Population Pharmacokinetics and Safety of Sildenafil in Premature Infants

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Background

- Sildenafil is a phosphodiesterase-5 inhibitor that reduces pulmonary vascular remodeling in animal models, raising the potential for a therapeutic role in the prevention or treatment of bronchopulmonary dysplasia (BPD) in premature infants.
- Sildenafil undergoes extensive cytochrome P450 3A (CYP3A)-mediated metabolism to an active metabolite (desmethylsildenafil [DMS]). Due to maturation in this metabolic pathway, changes in sildenafil clearance (CL) with age are expected.
- A sildenafil exposure target has not been established, however, one study noted that all infants with pulmonary hypertension that survived had an area under the concentration versus time curve (AUC) from 0 to 24 hours of 2650 ng*hr/mL (calculated as sildenafil plus 50% metabolite AUC).[1]
- Before clinical trials are performed in premature infants, population specific pharmacokinetic (PK) and safety data are needed to identify the optimal dose to study.

Objectives

- Characterize the PK and safety of sildenafil in premature infants.
- Perform dose-exposure simulations using the final model to identify the appropriateness of dosing selected for a follow-up phase 2 study.

Methods

- We performed a multi-center, open-label trial to characterize the PK of sildenafil in infants born at ≤28 weeks gestation with age <365 postnatal days (cohort 1) or born at <32 weeks gestation with age 3-42 postnatal days (cohort 2).
- In cohort 1, we enrolled infants receiving intravenous (IV) or enteral sildenafil per standard of care. In cohort 2, we administered a single IV dose of sildenafil.
- We analyzed PK samples for sildenafil and its active metabolite, DMS, concentrations using an HPLC/MS/MS validated assay.
- We performed a population PK analysis using the software NONMEM (version 7.3).
- We explored one and two compartment PK models for both sildenafil and DMS with linear elimination. We assumed complete conversion of sildenafil to DMS in order to obtain an identifiable model.
- We used a forward inclusion ($p<0.05$) and backward elimination ($p<0.01$) approach to identify covariates that explain inter-individual variability in sildenafil and DMS disposition.
- We used the final population PK model to perform dose-exposure simulations in premature infants.

Results

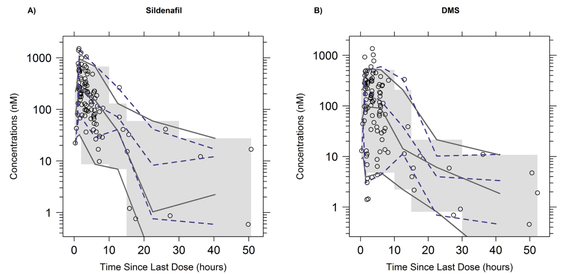
Table 1. Clinical data.

Variable	Cohort 1 (n=25)	Cohort 2 (n=9)	All (n=34)
Dosing (mg/kg/dose)	0.95 [0.42-2.09] [e]	0.25 [0.13-0.25]	0.79 [0.13-2.09]
Samples Per Infant	3 [3-4]	3 [2-4]	3 [2-4]
Weight (kg)	4.79 [1.36-8.06]	0.75 [0.59-1.24]	3.41 [0.59-8.06]
Birth Weight (g)	650 [450-1215]	800 [425-980]	666 [425-1215]
Gestational Age (weeks)	25 [22-28]	25 [23-27]	25 [22-28]
Postnatal Age (days)	166 [52-279]	18 [7-40]	125.5 [7-279]
Postmenstrual Age (weeks)	47.29 [31.43-62.86]	27.43 [26.00-32.43]	41.79 [26.00-62.86]
Serum Creatinine (mg/dL) [a]	0.2 [0.1-0.7]	0.65 [0.4-1.4]	0.3 [0.1-1.4]
Albumin (g/dL) [b]	3.7 [1.8-4.3]	2.75 [1.7-3.7]	3.1 [1.7-4.3]
BUN (mg/dL) [c]	11 [2-32]	25.5 [15-84]	15 [2-84]
Hematocrit (%) [d]	34.7 [26.5-46.0]	35.7 [26-49]	34.85 [26-49]
Fluconazole (%)	0	44.4	11.8

*Descriptive statistics were calculated based on the value at the time of the first record for each subject and reported as median [range]. Fluconazole (%) is reported as the percentage of concomitant use of fluconazole in each group. [a]Data available for 29 subjects; [b]Data available for 19 subjects; [c]Data available for 29 subjects; [d]Data available for 32 subjects. [e]All subjects but one received sildenafil via enteral administration.

- A two compartment model for sildenafil and one compartment model for DMS characterized the data well.
- Co-administration of fluconazole, a CYP3A inhibitor, resulted in an estimated ~80% decrease in sildenafil CL and its inclusion in the model led to a decrease in the inter-individual variability of sildenafil CL from 69.2% to 32.4%.

Figure 1. Visual predictive check for sildenafil and desmethylsildenafil (DMS) using the final population PK model. The shaded region denotes the 90% prediction interval of the simulated data. Dashed and solid lines represent the 5th, 50th, and 95th percentiles of the observed and model simulated data, respectively.



- Simulated exposures obtained with our model are in agreement with a previous population PK analysis[1] performed in infants that simulated similar dosing regimens (Table 2).

Table 2. Simulated steady-state area under the concentration versus time curve from 0 to 24 hours (AUC_{0-24}). Data presented as median [2.5th, 97.5th percentiles].

Intravenous Dosing			
Dose (every 8 hours)	0.125 mg/kg	0.5 mg/kg	1 mg/kg
Sildenafil (ng*hr/ml)	462 [232-2852]	1855 [926-10376]	3661 [1877-23393]
DMS (ng*hr/ml)	297 [91-979]	1187 [364-3914]	2374 [728-7830]
Sildenafil+50%DMS (ng*hr/ml)	640 [345-3070]	2563 [1382-11415]	5090 [2756-24856]
Enteral Dosing			
Dose (every 8 hours)	0.25 mg/kg	1 mg/kg	2 mg/kg
Sildenafil (ng*hr/ml)	397 [96-2644]	1637 [383-10149]	3141 [767-21134]
DMS (ng*hr/ml)	236 [51-870]	943 [204-3479]	1886 [407-6959]
Sildenafil+50%DMS (ng*hr/ml)	554 [146-2869]	2217 [568-11021]	4321 [1191-22925]

- Hypotension related to study drug occurred in one infant in cohort 2. This subject received a single IV dose of 0.236 mg/kg infused over 45 minutes compared to approximately 90 minutes in the rest of the patient sample. The sildenafil (0.36 and 0.29 ng/mL and BQL) and DMS (4.7, 5.12, 1.36, and 0.88 ng/mL) concentrations recorded were within the range of values observed for the other subjects in cohort 2 (median [range] sildenafil and DMS were 33.71 ng/mL [0.28-193.07] and 2.46 ng/mL [0.21-17.95], respectively).
- No further adverse events related to study drug were noted.

Conclusions

- A population PK model of sildenafil and DMS was developed. In agreement with a previously published infant population PK study[1], fluconazole, a CYP3A inhibitor, was found to explain a significant amount of the variability in sildenafil CL.
- With the exception of one infant with hypotension, we found that sildenafil was well tolerated at the dosing range studied.

References

1. Ahsman MJ, et al. Sildenafil exposure in neonates with pulmonary hypertension after administration via a nasogastric tube. *Arch Dis Child Fetal Neonatal Ed.* 2010;95:F109-14.

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