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CASE REPORT

PDE3 inhibition with enoximone as first-line therapy for severe persistent pulmonary hypertension of the newborn during neonatal transport: a case report

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Key Clinical Message

Severe Persistent pulmonary hypertension of the newborn (PPHN) can be effectively treated with a PDE3 inhibitor as first-line treatment during neonatal transport when iNO is not readily available. Starting iNO as soon as possible is strongly advised because of the complementary actions of both therapeutics.

Keywords

Enoximone; nitric oxide, neonatal transport, persistent pulmonary hypertension of the newborn, phosphodiesterase inhibitor.

Introduction

Persistent pulmonary hypertension of the newborn (PPHN) is a potentially life-threatening condition that occurs in conjunction with a variety of clinical illnesses including sepsis, asphyxia, meconium aspiration syndrome, congenital heart defects, congenital diaphragmatic hernia, and trisomy 21. Treatment includes treating the underlying clinical condition, open lung ventilation with targeted oxygen, sedation, increasing systemic blood pressure, and inhaled nitric oxide (iNO). Up to 40% of newborns are nonresponders to iNO and require additional treatment including phosphodiesterase-3 or phosphodiesterase-5 (PDE3; PDE5) inhibitors (usually milrinone or sildenafil) and extracorporeal membrane oxygenation (ECMO) [1].

We present a case of a septic newborn with severe PPHN treated with PDE3 inhibition as first-line therapy during neonatal transport.

Case

A term male newborn (GA 38 weeks) was vaginally delivered in a regional hospital with a birthweight of 3620 g. The APGAR scores were 8, 9, and 9. Shortly after delivery, the patient started grunting and he was admitted for nasal continuous positive airway pressure (nCPAP) treatment on the neonatology ward. Because the grunting persisted and the oxygen demand slowly increased, blood cultures were taken and antibiotics were started. Contact was made with the tertiary referral center for transportation to the Neonatal Intensive Care Unit (NICU) because the patient required progressively more oxygen. Vital parameters were within normal range with a FiO_2 of 0.4, and no differences were noted between pre- and postductal oxygen saturation. Capillary blood gas analysis revealed a pH of 7.20, pCO_2 of 55 mmHg, and a base excess of −7 mmol/L. On arrival of the transporting neonatologist, the baby had just been intubated because

of oxygen saturations of 90% despite an FiO_2 of 1.0 on nCPAP. Within minutes, the oxygen saturation dropped below 30%. Immediately, the diagnosis of PPHN was suspected (congenital heart defect was considered less likely because for hours, the oxygen saturation of the patient had been at 100%). Despite attempts to increase blood pressure with dobutamine and norepinephrine, sedation with midazolam and morphine and a trial with neuromuscular blockade (to remove the hypoxia-driven tachypnea) saturations remained well below 30% for 90 min. Heart rate remained at 150/min, and blood pressure did not drop below 50/35 mmHg. Because iNO was not available (this is not routinely installed on the transport incubators), the ICU in the regional hospital was contacted if they could provide milrinone, a PDE3 inhibitor we have experience with in the face of severe PPHN. They were able to provide enoximone, a PDE3 inhibitor more frequently used in adults (and occasionally children) for heart failure. On arrival of the enoximone, the patient was deteriorating: The heart rate of the patient was dropping to below 100 bpm, and the oxygen saturation was unmeasurable. A bolus of 3 mg/kg enoximone was given by hand, and a continuous infusion rate of 23 mcg/kg/min was started. Within minutes, the oxygen saturation started to increase slowly and the heart rate increased to 150 bpm. The patient was prepared for transport to the nearest available NICU (distance 147 km). During transport, the oxygen saturation further increased to 94%. Blood pressure decreased to 40/15 mmHg despite increase of norepinephrine to 0.6 mcg/kg/min and judicious volume expansion.

On arrival, iNO was started at 20 ppm after which the oxygen saturation increased to 100%. Hemodynamic management was optimized by further judicious volume expansion, dopamine (20 mcg/kg/min), and hydrocortisone (5 mg/kg/day). Enoximone was replaced with milrinone (1 mcg/kg/min) because of complete lack of experience with enoximone in terms of pharmacokinetic profile. Blood gas at admission: pH 7.05, pCO_2 48 mmHg, bicarbonate 13.3 mmol/L, base excess −17 mmol/L, PO_2 62 mmHg. The lactate was 14.1 mmol/L and brain natriuretic peptide 488 mcg/L.

