

## EFFECT OF SILDENAFIL IN PRIMARY PULMONARY HYPERTENSION

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### ABSTRACT

Primary pulmonary hypertension is a disorder with limited treatment options and poor outcome. We demonstrated a beneficial role of sildenafil, a phosphodiesterase 5 inhibitor, in a patient with primary pulmonary hypertension. After the initiation of sildenafil the pulmonary artery pressure decreased from 40/20mmHg to 16/6mmHg, while mean pulmonary arterial systolic pressure decreased from 25mmHg to 10mmHg. Sildenafil has a beneficial effect in patients with primary pulmonary hypertension in improving the functional class and decreasing the pulmonary artery pressures.

**KEY WORDS:** Sildenafil, Pulmonary Hypertension, Effectiveness.

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### INTRODUCTION

Primary pulmonary hypertension (PPH) is a disorder of unknown etiology with an annual incidence of 1-2 per million people and a median survival of 2.8 years.<sup>1</sup> Recently, various studies have shown promising results of sildenafil, a selective inhibitor of cyclic guanosine monophosphate-specific phosphodiesterase type 5, an enzyme that is abundant in both lung and penile tissues.<sup>2-5</sup> It is widely used to dilate penile arteries for the treatment of erectile dysfunction (ED). However, recent studies have suggested that it may also dilate pulmonary arteries in patients with pulmonary hypertension thereby decreasing pulmonary arterial pressure and increasing cardiac index

without affecting aortic pressure.<sup>6</sup> We are reporting a case of 50 year old female who benefited from oral sildenafil therapy with substantial improvement in exercise capacity.

### CASE REPORT

A 50 year-old female presented (in May 2003) with the history of progressive worsening of dyspnea on exertion. It has a ten years duration. Symptoms were assessed to be in New York Heart Association (NYHA)-IV. There was no significant past history or drug history. On examination there were signs of severe pulmonary hypertension with tricuspid regurgitation (TR) and congestive heart failure (CHF). On presentation electrocardiogram (ECG) revealed supra-ventricular tachycardia (SVT) which was successfully reverted to normal sinus rhythm with a single intra-venous dose of adenosine. On investigations the complete blood counts, urea, creatinine, electrolytes, calcium, magnesium, creatinine kinase and troponin-I were all normal. Screening for lupus anticoagulant and Thrombophilia were negative. Chest X-ray showed cardiomegaly with enlarged pulmonary artery. Transthoracic Doppler echocardiogram showed dilated pulmonary artery, right atrium, right ventricle

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(RV) and pulmonary arterial hypertension with right ventricular pressure of 45mmHg.

Based on the clinical features and investigations, diagnosis of primary pulmonary hypertension was made. Treatment with Flecainide, Clopidogrel, Frusemide, and low molecular weight heparin (LMWH) did not show any significant improvement. Therefore, sildenafil was started orally in a dose of 50mg BID and increased to 100mg BID. To evaluate the effect, pulmonary arterial pressure (PAP) was monitored which decreased from 40/20mmHg to 16/6mmHg, while mean pulmonary arterial systolic pressure decreased from 25mmHg to 10mmHg in next 4 days. There was no significant hypotension or decrease in arterial saturation. Patient was subjected to modified treadmill stress test and she achieved target heart rate without any symptom during 14 minute walk. On follow-up after 3 months she was asymptomatic and in NYHA-1.

## DISCUSSION

Primary pulmonary hypertension (PPH) is a rare disorder of unknown etiology with limited treatment options and poor outcome. The sub-acute course of the disease makes it difficult to have an early recognition and treatment. It is characterized by the chronic elevation of pulmonary artery pressure (PAP) and pulmonary vascular resistance (PVR) leading to right ventricular enlargement and hypertrophy. PPH is often characterized by a mean PAP >25mmHg at rest or >30mmHg during exercise, the pressure being measured invasively with a pulmonary artery catheter. Doppler echocardiography allows serial, non-invasive follow-up of PAPs and right heart function. The pathogenesis of pulmonary artery hypertension (PAH) remains unclear; however the pathological lesions of pulmonary arteries range from the early medial hypertrophy to the end-stage fibrotic plexiform lesions.<sup>1</sup> Elevated pulmonary vascular resistance seems to result from an imbalance between locally produced vasodilators and vasoconstrictors, in addition to vascular wall remodeling. Aim of therapy is to improve the functional capacity, quality of

life, and survival of patients with pulmonary hypertension. Nitric oxide (NO), prostacyclin, endothelin receptor blockers and dihydropyridine group of calcium-blockers have been widely used<sup>1</sup> with some beneficial effects on hemodynamics and right ventricular function and possibly increased survival in some cases. Sildenafil has been used in combination with iloprost, epoprostenol and nitric oxide.<sup>7-10</sup>

Although nitric oxide (NO) is a potent and selective pulmonary vasodilator, long-term use is limited by its short half-life, cost complicated mode of delivery and monitoring equipment. Nevertheless, sildenafil has been shown to augment and prolong the effect of NO when used in combination<sup>11,12</sup> and also to prevent rebound pulmonary vasoconstriction on withdrawal of inhaled NO. Thus, an ideal vasodilator would be pulmonary vascular specific which significantly reduces PA pressure rather than just increasing cardiac output.

Sildenafil selectively inhibits phosphodiesterase 5 (PDE5), which is abundant in pulmonary and penile tissue and has important vasodilatory properties. This results in increasing nitric oxide (NO) at tissue level leading to pulmonary vasodilatation. Sildenafil is well tolerated with no adverse effects in severe pulmonary hypertension. It reduces symptoms, improves effort tolerance and controls refractory heart failure significantly by 2 weeks in 70% of patients.<sup>13</sup> Some studies have shown improvement in both pulmonary haemodynamics and the clinical status of patients with pulmonary hypertension after three months of oral therapy.<sup>14</sup> Sildenafil significantly improved the symptomatic status, exercise capacity, NYHA class, and hemodynamic parameters of patients with severe PAH and can be safely used as a primary or adjunctive treatment of the same.<sup>15</sup>

Sildenafil decreases pulmonary artery pressure, either alone or in combination with inhaled iloprost or NO. At the same line, sildenafil decreases hypoxia-induced pulmonary hypertension in normal volunteers. These findings, together with reports of long-term improvement in symptoms and levels of pulmonary

artery pressure in patients with primary pulmonary hypertension, warranted us to use sildenafil alone in our patient and this showed a persistent reduction in mean PAP and improvement in NYHA functional class with substantial improvement in exercise capacity as demonstrated by the modified treadmill exercise test. Recent studies have also stressed the prognostic values of exercise capacity,<sup>7,8</sup> right atrial pressure, stroke index and vasodilator challenge responses. In the evaluation of the clinical relevance of exercise capacity improvements, additional elements need to be considered, such as baseline functional class and concomitant favorable effects on combined clinical events (including hospitalizations, mortality and rescue therapies), and quality of life.

The data strongly suggest that sildenafil when used alone as a pulmonary vasodilator in patients with pulmonary hypertension has good long-term hemodynamic effects and safety,<sup>16</sup> and may be superior to NO as it increases cardiac output without increase in wedge pressure.<sup>11</sup> Overall, sildenafil is a promising and well-tolerated agent for management of pulmonary hypertension. Further well-designed trials are warranted to establish its place in the treatment of pulmonary hypertension.

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