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Population Pharmacokinetics of Valproic Acid in Pediatric Patients With Epilepsy: Considerations for Dosing Spinal Muscular Atrophy Patients

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Abstract

Valproic acid (VPA) dosing strategies used in recent clinical trials in patients with spinal muscular atrophy (SMA) have utilized a paradigm of monitoring trough levels to estimate drug exposure with subsequent dose titration. The validity of this approach remains uncertain and could be improved by understanding sources of pharmacokinetic variability. A population pharmacokinetic analysis of VPA in pediatric patients with epilepsy was recently performed. The pooled data set included 52 subjects with epilepsy, ages 1 to 17 years, who received intravenous and/or various oral formulations. The data was best fit by a 2-compartment model; inclusion of age and weight reduced intersubject variability for clearance (41%), central volume (70%), and peripheral volume (42%) over the base model. The final model for clearance and volume parameters was clearance = $0.854 \cdot (\text{weight}/70)^{0.75}$; central volume of distribution = $10.3 \cdot (\text{weight}/70)^{1.0} \cdot (\text{age}/8.5)^{-0.267}$; peripheral volume of distribution = $4.08 \cdot (\text{weight}/70)^{1.0}$; and intercompartmental clearance = $5.34 \cdot (\text{weight}/70)^{0.75}$. Application of the model to data from a clinical trial in SMA patients suggests altered kinetics, perhaps based on underlying physiologic differences such as alterations in lean body mass. Future studies in SMA should incorporate modeling and simulation techniques to support individualized dosing and further assess if additional patient-specific factors necessitate alternative dosing strategies.

Keywords

Pediatrics; valproic acid; pharmacokinetics; spinal muscular atrophy; SMA

Valproic acid (VPA), 2-propylpentanoic acid, $\text{C}_8\text{H}_{16}\text{O}_2$, is a 144 Da small-branched chain fatty acid administered intravenously or orally as sodium valproate or as divalproex sodium, composed of sodium valproate and VPA in a 1:1 molar ratio, ie, sodium hydrogen bis(2-propylpentanoate). As a small free fatty acid, VPA is largely hydrophobic, imparting efficient entry to the central nervous system with good oral bioavailability. In the blood, VPA exists in its free form as the valproate ion but is highly bound to serum proteins in a saturable manner, with the unbound fraction increasing linearly from approximately 10% at 50 mg/L to approximately 30% at 200 mg/L total concentrations.¹

Metabolism is primarily via microsomal glucuronide conjugation and to a lesser extent by mitochondrial beta-oxidation and cytochrome P450-dependent oxidation. During monotherapy, half-life is 9 to 18 hours. Clearance may increase up to 60% higher for those on multiple antiepileptic drugs, presumably due to induction of CYP-dependent metabolism.²

Clinical effectiveness in epilepsy has been hypothesized to be related to increased brain concentrations of gamma-amino butyric acid. In addition, VPA may act to reduce release and/or the effects of excitatory amino acids, block voltage-gated sodium channels, and modulate dopaminergic and serotonergic transmission.³ Its broad scope of action has led to an assessment of the benefit of prophylactic use for migraine and as a mood-stabilizing agent in bipolar/mania. As a histone deacetylase (HDAC) inhibitor, VPA offers a promising treatment approach in various indications with currently unmet needs including neurodegenerative conditions⁴ and malignancies.^{5,6} Of the potential novel indications in pediatrics, spinal muscular atrophy (SMA) is an autosomal recessive neurodegenerative disease that predominantly affects motor neurons, resulting in progressive muscular atrophy and weakness. Clinical manifestation of the disease is due to insufficient survival motor neuron (SMN) protein levels as a result of homozygous disruption of the *SMN1* gene. Initial studies have focused on the potential benefit for VPA to upregulate SMN protein expression in patients with SMA and protect against motor neuron degeneration.⁷⁻¹¹ Larger trials have aimed at assessing safety and tolerability while obtaining evidence for clinical efficacy in distinct SMA subtypes based on age and ambulatory status.^{11,12} General difficulties have been met in SMA trials, including lack of robust biomarkers to predict long-term clinical effectiveness over a reasonable time frame and confounding factors during analysis of clinical endpoints evaluated over a longer time period. In addition to these concerns, dosing strategies for patients with epilepsy have been used for patients with SMA under the assumption that the pharmacokinetic profile of VPA is similar.

In the analysis discussed herein, we characterize the population pharmacokinetics (PopPK) of VPA in pediatric patients with epilepsy, using a nonlinear mixed-effects model, and apply the final model to estimate pharmacokinetic (PK) parameters from data collected during a clinical trial in SMA using VPA. Our long-term goal is to extend the knowledge of the VPA therapeutic window in SMA for designing more rigorous trials in the future.

