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Population pharmacokinetics of phenytoin in epileptic children and dosage regimens using Monte Carlo simulation

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ABSTRACT

Objective: The study aimed at a population pharmacokinetic analysis of phenytoin in epileptic children so as to determine optimal dosage regimen for achieving the therapeutic range. **Materials and Methods**: A total of 370 blood level concentrations from 225 patients were collected retrospectively from clinical routine therapeutic drug monitoring data. The data were analyzed based on population pharmacokinetics using NONMEM software.A base model was developed to handle covariates, including age, gender, weight, liver function test results, and co-anticonvulsants. The final model was done until the precision of parameters with minimum objective function value achieved. Monte Carlo simulation was utilized to determine the optimal dosage regimen. **Results:** The data were sufficiently described by the one-compartment model with Michaelis-Menten elimination. The most significant covariates on phenytoin's Vm were body weight and aspartate aminotransferase (AST) level. The optimal dosage regimen for achieving target steady state concentration of 5, 10, 20 mg/L was determined. **Conclusions:** A population pharmacokinetic model of phenytoin in epileptic children was developed. Body weight and AST level could partially affect the inter-individual variability in the Vm of phenytoin. The final model could be used to predict phenytoin individual pharmacokinetic parameters and to assist in dosage optimization.

Keywords: Children, phenytoin, population pharmacokinetics, simulation

INTRODUCTION

Epilepsy is a chronic non-communicable disease of the brain that affects people of all ages. Globally, more than 50 million people have epilepsy, and the estimated 2.4 million people are diagnosed with epilepsy each year.[1] The age groups of 5–9 and 25–34 years have been the highest prevalence of epilepsy in a rural population in Thailand.[2] Phenytoin is considered to be the drug of choice for treatment focal/partial seizure and generalized tonic-clonic seizure in children and adults.[3] The dosage regimen in children and adults is different due to different pharmacokinetics. The dosage adjustment in each patient depends on clinical response and phenytoin plasma concentration.[4,5] Phenytoin is a drug with narrow therapeutic index in which the total phenytoin plasma concentrations are between 5 and 10 mg/L (in some patients) and 10–20 mg/L (in general patients).[5,6] It is challenging to maintain the total phenytoin plasma concentrations within the therapeutic range to ensure the efficacy with acceptably low adverse effect. Furthermore, phenytoin displays the characteristic Michaelis-Menten pharmacokinetics where its elimination is dependent on the maximum rate of metabolism (Vm) and Michaelis-Menten constant (Km).[7,8] However, the Vm and Km values from the previous population pharmacokinetics studies in many countries were different.[9-17] Most of these studies included the data from groups of infants, children, and adults. As a consequent, the influence of covariates on a pharmacokinetic parameter for children could be obscured by the adult's group.[9-14,16] In Thailand, the population pharmacokinetics study of phenytoin in children were rare. To the best of our knowledge, a couple of studies on population pharmacokinetics of phenytoin were conducted in children patients[14,15] which present some limitations such as pool data[14] and small number of patients.[15] Moreover, the

search for optimal dosage regimen to achieve the therapeutic range is necessary for the prescribers.

The aim of this study is to conduct a population pharmacokinetic analysis of phenytoin in epileptic children and to investigate dosage regimen achieving steady state concentrations within therapeutic range by the aid of computer simulation.

PATIENTS AND METHODS

Patients and Data Collection

Data were collected retrospectively from epileptic children who received oral phenytoin in the form of chewable tablet (Dilantin, Pfizer Co. Ltd., Thailand) and capsule (Dilantin, Pfizer Co. Ltd., Thailand and Ditoin, Atlantic Pharmaceutical Co. Ltd., Thailand) for treatment epilepsy from the out-patient department between January 2007 and May 2018 at Queen Sirikit National Institute of Child Health, Bangkok, Thailand. The study protocol was approved by the institutional review board of Queen Sirikit National Institute of Child Health. Phenytoin concentrations were collected during routine therapeutic drug monitoring. Blood sampling was ordered as required clinically. Trough concentrations at steady state were normally drawn. Patients aged 1–16 years with oral administration of phenytoin for at least 3 weeks after dosage adjustments at the time of blood sampling were included in this study. Patients who were documented as noncompliant by doctors in the medical record, and patients with severe liver disease (aspartate aminotransferase [AST] or alkaline phosphatase [ALT] level > 3 times from normal upper level) or renal failure (GFR <30 ml/min/1.73m^2) were excluded from this study. The following data were retrieved from each patient's medical records: Characteristics such as sex, age, body weight, height, and laboratory results such as AST and ALT. Clinical data, such as underlying diseases and concomitant medications, were also recorded.

