REVIEW ARTICLE

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Therapeutic Applications of Sildenafil Citrate in the Management of Paediatric Pulmonary Hypertension

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Abstract

Pulmonary hypertension is characterised by a progressive increase in pulmonary vascular resistance and a poor prognosis. The exact underlying mechanisms are still poorly understood; however, it is hypothesised that pulmonary medial hypertrophy and endothelial dysfunction lead to impaired production of vasodilators such as nitric oxide (NO) and prostacyclin, and increased expression of vasoconstrictors such as endothelin-1. The current treatment modalities for pulmonary hypertension include conventional supportive therapies and more specific phar-

macological therapies that are targeted at abnormalities of endothelial function. NO and phosphodiesterase type 5 (PDE5) inhibitors induce pulmonary vasodilation by increasing intracellular cyclic guanosine monophosphate (cGMP) concentrations.

Sildenafil citrate is a highly selective inhibitor of PDE5. Investigations in animal models and recent clinical case reports with some studies in the paediatric population suggest that sildenafil may be a promising agent in treating pulmonary hypertension. The effect of sildenafil on pulmonary vasculature appears to be independent of the underlying cause, thereby providing a role in idiopathic pulmonary arterial hypertension (PAH), PAH associated with congenital heart disease, pulmonary hypertension secondary to lung disease or persistent pulmonary hypertension of the newborn. It may also be beneficial in postoperative pulmonary hypertension and in neonates who are difficult to wean from inhaled NO. It is easily administered and effective, and has minimal systemic adverse effects. Although the reported results in children with pulmonary hypertension are promising, it is an experimental drug and large-scale randomised controlled studies are required to validate the safety, efficacy and dosage in the paediatric population.

Pulmonary hypertension is an important clinical presentation of various paediatric and neonatal diseases, including congenital heart disease, lung disease and liver disease, all of which cause high morbidity and mortality. The disease is characterised by a progressive increase in pulmonary vascular resistance, leading to right ventricular failure. Pulmonary hypertension has similar characteristics in adults and children; however, some differences exist[1] and they are summarised in table I. Previously, the prognosis of patients with pulmonary hypertension was poor.[2] Fortunately, significant advances in pharmacological treatments have improved quality of life and patient survival.[3]

The most recent classification of pulmonary hypertension was established during the 2003 World Symposium (table II) and applies to both adults and children.[4] This classification separates the causes of pulmonary hypertension into five main categories: pulmonary arterial hypertension (PAH), pulmonary venous hypertension associated with left-sided heart disease, pulmonary hypertension associ-

Table I. Main differences between adults and children with pulmonary hypertension

Characteristic	Adults	Children
Main aetiologies	Idiopathic and familial PAH, thromboembolic and autoimmune diseases	Most common aetiologies outside immediate neonatal period are chronic lung disease and congenital heart disease
Histopathology	Advanced pulmonary vascular obstructive disease with intimal fibrosis and plexiform lesions	Severe pulmonary arterial medial hypertrophy with marked intimal proliferation
Presenting symptoms	Exertional dyspnoea, chest pain	Failure to thrive, poor appetite, cyanotic events, syncope, epilepsy-like attacks
The positive response rate to acute vasodilator testing with orally administered vasodilator drugs	About 12%	About 40%
Gene mutation (BMPR2)	Up to 50% in familial PAH have mutation in the gene	About 8% of the children with familial history have mutation in the gene

PAH = pulmonary arterial hypertension.

ated with lung disease and/or hypoxaemia, pulmonary hypertension due to chronic thrombotic and/or embolic disease, and miscellaneous.

In the paediatric population, PAH and pulmonary hypertension associated with lung disease and hypoxia are the two most common categories.

PAH can be either idiopathic, familial or associated with other underlying causes, such as connective tissue disease, congenital heart disease, portal hypertension, drugs and toxins, and persistent pulmonary hypertension of the newborn.[3] Lung diseases associated with pulmonary hypertension include respiratory distress syndrome, meconium aspiration syndrome, bronchopulmonary dysplasia, congenital diaphragmatic hernia, pulmonary hypoplasia, interstitial lung disease and others.[3]

In the last three decades, there has been significant progress in understanding the pathogenic mechanisms involved in the development of PAH. As a result of this extensive research, new and effective drugs, such as prostanoids, endothelin receptor inhibitors and phosphodiesterase inhibitors, were developed. These drugs show improvement in exercise capacity, quality of life and survival of these patients.[5,6]

Sildenafil is a highly selective inhibitor of phosphodiesterase (PDE)-5 which was recently discovered as a convenient and effective oral treatment for patients with pulmonary hypertension, mainly those with idiopathic PAH or PAH secondary to an underlying disease. This review highlights the recent therapeutic applications of sildenafil in pulmonary hypertension of children and neonates.

We reviewed the relevant medical literature by searching MEDLINE (1995 to April 2006), using the keyword 'sildenafil' and the combinations with the following keywords: 'pulmonary hypertension in children', 'pulmonary hypertension in neonates', 'pulmonary arterial hypertension in children', 'pulmonary arterial hypertension in neonates' and 'pulmonary hypertension of the newborn'. Our search was mainly on human studies, as well as experimental models in animals, and preference was given to manuscripts published in English.

