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Original Article

Association between oral sildenafil dosing, predicted exposure, and systemic hypotension in hospitalised infants

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Abstract *Background:* The relationship between sildenafil dosing, exposure, and systemic hypotension in infants is incompletely understood. *Objectives:* The aim of this study was to characterise the relationship between predicted sildenafil exposure and hypotension in hospitalised infants. *Methods:* We extracted information on sildenafil dosing and clinical characteristics from electronic health records of 348 neonatal ICUs from 1997 to 2013, and we predicted drug exposure using a population pharmacokinetic model. *Results:* We identified 232 infants receiving sildenafil at a median dose of 3.2 mg/kg/day (2.0, 6.0). The median steady-state area under the concentration–time curve over 24 hours ($AUC_{24,SS}$) and maximum concentration of sildenafil ($C_{max,SS,SIL}$) were 712 ng × hour/ml (401, 1561) and 129 ng/ml (69, 293), respectively. Systemic hypotension occurred in 9% of the cohort. In multivariable analysis, neither dosing nor exposure were associated with systemic hypotension: odds ratio = 0.96 (95% confidence interval: 0.81, 1.14) for sildenafil dose; 0.87 (0.59, 1.28) for $AUC_{24,SS}$; 1.19 (0.78, 1.82) for $C_{max,SS,SIL}$. *Conclusions:* We found no association between sildenafil dosing or exposure with systemic hypotension. Continued assessment of sildenafil's safety profile in infants is warranted.

Keywords: Dosing; exposure; systemic hypotension; infant; sildenafil

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Sildenafil is a potent type-5 phosphodiesterase inhibitor increasingly used off-label in infants.[1,2] Despite this increasing use, the safety profile of sildenafil in infants remains poorly defined. Anecdotally reported adverse events associated with sildenafil therapy include bleeding, ocular anomalies, changes in cerebral blood flow, and systemic hypotension.[3,4]

Systemic hypotension is particularly significant, given the haemodynamic instability frequently present in infants receiving sildenafil.[5–7] Findings from previous studies evaluating sildenafil's safety in infants are contradictory.[5,7–10] These findings may be due to differences in dosing and drug exposure, as evidenced by the wide range of observed plasma concentrations of sildenafil in previous pharmacokinetic studies.[11,12] Because of this variability, a complete investigation of the cardiovascular safety profile of sildenafil in infants will require evaluation of drug dosing and exposure.

Safety studies in infants are challenging, and evaluation of drug exposure adds to the complexity.[13] Novel strategies are urgently needed to overcome limitations of traditional studies, including large sample sizes and the use of blood samples to measure drug concentrations.[14] As a potential solution, we predicted individual sildenafil exposures using a published population pharmacokinetic model and combined them with electronic health record data from a large cohort of hospitalised infants. We hypothesised that increasing exposure to sildenafil

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will be associated with clinically significant systemic hypotension.

Materials and methods

Data source and patient population

We used an electronic health record-derived database populated using admission notes, discharge summaries, and progress notes written by neonatologists caring for infants admitted to 1 of 348 Pediatrix Medical Group neonatal ICUs in North America from 1997 to 2013. Clinical data routinely collected during hospitalisation are captured in a data warehouse maintained by the Pediatrix Medical Group for quality-improvement and research purposes.[15] We included all infants of 24–41 weeks' gestational age at birth who received enteral sildenafil for at least 1 day during their hospitalisation, in order to match the demographics of infants included in a published population pharmacokinetic model (Fig 1).[11] We excluded intravenous doses of sildenafil, and infants with incomplete dosing records or missing information on survival status at discharge. This study was approved by the Duke University Institutional Review Board without the need for written informed consent.

