

Sildenafil for the Treatment of Pulmonary Hypertension in Pediatric Patients

Alice J. Huddleston · Chad A. Knoderer ·
Jennifer L. Morris · Eric S. Ebenroth

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Abstract Sildenafil is a phosphodiesterase 5 inhibitor widely used for the treatment of pulmonary hypertension in children. Despite limited available safety and efficacy evidence, use of sildenafil continues to increase. To date, sildenafil use for pediatric pulmonary hypertension has been characterized for 193 children through 16 studies and 28 case series and reports. The primary efficacy data suggest that sildenafil is beneficial for facilitating the weaning of inhaled nitric oxide in children after cardiac surgery. Compiled safety data suggest that sildenafil is well tolerated among children with idiopathic pulmonary arterial hypertension and pulmonary arterial hypertension associated with congenital heart disease. This review summarizes the available data describing the use, safety, and efficacy of sildenafil for children with pulmonary hypertension.

Keywords Children · Phosphodiesterase inhibitor · Pulmonary hypertension · Sildenafil

Idiopathic pulmonary arterial hypertension (IPAH) was first described by Romberg [66] more than 100 years ago as “sclerosis of the pulmonary arteries.” In recent decades, growing interest and advanced research in pulmonary hypertension (PHTN) has led to a better understanding of the disease process. A rare condition, PHTN is characterized by a progressive increase in pulmonary vascular resistance leading to right ventricular failure and premature death [21]. Often, PHTN is associated with underlying conditions such as congenital heart disease, connective tissue disease, congenital diaphragmatic hernia, and others. When PHTN is present in conjunction with these processes, it is referred to as associated pulmonary arterial hypertension (APAH). Previously referred to as primary pulmonary hypertension, IPAH is defined as PHTN in which the underlying cause is unknown or of sporadic onset [67]. Although the true incidence of IPAH is unknown, it is estimated to occur in one to two cases per million people [81].

In the early 1980s, before the development of our current and more advanced treatment methods, the Primary Pulmonary Hypertension NIH Registry reported a median survival time of 2.8 years after a diagnosis of PHTN for adults but only 10 months for children [17]. Whereas the historical prognosis of a patient with PHTN had been very poor, significant advances in early diagnosis and advanced treatment options not only have extended survival but also have improved quality of life, exercise capacity, and hemodynamics [7, 32, 65].

A recent United Kingdom treatment and survival study reviewed 216 patients with PHTN and found survival rates of 85.6% at 1 year, 79.9% at 3 years, and 71.9% at 5 years

A. J. Huddleston · C. A. Knoderer (✉) · J. L. Morris
Department of Pharmacy, Riley Hospital for Children,
Clarian Health, 702 Barnhill Drive, Room 1016,
Indianapolis, IN 46202, USA
e-mail: cknoderer@clarian.org

C. A. Knoderer
Department of Pharmacy Practice, College of Pharmacy
and Health Sciences, Butler University, Indianapolis, IN, USA

C. A. Knoderer
Department of Pediatrics, Ryan White Center for Pediatric
Infectious Diseases, Indiana University School of Medicine,
Indianapolis, IN, USA

J. L. Morris
Department of Pharmacy Practice, Purdue University School
of Pharmacy and Pharmaceutical Sciences, Indianapolis,
IN, USA

E. S. Ebenroth
Department of Pediatrics, Section of Pediatric Cardiology,
Indiana University School of Medicine, Indianapolis, IN, USA

for patients with IPAH and 92.3% at 1 year, 83.8% at 3 years, and 56.9% at 5 years for patients with APAH. The prolonged survival found in this study can be attributed in part to advancements in pharmacologic treatment options including epoprostenol, bosentan, and sildenafil [31].

To date, sildenafil has been the most studied phosphodiesterase 5 (PDE-5) inhibitor and the most widely used treatment option among pediatric patients with PHTN. The available information supporting the use of sildenafil for pediatric PHTN is growing. Since the first reports describing the use of sildenafil for children, clinicians have continued to gain experience and have contributed further to the availability of safety and efficacy data through small, uncontrolled trials [6, 23, 36, 45, 49, 52, 55, 58–60, 62, 63, 69, 72, 75, 77], published reviews [3, 16, 34, 51], and uncontrolled case reports [1, 2, 4, 5, 8–10, 12, 14, 18, 20, 24, 29, 30, 37–42, 44, 46–48, 54, 56, 70, 82]. This article aims to review the available safety and efficacy data regarding sildenafil for the treatment of PHTN in pediatric patients.

