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SILDENAFIL IN MANAGEMENT OF PERSISTENT PULMONARY HYPERTENSION OF THE NEWBORN: REPORT OF TWO CASES

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SUMMARY

Persistent pulmonary hypertension of the newborn (PPHN) was described in 1969 by Gersomy and co-workers as persistent foetal circulation. Supra - systemic pulmonary artery pressures result in right to left shunting of blood through the ductus arteriosus and/or foramen ovale. This results from failure of the normal adaptation to extra uterine life of the foetal heart/lung system. The incidence is estimated at about 0.1-0.2% of live born infants, majority being term or post term. There is no race or gender related predisposition. Management was always difficult before the advent of nitric oxide (and now sildenafil). We report two newborn infants born at The Mater Hospital with perinatal asphyxia resulting in persistent pulmonary hypertension that were successfully managed with sildenafil.

INTRODUCTION

Persistent pulmonary hypertension of the newborn (PPHN) can be idiopathic but often follows adverse perinatal events such as sepsis, pneumonia, meconium aspiration, asphyxia, respiratory distress syndrome, congenital diaphragmatic hernia, primary pulmonary hypoplasia and pulmonary hypoplasia resulting from oligohydramnios (1).

There is maladaptation to extrauterine environment such that the normal fall in pulmonary vascular pressures on clamping of the cord and breathing of air by the newborn does not occur (2,3).

The persistence of raised pulmonary pressure results in right to left shunting of blood across the ductus arteriosus and/or foramen ovale. The resultant anoxia is only corrected by lowering the pulmonary pressures. Selective pulmonary vasodilation would be the most ideal but has not always been successful. In neonates, use of inhaled nitric oxide has met varied degrees of response in different circumstances (1). Sildenafil on the other hand appears to be a potent selective pulmonary vasodilator that needs controlled evaluation in infants with PPHN. No suitable parenteral formulation of this drug has been manufactured. However the tablet (oral) form of the drug can be made into a solution. Sildenafil citrate solution can be made extemporaneously and whether stored under refrigeration or at room temperature can remain stable for one month (4).

The sildenafil citrate solution used in the two cases was made by the hospital pharmacist by crushing one 25mg tablet of viagra and dissolving the powder in simple syrup made up to 50mls. This provided a solution of sildenafil citrate of 0.5mg/ml. The solution was stored in an amber coloured container away from light and used within one week.

The use of sildenafil in both cases was as a rescue when it became apparent from their clinical state that without additional intervention to reduce pulmonary pressures, their hypoxia was not being

improved by available means and no suitable alternative therapies were at hand. During discussions between the clinical team and parents, the possibility of use of sildenafil was explained to the parents who were made aware that it was not registered for use in the condition that we were going to administer it. The side effects of the drug when used in newborns were unknown and that the drug has been used in the form we proposed to use it for similar indication but in different circumstances. Only after verbal consent of both parents was obtained, was the drug prepared by the pharmacist and administered.

CASE REPORTS

Case 1: J.W., Date of birth 10.10.2004, date of discharge 31.10.2004, birth weight 3160g, discharge weight 3080g. A female infant delivered by emergency Caeserian section to a 34 year-old para 2^{+2} mother. Indication for Caeserian section was pregnancy-induced hypertension, foetal distress with meconium stained liquor at 39 weeks gestation by dates and ultra sonography. A post-dates infant was delivered with APGAR score of four at one, six at five, and ten minutes respectively. Meconium was suctioned from the airway through endotracheal intubation. Active rescusitation was necessary to save the infant.

The infant was admitted directly to ICU from theatre with a working diagnosis of post -datism, asphyxia and possible meconium aspiration syndrome. Mechanical ventilation was instituted with necessary supportive measures. Day one through to three, the arterial PO_2 remained marginal with labile blood pressure requiring dopamine infusion.

A cardiac evaluation was requested to rule out PPHN on day three. A 2D-echocardiography confirmed severe pulmonary hypertension (110mm Hg) with shunting across the foramen ovale/ductus arteriosus, enlarged right ventricle with poor contractility. Laboratory tests revealed haemoglobin concentration of 17.5g/dl with hypocalcaemia of 1.7mmol.