Drug Analysis

Phenytoin plasma concentration assays were performed as part of routine clinical monitoring. Phenytoin concentrations were measured using fluorescence polarization technique by COBAS INTEGRA® 400 (Roche Diagnostics, Indianapolis, IN, USA). The quantification range of the assay for phenytoin was between 0.42 and 40 mg/L. The coefficient of variation was 2.1 and 2.3% over the entire calibration range of 5.6–27.8 mg/L.

Population Pharmacokinetic Analysis

Pharmacokinetics modeling was analyzed using NONMEM software package version 7.3.0 (Icon Development Solutions, Ellicott City, MD, USA) with gFortran compiler. The NONMEM runs were executed with PDx-Pop version 5.2.1 (Icon Development Solutions, Ellicott City, MD, USA). The normalized prediction distribution error (NPDE) plots were performed by R software (version 3.6.2; The R Foundation for Statistical Computing, http://www.r-project.org/) using R package ggplot. As the trough levels collected from routine therapeutic drug monitoring did not allow the direct estimation of Km and volume of distribution (Vd) of phenytoin, a sensitivity analysis for Km values: 1–17 mg/L[9-14,16] and Vd values: 7–36 L[13-15] were performed to assess influence of these fixed parameters on final estimates of Vm. The optimization model was selected by the precision of the parameter estimates (the lowest relative standard error, %RSE) and minimum objective function value (OFV). As a result, Km and Vd were fixed to 2 mg/L and 9 L, respectively. The program subroutine ADVAN10 TRANS1, which implements a one compartment model with Michaelis-Menten elimination using first-order conditional estimation method with interaction, was selected to define the pharmacokinetic model. Exponential and additive error models were used to describe the inter-individual variability and residual unexplained variability, respectively.

For the development of the covariate model of Vm, a preliminary screening step was done by plotting the *post hoc* pharmacokinetic parameters against the covariates to assess the relationship. The potential covariates influencing phenytoin pharmacokinetics including sex, age, body weight, AST, ALT, and concomitant drugs (carbamazepine, phenobarbital, and valproic acid) were tested. The covariate models were analyzed by the stepwise approach including stepwise forward addition and stepwise backward elimination to identify their potential influence on phenytoin parameters. The stepwise forward additional was conducted to add each covariate one by one into the basic model to build the full model. The covariates were selected into the full model if the decrease of the OFV was >3.84 ($P < 0.05$, degrees of freedom = 1). The final model was obtained by removing covariates from the full model by the backward elimination method. A covariate causing an increase of OFV smaller than 6.64 ($P < 0.01$, degrees of freedom = 1) was rejected. The continuous covariates (such as age, body weight, AST, and ALT level) were tested through linear model, power model, and exponential model where the relationship was centered on the median value. The categorical covariates (such as sex and concomitant medications) were also tested with linear model, proportional model, power model, and exponential model.

Model Evaluation

The performance of the final model was evaluated on the basis of goodness of fit plots. A series of scatterplots compared the measured values and corresponding predictive values population predicted levetiracetam concentrations (PRED) in the base model and final model. The plots were evaluated by viewing the symmetry of point distribution around the unit slope line (y = x). Other plots illustrative of the overall goodness- of-fit of the model were the scatterplots of the conditional weighted residual errors (CWRES) and the NPDE versus the predicted values and time as model diagnostics to determine model misspecification.

Bootstrap analysis and visual predictive check (VPC) were performed to assess the accuracy and robustness of the estimation parameters from the final model. 1000 bootstrap data set were generated by resampling with replacement from the original data set. By comparing the mean of parameter estimations between the final model from the original data set and the median, 95% percentile confidence interval (2.5th–97.5th percentiles) of bootstrap was obtained from model evaluation methods. The VPC was performed by simulating 10,000 subjects to evaluate the predictive performance of the

final model. A 90% prediction interval was selected for VPC from the fifth and ninety-fifth percentiles of the simulated dependent data at each time point, and was compared with the original data set. The VPC was performed from the model evaluation method using the PDx-Pop program.