Definitions

The unit of observation for analysis was a course of sildenafil therapy. A course was defined as consecutive days of therapy with sildenafil at the same dose, for the same dosing interval, and through the same route of administration. Any change or interruption in dosing for one or more days constituted a new course. We extracted total daily sildenafil dose in mg/kg/day and also extracted the dosing interval. We defined "small for gestational age" as previously described.[16] We identified surrogates for severity of illness, including daily use of mechanical ventilation, any inotrope such as amrinone, dobutamine, dopamine, epinephrine, milrinone, norepinephrine, or phenylephrine, any other pulmonary vasodilator such as inhaled nitric oxide, bosentan, or epoprostenol, and the presence of a positive blood culture with organisms not typically considered contaminants. We defined exposure to cytochrome P450 3A4 (CYP3A4) inducers as concomitant exposure to either rifampin or bosentan. We defined exposure to CYP3A4 inhibitors as concomitant exposure to either fluconazole, ketoconazole, voriconazole, clarithromycin, or erythromycin.

The primary outcome was systemic hypotension, diagnosed during a sildenafil treatment course. We defined systemic hypotension as either new exposure to a vasopressor, namely dobutamine, dopamine, epinephrine, norepinephrine, or phenylephrine, or as discontinuation of an antihypertensive, namely angiotensin-converting enzyme inhibitor, β-blocker, calcium-channel blocker, tolazoline, phentolamine, nitroprusside, nitroglycerin, hydralazine, or clonidine. We performed a sensitivity analysis defining systemic hypotension as new exposure only to vasopressors.

Exposure predictions

To simulate sildenafil exposure, we used a published population pharmacokinetic model for infants, consisting of a one-compartment structural model for sildenafil and its primary active metabolite desmethylsildenafil with combined additive and proportional residual errors.[11] Using non-linear mixed-effects modelling methods, this model quantifies the different sources of variability in the dose–concentration relationship, including within- and between-subject variability and residual variability, and seeks to identify the measurable pathophysiological factors responsible for the differences observed between subjects. When dose–concentration relationships vary between subjects, as is common in critically ill infants,

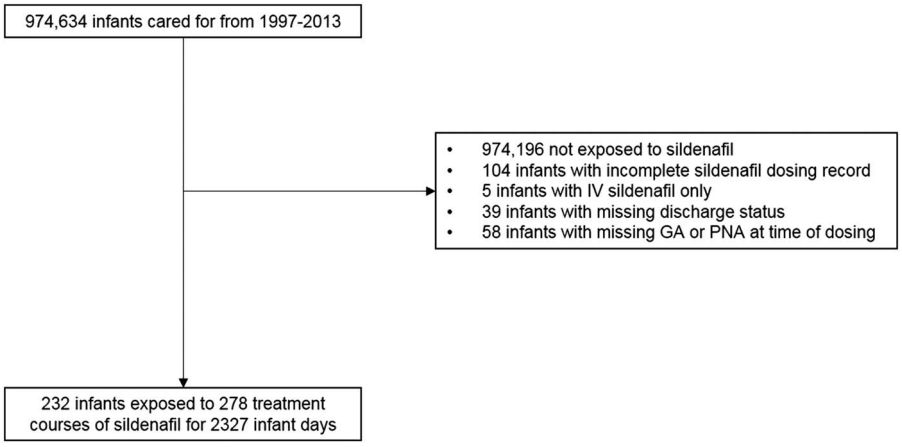

Figure 1.
Study flow chart. GA = gestational age; PNA = postnatal age.

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the population pharmacokinetic model can predict concentrations of sildenafil based on dose received and specific clinical characteristics, rather than simply having to assume that concentrations achieved depend only on the dose administered. The final model included weight (WT) as an allometrically scaled covariate for clearance (CL) and volume of distribution (V) for both the parent drug and the metabolite: sildenafil $CL(L/hour/70\,kg) = 62 \times \left(\frac{WT}{70}\right)^{0.75}$; sildenafil $V(L/70\,kg) = 596 \times (WT/70)$; desmethylsildenafil $CL(L/hour/70\,kg) = 83 \times \left(\frac{WT}{70}\right)^{0.75}$; desmethylsildenafil $V(L/70\,kg) = 245 \times (WT/70)$. The first-order absorption rate constant was fixed at 2.4/hour. Inter-individual variability was included for sildenafil clearance and volume of distribution, and for desmethylsildenafil clearance, with separate residual variabilities for the parent drug and the metabolite. We used the infant's daily weight and dosing information from the electronic health record to simulate daily sildenafil and desmethylsildenafil exposure as maximum concentration at steady-state ($C_{max,SS,SIL}$ and $C_{max,SS,DMS}$) and to simulate the area under the concentration versus time curve from 0 to 24 hours at steady-state using NONMEM version 7.3 (Icon Development Solutions, Ellicott City, Maryland, United States of America) (Supplementary Table S1).

