Sildenafil Use in Children with Pulmonary Hypertension

Jennifer L. Cohen, MD, Shannon N. Nees, MD, Gerson A. Valencia, MD, Erika B. Rosenzweig, MD, and Usha S. Krishnan, MD, DM

Objective To assess the demographics, treatment algorithm, and outcomes in a large cohort of children treated with sildenafil.

Study design A retrospective cohort study of children with pulmonary hypertension (PH) treated with sildenafil at a single institution between 2004 and 2015. Baseline and follow-up data collected by chart review.

Results There were 269 children included in this study: 47 with idiopathic pulmonary arterial hypertension, 53 with congenital heart disease, 135 with bronchopulmonary dysplasia, 24 with congenital diaphragmatic hernia, and 7 with other causes. Sildenafil was initial monotherapy in 84.8% and add-on therapy in 15.2%. Median follow-up time was 3.1 years (2 weeks-12.4 years). On follow-up, 99 (37%) remained on sildenafil or transitioned to tadalafil, 93 (35%) stopped sildenafil for improvement in PH, 54 (20%) died, and 20 (7%) were lost to follow-up. PH was most likely to improve in those with bronchopulmonary dysplasia, allowing for the discontinuation of sildenafil in 45%. Eighteen deaths were related to PH and 36 from other systemic causes. Two patients stopped sildenafil owing to airway spasm with desaturation. Overall survival was significantly lower in World Health Organization group 3 PH (bronchopulmonary dysplasia and congenital diaphragmatic hernia) vs group 1 (idiopathic pulmonary arterial hypertension and congenital heart disease), $P = .02$.

Conclusions In this retrospective experience in children with mainly World Health Organization groups 1 and 3 PH, low-dose sildenafil was well-tolerated, safe, and had an acceptable side effect profile. Although patients with group 3 PH have high mortality, survivors have a high likelihood of PH improving. *(J Pediatr 2019;205:29-34).*

Pulmonary hypertension (PH) is characterized by a progressive increase in pulmonary vascular resistance leading to right ventricular failure and premature death.[1-4] Sildenafil is a phosphodiesterase (PDE) type 5 inhibitor approved for treatment of pulmonary arterial hypertension (PAH) in adults. PDE-5 inhibitors have vasodilatory effects in the pulmonary vasculature via an increase in cyclic guanosine monophosphate.[5,6] Sildenafil is not currently US Food and Drug Administration (FDA) approved in the pediatric population; however, it has been extensively used off-label for pediatric PH since 2005, mostly based on adult studies because there are limited pediatric data.[7-11]

The Sildenafil in Treatment-Naïve Children, Aged 1-17 Years with Pulmonary Arterial Hypertension (STARTS-1) trial, a 16-week randomized, double-blind, placebo-controlled study, examined the effects of oral sildenafil monotherapy in pediatric patients with PAH, including idiopathic PAH (IPAH), and PAH associated with connective tissue disease and congenital heart disease (CHD). The peak oxygen consumption, mean pulmonary artery pressure, and pulmonary vascular resistance index improved with the medium- and high-dose sildenafil, and there was no significant change with low-dose sildenafil.[12] In the long-term extension study (STARTS-2), there was increased mortality noted at 3 years of age associated with high-dose sildenafil in children with IPAH, but not in children with PAH associated with CHD.[13] Review of these data by the FDA and European Medicines Agency resulted in contradictory recommendations; sildenafil was approved by the European Medicines Agency in 2011 with a later warning on avoidance of the use of high-dose sildenafil, and the FDA released a black box warning against the use of sildenafil in pediatric patients aged 1-17. The Pediatric Pulmonary Hypertension Network put forth a consensus statement highlighting the limitations of the START-2 extension study and the FDA warning was later revised to add that healthcare providers should consider the risk and benefits of sildenafil for the individual patient.[14-16]

Given the controversy and limited data on the treatment of pediatric PH with sildenafil, our aim was to describe our large, single-center experience with the use of sildenafil in infants and children with PH.

BPD	Bronchopulmonary dysplasia
CDH	Congenital diaphragmatic hernia
CHD	Congenital heart disease
FDA	US Food and Drug Administration
IPAH	Idiopathic PAH
PAH	Pulmonary arterial hypertension
PDE	Phosphodiesterase
PH	Pulmonary hypertension
WHO	World Health Organization

From the Division of Pediatric Cardiology, Department of Pediatrics, Columbia University Vagelos College of Physicians and Surgeons, New York Presbyterian Hospital, New York, NY

S.N. receives salary support through a Ruth L. Kirschstein National Research Service Award of the National Institutes of Health (5T32HL007854-22). The authors declare no conflicts of interest.

