Population Pharmacokinetics of Valsartan in Pediatrics

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Summary: The objective of this work was to develop a population pharmacokinetic model to assess the influence of subject covariates on the pharmacokinetics of valsartan in children. Data were collected from a single dose study in 26 hypertensive children ages 1 to 16 years. Subjects received 2 mg/kg valsartan suspension up to a maximum dose of 80 mg. Plasma samples were collected and analyzed using LC/MS/MS. Several structural pharmacokinetic models were evaluated for appropriateness. Allometric scaling and standard covariate analyses were performed to explain interindividual variabilities. Objective function values and goodness of fit plots were used for model selection. A posterior predictive check was used for model evaluation. A linear 2-compartment first-order elimination model with zero-order absorption and lag-time best described the disposition of valsartan. Allometric scaling and standard covariate analysis revealed that age and body size have similar influence; however, after adjustment for body size using fat free mass (FFM), the effect of increasing age was no longer significant on valsartan clearance (2% per year relative to a typical 8 year old with FFM of 30 kg). The population pharmacokinetic model reveals that increase in age has minimal influence on body size dependent clearance of valsartan in children.

Keywords: valsartan; pediatrics; hypertension; pharmacokinetics; NONMEM; NLME

Introduction

Valsartan is an angiotensin II receptor antagonist that blocks the binding of angiotensin II at the AT1 receptor. By blocking the angiotensin II-AT1 interaction, valsartan inhibits vasoconstriction, renin release and synthesis of aldosterone which in turn results in lower blood pressure and fluid retention. In adults, high blood pressure is a major risk factor for myocardial infarction, heart failure, and stroke. Thus, by lowering blood pressure, valsartan reduces the risk of major cardiovascular diseases.

The prevalence of hypertension in children ages 10 to 15 was determined to be 1% using 1996 data. In children, high blood pressure is defined as systolic or diastolic blood pressure higher than the 95th percentile for gender, age, and height measured on at least three separate occasions. Unlike adults, hypertension in children is usually secondary to identifiable causes such as obesity, diabetes and kidney diseases. Currently, there is no specific treatment guideline that promotes any class of antihypertensive agent over another for pediatrics. Rather, the choice of pharmacologic treatment tends to depend on physician’s preference, regulatory labeling or indication and availability of a suitable formulation such as a solution or suspension formulations. Valsartan is an attractive choice for the treatment of hypertension in children due to the availability of a suspension formulation and regulatory approval for pediatric use.

Early ADME studies show that absolute bioavailability following oral administration was 23% and 39% for capsule and solution formulations, respectively. It was also shown that valsartan undergoes little hepatic metabolism and that 81% of the drug is excreted unchanged via biliary elimination. Most of the administered drug is excreted through the feces while renal clearance accounts for about 30% and 13% of systemic clearance following intravenous and oral administrations, respectively.

The pharmacokinetics (PK) of valsartan have been studied for different adult demographic groups using various formulations. Noncompartmental analysis of in-
travenous, capsule and suspension formulations showed that valsartan has a half-life of 9.45, 7.05, and 7.50 hours for the intravenous, capsule and suspension formulations, respectively. In a population analysis using healthy volunteer data, valsartan was reported to follow two-compartment disposition with zero order absorption. Central volume of distribution was reported to increase with weight. Covariate analysis using patient data revealed that both clearance and central volume of distribution decrease with increasing age. The central volume-weight relationship observed in the healthy volunteers analysis was absent in the patient analysis.

PK of valsartan was also evaluated in special populations such as patients with moderate liver impairment, renal failure and heart failure patients. However, there are no reports in the literature specifically addressing PK of valsartan in a pediatric population. In the present work, we report the population pharmacokinetics of valsartan in hypertensive pediatric patients ages 1 to 16. Several structural models were explored and the effects of patient descriptors on the pharmacokinetics of valsartan were evaluated.

Materials and methods

Data: Data for the population PK analysis were obtained from a multi-center, open label, single dose study conducted in hypertensive children. The study protocol was approved by the respective Institutional Review Boards or Ethics Committees. The exclusion criteria included patients with preexisting conditions that could alter the pharmacokinetic profiles of valsartan. Exclusion criteria included presence of increased liver enzyme (aspartate aminotransferase, alanine aminotransferase) and bilirubin values by greater than twice the normal limit, as well as presence of creatinine clearance less than 40 mL/min/1.73 m². Patients with unstable medical conditions, abnormal electrolyte and hematological values were excluded.

