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Sildenafil in the management of neonates with PPHN: A rural regional hospital experience

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Introduction. Persistent pulmonary hypertension of the newborn (PPHN) can occur as a primary or secondary neonatal emergency and remains a serious management challenge with a high mortality rate. The failure of a rapid fall in pulmonary vascular resistance in the early postnatal period that characterises PPHN can progress into a vicious pulmonary vasoconstrictive cycle if not promptly managed. In the past 5 years sildenafil citrate (Viagra; Pfizer), with its selective pulmonary vasodilator properties, has emerged as a potential treatment modality for PPHN.

Objectives and methods. To describe our experience with the use of sildenafil in 2 non-ventilated neonates with moderate to severe PPHN. The patients were managed at Worcester Hospital, a rural regional hospital in the Western Cape, South Africa.

Results. In both cases the addition of sildenafil to the treatment regimen resulted in: (*i*) a significant increase in haemoglobin oxygen saturation as measured by pulse oximetry; (*ii*) ability to wean the fraction of inspired oxygen; and (*iii*) avoidance of mechanical ventilation and referral to a tertiary intensive care unit.

Conclusion. Sildenafil appears to be beneficial in the treatment of PPHN and its use can be considered in the management of selected cases, even in a resource-limited setting; however, this still needs to be validated by more controlled studies.

Persistent pulmonary hypertension of the newborn (PPHN) remains a difficult neonatal emergency to manage, despite novel management modalities. The condition occurs in near-term, term and post-term infants with an incidence of 0.43 - 6.8/1 000 live births and carries a high risk of mortality (10 - 20%).[1] The disruption in the normal perinatal fetal-neonatal circulatory transition that results in PPHN can be due to intrauterine pulmonary vascular underdevelopment (decreased vascular growth), maldevelopment (abnormal vascular structure) and/or maladaptation (perinatal hypoxia-induced pulmonary vasospasm).[2] Intrauterine or perinatal asphyxia and meconium aspiration syndrome remain the most common associated diagnoses.

Normal perinatal circulatory transition depends on the rapid fall of pulmonary vascular resistance (PVR) that occurs with the first breath and the marked rise in systemic vascular resistance (SVR) that follows clamping of the umbilical cord. The pathophysiology of PPHN resembles the fetal circulation (PVR>SVR), with extrapulmonary right-to-left shunting through the foramen ovale and/or ductus arteriosus resulting in diminished pulmonary perfusion and hypoxaemia.[2] If this is not interrupted a vicious pulmonary vasoconstrictive cycle can develop, further increasing PVR, diminishing pulmonary perfusion and resulting in refractory hypoxaemia and acidosis.

Preventing this cycle, or breaking it if already present, is essential in reducing hypoxic-ischaemic end-organ damage and mortality. Management efforts are therefore aimed at: (*i*) preventing and anticipating PPHN; (*ii*) ventilatory support to achieve optimal lung volume; (*iii*) haemodynamic support to maintain adequate cardiac output and optimal systemic blood pressure; and/or (*iv*) reducing the raised PVR.

At Worcester Hospital, PPHN occurs in approximately 2.9/1 000 liveborn infants of gestational age >34 weeks. Treatment is generally limited to ventilation and haemodynamic support as no PVR-reducing agents such as inhaled nitric oxide (iNO),[3,4] high-frequency oscillation ventilation (HFOV)[4] or extracorporeal membrane oxygenation (ECMO)[4] are readily available. Echocardiography is not available at our hospital for confirmation of pulmonary hypertension and exclusion of congenital heart disease, so diagnosis of PPHN depends on clinical assessment supported by limited special investigations including measurement of pre- and postductal haemoglobin oxygen saturation (SpO_2), arterial blood gases (pH 7.33 - 7.45), partial pressure of carbon dioxide ($PaCO_2$) (4.5 - 6 kPa), partial pressure of oxygen (PaO_2) (8 - 12 kPa), total dissolved carbon dioxide (TCO_2) (18 - 27 mmol/l) and base excess (BE) (–4 to +3 mEq/l), electrocardiography and chest radiography.

