

# Is Sildenafil an Effective Therapy in the Management of Persistent Pulmonary Hypertension?

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## ABSTRACT

Persistent pulmonary hypertension of the newborn (PPHN) is a life-threatening neonatal pathology resulting from poor hemodynamic and respiratory transition to extra uterine life. Inhaled nitric oxide (iNO) is a current, commonly used treatment of PPHN. However, iNO is not available therapy in many developing countries and around 50% of infants with PPHN do not respond to iNO therapy. Sildenafil is a phosphodiesterase inhibitor type 5 (PDE5) that has been shown to selectively reduce pulmonary vascular resistance in both animal models and adult humans. Recent studies have found that in PPHN, administration of Sildenafil was associated with a significant increase in the oxygenation and a reduction in mortality with no clinically important side effects.

### Key words:

Neonate, persistent pulmonary hypertension, sildenafil

## INTRODUCTION

Persistent pulmonary hypertension of the newborns (PPHN) is a syndrome characterized by an increased pulmonary vascular resistance, right-to-left shunt and severe hypoxemia without evidence of congenital heart disease.<sup>[1]</sup>

The incidence of neonatal refractory hypoxemia and/or PPHN in term or near-term infants is reported to reach around 6.8 per 1000 live births. The treatment for PPHN has evolved over the past 10 to 15 years but reported mortality remains at 10% to 20% in newborns with PPHN.<sup>[2]</sup>

The principal goal of PPHN treatment is selective pulmonary vasodilatation. Various methods of PPHN treatment include: Ventilation strategies (high-frequency oscillatory ventilation-HFOV),<sup>[3]</sup> and pulmonary vasodilators such as Magnesium sulfate,<sup>[4]</sup> Sildenafil,<sup>[2]</sup> Adenosine,<sup>[5]</sup> Bosentan,<sup>[6]</sup> Prostacyclin,<sup>[7]</sup> and specific agents: Inhaled nitric oxide (iNO).<sup>[8]</sup> Although iNO and ECMO are the gold standards of the PPHN therapy,<sup>[8,9]</sup> they are expensive therapeutic modalities associated with technical difficulties in developing countries.<sup>[10]</sup> The fact that there are up to 50-60% of patients who do not improve their oxygenation index with iNO, depending of the series and the pathology involved, making it necessary to search for cheaper therapies, assuring quick effectiveness and stabilization of the patient going through a very high-risk situation.

Sildenafil is a phosphodiesterase inhibitor type 5 (PDE5) that has been shown to selectively reduce pulmonary vascular resistance in both animal models and adult humans.<sup>[11,12]</sup>

Sildenafil produces vasodilatation by increasing cyclic guanosinemonophosphate (cGMP) through inhibition of the phosphodiesterase involved in the degradation of cGMP to guanosinemonophosphate.<sup>[13]</sup>

Sildenafil has been used for the treatment of pulmonary hypertension in adults.<sup>[14]</sup> It has been used in intravenous, oral or inhaled form. In uncontrolled experiments in children, Sildenafil was shown to reduce pulmonary vascular resistance and improve exercise capacity.<sup>[15]</sup>

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 highly protein bound 96% and extensively distributed throughout the body. It is metabolized via the hepatic cytochrome P450 enzyme system, has an elimination half-life of approximately 4 hours in adults, and is excreted in feces 80% and urine 13%.<sup>[16]</sup>

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This review of the recent literature focuses on the efficacy/safety of the Sildenafil in newborns with persistent pulmonary hypertension.

### ANTENATAL SILDENAFIL IN EXPERIMENTAL CONGENITAL DIAPHRAGMATIC HERNIA

In experimentally induced fetal congenital diaphragmatic hernia (CDH), antenatal Sildenafil administered to the pregnant rat from embryonic day 11.5 to embryonic day 20.5 crossed the placenta, increased fetal lung cyclic GMP and decreased active PDE5 expression.<sup>[12]</sup> Antenatal Sildenafil improved lung structure, increased pulmonary vessel density, reduced right ventricular hypertrophy, and improved postnatal NO which induced pulmonary artery relaxation.<sup>[17]</sup> Antenatal Sildenafil was not associated with adverse effect on retinal structure/function and brain development. The authors concluded that antenatal Sildenafil improves pathological features of persistent pulmonary hypertension of the newborn in experimental CDH and does not alter the development of other PDE5-expressing organs.<sup>[12,17]</sup>

### SILDENAFIL FOR PPHN: CASE REPORTS AND CLINICAL TRIALS

Several case reports;<sup>[9,18,19]</sup> and controlled studies;<sup>[2,20]</sup> document improved oxygenation as well as echocardiographic evidence of reduced pulmonary arterial pressures following the administration of Sildenafil therapy in newborns who had PPHN.

From South Africa, Engelbrecht;<sup>[16]</sup> described their experience with the use of Sildenafil in two non-ventilated neonates with moderate to severe PPHN. In both cases the addition of Sildenafil to the treatment regimen resulted in: A significant increase in hemoglobin oxygen saturation as measured by pulse oximetry; ability to wean off oxygen; and avoidance of mechanical ventilation.

