Government of **Western Australia**
North Metropolitan Health Service
Women and Newborn Health Service

IV Sildenafil for PPHN: Practice Implications for the Neonatal Pharmacist

Claire Kendrick
Claire.Kendrick@health.wa.gov.au
King Edward Memorial Hospital, Western Australia

Aim

To evaluate the effectiveness of IV sildenafil for PPH in an extremely premature neonate and its implications on neonatal pharmacy practice.

Background

Persistent pulmonary hypertension of the newborn (PPHN) manifests as severe pulmonary hypertension with hypoxaemia refractory to oxygen therapy and lung recruitment strategies due to high pulmonary vascular resistance (PVR) (1, 2). Treatments target the cardiopulmonary interactions in PPHN, seen in Figure 1. Sildenafil increases cyclic adenosine and guanosine monophosphate (cAMP and cGMP) concentrations, causing smooth muscle relaxation in the pulmonary vasculature and improved pulmonary blood flow(1, 2). In a tertiary hospital for women and newborns, oral sildenafil suspension has been used off-label for PPHN(3). Recently, intravenous (IV) sildenafil has emerged as an option for PPHN.

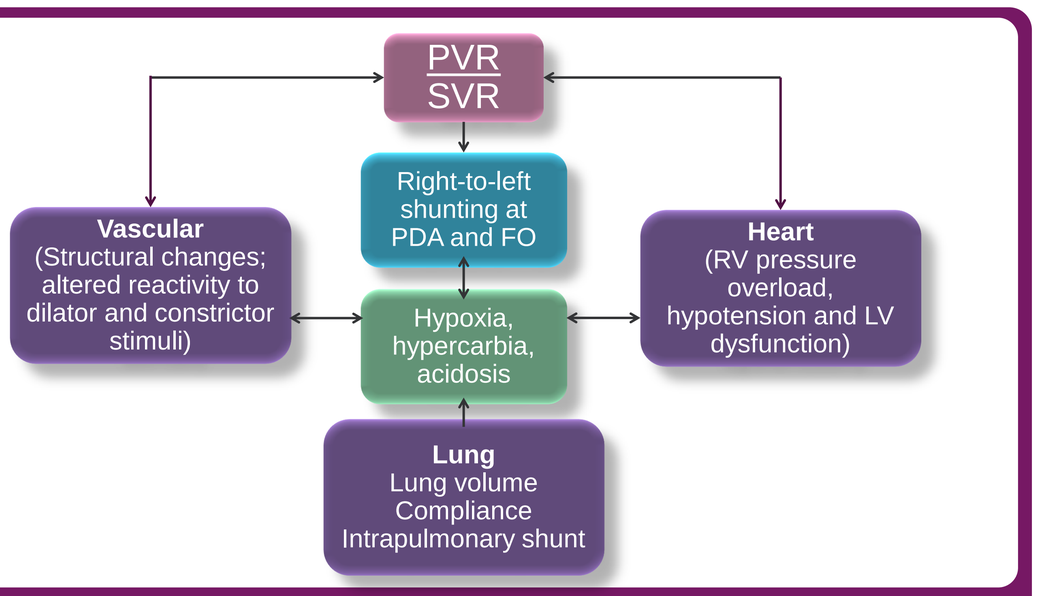

Figure 1: *Cardiopulmonary interactions in PPHN.* PVR, *pulmonary vascular resistance;* SVR, *systemic vascular resistance;* RV, *right ventricle;* LV, *left ventricle;* PDA, *patent ductus arteriosus;* FO, *foramen ovale(4).*

Clinical Presentation

OH was born at 22+6 gestation with no heart rate (HR), respiration rate (RR) and poor oxygen saturation (SpO2 50-60%) despite intermittent positive pressure ventilation with 100% fraction of inspired oxygen (FiO2). OH was diagnosed with extreme prematurity, PPHN, right pneumothorax, respiratory distress syndrome (RDS), patent ductus arteriosus (PDA), presumed sepsis and anaemia.

PPHN Management

OH received continuous oxygen supplementation and high frequency jet ventilation (HFJV) followed by continuous positive aware pressure (CPAP). She received three doses of pulmonary surfactant. Continuous IV infusions of dobutamine and noradrenaline were administered to increase SVR and improve cardiac performance. OH received inhaled nitric oxide (iNO), a selective pulmonary vasodilator that increases cGMP concentrations, for the first four days of life. As 30-50% of neonates do not respond to iNO therapy, vasodilators such as sildenafil are used as iNO alternates, supplements or weaning agents(1, 2, 5-7).

IV Sildenafil

There are no studies that have evaluated the efficacy of IV sildenafil, especially in preterm infants; its use is currently experimental(1). There are only three medication protocols for neonatal use of sildenafil in Australia(3, 8, 9). The IV dose in these guidelines is based on a small, open-label pharmacokinetic study(6). The Western Australia guideline includes a regimen for infants <37 weeks gestation. OH received this dose; a continuous infusion of 0.5mg/kg/day for 72 hours.

