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Safety of Sildenafil in Infants*

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Abstract

Objective—In view of the recent U.S. Food and Drug Administration's warning against the use of sildenafil in pediatric patients, we aimed to provide an updated overview of the dosing and safety of sildenafil in infants and to explore the relevance of the present safety concerns to the infant population.

Data Source—The National Library of Medicine PubMed and Cochrane Database of Systematic Reviews were searched using the following terms: Sildenafil AND (infant OR infants OR newborn OR newborns OR child OR children OR childhood OR pediatric OR pediatrics OR paediatric OR paediatrics).

Study Selection—Studies presenting original clinical data regarding the dosing, use, or safety of sildenafil in infants with pulmonary hypertension would be included.

Data Extraction—Of the 49 included studies, case reports and case series were the most common type of publications ($n = 25$). The identified trials included 625 children, with more than 140 infants. Persistent pulmonary hypertension of the newborn and pulmonary hypertension associated with other conditions were the most common underlying diagnoses.

Conclusion—There is currently no evidence of serious adverse event in infants exposed to sildenafil. Present safety concerns regarding the use of sildenafil in pediatric patients should be further explored before being applied to infant population. Sildenafil remains a valuable option for the treatment of pulmonary hypertension in young infants. Prospective studies should be designed in such a way that they include a safety assessment to evaluate potential adverse outcomes of sildenafil therapy in this population.

Keywords

adverse events; infants; off-label; pulmonary hypertension; safety; sildenafil

Sildenafil citrate is a selective and potent inhibitor of phosphodiesterase type 5 (PDE5). PDE5 is a cyclic guanosine monophosphate (cGMP) specific degrading enzyme that is highly present in the corpus cavernosum, vascular, and visceral smooth muscles. The inhibitory effect of sildenafil on PDE5 results in an increased level of cGMP and enhances nitric oxide (NO)-mediated vasodilation. The selective vasodilatory effect of sildenafil is a key feature in its evolving role in the treatment of pulmonary hypertension (PH) (1–3).

In 1998, the U.S. Food and Drug Administration (FDA) approved the use of sildenafil for the treatment of erectile dysfunction (1). An increased understanding of the physiology of PH and mechanism of action of sildenafil resulted in its approval for the treatment of PH in adults in 2005 (4). During the past decade, there has been a growing interest in the off-label use of sildenafil for the treatment of PH of various etiologies in infants. In 2012, however, the FDA issued a warning against the use of sildenafil in pediatric patients. This warning was based on the results of a clinical trial showing a higher risk of mortality after 2 years of treatment among children of 1–17 years randomized to high-dose sildenafil versus low-dose sildenafil. The majority of deaths were reported among children with idiopathic or hereditary PH with above median baseline values for features of disease severity (5).

Considering the new safety warning regarding the use of sildenafil in pediatric patients, we summarized the currently available evidence concerning the dosing and safety of the use of sildenafil in infants and we explored the relevancy of the recent FDA's warning to infant population.

METHODS

The National Library of Medicine PubMed and Cochrane Database of Systematic Reviews were searched systematically for articles published from January 1, 1999, to April 30, 2013, to identify publications concerning the use of oral or IV sildenafil for the treatment of PH in infants. Publications were initially screened using the following search terminologies: sildenafil AND (infant OR infants OR newborn OR newborns OR child OR children OR childhood OR pediatric OR pediatrics OR paediatric OR paediatrics). Identified studies were reviewed so that only those presenting original clinical data regarding the dosing, use, or safety of sildenafil in infants with PH of various etiologies would be included.

RESULTS

The literature search identified 367 studies, from which 49 met the review inclusion criteria. Case reports and case series were the most common type of publications ($n = 25$), followed by retrospective ($n = 10$), prospective ($n = 9$), and randomized controlled trials ($n = 5$). Eligible studies presented 625 children, which included more than 140 infants. Persistent PH of the newborn (PPHN) and PH associated with congenital heart defect, meconium

aspiration syndrome, congenital diaphragmatic hernia, or bronchopulmonary dysplasia were the most common underlying diagnoses.