Portions of this study were presented as an oral presentation at the Pediatric Academic Societies annual meeting, May 6-9, 2017, San Francisco, California.

0022-3476/$ - see front matter. Published by Elsevier Inc.
https://doi.org10.1016/j.jpeds.2018.09.067

Methods

This retrospective cohort study included 269 pediatric patients with PH (≤18 years of age) who initiated treatment with sildenafil between December 1, 2004, and December 31, 2015, with or without preexisting targeted PH therapy. Patients were excluded if the patient had group 2 PH including cardiomyopathy, and those with single ventricle physiology. Baseline and follow-up data were collected retrospectively from medical charts; data collection ended on December 31, 2016, giving a ≥1 year follow-up period for patients on sildenafil.

The addition of other PH-specific therapy was recorded. Survival status and treatments were assessed for all patients at the end of data collection, regardless of whether sildenafil was continued or discontinued. Events leading to discontinuation were collected to understand the reasons for stopping and side effects.

Statistical analyses were performed using Stata software, version 14.0 (StataCorp, College Station, Texas). Clinical variables were described using standard summary statistics including median with range for non-parametric data. Mann-Whitney *U* test, χ^2 test, and log-rank test were used to compare medians, proportions, and mortality, respectively. A *P* value of <.05 was considered statistically significant. This study was approved by the Columbia University Medical Center's Institutional Review Board.

Results

There were 269 patients who met inclusion criteria (134 male, 135 female). Forty-seven patients (17%) had IPAH, 53 (20%) had PH associated with CHD, 3 (1%) had PH associated with connective tissue disease, 135 (50%) had PH associated with bronchopulmonary dysplasia (BPD), and 24 (9%) had PH associated with congenital diaphragmatic hernia (CDH). Seven patients were classified as other. Three of these patients had glycogen storage diseases, 2 had mucopolysaccharidosis type 1 (Hurler syndrome), and 2 had skeletal abnormalities with associated restrictive lung disease.

The median age at PH diagnosis was 6 months (range, 1 week-16.3 years) and the median age at sildenafil initiation was 7 months (range, 1 week-17.1 years). The median follow-up time after sildenafil initiation was 3.1 years (2 range, weeks-12.4 years) (**Table I**). The maintenance dosing range for all patients was 1 mg/kg per dose given enterally every 8 hours. There were 5 patients early in the study period transferred to our institution on sildenafil every 6 hours, but were changed to every 8-hour dosing during the hospitalization as soon as possible. Patients were not discharged on every 6-hour dosing. If parenteral dosing was needed, the dose was 50% of the enteral dose. As shown in **Table II**, the majority of patients (84.8%) started sildenafil as monotherapy, 38 patients (14.1%) started sildenafil as add-on therapy, and 3 patients (1.1%) started sildenafil concurrently with other PH-specific medications. Thirty-nine percent of patients required an additional medication added to sildenafil, with a median time to additional medication of 6 months (range, 1 week-10.5 years). As an institutional protocol, patients with World Health Organization (WHO) functional class III or IV symptoms were started on a continuous prostanoid infusion as first-line therapy for PH, and those patients in functional class I or II were usually started on sildenafil as first-line therapy. Most patients with IPAH had a cardiac catheterization before the initiation of pulmonary vasodilator therapy (43/47 [93%]). About two-thirds of patients with CHD had a catheterization before the initiation of sildenafil (33/53 [62.3%]). It was rare for patients with PH associated with BPD to have a cardiac catheterization before sildenafil initiation, often owing to the small patient size and patient fragility, with only 20 of the 135 infants (14.8%) undergoing cardiac catheterization before sildenafil initiation. Similarly patients with CDH and PH rarely had cardiac catheterization before sildenafil initiation (2/24 [8.3%]). If patients with BPD and patients with CDH were not able to be weaned off sildenafil within 1 year, then a cardiac catheterization was performed to assess pulmonary artery pressure, evaluate intracardiac or extracardiac shunting, rule out pulmonary vein stenosis, and evaluate for left ventricular diastolic dysfunction. Patients with IPAH had follow-up cardiac catheterizations every 1-3 years, with the frequency determined by clinical status and changes in therapy.