Sildenafil citrate (Viagra; Pfizer), a relatively new drug, is a phosphodiesterase type 5 (PDE5) inhibitor that selectively reduces pulmonary vascular resistance.[5] To date there are about 10 case reports,[6-15] 2 uncontrolled[16-17] and 2 randomised controlled studies[18-19] reporting its efficacy as an oral preparation in neonates with PPHN. The dosage range generally used was 0.5 - 2 mg/kg/dose at 6-hourly intervals with dose titration based on response.[20] Apart from oral administration of sildenafil to patients with PPHN there are published cases of intravenous[21] and intratracheal[22] or nebulised[23] administration in humans and animal models. The pharmacokinetic profile of oral sildenafil has not been formally evaluated in children. In adults it is rapidly absorbed after administration, with a bioavailability of approximately 40%. Maximum serum concentrations occur 0.5 - 2 hours after an oral dose. Sildenafil is highly protein bound (96%) and extensively distributed throughout the body. It is metabolised via the hepatic cytochrome P450 enzyme system, has an elimination half-life of approximately 4 hours in adults, and is excreted in faeces (80%) and urine (13%).[24]

Having read of successful treatment of PPHN with sildenafil,[6-19] our first limited, unlabelled use of the drug was to assist in stabilising infants with PPHN before transfer to a tertiary level unit. Early stabilisation before transfer is attempted is advisable in patients with severe PPHN, as a delay

in instituting PVR-reducing management, even with optimal supportive treatment, can be disastrous.

Case reports

We report the efficacy and safety of an orally administered PVR-reducing agent, sildenafil citrate, in 2 neonatal cases. Detailed clinical characteristics and responses to management are listed in Table I.

Discussion

Published reports of oral sildenafil use suggest that it may be beneficial in the treatment of PPHN in newborn infants, and it is being used with increasing frequency.[20] At least 10 case reports[6-15] and 2 uncontrolled studies[16,17] document improved oxygenation as well as echocardiographic evidence of reduced pulmonary arterial pressures. One report,[25] however, failed to demonstrate beneficial responses in 2 neonates, which may have been related to the time of introduction of the drug and the context and clinical condition of the baby.

Published reports suggest that oral sildenafil may be beneficial in the treatment of PPHN in newborn infants.

A Cochrane review on sildenafil for pulmonary hypertension in neonates[26] included 2 randomised controlled trials conducted in resource-limited settings where iNO and HFOV are not available. Both included neonates in need of mechanical ventilation (with oxygenation index (OI) ≥25) and echocardiographically confirmed PPHN. Baquero *et al*.[18] compared oral sildenafil with placebo and evaluated its effect on oxygenation in PPHN in 13 neonates ≥35.5 weeks' gestation with severe hypoxaemia. Neonates in the treatment group were found to have improved OI and SpO_2 and a markedly lower mortality rate.

Herrera *et al*.[19] compared conventional management of newborn infants with PPHN with and without the addition of sildenafil (sildenafil 13 cases, placebo 11) and showed significant improvement in OI in the treatment group. In addition the PaO_2 at 72 hours was better and mean airway pressure and number of ventilation days lower in the sildenafil group.

Most published studies have evaluated sildenafil use in patients with severe PPHN who were already receiving mechanical ventilation. Use of the drug enabled us to manage our 2 patients with moderate to severe PPHN without ventilation and its potential associated complications, and to avoid their transfer to a tertiary neonatal ICU. In a recent observational case study by Daga *et al*.,[15] also conducted in a resource-limited setting, a decrease in the pulmonary arterial pressures of non-ventilated premature neonates with PPHN was demonstrated by pre- and post-sildenafil echocardiography. No short-term adverse effects were reported, and the importance of long-term follow-up was emphasised.