On day four, the condition was deteriorating despite hyperventilation on 100% $Fi0_2$ and correction of the hypocalcaemia. In view of the labile systemic blood pressure, use of tolazoline was considered inappropriate and yet there is no facility for nitric oxide therapy or extra corporeal membrane oxygenation (ECMO). A decision was reached to attempt rescue trial of sildenafil at an initial dose of 0.5mg/kg six hourly = 1.5mg six hourly. Informed verbal consent was obtained from both parents.

On day five, pulse oximetry revealed improved and stable oxygen saturation consistently above 96%. This was corroborated by arterial blood gas analysis that revealed improved $P0_2$ from 56 to 85 and PCO_2 from 50 to 42. This improvement was sustained. With this sustained improvement in blood gas status, a 2D echocardiogram was repeated after eight doses of sildenafil (two days) and revealed reduction of pulmonary pressure to 55mmHg and no shunting across the ductus arteriosus and/or foramen ovale. Oxygen (FiO_2) requirement continued to diminish and with appropriate ventilator adjustments, the infant was successfully weaned and extubated on day eight. A repeat echocardiogram revealed normal pulmonary pressure and myocardial function. Sildenafil was discontinued.

Concurrent events during these first eight days were development of necrotising enterocolitis with haemogram features of sepsis that was managed with empirical use of antibiotics including intravenous metronidazole and resting the gut. The infant was on phenobarbitone to prevent convulsions resulting from ischaemic encephalopathy.

The infant developed apnoiec attacks and respiratory failure on day ten at which time there was severe electrolyte imbalance with hyponatremia, hypokalemia and hypocalcaemia. The infant was ventilated for another two days from day 10 to 12. The electrolyte imbalance was corrected. Repeat echocardiography still showed normal pulmonary pressures and myocardial function. She was discharged to the special care baby unit on day 15 and discharged home on day 22 with no cardio-respiratory symptoms or signs. She is presently on outpatient follow up.

Case 2: A.N., Date of birth 12.1.2005, date of discharge 21.1.2005, birth weight 3510g, discharge weight 3250g. A female infant delivered by emergency Caeserian section to a 28 year old primigravid mother whose antenatal period was uneventful and gestation was at term. Indication for Caeserian section was delayed second stage (about one hour) with foetal distress. APGAR score was five at one, six at five, and eight at ten minutes respectively. The infant was admitted to the special care unit in respiratory distress with a working diagnosis of

moderate asphyxia. The respiratory distress persisted and the infant was on oxygen by face mask at a flow of 10 L/min. On examination, apart from the respiratory distress, the infant was hypertonic with a brief sharp cry. On day two, the infant developed generalised convulsions and was started on phenobarbitone (in addition to fluid restriction to 80 ml/kg/day and zinacef that she was on from admission). At this point, the neonatologist was requested to attend to the infant. A chest X-ray revealed a right sided enlarged heart (dextrocardia), full blood count showed neutrophilia of 90% and thrombocytopenia of 96,000. Antibiotics were empirically changed to ceftazidin and amikacin and a loading dose of intravenous phenobarbitone given with subsequent maintenance dose. An echocardiogram confirmed the dextrocardia and pulmonary hypertension of 120mmHg with shunting across the foramen ovale. There was no structural intracardiac anomaly. On day three, continous pulse oximetry revealed oxygen dependance at 15L/min flow rate by face mask to maintain saturation above 90%. The convulsions were still occurring though with reduced frequency. Phenytoin sodium was added to the treatment and this controlled the convulsions. The respiratory distress deteriorated to impending respiratory failure. However the parents could not afford ICU care hence a decision to start sildenafil to lower pulmonary pressure was made. Informed consent was obtained from the parents and sildenafil started at a dose of 0.5mg/kg six hourly (2mg Q1D). This was continued for four days and a gradual improvement in the respiratory function was noted with oxygen requirement reducing to less than 5L/min flow rate on face mask to maintain saturation above 95%. On day seven the infant did not require any supplemental oxygen and a repeat echocardiogram revealed reduction in pulmonary arterial pressure to 35mmHg and no shunting. Though the infant was still mildly tachypnoec (45 breaths per minute) the sildenafil was discontinued. At this point the infant had no convulsions and phenobarbitone was discontinued leaving her on epanutin alone and antibiotics. The consciousness level then improved rapidly. Limited assay of electrolytes revealed a hyponatremia that was corrected with normal saline.