Table II. Revised clinical classification of pulmonary hypertension[a]

Classification
Pulmonary arterial hypertension
Idiopathic
Familial
Associated with collagen vascular disease, congenital systemic-to-pulmonary shunts, portal hypertension, HIV infection, drugs and toxins, thyroid disorders, glycogen storage disease, Gaucher's disease, hereditary haemorrhagic telangiectasia, haemoglobinopathies, myeloproliferative disorders
Associated with significant venous or capillary involvement: pulmonary veno-occlusive disease, pulmonary capillary haemangiomatosis
Persistent pulmonary hypertension of the newborn
Pulmonary hypertension with left heart disease
Left-sided atrial or ventricular heart disease
Left-sided valvular heart disease
Pulmonary hypertension associated with lung diseases and/or hypoxaemia
Chronic obstructive pulmonary disease
Interstitial lung disease
Sleep-disordered breathing
Alveolar hypoventilation disorders
Chronic exposure to high altitude
Developmental abnormalities
Pulmonary hypertension due to chronic thrombotic and/or embolic disease
Thromboembolic obstruction of proximal pulmonary arteries
Thromboembolic obstruction of distal pulmonary arteries
Non-thrombotic pulmonary embolism (tumour, parasites, foreign material)
Miscellaneous
Sarcoidosis, histiocytosis X, lymphangiomatosis, compression of pulmonary vessels (adenopathy, tumour, fibrosing mediastinitis)

a This classification was adapted from the 2003 World Symposium on Pulmonary Hypertension (Venice 2003).[4]

1. Definition of Pulmonary Hypertension

The definition of pulmonary hypertension in children is the same as for adult patients. It is defined as a mean pulmonary artery pressure ≥25mm Hg at rest or ≥30mm Hg during exercise, with normal pulmonary artery wedge pressure (≤15mm Hg) and an increased pulmonary vascular resistance index (≥3 Wood units/m^2).[2] The inclusion of exercise-induced haemodynamic abnormalities in the definition of pulmonary hypertension is important, since the vasoactive response to triggers such as exercise and hypoventilation is greater in children than in adults.[3,7] This difference probably stems from the

characteristic increased vascular medial hypertrophy that is more pronounced in young children and results in dynamic vasoactivity. The increase in intimal fibrosis and plexiform lesions reduces this dynamic component in adults.[7]

2. Subcategories of Pulmonary Hypertension

2.1 Idiopathic and Familial Pulmonary Arterial Hypertension (PAH)

Idiopathic PAH is a rare disease that is diagnosed after exclusion of all known causes.[5] It is a new terminology for the subcategory that previously was known as primary pulmonary hypertension, and was officially changed in the 2003 World Pulmonary Hypertension Symposium.[4,5]

The estimated incidence of idiopathic PAH ranges from 1 to 2 cases per 1 million people in the general population.[8,9] Idiopathic PAH occurs most frequently in young adult women[8,10] and is characterised by progressive, sustained elevation in pulmonary arterial pressure without a defined cause.

Like other pulmonary hypertensive disorders, the average time to diagnosis is 1–2 years. The major difficulties in establishing the diagnosis of the idiopathic type include the subtle presentation and crossover of symptoms with other diseases. Symptoms include dyspnoea, syncope, fatigability and chest pain. In infants, children and young adults, moderate pulmonary hypertension can be tolerated well without manifesting these symptoms.

The familial form of what was previously called 'primary pulmonary hypertension', and which accounts for only a small percentage of cases, is now categorised as familial PAH. This form is inherited as an autosomal dominant trait, with a pattern of genetic anticipation. It is found in about 6% of patients with primary pulmonary hypertension.[8,11] Recently, the gene for the familial form was mapped to chromosome 2q33 and named BMPR2 (bone morphogenic protein receptor-2).[12,13]

Although the cause of idiopathic PAH is unknown, several physiological and pathological features are commonly observed. Nearly all patients have abnormalities in endothelial function which results in impaired release of vasodilators, such as nitric oxide (NO) and prostacyclin, or an enhanced production of vasoconstrictors, such as endothelin and thromboxane.[9]

2.2 Pulmonary Hypertension Secondary to Underlying Diseases

Pulmonary hypertension in children and neonates is usually secondary to an underlying disease such as congenital heart disease, respiratory disease, persistent pulmonary hypertension of the newborn, or other less common causes.

There is a wide spectrum of congenital heart diseases that result in PAH[9] (table III), and the age at which these pathologies cause irreversible pulmonary vascular disease varies significantly. It seems that a combination of high pressure and high flow causes more rapid development of severe vascular remodelling.[9]

Hypoxia plays an important role in the development of pulmonary hypertension. Respiratory pathologies that result in hypoxia can be either bronchial (obstructive or restrictive) or parenchymal diseases (table III).

Persistent pulmonary hypertension of the newborn is a syndrome characterised by increased pulmonary vascular resistance, extrapulmonary right-to-left shunting and severe hypoxaemia. Symptoms usually present within 12 hours of birth.[3] It is frequently associated with meconium aspiration, pneumonia, respiratory distress syndrome, sepsis, congenital diaphragmatic hernia, or pulmonary hypoplasia.[15]

3. Diagnosis and Assessment of Pulmonary Hypertension

The presenting signs and symptoms of patients with pulmonary hypertension are age-specific and consist of nonspecific presentations.[9] Newborns with persistent pulmonary hypertension present with cyanosis and respiratory distress.[15,16] Infants with pulmonary hypertension often present with signs of low cardiac output, such as poor appetite, failure to thrive, lethargy, diaphoresis, tachypnoea, tachycar-

Table III. Causes of pulmonary hypertension in the paediatric population (adapted from Tulloh,[14] with permission)

Cause
Neonates
persistent pulmonary hypertension of the newborn (idiopathic)
respiratory distress syndrome and bronchopulmonary dysplasia
structural disease: congenital diaphragmatic hernia, pulmonary hypoplasia, alveolar capillary dysplasia
interstitial disease: meconium aspiration syndrome, infection
Cardiac
congenital heart disease: left-to-right shunt (ASD, VSD, AVSD, PDA)
transposition of the great arteries
obstructive anomalies (TAPVC, MS, HLHS, HOCM, DCM)
Acquired
interstitial lung disease
cystic fibrosis
scoliosis
neuromuscular disease
chronic obstructive pulmonary disease
vasculitis
hypercoagulability states (protein C and protein S deficiency, factor V Leiden)
sleep-disordered breathing
Idiopathic (sporadic, familial)

