An update on sildenafil in the treatment of pulmonary arterial hypertension in the neonate

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Abstract

Pulmonary arterial hypertension (PAH) refers to a group of diseases that are characterised by high pressure in the pulmonary artery and by pulmonary vascular resistance. Persistent PAH in the newborn is a condition whereby the pulmonary artery pressure does not decrease after birth, and may occur in as many as 6.8 in 1 000 live births. Phosphodiesterase type 5 (PDE-5) is the predominant PDE isoform in the lung which metabolises cyclic guanosine monophosphate (cGMP), and is upregulated in conditions associated with PAH. Thus, by selectively inhibiting PDE-5, the accumulation of intracellular cGMP is promoted by sildenafil citrate and nitric oxide-mediated vasodilatation is also enhanced. The article provides information on associated dosing regimens and reconstitution guidelines.

Introduction

Pulmonary arterial hypertension (PAH) refers to a group of diseases characterised by high pressure in the pulmonary artery and by pulmonary vascular resistance. Pulmonary vascular resistance is caused by vasoconstriction, thrombosis and the structural remodelling of pulmonary arterioles, after which occlusion of the lumens takes place in some of these vessels. The progressive increase in pulmonary vascular resistance can lead to right ventricular failure and premature death.1,2

Pulmonary artery pressure does not decrease after the birth of a newborn with persistent PAH, and may occur in as many as 6.8 in every 1 000 live births.1,3

A rapid cardiopulmonary transition, characterised by a decrease in pulmonary vascular resistance, occurs in the foetus during the birthing process, with a tenfold increase in pulmonary blood, which is normal. However, hypoxaemic respiratory failure or persistent pulmonary hypertension in the newborn (PPHN) results if there is disruption to the normal physiology.4

Nitric oxide (NO) is the current first-line treatment option for neonates with PAH, but there is interest in understanding and targeting other biochemical pathways which regulate pulmonary vasoconstriction and remodelling in PPHN because NO is not universally effective.3,4

The restoration of normal vascular reactivity and responsiveness to NO might be possible by therapeutic strategies which increase cyclic guanosine monophosphate (cGMP).4

The pulmonary vasodilatory effects of NO are mediated through cGMP, the second messenger of NO, after which it is rapidly degraded by phosphodiesterase (PDE). PDE-5 is the predominant PDE isoform in the lung which metabolises cGMP, and is upregulated in conditions associated with PAH. Thus, by selectively inhibiting PDE-5, the accumulation of intracellular cGMP is promoted by sildenafil citrate. NO-mediated vasodilatation is also enhanced, and there can be antiproliferative effects on the pulmonary vascular smooth muscle.5

Factors that cause pulmonary arterial hypertension in neonates

Pulmonary PAH in neonates can present as a primary pathology without any identifiable underlying cause, or it may present secondary to an identifiable underlying disease, i.e. pulmonary, cardiac or systemic disease.1

The management of primary PAH remains limited because of poor understanding of the exact pathogenesis of PPHN, which is compounded by the lack of a suitable, selective vasodilator.1

The pathophysiological mechanism of the disease includes pulmonary endothelial dysfunction, which leads to the impaired production of vasodilators, for example, NO and prostacyclin, as well as the overexpression of endothelin-1, a potent vasoconstrictor.1

Pulmonary vasoconstriction is caused by alveolar hypoxia, and this subsequently leads to the structural remodelling of the blood flow.
vessel walls. This is most pronounced in the distal pulmonary arterioles, and plays a considerable role in the pathogenesis of PAH, which is also accompanied by chronic obstructive airway disease.6

**Pathogenesis of pulmonary arterial hypertension**

The pathogenesis of PAH consists of several biological factors, i.e. endothelial cell dysfunction, a procoagulant state, platelet activation, constricting factors, loss of relaxing factors, cellular proliferation, hypertrophy, fibrosis and inflammation. All of these factors invariably combine and produce progressive and deleterious pulmonary vascular remodelling.7

Thromboxane and endothelin-1 levels are increased in PAH. Both are vasoconstrictors, and endothelin-1 also has mitogenic effects. Vascular smooth muscle proliferation and vasoconstriction are promoted via the endothelin receptor system. Vasodilatation is promoted by calcium-channel inhibition, which NO inhibits. Thus, there is a decrease in NO synthase expression in PAH, which then leads to vasoconstriction and cell proliferation.7