Adverse effects of sildenafil include gastro-intestinal, cardiovascular, visual, auditory, central nervous system and possibly haemostatic disturbances. Portal hypertension in a patient with cirrhosis and portopulmonary hypertension was possibly exacerbated by sildenafil.[27] Because it is eliminated primarily by the hepatic route, caution is needed when it is used concomitantly with P450 inhibitors such as erythromycin, clarithromycin, cimetidine and ketoconazole.[28] Dose reduction is also necessary in patients with liver dysfunction or renal failure. Small, clinically insignificant reductions in blood pressure have been found in neonates treated with sildenafil for PPHN.[18] A potential risk of irreversible retinal damage linked to PDE6 inhibition has been documented with the use of sildenafil, and a case of severe retinopathy was reported in a 31-week premature baby treated with sildenafil acetate for pulmonary hypertension.[29] In a study evaluating the effects of sildenafil on platelet function, the PDE5 in platelets was inhibited by 50%, but no direct effect on platelet function could be demonstrated.[30] Bleeding after circumcision in a newborn receiving sildenafil has been reported,[13] and the vasodilatory effects of the drug on the penile vasculature were postulated as having contributed to the postoperative bleeding. Sudden decreases in or loss of hearing following PDE5 inhibitor therapy have also been reported.[31]

Making the decision whether to treat a neonate with sildenafil confronts the clinician with an array of as yet incompletely answered questions, including which patients to give the drug to, when to start, how to prepare it and how much to give, how to evaluate for a response and how long to treat. Sola *et al*.[20] have attempted to give some direction in this regard. Potential candidates to be considered would be term or near-term infants with severe PPHN and refractory hypoxaemia where the benefits of treatment would be most likely to outweigh the potential drawbacks. It could be considered when an infant's clinical condition worsens despite optimal available management. Preparing sildenafil for neonatal administration is best done by the pharmacy to ensure accurate dilution and sterile preparation. Methods of preparation include: (*i*) dissolve a crushed and powdered 50 mg tablet of sildenafil in Orobase, making a concentration of 2 mg/ml (if refrigerated, this is safe for 1 month after preparation);[20] (*ii*) dissolve a 50 mg tablet in 10 ml 1:1 mixture of 1% methyl cellulose and simple syrup, making 5 mg/ml, and dilute with 4 parts water before administration (stable refrigerated for 3 months);[32] or (*iii*) dissolve a 50 mg (or 25 mg) tablet in 25 ml (or 12.5 ml) sterile water, making 2 mg/ml (stability unknown).[20] Until further evidence is available the dosing strategy would include initiating therapy with intragastric sildenafil at 0.5 mg/kg/dose 6-hourly and considering, if there is no response, doubling the dose up to a maximum of 2 mg/kg/dose. Clinical indicators of a successful response would be improved oxygenation indices, namely a ≥10% increase in SaO_2 with a reduced differential between pre- and postductal values, a 3 kPa increase in PaO_2, ability to wean FiO_2, an increase in the a/APO_2 ratio (normal 0.75 - 1.0; a ratio <0.15 on FiO_2 >0.8 is indicative of PPHN[4]) and a decrease in OI. Response time can vary from 20 minutes to 3 hours after oral administration. Duration of treatment is not yet well defined, and one approach is to observe the individual response and stop the medication after a clear response and improvement. The treatment should also be discontinued after 6 - 8 doses if there is no improvement, and reduction in dose or cessation of treatment is necessary if hypotension develops despite inotropic support.

Taking into account ethical considerations regarding the unlabelled or investigational use of medicine,[33] informed consent from parents is essential and accurate data on outcomes of treated infants need to be diligently documented.