ASD = atrial septal defect; **AVSD** = atrioventricular septal defect; **DCM** = dilated cardiomyopathy; **HLHS** = hypoplastic left heart syndrome; **HOCM** = hypertrophic obstructive cardiomyopathy; **MS** = mitral stenosis; **PDA** = persistent ductus arteriosus; **TAPVC** = total anomalous pulmonary venous connection; **VSD** = ventricular septal defect.

dia and irritability. Toddlers and children may have cyanotic events with exertion, which are caused by right-to-left shunting through a patent foramen ovale. Without adequate shunting, the patients may present with syncope. After early childhood, children present with similar symptoms to those in adults, mainly exertional dyspnoea and chest pain.[7]

Patient history, physical examination and routine tests such as electrocardiography and chest radiography provide important clues to the diagnosis. However, the final diagnosis is established by right (and left) heart catheterisation, including haemodynamic testing. Echocardiography confirms the presence of pulmonary hypertension by demonstrating increased right ventricular pressure and rules out or confirms the presence of congenital heart disease, pulmonary venous disease or left ventricular dysfunction.[9] Cardiac catheterisation remains the diagnostic gold standard, as it allows accurate measurement of pulmonary artery pressure and pulmonary vascular resistance.[5,14] The degree of the pulmonary hypertension reversibility is determined by a short-acting vasodilator test (intravenous epoprostenol, inhaled NO, intravenous adenosine or inhaled iloprost) that is performed during the catheterisation.[5] Patients who are responsive to acute vasodilator testing (reduction of 20% in the mean pulmonary artery pressure with no change or increase in cardiac output) are likely to have a favourable response to calcium channel antagonist therapy.[7]

The modified New York Heart Association (NYHA) functional classification or the WHO classification is used to clinically assess the severity of pulmonary hypertension (table IV). These classifications determine the degree of a patient's daily function and are helpful in guiding treatment.[17] Another clinical test is the 6-minute walk test (6-MWT), which is an independent predictor of death in adult patients with idiopathic PAH and has been used as the primary endpoint in many clinical trials. It measures the distance that the patient can walk in 6 minutes, and it is used to compare the exercise capacity during the course of the disease and the response to treatment. The WHO classification and the 6-MWT were adapted from adults and are used as clinical comparison tools.

4. Treatment Modalities for Pulmonary Hypertension

4.1 Conventional Supportive Therapy

The conventional treatments for pulmonary hypertension include diuretics (to control symptoms of volume overload from right ventricular failure), supplemental oxygen and digoxin (which has a beneficial effect in some patients).[18] Anticoagulant therapy in children is based on studies in adults. Clinical data on their long-term use in children is limited, but supportive.[3]

Syncope and intractable right-sided heart failure are indications for atrial septostomy in patients who are treated with vasodilators, but whose pulmonary hypertension remains refractory to treatment. In patients who do not respond to prolonged vasodilator treatment, and in those with certain types of lesions, such as pulmonary vein stenosis, lung transplantation has been offered as the last treatment option.[7]

4.2 Specific Pharmacological Therapies

In the last three decades, new and effective drugs for pulmonary hypertension have emerged as a result of improved understanding of the pathogenesis of the disease. The main categories of pharmacological agents include calcium channel antagonists, inhaled NO, prostaglandins, endothelin receptor inhibitors and phosphodiesterase inhibitors. These drugs show improvement in exercise capacity, quality of life and survival in patients with pulmonary hypertension, mainly in patients with PAH.[6]

4.2.1 Calcium Channel Antagonists

Calcium channel antagonists are used as the initial treatment option in children with pulmonary hypertension who are acute responders to the short-acting vasodilator test (about 40% of the children and the percentage of responders falls with time).[3] The frequent occurrence of significant adverse effects prevents the use of these drugs empirically or in patients who are not responders.[7,19]

4.2.2 Nitric Oxide

NO is an inhaled agent which acts as a selective and potent vasodilator of the pulmonary vasculature.[20] Inhaled NO is additional to or replacement of the endogenous NO. It diffuses to the pulmonary arterial smooth muscle cells and activates soluble guanylate cyclase, resulting in an increase in cyclic guanosine monophosphate (cGMP), which activates a cascade of events leading to smooth muscle relaxation[3,9,20] (figure 1). Studies show that inhaled NO is safely used and effective in treating different forms of pulmonary hypertension, including exacerbations of idiopathic PAH, persistent pulmonary hypertension of the newborn, and pulmonary hypertension following cardiac surgery.[21,22]

4.2.3 Prostaglandins

Epoprostenol (prostacyclin) has been used for two decades for the treatment of patients with PAH and has shown improvement in haemodynamics,

Table IV. World Health Organization classification of pulmonary hypertension (adapted from Hoeper,[6] with permission)

Classification	
Class I	Patients with pulmonary hypertension but with no limitations of usual physical activity Ordinary physical activity does not cause increased dyspnoea or fatigue, chest pain or near syncope
Class II	Patients with pulmonary hypertension resulting in mild limitation of physical activity They are comfortable at rest Ordinary physical activity causes increased dyspnoea or fatigue, chest pain or near syncope
Class III	Patients with pulmonary hypertension resulting in marked limitation of physical activity They are comfortable at rest Less than ordinary activity causes increased dyspnoea or fatigue, chest pain or near syncope
Class IV	Patients with pulmonary hypertension with inability to perform any physical activity without symptoms These patients manifest signs of right heart failure Dyspnoea and/or fatigue may even be present at rest Discomfort is increased by any physical activity