Outcomes at the end of data collection were assessed (**Table III**). Thirty-three percent of patients continued on sildenafil, 4% transitioned to tadalafil, and 35% discontinued sildenafil owing to improvement in PH. For patients who were able to stop sildenafil owing to improvement in PH, the median time of sildenafil use was 1.7 years (range, 2 weeks-8.6 years). Two patients with BPD discontinued sildenafil owing to side effects, specifically desaturations owing to airway spasm. No patient stopped sildenafil owing to a perceived lack of

Table I. Patient characteristics of overall cohort and by type of PH

	All patients (n = 269)	Patients with IPAH (n = 47)	Patients with PAH-CHD (n = 53)	Patients with BPD (n = 135)	Patients with CDH (n = 24)
Male/female	134/135	16/31	25/28	76/59	10/14
Age at PH diagnosis	6 mo (1 wk-16.3 y)	3.9 y* (1 mo-16.3 y)	10 mo (1 mo-15.8 y)	4 mo* (1 wk-6.7 y)	1 mo* (1 wk-9 mo)
Age at sildenafil initiation	7 mo (1 wk-17.1 y)	7.6 y* (2 mo-17.1 y)	1.2 y (3 wk-16.8 y)	4 mo* (1 wk-6.9 y)	1.5 mo* (1 wk-9 mo)
Follow-up time	3.1 y (2 wk-12.4 y)	5.7 y* (2 mo-12.4 y)	3.9 y (1 mo-11.9 y)	1.9 y* (2 wk-11.5 y)	3.7 y (6 mo-10 y)

PAH-CHD, PAH associated with CHD.
Amount of time displayed as median (range).
*Indicates statistically different from remainder of cohort based on Mann-Whitney test ($P < .05$).

Table II. Sildenafil initiation and add-on medications

	All patients (n = 269)	Patients with IPAH (n = 47)	Patients with PAH-CHD (n = 53)	Patients with BPD (n = 135)	Patients with CDH (n = 24)
Sildenafil initiation					
Monotherapy	228 (84.8)	26 (55.3)*	49 (92.5)	121 (90)	22 (91.7)
Started concurrently with other PH-specific medication	3 (1.1)	1 (2.1)	0 (0)	2 (1.5)	0 (0)
Add-on therapy	38 (14.1)	20 (42.6)*	4 (7.5)	12 (8.5)	2 (8.3)
Additional medication added to sildenafil	105 (39.0)	39 (83.0)*	19 (35.8)	33 (24.4)	13 (54.2)
Time from sildenafil initiation to add-on medication	6 mo (1 wk-10.5 y)	7 mo (2 wk-8.8 y)	1.1 y* (2 wk-10.5 wk)	4 mo (1 wk-4.5 y)	7 mo (2 mo-4.5 y)

Values are n (%) unless or median (range).
*Indicates significant difference compared to remainder of cohort using χ^2 or Mann-Whitney test ($P < .05$).

efficacy. There were no patients who had to decrease sildenafil dose owing to other side effects; however, some patients with priapism underwent a slower uptitration of the sildenafil dose. One patient received a lung transplant, 20% (n = 54) died, with 18 of 54 deaths related to PH, and the remaining 36 deaths were thought to be due to respiratory failure or an infectious etiology. Sildenafil had been stopped in 1 patient before death some weeks later, and the remaining patients died while on sildenafil. Seven percent of patients were lost to follow-up. The overall survival starting from sildenafil initiation is shown in the Kaplan-Meier curve in the **Figure**, comparing survival of WHO group 1 PH (IPAH, CHD, and connective tissue disease) and group 3 PH (BPD and CDH). The 1-, 3-, and 5-year survivals after sildenafil initiation overall were 90%, 86%, and 84%, respectively. In group 1 patients the 1-, 3-, and 5-year survivals after sildenafil initiation were 98%, 94%, and 90%, respectively. In group 3 patients, the 1-, 3-, and 5-year survivals after sildenafil initiation were 84%, 80%, and 78%, respectively. Survival was significantly worse in group 3 PH vs group 1 PH ($P = .02$) and mortality was mainly related to systemic complications of prematurity and BPD. There was no difference in survival for the inpatients initially treated with sildenafil every 6 hours compared with those treated every 8 hours, although this was a very small sample size.