On day eight, though still tachypnoec, the infant was breast feeding adequately and digesting the feeds with good bowel action and passing adequate amounts of urine. On day nine, due to financial constraints, the infant had to be discharged for out patient follow up while still on oral phenytoin sodium.

DISCUSSION

Asphyxia, sepsis, meconium aspiration and post - datism have all been associated with PPHN (1). Both the cases presented here had perinatal asphyxia and probable sepsis. Case 1 also had meconium aspiration and post - datism.

Persistent hypoxia out of proportion to the expected degree of parenchymal lung disease should be investigated for possible PPHN (1). Both cases exhibited this by the need for high FiO_2 in Case 1 and high O_2 flow rate for Case 2. This prompted the echocardiography that revealed PPHN. Clinically, this can present as intermittent cyanotic spells as systemic PaO_2 alters with the amount of shunting. Clinical examination of the heart may reveal a single loud S_2 (normal "splitting" resumes when pulmonary hypertension subsides). These clinical features may be the only diagnostic tool available in developing countries. Hyperoxia test, preductal and post ductal PaO_2 analysis and hyperoxia — hyperventilation test may be useful. Echocardiography when available is confirmatory (4).

Attempts at management of PPHN have of necessity aimed at reduction in pulmonary pressure to stop the shunting. Drug therapy with tolazoline results in undesirable alteration of systemic blood pressure and hence the drug has not been popular in neonates (5). Hyperventilation by causing high PaO_2 has been shown to lower pulmonary pressure though marginally and inconsistently (8). Inhaled nitric oxide a potent pulmonary vascular dilator is useful but requires special equipment (1,6). Extra-corporeal membrane oxygenation — (ECMO) has also been used where it is available but the advent of nitric oxide inhalation removed the need for ECMO in management of PPHN (7).

More selective vasodilation of pulmonary vasculature is a desirable goal and several products have been tried alone or in combination such as inhaled iloprost alone or in combination with sildenafil, bosentan and sildenafil alone or in combination with inhaled nitric oxide (9-13). Most of the studies have been in children or adults with few in neonates. The use of inhaled nitric oxide

requires special equipment with a ventilator (1,3,6) which is often not available in developing countries.

Sildenafil was originally marketed for treatment of male sexual dysfunction which remains its main use. It is a potent oral medication that is a specific inhibitor of phosphodiesterase – 5 (PDE – 5), an enzyme that hydrolyses cyclic guanosine monophosphate (cGMP). Cyclic - GMP mediates pulmonary vasodilation possibly as a second messenger for endogenous nitric oxide production. PDE – 5 is in high concentration in the lungs. It's inhibition by sildenafil results in a sustained rise in cGMP and subsequent pulmonary vasodilatation. The effect of sildenafil on pulmonary vasculature appears to be independent of the underlying cause of the raised pulmonary pressure. Due to this, it may be useful in a range of settings of pulmonary hypertension including PPHN (10). In combination with inhaled iloprost, sildenafil appears to improve the efficacy of therapy several times (13).

We used sildenafil as monotherapy starting at 0.5mg/kg/six hourly and had remarkably good response without increasing the dose (10). The therapy was a last resort when other available means had apparently failed or were inappropriate. The pulmonary pressure reduced rapidly in two to three days and remained normal after withdrawal of the drug. The use of sildenafil removes the need for sophisticated equipment such as a ventilator or infusion pumps that are in short supply in developing countries. It is not possible from these cases to ascertain whether the use of sildenafil had any undesirable side effects. Occurance of electrolyte inbalance in both cases was attributed to inadequate attention to fluid electrolyte therapy rather than the sildenafil which has been shown to have no effect on systemic blood pressure (10,11,13). While sildenafil is an expensive drug even by developed country standards, its use removes the need for extra expense in sophisticated equipment hence may be useful in developing countries if it is used for a brief period in the neonate as we have done.

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