PHARMACOKINETICS AND PHARMACODYNAMICS

Adults and Children

The majority of pharmacokinetics (PK) data of sildenafil in adults and children are from oral dosing of sildenafil. After oral administration in adults, there is a rapid absorption with a maximum plasma concentration reached after 0.5–2.5 hours (6–9). The bioavailability of sildenafil is 38–41% in the fasted state (7, 8, 10, 12). Sildenafil is highly metabolized in the liver via CYP3A4 (79%) and CYP2C9 (20%) into its major circulating metabolite, UK-103 320, which possesses 50% of the potency of its parent drug (10, 12, 13). Sildenafil is known to be a relatively short-acting drug with a half-life of approximately 2–4 hours for both IV and oral preparations (7, 8). Patients with severe renal insufficiency (creatinine clearance < 30 mL/min) or hepatic impairment have a significantly decreased sildenafil clearance (13). Patients with PH have lower clearance and higher bioavailability as compared with healthy volunteers. Investigating the effect of age, race, gender, and renal or hepatic function, in these patients, did not show any significant impact on the metabolism of oral sildenafil (4). A 10-mg sildenafil IV bolus, in adult patients with PH, provides an exposure similar to that seen after a 20-mg oral tablet (14).

The PK characteristics of oral sildenafil in children were determined in a 16-week dose ranging study of treatment-naïve children of 1–17 years with PH (5, 11). After adjusting for body weight, the PK of sildenafil was found to be similar to adults. Comparison of steady-state concentrations in children with adults showed an overall decreased exposure in children, so that the 20–40 mg tid dosing of sildenafil in children provides an exposure comparable to 20 mg tid dosing in adults. This has been related to the relatively high oral plasma clearance in children older than 1 year (5, 11).

The widely accepted target plasma concentration for sildenafil is approximately 50–400 ng/mL. This range is derived from in vitro studies, showing 53–90% inhibition of PDE5 activity with a plasma concentration of 47–373 ng/mL (3, 5, 15). Despite this high selectivity, sildenafil also inhibits PDE1, PDE6, and PDE11 with a ratio of 1/41, 1/7, and 1/203, respectively (10). Animal and human studies have shown that PDE1 is mainly localized in the brain, kidney, liver, pancreas, and thyroid gland. PDE6 receptors are present in rod cells and cone cells of the retina, and PDE11 expression is high in the prostate and modest in the testis, skeletal muscle, and several other tissues (2, 16). This relative selectivity may result in potential side effects during treatment with PDE5 inhibitors (10).

Infants

The first PK study of sildenafil in infants was an open-label dose-escalation trial in 36 term and late preterm neonates with PH who received IV sildenafil during the first 10 days of life (9). Sildenafil was administered in eight step-up treatment groups. The investigators observed a higher volume of distribution and longer serum elimination half-life (48–56 hr) of sildenafil in the studied infants compared to adults. There was also a fourfold increase, to the level observed in adults, in the clearance of sildenafil within the first week of life. This

finding was linked to rapid developmental changes of hepatic CYP enzymes activity (13, 17, 18). Administration of an IV bolus dose of approximately 0.4 mg/kg over 3 hours followed by a maintenance dose of 1.5 mg/kg/hr provided sildenafil plasma concentration of 70–400 ng/mL (9). The use of an initial loading dose was deemed necessary, in this trial, to achieve and maintain the target concentration within a reasonable time, but it was found to cause hypotension if given too rapidly. An additional study investigated the metabolism of sildenafil, after oral administration of 1.3–10 mg/kg/24 hr, in 11 post-extracorporeal cardiopulmonary infants. The mean observed sildenafil plasma concentration was 300 and 100 ng/mL at 1 and 6 hours post dose with very high intra- and interpatient variability. It was suggested that the dose regimen of 0.5–2.0 mg/kg four times a day would provide an exposure comparable to the recommended adult dose of 20 mg four times a day (19). The accepted target sildenafil plasma concentration in infants is based on the available data from in vitro studies, indicating that the plasma concentrations of 47, 140, and 373 ng/mL, at steady state, produce 53%, 77%, and 90% inhibition of PDE5 activity, respectively (3, 15). There is currently an ongoing trial on the PK of sildenafil in premature infants, which should increase the knowledge about the metabolism of this drug in infant population (20).

SAFETY AND TOLERABILITY

Adult and Children

Sildenafil is a generally well-tolerated drug in adults. The most commonly reported adverse events (AE) at the recommended 20 mg tid oral dose are epistaxis, headache, dyspepsia, and flushing with more than or equal to 6% higher prevalence among patients receiving sildenafil therapy. Among the reported serious AEs (SAEs) in patients on standard dose oral therapy are the report of cardiovascular and cerebrovascular events, retinal hemorrhage, and sudden decrease or loss of hearing in temporal association with the use of this drug (4, 21). As the recommended IV and oral sildenafil dosing provides equivalent exposure, this safety data can also be applied to the IV formulation (4).