Patients with IPAH were significantly older at PH diagnosis and sildenafil initiation, and had a longer follow-up time compared with the remainder of the cohort (**Table I**). These patients were much more likely to require the addition of another PH-specific medication, with 83% of patients requiring an additional medication (83% vs 43%; $P < .001$). Twenty-four patients needed 1 additional medication during the follow-up period, and 15 patients required 2 additional medications. The median time to an additional medication was 7 months (range, 2 weeks-8.8 years). Five of the patients who were started on sildenafil as add-on therapy to epoprostenol were eventually able to have epoprostenol weaned off. Four of these 5 patients were started on an oral endothelin antagonist in addition to sildenafil.[17] Patients with IPAH were more likely to continue on a PDE-5 inhibitor (sildenafil or tadalafil) throughout the follow-up period, compared with the remainder of the cohort (77% vs 33%; $P < .001$). As expected, no patients with IPAH discontinued sildenafil owing to improvement in PH.

Patients with PAH associated with CHD had a median age at PH diagnosis of 10 months (range, 1 month-15.8 years), with median age at sildenafil initiation of 1.2 years. Most patients (92.5%) started sildenafil as first-line therapy for PH. Nineteen patients (36%) required additional medication added, with a median time to additional medication of 1.1 years (range, 2 weeks-10.5 years). This time to additional medication was significantly longer than the remainder of the cohort (1.1 years vs 6 months; $P < .01$). Fifteen patients had 1 medication added, and 4 patients received 2 additional medications. There were 3 patients on continuous systemic therapy with epoprostenol or treprostinil, 2 of whom died from PH during the study period; the other is currently undergoing evaluation for a lung transplant. About one-half of the patients (49%) were still on a PDE-5 inhibitor at last follow-up. Thirty-six percent were weaned off sildenafil for improvement in PH with a median

Table III. Outcome at last follow-up based on type of PH

Types of PH	Total no. of patients	On sildenafil or tadalafil	Off sildenafil (PH improved)	Died (all cause)	Died secondary to PH	Lost to follow-up
IPAH	47	36 (77)*	0 (0)*	6 (13)	4 (9)	4 (9)
PAH-CHD	53	26 (49)	19 (36)	5 (9)	3 (6)	3 (6)
PAH-CTD	3	3 (100)	0 (0)	0 (0)	0 (0)	0 (0)
PH-BPD	135	24 (18)*	61 (45)*	35 (26)*	9 (7)	13 (10)
PH-CDH	24	7 (29)	12 (50)	5 (21)	2 (8)	0 (0)
Other	7	3 (43)	1 (14)	3 (43)	0 (0)	0 (0)
Overall	269	99 (37)	93 (35)	54 (20)	18 (7)	20 (7)

CTD, connective tissue disease.
Values are n (%) unless otherwise indicated.
*Indicates significant difference compared to remainder of cohort using χ^2 ($P < .01$).

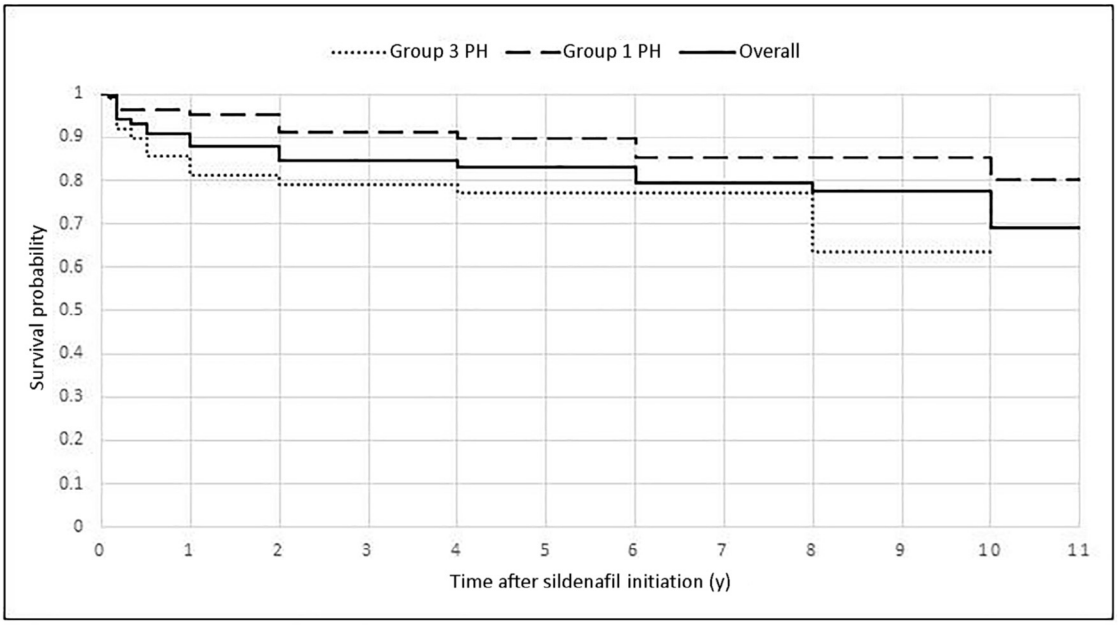

Figure. Kaplan-Meier curve demonstrates overall survival and compares the survival of WHO group 1 PH (IPAH, CHD, and connective tissue disease) and group 3 PH (BPD and CDH). Survival was worse in group 3 PH vs group 1 PH ($P = .02$).