Pediatric PHTN

Definition

The diagnostic classification of PHTN was revised at the 2003 World Pulmonary Hypertension Symposium and reflects new understanding of the disease (Table 1) [73]. Unlike adults, children most often present with APAH secondary to other pathologies, with IPAH being much less common. Frequent causes of PHTN in children include congenital cardiac and vascular disease, chronic lung disease, persistent PHTN of the newborn, and metabolic and genetic factors [73].

Pulmonary hypertension has been defined as a mean pulmonary artery pressure (PAP) of 25 mmHg or more at rest and 30 mmHg or more with exercise, in conjunction with a pulmonary vascular resistance of 3 Woods units/m² or more and a normal pulmonary artery wedge pressure of 15 mmHg or less [67]. Although this definition is the same for both adults and children, the disease process often is very different within the pediatric population. Whereas adults typically present with a diminished cardiac index, the cardiac index of children often is normal at presentation [67]. Additionally, exercise hemodynamic abnormalities appear to be amplified in pediatric patients due to diminished vasoactive responses. Normally, the pulmonary vascular bed has the ability to accommodate for increases in blood flow during exercise via vasodilation and recruitment of unused vasculature. This capacity is lost with PHTN, resulting in further elevations in pulmonary artery pressure with exercise. The inability to increase cardiac output in response to increases in oxygen demand can manifest as

Table 1 Pulmonary arterial hypertension in children

Diagnostic classification of pulmonary hypertension
Pulmonary arterial hypertension (PAH)
Idiopathic (IPAH)
Familial (FPAH)
Associated with (APAH)
Collagen vascular disease
Congenital systemic-to-pulmonary shunts
Portal hypertension
HIV infection
Drugs and toxins
Other (thyroid disorders, glycogen storage disease, Gaucher disease, hereditary hemorrhagic telangiectasia, hemoglobinopathies, myeloproliferative disorders, splenectomy)
Associated with significant venous or capillary involvement
Pulmonary veno-occlusive disease (PVOD)
Pulmonary capillary hemangiomatosis (PCH)
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 hypoxemia
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
Nonthrombotic pulmonary embolism (tumor, parasites, foreign material)
Miscellaneous
Sarcoidosis, histiocytosis X, lymphangiomatosis, compression of pulmonary vessels (adenopathy, tumor, fibrosing mediastinitis)

From the 2003 Third World Symposium on Pulmonary Arterial Hypertension 2003 [73]

HIV human immunodeficiency virus

dyspnea and syncope. Exertional and postexertional syncope episodes occur more commonly with children, manifesting this lack of compensation in cardiac output and resulting in diminished cerebral blood flow.

Pathophysiology of PHTN

Irrespective of the etiology of PHTN, pathophysiologic alterations are common among all types. The principal

mechanism of PHTN is a combination of vasoconstriction, vascular remodeling, and thrombus formation within the pulmonary vasculature. Advanced pathophysiologic studies have identified vasoconstriction and vascular remodeling associated with endothelial dysfunction as playing a key role in the development of PHTN [35]. Extensive animal and human models have established the role of endogenous nitric oxide (NO) and the cyclic guanosine monophosphate (cGMP) signaling pathway in the regulation of pulmonary vasodilation. Endogenous NO activates soluble guanylate cyclase, which in turn increases intracellular cGMP. Interactions between cGMP and cGMP-dependent protein kinases subsequently result in vasodilation [43]. Further understanding of this pathway has led to clinically important treatment options including inhaled NO (iNO) administration and drugs such as sildenafil that inhibit metabolism of cGMP.

Congenital heart defects causing increased pulmonary blood flow (often via left-to-right shunting), pulmonary vein obstruction, and cyanosis are most likely to be associated with PHTN. Many surgeries for congenital heart disease require the use of cardiopulmonary bypass. A study of pediatric patients after cardiopulmonary bypass has demonstrated an association with temporary pulmonary endothelial dysfunction and suppression of endogenous NO production [13]. Additionally, the systemic inflammatory response to cardiopulmonary bypass is associated with increased production of endothelin, a potent pulmonary vasoconstrictor [13, 71, 80].

Further confounding the general pathophysiologic process of PHTN is the impact of iNO. Children born with total anomalous pulmonary venous connection, transposition of the great arteries, large ventricular septal defects, and atrioventricular canal are at significant risk for both pre- and postoperative PHTN [71, 80]. These children may be managed preoperatively with iNO, and treatment often is continued for postoperative PHTN. The presence of exogenous or inhaled NO has been associated with a downregulation of endothelial NO synthase. Prolonged impaired production of vasoactive mediators such as NO and prostacyclin and overexpression of vasoconstrictors such as endothelin-1 lead to changes in vascular tone and pulmonary arterial smooth muscle hypertrophy [15, 26, 27, 35]. All these factors contribute to the risk of PHTN development in children with significant congenital heart disease after surgical repair.