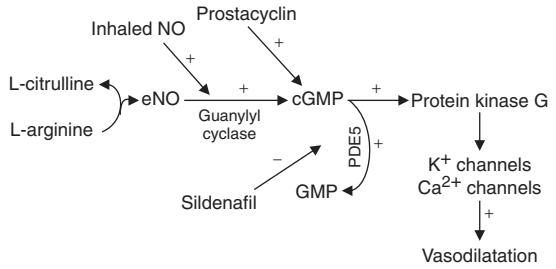

Fig. 1. Schematic illustration of the pathways involving endogenous nitric oxide (eNO) and cyclic guanosine monophosphate (cGMP) and the interaction with the pharmacological agents. **GMP** = guanosine monophosphate; **NO** = nitric oxide; **PDE5** = phosphodiesterase type 5.

quality of life and exercise capacity in these patients.[3,5,9]

The chemical instability of this medication at neutral pH and room temperature (half-life of 1–2 minutes) requires a continuous intravenous delivery system with cold packs to maintain stability. These requirements make the drug delivery cumbersome, inconvenient and associated with complications. Therefore, a search for alternative routes of drug delivery led to the clinical investigation of oral (beraprost, not approved in the US or Europe), inhaled (iloprost, approved in the US and UK) and subcutaneous (treprostinil, not registered in Europe, but approved recently in the US for long-term administration) epoprostenol analogues. Thus far, none has been proven to be as efficacious as intravenous epoprostenol.[3]

4.2.4 Endothelin Receptor Antagonists

Endothelin-1 is a very potent vasoconstrictor and a promoter of cell proliferation. Plasma endothelin-1 levels are increased in patients with idiopathic PAH, both in adults and paediatric patients,[23] and are correlated inversely with prognosis.[3] Thus, endothelin receptor antagonists are promising drugs for the treatment of PAH. To date, there are at least two different known receptor subtypes; A and B.[3] The A receptors are localised on smooth muscle cells and mediate vasoconstriction and proliferation,[3] while B receptors are found predominantly on endothelial cells and are associated with vasodilation through the release of vasodilators and clearance of endothelin-1.[3]

Bosentan (approved in the US and Europe) is an oral dual endothelin receptor antagonist that was shown to improve exercise capacity, quality of life and cardiopulmonary haemodynamics in adult patients with PAH.[24] There are recent publications on bosentan in children with PAH, suggesting that it is safely used and efficacious, and resulting in haemodynamic improvement.[23,25]

Sitaxsentan sodium is an experimental drug that acts as a highly selective antagonist of the A receptor, thereby blocking the vasoconstricting effects of the A receptor, while maintaining vasodilation through the B receptor.[2] The experience with this medication in the paediatric population is very limited.

4.2.5 Phosphodiesterase Inhibitors

PDEs are a large family of enzymes that catalyse hydrolytic cleavage of the 3′-phosphodiester bond of the cyclic nucleotides (e.g. cyclic adenosine monophosphate [cAMP], cGMP), controlling their intracellular levels.[26] PDE inhibitors block this hydrolytic cleavage, causing an accumulation of cAMP or cGMP, which finally leads to vasodilation.

Nonspecific PDE inhibitors include caffeine, theophylline, dipyridamole and pentoxifylline. Milrinone is a specific inhibitor of PDE3, whereas zaprinast and sildenafil are specific inhibitors of PDE5.[15] There is a high concentration of PDE5 in smooth muscle cells of the pulmonary vasculature.[27] Therefore, specific inhibition of this enzyme enhances the accumulation of cGMP and results in pulmonary vasodilation.

5. Sildenafil

Sildenafil is a potent and highly selective inhibitor of PDE5.[28] Since pulmonary arterial medial hypertrophy and vasoconstriction is the main mechanism of PAH in the paediatric population, inhibiting PDE5 (thereby increasing the concentration of secondary messenger cGMP and enhancing NO-mediated vasodilation) is a promising mode of targeting the medial muscular hypertrophy and inducing vasodilation.[29]

Although sildenafil can be used intravenously, it is unique for its oral preparation.[28] Oral sildenafil,

20mg three times daily, was recently approved by the US FDA for the treatment of adults with PAH without functional class restriction.[18] In children, it is used as rescue therapy or in experimental protocols. There is no recommended dosage for children with PAH and the current dosages used are extrapolated from the adult dose range. Nevertheless, dosages of 0.5–2.0 mg/kg/dose might be considered as therapeutic in children, as the plasma concentrations measured 1 hour after oral ingestion were similar to the peak plasma concentrations achieved in adults after a single dose of 25–100mg, and the patients demonstrated clinical improvement.[30,31]

Sildenafil is rapidly absorbed after oral administration, with absolute bioavailability of about 40%.[32] In healthy adults, maximum observed plasma concentrations are reached within 30–120 minutes (median 60 minutes) of oral administration in the fasted state.[6,32] Karatza and colleagues showed that the maximum serum concentrations of the drug in children are reached an hour after administration and are dose-dependent.[31] Sildenafil is eliminated predominantly by hepatic microsomal isoenzymes of cytochrome P450 (CYP) [3A4 (major route) and CYP2C9 (minor route)]. It is converted to *N*-desmethyl sildenafil, which is an active metabolite with properties similar to sildenafil. Plasma concentrations of this metabolite account for about 20% of the pharmacological effects of sildenafil. Both sildenafil and its major circulating *N*-desmethyl metabolite are almost completely bound to plasma proteins (96%). Protein binding is independent of total drug concentrations. Both sildenafil and its metabolite have terminal half-lives of about 4 hours.[6] The concomitant use of potent CYP3A4 inhibitors (e.g. erythromycin, ketoconazole, itraconazole), as well as the nonspecific inhibitor of CYP, cimetidine, is associated with increased plasma sildenafil concentrations. After either oral or intravenous administration, sildenafil is excreted as metabolites predominantly in the faeces (approximately 80% of administered oral dose) and to a lesser extent in the urine (approximately 13% of the administered oral dose).