Simulation

Monte Carlo simulation with 10,000 values based on the estimated parameters in the final model was performed using Crystal Ball software version 11.1.2.4 (Oracle Corporation, USA). The estimated mean values and the inter-individual variability of parameter were used to the simulation. The maintenance dose within the therapeutic range of 5–20 mg/L was calculated by the following formula: [18]

$$MD = \frac{Vm \times Css}{Km + Css}$$

where, MD is the maintenance dose (mg/day), Vm (mg/day), Km (mg/L), Css is the steady-state concentration (mg/L). Km and Vm values were received from the final model.

The maintenance dosage for a given children patient who achieved the target phenytoin concentration of 5–20 mg/L was set as 80–100 mg/day. Simulated maintenance dosage regimens were 80, 85, 90, 95, and 100 mg/day. Optimal dosing regimens were defined as the maximum probabilities of target attainment to those achieving Css within the target therapeutic range (5-10 and 10-20 mg/L) to minimize the risk of toxicity. The Css was calculated with the following formula: [18]

$$\text{Css} = \frac{\text{MD} \times \text{Km}}{\text{Vm} - \text{MD}}$$

where, Css (mg/L), MD is the maintenance dose (mg/day), Vm (mg/day), Km (mg/L).

RESULTS

Patient Characteristics

A total of 225 epileptic children enrolled in this study. The patient demographics and clinical characteristics are shown in Table 1. These characteristics were also utilized as the potential covariates in the model. The patients were treated with oral phenytoin (chewable tablet or capsule). The dosage was calculated as phenytoin in acidic form according to the following equation:

Phenytoin acid (mg) = S × F × D

where S is the salt factor, F is oral bioavailability, and D is phenytoin dose (mg).

The total of 370 concentration-time points during clinical routine therapeutic drug monitoring was collected. Phenytoin was administered orally up to 3 times a day. The time after the last dose covered a wide range from 9.55 to16.28 h with a median of 12.74 h [Figure 1].

Population Pharmacokinetic Analysis

One compartment model with Michaelis-Menten elimination by ADVAN10 TRANS1 subroutine was selected as a base model.

Table 1: The patient characteristics of epileptic children

Characteristic	Values or median (range); mean±SD
Sex (%)	
Male	133 (59.11)
Female	92 (40.89)
Age (years)	8.0 (1-16); 7.61±4.02
Total body weight (kg)	23.8 (8.3-100); 28.59±16.20
AST (unit/L)	26 (11-77); 29.05±11.86
ALT (unit/L)	22 (4-129); 27.48±20.78
Dosage[a] (mg/kg/day)	6.28 (1.45-17.70); 6.83±2.52
Sampling point (%)	
1 sampling point	130 (57.78)
>1 sampling points	95 (42.22)
Concomitant other AEDs (%)	
PHT alone	144 (38.92)
PHT+other AEDs	226 (61.08)
PHT+CBZ	24 (10.62)
PHT+PB	22 (9.73)
PHT+VPA	149 (65.93)
PHT+CBZ+PB	1 (0.44)
PHT+CBZ+VPA	7 (3.10)
PHT+PB+VPA	22 (9.73)
PHT+CBZ+PB+VPA	1 (0.44)
Phenytoin trough concentration (%)	
Sub-therapeutic (< 5 mg/L)	123 (33.24)
Therapeutic (5-20 mg/L)	190 (51.35)
Supra-therapeutic (>20 mg/L)	57 (15.41)

[a]calculated as phenytoin acid form, AST: Aspartate aminotransferase, ALT: Alkaline phosphatase, AED: Antiepileptic drug, PHT: Phenytoin, CBZ: Carbamazepine, PB: Phenobarbital, VPA: Valproate

The population value for Vm was estimated to be 6.10 mg/h while the values of Km and Vd were fixed at 2 mg/L and 9 L, respectively.The inter-individual variability (IIV) of Vm was estimated to be 67.2%. The covariate models were analyzed by the stepwise approach that included stepwise forward addition and stepwise backward elimination methods. The model building process is summarized in Table 2.