Treatment Options

Currently, no pharmacologic cure exists for PHTN. Treatment is aimed at relieving symptoms and slowing disease progression. Fewer than 10 years ago, management of infants and children with PHTN was limited to

aggressive ventilator strategies and iNO for critically ill inpatients, whereas outpatients were treated with calcium-channel blockers, anticoagulation, and continuous infusions of intravenous (IV) epoprostenol [79]. Subsequent clinical trials demonstrated the therapeutic efficacy of endothelin-receptor blockers and aerosolized prostacyclins and their analogs [33]. Because of serious side effects, complicated administration techniques, and difficulty obtaining these medications, the application of these treatment options often is limited to specialized PHTN treatment centers [33].

Sildenafil for PHTN

Mechanism of Action/Pharmacology

Sildenafil is a phosphodiesterase inhibitor with high selectivity against isoform 5. Expression of PDE-5, located largely in pulmonary vascular smooth muscle, is responsible for the breakdown of cGMP to guanosine 3'-cyclic phosphate (5'-GMP). Thus, inhibition of PDE-5 results in an increased endothelial level of cGMP and vascular smooth muscle relaxation. Pharmacotherapy with PDE-5 inhibitors, such as sildenafil, is a rational treatment option given the endothelial cell dysfunction and vasoconstriction within the pulmonary vasculature that contribute to PHTN. This specific mechanism of sildenafil action also makes it an ideal drug to consider for weaning iNO, as discussed later in this review.

Pharmacokinetics

The pharmacokinetic and metabolic profiles of sildenafil are based on studies with adult patients of varying ages, genders, races, and renal and hepatic functions [64]. The pharmacokinetics and pharmacodynamics of sildenafil in children with PHTN have not been studied to date. Sildenafil is absorbed rapidly, with onset of action in 30–120 min (mean, 60 min) for a fasting patient. When given in combination with fatty meals, the time to onset is delayed an additional 60 min, and the achieved peak concentration is reduced by 29% due to decreased absorption [64].

Sildenafil undergoes extensive first-pass metabolism, and the oral bioavailability is 40%. Hepatic metabolism is via cytochrome P (CYP) 3A4 (major) and CYP 2C9 (minor) into active metabolites. The active metabolite N-desmethyl sildenafil makes up 40% of serum concentrations and is responsible for 20% of the pharmacologic activity [64]. Both sildenafil and N-desmethyl sildenafil are approximately 96% plasma protein bound, with terminal half-lives of approximately 4 h. Sildenafil is eliminated as

metabolites primarily in the feces (approximately 80% of the administered dose), with approximately 13% excreted in the urine [64].

Drug Interactions

Because metabolism of sildenafil is mostly via CYP 3A4 and to a lesser extent via CYP 2C9, any inhibitor or inducer of these enzymes may potentially alter the clearance of sildenafil. Ritonavir, ketoconazole, itraconazole, and other potent CYP 3A4 inhibitors as well as other nonspecific CYP inhibitors given concomitantly are associated with increases in sildenafil plasma levels [64]. Fluconazole, a drug commonly used for children, moderately inhibits CYP 3A4. The pharmacologic effects of sildenafil are potentially increased when it is used in combination with fluconazole or any of the other CYP inhibitors. One case report in the literature describes the safe use of fluconazole and sildenafil concomitantly in an infant [19].

Bosentan, a CYP 3A4 and 2C9 inducer, given in conjunction with sildenafil causes a decrease in sildenafil plasma concentrations. Interestingly, this drug combination can be characterized as a mutual pharmacokinetic interaction due to the simultaneous decrease in sildenafil and increase in bosentan concentrations. In one study, sildenafil plasma concentrations were monitored in healthy volunteers given sildenafil 80 mg three times daily and bosentan 125 mg twice daily [61]. The sildenafil dose-interval area under the curve (AUC) was shown to decrease as much as 62.6% and the bosentan dose-interval AUC to increase as much as 49.8% [11].

In a study of 10 patients with PHTN, a 50% reduction in sildenafil AUC was noted after a single 100-mg dose in conjunction with bosentan 62.5 mg twice daily. This small study found the combination of sildenafil and bosentan to be safe and effective. Because clinical data on the use of sildenafil and bosentan in combination are minimal, no current recommendations exist for adjusting doses of either drug. Caution is warranted when the agents are used simultaneously [64].

Dosage and Administration Considerations

In the United States, sildenafil is available only in oral tablet formulation at select strengths (Revatio 20 mg; Viagra 25, 50, and 100 mg). To obtain patient-specific weight-based dosages in a more child-friendly preparation, an oral solution of sildenafil can be extemporaneously compounded [57]. The stability of a compounded suspension has been validated for up to 91 days at temperatures of 4°C and 25°C [57]. Notably, this specific formulation was developed using the Viagra dosage form. Compounding data for the Revatio dosing form are not available. Because

Revatio is the Food and Drug Administration (FDA)-approved sildenafil dosage form for PHTN, the potential exists for issues with medical insurance reimbursement for liquid formulations prepared using a non-FDA-approved sildenafil form.