time on sildenafil of 1.1 years (range, 1 months-7.5 years). The type of CHD and whether they were repaired is shown in **Table IV** (available at www.jpeds.com). The most common type of CHD in this cohort was atrioventricular canal defect (22/57 patients). Patients with unrepaired shunts on sildenafil were deemed candidates for repair when their pulmonary vascular resistance index was <6 Wood units*m^2 and the ratio of pulmonary to systemic resistance of <0.33.

There were 29 patients in our cohort with trisomy 21. The majority of these patients (n = 18) had PAH associated with CHD (15 atrioventricular canals, 2 ventricular septal defects, and 1 patent ductus arteriosus). Of these patients, 6 had unrepaired shunts when started on sildenafil, and 4 of these 6 subsequently underwent successful repair of the shunt. The remainder (n = 12) were patients with PAH after shunts were repaired. There were 4 patients with IPAH with no associated CHD or significant lung disease. Seven patients had PAH associated with BPD and all of these infants were premature with gestational ages ranging from 28-32 weeks with significant lung disease. Two of these patients with BPD had minor CHD (one with a small atrial septal defect and one with a small patent ductus arteriosus). Outcomes for these patients are shown in **Table V** (available at www.jpeds.com). About one-half of the patients on sildenafil or tadalafil at last follow-up—24.1% stopped sildenafil owing to improvement in PH, 10.3% were lost to follow-up, and 17.2% died. None of these outcomes were statistically significantly different from patients in our cohort without trisomy 21. Similar to the patients without trisomy 21 with IPAH, no patient with IPAH and trisomy 21 stopped sildenafil owing to improvement in PH. The mortality was high in patients with trisomy 21 and BPD (42.9%). One of these infants had sildenafil stopped owing to airway spasms, which may have been attributable to airway congestion from sildenafil in the presence of significant baseline tracheobronchomalacia. This infant died of sepsis and respiratory failure a few weeks after sildenafil was stopped. Two other patients died from respiratory failure as a primary cause of death.

Patients with PH associated with BPD made up a large proportion of the cohort, with 135 patients included. There was some overlap between the various groups of PH, with 23 patients with BPD having associated CHD, some with >1 lesion (11 patients with significant atrial septal defect, 10 with a patent ductus arteriosus, 4 with a ventricular septal defect, and 2 with pulmonary vein stenosis). The median age of PH diagnosis was 4 months (range, 1 week-6.7 years). There was not a significant amount of time between diagnosis and treatment, with a median age at sildenafil initiation of 4 months (range, 1 week-6.9 years). The majority of these patients (90%) started sildenafil as monotherapy, and one-quarter required an additional medication added to sildenafil, with a median time to add-on medication of 4 months (range, 1 week-4.5 years). Forty-five percent of patients with BPD were able to be weaned off sildenafil owing to improvement in PH during the follow-up period, with median time on sildenafil of 1.75 years (range, 2 weeks-5.7 years). There was the highest overall mortality in this cohort, with 26% of patients (n = 35) dying during the follow-up period and 9 of the 35 deaths had death attributed to PH and the rest from sepsis or worsening lung disease and respiratory failure.

There were 24 patients with PH associated with CDH. The median age at PH diagnosis was significantly younger than the remainder of the cohort at 1 month (range, 1 week-9 months) with a median age at sildenafil initiation of 1.5 months (range,

1 week-9 months). The majority of patients (91.7%) started sildenafil as monotherapy, and a large proportion (54.2%) required an additional medication, with a median time to add-on medication of 7 months (range, 1 month-4.5 years). One-half of the patients with CDH (50%) were able to wean off sildenafil after PH improved, with median time to sildenafil discontinuation of 2.1 years (range, 4 months-4.75 years). Twenty-nine percent continued on a PDE-5 inhibitor at last follow-up. Patients with CDH and PH also had a high mortality, with 5 deaths (21%), 2 of which were due to PH and the remaining due to other systemic causes.

