Case Report

Inhaled Iloprost for Severe Persistent Pulmonary Hypertension of the Newborn

Uraiwan Chotigeat MD*,
Santiwan Jaratwashirakul MD*

** Neonatal Unit, Department of Pediatrics, Queen Sirikit National Institute of Child Health*

The authors report one case of persistent pulmonary hypertension that had hypoxia although receiving treatment with high frequency oscillation, inotropic drugs, blood transfusion, and oral sildenafil for pulmonary vasodilatation. The patient developed hypotension after two doses of oral sildenafil and no response to high dose of inotropic drugs. So aerosolized iloprost was given via endotracheal tube and oxygen saturation improved within 10 minutes. Oxygen was weaned at 36 hours after treatment with this drug and no any side effect was found.

Keywords: *Iloprost, PPHN, Sildenafil*

J Med Assoc Thai 2007; 90 (1): 167-70
Full text. e-Journal: *http://www.medassocthai.org/journal*

Aerosolized iloprost is now used as a therapeutic option in pulmonary hypertension especially in adults[1-3]. However, there have been only a few reports from Europe on the use of this drug for pulmonary hypertension of the newborn[4-6]. The authors report the administration of this derivative of prostacyline in treating severe pulmonary hypertension of the newborn. The combination of iloprost inhaled was chosen as a last resort for treatment in a critically ill patient who did not respond to advanced conventional treatments, including high frequency oscillation and oral phosphodiesterase 5 inhibitors, sildenafil. The use of iloprost reversed permanently the right to left shunting, leading to a substantial improvement in oxygenation.

Case Report

A term female newborn, birth weight 2870 gm, was born via vaginal route from an uneventful pregnancy and good antenatal care from a private hospital. The mother received pethidine two and a half hours before delivery. The baby did not require any resuscitation at birth but was given intravenous naloxone at one and a half hours after delivery because of grunting and breathing difficulty. Physical examination at that time revealed grunting and slow breathing with mild retraction. Nasal continuous positive airway pressure (nCPAP) was applied with good response. Capillary blood gases showed respiratory acidosis at two and four hours after nCPAP application, after which the patient was intubated and started on conventional mechanical ventilation. Chest radiography showed right lung pnuemothorax. Needle aspiration was done and oxygen saturation improved except right lower lung pneumonia after being on endotracheal tube CPAP with 100 percent oxygen again. Due to progressive desaturation, the patient was switched to high frequency ventilation at age of nine hours. Despite optimal support with inotropics, antibiotics, blood transfusion and fluid bolus, the patient continued to deteriorate. Echocar-diogram demonstrated normal structural heart, right to left shunt at foramen ovale, pulmonary pressure was 56 mmHg, and systemic blood pressure was 62 mmHg. Persistent pulmonary hypertension was diagnosed at 46 hours of age and oral sildenafil was prescribed. Three doses were given at one-hour intervals, the patient developed hypotension with persistent desaturation. Inotropes were increased to maximum dose. The patient developed desaturation all the time for six hours while on high frequency ventilation again, so aerosolized iloprost (0.5 microgram per kilogram) was prescribed at, 59 hours of age. Oxygen saturation improved within 10 minutes, from 85%

Correspondence to : Chotigeat U, Neonatal Unit, Department of Pediatrics, Queen Sirikit National Institute of Child Health, Bangkok 10400, Thailand.

