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 (desmethysildenafil (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)0-24h from 0 to 24 hours of 2650 ng•hr/mL (calculated as sildenafil plus 50% metabolite DMS).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 ≤50 postnatal days (cohort 1) or born at ≤32 weeks gestation with age ≤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 a high performance liquid chromatography/mass spectrometry (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.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cohort 1 (n=34)</th>
<th>Cohort 2 (n=9)</th>
<th>Total (n=43)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postmenstrual Age (weeks)</td>
<td>39.79 [26.40]</td>
<td>65.00 [45.00]</td>
<td>58.26 [40.76]</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>2.46 [1.4]</td>
<td>2.09 [1.4]</td>
<td>2.30 [1.4]</td>
</tr>
<tr>
<td>Serum Creatinine (mg/dL)</td>
<td>1.07 [0.7]</td>
<td>0.79 [0.25]</td>
<td>0.89 [0.25]</td>
</tr>
<tr>
<td>Fluconazole (%)*</td>
<td>80.86 [10.36]</td>
<td>72.00 [10.36]</td>
<td>77.44 [10.36]</td>
</tr>
</tbody>
</table>

Variable values observed for the other clinical trial subjects were similar. *Descriptive values are reported as the percentage of concomitant use of fluconazole in each group. The dose of fluconazole was 4 mg/kg/dose administered via a nasogastric tube.

- 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 62.86% to 32.4%.

Figure 1. Visual predictive check for sildenafil and desmethysildenafil (DMS) using the final population PK model. The shaded region denotes the 95% 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 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 (AUC0-24h). Data presented as median (2.5%, 97.5% percentiles).

<table>
<thead>
<tr>
<th>Dose (mg/kg)</th>
<th>Sildenafil (ng•hr/ml)</th>
<th>Sildenafil+50%DMS (ng•hr/ml)</th>
<th>DMS (ng•hr/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.25 mg/kg</td>
<td>682.69 [772.23, 853.15]</td>
<td>193.07 [96.64, 285.50]</td>
<td>1.42 [0.29, 2.46]</td>
</tr>
<tr>
<td>0.5 mg/kg</td>
<td>1370.31 [1464.52, 2292.50]</td>
<td>391.40 [203.23, 624.57]</td>
<td>2.89 [1.01, 4.87]</td>
</tr>
<tr>
<td>1 mg/kg</td>
<td>2740.63 [2852.00, 3914.00]</td>
<td>782.80 [4321.00, 10149.00]</td>
<td>5.74 [3.14, 9.34]</td>
</tr>
</tbody>
</table>

- 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 mg/L) and DMS (4.7, 5.12, 3.96, and 0.88 mg/mL) concentrations measured were within the range of values observed for the other subjects in cohort 2 (median [range] sildenafil and DMS were 33.71 µg/mL [0.28-193.07]) and 2.46 mg/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 variability in sildenafil concentration.
• With the exception of one infant with hypotension, we found that sildenafil was well tolerated at the dosing range studied.

References