Prior to inclusion, parents or legal guardians of the children provided written informed consent. Children also provided Assent to Participate, when appropriate. Twenty six children received 2 mg per kg body weight of Valsartan suspension (4 mg/mL), to a maximum dose of 80 mg. Doses were administered under fasting conditions between 6:00 AM and 12:00 PM (noon) and the exact time of dosing was recorded. For children less than 6 years of age, plasma concentration samples were collected at predose and 0.5, 1, 2, 4, 8, 12 and 24 hour postdose and for those 6 to 16 years of age, 2 additional samples were collected at 3 and 6 hours post dosing. A total of 198 plasma concentrations was available for analysis. Table 1 summarizes the demographic characteristics of the study population. There was no missing demographic information.

Bioanalytics: Plasma concentration samples of valsartan were analyzed using liquid chromatography/tandem mass spectrometry (HPLC-MS/MS) using turbo ion spray (TIS) positive ion mode. The lower limit of quantitation of the assay was 2 ng/mL. Details of the bioanalytical methods appear in a pervious publication.

Table 1. Demographics details of subjects (N = 26) used in the development of pharmacostatistical model for valsartan pediatric PK

<table>
<thead>
<tr>
<th>Parameter</th>
<th>N</th>
<th>Mean</th>
<th>SD</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>26</td>
<td>7.81</td>
<td>4.86</td>
<td>1</td>
<td>15</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>26</td>
<td>128</td>
<td>32.2</td>
<td>74</td>
<td>194</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>26</td>
<td>50.3</td>
<td>45.8</td>
<td>9.3</td>
<td>192</td>
</tr>
<tr>
<td>FFM (kg)</td>
<td>26</td>
<td>31.2</td>
<td>21.1</td>
<td>6.77</td>
<td>79.5</td>
</tr>
</tbody>
</table>

FFM = fat free mass, calculated using Eqs. (3) and (4).

Model development and simulation were performed using non-linear mixed-effect modeling within the program NONMEM, version VI (ICON Development Solutions, MD, USA). NONMEM (‘Non-linear Mixed Effects Model’) was designed to fit general statistical (non-linear) regression models to data e.g. PK data from a population of subjects. First-order conditional estimation (FOCE) was specified for parameter estimation. Specifics of the pharmacostatistical model for valsartan are described below. The NONMEM data file was prepared using SAS version 8.2 (SAS Institute, Cary, USA), while post-processing of the NONMEM output (e.g. diagnostic graphics) used S-PLUS (Insightful Corporation).

Pharmacostatistical disposition model: Several structural PK models including one-compartment and two-compartment models with first or zero order absorption kinetics and a lag-time were evaluated. Standard model-fitting criteria such as objective function and graphical diagnostic plots were used to guide selection of the structural model. Pharmacokinetic parameters, such as absorption rate constant (Ka), apparent clearance (CL/F), apparent central volume of distribution (Vc/F), apparent inter-compartmental distributional clearance (CLp/F), apparent peripheral volume of distribution (Vp/F), duration for a zero-order absorption, and absorption lag-time were estimated for the one- and two-compartment models. Concentration measurements below the LLOQ were treated as missing in the analyses.

Unexplained between subject variability (BSV) in the structural model parameters was estimated using the following model with random effect $\eta_j$:

$$p_j = TVP \cdot \exp (\eta_j)$$  \hspace{1cm} Eq. (1)

where TVP is the typical value of the PK parameter $P$ (e.g., CL/F) in the population, $p_j$ is the individual value for $P$ in the $j^{th}$ individual and $\eta_j$ is a random variable with a mean of zero and variance $\omega^2_j$. 
This model assumes a log normal distribution for $P_i$ values. Estimates of between subject variability (BSV) in $P$ are presented as square roots of $\omega_i^2$, an approximation of the coefficient of variation of $P$ for a log-normally distributed quantity.

A constant coefficient of variation error model for predictions was used:

$$C_{ij} = C_{ij}^* (1 + \varepsilon_i)$$  \hspace{1cm} Eq. (2)

where $C_{ij}$ is the $i$th concentration measured in the $j$th individual. $C_{ij}^*$ is the respective model predicted concentration and $\varepsilon_i$ is a normally distributed error term with mean of zero and variance $\sigma^2$. Potential sources of residual unexplained variability include assay error, incorrect model specification and incorrect dose and/or sample records.

