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Research Article

Semi-Physiological based Population Pharmacokinetic Model for Methylphenidate Hydrochloride Multi-Layer Extended Release (Aptensio XR®) Capsules in Children ages 4-12 and Adults

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ABSTRACT

Aptensio XR® is an Extended-Release (ER) Methylphenidate (MPH) capsule drug product, approved for use in patients 6 years and above. Clinical studies have been conducted in adults (N=24), children ages 6-12 (N=15), and pre-school children ages 4-5 (N=9) with approved doses in children aged 6 and above at 10, 15, 20, 30, 40, 50, and 60 mg. The purpose of this investigation is to determine if a semi-physiological model for ER MPH can adequately describe Aptensio XR® (bead formulation) clinical data in children ages 4-12 and adults. Absorption of Aptensio XR® in children has been characterized by two fast first-order releases and a delayed slow first-order release and in adults by a fast zero-order release and a delayed first-order release. Both are consistent with published MPH models for these demographic groups. Subject body weight, sex and age were important covariates. Model bioequivalence parameters in children and adults had 15% or less bias, except for $pAUC_{0-3}$ hours (partial area-under-the curve 0-3 hours) which was greater than 15% in children less than 6. The recommended starting dose of Aptensio XR for patients aged 6 years and above is 10 mg once daily in the morning with or without food. The model parameters in children were used for simulations to determine that the 10 mg dose was the best dose for the 4-5 year old children.

Keywords: Semi-physiological model; Extended-release methylphenidate; NONMEM; Aptensio XR® dosing

INTRODUCTION

A relationship has been established between Methylphenidate (MPH) blood plasma concentration levels, their time course, and clinical effect in treating Attention Deficit Hyperactivity Disorder (ADHD) [1]. Today, there exist many approved ER (Extended-Release) MPH drug products effective for 12 hours with a single daily dose. Some show more efficacy in the morning whereas others have more efficacy in the afternoon. It is now also apparent that not only is the overall extended course of release of MPH ER drug products clinically important, but also that the pattern of release can impact the time course of efficacy throughout the day [2]. Recently, many new MPH ER drug products have been marketed that are formulated especially for children age 6 and above, as indicated in product labeling for the following:

- Aptensio XR®
- Cotempla XR-ODT®
- Jornay PM®
- Quillivant®
- Adhansia XR®

A close inspection of the Food and Drug Administration (FDA)-approved product labeling (in product labeling section 12.3 Pharmacokinetics) for these formulations shows similar language among these products regarding PK in children age 6 and above [3-7].

There are published compartmental models and other models based upon deconvolution of adult data for formulation optimization and possible covariate inclusion [8-10]. In addition, a recently-published study for an orally-disintegrating MPH tablet investigated its PK and Pharmacodynamics (PD) in subjects 6-17 years of age using a 3-compartment empirical model with slow and rapid absorption sites. However, it would be useful to have a

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semi-physiological model that would allow one to look at drug time course in specific tissues (e.g., brain) based upon the fitted model and if these levels can be impacted by changes in formulation or absorption.

A paucity of individual data in the literature has resulted in several current PK models relying solely on mean data, which can provide some useful determinations of maximum plasma concentrations (C_{max}), but may lack the ability to provide some other useful PK determinants. While individual data can provide additional useful PK information, on occasion, modeling individual data can be challenging, especially when one has very high variation in C_{max} [9,11,12]. It is generally accepted that establishing the overall PK time course is essential for the valid determination of MPH efficacy. Therefore, to improve methods for determining the PK metrics for oral ER methylphenidates, the current draft FDA ER MPH guidance recommends the determination of several partial area-under-the-curve (pAUC) values ($pAUC_{0-3}$, $pAUC_{3-7}$, and $pAUC_{7-12}$) in addition to AUC_{0-inf} and C_{max} to assure curve shape adherence in these formulations [13].

An ER MPH physiological model based upon individual subject data would provide another useful method for conducting simulation studies, especially those related to Bioequivalence (BE), PK, and PD in other populations of interest (e.g., pediatrics), particularly considering that many of the previously discussed ER MPH drug products in the market have been approved for administration to children [14]. Many of these products are also being prescribed off label for children under the age of 6.

The purpose of this paper is to use a semi-physiological population model for oral ER MPH and apply it to the available individual subject data for Aptensio XR® in children and adults because bioequivalence studies are done in adults and extrapolated to children [15-17]. Therefore, questions to be addressed in this manuscript include:

- Does the semi-physiological population model have the same structure for adults and children and if they are major differences.
- How rigorously does the model determines exposure in both groups as currently measured by partial area values ($pAUC_{0-3}$, $pAUC_{3-7}$, $pAUC_{7-12}$), in these subjects.
- Appropriate application of the model for weight-based dosing in 4 to 5 years olds.