Herrera *et al.*;<sup>[20]</sup> compared conventional management of newborn infants with PPHN with and without the addition of Sildenafil (Sildenafil 13 cases, placebo 11 cases) and showed significant improvement in OI (Oxygenation Index) in the treatment group. In addition, the PaO<sub>2</sub> at 72 hours was better, mean airway pressure and number of ventilation days was lower in the Sildenafil group.

In order to evaluate the effect of Sildenafil on oxygenation in newborns with PPHN, Baquero *et al.*;<sup>[2]</sup> conducted a pilot randomized blinded study in infants with severe PPHN and oxygenation index (OI) >25 who received oral Sildenafil (7 infants) or placebo (6 infants). In the treatment group, OI improved in all infants within 6 to 30 hours, all showed a steady improvement in pulse oxygen saturation over time,

and none had noticeable effect on blood pressure. In the Sildenafil group 6 of 7 survived compared to 1 of 6 infants who survived in the placebo group.

In a retrospective study, Khorana *et al.*;<sup>[19]</sup> recorded a total of 40 infants with PPHN, of which 11 infants were treated with oral Sildenafil. The initial median oxygenation index (OI) was 31.95 (24.25-48.25). All infants received standard therapy with mechanical ventilation, sedation and inotropic drugs. Out of the 11 infants, 6 infants responded to Sildenafil whilst 5 did not. Comparison between the groups showed the OI to be significantly higher in the non-responders, with a median of 46.12 versus 29.31 in the responders indicating a greater severity of disease in the former. In the Sildenafil responded group OI decreased 4.6% from base line after the first hour of starting oral Sildenafil and progressively decreased by 90% at 24 hours. Three out of the 5 non-responders showed an improvement in their oxygenation when their treatment was combined with other vasodilators. This conformed to other studies that have shown that oral Sildenafil acts synergistically with other vasodilators such as inhaled iloprost or nitric oxide. Oral Sildenafil was discontinued in one infant due to systemic hypotension.<sup>[19]</sup> To assess the efficacy and safety of Sildenafil in the treatment of PPHN, Shah and Ohlsson;<sup>[21]</sup> conducted a Meta-analysis study including three eligible trials that enrolled 77 infants in a randomized or quasi-randomized trials of Sildenafil compared with placebo in neonates with PPHN. All studies were performed in resource-limited settings where iNO and high frequency ventilation were not available at the time of study. First study<sup>[2]</sup> enrolled term neonates at a very high risk of mortality. The study was halted prematurely due to death in six enrolled patients. Decoding showed that 5 of the deaths occurred in the placebo group and there was a statistically significant reduction in oxygenation indices both at 24 hours and at the end of the treatment. The reduction in the absolute values of OI was evident from the first dose. The 2<sup>nd</sup> study<sup>[20]</sup> enrolled moderately sick patients (OI > 25), and reported improvement in oxygenation from the first dose. The 3<sup>rd</sup> study<sup>[22]</sup> enrolled 40 patients and reported improvement in mortality and physiological parameters starting from the first dose. Mortality was significantly reduced in this meta-analysis with 20% in Sildenafil group compared to 54% in control group. Overall reduction in mortality in the Sildenafil group was significant with (typical RR 0.20, 95% CI 0.07 to 0.57; typical RD -0.38, 95% CI -0.60 to -0.16; number needed to treat to benefit 3, 95% CI 2 to 6). They also found a steady improvement of the physiological parameters of oxygenation (oxygenation index, PaO<sub>2</sub>) after the first dose of Sildenafil with no significant clinical side effects.<sup>[21]</sup> However, we must realize that overall number of enrolled patients is small and long-term effects are unknown. These three studies and several case reports, justify a call for a larger multicenter randomized controlled study. Studies of this kind would require sample size in the range of approximately 100 to 400 patients.

Further issues to address include clear documentation of short and long-term benefits and side effects, neurodevelopmental follow up, the optimum dose, optimum route of administration; incidence of rebound pulmonary hypertension and effectiveness of Sildenafil in the rebound pulmonary hypertension cases.

### Intravenous sildenafil treatment in PPHN

To evaluate the safety of intravenous Sildenafil, an open-label, dose-escalation trial was conducted in newborns with PPHN and an oxygenation index (OI) >15. Sildenafil was delivered by continuous IV infusion with 8 sequential “step-up” dosing groups for at least 48 hours and up to 7 days. Five centers enrolled a total of 36 neonates, 29 of these neonates were already receiving inhaled nitric oxide (iNO). A significant improvement in OI (28.7 to 19.3;  $P=0.0002$ ) was observed after 4 hours of Sildenafil infusion in the higher dose cohorts. Out of the 36 infants, there was only one death.<sup>[23]</sup>