Sildenafil Efficacy

Sildenafil was first FDA approved in 2005 for the treatment of adult patients with PHTN after the results from SUPER-1, a large, multinational placebo-controlled trial [21]. Numerous clinical studies have demonstrated the efficacy of sildenafil for adults with PHTN, but few studies have evaluated the efficacy of sildenafil for children (Table 2). Total pediatric efficacy data, available through prospective and retrospective studies as well as observational reports, include 193 infants and children with both IPAH and APAH. Of these, the retrospective and prospective studies account for approximately 80% of the efficacy data and include 156 children.

The pediatric studies have included patients with PHTN of various etiologies. Eight prospective studies, including a series of 87 children (ages ranging from infancy to 19 years) taking oral sildenafil, describe sildenafil's efficacy for improving hemodynamics and exercise tolerance [6, 36, 45, 58, 59, 62, 63, 69]. Three of the prospective studies were randomized controlled trials involving pediatric patients with either persistent PHTN of the newborn or PHTN related to congenital heart disease [6, 58, 62]. Sildenafil improved the oxygenation index (calculated as fraction of inspired oxygen \times mean airway pressure/arterial partial pressure of oxygen) compared with baseline and placebo values for seven infants within 6–30 h after initiation of treatment [6]. Significant improvements in oxygen saturation also were observed in the sildenafil-treated infants compared with baseline and placebo values ($P < 0.05$). Sildenafil was shown to decrease postoperative systolic PAP significantly compared with the PAP of placebo-treated children [62]. An important measure of PHTN severity is the ratio of PAP to aortic pressure, which was significantly lower with sildenafil than with placebo ($P = 0.001$). Effective doses of sildenafil in these prospective studies ranged from 0.3 to 8 mg/kg/day [6, 58, 62].

Inhaled Nitric Oxide Weaning

Many children are benefited by the use of iNO, but the downregulation of endothelial NO can make it difficult to wean patients from iNO in a timely fashion. For this reason, iNO typically is weaned slowly and not stopped abruptly in the clinical setting. Rebound PHTN, presenting

Table 2 Efficacy data

Study, design	n	Age (years)	Dosage/route	Indication	Treatment duration	Outcomes
Peiravian [62], RCT	20	1–16	Oral: 0.3 mg/kg q3 h	PHTN–CHD: VSD, PDA, ASD, APW, SAW	24–48 h	Improved postoperative PAP and PA/Ao
Namachivayam [58], RCT	15	0.1–1.31	Oral: 0.3–0.5 mg/kg	All patients intubated, sedated, on iNO	1 dose	Successful wean off iNO; no rebound PHTN ($P < 0.001$); reduced elevation of PAP mechanical ventilation: 28.2 vs. 137 h in sildenafil vs. placebo groups ($P = 0.024$); total ICU stay: 47.8 vs. 189 h in sildenafil vs. placebo groups ($P = 0.004$)
Baquero [6], RCT	7	>35.5 weeks gestation & <3 days	Enteral: 1–2 mg/kg q6 h	PPHN	36 h	Improved oxygenation index ($P < 0.05$); improved pulse oxygen saturation ($P < 0.05$)
Raposo-Sonnenfeld [63], PT	9	1–17 yr	Oral: 1–2 mg/kg divided TID	Group A: IPAH, PHTN–CHD Group B: ES plus CHD with nonrestrictive VSD	2 years	Improved exercise capacity (6-MWD); improved functional class
Hump[36], PT	14	5.3–18	Oral: 0.25–1 mg/kg 4 × daily	IPAH, PHTN–CHD s/p repair, PFO	6–15.3 months	Improved 6-MWD; improved hemodynamics
Oliveira [59], PT	6	3–19	Oral: 2–8 mg/kg/day or 100–500 mg/day (4–6 doses/day)	IPAH	4–36 months	Improved functional class; improved systemic saturation
Stocker [77], PT	15	0.11–0.7	IV: 0.35 mg/kg × 1 dose, before or after iNO	PHTN–CHD s/p VSD or ASD defect repair/closure; stable patients at risk of PHTN	1 dose	Improved hemodynamics; SBP decreased significantly ($P < 0.05$); sildenafil-augmented pulmonary vasodilator effects of iNO
Schulze-Neick [72], PT	12	0.11–15.7	IV: In cath, 0.33 and 0.66 mg/kg; postop, 0.025, 0.1, and 0.25 mg/kg	Increased PVR, CHD	2 or 3 doses	Improved hemodynamics; increased intrapulmonary shunting ($P = 0.04$)
Kothari [45], PT	9	5–18	Oral: 5.5 mg/kg/day–150 mg/day TID	IPAH, PHTN–CHD s/p repair	3.5–8 months	Improved NYHA functional class; improved 6-MWD; improved hemodynamics
Sastry [69], PT	7	4–16	Oral: 25–100 mg q8 h	IPAH	5–20 months	Improved functional class; improved 6-MWD; improved hemodynamics
Otero Gonzalez [60], OS	2	12 and 15	Oral: 25 mg q8 h, increased to 50 mg q8 h	IPAH	12 months	Improved exercise tolerance (6-MWD); improved functional class
Lunze [52], OS	8	5.5–17.5	Oral: 1.2–3 mg/kg 3–4 times daily	IPAH, PHTN–CHD Combination therapy with bosentan	0.4–2.5 years	Improved oxygen saturation; improved 6-MWD and mean PAP
Mourani [55], RS	25	14–673 days (mean, 171 days)	Oral: 1.5–8.0 mg/kg/day	Chronic lung disease	Mean duration, 241 days (range, 28–950 days)	Improved hemodynamics