TABLE I. SUMMARY OF CASE REPORTS

	Case 1	**Case 2**
Gestational age	Term	Term
Birth weight	3 455 g	3 700 g
Mode of delivery	Caesarean section	Normal vaginal
Meconium-stained amniotic fluid	Present	Present
Apgar scores		
1 min	4	6
5 min	7	8
10 min	7	8
Immediate postnatal resuscitation	Airway suctioned under direct vision Bag-and-mask ventilation with 100% O_2	Airway suctioned under direct vision Bag-and-mask ventilation with 100% O_2
Ventilation support	Nasal continuous positive airway pressure (nCPAP)	Nasal continuous positive airway pressure (nCPAP)
Chest radiography	Diffuse patchy infiltrates Normal cardiothoracic ratio and cardiac shadow	Oligaemic lung fields Normal cardiothoracic ratio and cardiac shadow
First arterial blood gas	Postductal	Postductal
pH	7.08	7.19
$PaCO_2$	8.7 kPa	5.6 kPa
PaO_2	2.7 kPa	3.3 kPa
TCO_2	21.5 mmol/l	17.3 mmol/l
BE	-12 mEq/l	-12 mEq/l
Haemodynamic support	Dobutamine infusion of 5 - 15 µg/kg/min 0.9% sodium chloride intravenous boluses	Dobutamine infusion of 5 - 15 µg/kg/min 0.9% sodium chloride intravenous boluses
Acid base management	4.2% sodium bicarbonate 3 ml/kg given once with 0.9% sodium chloride 5 ml/kg as an infusion over 3 hours	4.2% sodium bicarbonate 1 ml/kg given twice with 0.9% sodium chloride (10 ml/kg and 5 ml/kg respectively) as boluses
PPHN diagnosis based on	*History* MSAF Perinatal asphyxia (low Apgar scores and significant haematuria indicative of ATN) *Clinical examination* (at time of diagnosis) Loud second heart sound Prominent pre-cordial impulse Refractory hypoxaemia	*History* MSAF Perinatal asphyxia (low Apgar scores) *Clinical examination* (at time of diagnosis) 20% differential between pre- and postductal SpO_2 (91% v. 71%) *Special investigations* (at time of diagnosis) 2.9 kPa differential between pre- and postductal PaO_2 (9.6 kPa v. 6.7 kPa) a/APO_2 ratio of 0.11 on FiO_2 1.0
Sildenafil administration		
Age at time of initial dose	11 h	3 h
Initial dose	1.0 mg/kg	0.5 mg/kg
Route of administration	Oro-gastric	Oro-gastric
Response	None	SpO_2 increased from 87% to 93% FiO_2 weaned to 0.9 over the next 3 hours
Response time after administration	-	1 hour
Incremented dose	2.0 mg/kg	1.0 mg/kg
Response	SpO_2 increased from 87% to 96%	SpO_2 increased from 87% to 97%
Response time after administration	30 min	40 min
Maintenance 6-hourly dose	2.0 mg/kg	1.0 mg/kg
Weaning	1.0 - 0.7 within 1 hour	0.9 - 0.4 over 12 hours
FiO_2	0.5 5 hours later	
Ventilation support	nCPAP discontinued on day 3 and nasal prong O_2 on day 6	nCPAP discontinued on day 3
Inotropic support stopped	Day 5	Day 2
Sildenafil	1.0 mg/kg 6-hourly on day 5, 1.0 mg/kg 12-hourly on day 7 Stopped on day 9	0.5 mg/kg/dose 6-hourly on day 5 Stopped on day 7

Conclusion

Sildenafil administered via the oro-gastric route was well tolerated in both our cases, and no adverse events were documented during treatment. Improved oxygenation was demonstrated by an increase in the SpO_2 and ability to wean FiO_2 after sildenafil was added to the conventional management of PPHN. Our results support published reports suggesting that sildenafil, with its ease of availability and low cost in comparison with other intensive care modalities, may be beneficial in the treatment of PPHN in newborn infants, including in resource-limited settings. However, lack of systematic evaluation calls for further studies on safety and efficacy before its widespread 'routine' use in neonatal medicine can be advocated.

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