Intravenous Prostacyclin in the Treatment of Persistent Pulmonary Hypertension of the Newborn Refractory to Inhaled Nitric Oxide

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Failure of the fetal pulmonary arterial adaptation to extrauterine life may result in supra-systemic pulmonary arterial pressures leading to right-to-left shunting of blood through the patent ductus arteriosus and/or patent foramen ovale, and the development of persistent pulmonary hypertension of the newborn. Infants with PPHN are hypoxemic because of reduced pulmonary perfusion and can develop myocardial failure secondary to oxygen depletion in the face of increased right ventricular overload.

Treatment with inhaled nitric oxide stimulates soluble guanylyl cyclase in the smooth muscle cells of the pulmonary arterioles to produce cGMP, leading to selective pulmonary vasodilatation. Though this modality of treatment is currently regarded as the gold standard therapy that decreases the need for extracorporeal membrane oxygenation in infants with PPHN, an inadequate response is still encountered in a considerable number of infants [1].

Prostacyclin is an arachidonic acid metabolite that causes vasodilatation in the systemic and pulmonary circulation by stimulating adenylyl cyclase in the vascular smooth muscle cells to produce cAMP. It has been extensively used in adults and children with pulmonary hypertension, but its use in infants with PPHN has been limited by systemic hypotension. Several studies have indicated, however, that the hypotensive effect could be prevented or mitigated by adequate inotropic medication [2]. Most experience with intravenous prostacyclin treatment was gained prior to the advent of inhaled nitric oxide [2]. Parker et al. [3] treated a neonate with alveolar-capillary dysplasia concurrently with inhaled nitric oxide and intravenous prostacyclin, and were the first to suggest that this combination may have a possible role in severe PPHN. In view of the scarcity of information on such combined therapy in the treatment of PPHN [4], we describe a neonate with severe PPHN refractory to nitric oxide inhalation, who was successfully treated with intravenous prostacyclin.

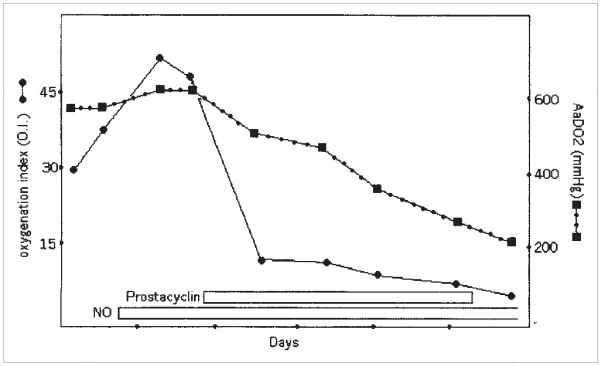
PPHN = persistent pulmonary hypertension
PDA = patent ductus arteriosus
PFO = patent foramen ovale
NICU = neonatal intensive care unit

Patient Description

A 4,155 g male infant was born to a multiparous, A+, 39 year old mother at 41 weeks gestation following a precipitous vaginal delivery in another hospital. Pregnancy was complicated by mild gestational diabetes and by dilatation of the fetal urinary collecting system as demonstrated by ultrasonography. Apgar scores were 9 and 9 at 1 and 5 minutes respectively. Initial physical examination was normal apart from moderate respiratory distress. Blood count was normal. Arterial blood gases analysis at 60% oxygen revealed hypercarbemia and moderate metabolic acidosis. Chest X-ray showed mild hyperinflation of the chest with granularity of lung apices. Central umbilical lines were inserted, blood cultures obtained (negative) and broad-spectrum antibiotic treatment was initiated. Because of increasing dyspnea and oxygen requirement up to 100%, mechanical ventilation was begun and the infant was transferred at 12 hours of age to our neonatal intensive care unit. Echocardiography performed prior to his transport demonstrated no structural abnormalities of the heart and a left-to-right shunt through both the PDA and PFO.