Table 2 continued

Study, design	n	Age (years)	Dosage/route	Indication	Treatment duration	Outcomes
Lee [49], RS	7	3 days–21 months (median, 12 months)	0.22–0.47 mg/kg 4 times daily	Patient with previous failed wean from iNO, PAH–CHD	Mean duration, 28 days	No rebound with sildenafil; mean time to iNO discontinuation 4.4 days after sildenafil; reduced iNO requirement after sildenafil initiation ($P = 0.024$); facilitated wean off iNO

RCT randomized controlled trial, PHTN-CHD pulmonary hypertension associated with congenital heart disease, VSD ventricular septal defect, PDA patent ductus arteriosus, ASD atrial septal defect, APW aortopulmonary window, SAW subaortic web, PAP pulmonary artery pressure, PA/Ao pulmonary artery to aortic pressure ratio, iNO inhaled nitric oxide, ICU intensive care unit, PPHN persistent pulmonary hypertension of the newborn, TID three times a day, IPAHA idiopathic pulmonary arterial hypertension, PT prospective trial, ES Eisenmenger syndrome, 6-MWLD 6-min walk time, PFO patent foramen ovale, IV intravenous, SBP systolic blood pressure, PVR pulmonary vascular resistance, NYHA New York Heart Association, OS observational study, RS retrospective study, s/p status-post

as an acute increase in PAP and cardiopulmonary instability, can complicate the withdrawal of iNO.

Two small studies [49, 58] in addition to several case reports [4, 5, 42, 70] have identified sildenafil as a means for minimizing rebound PHTN and the need for prolonged iNO therapy. Namachivayam et al. [58] demonstrated sildenafil's efficacy to facilitate iNO weaning of 29 infants and children. In this study, clinical rebound PHTN was defined as an increase of 20% or more in PAP or failure to discontinue iNO. None of the 15 sildenafil-treated patients (0.4 mg/kg times 1 dose) experienced clinical rebound PHTN, and all 15 were successfully weaned from iNO. Of 14 placebo-treated patients, 10 did experience clinical rebound PHTN ($P < 0.001$), with 4 of them failing to be weaned from iNO. Mean PAP increased by 1% in the sildenafil group and 25% in the placebo group at withdrawal of iNO ($P < 0.001$) [58].

A recent study by Lee et al. [49] examined seven children with congenital heart disease who previously had failed iNO weaning attempts before the initiation of oral sildenafil (0.22–0.47 mg/kg 4 times daily). Treatment with sildenafil significantly reduced iNO requirements within 24 h and facilitated iNO weaning for all seven patients [49]. Case reports describe similar observations [4, 5, 56, 70]. Reported effective doses of sildenafil used to assist in weaning iNO ranged from 0.2 to 1 mg/kg/dose (average, 0.5 mg/kg/dose) administered once or up to every 4–6 h.

Long-Term Outpatient Therapy

Inpatient sildenafil use has been widely adopted in pediatric hospitals, and this has encouraged the growth of outpatient sildenafil use. Long-term or chronic sildenafil administration for PHTN is becoming common despite the limited efficacy of this type of therapy for children. In 2005, Humpl et al. [36] published an open-label, single-drug pilot study of 14 outpatients with IPAHA, PHTN secondary to congenital heart disease, or Eisenmenger syndrome. At the 12-month follow-up assessment, the patients demonstrated sustained benefit in exercise tolerance, as measured by the 6-min walk distance of 278 ± 114 – 432 ± 156 m ($P = 0.005$). Improvements were shown in hemodynamic parameters through a mean PAP reduction from a median of 60 mmHg to a median of 50 mmHg ($P = 0.014$) and a median pulmonary vascular resistance decrease from 15 to 12 Woods units/m² ($P = 0.024$).