METHODS

Epilepsy Patient Data

Rich sampling data were obtained from 10 pediatric subjects with epilepsy enrolled in the open-label, prospective, randomized, phase IIIB, parallel group, multicenter trial of intravenous Depacon (Abbott Laboratories). The design and results of this study conducted in a larger population of mostly adult subjects were described previously.^{13,14} Briefly, subjects were randomized to receive 3.0 or 1.5 mg/kg/minute valproate sodium injection, for a total dose of up to 15 mg/kg per infusion. During the infusion phase, 3-mL blood samples were collected by venipuncture or indwelling catheter into appropriately labeled collection tubes prior to infusion (0 hour), at 5 minutes, 30 minutes (optional), and 1, 2, 3, 4, 5, and 6 hours after termination of the infusion.

Sparse PK data were obtained from The Children's Hospital of Philadelphia medical records database and Chartmaxx, which included 42 pediatric patients admitted for treatment of acute seizures between 2004 and 2006 and undergoing therapeutic drug monitoring (TDM) of VPA concentrations. Dosing for these patients was based on the institution standard of care for the treatment of seizure. Laboratory guidelines for monitoring VPA concentrations state that blood samples should be drawn after steady-state conditions have been reached;

for patients receiving VPA orally, blood samples should be drawn immediately before the next dose; and VPA samples should be monitored at a consistent time of day because concentration is affected by circadian rhythm. However, per discussion with prescribing physicians, these guidelines are not adhered to in all cases. Prescribing physicians described that sampling may be done at different times, depending on the circumstance: Trough values would be taken if the physician was evaluating options to increase dose due to lack of effectiveness; if the patient is in a steady state and there is no need for maximum effect, a random level would be taken; and if toxicity is expected, a peak value may be more informative for estimating exposure.

Collection of data from medical records and analysis of retrospectively collected data were approved by the investigational review board at The Children's Hospital of Philadelphia. Previously conducted studies were approved under separate investigational review boards.¹³

Bioanalytical Analysis

Pharmacokinetic samples collected during the clinical trial were analyzed for total and unbound VPA plasma concentrations and were determined using a commercially available fluorescence polarization immunoassay on the TDx/TDxFLx system using a validated method at Covance Laboratories, Inc, Vienna, Virginia. Ultrafiltration was used to separate unbound drug. The lower limits of quantification for total and unbound VPA in plasma were 12.5 mg/L and 2 mg/L, respectively. For those collected during routine TDM, specimens were analyzed for total VPA plasma concentrations using the VITROS VALP assay-validated method at The Children's Hospital of Philadelphia Chemistry Laboratory. The VITROS VALP assay was performed using VITROS Chemistry Products VALP Reagent in conjunction with the VITROS Chemistry Products Calibrator Kit 12 on VITROS 5,1 FS Chemistry Systems. Precision of the assay was less than 5% (coefficient of variation [CV] %), determined at VPA concentrations of 22.6 µg/mL, 61.3 µg/mL, and 103.4 µg/mL, and the reportable range was 10.0 to 150.0 µg/mL.

Data Assembly

A PopPK database was developed from 2 sources, which included individual dosing, total VPA concentration observation, and demographic covariate factors. An indicator variable was added that specified intravenous, syrup, capsule, divalproex sodium enteric-coated sprinkle tablet, divalproex sodium enteric-coated delayed release tablet, or extended release tablet. The dosing, covariate, and PK data were merged, formatted for the PK analyses, and saved as csv files, using SAS software (v9.2, SAS, Cary, North Carolina). The final analysis data set consisted of 52 subjects with 231 observations, with a range of 1 to 15 observations per subject.

Only a limited number of subjects in the final PopPK database had available free VPA and albumin concentrations; thus, only total VPA was analyzed in the current study. Given the limited number of extended release dosing, observations following extended release tablets were excluded. Because of the uncertainty in accuracy of dosing time in the TDM data set, observations greater than 15 hours (1-2 half-lives) post dose were excluded. Potential covariates in the final data set included age, weight, concomitant use of other antiepileptic drugs (ie induction status), and race. Potential covariates (ie race, height, and body mass index) were not included in the analysis if greater than 10% of the subject-level covariate records were missing. Of the covariates included in the analysis, there were 0% missing values, and thus imputation was not necessary.

Model Development

The PopPK analysis was conducted using nonlinear mixed-effects modeling (NONMEM version VI level 2.0, ICON Development Solutions, Ellicott City, Maryland) installed with NMQual 6.2.4 (NMQual, Metrum Institute, 2008, <http://nmqual.googlecode.com>). The first-order conditional estimation method with η - ϵ interaction (FOCE-INT) was used for all model runs.