During the stepwise forward addition, the body weight, age, AST, and ALT level decreased the OFV significantly. Other covariates including sex and concomitant antiepileptic medication (carbamazepine, phenobarbital, and valproic acid) appeared not to have effect on the Vm of phenytoin. After test for collinearity of these covariates, we found the inter-relationship between body weight and age, and between AST and ALT level. In comparison between body weight and age, it was found that Δ OFV of body weight decreased in higher rate (−165.490 vs. −61.511). Furthermore, decreased Δ OFV of AST level was higher than that of ALT level (−38.301 vs. −8.138). Both body weight and AST level led to the maximum drop in ΔOFV (−165.490 and −38.301). Hence, the body weight and AST level were analyzed using the stepwise

Table 2: Summary of the covariate models development

Model	Covariate	Model equation	OFV	ΔOFV	*P*
Base	-	Vm (mg/h) = θ_1	2024.984	-	-
Forward	AGE	Vm (mg/h) = $\theta_1 \times (AGE/8)^{\theta_4}$	1963.474	−61.510	<0.05
	BW	Vm (mg/h) = $\theta_1 \times (BW/23.8)^{\theta_4}$	1859.494	−165.490	<0.05
	AST	Vm (mg/h) = $\theta_1 \times (AST/26)^{\theta_4}$	1986.683	−38.301	<0.05
	ALT	Vm (mg/h) = $\theta_1 \times (ALT/22)^{\theta_4}$	2016.846	−8.138	<0.05
	SEX	Vm (mg/h) = $\theta_1 + (\theta_4 \times SEX)$	2024.548	−0.436	NS
	CBZ	Vm (mg/h) = $\theta_1 + (\theta_4 \times CBZ)$	2004.245	−0.739	NS
	PB	Vm (mg/h) = $\theta_1 + (\theta_4 \times PB)$	2022.751	−2.233	NS
	VPA	Vm (mg/h) = $\theta_1 + (\theta_4 \times VPA)$	2023.112	−1.872	NS
Full	AST	Vm (mg/h) = $\theta_1 \times (BW/23.8)^{\theta_4} \times (AST/26)^{\theta_5}$	1850.094	−9.400	<0.05
Backward	BW	Vm (mg/h) = $\theta_1 \times (AST/26)^{\theta_5}$	1986.686	+136.592	<0.01
	AST	Vm (mg/h) = $\theta_1 \times (BW/23.8)^{\theta_4}$	1859.494	+9.400	<0.01

ΔOFV: Difference of objective function values, Vm: Maximum rate of metabolism (mg/h), AGE: Age (year), BW: Body weight (kg), AST: Aspartate aminotransferase (unit/L), ALT: Alanine aminotransferase (unit/L), SEX (male=0, female=1), CBZ: Carbamazepine (no=0, yes=1), Phenobarbital (no=0, yes=1), Valproic acid (no=0, yes=1), NS: Not significant

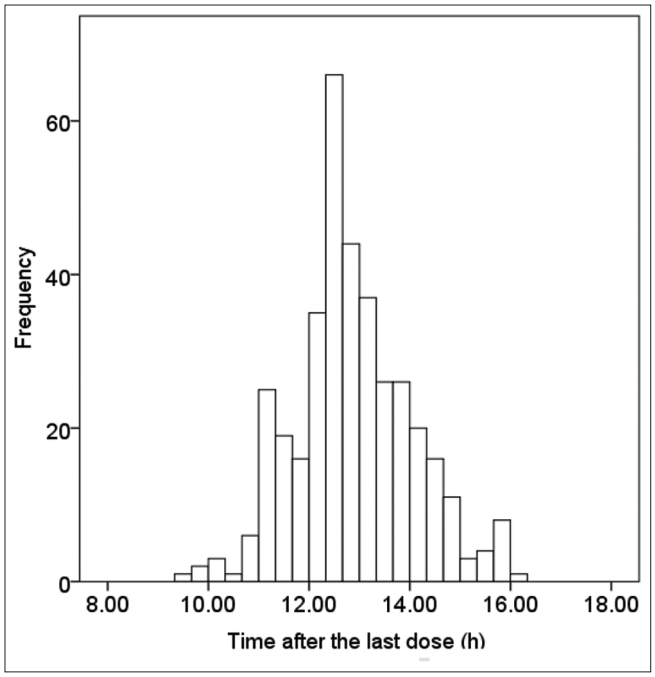

Figure 1: Histogram of the distribution of time after the last dose

backward elimination process. It was also demonstrated that body weight and AST level should be included in the final model. Thus, the final model parameter of phenytoin was described as follows:

$$Vm\ (mg/h) = 4.60 \times (BW/23.8)^{1.33} \times (AST/26)^{-0.374}$$

where Vm is the maximum rate of metabolism (mg/h), BW is body weight (kg), AST is aspartate aminotransferase (unit/L). The median of body weight (in kg) and AST (in unit/L) are 23.8 and 26, respectively.