Raposo-Sonnenfeld et al. [63] studied 10 children with IPAHA ($n = 5$) or PHTN associated with congenital heart disease ($n = 5$) treated with sildenafil for a minimum of 2 years. The patients treated with sildenafil showed significant improvement in exercise capacity and World Health Organization functional classification. This was most notable for the patients with IPAHA. In this group, the

Table 3 Adverse events

Adverse event	Description	<i>n</i>	Incidence (%) ^a
Hypotension [37, 49, 77]	Significant blood pressure reduction and impaired oxygenation with IV, transient with PO	15	5.9
Erection [12, 55, 62]	Mostly short-lived erection, one recurrent	6	2.6
Nasal congestion [60, 62]	Transient, resolved upon discontinuation (5)	6	2.3
Headache [23, 36, 45, 60, 69]	Persistent (sildenafil suspended 4 mo) One only with dose >125 mg	4	1.6
Dizziness [36, 45]	Resolved with dose reduction; one only with dose >125 mg	3	1.2
Flushing [36, 45, 69]	Resolved with dose reduction; one only with dose >125 mg	3	1.2
Bleeding [22]	Circumferential oozing after circumcision requiring cauterization and sutures; penis was erect	1	<1
Body ache [23]	Mild, self-limiting	1	<1
Epistaxis [36]	Self-limiting	2	<1
GI upset [62]	Not otherwise described	2	<1
Heavy menstrual flow [36]	With menarche, responded to progesterone therapy	2	<1
Optic neuropathy [76]	Monocular visual loss	1	<1
Pneumothorax [18]	Questioned relatedness	1	<1
Retinopathy [53]	Retinopathy of prematurity	1	<1
Rhinorrhea [23]	Resolved with dose reduction	2	<1
Intestinal pneumatosis [55]	Temporarily discontinued, safely restarted without other documented adverse event (continued 688 days)	1	<1
Abdominal discomfort [69]	Not otherwise described	NR	

IV intravenous; PO by mouth, NR not reported

^a % incidence calculated by utilizing sum of all pediatric studies and case reports

6-min walk distance improved from 394.2 ± 55.2 m at baseline to 526.7 ± 44.6 m at 2 years. The functional classification of patients with IPAH improved for six of seven patients in class 3 or 4 at baseline and for no patients in class 3 or 4 at 2 years. Side effects were minimal, consisting menorrhagia experienced by two female patients, ages 11 and 12 years. The symptoms resolved after regulation of the patients' menstruation and treatment of their anemia [63].

Mourani et al. [55] reviewed 25 patients younger than 2 years with chronic lung disease who were being treated with sildenafil for the management of PHTN. The patients were treated a median of 241 days (range, 28–950 days), with 88% of the patients achieving hemodynamic improvement after a median of 40 days. Hemodynamic improvement in this study was defined as a 20% decrease or more in the ratio of pulmonary to systemic systolic arterial pressure or improvement in the degree of ventricular septal flattening on serial echocardiograms. Sildenafil was well tolerated in this group. One patient discontinued therapy after 950 days due to frequent erections. Another

patient's therapy was briefly interrupted due to intestinal pneumatosis. During the follow-up period, five patients died: one of sepsis and the remaining four when support was withdrawn due to respiratory futility ($n = 3$) or neurologic devastation ($n = 1$). In each of these five patients, progressive improvement in PHTN had been demonstrated through serial echocardiographic assessments, and none of the deaths were the result of refractory PHTN or right heart failure.

Sildenafil Combination Therapy

For patients whose treatment with monotherapy has been ineffective, combination therapy can be used. Recent published adult data have shown successes with combination therapy [25, 28, 68, 74, 78]. Evidence for pediatrics, however, still is lacking. Successful use of prostaglandin E1, iNO, and sildenafil was described for an infant with congenital diaphragmatic hernia, with oxygen saturation improved from 60 to 90% within 24 h. The patient showed continued improvement, with uneventful discontinuation of

iNO at 4 days and prostaglandin E1 at 8 days. This patient was discharged home after 54 days of therapy, with sildenafil discontinued [20]. No additional published data describing this combination for children are available.

Bosentan and sildenafil have demonstrated efficacy individually for managing various forms of PHTN, but again, few studies characterize their combined use for children. A 2007 observational study included eight children with PHTN related to congenital heart disease who were treated with bosentan and sildenafil. This combination brought about significant improvement in functional class (mean, 2.8 ± 0.4 to 1.6 ± 0.8 ; $P = 0.001$). Improvements also were seen in oxygen saturation ($89.9 \pm 9.9\%$ to $92.3 \pm 7.1\%$; $P = 0.037$), 6-min walk distance (351 ± 58 to 451 ± 119 m; $P = 0.039$) and mean PAP (62 ± 12 to 46 ± 18 mmHg; $P = 0.041$) [52].