In consideration that the basic model-building tasks already have been performed previously, as cited, the authors determined that there was no need here to develop any truly *de novo* model, but rather, the intent was to investigate the ability of a derived semi-physiological model to assess its performance generally, and especially in pediatric populations. We think that this research will yield a more specific approach to analyze PK performance, since specific body organs, such as the brain, are considered in the model development. In addition, the results could also prove useful to inform BE studies of proposed MPH generic drugs which use adult PK data to predict pediatric PK performance.

MATERIALS AND METHODS

Patients

Concentration-time data from three clinical PK trials were available for analysis. Two trials were conducted in children diagnosed with ADHD and one study was conducted in adults.

Both studies on children were conducted under fed conditions in which the children were administered a standard breakfast (e.g., toast, jam, cereal with 2% milk, and orange juice) prior to being administered a single dose as sprinkles over applesauce, as described in the drug labeling. Study RP-BP-PK003 was done in pre-school children (N=9) 4-5 years of age while study 022-011 was done in children (N=15) 6-12 years of age [18,19].

In study RP-BP-PK003, doses of 10, 15 and 20 mg were administered, with blood samples collected from each subject at 0, 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, and 24 hours post dose. In study 022-011, doses of 20, 30, 40, 50, and 80 mg were administered, with blood samples taken at 0, 1, 1.5, 2, 2.5, 3, 4, 4.5, 5, 5.5, 6, 6.5, 7, 8, 8.5, 9, 9.5, 10, 10.5, 12, 15, 19, and 24 hours post-dose. In the PK study conducted in adults RP-BP-PK001 (N=24), each subject was fasted overnight and then received a single 80 mg capsule of Aptensio XR® administered as sprinkles over applesauce. Blood samples were taken at 0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 4.5, 5, 5.5, 6, 6.5, 7, 8, 8.5, 9, 9.5, 10, 10.5, 12, 15, 19 and 24 hours post-dose.

Ethics

This research was carried out in accordance with the clinical research guidelines established by the Basic Principles defined in the U.S. 21 CFR Parts 50, 56, and 312, the principles enunciated in the Declaration of Helsinki (and its amendments), and the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use. All protocols, protocol amendments, informed consents and other study documents were reviewed and approved by either the Integ Review Ethics Review Board or the Western Institutional Review Board (WIRB). Written informed consent was obtained from each subject or parents/legal guardians at the screening visit prior to performing any procedures or collecting any information. Studies PK001 used the Integ Review board while PK003 used WIRB. The study 022-011 was done as early phase 2 studies. The data for this study is the property of Rhode's Pharmaceutical and can't be shared to protect study participant privacy.

Analytical methods

Plasma from blood samples obtained in all three studies was extracted and analyzed to determine MPH concentration using a fully validated liquid chromatography method with tandem mass spectrometry (LC/MS/MS) analysis (calibration range 0.05 ng/mL–25 ng/mL). Details were presented in a previous publication [8,18]. The d-threo-enantiomer of MPH is ten times more potent than the l-form and accounts for approximately 95% of observed total MPH plasma concentrations [20]. Srinivas et al. determined the d/l ratio for total MPH as a function of time [21]. These results were used here to calculate the d/l MPH enantiomer ratio at each time point from the total MPH data provided for the individual child and adult subjects.

Data analysis

Base model: A physiological PK model was previously developed for adults and children for intravenous MPH formulations [15]. Subsequent model development investigated its application to the oral ER formulations Meta-date CD® and Ritalin LA® in adults [16].

The semi-physiological model used in the present study applied the parameters from the prior publications cited immediately above, but on the NONMEM platform based upon the population kinetics of the oral ER MPH drug product Concerta® [17]. The

model contains covariates for weight and sex which are important factors for describing drug absorption, drug distribution and elimination. Therefore, there was no need to further investigate additional covariates. Cofactors to account for gender and weight were entered as:

IF(SEX.Male) Volume=0.213*WT

IF(SEX.Female) Volume=0.327*WT

The base model for children related to Aptensio XR® absorption only was derived from a published 3-compartment body model with first-order rapid absorption followed by delayed first-order absorption [8].

Final model: For the children's model, the Aptensio XR® first-order fast absorption required two populations, one with a larger absorption value (K13F) and the other with a smaller absorption value (K13S), with (K13S) having a fixed variance (omega), Figure 1. The two populations were based upon visual inspection of the individual children's PK curves and difficulty of curve fitting. The population value for delayed absorption (K23) was estimated, but the variance was also fixed in the semi-physiological model to avoid numerical difficulties during parameter estimation.

