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ORIGINAL PAPER

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Severe persistent pulmonary hypertension of the newborn in a setting where limited resources exclude the use of inhaled nitric oxide: successful treatment with sildenafil

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Abstract We present the case of a full term neonate with severe persistent pulmonary hypertension of the newborn (PPHN) after birth asphyxia cared for at the St. Elizabeth Hospital in Curacao, Netherlands Antilles. Although the child was ventilated with high pressures and was given high doses of cardiovascular pressors, the arterial oxygen levels remained low with an alveolar-arterial O_2 gradient of 651 mmHg. As a last resort, sildenafil (1.5 mg/kg) was given via a nasogastric tube. This resulted in an immediate and sustained elevation of arterial oxygenation and subsequent complete recovery. After administration of sildenafil there was a transient hypotension which was corrected by a single bolus of saline. *Conclusion*: We discuss the current treatment modalities of persistent pulmonary hypertension of the newborn and the potential use of phosphodiesterase 5 inhibitors such as sildenafil in a situation where the standard of practice with inhaled nitric oxide and extracorporeal membrane oxygenation is not available.

Keywords Persistent pulmonary hypertension of the newborn · Sildenafil

Abbreviations ECMO: extracorporeal membrane oxygenation · iNO: inhaled nitric oxide · PDE: phosphodiesterase · PPHN: persistent pulmonary hypertension of the newborn

Introduction

Persistant pulmonary hypertension of the newborn (PPHN) is a serious disorder with high mortality. The introduction of inhaled nitric oxide (iNO) has greatly improved survival and reduced morbidity; however, in many countries this form of treatment is not readily available. Here we describe our experience of using sildenafil in a neonate with severe PPHN.

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Case report

The patient was the 3215 g product of a 38 week gestation pregnancy born to a 22-year-old G1P0 female. Pregnancy was complicated by oligohydramnios, which was detected 5 days before delivery. Leakage of amniotic fluid could not be detected, therefore the mother was admitted for fetal monitoring. The mother denied any use of drugs/medications during pregnancy. Labour was induced due to oligohydramnios. The mother received two doses of pethidine (100 mg/dose)7 h and 5 h before birth. Due to fetal heart beat decelerations with slow recovery, vacuum extraction was performed. There was a tight nuchal cord but no meconium staining of the amniotic fluid.

The birth weight was 3215 g (50th percentile), length 47 cm (10th percentile), and head circumference 36 cm (50th percentile). There were no dysmorphic signs. There was central cyanosis, and no spontaneous respiratory movements. The heart rate was approximately 40 per minute, with normal heart sounds and no murmurs during auscultation. The abdomen was flat with no apparent organomegaly on palpation. There were two umbilical arteries and one vein. In both elbows and both knees there was a mildly decreased passive extension. The infant was hypotonic, and showed no spontaneous movements. Laboratory findings 30 min after birth revealed: Hb 16 g/dl, WBC 25×10^9/l, platelets 347×10^9/l, arterial blood gases: pH 6,88, pCO_2 96 mmHg, pO_2 53 mmHg, HCO_3 17.4 mmol/l, and BE −16 mmol/l. A chest X-ray film showed decreased pulmonary vascular markings.

After mask and bag ventilation, the infant was intubated and mechanical positive pressure ventilation

started. The Apgar scores were 3, 5 and 7 after 1, 5 and 10 min. Initially high pressures (PIP 26 cm H_2O), (PEEP 5 cm H_2O, frequency 60/min)) and 100% oxygen were needed to achieve and maintain adequate oxygenation. Blood pressures were 75/54 mmHg initially. Blood cultures were obtained and ampicillin and gentamycin were started for a possible perinatal infection. Umbilical catheters were inserted. After an initial mild recovery with normal blood gases and lowering of the ventilation pressures and oxygen requirement (FiO_2 0.3), the baby deteriorated with a decrease in oxygen saturation to 80%. The post-ductal saturation was 10% points lower than the preductal measurement, raising the suspicion of PPHN with right-to-left shunting at the ductus arteriosus. A cardiac ultrasound scan excluded any anatomical cardiac abnormalities, and confirmed increased pulmonary arterial pressure at the systemic level and right-to-left shunt through the open arterial duct. The mechanical ventilation was intensified with maximum pressures of 35 cm H_2O PIP and 6 cm H_2O PEEP. Ventilation was not the problem as very low PCO_2 levels between 15 and 20 mmHg were achieved; however, every attempt to lower frequency or ventilation pressure in order to elevate the PCO_2 resulted in decreased oxygen saturation. Due to arterial hypotension (lowest 45/32 mmHg) and the need for optimal systemic pressures, the patient received numerous normal saline boluses with a total of 150 ml/kg in 24 h. After every bolus there was a short-lived increase in oxygen saturation. Dopamine and dobutamine were titrated to high doses with a maximum of 25 μg/kg per min each. Noradrenalin was also added for a few hours with no beneficial effect. Adequate sedation was achieved with morphine (20 μg/kg/h) and midazolam (max 200 μg/kg/h). When entering the 3rd day of life, the prognosis looked bleak with ongoing low oxygen saturations around 80%, and frequent dips to 70% ($PaO_2 \sim 40$ mmHg, alveolar-arterial O_2 gradient 651 mmHg). In our setting, iNO and extracorporeal membrane oxygenation (ECMO) were lacking due to the high costs of such treatments. As a last resort, one dose of sildenafil (1.5 mg/kg) was administered through a nasogastric tube (suspension made out of a 50 mg tablet). Ten minutes after administration of sildenafil the oxygen saturation rose rapidly to 99% and the PaO_2 to 287 mmHg (alveolar-arterial O_2 gradient 406 mmHg). With this there was an associated flushing of the face and abdomen accompanied by a drop in systemic pressure (from 76/55 to 50/32 mmHg). After a bolus of 20 ml/kg normal saline, the pressure recovered within 7 min and remained adequate thereafter. Subsequently, the ventilation pressure and frequency could be lowered significantly (20/5 cm H_2O, frequency 30/min, FiO_2 0,6), and extubation followed 2 days later (6th day of life). Dopamine and dobutamine could be tapered of over a 2-day period.