### Intratracheal sildenafil treatment in PPHN

The selectivity of Sildenafil in lung tissue makes it attractive as an anti-PPHN drug. In these sense, to obtain a quick response in pulmonary circulation and as an alternative procedure, Martell *et al.* explored its effects in a model of PPHN induced by meconium aspiration in newborn piglets. Sildenafil (0.75 or 1.5 mg/kg per dose administered intratracheally) induced a rapid decrease in mean pulmonary arterial pressure (PAP), which occurred as soon as 2 minutes and lasted for 120 minutes.<sup>[24]</sup>

### Is sildenafil more effective than Mg SO<sub>4</sub> in management of PPHN?

In a prospective, randomized and controlled study, Uslu *et al.*<sup>[25]</sup> investigated the clinical efficacy of intravenous magnesium sulfate (MgSO<sub>4</sub>) versus oral Sildenafil therapies in infants with PPHN. They found that Sildenafil was more effective than MgSO<sub>4</sub> in the treatment of PPHN with regard to time to adequate clinical response, duration of mechanical ventilation with fewer requirements for inotropic support.

### Long sildenafil treatment for pulmonary hypertension in infants with chronic lung disease

In animal models of chronic lung disease CLD, Sildenafil has been shown to benefit alveolar growth, pulmonary angiogenesis and survival, and reduce pulmonary inflammation in addition to the well-documented effects on pulmonary vascular resistance. A recently published retrospective series of 25 patients with BPD aged <2 years showed hemodynamic improvement in by a decrease in pulmonary hypertension in 88%, with adverse events in two patients.<sup>[26]</sup>

### Sildenafil pharmacodynamics preparation, dosage, administration and safety

From different studies it can be concluded that the time of maximum action and duration of the effect varies depending on the dose, the route of administration, and the model or clinical situation in which Sildenafil has been used. The most used route of administration has been oral, and the duration of the effect goes from 20 minutes to 6 hours afterward.<sup>[24,27]</sup>

The calculated exposure and the measured plasma concentrations of Sildenafil was highly variable between one patient and the next, which might lead to inadvertent under dosing or overdosing upon administration of a standard dose. The underlying variation in pharmacodynamic parameters could be explained by variable gut absorption.<sup>[17]</sup> Another explanation could be flow-limited hepatic clearance in combination with hemodynamic changes.<sup>[27]</sup> This high variability in exposure implies that careful dose titration is necessary.

Sildenafil administration is best carried out by the pharmacy to ensure accurate dilution and sterile preparation. Methods of preparation include: Dissolve a crushed and powdered 50 mg tablet of Sildenafil in Orobace, making a concentration of 2 mg/ml (if refrigerated, this is safe for 1 month after preparation). Until further evidence is available the initial dosing strategy would include initiating therapy with intra-gastric 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.<sup>[16]</sup>

To date there are about 10 case reports,<sup>[6-15]</sup> 2 uncontrolled,<sup>[16,18]</sup> and 2 randomized controlled studies;<sup>[9,19]</sup> reporting its efficacy as an oral preparation in neonates with PPHN. Apart from oral administration of Sildenafil to patients with PPHN there are published cases of intravenous;<sup>[23]</sup> and or nebulised administration in humans and animal models.<sup>[24]</sup>

The optimal dose of oral Sildenafil in neonates and children is still not entirely clear. The British National Formulary for Children advises starting doses of 0.5 mg/kg/dose up to a maximum of 2 mg/kg/dose/every 6 hours.<sup>[28]</sup> Because of a relatively short half-life, Sildenafil may be given up to 4 hourly although it is usually administered 6 hourly.<sup>[29]</sup>

Clinical indicators of a successful response would be improved oxygenation indices, namely a  $\geq 10\%$  increase in SaO<sub>2</sub> with a reduced differential between pre- and post ductal values, a 3 kPa increase in PaO<sub>2</sub>, ability to wean FiO<sub>2</sub>, an increase in the a/APO<sub>2</sub> ratio 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.<sup>[29]</sup>

There has been a report of severe retinopathy of prematurity in one study following the use of Sildenafil in a neonate with PPHN.<sup>[30]</sup> An animal study by Shekerdeman *et al.*, showed that even though there was improvement of pulmonary vascular resistance, there was also an associated systemic vasodilatation and deterioration of oxygenation when Sildenafil was administered with iNO.<sup>[31]</sup>

## CONCLUSION

Recent studies found that in PPHN, administration of Sildenafil was an effective treatment associated with a significant increase in the oxygenation and a reduction in mortality with no clinically important side effects. At this stage, Sildenafil may be considered as a first-line treatment in settings where iNO, HFV (High Frequency Ventilation), and ECMO are unavailable, although its use should not replace transport of the infant to a center where these therapies are available. However Sildenafil dosage, timing, and route of administration vary in the current literature. Discrepancies exist regarding which patients benefit most from the use of Sildenafil and those to whom Sildenafil could not be administered. Discrepancies also exist between sources regarding the use of Sildenafil in conjunction with iNO and other pharmacologic therapies. Additional large randomized controlled studies are needed to assess the pharmacokinetics, efficacy and safety of Sildenafil treatment in PPHN. Further randomized controlled trials of adequate power comparing Sildenafil with other pulmonary vasodilators are also need in infants with PPHN.

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