

Population Pharmacokinetics of Phenytoin in Japanese Patients with Epilepsy: Analysis with a Dose-Dependent Clearance Model

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The population pharmacokinetic parameters of phenytoin were estimated using routine therapeutic drug monitoring data from 116 epileptic patients. The 531 serum concentration values at steady-state after repetitive oral administration were analyzed using a nonlinear mixed effects model (NONMEM) program designed for estimation of population pharmacokinetic parameters. A one-compartment model with dose-dependent clearance was used for the pharmacokinetic analysis of phenytoin. The volume of distribution (V) was estimated to be 1.23 l/kg in a typical 42-kg patient, assuming that the bioavailability of orally administered phenytoin is 100%. The maximal elimination rate (V_{\max}) and the Michaelis-Menten constant (K_m) were 9.80 mg/d/kg and 9.19 μ g/ml, respectively. The parameter of power function of weight to adjust V and V_{\max} was estimated to be 0.463. In addition, K_m for phenytoin appeared to be 16% increased in patients receiving zonisamide concurrently. The population pharmacokinetic parameters of phenytoin will be useful for designing dosage regimens in epileptic patients.

Key words phenytoin; population pharmacokinetics; Michaelis-Menten elimination; zonisamide; nonlinear mixed effects model (NONMEM)

The population pharmacokinetic parameters not only provide the information required to decide the rational initial dose for a given patient, but also constitute the prior information required for bayesian forecasting, where one predicts the patient's pharmacokinetic parameters and the drug concentration at some future hypothesized dose, given the patient's observed concentration at some particular dose.²⁾ Various nomograms and bayesian regression programs are available for dosage computation for phenytoin exhibiting Michaelis-Menten elimination kinetics. However, the utility of dose-adjustment methods can be highly dependent on the pharmacokinetic model used and on the accuracy of the population pharmacokinetic parameters.^{3,4)}

Population analyses of dose-dependent pharmacokinetics of phenytoin have been performed using the well-known Michaelis-Menten model (MM) or the Lineweaver-Burk form of MM, where the dosing rate is assumed to be equivalent to the elimination rate at steady-state after repetitive drug administration.^{5–8)} The MM and its variants provide estimates of the maximal elimination rate (V_{\max}) and Michaelis-Menten constant (K_m), but no estimate of the volume of distribution (V). Therefore, the bayesian regression program implementing the MM model and its population parameters does not apply in many clinical situations where steady-state phenytoin concentrations are not available.^{3,4)} On the other hand, Beal published an algorithm for explicitly computing phenytoin concentrations as a function of time when a one-compartment model with Michaelis-Menten elimination is assumed.⁹⁾ This permitted the development of a bayesian (individual) analysis program for non-steady state phenytoin data.^{3,10–13)} However, the population pharmacokinetic parameters of phenytoin (mean values of V_{\max} , K_m , and V , and their variabilities) have not been estimated by a one-compartment model with Michaelis-Menten elimination, probably due to difficulties in the

population pharmacokinetic analysis using explicit (exact numerical) solutions to the differential equation for a one-compartment model with Michaelis-Menten elimination (TRUE).⁴⁾ Thus, the population parameters to be implemented in the bayesian regression program remain uncertain.³⁾

We have recently performed a simulation study for the population analysis of pharmacokinetic data arising from a one-compartment model with Michaelis-Menten elimination.⁴⁾ The findings showed that the TRUE model requires a precise analysis method for estimation of population pharmacokinetic parameters (the first-order conditional estimation method) and also considerable computational time to estimate population mean parameters (V_{\max} , K_m , and V) accurately. On the other hand, the one-compartment model with dose-dependent clearance (DDCL) runs approximately 20-fold faster than the TRUE and gives accurate population mean parameters for the steady-state pharmacokinetic data of drugs having a long biological half-life relative to the dosing interval.⁴⁾ These findings suggested that the DDCL model is a promising alternative to TRUE for estimating population pharmacokinetic parameters of drugs exhibiting Michaelis-Menten elimination kinetics. In the present study, we collected the routine therapeutic drug monitoring data of phenytoin to estimate the population pharmacokinetic parameters in Japanese epileptic patients. The concentration data at steady-state after repetitive oral administration were analyzed with the DDCL model using the nonlinear mixed effect model (NONMEM) program, which implements precise analysis methods for estimation of population pharmacokinetic parameters (including the first-order conditional estimation method).¹⁴⁾