Both 1- and 2-compartment structural models were evaluated with various inter- and intrasubject variability expressions to identify the appropriate base model. Selection of the final covariate model was determined by stepwise addition/deletion method via the likelihood ratio test. Briefly, additional covariates were included in the model if deemed significant ($P < .05$), observed as a reduction in the objective function value (OFV) of greater than 3.84 (χ^2 distribution, $df = 1$). Subsequently, covariates were retained in the model if fixing their value to zero resulted in a greater than 10.84 (χ^2 distribution, $df = 1$) increase in the OFV at a higher level of stringency ($P < .001$). Both additive and normalized power model relationships between covariate and parameter were tested. Ultimately, the final model was selected using a combination of goodness-of-fit criteria including diagnostic scatter plots, convergence with at least 3 significant digits, reasonable parameter estimates, and precision of parameter estimates.

Model Evaluation

Two methods were used to evaluate the performance of the final PopPK model and were based on an internal validation strategy. A stratified non-parametric bootstrap was performed to investigate the precision of model parameters¹⁵ implemented in R software (<http://www.r-project.org/>) using the Mifuns package (<http://mifuns.googlecode.com>). Five hundred replicate data sets were generated by random sampling with replacement and were stratified by study population to ensure a representative study population distribution using the individual as the sampling unit. Population parameters for each data set were subsequently estimated as described for the original estimation procedure. A visual predictive check was performed to evaluate model performance with respect to predicting the VPA concentration time profile following an intravenous (IV) infusion of 15 mg/kg. Monte Carlo simulations ($n = 1000$) were performed including both the fixed-effect and random-effects final model estimates applied to the original data set, and various predicted quantiles were calculated in R software.

Model Application I: Simulations

There were 2 main objectives for the current set of simulations. The first objective was to compare the absorption profiles of 4 oral formulations of VPA for a typical subject in the PopPK data set receiving a single dose of 250 mg. For this simulation, random variability was not included (fixed to zero) for ease of comparison. The simulation data set consisted of 4 typical age (8.5 years) and weight (27.5 kg) subjects, each receiving a different formulation at time zero. VPA concentrations were simulated from 0 to 6 hours.

The second objective was to compare the effect of (a) different dosing intervals, (b) age, (c) weight for age, and (d) random variability on predicted VPA concentrations. In all cases, it was assumed that multiple doses of sprinkle tablets were administered at regular intervals and that steady state had been reached prior to PK sampling. Valproic acid concentrations were simulated frequently from 0 to 24 hours. For this objective, (a) and (b) utilized the same population of 17 subjects, ages 1 to 17 years, each having a typical weight for age. Simulations were done following twice-daily dosing at milligram-per-day amounts of 250, 500, 750, 1000, 1250, 1500, 1750, and 2000, or three times daily at milligram-per-day amounts of 375, 750, 1500, and 1875. These dose amounts were chosen based on

administration of an equal number of 125-mg sprinkle tablets at each dose. For ease of comparison, a single simulation with no random variability was performed, and only ages 2, 6, 12, and 17 are shown.

For (c) and (d), only 3-times-daily dosing was considered. For (c), the data set included 9 subjects who were ages 2, 10, or 17 years and at each age 5th, 50th, or 95th percentile weight for age based on the National Health and Nutrition Examination Survey (<http://www.cdc.gov/nchs/nhanes.htm>). For age 2 years, the dose was 375 mg/d; for age 10 years, the dose was 750 mg/d; and for age 17 years, the dose was 1500 mg/d. These doses were chosen based on the results from (b). For (d), Monte Carlo simulations ($n = 1000$) were performed for 3 typical weight-for-age subjects ages 2, 10, or 17 years and included the random variability (inter- and intrasubject) component of the final model. From this, various predicted quantiles were calculated in R software.

Model Application II: SMA Patient Data

The CARNI-VAL trial was a multicenter phase II double-blind, randomized, placebo-controlled trial of L-carnitine and VPA in patients with SMA. This trial consisted of 2 parallel multicenter studies, targeting different SMA cohorts (Clinicaltrials.gov ID NCT00227266). The study was approved by the University of Utah Institutional Review Board and at each participating clinical trial site (University of Wisconsin-Madison Health Sciences, Wayne State University, Ohio State Biomedical, Johns Hopkins Medical, and St Justine Hospital). Part 1 was a prospective, double-blind, placebo-controlled randomized intention-to-treat protocol to assess safety and efficacy of VPA and L-carnitine in nonambulatory SMA type II or III “sitters” 2 to 8 years of age (cohort 1). Part 2 was a parallel open-label trial in SMA type II or III “standers and walkers” 3 to 17 years of age (cohort 2). Additional details of the study design, study population, and methodology for analysis of clinical endpoints are described elsewhere.^{11,12}