**Covariate model:** Initial patient covariate-PK relationships were explored graphically by plotting estimates of interindividual variability parameters against patient covariates such as age and weight. The covariates evaluated were gender, age, weight (WT) and fat free mass (FFM).\(^{10}\) Fat free mass represents the lean portion of the body consisting of muscle, bone, heart, kidney and extracellular fluids.\(^{10}\) The calculation of FFM incorporates height, weight and gender as shown on Eq. (3) and Eq. (4). Based on allometric principles, WT and FFM were alternatively introduced to the structural model as base covariates of clearance ($CL/F$ and $CL_d/F$) and volume ($V_c/F$ and $V_p/F$) parameters as advocated by others.\(^{17–19}\) It has been shown that flow dependent parameters follow an allometric exponent of 0.75 and volume-like parameters follow an allometric exponent of 1 and surprisingly, this relationship apparently holds true to nearly all organisms.\(^{20,21}\) Application of the allometric clearance model for 91 different xenobiotics showed that the mean allometric coefficient was 0.75 for all drugs and 0.65 for drug primarily cleared by the kidneys.\(^{22}\) Furthermore, attempts to estimate the allometric exponents were shown to lead towards unstable numerical estimates.\(^{19}\) Therefore, allometric exponents of 0.75 and 1 were used for clearance and volume parameters of valsartan, respectively, and were not estimated in the model (Eq. (5)). Additional patient covariates were evaluated using a centered linear (Eq. (6)) and centered power (Eq. (7)) for continuous covariate age and additive shift (Eq. (8)) models for categorical covariates gender.

\[
\begin{align*}
\text{FFM (Male)} &= 9270 \cdot \text{WT}/(6680 + 216 \cdot \text{BMI}) \quad \text{Eq. (3)} \\
\text{FFM (Female)} &= 9270 \cdot \text{WT}/(8780 + 244 \cdot \text{BMI}) \\
\text{TVP}_j &= \theta_1 \cdot (x/x_{avg})^{\theta_2} \quad \text{Eq. (4)} \\
\text{TVP}_j &= \theta_1 + \theta_2 \cdot (x - x_{avg}) \\
\text{TVP}_j &= \theta_1 \cdot (x/x_{avg})^{\theta_2} \quad \text{Eq. (5)} \\
\text{TVP}_j &= \theta_1 + \theta_2 \cdot X_j \quad \text{Eq. (6)} \\
\text{TVP}_j &= \theta_1 + \theta_2 \cdot X_j \quad \text{Eq. (7)} \\
\text{TVP}_j &= \theta_1 + \theta_2 \cdot X_j \quad \text{Eq. (8)}
\end{align*}
\]

Where:

- $WT$ = Total body weight in kg
- $BMI$ = Body mass index, calculated as kg/m$^2$
- $TVP_j$ = Typical population parameter value for the $j$th subject
- $x_{avg}$ = Population average values for WT and FM, 70 and 44, respectively equation (5), and mean covariate values for equations (6) and (7)
- $\theta_1$ = Represents value of TVP$_j$ when $x = x_{avg}$ for equations (4)–(7), and $x = 0$ for equations (8).
- $\theta_2$ = Represents values of allometric/power exponents for equations (4) and (7), slope of covariate effect for equation (6) and magnitude of covariate effect brought by a categorical covariate for equation (8)
- $x_j$ = The covariate value for the $j$th subject with values $> 0$ for equations (4)–(7) and 0 or 1 for equation (8)

The identification of covariates with impact on the parameters of the PK model was performed in a stepwise manner, initially evaluated by univariate analysis followed by a comprehensive forward addition backward elimination procedure to build the final covariate model. For the forward addition process, decrease in objective function of at least 3.84 ($p = 0.05$, 1 degree of freedom) was used to incorporate a covariate into the model. For the backward elimination step, increase in objective function of at least 10.83 ($p = 0.001$, 1 degree of freedom) was required to retain the covariate. The general requirements for accepting a NONMEM model estimation were a ‘successful minimization’ statement by the NONMEM program, a number of significant digits ≥ 3 for all fixed effect parameters and a successful covariance step.

**Model qualification:** Qualification of the PK model was performed using a visual predictive check methodology (VPC), as implemented by Jadhav et al based on initial recommendations by Yano et al.\(^{23}\) The primary aim of these predictive checks is to verify the agreement between the observed data and model-based simulated values. Parameters were simulated by random sampling from the distributions of the BSV, ignoring parameter uncertainty. Valsartan concentrations were predicted based on estimated parameter values and the same study design characteristics as the observed data. This was repeated 1000 times for the whole dataset. Prediction intervals were created by taking the 5th, 50th (median) and 95th percentile of the simulated data at each observation time point. The observed data were then graphically compared to this prediction interval.

