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BRIEF REPORT

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The use of phosphodiesterase inhibitor (dipyridamole) to wean from inhaled nitric oxide

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Abstract A full-term, male neonate developed persistent pulmonary hypertension, and responded to high-frequency oscillatory ventilation and inhaled nitric oxide (INO). Discontinuation of INO was attempted three times and was followed by severe desaturations due to right-to-left shunt through the patent ductus arteriosus and patent foramen ovale. As a result of this rebound pulmonary hypertension, the neonate was maintained on INO therapy for 6 days. Successful discontinuation was achieved by using the phosphodiesterase inhibitor, dipyridamole. We speculate that during exogenous INO therapy, endogenous nitric oxide was inhibited, thus cyclic guanosine 3′,5′-monophophate, the smooth muscle relaxant, was rapidly hydrolyzed. By inhibiting phosphodiesterase, smooth muscle relaxation occurred, and consequently weaning from INO was achieved.

Key words Neonates · Phosphodi-esterase inhibitor · Nitric oxide · Pulmonary hypertension

Introduction

Inhaled nitric oxide has been shown to improve oxygenation in neonates with severe persistent pulmonary hypertension [1–3]. However, a small subset of neonates who continue to improve while they are receiving INO progressively deteriorate when INO is discontinued. We speculate that this deterioration is due to an elevated level of phosphodiesterase, which hydrolyzes cyclic guanosine 3′,5′-monophosphate (cGMP) and results in smooth muscle constriction. We report on a full-term neonate who responded to INO, but became NO-dependent by the 6th day of treatment. Discontinuation of INO was successful using dipyridamole, a phosphodiesterase inhibitor.

Case report

A male neonate weighing 3170 g was born at full-term to a primigravida mother by cesarean section due to fetal distress. Upon delivery, he was intubated and thick meconium was found below the vocal cords. Apgar scores were 1 and 5 at 1 and 5 min, respectively. He was mechanically ventilated and, despite the use of high ventilatory support, he remained hypoxic. The neonate was transferred to our institution in the first few hours of life. Physical examination revealed central cyanosis, contractures of knee joints, undescended testicles, and palpable kidneys. Ultrasound examination of the abdomen showed cystic dilatation of the kidneys and bilateral tortuosity and dilatation of the uterus. The difference between preductal and postductal saturations was more than 30. Persistent pulmonary hypertension of the newborn was diagnosed and confirmed by echocardiogram, which showed right-to-left shunting through the patent ductus arteriosus (PDA) and patent foramen ovale (PFO) with tricuspid regurgitation. Right-sided pneumothorax occurred

and was drained successfully by a chest tube. The patient experienced clonic seizure activity, most likely secondary to asphyxia, which was controlled by phenobarbitone. Blood pressure was maintained at normal level by using volume expanders and dopamine (15 μg per kg per min) and dobutamine infusions (10 μg/kg min). Initial arterial pH was 7.09 with partial pressure of carbon dioxide in arterial blood ($PaCO_2$) of 60 mm Hg, partial pressure of oxygen in arterial blood (PaO_2) of 37.5 mm Hg, and bicarbonate (HCO_3^-) of 18 mEq/l. Despite increased support on conventional ventilation (PIP 37 cm H_2O, positive end-expiratory pressure 3 cm H_2O, rate 60/min, and fractional inspired oxygen (FIO_2) 1.00), oxygenation did not improve and 3100A high-frequency oscillatory ventilation (HFOV) (Sensor Medics, Yorba Linda, Calif., USA) was used. Arterial blood gas on HFOV showed pH 7.23, $PaCO_2$ 54 mm Hg, PaO_2 33.8 mm Hg, and HCO_3^- 22 mEq/l. HFOV support was progressively increased to deliver 100% oxygen with a mean airway pressure of 24 cm H_2O and pressure amplitude (ΔP) of 35 cm H_2O, but there was little improvement in oxygenation. Chest X-ray showed normal lung expansion. A few hours after initiating the HFOV, inhaled nitric oxide (INO) was started. The INO was obtained as a gas in balance nitrogen in a certified concentration of 841 ppm (Canadian Liquid Air, Montreal, Quebec, Canada) with < 5 ppm nitrogen dioxide. The NO mixture was connected at a pressure of 30 psi to the flowmeter and injected into the inspiratory line of the HFOV. The gas mixture was analyzed for NO, NO_2, with an electrochemical sensor (Pulmonox, Tofield, Alberta, Canada). Exhaled gas was scavenged. The neonate was treated with an initial dose of 80 ppm and attempts were made to lower the dose every 1–2 h after administration by reducing the concentration by 5 ppm. Twenty-four hours after initiating INO therapy the neonate was maintained on a dose of 10 ppm. PaO_2 increased from 33.8 to 150 mm Hg. Ventilator support was progressively weaned over the first 24 h, from an FIO_2 of 1.00 to 0.50, mean arterial pressure from 24 to 18 cm H_2O, and ΔP from 31 to 26 cm H_2O. At 40 h of age an attempt to discontinue INO failed and the neonate developed severe desaturation with significant right-to-left shunting through PDA and PFO, which was confirmed by echocardiogram. INO was restarted at 80 ppm then weaned gradually to 10 ppm. During the INO, methemoglobin concentration was measured every 8 h (270Co-oxime, Ciba-Corning, Diagnostics, Medfield, Mass., USA) and was < 5%. At 60 h of INO therapy, discontinuation was again attempted but was followed by severe desaturation with a preductal and postductal saturation difference of 45. The neonate then was restarted on 80 ppm of INO and weaned to 10 ppm, which was continued for 24 h. A third attempt to stop the INO also failed. Thirty hours after the last attempt, dipyridamole (phosphodiesterase inhibitor) was administered intravenously at 0.4 mg/kg per min over 10 min and repeated every 12 h for a total of three doses. Before dipyridamole was administered, INO was weaned to 5 ppm and the saturation dropped from 98 to 90%. After the administration of dipyridamole, there was a striking improvement in saturation (Fig. 1). No adverse side effects of dipyridamole were observed. The neonate's mean blood pressure was 61 mm Hg (range 52–59) and 69 mm Hg (range 59–89), respectively, before and during the administration of dipyridamole. Arterial blood gas following discontinuation of INO showed pH 7.45, PCO_2 30 mm Hg, and PO_2 142.5 mm Hg. Ventilator support was further weaned and the neonate thereafter continued to maintain normal saturation with no significant difference between the pre- and postductal saturation. At 15 days of age, HFOV was replaced by conventional ventilation and the neonate was extubated to nasal continuous positive airway pressure (CPAP). Nasal CPAP was replaced by nasal cannula to deliver the small amount of oxygen sufficient to keep oxygen saturation above 95%. The neonate's serum urea and creatinine concentrations were elevated (19 mmol/l and 266 μmol/l), but conservative measures were recommended by the nephrology team. He was then transferred back to the referring hospital in a stable condition.

