Sildenafil for Pulmonary Arterial Hypertension Complicating Respiratory Diseases

UK98240 (now known as Sildenafil), a selective type 5 phosphodiesterase (PDE5) inhibitor, was first chosen as a candidate drug for clinical development for cardiovascular indications in 1989. By blocking PDE5, sildenafil reduces the catabolism of cyclic guanosine monophosphate (GMP). Through a cascade of intracellular events, cyclic GMP promotes smooth muscle relaxation and diminishes cellular proliferation. Although initial studies were quite discouraging for both hypertension and angina, observation of an unusual side effect led to further studies in male impotence, and oral sildenafil was approved by US FDA for treatment of erectile dysfunction in 1998. A considerably high expression of PDE5 in lung tissue was already known, and it was only logical that a series of pre-clinical and clinical trials were subsequently designed to evaluate the efficacy and safety of sildenafil in pulmonary vascular disorders. A large randomised, controlled, multi-national phase III trial [Sildenafil Use in Pulmonary Hypertension (SUPER)] was initiated in 2002. This study included 278 patients with symptomatic pulmonary arterial hypertension (PAH) who received either placebo or oral, sildenafil (20, 40 or 80 mg) thrice daily for 12 weeks. Significant improvement was demonstrated in exercise capacity, functional class and pulmonary haemodynamics in this study. Based on results from this study and information from previous smaller reports, sildenafil was approved by US FDA in 2005 for the treatment of patients with PAH.

Although the SUPER trial was a great effort, more than 65% of enrolled patients had idiopathic PAH, and more than 30% had PAH associated with connective tissue disorders (scleroderma, systemic lupus erythematosus and others). The vast majority of pulmonary disorders that get complicated by PAH, and are commonly evaluated and managed by pulmonary physicians were, therefore, not represented in this data. So can we extrapolate the results of SUPER study and start prescribing oral sildenafil to patients suffering from PAH secondary to lung diseases? Unfortunately, the evidence on this count is rather sketchy and conflicting, and no clear answers are currently available.

In a study on seven patients with PAH secondary to parenchymal lung diseases (four with chronic obstructive pulmonary disease (COPD) and three with idiopathic interstitial fibrosis), oral sildenafil was administered in a dose of 50 mg thrice daily. After eight weeks of therapy, pulmonary arterial pressure (PAP) fell in five patients, and pulmonary vascular resistance (PVR) was reduced in six, but the change was statistically insignificant. Six-minute walk distance (6MWD) increased in six patients. However, the increment in distance walked exceeded 70 metres in only one patient. It has been suggested that the smallest difference in 6MWD, that is associated with a noticeable clinical difference in the patients perception of exercise performance, is 54 metres for mean values from patient groups, and 70 metres for individual patients.

Three studies have assessed sildenafil use in patients with lung fibrosis. In a randomised and controlled open label study on 16 patients, with advanced lung fibrosis due to several aetiologies (idiopathic pulmonary fibrosis, scleroderma, CREST syndrome, silicosis, extrinsic allergic alveolitis), were given a single dose of oral sildenafil (50 mg) or maximally tolerated dose of intravenous epoprostenol. Vasodilatory response to sildenafil was observed within 15 minutes, with a plateau after 45-60 minutes. A significant decrease in PVR and improvement in oxygenation were noted. In another study, 14 patients with PAH secondary to idiopathic interstitial fibrosis received sildenafil in a dose of 20-50 mg thrice daily for three months. Eight patients showed significant improvement in 6MWD (defined in the study as more than 20% increment), but only two improved the distance walked by more than 70 metres. Pulmonary haemodynamics were not assessed in this study, and two of the 14 patients enrolled discontinued treatment due to adverse events. More recently, 12 patients with advanced sarcoidosis and PAH, being considered for lung transplantation, were treated with sildenafil in doses ranging from 75 to 225 mg per day for 1-12 months. Evaluation during treatment revealed significant reduction in mean PAP (18.8%) and PVR (47.7%), with a significant improvement in arterial oxygen saturation, both at rest and after exercise. However, improvement in 6MWD was variable and insignificant.

