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Brief Report

Iloprost in persistent pulmonary hypertension of the newborn

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Abstract Aerosolized iloprost is now used as a therapeutic option in the treatment of pulmonary hypertension. We report on the administration of this derivative of prostacycline in treating severe pulmonary hypertension of the newborn. The combination of iloprost instilled endotracheally and inhaled was chosen as a last attempt at treatment in a critically ill patient who did not respond to advanced conventional treatments, including high frequency oscillation and inhalation of nitric oxide. The use of iloprost converted permanently the right-to-left shunting, leading to a substantial improvement in oxygenation.

Keywords: Prostacycline; inhaled therapy; right-to-left shunting

AEROSOLIZED ILOPROST, A STABLE ANALOGUE OF prostacycline, has recently been introduced in the treatment of pulmonary hypertension. Single case reports suggest new indications for its use as an inhaled agent, such as acute pulmonary hypertension and respiratory failure in childhood.[1] Case reports describing its use in the treatment of severe persistent pulmonary hypertension of the newborn, however, are rare. Möller[2] reported on the successful inhalation of aerosolized iloprost in neonates with persistent pulmonary hypertension, but these patients were not mechanically ventilated. Köster and coworkers[3] administered the agent to neonates with echocardiographic findings of pulmonary hypertension, and presumed a reduced incidence of intubation. This, as far as we know, is the first report on the combined use of endotracheally instilled and inhaled iloprost in a mechanically ventilated neonate with severe persistent pulmonary hypertension who did not respond to established treatments, including inhalation of nitric oxide. We combined the endotracheal instillation with inhalation as a rescue attempt in a critically ill patient, achieving a prompt and substantial improvement of oxygenation and a persistent conversion of the initial right-to-left shunt.

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Case report

A 3470 g male infant was delivered spontaneously at 37 + 6 weeks gestation after a normal pregnancy. Apgar scores were 9, 10, and 10, with the umbilical blood gases being within normal range. The neonate showed the characteristic features of Down's syndrome. The clinical diagnosis was confirmed by chromosomal analysis, showing trisomy 21. The infant developed respiratory distress and required intubation at 90 min of age. Initially, sufficient oxygenation was achieved on conventional ventilation, with approximately 50% inspired oxygen. Chest radiography on admission showed diffuse septic infiltrations in both lung fields, but laboratory findings were normal. Antibiotic treatment was commenced with ampicillin, gentamicin and cefotaxime. Analgesia and sedation were accomplished by fentanyl and midazolam. Arterial hypotension was initially treated with repeated expansion of volume, followed by high-dose intravenous vasopressors. Repeated echocardiography revealed a combined shunt over a patent arterial duct. At the age of 9 h, the patient deteriorated rapidly due to severe pulmonary haemorrhage. Echocardiography then showed a right-to-left ductal shunt. We commenced high frequency oscillation using a SensorMedics 3100A machine, with a maximal mean airway pressure of 35 cm water, and 100% oxygen. The high frequency oscillation was combined with inhalation of nitric oxide, given in an initial concentration of 40 ppm, followed by 20 ppm. Surfactant was applied in a dosage of

86 mg/kg, and the pulmonary haemorrhage ceased after repeated surfactant lavages. The mean arterial blood pressure was maintained above 50 mmHg by high dose intravenous vasopressors, composed of dopamine 8 µg/kg/min, norepinephrine 1.5 µg/kg/min and epinephrine 1 µg/kg/min and by dexamethasone. Sodium bicarbonate and tromethamine was given to maintain a blood pH greater than 7.4, and a positive base excess. Despite all these efforts, the achieved arterial oxygen tensions lay only within the range of 23–65 mmHg. No obvious effect of the inhaled nitric oxide was observed. At 24 h of age, cerebral ultrasound revealed bilateral intraventricular haemorrhage, graded at two to three.

