Persistent pulmonary hypertension of the newborn (PPHN) is defined as failure of normal pulmonary vascular relaxation at or shortly after birth manifesting as progressive and potentially fatal hypoxemic respiratory failure. PPHN represents a common outcome of vascular injury secondary to numerous perinatal stresses. The current standard therapy consists of selective vasodilatation with inhaled nitric oxide (iNO). However, approximately 40% of near-term infants treated with iNO fail to respond. Several animal studies have demonstrated that milrinone, a phosphodiesterase (PDE) III inhibitor, dilates the pulmonary vessels. We describe a case of PPHN treated with a combination of iNO and intravenous milrinone.

Case Report

B.A. was born by elective cesarean section (CS) at 38 weeks of gestation because of a previous CS and after a normal pregnancy (APGAR score 9/10, birth weight 3680 g). Progressive respiratory failure occurred shortly after birth. Echocardiography confirmed PPHN with right ventricular systolic pressure (pulmonary artery pressure, PAP) estimated at the tricuspid valve as 64 mmHg, and bidirectional flow through a patent foramen ovale and ductus arteriosus with normal biventricular function. The patient was intubated, started on antibiotic therapy and transported to our unit on the second day of life. On admission to our unit, the following findings were recorded: temperature 38.5°C, general condition extremely compromised, oxygen arterial saturation (SaO2) 77% with FIO2 100%, heart rate 165 bpm, blood pressure 86/41 (57) mmHg, phosphorus (P) 7.35, PO2 22.3, PCO2 40.8, base excess (BE) -2.3, and oxygenation index (OI) = 59. Neutropenia and increased C-reactive protein (CRP) also developed but no signs of septic shock were present at admission. Chest X-ray demonstrated signs of respiratory distress: diffuse fine granularity and air bronchograms. Antibiotic therapy with ampicillin, gentamicin and ceftazidime, cardiovascular support therapy with dopamine, recombinant human granulocyte colony-stimulating factor and iNO at a maximum dose of 20 ppm were initiated. An initial good response was obtained (O2 saturation >90%), but a few hours later despite optimal ventilation and proper hemodynamic support, the infant’s condition became refractory to iNO (OI 68, estimated right ventricular systolic pressure 87 mmHg). Milrinone was started by continuous infusion (maximum
dose 0.75 µg/kg/min). Reduced right ventricle systolic pressure estimated as 37 mmHg on echocardiography and improved oxygenation (OI 17) were observed within two hours. Both milrinone and iNO were discontinued eight days later (OI 4) and the infant was extubated. Cultures (blood, urine, cerebrospinal fluid, tracheal washing) performed on admission were negative and antibiotics were discontinued after CRP normalization. During milrinone therapy, the infant developed systemic hypotension refractory to dopamine (max dose 15 µg/kg/min), but responsive to adrenaline (0.1 µg/kg/min). Cranial ultrasound showed no signs of intracranial hemorrhage (IVH).

**Discussion**

Vascular smooth muscle relaxation may be produced by two distinct pathways: 1) Increases in the intracellular concentration of cyclic guanosine monophosphate (cGMP pathway) - NO molecules released from the endothelium increase concentrations of cGMP in the adjacent vascular smooth muscle cells and produce vascular relaxation; or 2) Increased concentration of intracellular cyclic adenosine monophosphate (cAMP pathway) as a result of increased cAMP production or decreased cAMP metabolism (PDE inhibition). Inhaled NO is widely accepted as the gold standard treatment for PPHN because of its selective vasodilator effects on the pulmonary vascular bed. However, approximately 40% of near-term infants treated with iNO still require extracorporeal membrane oxygenation to prevent death and moreover, prolonged high-dose iNO therapy is associated with the development of methemoglobinemia, organ injury due to higher oxides and cell membrane damage due to peroxynitrites.

Phosphodiesterases (PDEs) are enzymes that control intracellular levels of cyclic nucleotides and are extensively distributed in normal tissues. Currently, 50 different isoforms have been identified. The predominant isoenzymes in the pulmonary arteries are PDE-5 (cGMP-specific) and PDE-3 (cAMP-specific, cGMP-inhibitable).

Phosphodiesterase inhibitors prevent the breakdown of cGMP and cAMP. These agents are therefore potentially useful in clinical situations where active pulmonary vasoconstriction is one of the pathophysiological features. PDE-3 inhibitors increase intracellular levels of cAMP in cardiac myocytes and vascular smooth muscle, thus achieving a positive inotropic and lusitropic myocardial effect and systemic and pulmonary vasorelaxation.

Milrinone, a PDE-3 inhibitor, induces pulmonary vasodilation directly through a cAMP-mediated signalling pathway and an additive/synergic effect in combination with iNO, as demonstrated in different animal models. The addition of milrinone to iNO therapy in experimental models of pulmonary hypertension led to reductions in PAP and systemic vascular resistance as well as to improved right ventricular compliance and cardiac output compared with iNO alone.

Experience with this drug in neonates is limited. Studies of milrinone in newborns are largely reports on postoperative cardiac patients where the use of milrinone reduced the development of postoperative low cardiac output syndrome and improved pulmonary hemodynamics. Recently, in two case series, it was shown that the coadministration of intravenous milrinone in neonates with severe PPHN and poor iNO responsiveness led to sustained improvements in oxygenation.

In the first of these series, the authors presented four cases with severe PPHN unresponsive to therapy with iNO, with a mean OI of 40 (SD 12) before milrinone and a substantial improvement in OI (mean 28; SD 16) after the introduction of milrinone. In that report, two of the four cases described suffered from IVH without any firm relationship with the therapy. There was no description of systemic hypotension following milrinone in any of the four cases.

McNamara et al., in a retrospective study, described nine full-term (>37 weeks) neonates with severe PPHN and a baseline OI of 28.1±5.9 who received milrinone treatment after a poor initial response to iNO treatment. They showed a significant reduction in OI after milrinone treatment, particularly in the first 24 hours of treatment with the drug (OI 8.0±6.6, p<0.001) without development of systemic hypotension.

In conclusion, in the presented case, PPHN was secondary to clinical sepsis and no sustained response was achieved with iNO.
alone. Based on recent reports, intravenous milrinone was co-administered, leading to an early improvement in oxygenation. No adverse effects have been described at the cerebral level according to the literature. However, systemic dose-dependent hypotension developed following a milrinone dose of 0.65 µg/kg/min and was promptly resolved with the start of continuous intravenous infusion of adrenaline. The prompt resolution of the clinical picture in the presented case after the introduction of milrinone confirms that the drug may be a useful adjunctive treatment in the management of severe PPHN.

REFERENCES