment right ventricle diameter (RVD) decreased for average 0.3 cm (from 3.2±1.1 cm to 2.9±0.9 cm; $p<0.05$), and then further for another 0.14 cm (to 2.76±0.86 cm; $p<0.05$). In total, after 12 months of treatment RVD decreased by 0.44 cm ($p<0.01$) (Figure 3).

Arterial blood gas analyses and safety

In all 10 patients who completed the study we notice slightly improvement in PaO_2 at rest and after exertion. However, this improvement was not statistically significant. There were no changes in lung capacity for carbon monoxide diffusion.

During the study we notice only minor side effects. One patient complaint for headache during first months of treatment; one patient had muscle pain in the last two

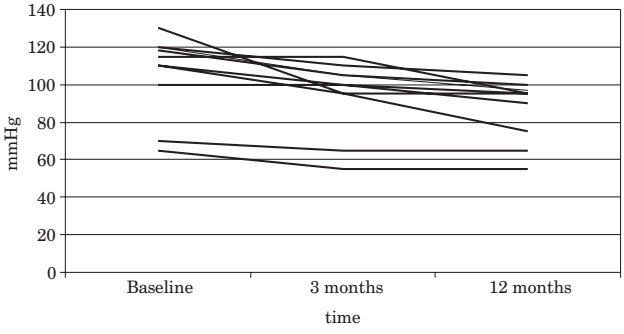

Fig. 2. Change in right ventricle pressure from baseline to three and twelve months of sildenafil treatment (each line represent one patient).

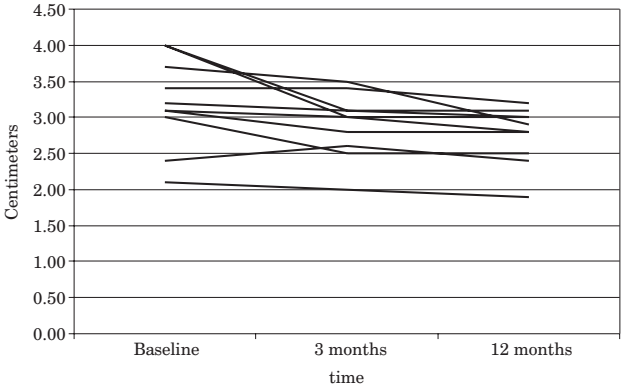

Fig. 3. Change in right ventricle diameter from baseline to three and twelve months of sildenafil treatment. (each line represent one patient).

months of the study. There were no withdrawals during the study caused by drug – related adverse events.

Discussion

Most of the clinical trials use functional capacity testing measured by a 6-minute walking test as primary end point[12–18,30–32,36,37,39]. Six-minute walk distance commonly used in clinical trials for the assessment of exercise capacity and as independent predictor of mortality[44].

In this small, open study, sildenafil significantly improved functional capacity measured by 6-minute walk test, after three and then further after twelve months of treatment. Increase in 6-minute walk distance noticed in this study was significantly better than increase noticed in SUPER trial (74 m to 48 after three months, and 144 m to 51 m after twelve months, $p<0.001$ for all comparisons)[37]. The much higher improvement in our study is most likely the result of small number of patients. In SERAPH study improvement in 6-minute walk distance was similar to our findings (114 m after 16 weeks of sildenafil treatment[39]). The most important observation in our study is sustained and prolonged benefit of sildenafil treatment. However, Galie et al. in SUPER trial did not found significant improvement in functional capacity between months three and twelve[37]. Similar finding was showed in study by Barst et al. The early improvement in 6-minute walk distance was lost after six months of beraprost therapy[45]. On the contrary, in our study 6-minute walk distance significantly improved between months three and twelve by another 70 m.

Consistent and significant improvement during twelve months sildenafil treatment period may suggest chronic effects and additional benefits possibly via reversal of pulmonary vascular remodeling. Improvement in NYHA class and Borg score were noticed already after three months and remained improved during the treatment period. Our study showed that sildenafil significantly reduced right ventricle pressure already after three months of treatment and there was further decrease noticed after twelve months of treatment.