The plots of goodness of fit for the final model are shown in Figure 2. It was observed that coordinates of PRED and IPRED versus observed concentration symmetric distributed around the identity line [Figure 2a and b]. Besides, the scatterplot of PRED and time after dose versus CWRES demonstrated a good distribution of the point around the zero lines, and most of the points were within the range of -3 and 3, indicating that the model was significantly well fitted [Figure 2c and d].[19] The scatterplot of PRED and time after dose versus NPDE demonstrated a good distribution of the point around the zero lines [Figure 2e and f].

Bootstrap analysis was performed to assess the accuracy and robustness of the estimation parameters from the final model. 1000 bootstrap data set was generated by resampling with successful rate of 91.4%. The result of the bootstrap analysis is shown in Table 3. The median values of parameter estimates from the bootstrap were close to the population estimates in the final model, and the significance of covariates was further verified by the results showing that the 95% confidence intervals of all parameters did not include null. The symmetric 95% confidence intervals of final model were also consistent with the 2.5th–97.5th percentile of bootstrap estimates indicating the accuracy and robustness of the proposed model. The results of the VPC are shown in Figure 3. As shown in Figure 3, <10% (8.92%) of observed data points fall outside a 90% prediction interval. It was demonstrated that the model and parameter estimates adequately described the observed data. Moreover, the VPC with the final covariate model confirmed the goodness of fit of the model to the observed data.

Simulation

The results revealed that body weight significantly affected the pharmacokinetics of phenytoin in children patients, and it should be considered in dosage optimization. Monte Carlo simulation was carried out obtaining 10,000 Vm estimated values having mean and standard deviation of 4.60 ± 0.8326 mg/h (110.4 ± 19.9824 mg/day). We then simulated phenytoin concentrations to achieving Css using this Vm estimation. The results of probabilities of target attainment to achieving Css as simulated maintenance dose are summarized

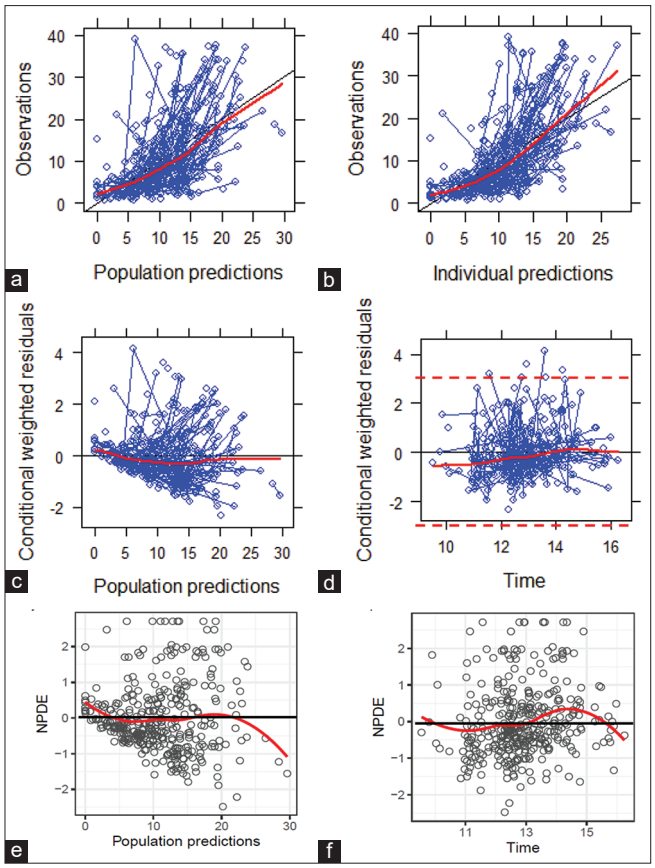

Figure 2: Goodness of fit plots from final model: Population predicted levetiracetam concentrations (PRED) versus observed concentration (a), individual PRED versus observed concentration (b), PRED versus conditional weighted residual errors (CWRES) (c), time after dose versus CWRES (d), PRED versus NPDE (e), and time after dose versus NPDE (f), and identity lines (black solid line), trend lines (red solid line), x = ±3 criteria for proper distribution of the CWRES (red dotted line)

