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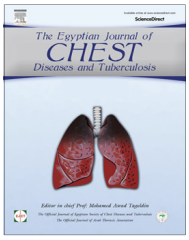

Sildenafil citrate therapy for secondary pulmonary arterial hypertension due to chronic obstructive lung disease

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KEYWORDS

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Abstract Pulmonary arterial hypertension is defined as a group of diseases characterized by a progressive increase in pulmonary vascular resistance, leading to right ventricular failure and premature death. Pathobiologic mechanisms of the disease include pulmonary endothelial dysfunction, which leads to impaired production of vasodilators, such as nitric oxide and prostacyclin, and overexpression of vasoconstrictors, such as endothelin-1.

Sildenafil inhibits phosphodiesterase type 5, an enzyme that metabolizes cyclic guanosine monophosphate, thereby enhancing the cyclic guanosine monophosphate-mediated relaxation and growth inhibition of vascular smooth-muscle cells, including those in the lung.

Methods: In this prospective study 139 patients with symptomatic pulmonary arterial hypertension (2ry to COPD) received placebo or sildenafil (20 mg) orally three times daily for 12 weeks. The end point was the change from baseline to week 12 in the distance walked in six minutes. The change in mean pulmonary-artery pressure and the incidence of clinical worsening were also assessed, but the study was not powered to assess mortality.

Results: The distance walked in six minutes increased from baseline in sildenafil group; the mean placebo-corrected treatment effects were 51 m (+13.0 percent), for 20 mg of sildenafil, ($P < 0.001$). Sildenafil dose reduced the mean pulmonary-artery pressure ($P = 0.04$), and was associated with side effects such as flushing, dyspepsia, and diarrhea. The incidence of clinical worsening did not differ significantly between the patients treated with sildenafil and those treated with placebo.

Conclusion: Sildenafil improves exercise capacity, and hemodynamic in patients with symptomatic pulmonary arterial hypertension.

Introduction

Pulmonary arterial hypertension is defined as a group of diseases characterized by a progressive increase in pulmonary

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vascular resistance, leading to right ventricular failure and premature death [1,2]. Pathobiologic mechanism of the disease includes pulmonary endothelial dysfunction, which leads to impaired production of vasodilators, such as nitric oxide and prostacyclin, and overexpression of vasoconstrictors, such as endothelin-1 [3,4].

Treatment includes conventional agents (anticoagulants, diuretics, digoxin, and supplemental oxygen, as well as calcium-channel blockers in selected patients), vasodilators, and antiproliferative agents such as prostanoids and endothelin-receptor antagonists, which are targeted at abnormalities of endothelial function [5,6]. Four agents are currently approved for the treatment of pulmonary arterial hypertension in the United States and Europe: intravenous epoprostenol, the inhaled prostacyclin analog iloprost, the subcutaneously and intravenously administered prostacyclin analog treprostinil, and the oral endothelin-receptor antagonist bosentan. Although these drugs are efficacious, adverse effects in terms of safety, tolerability, drug delivery, or all of these factors occur with all of these agents [5,6]. In addition, some medical therapy may fail in some patients in which case they may be considered for lung transplantation [7].

Changes in nitric oxide pathways have been detected in patients with pulmonary arterial hypertension, and although inhaled nitric oxide is used for testing acute vasoreactivity, the long-term administration of this agent is cumbersome and requires a complex delivery system [8,9].

The pulmonary vasodilating effects of nitric oxide are mediated through its second messenger, cyclic guanosine monophosphate (cGMP), which is rapidly degraded by phosphodiesterase. Phosphodiesterase type 5 is the predominant phosphodiesterase isoform in the lung that metabolizes cGMP, and it has been shown to be up-regulated in conditions associated with pulmonary hypertension. By selectively inhibiting phosphodiesterase type 5, sildenafil citrate (Revatio, Pfizer) promotes the accumulation of intracellular cGMP and thereby enhances nitric oxide-mediated vasodilatation; it may also have antiproliferative effects on pulmonary vascular smooth-muscle cells. Initial studies involving animal models, data from open label, uncontrolled trials involving patients with pulmonary arterial hypertension, and a small randomized, controlled study involving patients with idiopathic pulmonary arterial hypertension suggest that sildenafil is beneficial in the treatment of pulmonary arterial hypertension [10,11]. The objectives of our trial were to assess the efficacy and tolerability of sildenafil 20 mg given orally three times daily in patients with secondary pulmonary arterial hypertension.

Selection of patients

Patients were included if they had pulmonary arterial hypertension (2ry to COPD). Pulmonary arterial hypertension was defined as a mean pulmonary-artery pressure of 25 mm Hg or more as measured indirectly by echocardiography Study, medication was added to the patient's conventional therapy. Treatment with intravenous epoprostenol, oral bosentan, intravenous or inhaled iloprost, or subcutaneous treprostinil and supplementation with L-arginine were prohibited. Patients with a six-minute walking distance of less than 100 m or more than 450 m were excluded.

Echocardiographic assessment

The diagnosis of pulmonary arterial hypertension depends on direct measurement of the mean PAP by right heart catheterization but in our study we measured PAP indirectly by echocardiography. Echocardiography can provide an estimate of the pulmonary artery systolic pressure (PASP). PASP was determined by measuring the peak systolic pressure gradient from the right ventricle to the right atrium. This was calculated using the modified Bernoulli equation: $4v2$, where v is the maximum velocity of the tricuspid valve regurgitant jet, measured by continuous wave Doppler, added to the estimated right atrial pressure. The following formula was derived to estimate mean PAP: mean PAP = 0.65 PASP + 0.55 mmHg.

Study design

Prospective study was done for 12-weeks, from January 2015 and January 2016. Patients were classified into two groups: 1st (69) patients received sildenafil 20 mg 3 times daily for 12 weeks and 2nd group received placebo. All patients received the conventional therapy for COPD. Echocardiography was done for all patients for diagnosis of pulmonary hypertension and every 4 weeks as a follow up. Baseline walking distance in six minutes was done at first then every 4 weeks.

Outcome measures

The primary measure of efficacy was the change in exercise capacity, as measured by the total distance walked in six minutes, from baseline to week 12. Other measures of efficacy were the changes in mean pulmonary-artery pressure, and time from study to clinical worsening (defined as death, transplantation, hospitalization for pulmonary arterial hypertension, or initiation of additional therapies for pulmonary arterial hypertension, such as intravenous epoprostenol or oral bosentan). Physical examinations and laboratory tests were performed, and investigators recorded adverse events throughout study.

Statistical analysis

The primary end point was evaluated with the use of a sequential step-down, closed testing procedure, in which the mean response in group receiving sildenafil was compared with that in the placebo group. All pair wise comparisons for the primary end point were carried out at the prespecified two sided alpha level of 0.01 with the use of a two-samplet-test, stratified for baseline walking distance. Assuming that there was a treatment effect from sildenafil of 51 m, as compared with placebo, and a standard deviation of 75 m. Mean pulmonary-artery pressure was analyzed with the use of a stratified t-test; the time to clinical worsening was analyzed with the use of a stratified log-rank test (data for patients with no documentation of clinical worsening were included in the analysis as censored observations); and the mean pulmonary-artery pressure, a patient must have received the study drug and had both a baseline and at least one post-baseline measurement of the specific end point. To be included in the intention-to-treat analysis for time to clinical worsening, a patient must have received the study drug (see Table 1).