Combination therapy using sildenafil and bosentan as an oral treatment alternative to IV prostacyclin therapy offers potential benefit. Brancaccio et al. [9] reported successful discontinuation of IV prostacyclin without the need for reinitiation at the 4-year follow-up assessment when combination bosentan and sildenafil was used with a 7-year-old. Although combination therapy has anecdotally proved to be a benefit for a few patients, additional larger studies are needed to address the use of combination therapy as a more effective alternative to monotherapy.

Sildenafil Safety

The adverse event profile observed and reported for the adult population depicts sildenafil as a generally safe and well-tolerated medication. In the SUPER-1 trial, the most frequent adverse events observed with the FDA-approved dosage of 20 mg orally 3 times daily included epistaxis (8%), headache (7%), dyspepsia (6%), insomnia (6%), and flushing (6%) [21]. At doses exceeding the FDA-approved doses, the incidence of flushing, myalgia, diarrhea, and visual disturbances (described as color-tinged vision, increased sensitivity to light, and blurred vision) are increased [21]. In comparison, the limited pediatric data available show a parallel among adverse events reported. Table 3 summarizes the adverse events noted in pediatric studies and case reports.

For this review, the incidence of each reported adverse event was calculated using the sum of all the patients receiving sildenafil in the studies and case reports. All the studies and case reports made reference to adverse events, often noting that no event was experienced, although few investigations specifically stated how or which adverse events were monitored. The calculated incidences of these adverse events are low, but this may be a reflection of the limited reporting within published data. Thus, the lack of toxicities

from the available data may not necessarily reflect the general safety of the drug, and continued prudent use is warranted.

A notable concern with sildenafil is the risk for optic changes including visual disturbances, retinal hemorrhage, and optic neuropathy. The color-tinged vision experienced by some patients is the result of sildenafil's effect on phosphodiesterase-6, resulting in an alteration of the GMP level in the retina [76]. In the SUPER-1 trial, the incidence of retinal hemorrhage was 1.4% of patients receiving the recommended treatment dose of 20 mg orally 3 times daily (1.9% for all groups) compared with 0% of patients receiving a placebo [21]. Notably, most of these patients were concomitantly receiving anticoagulation therapy, increasing the risk of bleeding. Only minimal pediatric data support an association of retinal hemorrhage with sildenafil use. Two case reports describe ischemic optic neuropathy in a 6-year-old and retinopathy of prematurity in a 26-week-gestation neonate loosely correlating with the use of sildenafil [53, 76]. The nonspecific temporal association and the multitude of potential alternate causes, especially the risk of retinopathy for a premature neonate, limits conclusions of a causal relationship. To date, no strong evidence has associated sildenafil with retinal or choroidal blood changes in children.

Intravenous Sildenafil

Sildenafil is available as an IV injection in various countries outside the United States, but available data on use of the IV form for children are limited. Lammers et al. [48] reported the successful use of IV sildenafil for a 7-month-old with known PHTN in acute respiratory failure after an episode of aspiration. Oral sildenafil was changed to an IV infusion of 0.3 mg/kg/min due to perceived ineffective absorption. The change resulted in stabilization of the patient's clinical condition without a reduction in systemic arterial pressure or an increased need for inotropic support throughout the duration of the sildenafil infusion.

Stocker et al. [77] studied the acute effects of IV sildenafil and its interaction with iNO on hemodynamics and oxygenation for 15 infants at risk for PHTN after cardiac surgery. Intravenous sildenafil was shown to augment the beneficial pulmonary vasodilatory effects of iNO, as evident by reductions in the pulmonary vascular resistance index from 2.95 to 2.45 U ($P < 0.05$) when iNO was given before sildenafil. For patients receiving sildenafil first, the pulmonary vascular resistance index decreased from 2.84 to 2.35 U ($P < 0.05$). However, sildenafil treatment also resulted in a significantly reduced systemic blood pressure and systemic vascular resistance ($P < 0.01$) in both groups. Infants receiving sildenafil in this study also experienced worsened arterial oxygenation and alveolar–arterial gradient

($P < 0.05$). The study was terminated early due to the significant reduction in systemic blood pressure and deterioration in oxygenation, which did not improve with iNO.