Discussion

Improvement or even resolution of PH during sildenafil therapy has been reported in patients with BPD and CDH.[18-21] This finding was true in our study as well, with about one-half of these patients weaned off of sildenafil owing to improvement in PH at the end of the study period. The median time to sildenafil discontinuation in this group was 1.75 years. Although mortality was highest in patients with BPD and CDH in our study, those patients that survive have a high likelihood of weaning off PH medications owing to improvement in PH associated with lung growth and maturation.

IPAH tends to be progressive, and all patients who were started on PDE-5 inhibitors remained on this medication throughout the study period. Patients with IPAH were the least likely to start sildenafil as first-line targeted PH therapy, because many of these patients were started on more aggressive first-line therapy with continuous prostanoid infusions. There were 5 patients who were initially on a continuous prostanoid infusion that were able to be weaned off once sildenafil was added, some of which were previously described by Melnick et al.[17]

The REVEAL registry including children with IPAH demonstrated a 1-, 3-, and 5-year estimated survival rates from diagnostic catheterization of 96 ± 4%, 84 ± 5%, and 74 ± 6%, respectively, with no significant difference in 5-year survival between IPAH and PAH associated with CHD (5-year survival of 71 ± 13%).[3,22] In our cohort the 1-, 3-, and 5-year survivals in patients with IPAH and PAH associated with CHD were 98%, 94%, and 90%, respectively, after sildenafil initiation, which is overall higher than reported previously.

PH associated with CHD was most common in patients with left to right shunts such as atrioventricular canal, ventricular septal defect, and patent ductus arteriosus. Most patients with an atrioventricular canal defect who were started on sildenafil were repaired, showing the propensity for postoperative PH in this cohort, and the patients with ventricular septal defects and patent ductus arteriosus were mostly unrepaired.

Our study also assessed the type of PH and outcome in patients with trisomy 21. Beghetti et al in a post hoc analysis of trisomy 21 patients in the STARTS-1 trial showed no effect of sildenafil treatment on the pulmonary vascular resistance index or mean pulmonary artery pressure.[23] Although our study did not directly assess the efficacy of sildenafil, comparing outcomes in our study between patients with and without trisomy 21 showed no statistically significant difference in outcome at last follow-up. In addition, 6 patients with trisomy 21 and CHD were unrepaired when started on sildenafil, and 4 of these patients had improvement in PH on sildenafil treatment that allowed them to subsequently undergo successful cardiac repair after a decrease in pulmonary vascular resistance index to <6 Wood units*m^2 and a ratio of pulmonary to systemic resistance of <0.33.

There are many targeted PH medications approved for adults, and many of these are used off-label in children. Bosentan is currently the only FDA approved targeted PH medication in children, approved in children age ≥3 years with IPAH. Despite the controversy surrounding the use of sildenafil in children, many institutions have continued to use sildenafil as first-line therapy in the majority of patients with PH; however, a large proportion (39%) require additional PH-specific medications.

Out of the 269 patients included in this study, only 2 patients needed to discontinue sildenafil owing to side effects, namely, desaturations associated with airway spasm. Both of these patients had PH associated with BPD with one having trisomy 21. This airway spasm was described as episodic desaturation associated with decreased air entry on physical examination, unresponsive to bronchodilators, and required aggressive bagging for resolution of symptoms. It is hypothesized that sildenafil may cause edema in the already compromised airways causing episodic airway occlusion. Although this side effect of sildenafil was rare, it should be monitored for, especially in patients with PH associated with BPD and in Down syndrome. Priapism, although mentioned by many parents of patients, was never severe enough to require discontinuation of the medication and could be managed by a slower uptitration of sildenafil to the ultimate dose. Additionally, facial flushing, headaches, nasal stuffiness, and irritability were other symptoms mentioned, without the need to modify therapy.

The STARTS-1 trial showed an increased mortality at 3 years associated with high-dose sildenafil in children with IPAH.[12] Patients at our institution received low-dose sildenafil, and the overall mortality in our cohort was lower than previously reported data.

The main limitation of this study is the retrospective design. Measurement of efficacy of sildenafil was not deemed possible owing to the heterogeneity of the cohort, including many confounding factors including the addition of other medications during the study period and variable timing of echocardiograms and cardiac catheterizations in relationship to sildenafil initiation. Side effects that did not lead to sildenafil discontinuation were inconsistently documented; therefore, their true frequency could not be determined accurately.