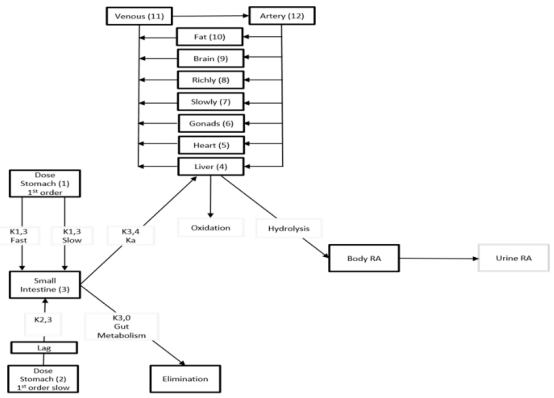

Figure 1: Semi-physiological model for Aptensio® in children. The model has K13 fast and K13 slow 1st order absorption from the stomach and delayed release absorption K23 from the stomach. Drug in the small intestine can undergo first pass gut metabolism or be absorbed *via* K34. The body has several compartments to predict drug levels. Drug from the liver can be either oxidized or hydrolyzed during elimination.

The final adult model and child model each incorporated a fast drug release and a delayed drug release. Covariates for both the child model and adult model were weight and sex. Both covariates were included in the published model and used in this model [16,17]. The difference in the two final models was that for children both drug releases were first-order while for adults the fast drug release was zero-order. Adult data and child data were analyzed separately.

The model was built using NONMEM version 7.3.0 (ICON Development Solutions, Dublin, Ireland) with GNU Fortran (GNU Compiler Collection version 4.7.2; Free Software Foundation, Boston, MA). Perl-speaks-NONMEM version 4.4.8 was used to manage NONMEM runs and perform some computational tasks. R version 3.2.2 and SAS 9.4 were used with X-pose version 4.5.3 for analysis, bootstrapping, and post processing of NONMEM output and for data manipulation.

Pharmacokinetic analysis

For the semi-physiological model, a first-order conditional method with interaction was employed for parameter estimation using Advan 13 and Trans 4. The individual concentration-versus-time d- and l-MPH data for the ER model for Aptensio XR® were simultaneously analyzed. The extent of shrinkage of empiric Bayesian parameter estimates obtained from NONMEM was determined for the PK parameters. Subject body weight was a covariate for all parameters. Scaled fractional tissue volumes and blood flows for organs had sex and weight as covariates (e.g., cardiac output=15.87*wt**0.75; male flow=0.038* cardiac output; female flow=0.047*cardiac output).

Pharmacostatistical model-children and adults

d-MPH: Since the d-MPH is the active species, it was modeled as follows.

The inter-subject variability for all d-MPH PK parameters was assumed to be log normally distributed:

$$P_{ij} = P_{typj}\exp\left(n_{ij}\right) \quad \text{.....(1)}$$

with

$$n_{ij} \sim \left(0, \omega_{pj}^{2}\right) \quad \text{..... (2)}$$

Where: P_j is the typical value for the j^{th} parameter in the population, P_{ij} is the individual value for the j^{th} parameter in the ith subject, and n_{ij} is a random variable in the j^{th} parameter with a mean of zero and a variance of ω_{pj}^2. The model assumes that the P_{ij} values are log-normally distributed. Inter-subject variability in P_j was modeled as the square root of ω_{pj}^2, which approximated the coefficient of variation P_j for a log-normally distributed quantity.

An additive residual error model, a proportional residual error model, and a combination of the two were tested for d-MPH. The theta values for all weights were fixed.

The standard deviation of the residual error (W) was obtained from the square root of the variance resulting in:

For children,

$$W = \text{SQRT}\left((\text{Theta 1}) + (\text{Theta 2})*F*F\right) \quad \text{..... (3)}$$

For adults,

$$W = \text{SQRT}\left((\text{Theta 1})**2 + (\text{Theta 2}*F)**2\right) \quad \text{..... (4)}$$

In each case, the W value was used to convert the residuals to the weighted residuals:

IWRES=((DV-F)/W)

The relative amounts of drug dose available from fast-release compartment-1 (F1) and the relative amount in the lagged compartment-2 (F2) were estimated by NONMEM where F2=1-F1.

Liver hydrolysis d-MPH: The d-MPH population rate of liver hydrolysis was estimated (no eta) in order to fit the terminal plasma concentration curve. All parameters were fixed except for KmD and V_{max} D, which were estimated. The hydrolysis rate was defined by equation 5:

$$RHYD = VmaxD*CpDLiv/\left(KmD*\left(1+\left(CpLLiv/KmL\right)+CpDLiv\right)\right) \quad \text{...(5)}$$

Where:

CpDLiv=Concentration of d-MPH in the Liver

CpLLiv=Concentration of l-MPH in the Liver

$V_{max}D=V_{max}$ for d-MPH liver hydrolysis

KmD=Km for d-MPH liver hydrolysis

KmL=Km for l-MPH liver hydrolysis.

l-MPH: Since this species is ten times less active and with reported AUC values 10 to 40-fold lower than for d-MPH, only population values were used to represent the l-MPH concentrations (i.e., $P_{ij}=P_{typ}$) in the model. An additive residual error model, a proportional residual error model, and a combination of the two were also tested for l-MPH, with the additive residual error model again best describing the data. Error models were the same as those used in children and adults for d-MPH. Population parameters were fixed to values similar to the best-fit values for d-MPH except for gut metabolism (K30) whose value was much larger for the l isomer.