The neonatal pharmacist is responsible for monitoring patients receiving IV sildenafil to ensure safety and efficacy. The pharmacist will recommend dose adjustments where needed and ensure IV sildenafil is weaned before cessation to prevent PPHN(3, 5, 10). Suggested monitoring parameters and OH's results are seen in Table 1(2, 3, 6, 8, 9). As OH's results remained stable during sildenafil therapy, no dosage adjustments were required.

Sildenafil is compatible with glucose 5% and sodium chloride 0.9%(3, 8) but there is no data for compatibility with other drugs. The neonatal pharmacist should recommend sildenafil administration through a dedicated IV line or ensure adequate flushes between drugs(11).

Outcomes

OH's respiratory condition improved and she has remained stable on CPAP. A chest X-ray showed resolution of the pneumothorax. OH's other treatments included oral caffeine for RDS and IV indometacin for PDA. Prophylactic IV antibiotics were ceased when negative blood cultures returned. One unit of packed red blood cells improved OH's haemoglobin from 100g/L on day two to 144g/L. OH will remain an inpatient until she reaches term gestation with ongoing therapy goals of improving nutrition.

Parameter: Reason for monitoring (units)	OH's results			
	Day 0	Day 1	Day 2	Day 3
BP: Risk of sildenafil-induced hypotension (mm Hg)	23/13 to 50/27	46/27 to 50/28	36/21 to 50/28	40/23 to 54/32
HR: Risk of sildenafil-induced bradycardia (beats per minute, bpm)	140-170	146-155 (4x bradycardias in high 80s)	138-143 (2x bradycardias in high 80s)	127-142
RR: Efficacy of sildenafil for PPHN (breaths per minute)	13-65 on HFJV	10-49 on HFJV	16-30 on HFJV	17-38 on HFJV
SpO_2: Efficacy of sildenafil for PPHN (%)	52-71; 94-96 after resus	92-96	93-97	93-96
PaO_2: Efficacy of sildenafil for PPHN (mm Hg)	38		40	
MAP: Efficacy of sildenafil for PPHN	10/13	10/12		
Eye tests: risk of sildenafil-induced retinopathy	Due day 28			

Conclusion

Despite lack of evidence, IV sildenafil was successfully used for PPHN in an extremely premature neonate. The neonatal pharmacist is integral to the care of a patient with PPHN, especially regarding sildenafil dosing, administration and monitoring.

References
1. Gardner SL CB, Hines ME, Hernandez JA,. Merenstein & Gardner's Handbook of Neonatal Intesive Care. 8th ed. St Louis, Missouri: Elsevier; 2016.
2. Kelly LE, Ohlsson A, Shah PS. Sildenafil for pulmonary hypertension in neonates. The Cochrane database of systematic reviews. 2017;8:Cd005494.
3. King Edward Memorial Hospital. Neonatal Drug Protocol: Sildenafil. Perth, WA: King Edward Memorial Hospital & Perth Children's Hospital Pharmacy, Neonatal Directorate; 2017.
4. Kinsella JP, Abman SH. Recent developments in the pathophysiology and treatment of persistent pulmonary hypertension of the newborn. The Journal of pediatrics. 1995;126(6):853-64.
5. Taketomo CK, Hodding JH, Kraus DM. Pediatric & Neonatal Dosage Handbook with Internation Trade Names Index. 23rd ed. United States: Lexicomp; 2016.
6. Steinhorn RH, Kinsella JP, Pierce C, Butrous G, Dilleen M, Oakes M, et al. Intravenous sildenafil in the treatment of neonates with persistent pulmonary hypertension. The Journal of pediatrics. 2009;155(6):841-7.e1.
7. Lakshminrusimha S, Mathew B, Leach CL. Pharmacologic strategies in neonatal pulmonary hypertension other than nitric oxide. Seminars in perinatology. 2016;40(3):160-73.
8. Royal Hospital for Women. Sildenafil. NSW: Neonatal Medicines Formulary Consensus Group,; 2017.
9. South Australia Health. South Australian Neonatal Medication Guidelines: Sildenafil. SA: South Australian Department for Health and Ageing; 2018.
10. Australian Medicines Handbook. Sildenafil (cardiovascular). 2018. In: Australian Medicines Handbook [Internet]. Adelaide, South Australia: Australian Medicines Handbook. Available from: https://amhonline.amh.net.au/.
11. King Edward Memorial Hospital. IV Compatibility in Neonates. Perth, WA: King Edward Memorial Hospital & Perth Children's Hospital Pharmacy, Neonatal Directorate; 2018.