6. Clinical Applications of Sildenafil in Pulmonary Hypertension

With the increased understanding of the mechanisms involved in the pathogenesis of pulmonary hypertension, and particularly in PAH, novel treatment options become available. Sildenafil represents one of the most recently recognised drugs with a significant therapeutic potential in pulmonary hypertension.[33] This drug has been used in various pathologies associated with PAH in children, and the outcome reported in a number of comparative studies, case series and case reports.

6.1 Idiopathic and Familial PAH

Fewer than 50% of patients with idiopathic PAH are found to be responsive to the vasodilator test and these patients will benefit from calcium channel antagonist therapy. In all other patients, intravenous infusion of epoprostenol is the mainstay of therapy.[3] However, continuous intravenous infusion is not the optimal modality in the paediatric population and is associated with potential complications such as line infections, catheter dislodgement and pump malfunction.[3] For these reasons, oral sildenafil offers an attractive and effective alternative.[28,34]

Several studies and case reports were published recently, investigating the effect of oral sildenafil in patients with PAH[10,35-39] (table V). Kothari and Duggal[35] conducted a prospective, uncontrolled study in nine children aged 5–18 years; six had primary pulmonary hypertension, and three had secondary causes. In all six children with primary pulmonary hypertension, who were graded as NYHA functional class 3 or 4, sildenafil was added to conventional therapy. The study showed a remarkable and sustained benefit of sildenafil in these patients. The improvement was subjective as well as objective, as reflected in the NYHA functional class and 6-MWT. The authors found that the mean pulmonary artery pressure decreased in three of the patients who underwent re-catheterisation after a mean period treatment with sildenafil of 7 months. In all patients, sildenafil was well tolerated and was associated with only minor adverse effects. Sastry et al.[36] evaluated the efficacy of sildenafil in six chil-

Table V. Summary of studies on sildenafil citrate in paediatric patients with pulmonary arterial hypertension (PAH)

Study (year)	Study type	No. of pts	Age (y)	Route of administration and dosage	Main indications	Treatment duration (mo)	Outcome	Follow-up period (mo)	Adverse reactions
Kothari & Duggal[35] (2002)	Prospective, uncontrolled	6	5–18	Oral, 5.5 mg/kg/day– 150 mg/day (divided in 3 doses)	Primary pulmonary hypertension	3.5–8	Improved NYHA functional class Improved 6-MWT Improved haemodynamics	3.5–8	Dizziness, flushing and headache (when dose >125mg) No visual symptoms No inconvenience due to erectile effect
Sastry et al.[36] (2002)	Prospective, uncontrolled	6	4–16	Oral, 25–100 mg/dose (8-hourly)	Primary pulmonary hypertension	5–20	Improved NYHA functional class Improved 6-MWT Improved haemodynamics	5–20	Minor headache, flushing, abdominal discomfort
Oliveira & Amaral[37] (2005)	Prospective, uncontrolled	6	3–19	Oral, 2–8 mg/kg/day or 100–500 mg/day (4–6 doses/day)	Idiopathic PAH	4–36	Improved NYHA functional class Improved systemic saturation	4–36	No adverse effects One death after abrupt and unplanned withdrawal of medication
Humpl et al.[38] (2005)	Prospective, uncontrolled	4	5–18	Oral, 0.25–1 mg/kg/dose (6-hourly)	Idiopathic PAH	12	Improved 6-MWT Improved haemodynamics	12	Self-limited nosebleeds, menstrual losses with the menarche, facial flushing, headache and dizziness
Abrams et al.[10] (2000)	Case report	1	4	Oral, 2 mg/kg (4-hourly)	Primary pulmonary hypertension	3	Improved exercise capacity	3	None
Karatza et al.[39] (2004)	Case report	1	14	Oral, 0.5 mg/kg, increased to 2 mg/kg (4-hourly)	Primary pulmonary hypertension	6	Increased exercise capacity Increased oxygen saturation	6	None

NYHA = New York Heart Association; **pts** = patients; **6-MWT** = 6-minute walk test.

Table VI. Summary of studies on sildenafil citrate in paediatric patients with congenital heart disease and pulmonary arterial hypertension (PAH)