Model evaluation-d MPH: A goodness-of-fit plot was generated for individual predictions, population predictions, and conditionally-weighted, residual-versus-time plots using R. The fixed and estimated parameters were delineated for Aptensio XR® d-MPH. The same parameters were fixed for l-MPH at the estimated population values for l-MPH.

Predictive performance

The model qualification for Aptensio XR® was done using a prediction-corrected, visual-predictive check [22]. This was performed by simulating 1,000 data sets using the parameter estimates from the final best-fit model in Perl Speaks NONMEM. The NONMEM-generated simulations (prediction corrected) were then analyzed using XPOSE 4 to give the respective 95% prediction percentiles. The 5th, 50th, and 97.5th percentile values of the observed data were calculated. The percentiles, around the 5th, 50th, and 97.5th prediction percentiles (95% CI) of the simulated data were plotted along with the observed data, and then overlaid on the plot of the prediction percentiles.

Estimation of parameter standard errors and confidence intervals

As a consequence of rounding errors, the NONMEM covariance step was not successful, which resulted in an inability to calculate asymptotic standard errors. NONMEM with the UNCOND option was also unsuccessful. However, the models ran successfully when the covariance was not implemented. Therefore, the standard errors for the parameter estimates were determined by bootstrapping (i.e., generating pseudo-samples using the same distribution as for the original samples). 500 bootstrap replicates were generated. Only 500 were done because of the run time of 2-3 days for a successful run. Runs that did not have at least three significant figures and minimized successfully were discarded. The 90% confidence intervals were calculated based upon the standard error values for each parameter.

Comparison of estimation bias in observed *vs.* model-predicted be metrics

The mean biases for the BE metrics $pAUC_{0-3}$, $pAUC_{3-7}$, $pAUC_{7-12}$, C_{max}, and AUC_{0-inf} were calculated for the experimental data and compared to those predicted by an N=1000 simulation from the model [23]. Each area metric was investigated separately for children (i.e., all ages, <6 (less than 6) and ≥ 6 (greater than or equal to 6)) and adults. C_{max} was compared for all children not different age groups. This allowed a comparison of the semi-physiological model-generated parameter estimation bias to the observed BE metrics for children and adults independently.

Dose determination in 4-5 year-old children

A PK-only approach was used to determine dose by comparing the 90% CIs for the observed plasma levels in all children (given doses of 10, 15, 20, 30, 40, 50, and 80 mg) with the simulated (N=1000 studies) C_p plasma levels for children less than 6 years of age (given a simulated 10 mg dose) [24,25]. The simulated C_p values for children less than 6 years old dosed at 10 mg were compared to the previously-described 90% CIs for the plasma concentrations in the observed data for all children.

Power and sample size estimation

We followed the method presented by Wang et al. for determination of 95% CIs within 60% and 140% of the geometric mean estimates for clearance and volume of distribution [25]. This method employed the Wang method to evaluate probability, as defined below:

$$P\left(S \le \frac{\sqrt{n}\, ln\ 1.4}{t_{0.975,n-1}}\right) \ge 0.80$$

Where: S is the sample standard deviation of the log-transformed parameter, n is the sample size, and $t_{0.975,\ n-1}$ is the critical value for the 95.7th percentile of the Student t-distribution with n-1 degrees of freedom. Power estimates for various values of n are obtained when replacing the population variance in the density function for S with estimates obtained from the PK simulations for volumes of distribution.

RESULTS

The graphs in supplementary Figure 1 clearly show that adults, children ages 6-12, and children ages 4-5 all have different mean curve shapes which are an expression of the individual curve differences.

Children and adults

Parameter estimation for d-Methylphenidate-Aptensio XR®: The parameter estimation process for Aptensio XR® converged successfully using the first-order conditional estimation method with interaction with three significant figures. The final parameter estimates are shown in Table 1 for Aptensio XR® in children with the corresponding estimates of standard error and 90% CIs. Standard error was estimated *via* bootstrapping. The population PK parameters were estimated with minimal shrinkage Table 1, except for K30, and K34 for Aptensio XR®, indicating that all other parameters would be informative [26]. Parameter estimates for adults are presented in Table 2 and none of the parameters' shrinkage values exceeded the acceptable level of 30%.