Transfer to a centre providing extracorporeal membrane oxygenation was not possible due to the critical clinical condition, with extracorporeal oxygenation also being contraindicated because of the intraventricular haemorrhage. Over the following hours, the oxygenation continued to deteriorate, with the maximal achieved oxygen saturation being 60 to 65%. As the clinical condition worsened progressively, we decided at 30 h of age to administer iloprost, having obtained informed parental consent.

Iloprost, the solution containing 20 µg in 1 ml, was instilled endotracheally by administering 2 µg iloprost diluted with 1 ml sodium chloride 0.9% via a nasogastral tube placed at the tip of the endotracheal tube, without disconnecting the high frequency oscillation. This was repeated after 90 min. Parallel to the second endotracheal application of iloprost, we commenced continuous administration of aerosolized iloprost, with an initial dosage 20 µg/kg/d, integrating a nebulizer into the ventilatory system.[1] As nebulizer, we used the Small Particle Aerosol Generator, SPAG-2® (ICN Pharmaceuticals, Inc.). Up to the age of 39 h, the infant received three more endotracheal instillations of iloprost every 90 to 120 min (Fig. 1). Thereafter, under continuous inhalation of aerosolized iloprost, we achieved satisfactory oxygenation, with arterial oxygen tensions of at least 60–80 mmHg (Fig. 2). The medication and ventilatory settings were maintained otherwise unchanged as mentioned above. The endotracheal application of iloprost was repeatedly followed by a reduction of the mean systemic arterial blood pressure of 10–20%. Echocardiography showed a complete conversion of the initial right-to-left ductal shunting, and a concomitant decrease of the right ventricular pressure. Subsequently, the satisfactory oxygenation was maintained, even when the mean airway pressure and the concentration of oxygen were reduced. Over the following days, however, there was multi-organ failure, with refractory circulatory failure, persisting anuria, and hepatic failure. The child died after 4 days. All microbiological cultures had remained sterile.

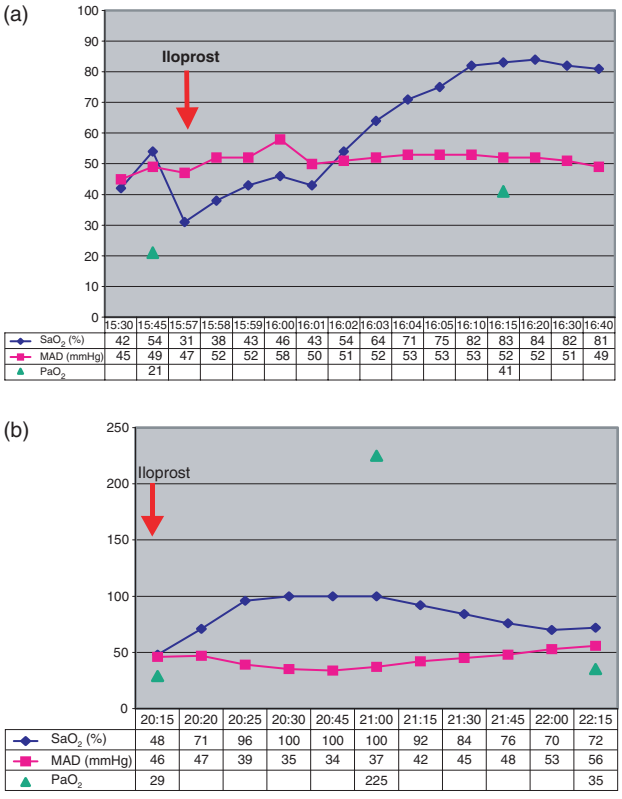

Figure 1.
The chart shows (a) the first endotracheal application of iloprost and (b) the effect of the third application (SaO_2: oxygen saturation; MAD: mean arterial blood pressure; PaO_2: arterial oxygen tension).