Study (year)	Study type	No. of pts	Age (y)	Route of administration and dosage	Main indications	Treatment duration	Outcome	Follow-up period	Adverse reactions
Schulze-Neick et al.[40] (2003)	Prospective, uncontrolled	12	0.2–15.7	IV, 1 mg/kg divided in 2 unequal doses, each over 10 min	Preoperative catheterisation	Stat doses	Decreased pulmonary resistance	No follow-up	No significant adverse reactions
		12	0.11–0.65	IV, 0.025, 0.1 & 0.25 mg/kg (in 10–15 min steps)	Postoperative PAH	Stat doses	Decreased pulmonary resistance Increased intrapulmonary shunting	No follow-up	No significant adverse reactions
Stocker et al.[41] (2003)	Prospective, randomised	15	0.11–0.7	IV, 0.35 mg/kg over 20 min + iNO	Stable infants at risk of PAH, early after cardiac surgery for VSD or ASD	20 min single dose	Sildenafil augmented pulmonary vasodilator effect of iNO	No follow-up	Sildenafil produced systemic hypotension and impaired oxygenation
Humpl et al.[38] (2005)	Prospective, uncontrolled	10	6–18	Oral, 0.25–1 mg/kg/dose (6-hourly)	PAH persisted after correction of congenital heart disease, or if considered inoperable	12mo	Improved 6-MWT Improved haemodynamics	12mo	Self-limited nosebleeds, menstrual losses with the menarche, facial flushing, headache and dizziness
Kothari & Duggal[35] (2002)	Prospective, uncontrolled	3	5–18	Oral, 5.5 mg/kg/day–150 mg/day (divided in 3 doses)	After cardiac surgery	3.5–8mo	Improved NYHA functional class Improved 6-MWT Improved haemodynamics	3.5–8mo	Dizziness, flushing and headache (when dose >125mg) No visual symptoms No inconvenience due to erectile effect
Karatza et al.[31] (2005)	Case reports	2	6.5, 10.5	Oral, 0.5–2 mg/kg/dose (4-hourly)	Pulmonary hypertension associated with congenital heart disease	6mo	Increased exercise capacity and increased saturation	6mo	No adverse effects noted
Carroll & Dhillon[28] (2003)	Case report	1	7	Oral, 0.5–2 mg/kg/dose (6-hourly)	Pulmonary hypertension associated with congenital heart disease	Unknown	Significant improvement of exercise test	Unknown	None

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Table VI. Contd

Study (year)	Study type	No. of pts	Age (y)	Route of administration and dosage	Main indications	Treatment duration	Outcome	Follow-up period	Adverse reactions
Saygili et al.[42] (2004)	Case report	1	9	Oral, 0.75 mg/kg/dose (6-hourly)	PAH associated with VSD correction	3wk	Enabled to wean iNO and pulmonary artery pressure decreased	12mo	None
Kulkarni et al.[43] (2004)	Case report	1	4	Oral, 0.25– 0.5 mg/kg/dose (4-hourly)	After heart transplantation for dilated cardiomyopathy	8wk	Decreased pulmonary pressures	8wk	None
Knoderer et al.[44] (2005)	Case report	1	1	Oral, 0.25–0.5 mg/kg (6-hourly)	Pulmonary hypertension associated with congenital heart disease	11mo	Normal pulmonary pressures and gaining weight	3y	None

ASD = atrial septal defect; **iNO** = inhaled nitric oxide; **IV** = intravenous; **NYHA** = New York Heart Association; **pts** = patients; **VSD** = ventricular septal defect; **6-MWT** = 6-minute walk test.

dren (aged 4–16 years) with primary pulmonary hypertension. They found an overall improvement in the echocardiographic and haemodynamic measurements in all patients, as well as improvements in the NYHA functional class and the 6-MWT. Their study also suggested a possible survival advantage, but this could not be confirmed based on their study design and small group of patients.

In a more recent prospective case series, Oliveira and Amaral[37] reported six patients aged 3–19 years with idiopathic PAH who had no response to previous conventional treatment. They were treated with oral sildenafil (2–8 mg/kg/day) during a period of 4–36 months. All patients achieved a good therapeutic response, with improvement by at least one functional class, and an increase in systemic arterial oxygen saturation. No major adverse effects were observed, but one patient died suddenly after unplanned withdrawal of sildenafil. Humpl et al.[38] conducted a 12-month single-drug, open-label clinical trial using oral sildenafil in 14 children; 4 of them with idiopathic PAH. Similar to the previous studies, this study also found an improvement in both exercise tolerance and pulmonary vascular haemodynamics. No adverse effects were reported. Although their study was not controlled, the authors' feeling was that these patients, treated with sildenafil, had a better survival curve than patients who were treated in their institution in the past.

Although all these studies are relatively small scale and uncontrolled, they suggest that sildenafil may be useful in the management of idiopathic PAH in the paediatric population. Large randomised and controlled studies will enable definite conclusions and optimal dosage recommendations.

6.2 PAH Associated with Congenital Heart Disease

There are several possible applications for sildenafil in children with congenital heart disease. In the immediate postoperative phase, sildenafil can be used to decrease the pulmonary arterial pressure. Another application is in patients who develop PAH associated with congenital heart disease, later in the course of the disease[28,31,35,38,40-44] (table VI).

Intravenous sildenafil has been used in pre-cardiac surgery catheterisation to evaluate the reversibility of PAH. Schulze-Neick et al.[40] compared the effects of intravenous sildenafil with inhaled NO in preoperative and postoperative patients with congenital heart disease and elevated pulmonary vascular resistance (table VI). They showed that intravenous sildenafil may be equal or superior to a standard dose of inhaled NO in reducing the elevated pulmonary vascular resistance in these patients, both during routine cardiac catheterisation and after open-heart surgery. They found no significant effect of sildenafil on intrapulmonary shunting in the preoperative group who underwent cardiac catheterisation. In the postoperative mechanically ventilated patients, the measured intrapulmonary shunting was statistically higher in the sildenafil-treated patients; however, this was not clinically significant. This is presumably related to vasodilation of pulmonary arterioles supplying non-ventilated areas of lung, a well described complication of intravenous, non-selective pulmonary vasodilation. These findings are in contrast to those with inhaled NO, where its effect is localised only to adequately ventilated areas of lung.[40]

Pulmonary endothelial dysfunction is failure of the endothelium to produce adequate amounts of endogenous NO.[45] Open heart surgery with cardiopulmonary bypass is known to amplify this failure,[45] and inhaled NO is an important therapeutic modality in these patients when they return from surgery. Stocker et al.[41] conducted a prospective, randomised trial with intravenous sildenafil and inhaled NO in infants after cardiac surgery. They investigated the acute effects of intravenous sildenafil on haemodynamics and oxygenation, and its interaction with inhaled NO in stable infants at risk of pulmonary hypertension, early after cardiac surgery with cardiopulmonary bypass. Their study revealed very similar conclusions to Schulze-Neick et al.,[40] showing that intravenous sildenafil reduced pulmonary vascular resistance and enhanced the pulmonary vasodilator effects of NO. They also demonstrated that intravenous sildenafil significantly reduced the systemic blood pressure with systemic vasodilation. The investigators terminated the study early, because they noticed a consistent deterioration in oxygenation and increased alveolar-arterial gradient, which indicated an increase in intrapulmonary shunting in the post-bypass lung.