**Results**

**Base model:** A linear 2-compartment disposition model with zero-order absorption and lag-time was selected as the most appropriate structural model to describe valsartan pharmacokinetics in this pediatric population. Equations describing the base structural
Fig. 1. Model diagnostic plots for base model
Table 2. Population PK parameters for typical subject [SE%] for base and final model

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Base Model with WT</th>
<th>Final Model with FFM</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TV (SE%)</td>
<td>BSV (SE%)</td>
</tr>
<tr>
<td>CL/F (L/hr)</td>
<td>2.87 (15.6)</td>
<td>131 (55.6)</td>
</tr>
<tr>
<td>Vc/F (L)</td>
<td>8.36 (14.7)</td>
<td>65.5 (31.5)</td>
</tr>
<tr>
<td>CL/F (L/hr)</td>
<td>0.227 (24.1)</td>
<td>130 (44.6)</td>
</tr>
<tr>
<td>Vc/F (L)</td>
<td>5.18 (32.2)</td>
<td>—</td>
</tr>
<tr>
<td>Duration (hr)</td>
<td>1.23 (8.04)</td>
<td>26.8 (53.9)</td>
</tr>
<tr>
<td>Lag-time (hr)</td>
<td>0.137 (30.5)</td>
<td>—</td>
</tr>
<tr>
<td>RUV (%CV)</td>
<td>22.6 (19.4)</td>
<td>—</td>
</tr>
<tr>
<td>Age on CL/F</td>
<td>0.0469 (74.6)</td>
<td>—</td>
</tr>
<tr>
<td>OFV</td>
<td>2653.7</td>
<td>—</td>
</tr>
</tbody>
</table>

WT: total body weight, FFM: fat free mass, TV: typical value, BSV: between subject variability (%CV), RUV: residual unexplained variability (%CV), SE%: standard error of estimate relative to estimate, Vc/F, Vp/F: volume of distribution of central (Vc/F) and peripheral compartments (Vp/F), CL/F, CL/F: drug elimination clearance (CL/F) and intercompartmental clearances (CL/F), Age on CL: 4.32 *(FFM/44)^0.75 + 0.0566 *(Age-7.8), OFV: NONMEM objective function value.

Fig. 2. Model diagnostic plots for the final model

impact on the PK parameters CL/F and was selected for inclusion into the model. Gender was not identified as a significant covariate. Following the stepwise selection of these influential covariates and formal covariate model development, the final PK model retained the effects of AGE on CL/F. The diagnostic plots and parameter estimates for the final model are shown in Figure 2 and Table 2.

Overall, there was a drop in the NONMEM objective function value by 229 units for the final model which indicates suitability of the covariate model on statistical grounds. Diagnostic plots for the final model (Fig. 2) revealed notable improvements relative to the base model (Fig. 1). Most noticeable was the tighter distribution of concentrations around the line of identity in the plot of population predicted versus observed concentrations. The trend of negative weighted residuals with high concentrations was improved in the final model. The fixed effect population PK parameters were estimated with reasonable precision (SE% ≤ 30%). After inclusion of
covariates in the final model, there was a substantial reduction in the BSV of CL/F (131% to 32.7%), VC/F (66% to 30.9%), and CLd/F (130% to 31.3%) compared with the base model. In contrast, the addition of WT and age to the base model resulted in a more modest reduction of BSV of CL/F (131% to 39.0%), VC/F (66% to 39.7%) and CLd/F (130% to 43.0%). This shows that FFM contributes significantly to BSV in these PK parameters.

Examination of individual model fits revealed reasonable correspondence between observed and population and individual model predicted data. Model qualification using VPC confirmed acceptable agreement between the observed data and model-based simulated values. Most of the observed values lay within the 90% prediction interval and the median trend line clearly reflected the midpoint within the data distributed at individual time points (Fig. 3).

The final model equations for CL/F, Vc/F, CLd/F, and Vp/F are:

\[
TVCL/F \text{ (L/hr)} = 4.32 \cdot (\text{FFM}/44)^{0.75} + 0.0566 \cdot (\text{Age} - 7.8) \quad \text{Eq. (11)}
\]

\[
VVc/F \text{ (L)} = 15.3 \cdot (\text{FFM}/44)^{1.0} \quad \text{Eq. (12)}
\]

\[
TVCLd/F \text{ (L/hr)} = 0.712 \cdot (\text{FFM}/44)^{0.75} \quad \text{Eq. (13)}
\]

\[
TVVp/F \text{ (L)} = 7.6 \cdot (\text{FFM}/44)^{1.0} \quad \text{Eq. (14)}
\]

An interpretation of the effects of FFM and age on CL/F is given in Figure 4. Due to correlation between body size and age in children, CL/F increases with age, and approaches that of adult CL values in the 12–15 years old age groups. However, after adjustment by FFM (right hand side plot of Fig. 4), the correlation between age and CL/F becomes less important as reflected in Eq. (11).

