Oral Sildenafil in the Management of Primary Pulmonary Hypertension

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Abstract
We report a case of primary pulmonary hypertension who benefited from oral Sildenafil therapy. Sildenafil, a selective phosphodiesterase type 5 inhibitor which acts as a pulmonary vasodilator, led to an improved clinical condition, exercise performance and haemodynamic parameters which were maintained at 6 months of follow up. Larger trials are warranted.

INTRODUCTION
Primary pulmonary hypertension (PPH) is a rare (1-2 cases per million people annually) progressive disorder of unknown etiology predominantly affecting women in early life and characterized by progressive elevation of mean pulmonary artery pressure (PAP) greater than 25 mm at rest, right ventricular failure and death.1 It is a vascular disease confined to small pulmonary arterioles where intimal fibrosis and medial hypertrophy leads sequentially to vascular obstruction, right ventricular decompensation which is manifested as reduced cardiac output and development of peripheral oedema.

CASE REPORT
An 18 year old female presented with five years history of worsening dyspnoea. At the time of admission she was NYHA class III symptomatic with absence of orthopnoea and cough in the supine position. There was also history of exertional presyncope since 2 years although patient never experienced any frank syncopal episodes. She had recently been complaining of swelling of feet and face since last 2 months. The patient had also been complaining of chest pain and palpitations off and on but never had any episode of haemoptysis. She had no history of exposure to toxic chemicals, appetite suppressant or collagen vascular disease. There was no history of similar problem in the family. Physical examination revealed raised jugular venous pressure with prominent a and v waves with bilateral pedal oedema. There was presence of persistent hypotension and tachycardia while patient was on calcium channel blockers without any symptomatic improvement. There was no evidence of cyanosis or clubbing. Cardiovascular examination revealed right ventricular heave, signs of tricuspid regurgitation and ejection systolic murmur in pulmonary area. There was a right ventricular S3 gallop indicative of right ventricular failure.

The routine biochemical parameters were within the normal limits and excluded hepatic dysfunction, HIV infection and collagen vascular diseases. Her electrocardiogram showed increased amplitude of P wave in lead II and inverted P wave in lead V1 creating the illusion of left atrial enlargement. This phenomenon is seen in extreme right atrial enlargement.2 There was also right axis deviation, right ventricular hypertrophy and T wave changes suggestive of strain (Fig. 1). Chest x-ray showed main pulmonary artery and right descending pulmonary artery dilatation with right heart enlargement. An echocardiogram revealed dilated right sided chambers and main pulmonary artery. The estimated systolic pulmonary artery (PA) pressure was 105 mm Hg and right atrial pressure of 20 mm Hg with marked shift of interatrial septum towards the left side (Fig. 2). Cardiac catheterization showed a normal left ventricular angiogram with no evidence of left to right
shunt and pulmonary artery angiogram revealed dilated pulmonary arteries with raised pulmonary artery (PA) systolic pressure (Table 1). Pulmonary embolism as a cause was ruled out with a normal ventilation-perfusion study (Fig. 3). A diagnosis of primary pulmonary hypertension with right ventricular failure was made.

The patient was started on digoxin, diuretics and warfarin and international normalized ratio (INR) was maintained at 2.0. Based on recent reports, therapy with oral sildenafil 25 mg thrice a day was started and gradually stepped up to a total dose of 150 mg/day.

A marked improvement was noted within 2 weeks and she showed progressive improvement in symptoms and functional capacity (6 minute walk test). Cardiac catheterization at the end of 1 month showed a remarkable reduction of PA systolic pressure (35% decrease) and right atrial pressure (40% decrease) with a significant increase of cardiac output.

**DISCUSSION**

Current therapeutic approaches of PPH mostly include limitation of physical activity, long term anticoagulation and vasodilator therapy. But only 25-30% of patients show improvement of symptoms and haemodynamics with long term use of oral calcium channel blockers. Continuous intravenous Epoprostenol3 (prostacyclin) use in non-responding PPH patients has led to improvement in functional capacity and survival but catheter infection, systemic effects, tachyphylaxis, non-availability in India and high cost involved limits its widespread use in developing countries like India. Prostacyclin analogues given by continuous subcutaneous infusion (Treprostinil), orally (Beraprost) or by intermittent aerosol (Iloprost) are under development as alternatives to the intravenous route.

The major advance in the treatment of the condition is due to development of two orally active agents bosentan (endothelin receptor antagonist) and sildenafil which demonstrate selectivity for the pulmonary vasculature. Sildenafil inhibits cyclic GMP specific phosphodiesterase,6 an enzyme that is abundantly present in pulmonary vasculature. This causes increased cyclic GMP levels in vascular smooth muscle leading to enhanced nitric-oxide-mediated vasodilation producing decrease in the elevated pulmonary artery pressure. The dose of Sildenafil for PPH remains unknown. Studies in awake lambs5 with PPH showed a dose-related (serial dose 12.5 mg, 25 mg and 50 mg) reduction of PAP by 21%, 28% and 43% and pulmonary vascular resistance.

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<th>Table 1: Haemodynamic parameters before and after sildenafil</th>
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<td>Before therapy</td>
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<td>RA</td>
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<td>RV systolic</td>
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<td>PA systolic</td>
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<td>Left to right shunt</td>
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<td>LV angiogram</td>
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RA : Right atrium; RV : Right ventricle; PA : Pulmonary artery; PCWP : Pulmonary capillary wedge pressure; LV : Left ventricle; CO : Cardiac output; CI : Cardiac index; PVR : Pulmonary vascular resistance
Resistance by 18%, 23% and 45% respectively. Human studies have shown that when administered alone (in doses of 50-300 mg) it causes reduction of pulmonary artery pressure, pulmonary vascular resistance and systemic vascular resistance with increased cardiac index. When administered in combination with inhaled nitric oxide (NO) it augmented and prolonged the pulmonary vasodilator effect of NO and prevented the rebound pulmonary vasoconstriction that occurred after NO inhalation in absence of sildenafil. It acts synergistically with inhaled iloprost to cause strong pulmonary vasodilatation in primary PPH. In the patient we studied there was significant clinical and haemodynamic improvement at the end of one month and now recent data has shown that acute efficacy of sildenafil is well-preserved after long term treatment with no evidence of any tolerance. Sildenafil is a cheap freely available drug with good oral efficacy. It could, become a very useful agent in the medical management of primary pulmonary hypertension in India. Hence we recommend that further studies are needed to determine long term safety of the drug and identify subset of patients who respond favourably.

REFERENCES


Announcement

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Joint Secretary : AK Jain, S Joshi
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XXXIII Annual National Conference of Indian Association of Physical Medicine and Rehabilitation (IAPMRCON 2005) will be held from 27th - 30th January, 2005 at Convention Center, National Institute of Medntal Health and Neuro Sciences (NIMHANS), Bangalore 560 029, Karnataka, India.

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26th Annual Conference of Association of Physicians of India - UP Chapter on 20th and 21st November 2004 at Motilal Nehru Medical College, Allahabad.
Theme of the Conference : "Trials, Tribulations and Triumphs of Modern Medicine".
For further details contact Conference Secretariat : Dr. Sarita Bajaj, 3/6 Panna Lal Road, Allahabad 211 002.
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