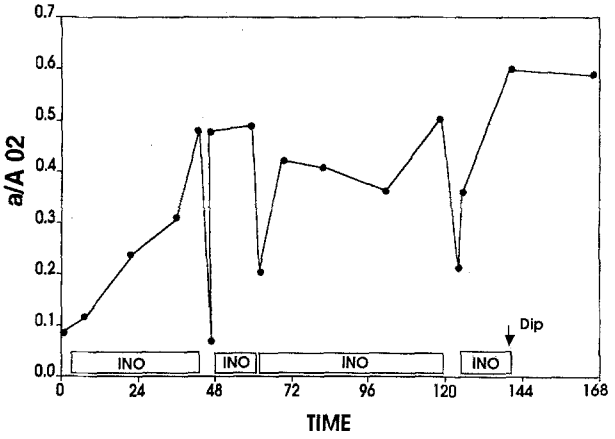

Fig. 1 Serial changes in arterial–alveolar oxygen ratio $a/A\ O_2$ before and during inhaled nitric oxide *INO* therapy in a full-term neonate with persistent hypertension of the newborn due to meconium aspiration syndrome. As shown, INO improved oxygenation and the three attempts at discontinuing INO were associated with rebound desaturation, which was reversed by dipyridamole *DIP*

Discussion

We report the clinical course of a full-term newborn treated with INO and HFOV for pulmonary hypertension due to asphyxia and meconium aspiration syndrome. There was dramatic improvement in oxygenation, as evidenced by blood gas results and pulse oximeter demonstrating no difference in pre- and postductal saturation. Three attempts to discontinue INO were made, but they were associated with rebound desaturation and right-to-left shunt across the ductus arteriosus, as demonstrated by echocardiography. Subsequently, discontinuation of INO was achieved by inhibiting phosphodiesterase, an enzyme that hydrolyzes cGMP. Since NO causes vasodilatation by increasing cGMP content in vascular smooth muscle cells [4], inhibition of cGMP phosphodiesterase activity may contribute to smooth muscle relaxation. In our case, we speculated that during INO, endogenous NO production was decreased. The decrease in endogenous NO may be responsible for the rebound pulmonary hypertension following weaning from INO. Bult et al. [5] found that exposure to large quantities of NO may lead to downregulation of the endogenous biosynthesis in the generator cells and diminished responsiveness of the effector cells.

Dipyridamole is a vasodilator which also exhibits antiplatelet effects. It has been used in patients with coronary artery disease, myocardial infarction, prosthetic heart valves, coronary bypass grafts, neurological diseases, and disorders of peripheral circulation. The specific mechanism by which dipyridamole exerts its hemodynamic and antiplatelet actions is not fully understood. Dipyridamole prevents the inactivation

of adenosine, a potent vasodilator, by adenosine deaminase in the red blood cells, lung, and myocardial tissue [6]. Studies have demonstrated that dipyridamole prevents adenosine from reaching the site of deamination in the tissues by inhibiting the facilitated diffusion uptake mechanism for adenosine [7, 8]. This leads to an accumulation of adenosine in the interstitial space around the arterioles, which results in vasodilatation.

Multiple phosphodiesterase isoenzymes have been isolated from a variety of tissues and, based on their kinetic characteristics and susceptibility to inhibition by selective inhibitors, have been divided into five distinct families [9].

Dipyridamole and zaprinast, cGMP-phosphodiesterase isoenzyme type 5 inhibitors, were found to cause dose-dependent pulmonary vasodilatation in the near-term, chronically prepared ovine fetus, which was not primarily due to their effects on adenosine [10]. Recently, Kinsella et al. [11] have reported a case in which dipyridamole was able to enhance the response to INO.

We hypothesize that the duration of action of dipyridamole was sufficient for the suppressed endogenous NO production system to recover. One might argue that the neonate was ready to be weaned from INO after the 6th day of treatment and the contribution of dipyridamole to the weaning process was negligible. As described above, the neonate failed three attempts to discontinue INO, despite low ventilatory support. Furthermore, his saturation dropped significantly when INO was reduced to 5 ppm before dipyridamole administration, and saturation returned to baseline immediately after dipyridamole was administered. INO was not discontinued completely before dipyridamole because of the past experience of severe desaturation when INO was discontinued.

We believe that with the increase in the use of INO more cases of INO dependency will be identified. We speculate that this INO dependency is most likely due to inhibition of endogenous NO by exogenous NO. Phosphodiesterase inhibitors, such as dipyridamole, may play a role in facilitating the weaning process from INO in cases of INO dependency.

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