

hydrophobic lipids, so this has long been an issue for developers of these drugs; however, some companies have not been put off. For example, Sanofi Aventis have their orally-dosed obesity drug, Acomplia (a CB1 antagonist), in Phase III clinical trials, with a back-up compound not far behind in Phase IIb. Novartis have a CB1 antagonist (SAB378) in Phase II trials for pain management. Water-soluble cannabinoid drugs are possible too. Pertwee's group recently developed O-1057, a non-selective but water-soluble cannabinoid antagonist. Ward also believes that a focus on

stability might reap rewards. 'By targeting the degradation and hydrolysis pathways of cannabinoids it might be possible to maintain the structure for longer.' Ward added, 'this in turn could improve efficacy'.

Although there is sustained and ongoing clinical interest in cannabinoid drugs, it is equally clear that the development of water-soluble, stable compounds is still in its infancy. That said, with the wide range of indications touted for treatment with cannabis-derived drugs, there seems to be a long future for cannabinoids in the clinic.

Significant improvements

The 14 children in the study were given a baseline assessment of hemodynamics by cardiac catheterization and distance walked in six minutes. Sildenafil was then given orally at 0.25–1 mg per kg of body weight four times daily. The six-minute walk was repeated at six weeks, three, six and 12 months and cardiac catheterization was redone after an average of 10.8 months of treatment. After six months therapy, the distance walked had increased from 278 ± 114 m to 443 ± 107 m. Little improvement was noted at 12 months; the six month point seemed herald a plateau. Mean pulmonary artery pressure and median pulmonary vascular resistance decreased during treatment [1].

Viagra eases symptoms of pulmonary arterial hypertension in children

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A preliminary clinical study involving 14 children with pulmonary arterial hypertension (PAH) has indicated that sildenafil (Viagra) can improve walking distance and hemodynamics for up to 12 months. Ian Adatia (Division of Cardiology, Hospital for Sick Children, University of Toronto Medical School, Canada) now thinks 'we absolutely need a larger trial in children with randomization and perhaps placebo-controlled if that can be justified now or at least in comparison with the drugs already used to treat PAH.'

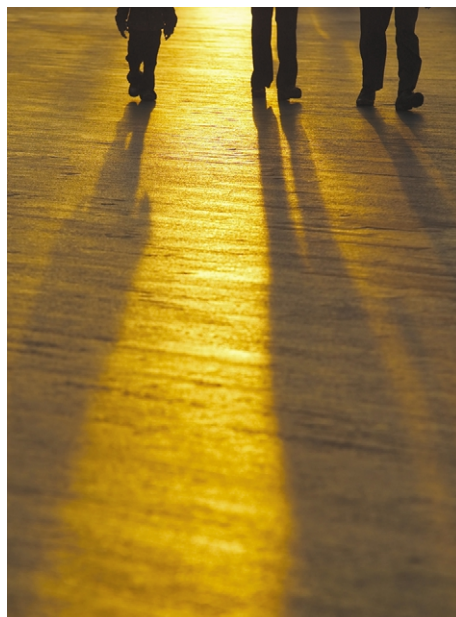
Mechanism of action

Sildenafil is a highly selective and potent inhibitor of the cGMP-specific type 5 phosphodiesterase isoenzyme. In the last four years various studies have shown that type 5 phosphodiesterase inhibitors can achieve pulmonary vasodilation in animals with experimental pulmonary hypertension, in humans with primary and secondary PAH and in healthy volunteers with hypoxic pulmonary vasoconstriction. This is the first study to show that the beneficial effect is also obtainable in children with PAH.

An inexorable progression

'Children with PAH face an unremitting disease that progresses inexorably to right ventricular failure and death. There are a few treatment

options, including continuous intravenous prostacyclin infusion, oral calcium channel blockers and anticoagulation, but their cost is high, they have serious side effects and most require prolonged intravenous access,' explains Adatia. Newer therapies such as endothelin receptor blockers, continuous inhalation of nitric oxide and aerosolized prostacyclin and analogues are becoming more widely used but none is ideal. 'PAH cannot be treated as such, in that we cannot reverse or slow its progression, but we can try to alleviate the symptoms for as long as possible,' adds Adatia.



'...new studies such as this will change the landscape in treating PAH...'

Future developments

In 2004, Pfizer (New York, NY, USA) submitted regulatory filings in the USA and Europe for Revatio™ (sildenafil citrate) as a treatment for PAH and in July this year, the FDA approved Revatio™ on the basis of results from a large randomized study of 277 adult PAH patients; Revatio™ is the first oral treatment approved for patients in the early stages of the disease. 'I think that the move by the FDA, the registration in the US by Pfizer and new studies such as this will change the landscape in treating PAH,' comments Michael Kirchengast (Vice President, Global Product Development Services, Therapeutic Unit Cardiovascular, PRA International, Mannheim, Germany). Kirchengast notes that Myogen (Westminster, CO, USA) is also developing the endothelin receptor antagonist ambrisentan and has just completed enrollment of 187 adult PAH patients in ARIES 2, a Phase III trial based primarily in Europe. Another 186 patients from North America will be enrolled in ARIES 1 by the end of 2005. 'This once-daily dosage drug has shown good results so far, so it will be interesting to see what the Phase III trials come up with,' he says.

References

- 1 Humpl, T. *et al.* (2005) Beneficial Effect of oral sildenafil therapy on childhood pulmonary arterial hypertension: twelve-month clinical trial of a single-drug, open-label, pilot study. *Circulation* 111, 3274–3280