Model evaluation for d-Methylphenidate-Aptensio XR®: The goodness-of-fit plots for Aptensio XR® (Figures 2 and 3) concentrations in children and adults showed reasonable correlation between predicted and observed data for population versus individual predictions over time. The plot of the Conditionally-Weighted Residuals (CWRES) also showed a reasonable uniform distribution between 0 and 24 hours for both children and adults.

Table 1: NONMEM Parameter Estimates for Aptensio® for children from the Final Model with η Shrinkage.

Parameter	Unit	Estimate	%RSE	90% CI	Shrinkage (%)
K13F	h-1	2.45	6.24	(0.10 3.95)	-
K13S	h-1	2.04	4.6	(0.05 3.19)	-
K23	h-1	0.62	2.27	(0.06 0.90)	-
K30	h-1	1.64	1.20	(1.22 7.24)	-
K34	h-1	0.03	0.067	(0.02 0.63)	-
K_m	mg/L	22.5	1.28	(20.0 30.0)	-
V_m	mg/hr/kg$^{0.75}$	38.6	0.87	(30.0 45.0)	-
Alag2	hr	10.9	1.82	(3.52 11.91)	-
F1	-	0.73	0.41	(0.62 0.83)	-
F2	-	0.26	1.16	(0.17 0.37)	-
V11	L	1.23	3.98	(0.18 2.50)	-
ω^2 K13F	-	0.26	6.24	(0.053 0.91)	22
ω^2 K13S Fixed	-	0.9	-	-	-
ω^2 K23 Fixed	-	0.9	-	-	-
ω^2 K30	-	0.09	3.04	(0.03 0.77)	93
ω^2 K34	-	0.08	3.1	(0.01 0.74)	50
ω^2 Alag2	-	0.03	13.6	(0.001 0.20)	25
ω^2 F1	-	0.38	3.74	(0.01 0.92)	27
[a]SD, RES prop Fixed	-	0.003	-	-	-

Note: [a]SD: Standard Deviation associated with the respective residual error. All are typical values with relative standard error, 90% confidence intervals, ω the variance estimate for inter-subject variability.

Table 2: NONMEM Parameter Estimates for Aptensio® for adults from the Final Model with η Shrinkage.

Parameter	Unit	Estimate	%RSE	90% CI	Shrinkage (%)
[a]K13	h-1	5.2	0.14	(5.11 5.33)	-
K23	h-1	0.78	0.77	(0.65 1.17)	-
K30	h-1	3.36	0.38	(2.47 3.50)	-
K34	h-1	0.63	0.69	(0.43 0.80)	-
D1	hr	0.82	0.37	(0.70 0.98)	-
K_mD	mg/L	9.20	0.04	(9.00 9.30)	-
V_{max}D	mg/hr/kg$^{0.75}$	41.1	0.16	(39.80 45.90)	-
Alag2 Fixed	hr	5.35	-	-	-
F1	-	0.54	0.09	(0.43 0.69)	-
F2	-	0.45	0.11	(0.31 0.56)	-
V11	L	2.52	0.6	(2.15 4.47)	-
ω^2 K13	-	0.7	0.14	(0.56 0.89)	22
ω^2 K23 Fixed	-	0.9	-	-	-

ω^2 K30	-	0.54	0.38	(0.40 0.65)	22
ω^2 K34	-	0.17	0.69	(0.06 0.79)	13
ω^2 D1	-	0.24	0.17	(0.05 0.44)	13
ω^2 Alag2 Fixed	-	0.05	-	-	-
ω^2 F1	-	0.56	0.1	(0.48 0.63)	6
[b]SD, RES_{prop} Fixed	-	1	-	-	-

Note: [a]Covariate is W_t^(-0.25) for all absorption parameters; [b]SD: Standard Deviation associated with the respective residual error. All are typical values with relative standard error, 90% confidence intervals, ω the variance estimate for inter-subject variability.