To represent total pharmacological exposure to sildenafil, the area under the sildenafil concentration–time curve from 0 to 24 hours at steady-state ($AUC_{24,SS,SIL}$) was added to half the area under the desmethylsildenafil concentration versus time curve from 0 to 24 hours at steady-state ($AUC_{24,SS,DMS}$) $\left(AUC_{24,SS,SIL+DMS} = AUC_{24,SS,SIL} + 0.5 \times AUC_{24,SS,DMS}\right)$, as was done in the original model publication.[11] Because of an insufficient number of infants exposed to fluconazole, we did not include it as a covariate effect; instead, we included concomitant exposure to any CYP3A4 inducer or inhibitor in the multivariable regression.

Statistical analysis

We used summary statistics including medians (interquartile ranges) and counts (percentages) to describe continuous and categorical variables. We compared the distribution of variables using the Wilcoxon rank-sum, χ^2, and Fisher's exact tests as appropriate. We used Spearman's rank correlation to describe relationships between sildenafil dose and $C_{max,SS,SIL}$ and $AUC_{24,SS,SIL+DMS}$. We used multivariable logistic regression with random effects for the neonatal ICU to evaluate associations between systemic hypotension and sildenafil dosing, $C_{max,SS,SIL}$, and $AUC_{24,SS,SIL+DMS}$, which were centred and scaled before inclusion in the regression analysis: for example, $C_{max,SS,SIL,center-scale} = (C_{max,SS,SIL} - \text{mean}(C_{max,SS,SIL})/\text{standard deviation}(C_{max,SS,SIL})$. We fit a total of three separate models for total daily sildenafil dose, $AUC_{24,SS,SIL+DMS}$, and $C_{max,SS,SIL}$, all including the following as covariates: postnatal age in days, weight, gestational age, small for gestational age, mechanical ventilation, inotropes, other pulmonary vasodilators, and exposure to CYP3A4 inducers or inhibitors. Because an association between systemic hypotension and younger postnatal age became apparent in our analysis, and because younger infants treated with sildenafil may be more likely to suffer from persistent pulmonary hypertension of the newborn, we conducted a second sensitivity analysis limited to infants with this diagnosis. We reported adjusted odds ratios and 95% confidence intervals for systemic hypotension. We conducted statistical analyses using STATA SE 14.1 (College Station, Texas, United States of America), and considered p values <0.05 to be statistically significant.

Results

We identified 232 infants exposed to 278 sildenafil courses for 2327 infant-days of therapy (Table 1). The median (interquartile range) gestational age and birth weight were 27 weeks (25, 36) and 775 g (593, 2368), respectively. The median postnatal age and postmenstrual age on the 1st day of sildenafil exposure were 85 days (21, 126) and 41 weeks (38, 44), respectively. Only 20% of infants were at <37 weeks of postmenstrual age when starting sildenafil. Over half of the infants (55%) were receiving mechanical ventilation, and 30% were exposed to another pulmonary vasodilator when starting sildenafil. The most commonly used pharmacologic pulmonary vasodilator other than sildenafil was inhaled nitric oxide, administered to 30% of infants, whereas bosentan (<1%) and epoprosterenol (1%) were administered less frequently. The median daily fraction of inspired oxygen on the 1st day of sildenafil therapy was 50% (35%, 100%), and 57% of infants were on >50% fraction of inspired oxygen. The median dose of sildenafil was 1.0 mg/kg/dose (0.6, 1.7) or 3.2 mg/kg/day (2.0, 6.0). The most common dosing intervals were every 6 hours (55%) and every 8 hours (27%). The mean (5th, 95th percentile) treatment course duration was 8.5 days (1, 46). The most common diagnoses potentially associated with sildenafil were persistent pulmonary hypertension of the newborn in 195/232 (84%) infants and bronchopulmonary dysplasia in 179/232 (77%) infants. Other diagnoses potentially associated with sildenafil use included congenital diaphragmatic hernia (24/232, 10%), pulmonary hypoplasia (20/232, 9%), and meconium aspiration syndrome (10/232, 4%).