Eight days postpartum, he developed a sepsis-meningitis for which he received meropenem for 3 weeks. Blood and cerebrospinal fluid cultures were positive for *Acinetobacter baumannii*. On discharge 1 month after admission, he was still slightly irritable but otherwise had a normal physical examination. At 4 months of age the brainstem electric response audiometry was normal and he had achieved appropriate developmental milestones. There was still a slight hypertonicity of the extremities.

Discussion

We present a case of severe PPHN refractory to the initiated supportive therapy, which in the absence of iNO and ECMO, was successfully treated with sildenafil.

According to data from the United States, the prevalence of PPHN of the newborn is widely variable and is estimated to be 1.9 per 1000 live births [18]. On the island of Curacao (approximately140,000 inhabitants) the annual incidence is 4 per year (unpublished data) and occurs mainly in term or near term infants. Under normal circumstances, a progressive fall in the pulmonary vascular resistance is accompanied by a rise in systemic vascular resistance within the first hours after birth. This leads to a steady increase in pulmonary blood flow. Factors that interfere with these events can cause the transitional circulation to persist.

In a major observational study (by the National Institute of Child Health and Human Development Neonatal Research Network) in the United States, clinical features were described of 385 infants with PPHN in 12 level III neonatal intensive care units [18]. The diagnoses associated with PPHN were meconium aspiration syndrome (41%), pneumonia (14%), RDS (13%), pneumonia and/or RDS (14%), congenital diaphragmatic hernia (10%), pulmonary hypoplasia (4%), and idiopathic (17%). In the infant described, perinatal depression due to hypoxia probably led to development of PPHN; however, oligohydramnios was detected at the very end of this pregnancy which might have led to pulmonary hypoplasia thereby also contributing to PPHN. It is rather unlikely that it played a significant role as the infant responded rapidly to sildenafil.

The treatment of PPHN is largely supportive and widely variable. Before the introduction of iNO therapy, the most commonly used modalities (often in combination) were hyperventilation (66%), continuous alkali infusion (75%), inotropic agents (84%), vasodilators including tolazoline (39%), sedation (94%), paralysis (73%), high frequency ventilation (39%) and ECMO (34%) [18]. It is important to note that most of these therapies (except for ECMO) were not evaluated by randomised controlled trials before implementation. The effects of iNO in PPHN, however, have been studied extensively. Since its introduction, iNO is currently regarded as the gold standard, and ECMO may be used as an escape therapy; however, in large parts of the world the last two treatments are often not available due to the high costs and lack of required infrastructure.

Inhaled NO improves oxygenation, reduces the need for ECMO in term and near term infants with severe PPHN and does not appear to have significant toxicity [1, 3, 4, 5, 6, 7, 10,13]. NO activates guanyl cyclase leading to production of c-GMP. This activates c-GMP dependent protein kinase, which increases the opening of calcium-sensitive potassium channels, in turn causing membrane hyperpolarisation, and inhibits calcium influx through the L-type calcium channel. This leads to relaxation of the vascular smooth muscle cell [2].

C-GMP is deactivated by phosphodiesterase (PDE). Recently interest has focused on PDE inhibitors because of their potent vasodilatation properties. There are ten families of PDE isoenzymes. PDE 5 is particularly prevalent in vascular smooth muscle, and PDE 5 inhibitors are widely known as a treatment for erectile dysfunction [12]. Studies in animal models with pulmonary hypertension have shown that PDE 5 inhibitors such as zaprinast and sildenafil are potent pulmonary vasodilators and augment the vasodilatation effect of iNO [8, 9, 17,19]; however, there is also a significant drop in systemic blood pressure with higher doses of both agents [14, 17,19]. Five minutes after a dose of 1.5 mg/kg administered through a gastric tube, our patient had a drop in systemic pressure which lasted for only 5–7 min and was not accompanied by significant tachycardia. In sepsis and septic shock, inflammatory mediators result in the production of increased concentrations of NO which are responsible for changes in vasomotor tone, decreased vasopressor responsiveness, and decreased myocardial function [15]. In the case of PPHN due to sepsis, the use of sildenafil may theoretically worsen the circulatory status. Another potential risk is the use of sildenafil in paryncymal lung disease (such as in meconium aspiration syndrome) where it might induce or worsen ventilation perfusion mismatch, resulting in a lower PaO_2. Administration in an aerosolised form lowers the potential systemic side-effects and might also prevent this ventilation perfusion mismatch [8,9]. In a recent review, the current clinical experience with sildenafil has been summarised [16]. In all the PPHN cases mentioned, sildenafil was used as an adjunct to iNO. We believe our case is novel due to the fact that sildenafil was used primarily and not in combination with iNO or other vasodilators. We chose the dosage based on literature data available at that moment [11, 14,19]. Although we do not advocate it as a standard therapy, we used sildenafil to successfully treat a case of severe PPHN. Further research is needed to determine optimum dose, safety, and route of administration. If found effective in randomised controlled trials, PDE 5 inhibitors could contribute greatly to the treatment of PPHN in countries with limited resources.

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