Paediatrics: Sildenafil in the treatment of pulmonary hypertension in the neonate

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Abstract
Pulmonary hypertension refers to a group of diseases that is characterised by high pressure in the pulmonary artery, and pulmonary vascular resistance. Persistent pulmonary hypertension in the newborn is a condition in which the pulmonary artery pressure does not decrease after birth. It may occur in as many as 6.8 in 1 000 live births. Phosphodiesterase type 5 (PDE5) is the predominant phosphodiesterase isoform that metabolises cyclic guanosine monophosphate (cGMP) in the lung. It is upregulated in conditions that are associated with pulmonary hypertension. Thus, by selectively inhibiting PDE5, the accumulation of intracellular cGMP is promoted by sildenafil citrate. The nitric oxide-mediated vasodilatation is also enhanced. It is recommended that more large-scale randomised, controlled clinical trials should be carried out to confirm the efficacy, safety and optimal dosage of sildenafil in the treatment of pulmonary hypertension in neonates and paediatric patients.

Introduction
Pulmonary hypertension refers to a group of diseases that are characterised by high pressure in the pulmonary artery, and pulmonary vascular resistance. Pulmonary vascular resistance is caused by vasoconstriction, thrombosis and structural remodelling of the pulmonary arterioles. 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

In the case of persistent pulmonary hypertension in the newborn, pulmonary artery pressure does not decrease after birth and may occur in as many as 6.8 in 1 000 live births.1,3

During birth, a rapid cardiopulmonary transition, characterised by a decrease in pulmonary vascular resistance, occurs in the foetus, with a tenfold increase in pulmonary blood. This is normal. However, hypoxaemic respiratory failure or persistent pulmonary hypertension of the newborn (PPHN) occurs if there is any disruption of the normal physiology.5

The current first-line treatment option for neonates with pulmonary hypertension is nitric oxide. However, interest has been shown in the understanding and targeting of other biochemical pathways that regulate pulmonary vasoconstriction and remodelling in PPHN, because nitric oxide is not universally effective.3,4

The restoration of normal vascular reactivity and responsiveness to nitric oxide could be possible using therapeutic strategies that increase cyclic guanosine monophosphate (cGMP).3 Through nitric oxide's second messenger, cGMP, the pulmonary vasodilatory effects of nitric oxide are mediated. It is then rapidly degraded by phosphodiesterase. Phosphodiesterase type 5 (PDE5) is the predominant phosphodiesterase isoform that metabolises cGMP in the lung. It is upregulated in conditions that are associated with pulmonary hypertension. Thus, by selectively inhibiting PDE5, the accumulation of intracellular cGMP is promoted by sildenafil citrate. Nitric oxide-mediated vasodilatation is also enhanced. Antiproliferative effects can take place on the pulmonary vascular smooth muscle.5

Factors associated with pulmonary hypertension in neonates
Pulmonary hypertension in neonates can present as a primary pathology without any identifiable underlying cause, or it may present secondary to an identifiable underlying disease, such as pulmonary, cardiac or systemic disease.3

Because of the poor understanding of the exact pathogenesis of pulmonary hypertension in neonates, the management of primary pulmonary hypertension remains limited. This is compounded by the lack of a suitable, selective vasodilator.1

The pathophysiological mechanism of the disease includes pulmonary endothelial dysfunction. This leads to impaired

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production of vasodilators, for example, nitric oxide and prostacyclin, as well as an overexpression of endothelin-1 (a potent vasoconstrictor).6

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

**Pathogenesis of pulmonary hypertension**

The pathogenesis of pulmonary hypertension consists of several biological factors, including 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 a progressive and deleterious pulmonary vascular remodelling.7

Thromboxane and endothelin-1 levels are increased in pulmonary arterial hypertension (PAH). Both are vasoconstrictors. Endothelin-1 also has mitogenic effects. Vascular smooth muscle proliferation and vasoconstriction are promoted via the endothelin receptor system. Vasodilatation is enhanced by calcium-channel inhibition, which nitric oxide inhibits. Thus, there is a decrease in nitric oxide-synthase expression in PAH, which then leads to vasoconstriction and cell proliferation.7

Other factors that may influence the pathogenesis of pulmonary hypertension are autoantibodies, proinflammatory cytokines and inflammatory infiltrates. Coagulation is affected in PAH, as is evidenced by increased levels of coagulation factors. The tissue plasminogen activator, thrombomodulin, nitric oxide, and prostacyclin (PGI2) levels are decreased. This leads to an imbalance that favours thrombus formation. It should be noted that the common denominator of PAH mechanisms is endothelial dysfunction.7

The four categories of pulmonary hypertension are:8

- PAH
- Pulmonary venous hypertension (PVH)
- Hypoxaemia-associated pulmonary hypertension
- Pulmonary hypertension due to embolic and chronic thrombotic diseases.8