Following admission in the NICU, high pressure ventilation with 100% oxygen was required to maintain adequate oxygenation of the infant. On the 3rd day of life, failure to maintain adequate oxygenation became evident and repeated echocardiography demonstrated supra-systemic pulmonary artery pressures and a right-to-left shunt through a small PDA, with a mean PA-AO gradient of 17 mmHg, confirming the diagnosis of persistent pulmonary hypertension of the newborn.

Treatment included high pressure mechanical ventilation with 100% oxygen, continuous administration of inotropic drugs, deep sedation, and moderate alkalinization with intravenous bicarbonate. In addition, inhaled nitric oxide therapy was started, increasing to 60 ppm with no effect on oxygenation. A trial of surfactant administration also failed. At around 72 hours of age the oxygenation indices were around 50 with an $AaDO_2$ of 603 mmHg. Intravenous infusion of prostacyclin (Flolan®) was begun, concurrently with nitric oxide inhalation, at an initial dose of 2 ng/kg/min and gradually increased to 20 ng/kg/min within 3 hours. A marked improvement in oxygenation was observed and the ventilatory settings were gradually reduced [Figure]. Eighteen hours following initiation of treatment with prostacyclin, the oxygenation index was calculated as 13.6 and the $AaDO_2$ was 505 mmHg. Following further respiratory improvement, a trial to decrease the prostacyclin dose at 36 hours of treatment resulted in respiratory deterioration; however, administration of the drug was gradually discontinued after 4 days of treatment with no further deterioration. Treatment with inhaled nitric oxide was stopped 2 days later. The



Oxygenation indices (O.I.) and AaDO2 values following treatment with intravenous prostacyclin. The small decline of O.I. prior to treatment was due to reduction of the ventilator rate with no effect on $AaDO_2$.

baby was extubated on the 10th day of his life and was weaned to room air 5 days later. A gradual decline of pulmonary arterial pressure was observed concomitantly by echocardiography. Adequate blood pressure values were maintained during his hospitalization and no bleeding tendency was evident. His neurologic examination was considered normal and he was returned subsequently to the referring hospital for further evaluation of his urologic condition.

Comment

Prostacyclin has been administered to infants with PPHN both intravenously and through inhalation [2,5]. Eronen and co-workers [2] utilized Doppler echocardiography during infusion of prostacyclin to eight newborn infants with severe PPHN to study its effect on pulmonary arterial pressure, systemic pressure and systemic oxygenation. Prostacyclin infusion at a starting dose of 20 ng/kg/min failed to reduce pulmonary and systemic arterial pressures and a mean dose of 65 ng/kg/min was required to significantly decrease the pulmonary arterial pressure, resulting in reversal of the ductal shunt.

In order to circumvent the systemic effect, inhaled prostacyclin was used to treat two term PPHN newborns [5]. An immediate improvement of oxygenation was observed, however the effect in one neonate was attributed to the reduction of intra-pulmonary shunting and not to the reversal of the fetal shunts.

Kelly and associates [4] were the first to use inhaled prostacyclin for the treatment of PPHN refractory to inhalation of nitric oxide. The oxygenation indices of their four treated neonates were between 24 and 36 despite treatment with inhaled nitric oxide, and a rapid improvement was observed following inhalation of prostacyclin.

In our case, the oxygen index was calculated above 50 and the $AaDO_2$ was above 600 mmHg despite treatment with inhaled nitric oxide, alkalinization and inotropic support. The observed response to prostacyclin infusion at a dose of 20 ng/kg/min was immediate but less dramatic than that observed following inhalation. A higher dose might have been more efficacious [2], but considering the possibility of potential side effects, probably unjustified. Prostacyclin is an arachidonic acid metabolite that may cause systemic vasodilatation and inhibition of platelet aggregation. No such untoward effects were observed in our case.

In conclusion, inhaled nitric oxide and prostacyclin, either inhaled or infused, affect pulmonary vasodilatation by different mechanisms. Therefore, a synergistic effect might be observed following their concurrent use in the treatment of PPHN. Our experience, though limited, supports the concomitant use of both drugs in neonates with PPHN whose response to inhaled nitric oxide is suboptimal.

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