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**Fig. 3.** Model qualification using visual predictive check
Plot contains observed concentrations (circle), median of predicted concentration (solid line), and 90% prediction interval (shaded area).

**Fig. 4.** Correlation between CL/F and Age, and FFM normalized CL/F and age
Plot on the left shows linear relationship of age and CL/F, however that relationship becomes less important after clearance is normalized by FFM as shown by plot on the right hand side.
Discussion

The pharmacokinetics of valsartan is adequately characterized by a linear two-compartment model along with zero order absorption and lag-time analyzed using a mixed effects analysis methodology. Fixed effect pharmacokinetic parameters were estimated with satisfactory precision, with consistently low standard error (SE% ≤ 30%) and goodness of fit plots showed the absence of any systematic bias. The multiphasic elimination of valsartan was consistent with the previous population PK analysis in adults.24)

The present clearance estimates were in close agreement with population clearance estimates obtained from healthy adult data. In healthy adults, population clearance estimate was reported to be 1.84 L/hr.11) After adjusting for a bioavailability factor of 39%,8 the present population clearance estimate of 4.32 would equal 1.68 L/hr for a typical adult with FFM of 44 kg. In the same publication, the population apparent volume of distribution was estimated to be 9.5 L, which is higher than the present estimate of 6.0 L after adjusting for the bioavailability factor.11) This discrepancy may be attributed to the fact that duration of absorption was fixed in the previous analysis.11,24) In hypertensive adults, population CL and Vc were reported as 1.44 L/hr and 9.0 L.11)

Allometric scaling and standard covariate analysis revealed age to have similar influence as body size as a single covariate of clearance in children. However, after adjustment for body size in the form of fat free mass, the effect of increasing age was small, with a clearance increase of only 2% per year relative to a typical 8 year old with FFM of 30 kg. The modest increase of clearance with age observed in the present work is opposite to the reported decrease of clearance with advancing age in older adult hypertensive patients (median age = 55)11,24) and heart failure13) (mean age = 63 patients) patients. The influence of age on clearance was not reported in younger adults (mean age = 30).11,24) The different relationships of clearance and age in the three age groups imply that clearance increases only slightly with age in children, then plateaus in young adults and declines in older patients. This differential relationship of clearance and age is consistent with the different dosing requirements of patients across different age groups as described by Rowland and Tozer.25)

Because the dosing scheme in the current study was based on total body weight and not FFM, total body weight was initially considered a potential size covariate. However, as shown in Table 2, the inclusion of total body weight in the PK model did not adequately decrease BSV values of both clearance and volume parameters. In contrast, the inclusion of FFM to the PK model further decreased the objective function by about 25 points and consistently decreased BSV for all parameters. The superior performance of FFM in describing the PK of valsartan is consistent with a previous observation stating that the fat portion of the body plays minimal role in drug elimination and consistent with the physico-chemical properties of valsartan.19,26) Valsartan is a polar compound with a log P of ~1.49 and oil/water partition coefficient of 0.033. As such, valsartan is expected to have minimal distribution in fatty tissues.26) Although dosing was based on total body weight, the maximum dose was capped at 80 mg, despite the fact that mean and maximum weights for these patients were 52 and 192 kg, respectively Table 1. Therefore, after considering the above factors, FFM was determined to be the most appropriate size covariate in describing the PK disposition of valsartan in children.

The final population PK model was validated using the visual predictive check (VPC) method.23) VPC uses simulated response from the posterior distribution of the parameters, which includes the uncertainty of the estimate in addition to the point estimates (theta, omega and sigma), to assess the model’s ability to represent the actual data. Exclusion of this uncertainty results in a degenerate posterior distribution or a simple predictive check.21) By simulating from the degenerate posterior distribution of the parameters and using the empirical distribution of the response, prediction intervals and median concentration versus time profiles are created, for example 5th, 50th and 95th percentiles. The final population PK model for valsartan provided a good prediction of concentration-time profiles, with most observed data lying within the 90% prediction interval and median trend line closely reflecting the midpoint within the data distribution at individual time points.

In conclusion, the pharmacokinetics of valsartan are well described by a linear 2-compartment population PK model that includes FFM as covariates on clearance and volume parameters consistent with allometric principles. Even though age is competitive to body size as a single predictor of clearance in children, after adjustment for body size, the effect of increasing age is estimated to have minimal impact on clearance. These results suggest that body weight based dosing, up to 80 mg, for valsartan in pediatrics may provide acceptable and comparable exposure to that seen in adult hypertension patients.

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