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Abstract

Primary pulmonary hypertension is a rare disease in childhood associated with a poor prognosis. However, during the past 10 years, pulmonary vasodilator treatment has somewhat improved its prognosis. Long term continuous infusion of prostacyclin (epoprostenol) has been shown to improve physical capacity and to reduce mortality in primary and secondary pulmonary hypertension. It has been reported in adults that daily repetitive inhalation of iloprost, a prostacyclin analogue, seems also suitable for long term therapy of pulmonary hypertension. Repetitive inhalation of iloprost was administered to a 5 year old boy with severe primary pulmonary hypertension. He showed continuous clinical improvement without any side effects over the three years of treatment. This treatment may offer an alternative to continuous intravenous prostacyclin infusion and obviates the need for a permanent central venous catheter.

Reference


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CASE REPORT

Long term inhalation of iloprost in a child with primary pulmonary hypertension: an alternative to continuous infusion

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Abstract

Primary pulmonary hypertension is a rare disease in childhood associated with a poor prognosis. However, during the past 10 years, pulmonary vasodilator treatment has somewhat improved its prognosis. Long term continuous infusion of prostanycin (epoprostenol) has been shown to improve physical capacity and to reduce mortality in primary and secondary pulmonary hypertension. It has been reported in adults that daily repetitive inhalation of iloprost, a prostanycin analogue, seems also suitable for long term therapy of pulmonary hypertension. Repetitive inhalation of iloprost was administered to a 5 year old boy with severe primary pulmonary hypertension. He showed continuous clinical improvement without any side effects over the three years of treatment. This treatment may offer an alternative to continuous intravenous prostanycin infusion and obviates the need for a permanent central venous catheter.

Keywords: iloprost; inhalation; prostanycin; pulmonary hypertension

Primary pulmonary hypertension is a rare disease whose natural course is associated with poor long term survival. However, during the past 10 years, pulmonary vasodilator treatment has somewhat improved its prognosis. Long term continuous infusion of prostanycin (epoprostenol) has been shown to improve physical capacity and to reduce mortality in primary and secondary pulmonary hypertension. This beneficial effect is thought to arise not only from the sole vasodilator effect, as most of the patients do not respond acutely to an infusion of prostanycin, but also from its antiproliferative and antiaggregant effects. Pharmacokinetic properties, with a short elimination half life of 2–3 minutes, require the drug to be given as a continuous infusion through a central venous line. The continuous infusion of a prostanycin analogue, iloprost, has shown the same efficacy in pulmonary hypertension.

Furthermore, inhaled iloprost is as effective as inhaled nitric oxide to assess the pulmonary vascular reactivity of patients with pulmonary hypertension and congenital heart disease as shown recently by our group. Daily repetitive inhalation of iloprost has also been reported to be suitable for long term treatment of pulmonary hypertension. Iloprost may have some advantages over inhaled prostanycin because of its sustained clinical effects over 60–120 minutes. Because extrapolation from adults to children may not be straightforward, we report the experience of long term daily repetitive inhalation of iloprost in a 5 year old boy with primary pulmonary hypertension.

Case presentation

A 3.5 year old boy, previously described as healthy, presented with dyspnoea and cyanosis following the inhalation of a peanut. Transcutaneous oxygen saturation (SaO₂) was 80% in room air. Clinical examination showed a loud second heart sound and a 3/6 diastolic murmur. Along with signs of severe right ventricular hypertrophy on the ECG, echocardiography showed dilatation and hypertrophy of the right ventricle and a small secundum atrial septal defect with a right to left shunt. Doppler measurements estimated the pulmonary systolic and diastolic pressure at 95/60 mm Hg (equal to systemic pressure).

He remained cyanotic (SaO₂ between 80% and 85% in room air) despite removal of the peanut. The diagnosis of primary pulmonary hypertension was retained after exclusion of all other causes. Cardiac catheterisation (table 1) confirmed the high pulmonary pressure and resistance, non-responsive to 30 ppm inhaled nitric oxide.