For the current analysis, dosing records, demographics, and VPA trough concentrations from SMA patients enrolled in cohorts 1 and 2 from the CARNI-VAL trial were merged into a single data set (“SMA data set”) and formatted for PopPK analysis. Dosing information was provided as the number of 125-mg sprinkle capsules per day and converted to milligram amount. The dosing interval was assumed to be every 12 hours, with 2 exceptions: Subjects taking 1 capsule per day were assumed to be every 24 hours, and subjects taking 3 capsules per day were assumed to be every 8 hours. To simplify the formatting, subjects receiving an odd number of tablets per day (eg, 5, 7) were assumed to be evenly dosed every 12 hours. The trough concentrations collected at each visit month (3, 6, or 12) were paired with each dosing record, and the time after dose was assumed to be 12 hours. Subjects were assumed to have reached steady state by the time of PK sample collection.

The SMA data set was used to further evaluate the performance of the final PopPK when applied to a novel patient population. This was achieved by fixing the parameter estimates from both the base and final PopPK model developed from epilepsy patients, fitting both models to the SMA data and comparing the resulting OFV and diagnostic plots. Based on the results of this validation method, it was prudent to subsequently estimate the PK parameters in SMA patients and compare these to estimates from patients with epilepsy. This was achieved by estimating clearance and central volume parameters as a fractional value of the estimated values determined from patients with epilepsy.

RESULTS

Epilepsy Patient Population and Data Characteristics

The clinical trial data set included 57 observations from 10 subjects, with at least 1 PK observation for each subject. The dose was administered via a single IV infusion with mean (range) of 14 (12-15) mg/kg/d. There were 2 subjects ages 1 to 2 years, no subjects ages 3 to 10 years, and 8 subjects ages 11 to 17 years. The TDM data set included 174 observations from 42 subjects, with at least 1 PK observation for each subject. The dose was administered via multiple doses of IV and/or oral formulations including syrup, capsule, sprinkle, and tablet, with mean (range) of 23 (3-60) mg/kg/d. The final PopPK data set contained 231 observations from 52 subjects approximately uniformly distributed from age 1 to 17 years. Thirty-six subjects were male, and 16 were female. Thirteen subjects were classified as being on other antiepileptic drugs (“induced”), whereas 39 subjects were on monotherapy (“noninduced”). Of the 10 subjects enrolled in the clinical trial, 4 were induced and 6 noninduced, whereas 9 subjects in the TDM subset were induced and 33 subjects were noninduced.

Pharmacokinetic samples collected during inpatient visits after multiple doses were uniformly distributed from 0 to 15 hours after the last dose. Pharmacokinetic samples collected during the clinical trial ranged from 0 to 6 hours after a single IV dose. Plasma VPA concentrations for the TDM subset were most often within the therapeutic range of 50 to 100 mg/L (63%) but below or above the therapeutic range 26% or 12% of the time, respectively. Only 3% of the concentrations were above 125 mg/L.

Epilepsy Population PK Modeling Results

The data were best described by a 2-compartment model parameterized in terms of clearance (CL), central volume of distribution (V_c), intercompartmental clearance (Q), and peripheral volume of distribution (V_p) and a first-order absorption rate constant for solid oral dosing and zero-order absorption rate constant for liquid oral dosing. The model was implemented using the PREDPP subroutine ADVAN4 TRANS4 in NONMEM software.

The base 2-compartment model was revised to account for the formulation effect on the absorption following oral administration. Because of lack of data in the absorption phase for each formulation and for the simulation purposes of the model, it was considered suitable to fix absorption parameters to previously characterized rates,¹⁶ and these are shown in Table I. An additional absorption lag-time parameter specifying the delay associated with enteric coating was utilized for sprinkle and tablet formulation.

Diagnostic plots of the base model indicated a strong correlation in PK parameters (clearance, volume) with bodyweight (kg), and thus an allometric model was considered during model development. The underlying basis for this type of model has been previously described as useful in pediatrics in that it incorporates known physiologic relationships in the covariate parameter model.¹⁷ Inclusion of covariates in the final model reduced intersubject variability by 41% for clearance, 70% for central volume, and 42% for peripheral volume (Table I). Goodness-of-fit diagnostic plots for the base and final 2-compartment models for all subjects indicated improved fit of observed versus population and individually predicted concentrations of VPA (Figure 1; only final model shown).