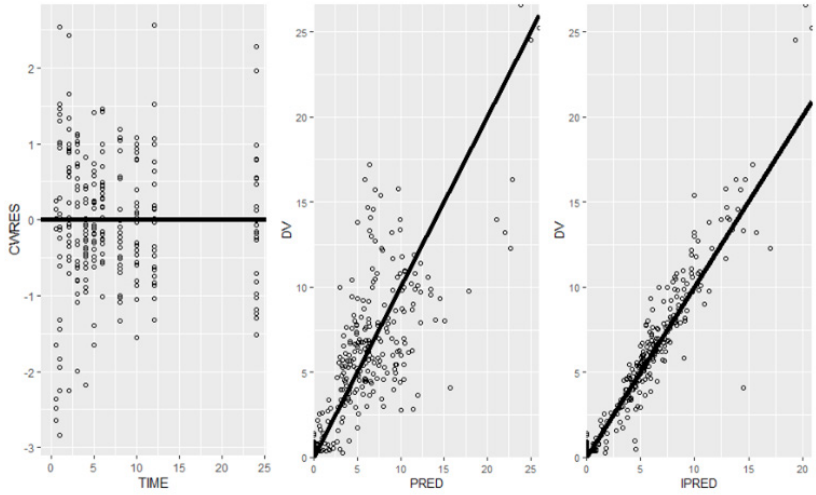

Figure 2: Diagnostic plots for children for Aptensio®. The three plots from left to right are Conditional Weighted Residuals (CWRES) *vs.* time, DV (Observations) *vs.* PRED (Predicted Concentrations), and DV *vs.* IPRED (Individual Predicted Concentrations). Open circles represent the CWRES values plotted against time and the observed data against the population.

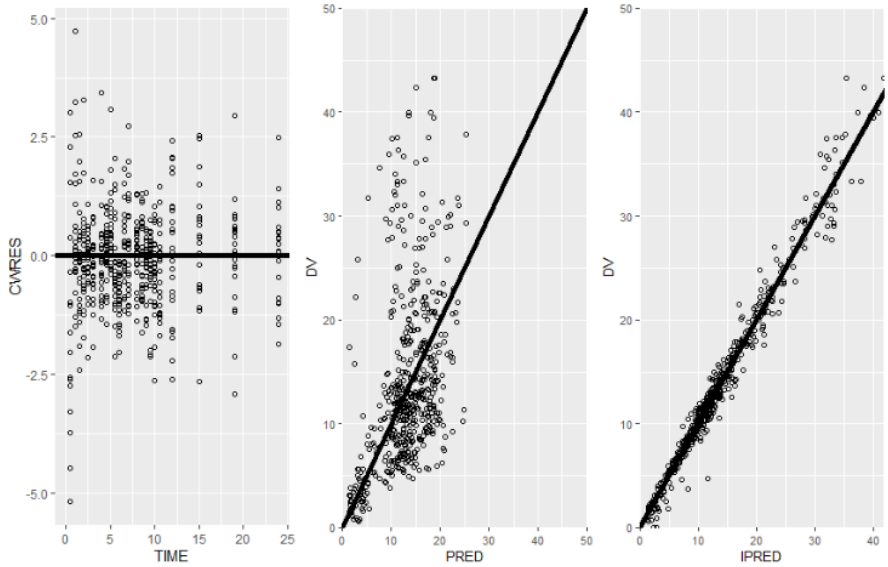

Figure 3: Diagnostic plots for adults for Aptensio®. The three plots from left to right are Conditional Weighted Residuals (CWRES) *vs.* time, DV (Observations) *vs.* PRED (Predicted Concentrations), and DV *vs.* IPRED (Individual Predicted Concentrations). Open circles represent the CWRES values plotted against time and the observed data against the population.

Model qualification

A visual predictive check indicated that the physiological model adequately described Aptensio XR® data (Figure 4) for children and adults. The Aptensio XR® model qualification plot is based on 1000 simulations (N=24 per simulation). Shaded blue areas are the 95% CIs of the 5th and 95th percentiles of the simulated data. The dashed lines are the 5th, 50th, and 95th percentiles for the observed data. Observed data are the open data points.

C_{max} and pAUC parameter precision

The 90% CIs were calculated for the observed and model-simulated (N=1000 studies) data for children and adults for all of the relevant BE parameters (C_{max}, $pAUC_{0-3}$, $pAUC_{3-7}$, $pAUC_{7-12}$) using best-fit parameters. Since the children's data had less than 30% of the 24 subjects with a reported non-zero value at 0.5 hours, this time point was not used in the simulations. The means of the simulated C_{max}, $pAUC_{0-3}$, $pAUC_{3-7}$, and $pAUC_{7-12}$ were then compared with the observed experimental data and the percent bias calculated. Results are presented in Table 3 for children and adults. Final bias values were all within the nominal value of 15% [27]. Some pAUC values in children were not obtained due to the sparseness of data at those times and fewer subjects.

Assessment of dosing for 4-5 year old children (N=9)

A graph of the observed 90% CIs for all children receiving a 10, 15, 20, 30, 40, 50, or 80 mg dose is overlaid with the experimental Cp values from subjects that received those doses. The graph also shows the simulated Cp values for subjects <6 years old overlaid on the same observed 90% CIs after receiving a 10 mg dose (Figure 5). The results from the power calculations for different N values is presented in Table 4 shows that for the N=9 for the current study the power is greater than 80% (e.g., children LT 6).