Echocardiographic evaluation of the heart showed a normal anatomy with a suprasystemic right ventricular pressure with bidirectional shunt over the arterial duct. The left ventricular function was adequate, and the contractility of the right anterior wall was decreased (Fig. 1).

After one hour, the PaO_2 decreased and surfactant was administered resulting in increasing PaO_2. Hypercapnia prompted a switch to high-frequency oscillation (HFO) ventilation. After 7 days, he was successfully extubated.

Because of the prolonged period of deep hypoxia, the patient was treated with total body cooling during 72 h at a temperature of 33.5°C for neuroprotection. Brain sonography at admission showed highlighting of the thalami. The MRI after 3 days showed a small ischemic lesion on the left anterior cortex.

Blood cultures as well as cultures of the mother showed Group B streptococci (GBS). The liquor culture after several days of treatment in a stable phase was negative. C-reactive protein was 52 mg/L on admission. He was initially treated with amoxicillin/cefotaxime and with cefotaxime monotherapy during 2 weeks. The otoacoustic emission (OAE) test was normal. At the age of 12 months, his mental and motor development is normal. He shows normal general movements, symmetrical normal muscle tone, and reflexes.

Discussion

This patient presented with PPHN in the context of neonatal sepsis in less than favorable circumstances responding well to first-line treatment with an unconventional PDE3 inhibitor in newborns. The initial outcome is favorable. Despite the prolonged period of deep hypoxemia, the MRI of the brain showed no gross abnormalities.

PDE inhibition as first-line therapy for PPHN has been described in the literature. Typically, a PDE5-inhibitor is used for this indication (sildenafil). Sildenafil inhibits the cGMP-degrading phosphodiesterase (PDE5), prolonging and/or enhancing the vasodilator effects of NO via soluble guanylate cyclase (sGC) [2]. A recent Cochrane review and several later reviews support the use of sildenafil as first-line therapy when iNO is not available, but a large-scale randomized trial is still needed to assess efficacy and safety [3].

Milrinone inhibits cAMP-degrading phosphodiesterase (PDE3) in the cyclooxygenase pathway, enhancing the vasodilator effect of endothelial-derived prostacyclin. Prevention of degradation of cAMP in cardiac myocytes improves both contractility (inotropy) and diastolic function (lusitropy) [4]. Gradually, case series, retrospective cohort studies, and pharmacological studies lend support for using this drug in the complex pathophysiology of PPHN, usually as additional treatment to iNO [5, 6]. A randomized controlled trial to evaluate the efficacy and safety of PDE3 inhibition for either LCOS or PPHN has never been conducted. The recommended dosage regime consists of a loading dose of 50 mcg/kg followed by continuous infusion of 0.33–1.0 mcg/kg/min. In a recent review of PPHN, Sharma et al. stated that milrinone might be the pulmonary vasodilator of choice when left ventricular function is compromised [7]. Enoximone is also a PDE3 inhibitor with comparable effects and pharmacokinetics. In children, it is mainly used in low cardiac