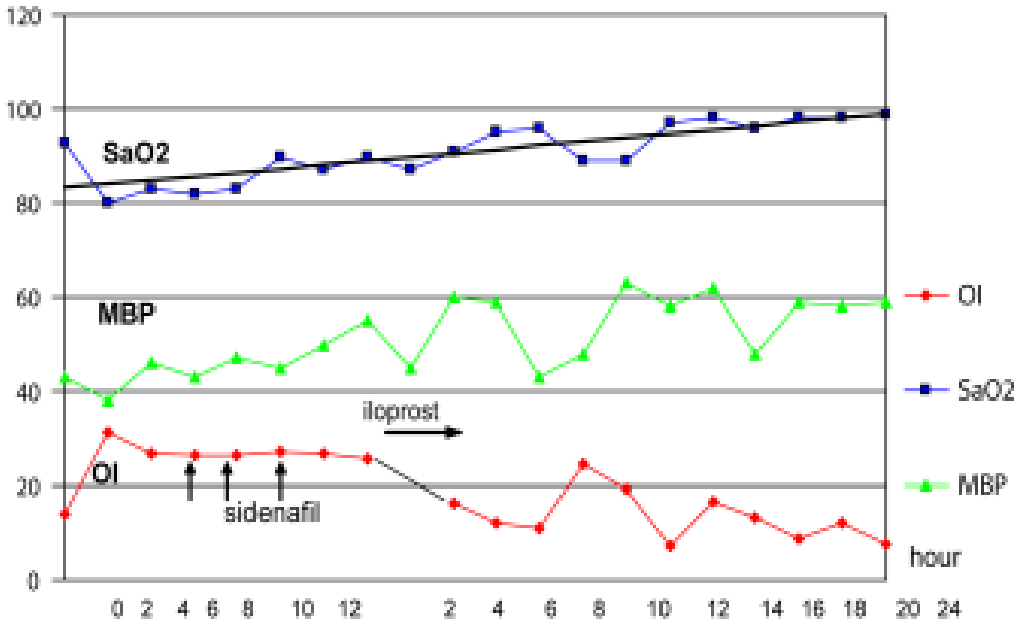

Fig. 1 The effect of sildenafil and iloprost treatment of pulmonary hypertension (OI, SaO_2, MBP)
OI = Oxygenation index, MBP = mean blood pressure, SaO_2 = Oxygen saturation

to 91% and reached 95% after two doses of iloprost (at two-hour intervals). Oxygenation saturation index decreased gradually and oxygen was weaned after 36 hours of treatment (total dosage 15 microgram). The patient was extubated at 7 days of life and discharged at 15 days old without any complications. No systemic hypotension occurred during treatment with iloprost (as Fig. 1).

Discussion

Due to the high cost of iNO (inhaled nitric oxide), other drugs such as sildenafil (phosphodiesterase 5 inhibitor) and magnesium sulfate are being tried in the treatment of persistent pulmonary hypertension of the newborn. Unfortunately, side effects such as systemic hypotension have been reported. Aerosolized iloprost has been used in the treatment of persistent pulmonary hypertension of the newborn in Europe[1]. This drug was approved by the European Commission for the treatment of pulmonary hypertension in adults since 2003. Aerosolized prostacyclin was found to be a potent pulmonary vasodilator in patients with acute respiratory failure, exerting preferential vasodilatation in well-ventilated lung regions[1,2,7,8]. These reports were mainly in adult patients but a few reports were from children and the newborn[4-6]. This is the first report in treatment of persistent pulmonary hypertension with this drug in Thailand. Iloprost is a stable analogue of prostacyclin that is associated with a longer duration of vasodilatation[9].When administered during a short aerosolization maneuver to patients with pulmonary hypertension, its pulmonary vasodilative potency was similar to that of prostacyclin but its effects lasted for 30 to 90 minutes, compared to 15 minutes[3,10-12]. The presented patient responded to this drug within 30 minutes and required 10 doses (15 microgram). The relatively short duration of action is a major disadvantage of this form of treatment because 6 to 12 inhalations per day may be needed to maintain the desired clinical effect[13]. This patient failed treatment after sildenafil. Then the authors decided to use this drug. The current study demonstrates that the phosphodiesterase (PDE) 1/5/6 inhibitor, sildenafil, may also amplify the pulmonary vasodilatory response to inhaled iloprost. Both indirect inhibition of PDE3 by increased cGMP and direct inhibition of PDE1 may explain the effects of sildenafil on the iloprost-induced vasodilation. Most interesting, when applied in subthreshold doses, all PDE inhibitors enhanced and markedly prolonged the vasodilatory response to inhaled iloprost, without any systemic pressure decline or deterioration of gas exchange being detectable[14]. A combination of low dose systemic PDE inhibitors might be considered for enhancement and in particular,

prolongation of the lung vasorelaxant response to inhaled iloprost. The patient was discharged from the hospital at 15 days old without any complication and normal development until now (nine months old).

In conclusion, the present report demonstrates the beneficial effect of aerosolized iloprost for the treatment of severe pulmonary hypertension. It may be a suitable alternative drug to inhaled NO for the treatment of persistent pulmonary hypertension of the newborn in developing countries.

