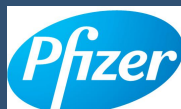


Pharmacokinetics of Sildenafil in Pulmonary Arterial Hypertension (PAH) Pediatrics One Month to One Year Old: Interpolation of Two Population Pharmacokinetic Models of Sildenafil in a PPHN population (11 hours to 10 Days) and in a Pediatric PAH population (1 to 17 Years)



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Introduction

- Sildenafil is indicated for the treatment of PAH in both adults and pediatrics (1 to 17 years old);
- Two population models of sildenafil pharmacokinetics (PK) have been developed in PPHN (11 hours to 10 days) and PAH pediatric populations (1 to 17 years), respectively;
- No PK data exists for 10 days to 1 year old children;
- The purpose of this research is to provide a rationale for the treatment of children with PAH between one month and 1 year of age, based on a PK bridging and modeling approach of available data;
- The resulting quantitative integration facilitated dose recommendation for one month to one year age range of children with PAH.

Objectives

- To predict sildenafil PK in children 1 to 12 months old with PAH;
- To derive the dose recommendation for 1 to 12 months old children with PAH using the above derived evidence.

Methodology

Sildenafil Population PK model for PPHN age from 11 hours to 10 days:¹

$$CL/F_{PPHN} (L/h) = CL_{TV} \left(\frac{Age}{3.5} \right)^{\theta_{age}} / 0.41$$

CL_{TV} : typical value of intravenous clearance at an age of 3.5 days; θ_{age} : power coefficient for age dependent effect on CL_{PPHN} ; 0.41: oral bioavailability³

Sildenafil Population PK model for PAH children age from 1 to 17 years old:²

$$CL/F_{PAH} (L/h) = \left(CL_0 + (CL_{max} - CL_0) \frac{WT^\gamma}{WT^\gamma + WT_{50}^\gamma} \right) \frac{DOSE^{DOSEEXP}}{29.5}$$

with CL_0 : apparent clearance extrapolated to a zero kg WT; WT: individual body weight; CL_{max} : maximum apparent clearance at a DOSE of 29.6 mg; γ : hill coefficient; $DOSEEXP$: power coefficient for dose dependency in clearance. For both models steady-state average concentration ($C_{ss,avg}$) follows as:

$$C_{ss,avg} (ng/mL) = DOSE \cdot 1000 / (8 \cdot CL/F)$$

with DOSE: sildenafil dose in mg given TID every 8 hours. The overall inter-subject variability for CL/F

$$\eta_{total} = \eta + \eta_{wt}$$

with η : inter-subject variability of CL/F, PPHN, η_{wt} , and pediatric PAH patients; η_{wt} : part of inter-subject variability of CL/F for weight distribution at a specific age.

Dose Regimen Simulation Schemes

Two simulation schemes:

- 1) 0.4 to 4 mg/kg TID, range commonly used in clinical practice; and
- 2) 2 to 20 mg TID, covering exposure range at the recommended dose in the treatment of PAH pediatric patients, i.e. 10 mg TID for WT $\leq$ 20 kg, and 20 mg TID for WT > 20 kg, 1 to 17 years old.

Derivation of Dose Recommendation

The PPHN PK parameters at one month, and the PAH PK parameters at one year were set as reference points.

The better of the two models was selected based on the closeness to the extrapolated clearance value to the predicted values of the alternative model. In other words comparing the value of the PPHN model extrapolated to 1 year to the predicted value for the PPHN model and the PPHN model extrapolated to 1 month to the predicted value for the PPHN model.

Using the selected model, two dose regimens were proposed, mg or mg/kg TID, producing the same or comparable exposure range as to that at the recommended dose in the treatment of pediatric PAH patients.

Sensitivity Analysis

To understand the predictability and inaccuracy using the selected model, the commonly used allometric scaling method⁴ was applied to extrapolate the two models into the 1 month to 1 year range as follows:

- a) the PPHN model CL/F_{PPHN} value for 1 month was extrapolated using allometric scaling to one year;
- b) the PAH model CL/F_{PAH} value from 1 year was extrapolated using allometric scaling to one month.