Conventional treatment including calcium channel blockers (nifedipine), anticoagulation,
and nocturnal oxygen was started. Over the next year, the child’s condition deteriorated with a decrease in physical capacity (New York Heart Association (NYHA) functional class III–IV) and his SaO₂ dropped to 75% at rest in room air. An exercise test had to be stopped as his saturation dropped to 60% after walking for less than one minute. At age 5 years, after approval by our local ethics committee and with parental informed consent, a compassionate use of aerosolised iloprost was started. Iloprost was administered at a daily dose of 2 μg, divided in six aerosols of 4 μg (every four hours) delivered by a PARI LC STAR nebulizer (PARI GmbH, Starnberg, Germany) driven by a PARI MASTER air compressor (PARI GmbH). This dosage was adapted from reported doses in adults. 5,6 Conventional treatment was continued. His physical capacity consistently improved over the next two years (NYHA II), and his SaO₂ increased to 85–90%. A repeated exercise test showed that he could now walk for 12 minutes at 3 km/h while maintaining an SaO₂ of > 75%. He was able to return to school and started light physical activities (for example, walking and swimming). A repeated catheterisation, after two years of treatment, documented the beneficial effect of aerosolised iloprost by a 25% decrease in baseline pulmonary vascular resistance (PVR) and PVR to systemic vascular resistance ratio (PVR:SVR), and an increase in systemic oxygen saturation, cardiac index, and mixed venous saturation (table 1). A mild degree of pulmonary vascular reactive activity was observed with inhaled nitric oxide and aerosolised iloprost. In search of adverse effects of chronic inhalation, a fibroptic bronchoscopy showed a normal tracheal and bronchial epithelium. Treatment is being continued with weight adapted doses.

Discussion
This is to our knowledge the first report documenting the beneficial effect of prolonged daily repetitive inhalation of iloprost in a child with pulmonary hypertension. Iloprost is a stable compound, pharmacologically similar to prostacyclin with the same vasodilatory, vascular remodelling, and platelet inhibitory properties, but with a longer half life. 7 Five years after diagnosis and three years after iloprost inhalation was started, our patient experiences a sustained clinical and haemodynamic improvement supported by objective data (improvement in SaO₂ and tolerance to exercise). This novel treatment also caused an objective decrease in PVR and PVR:SVR ratio by 25%. These results are in agreement with the data reported for adults. 5,6 However, our patient presented with more severe pulmonary hypertension characterised by a PVR of 26 WU × m⁻² and a PVR:SVR ratio of 2.4. On the basis of the literature and the natural history of paediatric patients with pulmonary hypertension taking conventional treatment alone (calculated channel blockers and anticoagulation), his estimated life expectancy would have ranged between 2–3 years before iloprost treatment was started. 3 Patients with an atrial septal defect or foramen ovale have been reported to live longer. 4 Furthermore, it has been reported that an atrial septostomy may improve the quality of life and survival in selected patients with pulmonary hypertension. 10 An atrial septal defect is present in our patient and may explain a longer survival. However, it would have been expected that quality of life and exercise tolerance should continue to deteriorate with time even if at a slower rate. The contrary occurred as he showed sustained and continuous clinical improvement. His quality of life has changed remarkably as he returned to school and practices light physical activities with friends and his family.

This report outlines several additional important points: daily repetitive inhalations of iloprost are feasible even in young children and seem to be free of local and systemic side effects; improvement in exercise capacity and quality of life may be expected rapidly but changes in PVR and pulmonary artery pressure may require prolonged treatment. This route of administration avoids complications associated with permanent central venous access (infec-

7 Grant SM, Goo KL. Iloprost: a review of its pharmacodynamic and pharmacokinetic properties and therapeutic potential in peripheral vascular disease, myocardial ischemia and extracorporeal circulation procedures. Drugs 1992;43:889–924.