Systemic hypotension occurred in 10% (24/232) of infants and 9% (25/278) of therapy courses. Of the 24

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Table 1. Demographics.

	Infants with hypotension	
	Yes (n = 24)	No (n = 208)
Gestational age at birth (weeks)		
⩽25	6 (25%)	79 (38%)
26–28	3 (13%)	46 (22%)
29–32	3 (13%)	22 (11%)
33–36	4 (17%)	12 (6%)
⩾37	8 (33%)	49 (24%)
Birth weight (g)		
<1000	8 (33%)	127 (61%)
1000–1499	3 (13%)	14 (8%)
1500–2499	2 (8%)	25 (12%)
2500–3499	8 (33%)	32 (15%)
⩾3500	3 (13%)	10 (5%)
Small for gestational age	2 (8%)	70 (34%)
Male gender	13 (54%)	117 (56%)
Inborn status	15 (63%)	163 (78%)
C-section	15 (63%)	149 (73%)
5-minute Apgar		
0–3	2 (9%)	17 (8%)
4–6	8 (36%)	50 (25%)
7–10	12 (55%)	135 (67%)
Age at first exposure (days)		
<7	8 (33%)	11 (5%)
7–29	5 (21%)	45 (22%)
30–59	2 (8%)	28 (13%)
60–119	5 (21%)	58 (28%)
⩾120	4 (17%)	66 (32%)

infants with hypotension, 18 were started on an inotrope or had an increase in the number of inotropes, and six infants had their antihypertensive medications discontinued or the number of antihypertensive medications decreased. Of the six infants who had a decrease in antihypertensive medications, angiotensin-converting enzyme inhibitors were discontinued in three infants, calcium-channel blockers in one, β-blockers in one, and other antihypertensives in one. Infants with systemic hypotension had a higher median birth weight (2108 g [870, 3071] versus 759 g [585, 2278], p = 0.004), but the median weight on the day of first exposure did not differ (median 3094 g [2313, 3547] versus 3081 g [2418, 3768], p = 0.79). There was no significant difference in the distribution of gestational age, but infants with systemic hypotension had lower median postmenstrual ages and postnatal ages on the day of first exposure (postmenstrual age: 39 weeks [37, 42] versus 41 weeks [38, 44], p = 0.03; postnatal age: 17 days [3, 96] versus 89 days [25, 129]; p = 0.002). Hypotension was diagnosed early in the course: at a median of 0.5 days (0, 4) after the start of therapy. The median dose and total daily dose did not differ between infants with systemic hypotension and those without (1.0 mg/kg [0.5, 1.4] versus 1.0 mg/kg [0.5, 1.5], p = 0.42; and 3.0 mg/kg/day [1.8, 5.8] versus 3.3 mg/kg/day [2.0, 6.2], p = 0.37. On the 1st day of therapy, 72% of infants diagnosed with systemic hypotension were receiving mechanical ventilation, and 40% were exposed to another pulmonary vasodilator.

Table 2. Median (interquartile range) total daily dose and daily simulated exposures.

	Courses with hypotension		
	Yes (n = 25)	No (n = 253)	p
Sildenafil dose (mg/kg/day)	3.0 (1.8, 5.8)	3.3 (2.0, 6.2)	0.37
$AUC_{24,SS,SIL+DMS}$ (ng × hour/ml)*	721 (400, 1614)	711 (401, 1540)	0.84
$C_{max,SS,SIL}$ (ng/ml)	101 (53, 373)	129 (69, 287)	0.88