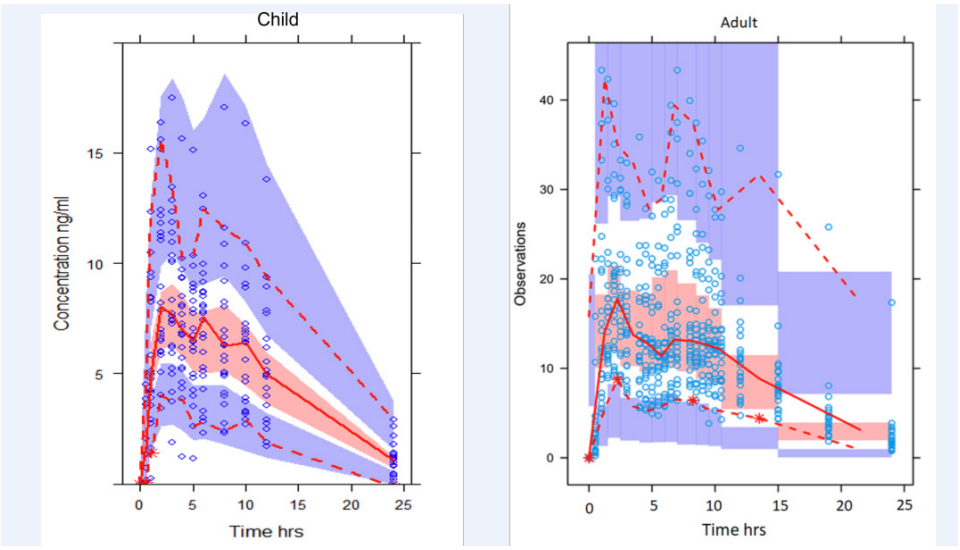

Figure 4: Visual predictive check model qualification plots for children and adults for Aptensio® Predicted corrected visual predictive check. Blue dots=prediction corrected observations, red dashed lines=median of the corrected observations, orange shaded area=95% Confidence Interval (CI) of the median prediction, blue shaded area=95% CI of the 5th and 97.5th prediction interval.

Table 3: Bias results for children's and adult's simulated (N=1000 studies) peak, and pAUC, values.

Children simulation	Percent bias
C_{max} All Ages	1
pAUC(0-3) hr LT6	10.6
pAUC(0-3) hr GT6	14.5
pAUC(0-3) hr All Ages	12.0
*pAUC(3-7) hr LT6	-
pAUC(3-7) hr GT6	7.7
pAUC(3-7) hr All Ages	7.7
*pAUC(7-12) hr LT6	-
*pAUC(7-12) hr GT6	-
*pAUC(7-12) hr All Ages	-
Adult simulation	**Percent bias**
C_{max}	4
pAUC(0-3) hr	1
pAUC(3-7) hr	-15
pAUC(7-12) hr	-5.3

Note: *Difficult to determine since missing for most children.

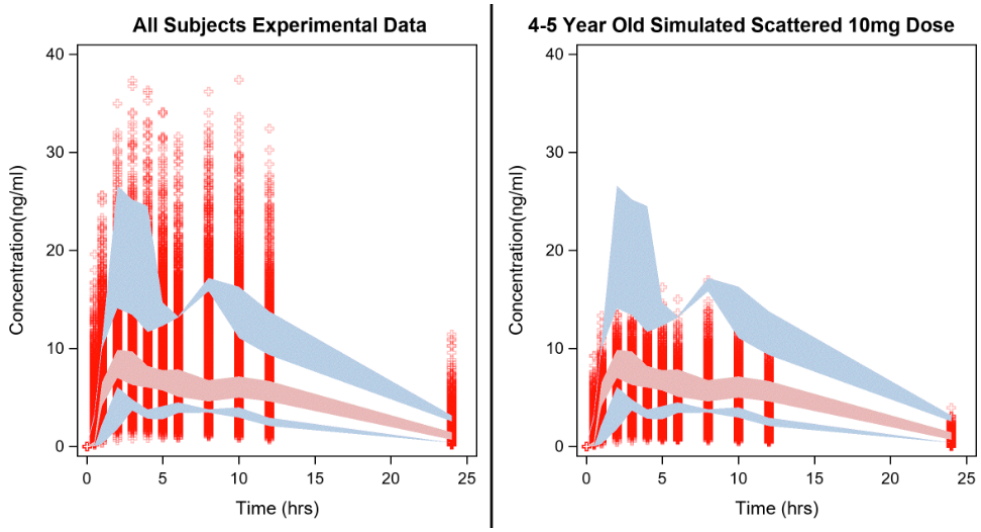

Figure 5: Observed 90% confidence intervals for (6-12 years old) dosed with all doses (10, 20, 30, 40, 50 and 80 mg) of Aptensio®. The simulated scattered concentration values for all doses (10, 20 and 30 mg) and for the 10 mg dose in children 4-5 yrs. The upper, lower, and median confidence intervals for all subjects are presented in blue and orange respectively. **Note:** (▫) SIMCP, (▫) 90%CLL ALL SUBJECTS, (▫) 90%CLM ALL SUBJECTS, (▫) 90%CLU ALL SUBJECTS

Table 4: Age group, number of subjects and the resulting study power based upon the standard deviation values from the simulated studies for the model volume parameter.