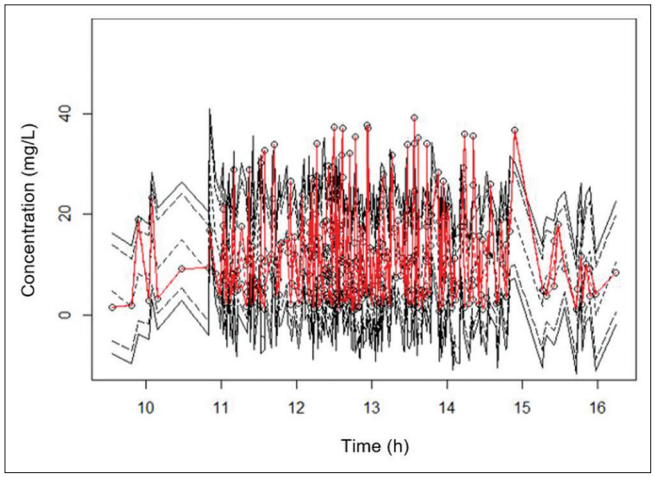

Figure 3: A visual predictive check for the final model. The black solid lines and dashed lines represent the 5th, 10th, 50th, 90th, and 95th percentiles for the simulated concentrations. The opened circles represent observed concentration, which outside the 90% confidence interval amounted to 8.92%

in Table 4. For the simulations, the body weight and AST level were fixed at 23.8 kg and 26 U/L, respectively. It was found for the patient with 23.8 kg-body weight and AST level of 26 U/L that a 90 mg/day dose rate was supposed to reach maximum probabilities of target therapeutic (69.6%) and supra-therapeutic range (0%) with the lowest probabilities of toxicity.

Table 3: The parameters estimated from the final model and bootstrap results

Parameter (unit)	Final model estimate (%RSE, %; 95% CI)	Bootstrap median (95% CI [a])
Fixed-effects parameters		
Vm[b] (mg/h)	4.60 (8.74; 3.81–5.39)	4.613 (3.810–5.340)
BW_Vm	1.33 (7.05; 1.15–1.51)	1.340 (1.130–1.540)
AST_Vm	−0.374 (32.9; −0.615–−0.133)	−0.393 (−0.717–−0.087)
Inter-individual variability parameters (IIV)		
Vm, %CV	18.06 (50.0; 2.55–25.40)	17.92 (0.30–25.83)
Residual unexplained variability parameters (RUV)		
Additive, SD (mg/L)	7.13 (10.5; 6.36–7.83)	7.11 (6.32–7.87)

Vm: Maximum rate of metabolism, BW: Body weight (kg), BW_Vm: BW effect on Vm (power relationship), AST: Aspartate aminotransferase (unit/L), AST_Vm: AST effect on Vm (power relationship), %CV: % Coefficient of variation=sqrt (estimate parameter) × 100, SD: Standard deviation=sqrt (estimation), %RSE: % relative standard error = (standard error/estimate parameter) × 100, 95%CI: 95% confident interval=parameter estimate ± (1.96×standard error), [a]95% CI (2.5th - 97th percentiles) of 1000 bootstrap, [b]Vm for median BW of patients (23.8 kg) and for median AST of patient (26 unit/L)