$C_{max,SS,SIL}$ = maximal sildenafil steady-state concentration
*$AUC_{24,SS,SIL+DMS}$ = 24-hour area under the concentration–time curve at steady-state, accounting for the contribution of the active desmethyl-sildenafil metabolite by adding 50% of this metabolite's AUC to the corresponding value for the parent drug ($AUC_{24,SS,SIL+DMS} = AUC_{24,SS,SIL} + 0.5 \times AUC_{24,SS,DMS}$)

The median predicted $AUC_{24,SS,SIL+DMS}$ and $C_{max,SS,SIL}$ were 712 ng × hour/ml (401, 1561) and 129 ng/ml (69, 293). None of the predicted exposures differed between courses with and without systemic hypotension (Table 2). As anticipated, we observed a significant positive correlation between total daily dose and $AUC_{24,SS,SIL+DMS}$ (R = 0.65, p < 0.001) and $C_{max,SS,SIL}$ (R = 0.69, p < 0.001). Concomitant administration of CYP3A4 inducers was rare (<1%), whereas CYP3A4 inhibitors were co-administered during 5% of treatment courses. The most commonly co-administered CYP3A4 inhibitor on days of sildenafil exposure was fluconazole (3%), followed by erythromycin (1%), whereas the most commonly co-administered CYP3A4 inducer was rifampin (<1%).

In multivariable analysis, the total daily sildenafil dose was not associated with systemic hypotension: odds ratio = 0.96, 95% confidence interval: 0.81, 1.14/1 SD increase in total daily dose. We also found no association between predicted sildenafil exposures and systemic hypotension (Table 3). Results were similar in a sensitivity analysis defining systemic hypotension as new exposure only to inotropes. Neither total daily dose – odds ratio = 1.34, 95% confidence interval: 0.90, 1.99/1 SD increase in total daily dose – $AUC_{24,SS,SIL+DMS}$ – odds ratio = 1.36, 95% confidence interval: 0.93, 1.97/1 SD increase in $AUC_{24,SS,SIL+DMS}$ – or $C_{max,SS,SIL}$ – odds ratio = 1.34, 95% confidence interval: 0.85, 2.10/1 SD increase in $C_{max,SS,SIL}$ – were associated with increased odds of systemic hypotension. Results were also unchanged when all three regressions were repeated in infants with persistent pulmonary hypertension of the newborn and when stratifying the study population by gestational age into term infants – that is, ⩾37 weeks

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Table 3. Adjusted odds of hypotension.

	Odds ratio** (95% confidence interval)
Sildenafil dose (mg/kg/day)	0.96 (0.81, 1.14)
$AUC_{24,SS,SIL+DMS}$ (ng × hour/ml)*	0.87 (0.59, 1.28)
$C_{max,SS,SIL}$ (ng/ml)	1.19 (0.78, 1.82)

$C_{max,SS,SIL}$ = maximal sildenafil steady-state concentration
*$AUC_{24,SS,SIL+DMS}$ = 24-hour area under the concentration–time curve at steady-state, accounting for the contribution of the active desmethyl-sildenafil metabolite by adding 50% of this metabolite's AUC to the corresponding value for the parent drug ($AUC_{24,SS,SIL+DMS} = AUC_{24,SS,SIL} + 0.5 \times AUC_{24,SS,DMS}$)
**Adjusted for postnatal age, daily weight, gestational age, small for gestational age status, exposure to inotropes, other pulmonary vasodilators, mechanical ventilation, cytochrome P450 3A4 inducers or inhibitors, and random effects for site

gestational age – versus preterm infants – that is, <37 weeks gestational age: odds ratio = 0.36 (0.18, 2.20) per 1 SD increase in total daily dose, odds ratio = 5.02 (0.59, 42.45) per 1 SD increase in $AUC_{24,SS,SIL+DMS}$, odds ratio = 7.12 (0.18, 285.88) per 1 SD increase in $C_{max,SS,SIL}$ for full-term infants, odds ratio = 1.01 (0.85, 1.21) per 1 SD increase in total daily dose, odds ratio = 1.22 (0.80, 1.85) per 1 SD increase in $AUC_{24,SS,SIL+DMS}$, odds ratio = 0.66 (0.27, 1.58) per 1 SD increase in $C_{max,SS,SIL}$ for preterm infants.