Until the recent FDA's warning advising against the use of sildenafil in children, sildenafil therapy was believed to be associated with mild-to-moderate AEs with high tolerability in pediatric patients (22). In a 16-week randomized double-blind placebo-controlled trial of The Sildenafil in Treatment-Naïve Children, Aged 1–17 Years, With Pulmonary Arterial Hypertension (STARTS-1) study, the most frequently reported AEs were headache, pyrexia, upper respiratory tract infections, vomiting, and diarrhea (5). SAEs were reported in 11 patients, two of which were considered to be treatment related (stridor and ventricular arrhythmias). However, only two patients needed to discontinue the treatment because of experiencing AEs (weight loss and stridor).

Concern was raised after the completion of the extension phase of the study (STARTS-2). Survival was significantly lower, after 2 years of treatment, among patients randomized to a high dose of sildenafil as compared with patients randomized to medium or low dose. After completion of 3–7 years of treatment, 29 deaths on sildenafil therapy and six deaths during follow-up were reported. Patients randomized to low-, medium-, and high-dose therapy experienced 9% (5 of 55), 14% (10 of 74), and 20% (20 of 100) rate of mortality, respectively. Seventy-four percent of deaths were reported in the patients with idiopathic or

hereditary PH, although pulmonary arterial hypertension associated with other conditions, such as congenital heart defect, represented 67% of the study population. Despite the fact that most deaths were investigator assessed as being associated with disease progression, and none were considered to be causally related to the study treatment, this finding resulted in an update in FDA's sildenafil labeling policy and an advice against any use of the drug in the pediatric population.

Infants

The use of sildenafil in infants has increased substantially in the past 10 years (23). To date, there are about 40 case reports and prospective or retrospective studies on the use of sildenafil, which include newborn or young infants with PH of various etiologies (Table 1). Of these reports, only the open-label dose-escalation trial of IV sildenafil in infants with PH was designed to record clinical and laboratory AEs during therapy with sildenafil (24). Hypotension and development of patent ductus arteriosus were the only treatment-related AEs reported. The small sample size and short duration of sildenafil therapy were the major limiting factors of this study in the assessment of safety. The Cochrane collaboration in 2011 performed a review of the three randomized controlled trials available on the use of sildenafil for PH of infants (25–28). All three studies reported improvement in oxygenation, no decline in the blood pressure, and a significant reduction in mortality in the sildenafil-treated infants. Only one study reported data on the neurodevelopmental outcome and found normal MRI, evoked potentials, electroencephalography (EEG), and neurological examination in all infants in the sildenafil therapy group (27). Considering the evolving physiology of an infant and the AE profile of sildenafil in adults and older children, we have reviewed the potential AEs that may pose an increased risk for SAE in the infant population.

NERVOUS SYSTEM DISORDERS

Although sildenafil has been found to increase the level of cGMP and cerebral blood flow (CBF) in the brain of healthy rats, this effect has not been detected in the brain of healthy human volunteers (29–32). A prospective study on the effect of sildenafil on cerebral oxygenation of infants on cardiopulmonary bypass, post corrective cardiac surgery, suggested that sildenafil might increase CBF (33). The pilot randomized blinded study of oral sildenafil in infants with PPHN found normal MRI, evoked potentials, EEG, and neurological examination in all infants exposed to sildenafil (27). There are currently a number of ongoing trials examining the neurodevelopmental outcome of infants exposed to sildenafil. The results of these trials should add to the safety information of sildenafil in the infant population (34, 35).

EYE DISORDERS

Although sildenafil is considered highly selective for PDE5 inhibitor, it is also a potent inhibitor of PDE6 receptors (12). PDE6 is the primary regulator of cytoplasmic cGMP concentration in rod and cone photoreceptors, and its precise regulation is essential for normal operation of the visual transduction cascade (16). This knowledge has raised a valid and physiologically relevant concern regarding the effect of sildenafil on the development of the immature retina of premature infants and the progression of retinopathy of prematurity

(ROP). Studies on the effect of sildenafil on ROP, however, have not found any significant increase in the risk of ROP. The currently available evidence is limited to three reports: a report of a case of an extremely premature newborn who developed severe ROP at 34 weeks' gestational age while receiving sildenafil; a prospective observational study of term and late preterm infants on more than 2 weeks of sildenafil; and a retrospective case-control study of 17 infants younger than 30 weeks gestation who had received sildenafil during hospitalization (38, 39). In the two latter studies, the investigators did not observe any ocular complications that could be directly linked to the use of sildenafil. These results, although encouraging, are in need of further confirmation with appropriately designed studies with an adequate sample size.

