Sildenafil as a selective pulmonary vasodilator in childhood primary pulmonary hypertension

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Abstract

Primary pulmonary hypertension is a rare disease of childhood, which carries a poor prognosis. Patients often present with severe exercise limitation, and untreated life expectancy is less than 1 year. Pharmacological intervention is directed towards reduction of the raised pulmonary artery pressure with vasodilator treatment, initially with calcium antagonists, although more recently long term prostacyclin treatment has shown benefit in some patients. Heart–lung transplantation remains an option for children with severe disease refractory to therapeutic treatment.

A 4 year old Bangladeshi girl with dyspnoea, cyanosis, and signs of a low cardiac output, is described. Initial treatment with prostacyclin was gradually reduced, and maintenance treatment with oral sildenafil (Viagra; Pfizer) instituted. At follow up 3 months later, her exercise capacity was greatly improved and she continues to enjoy a good quality of life without obvious side effects. In view of the encouraging initial results, this may become an acceptable adjunct in treating this patient group.

Keywords: primary pulmonary hypertension; sildenafil; prostacyclin

A 4 year old Bangladeshi girl with dyspnoea, cyanosis, and signs of a low cardiac output. She had been seen 18 months before with a cyanotic episode, and had been treated with supplemental oxygen, anticoagulation, and digoxin treatment. More recently, prostacyclin, a potent pulmonary vasodilator with a short half life, has been used with benefit in these patients. Maintenance treatment is dictated by the acute response to incremental doses of prostacyclin at cardiac catheterisation, allowing assessment of potential reversibility of the raised pulmonary vascular resistance. Patients are thereby divided into two groups: acute responders, many of whom can initially be managed with conventional treatment; and...
non-responders, in whom long term prostacyclin treatment is now the treatment of choice. A recent report by Barst et al demonstrated improved symptoms, haemodynamic data, and survival with long term prostacyclin, in children who failed to respond to acute vasodilatation. Survival at four years in this group was 92%, which compares favourably to historical controls in whom survival was only 29%, and to children who have undergone heart–lung transplantation where five year survival is approximately 40%.3 4 The mechanism by which prostacyclin achieves a sustained reduction in pulmonary vascular resistance in the absence of acute vasodilatation remains unclear. Although two prospective studies in adult patients5 6 demonstrated significantly improved quality of life and haemodynamic parameters with prolonged prostacyclin treatment, neither group could demonstrate the aetiology of the underlying vascular remodelling. In contrast, the long term use of calcium antagonists is frequently hampered by intolerable side effects, and may prove hazardous or even fatal.2

Sildenafil is a selective and potent inhibitor of cGMP-binding cGMP-specific phosphodiesterase (PDE5), which catalyses hydrolysis.7 Inhibition of PDE5 increases the cellular levels of cGMP, potentiating vascular smooth muscle relaxation (fig 1), particularly in the lung where PDE5 is found in high concentrations.8 It has been used to offset rebound pulmonary hypertension in infants on withdrawal of nitric oxide treatment, by maintaining raised levels of cGMP in the pulmonary vasculature.

The clinical response in this patient suggests sildenafil may play a role in the management of primary pulmonary hypertension. The tissue specific distribution of PDE5 makes it an attractive alternative or adjunct to current therapies and oral administration avoids the problems of long term prostacyclin infusion.

Figure 1 The mechanism of action of sildenafil. cGMP, cyclic guanosine monophosphate; GTP, guanosine triphosphate; GMP, guanosine monophosphate.