Discussion

In a large group of hospitalised infants, we found that neither dosing nor predicted sildenafil exposure were associated with systemic hypotension after adjusting for infant characteristics and surrogates of severity of illness. Although our study is retrospective, it is the largest evaluation of sildenafil safety in infants, and it is the first study to use predicted sildenafil exposure to characterise safety.[17]

Sildenafil induces vasodilation through inhibition of type-5 phosphodiesterase.[18] Because type-5 phosphodiesterase is predominantly expressed in the lungs, sildenafil is considered a selective pulmonary vasodilator.[19,20] Despite this perceived pulmonary selectivity, systemic hypotension can occur because of direct passage of sildenafil into the systemic circulation through intra- and extra-cardiac shunts, due to direct negative effects of sildenafil on the neonatal myocardium, or as a result of variable levels of type-5 phosphodiesterase expression in the lungs with the potential for off-target effects.[9,21] Treatment-related systemic hypotension was first reported in 5 of 36 (14%) infants >34 weeks gestational age exposed to escalating doses of sildenafil via intravenous infusion.[7] These findings are comparable to the 10% prevalence of hypotension found in our cohort. A total of two other prospective and one retrospective study of infants receiving enteral sildenafil failed to detect serious cardiovascular adverse events; however, they lacked the sample size necessary to identify rare adverse events and did not assess drug exposure.[5,9,22]

Systemic drug exposure mediates the relationship between dosing and its safety profile and may be variable in critically ill infants.[23,24] Early clinical studies suggested that this is the case for sildenafil. In the first open-label trial of intravenous sildenafil in infants, blood concentrations varied both between and within dose levels.[7] This variability in exposure was confirmed using population pharmacokinetic modelling. In a study of intravenous sildenafil in 36 term infants with persistent pulmonary hypertension of the newborn, sildenafil clearance increased from 0.84 L/hour for a 1-day-old infant to 2.58 L/hour at 7 days of age.[12] The authors concluded that sildenafil pharmacokinetics in infants were best characterised by a model that accounted for the relationship between clearance and postnatal age but noted that despite this age effect, interindividual variability in clearance remained high (>50%). Similar conclusions were drawn from a single-centre pharmacokinetic study of 11 infants receiving enteral sildenafil.[11] Concentrations from blood samples and calculated $AUC_{24,SS,SIL+DMS}$ varied, and interindividual variability in pharmacokinetic parameters predicted using a one-compartment model were >80% for both clearance and volume of distribution. More recently, 30 concentrations obtained from blood samples of six infants at 24–39 weeks' gestational age receiving a median (range) dose of 0.9 mg/kg (0.5–2.1) of sildenafil as per standard of care in an opportunistic pharmacokinetic study ranged from 2.6 to 434 ng/ml.[25] These findings support the notion of variability in sildenafil exposure owing to variable pharmacokinetics, and that assessments of the drug's safety require evaluation of drug exposure.

Performing a large-scale sildenafil safety study with concentration measurements from blood samples in infants would be challenging. Fortunately, published pharmacokinetic models allowed us to predict drug exposure using infant characteristics and dosing information collected in electronic health records. The predicted exposures for our study were within the range reported in one previous pharmacokinetic trial, but lower than that in the cohort of infants used to derive the pharmacokinetic model applied in our study.[11,12] This difference may be due to the higher doses administered to the pharmacokinetic model development cohort (mean 1.9 mg/kg/dose) compared with the electronic health record cohort (mean 1.2 mg/kg/dose), or due to the younger postnatal age at the time of sildenafil dosing: a mean value of 34 hours in the model development cohort versus a mean value of 3.5 days in the electronic health record cohort.