CARDIOVASCULAR DISORDERS

The data on cardiovascular effects of sildenafil in infants are contradictory. A double-blinded randomized controlled trial of 24 children and infants undergoing cardiac surgery suggested a negative impact of preoperative sildenafil therapy on ventricular function and oxygenation (41). The authors postulated that the elevated cGMP might decrease the myocardial calcium sensitivity and blunt the contractile response to adrenergic stimulation. It is important to note that the mean age of patients randomized to sildenafil therapy was 0.62 years and only the preoperative effect of sildenafil was assessed in this study. The change in the mean arterial blood pressure during sildenafil use in neonates with meconium aspiration syndrome or sepsis was assessed in a retrospective study. No significant decrease in mean blood pressure or increase in vasopressor/inotrope requirement occurred (42). Furthermore, none of the three randomized controlled trials on the use of sildenafil for PH of infants reported a decline in the blood pressure (25–28). The vasodilatory effect of sildenafil has also not shown to cause significant hypotension in adults or older children (4, 40). There is no doubt that presence of persistent patency between systemic and pulmonary circulation, the structure and physiology of premature myocardium, and its high dependency on adrenergic responses put the newborn infant at risk for the development of hemodynamic instability (43). To date, evidence of hypotension as AE of oral or IV sildenafil therapy is limited to sporadic reports of mild-to-moderate hypotension with no report of severe hemodynamic instability related to sildenafil therapy. Systemic administration of sildenafil especially together with inhaled NO has been found to generate vasodilatory effect through the pulmonary vasculature and results in a dose-dependent increase in ventilation-perfusion mismatch (44, 45). This effect, however, has not been consistent through animal or human studies and needs to be further explored in well-designed safety assessment trials.

BLEEDING DISORDERS

The fragility of the germinal matrix blood vessels along with the lack of autoregulatory capacity of the cerebral vessels of the brain of sick infant increases the risk of bleeding events in this population. Although the concurrent use of oral sildenafil with other anticoagulant agents can enhance the potential antiaggregatory effect of this drug, its isolated use has not shown any direct effect on the aggregation of human platelets (44, 46, 47). Case reports of variable hemorrhagic events during oral sildenafil therapy have been

loosely linking these events to the use of sildenafil (30, 36, 37, 48, 49). This AE, however, has not been observed to date.

MORTALITY

The effect of sildenafil on mortality in infants with PH is unknown. Although the recent FDA warning has brought major concern regarding sildenafil therapy in infants, the applicability of the result of the STARTS-2 trial to infant population is uncertain. Beside the clear difference in the age characteristics, the etiology, pathophysiology, and outcome of PH in most newborns and infants differ from those in children. In the majority of infants, PH is either secondary to PPHN or is associated pulmonary arterial hypertension (APAH) with conditions such as congenital heart disease or chronic lung disease. In the STARTS-2 trial, although APAH represented 67% of the study population, 74% of deaths were reported in the patients with idiopathic or hereditary PH, which are uncommon causes of PH in infants. Furthermore, of patients who died, the majority had above median baseline values for features of disease severity with 40% being classified as functional class II or IV, making the investigators not to consider any of the deaths to be causally related to the study treatment.

From all the available evidence in infants, the three randomized controlled trials on the use of oral and IV sildenafil for PH of infants showed a reduction in mortality in ones randomized to sildenafil (26–28). The available studies on long-term sildenafil therapy in infants and accessible data on mortality reported a mortality rate of 5–30% among the treated infants after a median of 119–343 days of treatment. None of the deaths was considered to be causally related to the sildenafil therapy in any of the studies (28, 50, 64). Out of all other existing evidence, 13 deaths have been reported among more than 100 infants who received sildenafil treatment for PH of various etiologies (Table 1). Therefore, to date, the data do not indicate an increased risk of mortality secondary to sildenafil therapy among infant population.

Most of the current ongoing trials on short- and long-term use of sildenafil in infants with PH have outlined mortality assessment as their primary or secondary outcome. These data, when available, will further clarify if the current worry around the use of sildenafil in pediatric patients can also be applied to infants.