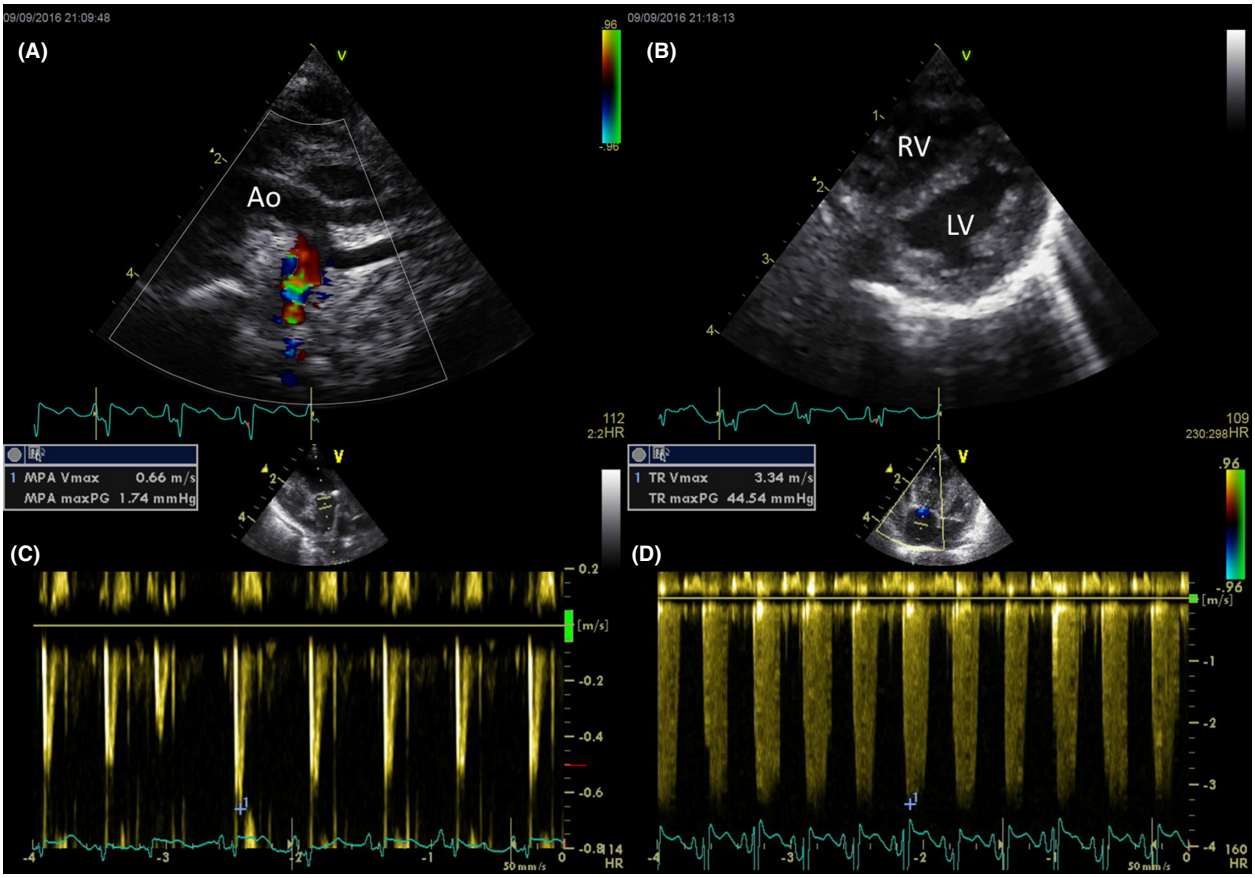

Figure 1. Composite illustration of PPHN as found in our patient. (A) reversed flow in the aortic arch due to right–left shunt over the ductus arteriosus; (B) D-shaped left ventricle (LV) due to elevated right ventricle (RV) pressure; (C) peaked flow signal in main pulmonary artery (MPA) as commonly seen in pulmonary hypertension; (D) tricuspid regurgitation with systemic level pressure gradient indicative of pulmonary hypertension.

output syndrome (LCOS) when β-adrenoceptors are downregulated as in major open-heart surgery and sepsis. Reported dosage regimes include a loading dose of 1–5 mg/kg followed by continuous infusion of 10–23 mcg/kg/min [8, 9]. Dosage regimes rely on adult data or the published small case series. Despite the absence of literature describing the use of enoximone as first-line treatment for PPHN in a term newborn, we felt its use in this particular case warranted as the only other outcome would have been death. Indeed, the rapid improvement in oxygen saturation seen after initiating enoximone infusion is in accordance with the literature describing the role of PDE3 inhibition in PPHN. What is new is that PDE3 inhibition was successfully used as first-line treatment for PPHN allowing this patient to safely reach the NICU for further treatment with iNO. The patient we described is normal on neurological examination and no significant damage is found on MRI. Despite a prolonged period of deep hypoxia, this patient maintained blood pressure and heart rate during this period. Together with total body cooling (and probably intact cerebral autoregulation), these factors may have secured continuous blood flow to the brain and thus preventing significant hypoxic damage.

In conclusion, this case underscores the value of PDE3 inhibition in PPHN and indicates that when nothing else is available, PDE3 inhibition can be used as first-line therapy for PPHN. As soon as possible, support with iNO (or PDE5-inhibition) should be added to maximize therapeutic effect. Hemodynamic stability is of paramount importance, not only for survival but also to prevent or limit hypoxic ischemic damage to the brain.

Conflict of Interest

Robin van der Lee, Barbara Peels, and Corine Koopman-Esseboom declare that they have no conflict of interest.

Informed Consent

Informed consent was obtained from the parents of the patient for being included in this report.

Authorship

RL: wrote the first draft of the manuscript. All authors participated in the concept and design and in drafting and critically revising the manuscript. All authors approved the manuscript as submitted.

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