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Despite the range of predicted sildenafil exposures in our study, we did not identify a relationship with systemic hypotension. Concerns about an exposure–safety relationship for sildenafil stem primarily from the results of the STARTS-2 trial.[26] This open-label extension to the pivotal STARTS-1 study found increased mortality after 2 years of high-dose sildenafil exposure in children weighing >20 kg.[26–28] Mortality was lower in children receiving low or medium dosing. Although exposure data were not available for the long-term extension study, predicted geometric mean AUC of the parent drug in children treated with high-dose sildenafil in the 16-week STARTS-1 study ranged from 941 to 2193.6 ng × hour/ml, which is higher than exposures in the medium- and low-dose groups (114.8–769.5 ng × hour/ml).[29] Interpreting these findings has proven to be challenging, and their significance for infants remains disputatious.[30,31] Even if one assumes that the observed exposure–safety relationship is true for older children, physiological and disease-specific differences may explain the reason this applies to infants. Disease states treated in infants, such as persistent pulmonary hypertension of the newborn and concomitant therapy with high fractions of inspired oxygen, may increase pulmonary type-5 phosphodiesterase activity and/or expression, resulting in improved on-target effects.[21] Children in the long-term STARTS-2 trial were receiving outpatient sildenafil therapy for various forms of pulmonary hypertension, but not for persistent pulmonary hypertension of the newborn, and they were not exposed to high fractions of inspired oxygen.[27] Given these differences and the potential benefits of sildenafil in infants, careful population-specific safety assessments are needed.

The strengths of our study included its novel, cost-effective, efficient, and minimal-risk design. Nevertheless, it is not without limitations. The dosing and safety data are derived from electronic health records, which have not undergone the development and scrutiny required for a prospective trial database. Clinically significant hypotension was defined based on pharmacologic interventions, as blood pressure measurements were not available. This methodology likely underestimates the true prevalence of hypotension, but may serve as an acceptable surrogate of the clinically significant events. This is particularly true in the neonatal population, in which defining hypotension on the basis of blood pressure measurements remains challenging. As a result, neonatal clinical trial experts of the National Institute of Child Health and Human Development-funded Pediatric Trials Network concluded that for the assessment of drug safety, hypotension should be defined based on the need for vasopressors and inotropes, as was done in our study.[32] Because the reason for discontinuing drugs is not provided in the electronic health record data available, we did not include discontinuation of sildenafil as a surrogate for hypotension but acknowledge that this may be a common first intervention for infants experiencing this complication. Overall, the limitations in hypotension definitions likely led us to underestimate the true prevalence of this complication in premature infants. To predict exposures we used a previously published population pharmacokinetic model derived for neonates, but we acknowledge that this model has not been externally validated.[11] Unfortunately, this limitation is common in paediatric pharmacokinetic models owing to the significant challenges of conducting prospective validation trials in this population. Further, we had to limit our study population to match the characteristics of the population used to develop the model, and therefore excluded infants receiving intravenous sildenafil. The original model publication does not provide information about gestational age, limiting our ability to compare it with the gestational age distribution in our cohort; however, the mean postnatal age and weight of the infants included in the model development cohort were 33 days and 3.6 kg, suggesting that they are predominantly premature. This is consistent with the finding for our study population.[11] Details on administration, such as formulations, concomitant nutrition, or use of a nasogastric tube, were not available. Further, the mean treatment duration for our cohort was short, limiting our ability to report on the long-term safety. Finally, although we were able to adjust for several characteristics in our regression analyses, other risk factors not available in the electronic health record may lead to residual bias.

In conclusion, this large, novel sildenafil exposure–safety study in hospitalised infants found that neither dosing nor predicted exposure were associated with systemic hypotension. Given the known dose–concentration variability observed in premature infants, the use of exposure predictions strengthens the lack of an observed association between sildenafil use and hypotension in this population. Our findings are consistent with the majority of those from recently conducted, smaller retrospective and prospective studies supporting the safety of sildenafil in hospitalised infants.

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Conflicts of Interest

Complete disclosure information for C.P.H., P.B.S., and M.C.-W. can be found at https://dcri.org/about-us/conflict-of-interest/. M.M.L., N.J.O., R.H.C., and D.G. have no conflicts of interest to disclose for this study.

Ethical Standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national guidelines on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008, and has been approved by Duke University Institutional Review Board.

Supplementary material

To view supplementary material for this article, please visit https://doi.org/10.1017/S1047951117001639

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