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

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**Figure 1:** The pathophysiology of pulmonary arterial hypertension

LA: left atrium, LV: left ventricle, RA: right atrium, RV: right ventricle
Use of sildenafil in pulmonary hypertension

Sildenafil can be used in PAH, primary pulmonary hypertension and in PPHN of the newborn baby that is refractory to treatment with nitric oxide. Nitric oxide causes vasodilatation in the vascular smooth muscle because it is an endogenous, endothelium-derived vasodilator. There is an increased production of cGMP through the stimulation of soluble guanylate cyclase.9

There are a few strategies with which to treat PAH in neonates, but the most recent one used to increase the activity of endogenous nitric oxide is enhancement of the nitric oxide-dependent, cGMP-mediated pulmonary vasodilatation. This can be achieved through the inhibition of the breakdown of cGMP by PDE5. Sildenafil has an acute pulmonary vasodilatory effect.9 Refer to Figure 2 for a schematic diagram of the mechanism of action of sildenafil.

In a study of a neonatal model, the effects of sildenafil on the vasorelaxation of the pulmonary arteries, and also on decreasing pulmonary arterial pressure and pulmonary vascular resistance, were shown. PDE5 is the key regulator of nitric oxide-induced vasodilatation in the postnatal pulmonary arteries. An exceptional characteristic of PDE5 is its ability to cause pulmonary vasodilatation, even in the absence of functional endothelium. It then potentiates the vasorelaxant response to exogenous nitric oxide and nitroprusside. It has been shown that sildenafil is a selective pulmonary vasodilator. It has no effect on systemic arterial pressure. This means that the effects of inhaled nitric oxide are potentiated when it is given orally.11

According to Sola et al, published reviews on oral sildenafil for adults and neonates, uncontrolled neonatal reports, abstracts in paediatric society annual meetings and verbal communications have all demonstrated that oral sildenafil is being used off-label without any precise protocol or clinical guideline worldwide. Sildenafil is unique because its oral preparation (20 mg three times a day) was approved by the US Food and Drug Administration in 2007 for the treatment of adults with PAH with no functional class restriction. There is no recommended dosage for children or neonates with PAH. A case study, conducted in the Western Cape, found that the dosing strategy may include initiation of sildenafil therapy via an intragastric tube at 0.5 mg/kg/dose four times a day. If no response is obtained, the dose may be doubled to a maximum of 2 mg/kg/dose. The current dosages are extrapolated from the adult dosing range, and 0.5-2 mg/kg/dose might be considered as 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 withdrawal of inhaled nitric oxide. The duration of mechanical ventilation is reduced.11-13

Sildenafil is rapidly absorbed after oral administration. The bioavailability is 40%. It was found that the maximum serum concentration of the drug in children was reached an hour after administration and that this was dosage-dependent.12

cGMP: cyclic guanosine monophosphate, GMP: guanosine monophosphate, GTP: guanosine triphosphate

Figure 2: Schematic representation of the mechanism of action of sildenafil9
It has also been reported that sildenafil may be nebulised. It acts as a selective pulmonary vasodilator and has no effect on systemic arterial pressure. This is 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 has been evaluated in a range of studies. It was found to be well tolerated in the neonates who received higher infusion dosages. Improvements in oxygenation in both acute and sustained patients were noted. The option of administering sildenafil via the endotracheal route has been considered for a 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 in neonates needs to be better defined.5,11,14

The side-effect profile of sildenafil has also been investigated, but it is exceedingly difficult to evaluate in the neonatal population. One of the most common side-effects is hypotension. Ocular complications are also a significant set of side-effects associated with sildenafil in adults. Sildenafil is also suspected of exacerbating retinopathy of prematurity (ROP). With the use of sildenafil, the risk of ocular complications has not yet been determined in neonates, who are not otherwise at risk of the development of ROP.15

Conclusion

In an array of studies, sildenafil proved to be very effective in treating PAH in neonates. It is likely that the use thereof will increase over time, but further assessment of its safety profile is needed. In term and near-term infants with severe PPHN and severe hypoxaemia, the dosage range of 1-2 mg/kg/dosage every six hours orally was shown to improve survival. It does not seem to cause hypotension or noticeable side-effects.11

Most of the data from the literature are very promising, but generally have been derived from small case series and single case reports. These findings were not similar, the different studies’ treatment regimens were not uniform, the dosages of sildenafil varied between studies and the follow-up period was not always sufficient. Therefore, it is recommended that more large-scale, randomised, controlled clinical trials should be carried out to confirm the efficacy, optimal dosing and safety profile of sildenafil when treating PAH in neonates and in the paediatric setting.12

References