DISCUSSION

The study of the population pharmacokinetic of phenytoin was conducted in Thai children patients. A one compartment model with Michaelis-Menten elimination and with body weight and AST level as the covariates was established. Notice that our study design was somewhat similar to the study of Kanjanasilp *et al*.[14] listed in Table 5. However, there were differences between the two. In Kanjanasilp *et al*'s study,[14] majority of the population was adult, having the estimated Vm of 279.82 mg/day which was not applicable to children patients. In addition, alcohol consumption showed a significant effect on Vm. This covariate was not relevant to our study as the target population was children. In our model, demographic information (e.g., body weight), biological factors (e.g., AST level), and concomitant medications were investigated as the potential covariates of Vm. And, body weight and AST level were found to have significant effect on Vm. The estimated Vm in our final model was 4.6 mg/h (110.4 mg/day), which was similar to the value of 122.81 mg/day, as reported by Wisuttiwong.[15] Lee *et al*.[17] founded that the AST and ALP levels acted as the significant covariates on the estimated Vm. The Vm value after adjustment made for the significant covariate was 0.525 mg/kg/h (352.94 mg/d), which was higher than the value in our study. In addition, our estimated Vm was lower than those in several other studies[9-13,16,17] with different ethnic groups. Genetic polymorphism of CYP2C9 and CYP2C19 that metabolizes phenytoin could have a possible

Table 4: Probabilities of target attainment to achieving steady- state concentration following a maintenance dose of either 80, 85, 90, 95, or 100 mg/day

Steady-state concentration	Dose/day				
	80 mg/day (%)	85 mg/day (%)	90 mg/day (%)	95 mg/day (%)	100 mg/day (%)
Sub-therapeutic<5 mg/L	64.83	46.36	30.39	19.64	11.83
Therapeutic					
−5−10 mg/L	35.17	50.57	47.17	40.25	32.03
−10−20 mg/L	0	3.07	22.43	28.64	27.63
Supra-therapeutic					
>20 mg/L	0	0	0	11.47	28.45

Dose per day: Calculated dose from phenytoin acid

Table 5: Previous population pharmacokinetic studies of phenytoin

Authors	Population	n (conc.)	Type of data	Covariates related to Vm	The estimated value of Vm
This study (Thailand)	children	225 (370)	C_{trough}	BW, AST	4.60 mg/h (110.4 mg/day)
Grasela *et al*.[9] (Germany, Japan, England)	children and adult	322 (780)	N/A	BW	217.24 mg/day
Miller *et al*.[10] (South Africa)	children and adult	37 (100)	N/A	-	154.7 mg/day
Yukawa *et al*.[11] (Japan)	children and adult	220 (505)	C_{peak}	BW	221.90 mg/day
Yukawa *et al*.[12] (Japan)	children and adult	334 (756)	C_{peak}	BW, co-anticonvulsant	177.56 mg/day
Odani *et al*.[13] (Japan)	children and adult	116 (531)	C_{peak} and C_{trough}	BW	179.21 mg/day
Kanjanasilp *et al*.[14] (Thailand)	children and adult	167 (197)	N/A	Alcohol	279.82 mg/day
Wisuttiwong[15] (Thailand)	children	39 (39)	C_{trough}	-	122.81 mg/day
Chan *et al*.[16] (Singapore)	children and adult	66 (174)	C_{peak}	BW	245.89 mg/day
Lee *et al*.[17] (Singapore)	children	66 (148)	N/A	BSA, AST, ALP	N/A

Vm: Maximum rate of metabolism, BW: Body weight (kg), AST: Aspartate aminotransferase (unit/L), ALP: Alkaline phosphatase (unit/L), N/A: Not available

influence on the Vm of phenytoin.[20-24] Ordani *et al*.[23] found that the Vm value in a patient with heterozygous CYP2C9 and CYP2C19 was lower by 33% and 14% compared with normal ones, respectively. Whereas the prevalence of poor metabolism in CYP2C19 was found between 2% and 5% in Caucasians,[25] 4–8% in Africans,[26,27] and 11–12% in Asian.[25,28] However, the genetic polymorphism was not possible to include as a covariate in the study because genotyping is not carried out routinely in our clinical setting.

The covariates that affected on Vm of phenytoin in the previous studies[9-17] are tabulated in Table 5. Body weight acted as a significant covariate on the Vm of phenytoin in some previous studies.[9,11-13,16] Body weight was also found to have a power function relationship with Vm as a physiological variable.In contrast to Miller *et al*.,[10] Kanjanasilp *et al*.[14] and Wisuttiwong[15] did not report the body weight as the covariate. However, analyzed in a small population (39 children patients), Wisuttiwong[15] found a linear relationship between body weight and Vm value ($r = 0.358$, $P = 0.025$). Lee *et al*.[17] also reported that the body surface area, which was calculated from body weight and height, played as a covariate on Vm. It was implied that body weight was vitally important factor that embodied many aspects of individual characteristics. In addition, AST level showed the characteristic of significant covariate on Vm of phenytoin with a power function relationship.[17] It may be because more than 95% of phenytoin was metabolized in the liver.[7] Increase in the AST level cause the Vm value to decrease with the power function.