Other factors which may influence the pathogenesis of PAH are autoantibodies, proinflammatory cytokines and inflammatory infiltrates. Coagulation is affected in PAH, as is evidenced by the increased levels of coagulation factors. The tissue plasminogen activator, thrombomodulin, NO and prostacyclin levels are decreased. This leads to an imbalance which favours thrombus formation. It should be noted that endothelial dysfunction is the common denominator of mechanisms pertaining to PAH.7

The four categories of PAH are:8

- PAH
- Pulmonary venous hypertension
- Hypoxaemia-associated PAH
- PAH embolic or chronic thrombotic disease.8

Refer to Figure 1 for a schematic description of the pathogenesis of PAH.

**The use of sildenafil in pulmonary arterial hypertension**

Sildenafil can be used in PAH, primary PAH, and in PPHN which is refractory to treatment with NO. NO causes vasodilatation in the vascular smooth muscle because it is an endogenous, endothelium-derived vasodilator. The increased production of cGMP occurs through the stimulation of soluble guanylate cyclase.9

A few strategies are used to treat PAH in neonates, but the most recent one for increasing the activity of endogenous NO is to enhance NO-dependent, cGMP-mediated pulmonary vasodilatation. This can be achieved through inhibition of the breakdown of cGMP by PDE-5. Sildenafil has an acute pulmonary vasodilatory effect.9

Refer to Figure 2 for a schematic diagram of sildenafil's mechanism of action.10

The effects of sildenafil in the vasorelaxation of the pulmonary arteries, and also in decreasing pulmonary arterial pressure and pulmonary vascular resistance, were shown in a study on a neonatal model. PDE-5 is the key regulator of NO-induced vasodilatation in the postnatal pulmonary arteries. The ability to cause pulmonary vasodilatation is an exceptional characteristic of PDE-5, even in the absence of a functional endothelium. It then potentiates the vasorelaxant response to exogenous NO and nitroprusside. It has been shown that sildenafil is a selective pulmonary vasodilator with no effect on systemic arterial pressure. This means that the effects of inhaled NO are potentiated when it is given orally.11

It has been demonstrated in published reviews on oral sildenafil

![Figure 1: The pathophysiology of pulmonary arterial hypertension](Image)

![Figure 2: Schematic representation of the mechanism of action of sildenafil](Image)
for adults and neonates, uncontrolled neonatal reports and abstracts from paediatric society annual meetings, as well as verbal communications, that oral sildenafil is being used off-label worldwide without any precise protocol or clinical guidelines. Sildenafil is unique because of its oral preparation. The US Food and Drug Administration approved 20 mg three times a day in 2007 for the treatment of adults with PAH with no functional class restriction. A case study was conducted in the Western Cape in which it was found that the dosing strategy may include the initiation of sildenafil therapy via an intragastric tube at 0.5 mg/kg/dose four times a day, and the dose may be doubled to a maximum of 2 mg/kg/dose in the event of no response. The current dosages are extrapolated from the adult dosing range. A dose of 0.5-2.0 mg/kg/dose is considered to be therapeutic in neonates and children. It has also been suggested that a single dose of 0.4 mg/kg of oral sildenafil can prevent rebound after the withdrawal of inhaled NO, and after the duration of mechanical ventilation has been reduced. A dosing strategy will now be outlined, based on the latest guidelines.

Sildenafil is rapidly absorbed after oral administration, with bioavailability of 40%. It was found that the maximum serum concentration of the drug is reached an hour after administration in children, and that this is dosage dependent.

It has also been reported that sildenafil can be nebulised. It acts as a selective pulmonary vasodilator with no effect on systemic arterial pressure, similar to it being given orally or as an intravenous infusion; but the expected pulmonary deposition varies, depending on the nebuliser. The intravenous administration of sildenafil was evaluated in a range of studies. It was found to be well tolerated, and improvements in oxygenation in both acute and sustained cases were noted in neonates who received a higher infusion dosage. The option of administering sildenafil via the endotracheal route has been considered for more rapid onset of action, but there is still much to be learned about sildenafil in neonates. Presently, the oral alternative appears to be considerably safer and more efficacious. The pharmacokinetics of sildenafil still needs to be better defined in neonates.