Population pharmacokinetic parameter estimates for the final model are shown in Table I. Clearance-and volume-related parameters in the final model are described as follows: CL = $0.854 \cdot (\text{weight}/70)^{0.75}$; V_c = $10.3 \cdot (\text{weight}/70)^{1.0} \cdot (\text{age}/8.5)^{-0.267}$; V_p = $4.08 \cdot (\text{weight}/70)^{1.0}$; Q = $5.34 \cdot (\text{weight}/70)^{0.75}$. The final model estimates a clearance of 0.424 L/h, central volume of 4.05 L, peripheral volume of 1.60 L, and intercompartmental clearance of

2.65 L for a typical 27.5-kg, 8.5-year-old subject (ie, median covariate value in final data set).

The clearance values estimated by the model were in agreement with reported values for pediatric patients having relatively large clearances, expressed in weight (L/h/kg), which decrease with maturation approximating those of adults by around 10 years of age.^{18,19} Extrapolation of clearance predictions to subjects younger than 1 year of age seemed comparable with clearance in neonates previously estimated to be 0.014 L/h/kg.²⁰ Expressed in liters, clearance values increased with body weight and/or age, which has been described in other VPA PopPK studies.^{2,21-23}

Inclusion of induction status on clearance resulted in a statistically significant improvement during model fitting but led to model instability and noticeable bias in diagnostic plots, which may have been due to the inability for the dichotomous indicator to represent the metabolic changes in subjects on polytherapy. Based on the purposes of predicting VPA concentrations, this covariate was not included in the final model.

Volume of distribution increased with increasing body weight based on the allometric expression but with a negative influence on central volume with increasing age. That is, when normalizing for weight, central volume decreased rapidly from 0 to 2 years of age and then gradually thereafter, which corresponds well with historical values in pediatrics.²⁴ Extrapolation of our model to central volume values in subjects younger than 1 year of age, the limit of our data set, was comparable with reported distribution volume in neonates.²⁰ Peripheral volume remained constant for all ages and had the largest intersubject variability, which may be attributed to the underlying intersubject variability in protein binding known to exist but not explicitly described in the model.

Proportional residual variability changed little from base to final model and was described separately for each data subset. Describing the intersubject random effects on PK parameters using a full block covariance matrix (Ω) significantly improved the fit (difference in OFV $\approx$ 12), as compared with a reduced diagonal matrix where covariance is assumed to be zero. Bootstrap confidence intervals contained zero for these covariance parameters, as well as the estimated exponent on the age covariate, indicating that the inclusion of these parameters in the final model should be interpreted with caution.

In terms of VPA kinetics, the final model predicted best in range of 50 to 100 mg/L but overpredicted observed concentrations above 100 mg/L, likely due to limited data above this range. The visual predictive check (Figure 2A) demonstrated a good fit to IV data in 10 subjects, with data evenly distributed around the median predicted value and most of the data contained within the 95% prediction interval. Given the objective of the current study, the model was considered suitable for optimization of VPA dosing in pediatrics, using a criteria of targeting the therapeutic range.

Simulation results

The rate of absorption, based on maximum plasma concentration ($C_{\max}$) and time to reach $C_{\max}$ ($T_{\max}$), has been previously characterized and may be rank ordered as syrup > capsule > sprinkle $\approx$ tablet.¹⁶ Simulations of each formulation recapitulate the characterized profiles and demonstrate the flexibility of the model (Figure 2B). Predicted peak plasma concentrations after a single dose were highest for syrup and lowest for divalproex sprinkle capsule.

Subsequent simulations were based on equal dosing regimens where the same number of 125-mg sprinkle tablets were administered at each dose given twice daily or 3 times daily

(Figure 3A). As expected, more frequent 3-times-daily dosing resulted in lower peaks and higher troughs, reflecting a more controlled concentration range. Peak-to-trough ratio following twice-daily dosing was approximately 0.5 and following 3-times-daily dosing was approximately 0.7. Given the peak-to-trough ratios, an unknown peak concentration would be approximately double the observed trough value after twice-daily dosing and approximately 1.5 times the trough after 3-times-daily dosing. Given the same milligram dose, older subjects had lower concentrations (Figure 3A and 3B). A doubling of the dose from age 2 to 10 years (375-750 mg) and from 10 to 17 years (750-1500 mg) was required to maintain therapeutic concentrations (not shown). Next, subjects with a higher weight for age resulted in lower VPA concentrations (Figure 3C).

The random variability for a typical weight-for-age subject (Figure 3D) was greater than the weight-for-age effect with no random variability (Figure 3C), indicating that significant unaccounted variability in VPA concentrations remain despite the identification of covariate factors in the model.