This study shows that sildenafil was well-tolerated. Treatment approaches and outcome differ based on type of PH, however, with sildenafil remaining as first-line treatment for pediatric patients with WHO functional class I and II PH. Mortality in our cohort was overall lower than previously published mortality associated with various types of PH.[3,18,22,24-27] Importantly, patients with group 3 PH have especially high mortality, but patients who survive have a high likelihood of PH improving over time. ■

Submitted for publication Jul 6, 2018; last revision received Sep 25, 2018; accepted Sep 26, 2018

Reprint requests: Usha S. Krishnan, MD, DM, Division of Pediatric Cardiology, Department of Pediatrics, CHN 2 North, # 255, 3959 Broadway, New York, NY 10032. E-mail: usk1@cumc.columbia.edu

References

1. Haworth SG, Hislop AA. Treatment and survival in children with pulmonary arterial hypertension: the UK Pulmonary Hypertension Service for Children 2001-2006. Heart 2009;95:312-7.
2. Galie N, Ghofrani HA, Torbicki A, Barst RJ, Rubin LJ, Badesch D, et al. Sildenafil citrate therapy for pulmonary arterial hypertension. N Engl J Med 2005;353:2148-57.
3. Barst RJ, McGoon MD, Elliott CG, Foreman AJ, Miller DP, Ivy DD. Survival in childhood pulmonary arterial hypertension: insights from the registry to evaluate early and long-term pulmonary arterial hypertension disease management. Circulation 2012;125:113-22.
4. Berger RM, Beghetti M, Humpl T, Raskob GE, Ivy DD, Jing ZC, et al. Clinical features of paediatric pulmonary hypertension: a registry study. Lancet 2012;379:537-46.
5. Barst RJ, Ertel SI, Beghetti M, Ivy DD. Pulmonary arterial hypertension: a comparison between children and adults. Eur Respir J 2011;37:665-77.
6. Cohen AH, Hanson K, Morris K, Fouty B, McMurtry IF, Clarke W, et al. Inhibition of cyclic 3′-5′-guanosine monophosphate-specific phosphodiesterase selectively vasodilates the pulmonary circulation in chronically hypoxic rats. J Clin Invest 1996;97:172-9.
7. Hanson KA, Ziegler JW, Rybalkin SD, Miller JW, Abman SH, Clarke WR. Chronic pulmonary hypertension increases fetal lung cGMP phosphodiesterase activity. Am J Physiol 1998;275:931-41.
8. Humpl T, Reyes JT, Holtby H, Stephens D, Adatia I. Beneficial effect of oral sildenafil therapy on childhood pulmonary arterial hypertension: twelve-month clinical trial of a single-drug, open-label, pilot study. Circulation 2005;111:3274-80.
9. Apitz C, Reyes JT, Holtby H, Humpl T, Redington AN. Pharmacokinetic and hemodynamic responses to oral sildenafil during invasive testing in children with pulmonary hypertension. J Am Coll Cardiol 2010;55:1456-62.
10. Abrams D, Schulze-Neick I, Magee AG. Sildenafil as a selective pulmonary vasodilator in childhood primary pulmonary hypertension. Heart 2000;84:e4.
11. Karatza AA, Bush A, Magee AG. Safety and efficacy of sildenafil therapy in children with pulmonary hypertension. Int J Cardiol 2005;100:267-73.
12. Barst RJ, Ivy DD, Gaitan G, Szatmari A, Rudzinski A, Garcia AE, et al. A randomized, double-blind, placebo-controlled, dose-ranging study of oral sildenafil citrate in treatment-naive children with pulmonary arterial hypertension. Circulation 2012;25:324-34.
13. Barst R, Layton G, Konourina I, Richardson H, Beghetti M, Ivy D. STARTS-2: long-term survival with oral sildenafil monotherapy in treatment-naive patients with pediatric pulmonary arterial hypertension. Circulation 2014;192:1914-23.
14. U.S. Food and Drug Administration. Revatio (sildenafil): drug safety communication—recommendation against use in children. Silver Spring (MD): U.S. Food and Drug Administration. https://www.fda.gov/Drugs/DrugSafety/ucm317123.htm. Accessed February 20, 2013. Updated 2012 Aug 30.
15. European Medicines Agency. Assessment report for Revatio. International non-proprietary name: sildenafil. Procedure No. EMEA/H/C/000638/II/0028. London (UK): European Medicines Agency; 2011 http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/000638/WC500107804.pdfGoogleScholar. Accessed February 20, 2013.
16. Abman SH, Kinsella JP, Rosenzweig EB, Krishnan U, Kulik T, Mullen M, et al. Implications of the U.S. Food and Drug Administration warning against the use of sildenafil for the treatment of pediatric pulmonary hypertension. Am J Respir Crit Care Med 2013;187:572-5.
17. Melnick L, Barst RJ, Rowan CA, Kerstein D, Rosenzweig EB. Effectiveness of transition from intravenous epoprostenol to oral/inhaled targeted pulmonary arterial hypertension therapy in pediatric idiopathic and familial pulmonary arterial hypertension. Am J Cardiol 2010;105:1485-9.
18. Spaggiari E, Stirnemann JJ, Sonigo P, Khen-Dunlop N, De Saint Blanquat L, Ville Y. Prenatal prediction of pulmonary arterial hypertension in congenital diaphragmatic hernia. Ultrasound Obstet Gynecol 2015;45:572-7.
19. Iocono JA, Cilley RE, Mauger DT, Krummel TM, Dillon PW. Postnatal pulmonary hypertension after repair of congenital diaphragmatic hernia: predicting risk and outcome. J Pediatr Surg 1999;34:349-53.
20. Mourani PM, Sontag MK, Ivy DD, Abman SH. Effects of long-term sildenafil treatment for pulmonary hypertension in infants with chronic lung disease. J Pediatr 2009;154:379-84.
21. Noori S, Friedlich P, Wong P, Garingo A, Seri I. Cardiovascular effects of sildenafil in neonates and infants with congenital diaphragmatic hernia and pulmonary hypertension. Neonatology 2007;91:92-100.
22. Benza RL, Miller DP, Gomberg-Maitland M, Frantz RP, Foreman AJ, Coffey CS, et al. Predicting survival in pulmonary arterial hypertension: insights from the Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management (REVEAL). Circulation 2010;122:164-72.
23. Beghetti M, Rudzinski A, Zhang M. Efficacy and safety of oral sildenafil in children with Down syndrome and pulmonary hypertension. BMC Cardiovasc Disord 2017;17:177.
24. Al-Ghanem G, Shah P, Thomas S, Banfield L, El Helou S, Fusch C. Bronchopulmonary dysplasia and pulmonary hypertension: a meta-analysis. J Perinatol 2017;37:414-9.
25. Khemani E, McElhinney D, Rhein L, Andrade O, Lacro RV, Thomas KC. Pulmonary artery hypertension in formerly premature infants with bronchopulmonary dysplasia: clinical features and outcomes in the surfactant era. Pediatrics 2007;120:1260-9.
26. Dillon PW, Cilley RE, Mauger D, Zachary C, Meier A. The relationship of pulmonary artery pressure and survival in congenital diaphragmatic hernia. J Pediatr Surg 2004;39:307-12.
27. Wynn J, Krishnan U, Aspelund G, Zhang Y, Duoong J, Stolar CJ, et al. Outcomes of congenital diaphragmatic hernia in the modern era of management. J Pediatr 2013;163:114-9.