External validation

To assess the predictability of the PPHN and PAH models, for each individual clearance estimate from a publication⁵, the prediction intervals based on the given individual weight and dose were calculated from the interpolated population PK models; and a semi statistical approach taken to assess their distribution in relation to the predicted distributions.

Assumptions

- The time course of the CYP3A maturation process⁶ is applicable to the elimination process of sildenafil from birth to 12 months in children:
 - unlikely violated, based on our knowledge of metabolic pathways of sildenafil (extensively metabolized via CYP3A);
- The underlying disease PPHN in neonates or PAH in children has an insignificant effect on the distribution and elimination of sildenafil:
 - may need further data support but there exist many common traits of PPHN and PAH diseases;
- Potential differences in absolute bioavailability between adult healthy volunteers and >1 year old children have an insignificant effect on exposure:
 - may not hold for children < 1 month. Since this research is focusing on the population greater than one month and less than one year, this is not of great concern.

Tables and Figures

Figure 1: Age weight relationship from the CDC chart growth data

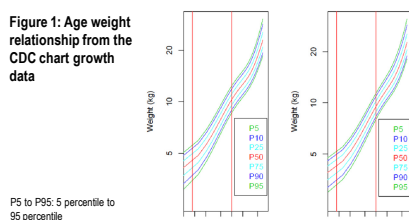


Figure 2: CL and C_{ss} vs Dose model predictions for PPHN and PAH population after 1 month and 1 year

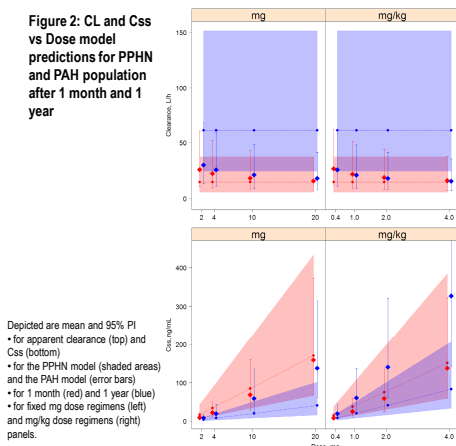


Figure 3: CL and C_{ss} vs age following sildenafil oral doses of 2 mg/kg and 20 mg, respectively

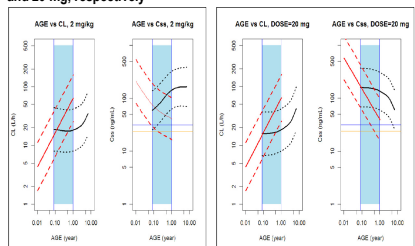
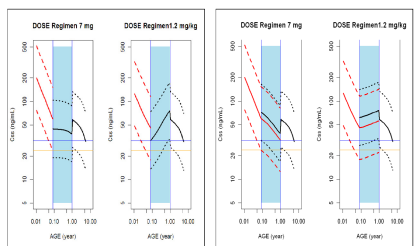


Figure 4: Contrast of two proposed dose regimens of 7 mg or 1.2 mg/kg TID
Left Panel: C_{ss} vs. Age by the PAH pop PK model extrapolated from 1 month to 1 year
Right Panel: C_{ss} vs. Age by allometric scaling from 1 month to 1 year

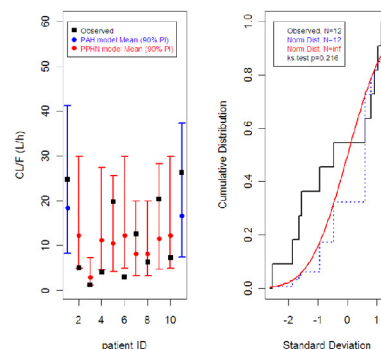


Left panel, same legend as Figure 3. Right panel: within 1 month and one year age group, C_{ss} extrapolated by allometric scaling; red lines were drawn using values at 1 month by the PPHN pop PK model and black lines were drawn using values at 1 year by the PAH pediatric population PK model.