Discussion

Nebulized iloprost has been shown to induce selective pulmonary vasodilatation in adults with pulmonary hypertension, with a low risk of systemic side-affects.[4] In children, an improvement of pulmonary hypertension has been demonstrated after longterm therapy with inhaled iloprost.[5] Case reports on the use of aerosolized iloprost in neonates and infants with pulmonary hypertension due to cardiac disease, or after cardiac surgery, are encouraging.[6] Reports on the administration of aerosolized iloprost in neonates and children in intensive care, however, are rare. Möller, as well as Köster and coworkers, studied the effects of inhaled iloprost in spontaneously breathing neonates with mild signs of persistent pulmonary hypertension, and they discussed a probable reduction of the incidence of intubation.[2,3] As far as we know, nonetheless, mechanically ventilated neonates with severe pulmonary hypertension have not previously been treated with inhaled iloprost. Several case reports on the successful treatment of this disease with inhaled prostacyclins encourage the use of iloprost.[7] Compared to the systemic application of prostacycline, the rate of adverse effects

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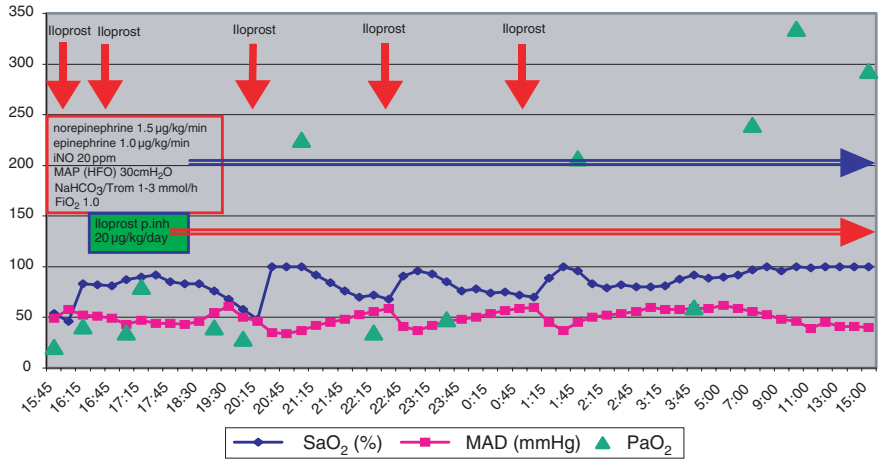

Figure 2.
Summary of clinical evolution of the patient undergoing a combined therapy of endotracheal and inhaled iloprost (SaO_2: oxygen saturation; MAD: mean arterial blood pressure; PaO_2: arterial oxygen tension; iNO: inhaled nitric oxide; MAP: mean airway pressure; FiO_2: fraction of inspired oxygen).

seems to be negligible.[8,9] Furthermore, prostacycline instilled endotracheally seems to have only mild systemic side-effects.[10]

Prostacyclins, and inhaled nitric oxide, show different mechanisms of interaction regarding the precapillary vascular resistance vessels of the lung.[9] Prostacyclins, including iloprost, interfere with the second messenger cyclic adenosine monophosphate, whereas inhaled nitric oxide interferes with cyclic guanosine monophospate. One could presume a beneficial effect of prostacyclins and iloprost regarding non-responders of inhaled nitric oxide, as well as an additive effect combining both agents.

One reason for the previous lack of treatment with aerosolized iloprost in newborns with persistent pulmonary hypertension could be due to the difficulties in practice of aerosolized application in ventilated newborns undergoing high frequency oscillation. On the other hand, the time required to achieve a significant effect of aerosolized iloprost seems to consist of several hours, a phenomenon also observed by own experience. A prompt improvement, as in the application of inhaled nitric oxide, is not probable. Due to the severe clinical condition of our patient, we decided to attempt treatment with iloprost, combining endotracheal instillation with the inhalation of the aerosolized agent. So far, studies on the dosage required in neonates do not exist.

The integration of the nebulizer into the ventilatory system, as well as the management of the high frequency oscillation, did not pose any problems.

It needs to be confirmed whether the application of nebulized iloprost, alone or in combination with an endotracheal instillation, might now be an option in the therapy of neonates with severe pulmonary hypertension.

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