References

1. Walmrath D, Schneider T, Pilch J, Grimminger F, Seeger W. Aerosolized prostacyclin in adult respiratory distress syndrome. Lancet 1993; 342: 961-2.
2. Zwissler B, Kemming G, Habler O, Kleen M, Merkel M, Haller M, et al. Inhaled prostacyclin (PGI2) versus inhaled nitric oxide in adult respiratory distress syndrome. Am J Respir Crit Care Med 1996; 154: 1671-7.
3. Olschewski H, Ghofrani HA, Walmrath D, Schermuly R, Temmesfeld-Wollbruck B, Grimminger F, et al. Inhaled prostacyclin and iloprost in severe pulmonary hypertension secondary to lung fibrosis. Am J Respir Crit Care Med 1999; 160: 600-7.
4. Ehlen M, Wiebe B. Iloprost in persistent pulmonary hypertension of the newborn. Cardiol Young 2003; 13: 361-3.
5. Lambert V, Serraf A, Durand P, Losay J. Aerosolized iloprost therapy in an infant with chronic pulmonary hypertension after a neonatal arterial switch operation. Arch Pediatr 2001; 8: 1218-21.
6. Concheiro GA, Sousa RC, Suarez TB, Paradela CA, Ocampo CS, Antelo CJ. Inhaled iloprost: a therapeutic alternative for persistent pulmonary hypertension of the newborn. An Pediatr (Barc) 2005; 63: 175-6.
7. Walmrath D, Schneider T, Pilch J, Schermuly R, Grimminger F, Seeger W. Effects of aerosolized prostacyclin in severe pneumonia. Impact of fibrosis. Am J Respir Crit Care Med 1995; 151: 724-30.
8. Walmrath D, Schneider T, Schermuly R, Olschewski H, Grimminger F, Seeger W. Direct comparison of inhaled nitric oxide and aerosolized prostacyclin in acute respiratory distress syndrome. Am J Respir Crit Care Med 1996; 153: 991-6.
9. Fitscha P, Tiso B, Krais T, Sinzinger H. Effect of iloprost on in vivo and in vitro platelet function in patients with peripheral vascular disease (PVD). Adv Prostaglandin Thromboxane Leukot Res 1987; 17A: 450-4.
10. Hoeper MM, Olschewski H, Ghofrani HA, Wilkens H, Winkler J, Borst MM, et al. A comparison of the acute hemodynamic effects of inhaled nitric oxide and aerosolized iloprost in primary pulmonary hypertension. German PPH study group. J Am Coll Cardiol 2000; 35: 176-82.
11. Olschewski H, Walmrath D, Schermuly R, Ghofrani A, Grimminger F, Seeger W. Aerosolized prostacyclin and iloprost in severe pulmonary hypertension. Ann Intern Med 1996; 124: 820-4.
12. Gessler T, Schmehl T, Hoeper MM, Rose F, Ghofrani HA, Olschewski H, et al. Ultrasonic versus jet nebulization of iloprost in severe pulmonary hypertension. Eur Respir J 2001; 17: 14-9.
13. Hoeper MM, Galie N, Simonneau G, Rubin LJ. New treatments for pulmonary arterial hypertension. Am J Respir Crit Care Med 2002; 165: 1209-16.
14. Schermuly RT, Inholte C, Ghofrani HA, Gall H, Weissmann N, Weidenbach A, et al. Lung vasodilatory response to inhaled iloprost in experimental pulmonary hypertension: amplification by different type phosphodiesterase inhibitors. Respir Res 2005; 6: 76-86.

การรักษาภาวะความดันเลือดปอดสูงในทารกแรกเกิดด้วยยาไอโลปรอส

อุไรวรรณ โชติเกียรติ, สันติวรรณ จรัสวชิรกุล

ผู้ศึกษาได้รายงานผู้ป่วยทารก 1 รายที่ได้รับการวินิจฉัยเป็น PPHN ซึ่งได้รับการรักษาด้วยเครื่องช่วยหายใจความถี่สูง การให้ยาเพิ่มความดันโลหิต การให้เลือดเพื่อรักษาภาวะซีด การให้ยา sildenafil เพื่อขยายเส้นเลือดในปอดแต่ทารก มีภาวะความดันโลหิตต่ำแม้ว่าจะเพิ่มยาinotropic drug แต่ความดันโลหิตไม่ดีขึ้น ผู้ป่วยตอบสนองต่อการให้ยาไอโลปรอสทางท่อทางเดินหายใจโดยการมีภาวะความเข้มข้นของออกซิเจนเพิ่มขึ้นใน 10 นาทีและสามารถลดออกซิเจนได้ใน36ชั่วโมงหลังให้ยา ไม่พบภาวะแทรกซ้อนจากการใช้ยานี้ในทารกที่มีภาวะ PPHN