Table 1 lists the PK parameters which were used for the simulations

Parameters	Unit	Values	95% Confidence Interval	Used in Equation
CL_{TV}	L/h	1.72	(1.45, 2.05)	PPHN model
θ_{age}	-	0.583	(0.38, 0.78)	
η_{in}	-	0.299	(0.17, 0.43)	
F	-	0.41	(0.36, 0.47)	
CL_0/F	L/h	14.3	(8.3, 20.3)	PAH ped model
CL_{max}	L/h	57.2	(51.4, 63.0)	
WT_{50}	Kg	21.7	(16.0, 27.4)	
γ	-	3.76	(2.46, 5.06)	
$DOSEEXP$	-	-0.217	(-0.357, -0.077)	Variance model
η_{in}	-	0.243	(0.20, 0.29)	
η_{wt}	-	0.04	(0.01, 0.06)	

Figure 5: The observed apparent clearance (CL/F) extracted from the publication by Ahsman et al and the corresponding predicted mean and 90% prediction interval using the PPHN (age < one month) and PAH model (age $\geq$ one month), and the test for normality



Results and Discussion

- PK parameter values used for simulation are shown in Table 1.
- Figure 1 shows the age and weight relationship across the age range from birth to 6 years.
- Figure 2 shows the simulation results for the two interpolation PK models for the dose regimens, i.e., 0.4, 1, 2, 4 mg/kg, and 2, 4, 10, 20 mg at one month and one year.
- Figure 3 shows the simulated CL/F and C_{ss} distributions for doses of 2 mg/kg and 20 mg across the age range from birth to 6 years.
- The CL/F and C_{ss} values extrapolated to 1 month, by the PAH population PK model for children from 1 to 17 years, are very close to the values predicted by the PPHN population PK model; whereas the CL/F and C_{ss} values extrapolated to 1 year by the PPHN population PK model deviated substantially from the values predicted by the PAH population PK model for children from 1 to 17 years (Figure 2). Hence, the PAH pediatric population PK model was selected in predicting PK in this age range.
- Two dose regimens, i.e., 1.2 mg/kg, or 7 mg TID, were proposed for the treatment of PAH pediatric patients from one month to one year old, and are expected to achieve clinically relevant concentrations in which central tendency and variability are similar to concentrations achieved at the recommended dose of 10 mg TID for PAH pediatric patients less than 20 kg corresponding to an approximate age range from 1 to 7 year.
- A mg based dose regimen predicts to produce more uniform concentrations across the particular age range of 1 month to 1 year, whereas a weight based regimen tends to produce rising concentrations with an increase in age.
- The estimated range for C_{ss} extrapolated allometrically from one year downwards to one month is similar to the estimated range for C_{ss} extrapolated allometrically upwards from 1 month to 1 year (Figure 4). In addition, the C_{ss} range by the two allometric scaling models (Figure 4) was comparable to the C_{ss} range by the PAH pediatric model. All together, this supports the adequacy of the PAH PK model to predict the PK from 1 month to 1 year in children.
- The limited external validation showed that the observed CL/F values⁵ for the two patients with age > 30 days were within the 90% prediction interval (PI) of the PAH model, and the observed CL/F values in 8 out 10 remaining patients with age < 30 days were within the 90% PI of the PPHN model, only two patients marginally missed the lower 90% PI boundary (Figure 5).

Conclusions

- We have conducted simulations, a sensitive analysis, and a predictability assessment using two population PK models for sildenafil in pediatrics spanning ages from birth to 14 days (PPHN model), and from one to 17 years (PAH model) to predict the sildenafil PK in PAH patients aged one month to one year.
- An oral dosing regimen of 1.2 mg/kg TID or a fixed dose of 7 mg TID can be recommended for this age group for the treatment of PAH. The recommended dose regimen would achieve a similar exposure to the labeled dose regimen for pediatric PAH patients from 1 to 17 years old.

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