CONCLUSION

Infants present a unique challenge when it comes to efficient and safe use of medications. Although the maturational physiology of infants makes them prone to safety concerns, the clear limit in available therapeutic options can also make this population prone to lack of beneficence practice (52). The current available evidence on PK, dosing, and safety of sildenafil has so far presented this drug as a valuable option for the treatment of PH in young infants. Any prospective study of sildenafil therapy should design a safety assessment to evaluate potential adverse outcomes in this underserved population.

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TABLE 1

Use of Sildenafil in Infants, Current Evidence

Study Design	n	Age	Dose (mg/kg/dose)	Duration	Inhaled Nitric Oxide	Indication	All-Cause Mortality (%)	Reported Adverse Event
Newborns								
RCT (27)	13	3–72 hr	1–2, oral	8 doses	No	PPHN	14	None
RCT (26)	24	Term infants	2 q6h, oral	72 hr	No	PPHN	0	None
PT (24)	36	34 ± 17 wk	1 → 0.25, IV (bolus and infusion)	2–7 d	Yes	PPHN	3	Labile BP, patent ductus arteriosus
RCT (28)	51	Term infants	3 q6h, oral	2–16 doses	No	PPHN	6	None
RT (42)	17	34–42 wk	3–5.7 ^a	12 ± 11 d	Yes	PH-meconium aspiration syndrome, PH-sepsis	18	None
Children								
PT (53)	16	3 d to 18 yr	0.25–0.5 q6h, Oral	SD, 12 wk	Yes	CDH, pulmonary vein stenosis, primary pulmonary hypertension, secondary pulmonary hypertension	NS	None
PT (45)	24	0.1–15 yr	0.025–0.66, IV	30 min	Yes	PH-CHD	NS	↑ Intrapulmonary shunt
RCT (54)	30	0–13 yr	0.4, oral	SD	Yes	PH	0	None
PT (33)	13	2–20 mo	0.025–0.25, IV	30 min	No	PH-CHD	NS	↑ Cerebral blood flow
PT (55)	10	4–6 mo	0.5–2.0 q4h	7–14 d	Yes	PH-CHD	0	None
PT (56)	15	0.9–17 yr	0.5, oral	SD	No	PH-CHD	NS	↓ BP
RT (57)	7	3 d to 21 mo	0.22–0.47 q6h, oral	28 d	Yes	PH-CHD	0	None
RT (50)	25	14–673 d	0.5–2 q6–8h	28–950 d	No	Chronic lung disease	20	Frequent erection, intestinal pneumatosis
RT (58)	22	< 1 yr	0.2–1 q4–6h	4–6 d	No	CDH	31	None
PT (51)	25	10–1,790 d	0.25–1 q6h, oral	9–1,002 d	Yes	PH	36	None
PT (19)	11	2–121 d	0.5–2.5, oral	54–528 hr	Yes	PPHN PH-CHD	18	None
RT (59)	45	6 d to 17 yr	0.6–0.12 q4h, oral	1–291 d	Yes	PH-CHD	10	↓ BP
RT (60)	100	0–10 yr	0.5–2	5–7 d	Yes	PH-CHD	NS	Facial flushing
PT (39)	22	14–280 d	400–1,000 ^b	2–36 wk	NS	PH	NS	None
RCT (41)	24	3–27 mo	0.5 q6h, oral	4 doses	No	PH-CHD	0	↓ Biventricular function
RT (61)	38	5–33 mo	0.35 q4h	1–2 wk	No	PH-CHD	NS	None
RCT (62)	17	3 mo to 14 yr	NS	24–72 hr	No	PH-CHD	0	None
RT (63)	21	82–307 d	0.25–1.5 q6h, oral	2 to > 30 d	No	PH-bronchopulmonary dysplasia	19	None

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Study Design	n	Age	Dose (mg/kg/dose)	Duration	Inhaled Nitric Oxide	Indication	All-Cause Mortality (%)	Reported Adverse Event
RT (64)	19	32–132 d	2–3 q3–6h, oral	105–671 d	No	PH-CDH	5	None

RCT = randomized controlled trial, PPHN = persistent pulmonary hypertension of the newborn, PT = prospective trial, BP = blood pressure, RT = retrospective trial, PH = pulmonary hypertension, CDH = congenital diaphragmatic hernia, SD = single dose, CHD = congenital heart disease, NS = not specified.

^aUnit, mg/kg/d.

^bAverage cumulative dose over 2–36 wk.