SMA Patient Population and Data Characteristics

A total of 86 subjects had at least 1 corresponding dose and subsequent trough concentration for the current analysis, and all other dosing or trough concentrations without corresponding records were excluded. The data consisted mostly of subjects ages 1 to 9 years but also included 5 subjects ages 10 to 16 years. Subjects received 8 to 48 mg/kg/d and were generally within the therapeutic range established for epilepsy (50-100 mg/L), although concentrations ranged from 0 to 122 mg/L. Specifically, doses were consistently lower than PopPK model-based recommendations for ages 3 to 16 years (Figure 4, solid line). While there exists the constraint of dosing sprinkle capsules at nominal multiples of 125 mg, it was also of interest to examine the approximated dose recommended range of 20 to 30 mg/kg/d. The dose administered (mg/kg/d) increased at each visit month and was at best overlapping the approximated dose recommended range at the last study visit (Figure 5). Median VPA concentrations were maintained within the target range (50-100 mg/L), but the range of concentrations extended well below the therapeutic range at all visit months. Evaluated as milligram per kilogram per day, the dose decreased with age because of an increase in weight, and subjects ages 1 to 8 years received a similar number of tablets per day.

SMA Population PK Modeling Results

When using the SMA data set as a validation data set, the final model, which incorporated weight and age on PK parameters, resulted in an improved fit to the data determined by reduction in the OFV and reduction in prediction error. However, a considerable bias in prediction error remained present that could not be explained by the final model. Thus, estimation of key PK parameters was performed to determine whether the estimates in patients with SMA differ from those with epilepsy. Estimating clearance and central volume rather than fixing these to values from subjects with epilepsy (ie traditional validation method) resulted in a large decrease in the OFV, the bias in predictions was corrected, and prediction error was reduced as evidenced by diagnostic plots (Supplemental Figure S1; only final model shown). Clearance was estimated to be 0.81 (4.7% CV), and volume was 11.1 (117% CV), which represent the fraction of the typical value for estimates in subjects with epilepsy. That is, the estimates indicate a 19% lower clearance and 11 times greater volume of distribution than in subjects with epilepsy. A corresponding base model with no covariates on PK parameters resulted in very poor fit (Supplemental Figure S2), and parameter estimates indicated an unaccounted trend in intersubject variability based on weight and/or age. Post hoc estimates from the base model suggested a trend based on SMA subtype (ie, type II or III) but was due to the correlation of subtype with weight and/or age, as there was no evidence for this from post hoc estimates from the final model. To be sure,

SMA subtype was included as a covariate on clearance and resulted in no statistical improvement in the final model.

DISCUSSION

The therapeutic range of total VPA plasma concentrations required to prevent seizures in the majority of subjects with epilepsy is narrow but well established. Targeting this range, model-based approaches have described through simulations optimal dosing schemes for various formulations.²⁵⁻²⁷ Monitoring of concentrations while titrating an individual's dose is recommended because of the high intersubject variability and risk of hepatotoxicity. Based on the potential use in novel pediatric indications such as SMA, it is important to identify the sources of variability and determine whether the overall PK profile is similar to that of patients with epilepsy.

There have been multiple studies examining the PopPk of VPA in children with epilepsy. In the first to utilize this approach, Botha et al analyzed 97 steady-state concentration measurements collected from 52 subjects and provided evidence that clearance increased with body weight and concomitant administration of additional antiepileptic medications.^{2,21-23,28-30} More recently, others studies have utilized data collected from hundreds of patients, providing greater precision for estimation of population PK parameters, and have supported some of these initial findings.^{21-23,30} For the most part, these studies have utilized steady-state trough concentrations sufficient for estimating clearance. The current study improves upon these by inclusion of rich PK data collected from pediatric subjects administered IV VPA, allowing for precise estimation of both clearance and volume of distribution parameters. While it would have been preferable to have a greater number of subjects in the analysis, the resulting model achieved good precision in parameter estimates comparable with historical values while simultaneously explaining the underlying changes associated with maturation including metabolism and body size/composition.

The nonlinear relationship between total and unbound VPA concentrations is not described here but has been previously explained by either a 1- or 2-site binding model taking into account albumin concentrations without additional covariate effects.^{1,14} Protein binding indirectly affects the clearance estimates from our model. That is, elimination of VPA occurs primarily by hepatic metabolism and is characterized as restrictive, such that only the unbound drug can be metabolized. Thus, total clearance is dependent on both the free fraction and intrinsic clearance. Clinical evidence indicates intrinsic clearance to be approximately 10 times that of total VPA clearance in neonates with intractable seizures²⁰ and in children on either monotherapy or polytherapy.¹⁹ The current model is limited in its ability to describe intrinsic clearance, but we suspect the changes observed in total clearance with increasing body weight/age are mostly due to metabolic changes and not by the effect of protein binding.¹⁹