As a secondary end point we used improvement in right ventricle diameter. To the best of our knowledge, there was only one study so far which analyzed impact of sildenafil treatment on right ventricle mass and volume[39]. However, to simplify the procedure, we used echocardiography to estimate diameter of the right ventricle. And indeed, we noticed significant decrease in right ventricle dimension already after three months of treatment, and then further decrease after twelve months of sildenafil treatment. These results are similar to the results of the SERAPH study which noticed significant reduction in right ventricle mass measured by cardiac MR[39].

So, part of our findings, improvement in a 6-minute walk distance and in NYHA class could be explainable with noticed improvement in right ventricle hemodynamics. Improvement in these patients is not only explainable by improvement of resting hemodynamics or by vasodilator effect of sildenafil[29]. Sildenafil also has anti – proliferative and anti – remodeling effect, and these effects could explain further changes in hemodynamics beyond just vasodilator effect[38,39]. Unfortunately, at the moment it is not known if this effect of reducing right ventricle diameter had an impact on improvement in functional capacity. There was no change in pO_2 at rest and after the exertion and in DL_{CO}.

In two patients with Eisenmenger syndrome there was no improvement in followed parameters. Nevertheless, in these patients we noticed deterioration in functional capacity and in followed parameters, so sildenafil treatment was discontinued after three months of the therapy.

In all patients in our study sildenafil was well tolerated, only minor side effects during the study period occurred (headache, muscle pain, nausea).

Some reports suggest additive effects of sildenafil added to other drugs[20,30,31,33,34] but further, larger, randomized, double-blind, clinical trails are necessary to establish additive effects of sildenafil to other drugs used in the therapy of pulmonary arterial hypertension. In our study patients did not use calcium-channel blockers or any other vasodilator so we were able to measure pure sildenafil treatment effects which is different to other published studies.

There are only few studies that estimated role of oral sildenafil alone in treatment of pulmonary arterial hypertension[32,35–37,39] and our results are in favor of these studies.

Data in present study showed no efficacy of sildenafil treatment in patients with Eisenmenger syndrome, so for these patients other treatment options should be considered, although only two patients in this group are insufficient for any general conclusions.

Limitation of our study was a small number of patient, lack of power-analysis and lack of control group (open-label design). An important observation from this trial is that early beneficial effects of sildenafil are consistent and further improved with prolonged use.

In conclusion, sildenafil significantly improved exercise capacity and hemodynamics in our small group of patients with severe pulmonary hypertension (both idiopathic and CEPTH). In these patients, sildenafil could be a reasonable option for the first line therapy[46,47] but further studies, on larger number of patients are needed to confirm our findings. Efficacy of sildenafil treatment in these patients was proportional to the duration of treatment. However, further trials are necessary to determine a position of sildenafil treatment in patients with pulmonary arterial hypertension as monotherapy or in combination with prostanoids and/or endothelin-receptor antagonists.

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UČINKOVITOST I SIGURNOST ORALNOG SILDENAFILA U BOLESNIKA S TEŠKOM PLUĆNOM HIPERTENZIJOM

SAŽETAK

Teška plućna hipertenzija je bolest koja značajno smanjuje funkcijski kapacitet bolesnika i ima lošu prognozu. U studiji smo ispitivali kratkoročni (3 mjeseca) i dugoročni (12 mjeseci) učinak sildenafila u bolesnika s teškom plućnom hipertenzijom. U studiju je bilo uključeno 12 bolesnika koji su praćeni prije početka liječenja, nakon 3 mjeseca te nakon 12 mjeseci liječenja. Primarni cilj praćenja je bilo poboljšanje u 6-minutnom testu hoda, a sekundarni pad talka u desnom ventrikulu. U bolesnika je došlo do značajnog poboljšanja hodne pruge nakon 3 te nakon 12 mjeseci praćenja. Također je došlo do smanjenja tlaka u desnom ventrikulu nakon 3 te nakon 12 mjeseci praćenja. Nisu zabilježene značajne nuspojave. U zaključku, sildenafil je siguran i učinkovit u liječenju kroz 12 mjeseci u bolesnika s teškom idioptaskom plućnom hipertnezijom, te plućnom hipertenzijom uzrokovanom kroničnim trombo-embolizmom.