CASE REPORT

Oral Sildenafil for Severe Pulmonary Hypertension Developing after Ibuprofen Use in a Neonate

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Background: Severe pulmonary hypertension may following ibuprofen administration for ductal closure. **Case characteristics:** An extremely preterm infant who developed severe pulmonary hypertension unresponsive to inhaled nitric oxide after ibuprofen administration. **Outcome:** Pulmonary hypertension reversed after the administration of oral sildenafil, but the infant died due to complications related to bronchopulmonary dysplasia. **Message:** Sildenafil may have a role in treatment of severe pulmonary hypertension after ibuprofen treatment for ductal closure.

Keywords: *Patent ductus arteriosus, Prematurity, Pulmonary vasodilators.*

Several cases of pulmonary hypertension after prophylactic and therapeutic use of ibuprofen for ductal closure have been reported [1-7]. In such cases, pulmonary vasodilators have been used with variable response. We report a positive response to the concomitant use of inhaled nitric oxide and oral sildenafil in an extremely premature neonate who developed severe pulmonary hypertension after ibuprofen administration.

Case Report

A preterm (26 weeks) neonate, second child of triplet pregnancy, weighing 750 g was born to a 18-year-old mother who received corticosteroids and magnesium sulfate before delivery. The infant was delivered via cesarean section. He was intubated in the delivery room. The initial course involved mechanical ventilation and surfactant therapy with poor response; he was placed on high-frequency oscillatory ventilation (HFOV) on day 5 and remained stable on moderate settings.

A functional echocardiography performed on day 6 demonstrated a hemodynamically significant patent ductus arteriousus (PDA) with continuous left-to-right shunt and no evidence of pulmonary hypertension. He was unsuccessfully treated with three doses of ibuprofen (L-lysine). A second course of ibuprofen was delayed because of late-onset enterococcal sepsis. On day 29, under stable conditions but still requiring mechanical ventilation, a repeat functional echocardiography evaluation revealed a PDA without signs of pulmonary hypertension, and a second course of ibuprofen was prescribed (10 mg/kg body weight first dose, then 2 doses of 5 mg/kg given 24 hours apart). After the third dose, the infant´s condition worsened; he became hypotensive and presented with frequent hypoxemic events requiring fluid boluses, vasopressors (dopamine, dobutamine and epinephrine) and aggressive ventilatory support on HFOV (FiO_2 1, mean airway pressure 24 cmH_2O). Chest *X*-ray showed no infiltrates or pneumothorax. Functional echocardiography revealed a large PDA with bidirectional shunt and septal wall flattening. Inhaled nitric oxide (iNO) was started and titrated to 20 ppm with no improvement in oxygenation.

On the 35th day of life, oral sildenafil (sildenafil citrate solution) was initiated at 0.5 mg/kg every 6 hours. Arterial oxygen saturation raised from 57% to 91% in the following hours. However, oxygen requirements remained above 80%. The dose was increased, 72 hours later, to 1 mg/kg every 6 hours. A marked improvement in oxygenation was then observed with decreasing FiO_2 needs (<0.4) allowing a gradual weaning of iNO until its discontinuation on the 41st day of life. Subsequent echocardiograpic valuations confirmed the resolution pulmonary hypertension and closure of the PDA. However, the infant became ventilator-dependent and was diagnosed as severe bronchopulmonary dysplasia (BPD) at 36 weeks of postconceptional age. He developed unilateral stage III retinopathy of prematurity (ROP). Magnetic resonance imaging of brain at 52 weeks of postconceptional age demonstrated cerebral atrophy and delayed myelination. Due to treatment futility and according to parents' wishes, reorientation of care was adopted and the infant died at the age of 6½ months.

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DISCUSSION

Pulmonary hypertension is a rare but potentially lethal adverse effect of ibuprofen administration for the treatment of PDA. It may be related either to early administration of the drug, that prevents a normal drop in pulmonary vascular resistance, or to acidification of the ibuprofen solution resulting in precipitation and secondary microembolism of the lung [3]. Although this effect was initially thought to be associated with prophylactic treatment or when ibuprofen was buffered with tromethamine [1], a few cases have been observed after therapeutic use of L-lysine ibuprofen.

Most reported cases responded well to the use of iNO but some infants died despite aggressive treatment. An earlier report of the concomitant use of iNO and sildenafil in this setting reported poor outcome [5]. Our patient did not respond to iNO but pulmonary hypertension reversed with the administration of oral sildenafil. Sildenafil is a selective phosphodiesterase 5 (PDE 5) inhibitor which increases cGMP levels inducing pulmonary vascular relaxation. Oral sildenafil is the standard treatment of chronic pulmonary hypertebnsion, and is also used to aid weaning from iNO therapy in term infants. However, its use as an emergency treatment of acute pulmonary hypertension is limited and dosing regimen is not clear [8].

Studies in neonates with pulmonary hypertension have shown that sildenafil selectively reduces pulmonary vascular resistance (PVR) with few systemic effects [9]. It has been shown to have an onset of action in 30 to 120 minutes and its potential side effects include arterial hypoxemia, hypotension and retinopathy of prematurity [9]. Our patient developed stage III ROP which regressed spontaneously.

We conclude that pulmonary hypertension is a rare but potentially lethal side effect in preterm infants receiving ibuprofen for PDA closure. In case of absent or partial response to iNO, the administration of oral sildenafil may be effective.

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