Humpl et al.[38] performed a 12-month, open-label clinical trial of oral sildenafil in 10 children with PAH secondary to congenital heart disease (table VI). They found that sildenafil was well tolerated and had no haematological, renal or hepatic functional impairments, as well as no vision-related abnormalities. Sildenafil was found to improve both exercise tolerance and pulmonary vascular haemodynamics. Kothari and Duggal[35] reported three patients who underwent surgery for congenital heart disease (ventricular septal defect or patent ductus arteriosus); all had severe pulmonary hypertension and received oral sildenafil in addition to conventional therapy. The authors concluded that the study showed a remarkable and sustained benefit of sildenafil, and it was well tolerated.

These studies show that the use of an efficacious oral pulmonary vasodilator, such as sildenafil, may have a role in the clinical setting of PAH associated with congenital heart disease. It may allow weaning of intravenous pulmonary vasodilator support and can be administered conveniently for several days, weeks or months, and result in improvement in both exercise tolerance and pulmonary vascular haemodynamics.

6.3 Pulmonary Hypertension Associated with Lung Diseases and/or Hypoxaemia

Chronic lung disease in children can be complicated by severe chronic pulmonary hypertension.[28] Sildenafil can offer a possible therapeutic option in these patients because of its effect on the pulmonary vasculature, which is independent of the underlying cause.[28] There are several single case reports in the literature that describe the use of sildenafil in various lung pathologies such as interstitial pneumonitis, pertussis, bronchopulmonary dysplasia and diaphragmatic hernia.

Carroll and Dhillon published their experience with oral sildenafil in two infants with chronic pul-

monary hypertension secondary to pneumonitis.[28] One infant was treated with sildenafil as palliative treatment to allow him some time at home. In the second patient, sildenafil was commenced because intravenous prostacyclin was impractical for home use. He showed improvement with no significant adverse effects. However, both patients died from progression of their underlying pulmonary disease. McEniery et al.[46] described an infant with pertussis who developed pulmonary hypertension. *Bordetella pertussis* produces a number of active toxins that impair cardiovascular function and inhibit endothelial NO production; hence, pertussis is associated with pulmonary hypertension. This patient was treated with a combination of sildenafil and inhaled NO, and his haemodynamic condition was stabilised. The authors postulated that this drug combination may offer potential treatment in patients with pertussis toxaemia. Hon et al.[47] reported the use of oral sildenafil in a 5-month-old preterm infant with severe bronchopulmonary dysplasia and PAH refractory to inhaled NO. The infant was treated with oral sildenafil for 6 months until complete resolution of PAH and oxygen supplement was weaned off. There were no adverse effects during the treatment period. Chaudhari et al.[48] reported on a neonate with severe pulmonary hypertension associated with impaired alveolarisation and plexiform pulmonary arteriopathy. The neonate was treated with oral sildenafil and inhaled NO, and this resulted in significant clinical improvement with recovery from the pulmonary hypertensive crisis.

Animal models may suggest another role of sildenafil in chronic lung disease. Ladha et al.[49] demonstrated that, in addition to its known vasodilatory effect, sildenafil also preserved alveolar growth and lung angiogenesis in rats. These findings suggest a role for the NO or cGMP pathway during alveolar development. If this hypothesis is validated, it might explain the beneficial effect of long-term treatment with sildenafil in patients with bronchopulmonary dysplasia, impaired alveolar structures and other parenchymal lung diseases.

6.4 Sildenafil and Inhaled Nitric Oxide

Severe rebound hypoxaemia and pulmonary hypertension are significant problems when weaning inhaled NO in some patients, mainly after prolonged inhaled NO therapy and abrupt cessation of treatment.[15] This clinical issue is frequently seen in the paediatric population, and is also well defined in newborns with persistent pulmonary hypertension.

Atz and Wessel[50] hypothesised that sildenafil may add to the pulmonary vasodilation effect of inhaled NO or blunt the rebound effect of abrupt discontinuation of inhaled NO. They reported their experience in three infants (aged 1 day, 6 weeks and 4 months) with pulmonary hypertension following surgery for congenital heart disease. Sildenafil was used after failed attempts to discontinue inhaled NO, and resulted in a rise in cGMP levels within 90 minutes of administration, with an associated drop in pulmonary arterial pressure, allowing successful weaning from NO. They found no adverse systemic effects. In another recent study,[15] oral sildenafil was used in five neonates and younger infants (age range 2–28 weeks) with refractory suprasystemic pulmonary hypertension after gradual withdrawal of inhaled NO, despite alkalinisation and inotropic support. Sildenafil permitted discontinuation of inhaled NO within 4–6 hours, without haemodynamic instability, allowing extubation in four of them within 48 hours. Mychaskiw et al.[51] reported a 17-year-old patient who had replacement of a biventricular assist device to support heart failure secondary to a viral cardiomyopathy. In this case, sildenafil ameliorated the rebound pulmonary hypertension that developed following withdrawal of inhaled NO.

The fact that sildenafil seems to be as effective as inhaled NO in improving pulmonary vasodilation, and may even have an additive effect,[52-54] makes it a useful tool in weaning patients after prolonged therapy with inhaled NO.