Age group: 4-5 years		Age group: 6-12 years	
n	Power	n	Power
4	0.9992844	4	0.298504
5	0.9999998	5	0.459329
6	1	6	0.634381
7	1	7	0.789149
8	1	8	0.898776
9	1	9	0.960337
10	1	10	0.987513
11	1	11	0.996881
12	1	12	0.999388

Note: SD=0.088898 for the 4-5 years of age group and SD=0.307649 for the 6-12 years of age group.

DISCUSSION

Although FDA-approved ER MPH products' PK profiles differ in their peak plasma concentrations and rate at which peak concentrations are attained, these products' data strongly suggest and support a conclusion that PK profile shape is a critical determinant of efficacy [17]. Based upon this, an evaluation of ER MPH PK model performance should always consider whether the model is able to successfully characterize (a) input rates and (b) therapeutic C_{max} values or partial areas inclusive of C_{max}. Lyauk et al. developed a population model for MPH using Ritalin LA® to study the impact of CES1 single nucleotide polymorphism on MPH metabolism. However, in the paper's Supplemental Materials section 3.2, the authors discussed their "inability to estimate variations in maximal plasma concentrations (C_{max}) due to the very sparse sampling used in study II." They concluded that this failure may be related to their reported model shrinkage and that their results "should therefore be viewed as preliminary and further studies need to be conducted to validate the findings."

Several approaches have been published to analyze ER MPH PK profiles. A novel method based upon deconvolution using mean data has been described by Gomeni et al. Another recent population model had slow and fast first-order release rates for an orally-disintegrating ER MPH tablet in children; however, the authors did not present any information related to the model's determination of C_{max}. Another publication on the population PK for Aptensio XR® also used dual first-order release from fast and slow depots. In it, the authors presented a ratio which was the geometric mean (test, 15 mg and 20 mg) divided by geometric mean (reference 10 mg) and for C_{max} the ratio was 0.85 and 0.97 for the 15 mg and 20 mg doses respectively. The 0.85 value was

much worse than the bias of C_{max} (1% children and 4% adults) in the current study. However, since they did no further analysis, the result is difficult to assess, although there was found to be a negative correlation between the two. The aforementioned studies either did not conduct a formal analysis of observed versus model-simulated C_{max} values or when they did, the results had a limitation related to the accuracy/precision of the result. A study using Meta data presented extensive PK-PD data for children but the lack of individual pediatric data did not allow estimation of the true parameters of the pediatric PK-PD relationship [28].

In our current study, we aimed to conduct a formal comparison between observed and model-simulated C_{max}, and partial area-under-the-curve (pAUC) values in children and adults. The current modification of the semi-physiologic model developed for the NONMEM platform and applied to the Aptensio XR® children's data predicts the true C_{max} in the generated base data for children greater than 6 and adults within the nominal limits. For children less than 6 due to the small number and variability, C_{max} values and $pAUC_{3-7}$ hr were more difficult to determine with $pAUC_{7-12}$ hr being absent due to the flatness of the curve (Supplementary Figure 1). For adults, many did have a clearly defined second peak which resulted in the $pAUC_{3-7}$ hr and $pAUC_{7-12}$ hr values being within the nominal limits.

These results are supported by the low shrinkage values associated with most of the absorption parameters for Aptensio XR® in children. In addition, the assumption that children's data are more variable is supported by the results presented in above mentioned Tables 1 and 3 of this study. These results show that the semi-physiologic model describes both children and adult data and that the structural models are similar except for parameter values and that children have first order absorption for both absorptions and adults have zero-order followed by first-order absorption.

CONCLUSION

Based upon the continued development of new MPH ER drug products, this semi-physiological ER MPH NONMEM model may provide an improved platform for data analysis due to its ability to more accurately determine C_{max} and pAUC values in children. Based upon the model simulations, a 10 mg dose seems most appropriate for children 4-5 years old and was sufficiently powered to assess the study validity. The results from this study can possibly be used to determine how well adult data could predict the outcome in children if PD data are included to predict the impact on efficacy for model-efficient parameters such as C_{max} and pAUC. This could be established by simulating a replicate crossover study involving two treatments, two sequences, and four periods using simulated plasma concentrations from this model.

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CONFLICT OF INTEREST

The authors other than Dr. Chaudhary have no financial associations with Rhodes' Pharmaceuticals. Dr. Chaudhary is an employee of Rhodes' Pharmaceuticals. There are no conflict of interest for the other authors.

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