Table IV. Type of CHD and timing of cardiac repair relative to sildenafil initiation

Types of CHD	No. of patients	Patients repaired before sildenafil initiation	Patients repaired after sildenafil initiation	Patients unrepaired at last follow-up
Atrioventricular canal	22	15	5	2
Ventricular septal defect	7	2	2	3
Patent ductus arteriosus	6	1	2	3
TOF/PA/MAPCAs	5	5	0	0
Truncus arteriosus	3	3	0	0
Aortic coarctation	3	3	0	0
D-TGA	2	2	0	0
Mitral stenosis	2	2	0	0
AP window	1	0	0	1
IAA/ventricular septal defect	1	1	0	0
Pulmonary vein stenosis	1	1	0	0

AP, aortopulmonary; *D-TGA*, D-transposition of the great arteries; *IAA*, interrupted aortic arch; *TOF/PA/MAPCAs*, tetralogy of Fallot with pulmonary atresia and major aortopulmonary collaterals.

Table V. Type of PH and outcome in patients with trisomy 21

		Outcome at last follow-up			
Types of PH	Total no. of patients	On sildenafil or tadalafil	Stopped sildenafil owing to PH improvement	Lost to follow-up	Died
IPAH	4 (13.8)	2 (50)	0 (0)	1 (25)	1 (25)
PH-BPD	7 (24.1)	2 (28.6)	2 (28.6)	0 (0)	3 (42.9)
PAH-CHD	18 (62.1)	10 (55.5)	5 (27.8)	2 (11.1)	1 (5.5)
Overall	29 (100)	14 (48.3)	7 (24.1)	3 (10.3)	5 (17.2)

PAH-CHD, PAH associated with CHD.
Values are n (%).