6.5 Persistent Pulmonary Hypertension of the Newborn

Inhaled NO is currently regarded as the gold standard therapy for pulmonary hypertension of the newborn, whereas the extracorporal membrane oxy-

genation (ECMO) is considered as a rescue therapy.[15] However, there are some difficulties which limit the use of NO: about 30% of the patients do not respond to this drug,[15] there is a risk of developing rebound pulmonary hypertension upon its withdrawal, even after relatively short periods of use, and its mode of delivery usually requires endotracheal intubation.[15] Other important considerations are the development of methaemoglobinaemia and cell membrane damage from peroxynitrites.[15] The high cost involved and the lack of infrastructure in some parts of the world makes NO and ECMO even less available. These limitations led to further studies on the possible role of sildenafil, which might overcome some of the difficulties mentioned.

Juliana and Abbad[55] published a successful case of sildenafil treatment for persistent pulmonary hypertension in an infant, where inhaled NO or ECMO were not available. Just recently, a pilot randomised, blinded study on oral sildenafil in infants with persistent pulmonary hypertension of the newborn was published.[56] This study was performed in a neonatal intensive care unit in Colombia. It was well equipped but there was no inhaled NO, high frequency oscillating ventilators or ECMO available. Seven infants were treated with oral sildenafil 1 mg/kg every 6 hours, whereas six infants received placebo. The main outcome variable was the effect of oral sildenafil on oxygenation. Oxygenation index improved in all infants within 6–30 hours. Sildenafil was well tolerated. In the treatment group no noticeable effect on blood pressure was observed. Six infants survived in the treatment group, whereas only one infant survived in the placebo group. The study showed that sildenafil may be effective in the treatment of persistent pulmonary hypertension of the newborn.

Sildenafil has been studied in animal models of neonatal pulmonary hypertension. It was shown to be a selective pulmonary vasodilator with no effect on the systemic arterial pressure, potentiating the effects of inhaled NO when given orally,[57] as an intravenous infusion[58] or in an aerosolised form.[59] In an experimental model of pulmonary hypertension associated with meconium aspiration syndrome, intravenously administered sildenafil completely reversed the increased pulmonary vascular resistance without affecting systemic haemodynamics.[55] These experimental models also showed that when sildenafil was added to inhaled NO it produced unacceptable deterioration in oxygenation, as a result of an increase in intrapulmonary shunting.[60] These models point to a possibly higher risk involved in using sildenafil in parenchymal lung disease, such as meconium aspiration syndrome. In such situations, sildenafil might induce or worsen ventilation perfusion mismatch, resulting in lower arterial oxygenation. Alternative administration in an aerosolised form may lower the risk of ventilation perfusion mismatch and the systemic adverse effects.[59] It is also important to remember that infants are at risk for sepsis and septic shock and developing associated pulmonary hypertension. Inflammatory mediators that are produced during the septic state increase the concentrations of endogenous NO, which cause changes in systemic vasomotor tone.[61] In these circumstances, sildenafil may theoretically worsen the circulatory status.

7. Adverse Events

Most of the studies and the reports on sildenafil in children and infants with pulmonary hypertension suggest that there is a very low incidence of adverse effects, and these are usually minor. Adverse effects that were reported in adults treated for pulmonary hypertension include headache, flushing, dizziness, postural hypotension, dyspepsia, constipation, backache, blurred vision, giddiness and short-lived erections.[34] In most of the paediatric patients reviewed here, no major adverse effects were noted. However, a few major concerns should be considered before treating patients with pulmonary hypertension with sildenafil. Intravenous sildenafil was found to significantly reduce the systemic blood pressure.[40,41,60] In some cases, the drop in systemic blood pressure was corrected with volume expanders,[55] whereas in others it was not clinically significant and did not require any specific treatment.[38] Another important consideration is the deterioration in arterial oxygenation and the increase in alveolar-

arterial gradient, which is probably due to an increase in intrapulmonary shunting.[40,41,58] This can be unacceptable in infants with parenchymal lung disease and low reserves.

Visual and ocular abnormalities were also reported with the use of sildenafil in pulmonary hypertension. Blurred vision, increased perception of light and blue-green colour-tinged vision are described as possible adverse effects.[45] In premature babies, retinopathy of prematurity (ROP) is a concern, but only one case report suggested that the use of sildenafil induced severe ROP in a preterm baby who had severe pulmonary hypertension.[62] However, that baby had many other risk factors for the development of ROP, as was discussed by Pierce et al.[63]

8. Conclusions

Pulmonary hypertension in the paediatric population remains an incurable disease, but the recent advances in understanding the mechanisms involved in the pathogenesis of the disease are an important step in developing new and effective therapies.[6] These newly available medications improve exercise capacity, quality of life and survival.[6]

Sildenafil, which is considered an experimental drug for children with pulmonary hypertension, appears as one of the most promising pulmonary vasodilator agents; it is relatively safe and simple to use,[52] and the effect it has on the pulmonary vasculature is independent of the underlying cause. There are reports of successful use of sildenafil in children with idiopathic PAH, PAH that results from congenital heart disease, or pulmonary hypertension secondary to lung disease; it may also be beneficial in postoperative pulmonary hypertension and in patients who are difficult to wean from inhaled NO.[45,50,51]

Although the data from the literature are promising, they are mainly from small case series and single case reports. Treatment regimens were not uniform, the dosage of sildenafil varied between studies, and the follow-up period was not always sufficient. Therefore, large-scale randomised, controlled clinical trials are required to confirm the efficacy, safety and optimal dosage of sildenafil as treatment of pulmonary hypertension in the paediatric population.

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