The side-effect profile of sildenafil has been investigated, but it is exceedingly difficult to evaluate in the neonatal population. Hypotension is one of the most common side-effects. Ocular complications are also an important set of side-effects associated with sildenafil in adults, and sildenafil is suspected to exacerbate retinopathy of prematurity (ROP). The risk of ocular complications with the use of sildenafil has not yet been determined in neonates who are not otherwise at risk of developing ROP.

### Dosing

Sildenafil is not licensed for use in children.

Determining dose adequacy is complicated since the dose is influenced by inter- and intrapatient variability with respect to the volume of distribution and drug clearance, as well as the rapid maturation of metabolic clearance in the early postnatal period. Hardly any pharmacokinetic information, with the exception of a few case reports or small studies, is available on the administration of either oral or intravenous sildenafil in neonates. Until such time as more definite pharmacokinetic data are available, it is recommended that intragastric therapy is started at a 1 mg/kg/dose, six hourly, increased to 2 mg/kg/dose if required, every six hours, in instances where alternative therapies, such as high-frequency ventilation, surfactant, inhaled NO and extracorporeal membrane oxygenation, have limited availability. Neonatal versus infant dosing of sildenafil for PAH is summarised in Table I.

### The reconstitution of sildenafil tablets

The current lack of a commercially available oral sildenafil product in South Africa has resulted in extemporaneous preparation. A powder for oral suspension (Revatio) is available in the USA and certain European countries. Sildenafil tablets can be crushed using a pestle and mortar, and the pulverised form reconstituted with a mixture of Ora-Sweet, a palatable flavoured syrup vehicle, and/or Ora-Plus, an aqueous suspending base, in a ratio of 1:1, or with equal amounts of methylcellulose 1% and simple syrup. A small amount of the liquid is gradually mixed into the powder to form a uniform paste, leading up to a suspension that is stable for 91 days when stored in a plastic amber container at room temperature (25 °C) or in a refrigerator (5 °C). The preparation should be shaken thoroughly before use. If a suitable syrup vehicle is not available, the pulverised sildenafil can be reconstituted daily with distilled water in order to provide a suitable dose for neonates.

This procedure is not ideal since potential formulation or dispensing errors can occur, and large interbatch variability can also result, but it will need to suffice until a suitable pharmaceutical product is commercially available.

### Table I: Neonate and infant dosing of sildenafil for pulmonary arterial hypertension

<table>
<thead>
<tr>
<th>Initial dose</th>
<th>Median dose</th>
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<tbody>
<tr>
<td>0.3 mg/kg/dose, 8-12 hourly or Doses of 0.25-0.5 mg/kg/dose, every 4-8 hours, have been used according to clinical response</td>
<td>Median dose: 7 mg/kg over the duration of the course or A maximum of 30 mg/day</td>
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<tr>
<td>0.25-0.5 mg/kg, 4-8 hourly or Doses as high as 2 mg/kg/dose, every 4 hours, have been reported</td>
<td>Increased if needed, and well tolerated to 1-2 mg/kg/dose, 4-8 hourly or A maximum of 30 mg/day</td>
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- A maximum of 30 mg/day
- A maximum of 30 mg/kg over the duration of the course
- A maximum of 30 mg/day

- 0.5 mg/kg/dose four times a day
- A maximum of 30 mg/kg/day

- A maximum of 30 mg/kg/day
- A maximum of 30 mg/kg/day

- A maximum of 30 mg/kg/day
- A maximum of 30 mg/kg/day
Conclusion

Sildenafil has been proven to be very effective in treating PAH and PPHN in neonates in an array of studies. It is likely that the use thereof will increase over time, but further assessment of the safety profile is still needed. It has been demonstrated that survival improved with the dosage range used in term and near-term infants with severe PPHN, PAH and severe hypoxaemia, and did not seem to cause hypotension or noticeable side-effects.

Most of the data from the literature are very promising, but have mostly derived from small case series and single-case reports. The findings were dissimilar, the treatment regimens were not uniform, the dosages of sildenafil varied, and the follow-up period was not always sufficient, in the various studies. Therefore, it is recommended that more large-scale, randomised, controlled clinical trials are required to confirm the efficacy, optimal dosing and safety profile of sildenafil in the treatment of PAH in neonates and in the paediatric setting.

References