In epilepsy, the extent of absorption (ie, systemic bioavailability) and not the rate of absorption is the main determinant of efficacy. Thus, the 4 formulations described in the current model are equivalent in terms of efficacy since they all exhibit approximately 100% bioavailability. For many novel indications such as SMA there is not a requirement for rapid achievement of therapeutic concentrations, and therefore it is preferable to choose formulations that result in lower peak plasma concentrations. Single-dose simulations recapitulate previous comparisons between formulation absorption rates, suggesting that sprinkle VPA would be optimal in this regard. In addition to enteric coating, sprinkle is often administered on food, which helps to alleviate the gastrointestinal side effects observed with syrup and capsules. Syrup is commonly administered via nasogastric feeding

tube in patients in the intensive care unit and is a viable option for many of the SMA patients requiring this intervention because of limited gastrointestinal motility or inability to swallow due to complications of the disease. For pediatrics, both syrup and sprinkle are preferable since they are available as smaller dosage amounts relative to capsules or tablets.

Primary efficacy results from the CARNI-VAL trial are reported elsewhere but generally indicated a lack of effectiveness over a 6-month treatment period.^{11,12} However, a post hoc subgroup analysis indicated potential benefit in the youngest cohort treated over a longer treatment period. Interestingly, we found that the youngest subjects were dosed in the recommended range for epilepsy but were below this range with increasing age. From the dosing data alone, it may be expected that trough concentrations would follow a similar pattern; however, this was not observed. In fact, trough concentrations indicated overall maintenance in the targeted therapeutic range over the duration of the study. This discrepancy may point to altered kinetics, which was subsequently quantified as a lower clearance and higher distribution volume relative to subjects with epilepsy. The magnitude of this difference is difficult to know for certain because of the various assumptions necessary for the current analysis but warrants further investigation into the source of this alteration.

Currently there is no evidence that suggests that deficiency of SMN protein, the underlying basis of SMA disease, would result in reduced metabolic activity of the liver enzymes responsible for elimination of drugs such as VPA. Indirect effects may be more likely a source of the alteration and may be explained by comparison of patient-specific factors between patients with epilepsy versus those with SMA. Epilepsy patients are relatively healthy subjects, whereas patients with SMA are often nonambulatory and may require ventilator support and/or nasogastric feeding. Malnutrition and obesity are both potential sequelae to proximal muscle weakness in SMA. During VPA therapy, appetite can be stimulated and can promote obesity in some or offset malnutrition in others; in fact, excessive weight gain was clearly more prevalent in the active treatment group in nonambulatory SMA patients. Dual-energy x-ray absorptiometry measurements confirmed that the associated weight gain was due largely to an increase in total body fat mass in the absence of an increase in lean mass.¹¹ An increase in body fat relative to lean mass would likely result in an increased peripheral volume (ie, fatty tissue) for VPA to distribute with a lower-than-expected clearance per body weight. In terms of efficacy, children with the greatest improvement in gross motor function gained less fat mass than did those with stable or worsening functional scores. The fact that the functional scores did not decline in light of substantial weight gain in the active treatment group suggests that VPA may indeed have a modest yet measurable biologic effect that is outweighed by its confounding effect of weight gain.

In summary, the current model offers an improved tool for applying a Bayesian approach for individualized dose adjustments, perhaps more robustly for patients with epilepsy. Evidence of considerable unaccounted variability in patients with epilepsy and altered kinetics in patients with SMA suggests that ongoing monitoring of VPA concentrations in patients concurrently with any model-based individualization approach is advised. The combination will serve to assess the validity of such a model for future applications and to improve upon such as more data become available. In general, future SMA studies should incorporate modeling and simulation to ensure dosing and sampling scheme match expectations and allow the sources of variability to be evaluated on precisely estimated PK parameters. Measurement of albumin concentrations and/or unbound VPA is advisable both to account for protein binding and to provide more accurate characterization of the exposure-response relationship, which will help to extend the knowledge of the VPA therapeutic window in SMA. Gaining a better understanding of the underlying differences observed here may

likewise benefit other novel indications applying VPA based on its HDACi mechanism of action.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Goodness of fit diagnostic plots of final VPA population PK model established in pediatric patients with epilepsy.

Figure 2. Simulations of single dose VPA concentrations. A, Visual predictive check of VPA concentrations in pediatric patients with epilepsy receiving 15 mg/kg IV infusion. B, Absorption kinetics of syrup, capsule, divalproex sprinkle or tablet after a single 250 mg dose.

Figure 3.