In agreement with the previous studies,[9,14-17] age was not found to be a significant covariate on Vm in our study. Moreover, other covariates such as sex and concomitant antiepileptic drugs (carbamazepine, phenobarbital, and valproic acid) were not found to have any effect on Vm. Sex was not significant covariate on Vm as the effect of sex on the activity of CYP2C9 and CYP2C19 which were responsible for phenytoin metabolism[29] were not clear in human.[30] In addition, the findings were consistent with many previous studies.[9,14,16,17]

The inter-individual variability in Vm-parameter was modeled using an exponential model with allometric scaling for body weight according to Grasela *et al*.,[9] Yukawa *et al*.,[11,12] Odani *et al*.,[13] and Chan *et al*.[16] Notice that the exponential model has been commonly used[19] with the residual unexplained variability as an additive error, according to Wisuttiwong.[15] It was recommended that the additive error model was an appropriated model to explain population pharmacokinetics having the fluctuation in the narrow

range.[19] The bootstrap analysis was performed to assess the accuracy and robustness of the mean of estimated parameters from the final model. The resulting parameter estimates were in similar values compared with those from the original data set where they were within the 95% percentile confidence intervals from bootstrapped results. Thus, it is suggested that the final model may have accuracy and robustness.

The phenytoin concentrations for epileptic children (23.8 kg in weight and AST level of 26 unit/L) were calculated to determine the probabilities of target attainment to achieving Css following a maintenance dose of 80, 85, 90, 95, and 100 mg/day. The results suggested that the dosage regimen of 90 mg/day attained a maximum probability to achieving Css within the therapeutic range with the lowest of toxicity from phenytoin. Moreover, the final model could be used to predict phenytoin individual pharmacokinetic parameters, and to support phenytoin dose individualization base on target concentrations.The estimated doses to achieve target Css of 5, 10, and 20 mg/L for the patients who have various body weight (ranging from 10 to 25 kg) and AST (ranging from 20 to 60 unit/L) are shown in Table 6. The estimated doses would provide a guideline, which can help physicians to decision making as target concentrations.

Nevertheless, the current study had several limitations. First, this study was a population analysis from the retrospective routine therapeutic drug monitoring data, and most recruited data were trough concentrations. The data might be insufficient for analyzing Km and Vd. Second, we did not perform the external validation of the final model, again, due to insufficient data. This study used only the VPC for the internal validation. Finally, clinical responses corresponded to the predicted doses to achieve target Css were not yet evaluated. A randomized controlled trial should be carried out to further verify the improvement of clinical outcomes in model-guided treatment.

Table 6: Maintenance dose to achieve target steady-state concentration

BW (kg)	Css (mg/L)	MD (mg/d)				
		AST (unit/L)				
		20	30	40	50	60
10	5	27.45	23.59	21.18	19.49	18.20
	10	32.03	27.52	24.72	22.74	21.24
	20	34.94	30.03	26.96	24.80	23.17
15	5	47.08	40.45	36.33	33.42	31.22
	10	54.92	47.20	42.38	38.99	36.42
	20	59.92	51.49	46.23	42.53	39.73
20	5	69.02	59.31	53.26	48.99	45.77
	10	80.52	69.19	62.14	57.16	53.39
	20	87.84	75.48	67.78	62.36	58.25
25	5	92.87	79.80	71.66	65.92	61.58
	10	108.35	93.10	83.60	76.91	71.84
	20	118.20	101.57	91.21	83.90	78.37

MD: Maintenance dose is calculated from phenytoin acid, BW: Body weight (kg), AST: Aspartate aminotransferase (unit/L), Css: Steady-state concentration

CONCLUSIONS

A population pharmacokinetic model of phenytoin for epileptic children as well as the optimal dosage regimen was developed in this study. It was observed that body weight and AST level may counted as the significant covariates for Vm estimation. The final model can provide helpful information to facilitate individualized phenytoin dosage regimen with similar patient population characteristics to achieving Css within the therapeutic range.

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