Schulze-Neick et al. [72] observed similar results among 24 patients treated with IV sildenafil either during cardiac catheterization or within 2 h after cardiac surgery. Pulmonary vascular resistance was reduced more effectively with sildenafil than with iNO (11.5% vs. 4.3% in the catheterized patient group [$P < 0.05$] and 25.8% vs. 14.6% in the postoperative patient group [$P = 0.09$]). Sildenafil also was noted to potentiate a cGMP increase in response to iNO. Neither treatment with iNO nor the infusion of sildenafil alone significantly increased plasma cGMP levels, but cGMP levels increased when treatment therapies were combined ($P < 0.001$). Increased intrapulmonary shunting in patients receiving IV sildenafil postoperatively compared with patients receiving iNO ($P = 0.04$) further supports the safety concerns with this dosage form.

The observed problems of systemic hypotension and impaired oxygenation experienced by patients receiving IV sildenafil raise concerns and could limit its use if it were to become available in the United States. Further studies evaluating the pharmacokinetics of IV sildenafil with children to explore therapeutic effects and toxicities related to IV administration are warranted.

Pharmacoeconomic Consideration

The development of advanced treatment methods for the management of PHTN has led to a growing financial

implication for both patients and the institutions caring for these patients. Special considerations including extemporaneous compounding and complex delivery systems further add to the staggering cost of long-term pharmacologic management of the disease. Table 4 outlines a cost comparison of pharmacologic treatment options for chronic PHTN management. Compared with alternative treatment options, sildenafil appears to be an affordable option. Based on average wholesale price, a typical 1-month supply of bosentan, epoprostenol, and inhaled iloprost for a 10-kg patient would easily total more than \$2,000 for each. For that same 10-kg patient, a sildenafil compounded solution would cost a fraction of that, at \$330 for a 1-month supply. This treatment option could save the patients and caregivers thousands of dollars annually.

Sildenafil often is used within the hospital inpatient setting, especially in conjunction with iNO. Namachivayam et al. [58] identified sildenafil not only as a means for preventing rebound PHTN, but also as a potential for cost savings. The duration of mechanical ventilation averaged 28.2 h for the 15 patients treated with sildenafil and 98 h for the 14 patients treated with placebo ($P = 0.024$). The total intensive care unit length of stay after study completion was reduced from a mean of 189 h for the placebo group to 47.8 h for the sildenafil group ($P = 0.004$) [58]. By affording patients an average of nearly 3 days less on the ventilator and an average shortened intensive care unit stay of 6 days, there is a potential for substantial cost savings to both the hospital and the patient. Future pharmacoeconomic studies are needed for further evaluation of these financial implications.

Table 4 Outpatient considerations

Drug	Cost per 30-day supply (average doses for 10-kg patient)	Special considerations	Special access
Sildenafil (Revatio, Viagra)	\$329.99 ^a (1 mg/kg/dose PO TID 480 ml)	Compounded ^b	Available at compounding pharmacies
Bosentan (Tracleer)	\$2,436.00 ^c (31.25 mg PO BID 62.5 mg 30 tablets)	Liquid not available; preparation before administration	Tracleer Access Program (TAP) enrollment required; access through specialty distributors
Epoprostenol (Flolan)	\$2,287.20 ^c (includes diluents) (0.5 mg vial × 20, 50-mL diluents × 60) Excludes cost for CVL maintenance + home nursing + cold packs	Administered through a central venous line; requires cooling to between 2° and 8°C; special diluents for reconstitution	Available only through Accredited specialty pharmacy
Inhaled iloprost (Ventavis)	\$8,823.60 ^c (30 × 6 of 10 µg/ml) (based on 5 µg inhaled 6 × day)	Ventavis I-neb AAD system	PAH Pathways (Actelion) enrollment program; requires specialty pharmacies; Sure Steps patient education program optional

PO by mouth, *TID* three times daily, *BID* twice daily, *CVL* central venous line, *AAD* adaptive aerosol delivery, *PAH* pulmonary arterial hypertension

^a Based on Riley Hospital for Children outpatient pharmacy

^b Viagra used for product compounding

^c Based on Red Book AWP [50]

Conclusions

Significant advances in early diagnosis and advanced pharmacologic treatment options for pediatric PHTN not only have extended survival but also have improved quality of life, exercise capacity, and hemodynamics [7, 32, 65]. With improved understanding of the pathophysiology of PHTN, novel pharmacologic agents inhibiting PDE-5, such as sildenafil, have been developed and quickly have become favored therapeutic options. Efficacy data from small case series, case reports, and small uncontrolled trials support the use of sildenafil. Although a wide range of doses were given in case reports and trials, the most-used effective dosing regimen ranges from 0.5 to 2 mg/kg given three times daily to a maximum dose of about 8 mg/kg/day. To confirm the overall safety and efficacy of sildenafil for the treatment of PHTN in the pediatric population, large-scale randomized, controlled trials are warranted.

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