Three recent studies have evaluated the role of sildenafil in COPD. In one, a single dose of sildenafil (50 mg) was administered to 18 stable patients, of whom five had resting PAH and six had exercise-induced PAH. Regardless of PAP at rest, at one hour the increase in PAP during submaximal exercise was attenuated. There was no improvement in exercise capacity or cardiac output after this single dose. In another study, 15 patients, nine of whom had PAH, received sildenafil (50 mg) thrice daily for three months. Treatment failed to improve exercise capacity (assessed by exercise testing and 6MWD) or stroke volume. Overall results were similar for patients with or without PAH. Clinical efficacy of sildenafil was also studied in six patients with severe COPD and documented PAH. A three-
month trial of 50 mg, sildenafil administered thrice daily resulted in a significant reduction in mean PAP (18.5%) and PVR (34.2%), and a significant increase in mean 6MWD (82 metres).

Finally, four studies\textsuperscript{10-13} have looked at patients with inoperable chronic thromboembolic pulmonary hypertension (CTEPH). In a preliminary study,\textsuperscript{10} 12 such patients were given sildenafil (50 mg) thrice daily for a mean duration of 6.5±1.1 months. A significant reduction in mean PAP (14.6%) and pulmonary vascular resistance index (PVRI, 22.4%), along with a significant increase in mean cardiac index (20.0%) was observed. Although the mean 6MWD increased significantly, and this increase was only 42 metres. There was no significant change in arterial or mixed venous oxygenation. In another study,\textsuperscript{11} six patients with severe CTEPH and co-existing left ventricular (LV) dysfunction received sildenafil (50 mg) thrice daily for six weeks. These patients had a significant reduction in mean PAP (16.8%) but not in mean PVRI (22.4%). There was also a significant increase in Medical Research Council (MRC) dyspnoea score, NYHA class and gas transfer.

In contrast, another large study on 104 patients of CTEPH noted a significant reduction in mean PVR (12.1%) but not in mean PVRI (22.4%), after three months of therapy with sildenafil (50 mg) thrice daily.\textsuperscript{12} There was also a significant improvement in mean 6MWD (51 metres). Perhaps the best quality evidence in patients with CTEPH was generated by a recently concluded double-blind, placebo-controlled pilot study.\textsuperscript{13} Of the 19 subjects enrolled, nine were randomized to receive sildenafil (40 mg) thrice daily. At the end of 12 weeks of treatment, sildenafil had resulted in a significant reduction in mean PAP (12.7%) and PVR (22.0%), but not in dyspnoea score or 6MWD (18 metres). After this initial phase, all patients received open label sildenafil till 12 months.\textsuperscript{13} At 12 months, significant improvement in 6MWD (36 m) symptom score, activity score, PVR, and blood NT-pro brain natriuretic peptide was observed. Because of these findings, the investigators suggested that sildenafil may favourably alter the natural history of CTEPH.

What does this evidence mean to a practicing pulmonologist? Looking back at these studies, it is obvious that, sildenafil therapy is associated with a modest and significant improvement in pulmonary haemodynamics in patients having PAH secondary to pulmonary disorders. The benefit also appears to be sustained over long-term administration. Sildenafil appears effective in this regard for a wide variety of primary pulmonary conditions. There is also no doubt that oral sildenafil therapy is much more convenient for the patient, as opposed to other drugs which need to be administered parenterally. In fact, sildenafil is the only such vasodilator currently available in India. The safety record of this molecule is excellent, based on previous data, as well as specific results from studies on patients with pulmonary hypertension. On the flip side, however, the data is rather limited and not of high scientific quality. Very few randomised trials have been conducted in patients with PAH, and data analysis has mostly been restricted to a few weeks or months of treatment. Another important point to note is that although consistent improvements have been observed in haemodynamic parameters across almost all trials, this improvement in most instances has not been accompanied by a parallel improvement in exercise capacity, respiratory symptoms, and/or oxygenation status.

The lack of quality data, and of significant clinical impact despite pulmonary vasodilation, makes it virtually impossible to decide which subset of patients of PAH secondary to pulmonary diseases are more likely to benefit with sildenafil. As of now, one can only suggest a cautious clinical trial in patients in whom severe PAH is refractory to standard conservative and pharmacological measures. The drug is now available in India. However, more clinical data is required before sildenafil can be incorporated into a standard management protocol for these patients.

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REFERENCES