Simulations of steady-state VPA concentrations for typical weight-for-age subjects administered (A) three 125 mg divalproex sprinkle capsules two-times daily or (B) two 125 mg divalproex sprinkle capsules three-times daily assuming no inter- or intra-subject variability. Simulations of steady-state VPA concentrations for a (C) typical, low and high weight-for-age 10 year old subject administered two 125 mg divalproex sprinkle capsules three-times daily assuming no inter- or intra-subject variability or a (D) typical weight-for-age subject including inter- and intra-subject variability.

Figure 4. Daily dose of divalproex sprinkle capsules versus age in patients with SMA enrolled in CARNI-VAL study. Solid black line indicates the recommended BID dose for each age given simulations from the final PopPK model and approximates a range of 20-30 mg/kg/day. The right axis is the number of sprinkle capsules per day.

Figure 5.

Daily dose of divalproex sprinkle capsules and subsequent trough concentrations in patients with SMA enrolled in CARNI-VAL study. Dotted lines indicate the approximated recommended dose range of 20-30 mg/kg/d (left) or target concentration range of 50-100 mg/L (right).

Table I

Valproic Acid Population Pharmacokinetic Parameter Estimates for Base and Final Models

Parameter	Parameter Estimate (% RSE)		Bootstrap Median (95% CI)
	Base Model	Final Model	Final Model
Syrup: K_0 , mg/h = Θ_1	410	410	–
Capsule: K_a , h ⁻¹ = Θ_2	2	2	–
Sprinkle: K_a , h ⁻¹ = Θ_3	1.2	1.2	–
Sprinkle: ALAG, h = Θ_4	1	1	–
Tablet: K_a , h ⁻¹ = Θ_5	4.1	4.1	–
Tablet: ALAG, h = Θ_6	2	2	–
CL (L/h) = Θ_7	0.410 (9.2)	0.854 (6.21)	0.839 (0.739-0.944)
V _c (L) = Θ_8	5.67 (9.54)	10.3 (6.77)	10.705 (8.942-18.534)
Q (L/h) = Θ_9	3.96 (8.99)	5.34 (20.0)	5.249 (2.105-7.789)
V _p (L) = Θ_{10}	1.33 (32.6)	4.08 (17.2)	3.759 (0.066-5.822)
AGE power V _c = Θ_{11}	–	-0.267 (18.2)	-0.208 (-0.378 to 0.211)
WT power CL	–	0.75	
WT power V _c	–	1.0	
WT power Q	–	0.75	
WT power V _p	–	1.0	
$\omega^2_{CL} = \omega_{11}$	0.371 (20.3), CV% = 60.9	0.129 (21.3), CV% = 35.9	0.128 (0.070-0.192)
COV _{CL-V_c} = ω_{21}	–	0.0397	0.042 (-0.023 to 0.237)
$\omega^2_{V_c} = \omega_{22}$	0.426 (28.6), CV% = 65.3	0.0384 (74.7), CV% = 19.6	0.035 (0.000-0.800)
COV _{CL-V_p} = ω_{31}	–	0.0777	-0.044 (-0.964 to 0.195)
COV _{V_c-V_p} = ω_{32}	–	0.144	0.004 (-3.585 to 0.265)
$\omega^2_{V_p} = \omega_{33}$	3.07 (33.9), CV% = 175	1.02 (62.3), CV% = 101.5	0.823 (0.122-19.108)
$\sigma^2_{prop [TDM]}$	0.121 (10.2), CV% = 34.8	0.121 (9.7), CV% = 34.8	0.126 (0.106-0.156)
$\sigma^2_{prop [TRIAL]}$	0.0019 (19.8), CV% = 4.4	0.00214(23.9), CV% = 4.6	0.002 (0.001-0.003)

RSE, relative standard error; CI, confidence interval; K_0 , zero-order rate constant; K_a , first-order rate constant; ALAG, absorption delay; CL, clearance; V_c, central volume of distribution; Q, intercompartmental clearance; V_p, peripheral volume of distribution; AGE, age in years; WT, weight in kg; $\omega^2_{CL} = \omega_{11}$, intersubject variability on clearance; CV, coefficient of variation; COV_{CL-V_c} = ω_{21} , covariance of intersubject variability between clearance and central volume; $\omega^2_{V_c} = \omega_{22}$, intersubject variability on central volume; COV_{CL-V_p} = ω_{31} , covariance of intersubject variability between clearance and peripheral volume; COV_{V_c-V_p} = ω_{32} , covariance of intersubject variability between central and peripheral volume; $\omega^2_{V_p} = \omega_{33}$, intersubject variability on peripheral volume; $\sigma^2_{prop [TDM]}$, intrasubject variability for subjects in the therapeutic drug monitoring (TDM) subset; $\sigma^2_{prop [TRIAL]}$, intrasubject variability for subjects in the intravenous infusion clinical trial subset.