METHODS

Patients and Data Description

Serum phenytoin con-

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centration data at steady-state after repetitive dosing (for more than 4 weeks) were collected from 116 epileptic patients, who were treated with oral administration of the conventional tablet (Aleviatin®, Dainippon Pharmaceutical Co., Osaka, Japan) and/or with the preformulated ground tablet at Kyoto University Hospital from November 1989 through September 1994. Table 1 depicts the characteristics of the 116 patients. Most of the patients were outpatients, and no patient had severe hepatic/renal failure. The age of patients ranged from 1 to 37 years old. Figure 1 shows the distribution of age in 116 epileptic patients. Ninety-five patients were also administered other antiepileptic drugs concurrently with phenytoin (Table 1). Fifty-nine patients were treated with only one dose level of phenytoin, whereas 33 patients received more than 3 dose levels. The mean daily dose of phenytoin was 200 mg, and phenytoin was administered orally at a 12-h interval in 87 patients. The serum concentration of phenytoin was measured by a fluorescence polarization immunoassay (TDX®, Dainabot Co., Tokyo, Japan). Five hundred thirty-one serum concentration values were used for the pharmacokinetic analysis; 263 serum samples were obtained for the measurement of approximate peak levels at 2.5 to 4 h after the dosing, while 54 samples were obtained for the measurement of trough levels at 8 to 24 h after the dosing. No significant absorption phase following oral administration was observed in the serum phenytoin concentration data, since serum samples were obtained for routine therapeutic drug monitoring purposes.

Pharmacostatistical Model The time course of drug concentration in an interdose interval at steady-state after repetitive dosing can be analyzed using the DDCL model, which gives an approximate solution to the TRUE model (the exact solution to the differential equation for a one-compartment model with Michaelis-Menten elimination).⁴⁾ That is, assuming that the biological half-life of the drug is long compared to the dosing interval, and that apparent clearance (CL_{ij}) for the j th observed serum phenytoin concentration in the i th subject (SPC_{ij}) is constant at an interdose interval at steady-state after repetitive dosing, CL_{ij} can be described as a function of dosing rate:

$$CL_{ij} = (V_{\max_i} - D_{ij}/\tau_{ij})/K_{m_i} \quad (1)$$

where D_{ij} and τ_{ij} are the dose and the dosing interval associated with SPC_{ij} , respectively. V_{\max_i} and K_{m_i} are the maximal elimination rate and the Michaelis-Menten constant in the i th subject, respectively. Assuming that the bioavailability is 100%, the one-compartment model with rapid absorption following oral administration is

$$SPC_{ij} = D_{ij}/V_i \cdot e^{-CL_{ij}/V_i \cdot t_{ij}} / (1 - e^{-CL_{ij}/V_i \cdot \tau_{ij}}) \cdot (1 + \varepsilon_{ij}) \quad (2)$$

where V_i is the volume of distribution in the i th individual, and t_{ij} is the time after dosing associated with SPC_{ij} . ε_{ij} is a random variable describing intraindividual (residual) variability with mean zero and variance σ^2 . In addition, the DDCL model always gives exact solutions to the TRUE for the peak ($t_{ij}=0$) and trough ($t_{ij}=\tau_{ij}$) levels at steady-state following repetitive bolus administration.⁴⁾

Table 1. Description of Patient Data Used in Population Analysis of Phenytoin Kinetics in the Epileptic Patient

Number of patients	116
Number of outpatients	112
Number of females	43
Age (years)	15.6 ± 6.6
Weight (kg)	42.4 ± 16.5
Number of patients taking phenytoin alone	21
Number of patients taking other anticonvulsants	
Zonisamide	39
Carbamazepine	43
Valproic acid	50
Phenobarbital	15
Others	22
Daily dose of phenytoin (mg)	200 ± 64
Number of measurements	531

Mean ± S.D.

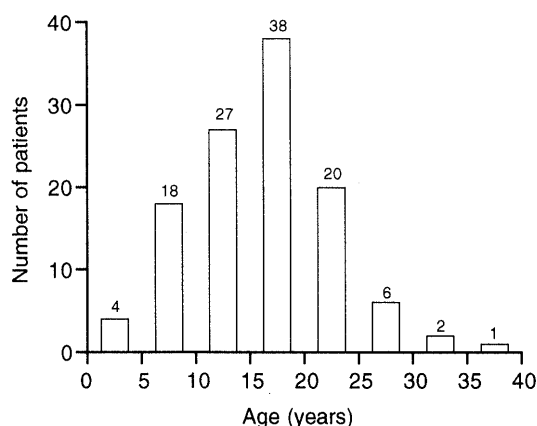


Fig. 1. Distribution of Age in 116 Epileptic Patients

The influence of body weight on V_{\max_i} and V_i of phenytoin and the interindividual variabilities of V_{\max_i} and V_i were modeled using the following equations:

$$SIZE_i = 42 \cdot (WT_i/42)^{\theta_{WT}} \quad (3)$$

$$V_{\max_i} = V_{\max} \cdot SIZE_i \cdot (1 + \eta_{V_{\max_i}}) \quad (4)$$

$$V_i = V \cdot SIZE_i \cdot (1 + \eta_{V_i}) \quad (5)$$

where $SIZE_i$ is the hypothetical body size to adjust V_{\max_i} and V_i in the i th individual, WT_i is the individual body weight in kg, and θ_{WT} is the model parameter to be estimated. V_{\max} and V is the population mean of the maximal elimination rate (in mg/d/kg) and the volume of distribution (in l/kg) in a typical 42-kg patient, respectively. $\eta_{V_{\max_i}}$ and η_{V_i} is a random variable describing interindividual variability with zero mean and variance equal to $\omega_{V_{\max}}^2$ and ω_V^2 , respectively. Modeling body size in this way allows the data to determine the optimal power function of weight to be used to adjust V_{\max_i} and V_i .^{6,15)} Note that when $\theta_{WT}=1$, $SIZE_i$ is simply linearly proportional to weight, and when $\theta_{WT}=0$, $SIZE_i$ is independent of weight.

During the routine therapeutic drug monitoring of phenytoin, the serum phenytoin concentration was sometimes high in patients administered zonisamide concurrently (unpublished observation). Thus, the influence of zonisamide on the K_{m_i} of phenytoin and the

interindividual variability of K_{m_i} were modeled using the following equation:

$$K_{m_i} = K_m \cdot (\theta_{ZNS})^{ZNS_i} \cdot (1 + \eta_{K_{m_i}}) \quad (6)$$

where K_m is the population mean of the Michaelis-Menten constant (in mg/l or $\mu\text{g/ml}$). θ_{ZNS} is the parameter to estimate the effect of concurrently administered zonisamide on the clearance of phenytoin: that is, $ZNS_i = 1$ for the coadministration of zonisamide, and otherwise $ZNS_i = 0$. $\eta_{K_{m_i}}$ is a random variable describing interindividual variability of K_{m_i} with zero mean and variance equal to $\omega_{K_m}^2$.

Data Analysis Data analysis was performed with the NONMEM software (double precision NONMEM Version IV Level 2.1 and NM-TRAN Version II Level 2.1)¹⁴⁾ on a FACOM M-1800 running under a UXP/M UNIX clone at the Kyoto University Data Processing Center. NONMEM pools data from all individuals but explicitly models and handles the complicated error structure arising from a proper accounting of the interindividual (η_i) and intraindividual (ε_{ij}) random effects; it allows us to estimate the population mean parameters, V_{\max} , K_m , V , θ_{WT} , θ_{ZNS} , and the interindividual variabilities, $\omega_{V_{\max}}^2$, $\omega_{K_m}^2$, ω_V^2 , and also the intraindividual variability, σ^2 , simultaneously. The first-order estimation method was the first estimation method available with NONMEM, whereas three precise analysis methods are now available with NONMEM software.¹⁴⁾ In the present study, we used the first-order conditional estimation method with η, ε -interaction.^{4,14)} NONMEM provides estimates of the standard error for all the parameters, and standard error can be used to define confidence intervals (CI) for true parameter values. Statistical significance of the parameters was also evaluated by the likelihood ratio test using the minimum value of the objective function ($-2 \log$ likelihood) produced by NONMEM.¹⁴⁾ That is, when the difference of $-2 \log$ likelihood (*l.l.d.*) between two models allowing a parameter of interest freely estimated vs. fixed to a hypothetical value was greater than 3.84, the parameter value was considered to be statistically significant ($p < 0.05$).

RESULTS

Table 2 shows the final estimates of the population pharmacokinetic parameters in Eqs. 1–6 and their 95% CI. V_{\max} was estimated to be 9.80 mg/d/kg in a typical 42-kg patient, assuming that the bioavailability of orally administered phenytoin is 100%. The estimated K_m value (concentration giving half maximal clearance) was 9.19 $\mu\text{g/ml}$ (mg/l). V was estimated to be 1.23 l/kg in a typical 42-kg patient; however, the 95% CI was relatively large. The estimated θ_{WT} value, 0.463, in conjunction with the small 95% CI, suggested that body weight has a significant influence on V_{\max_i} and V_i , and that these values are not linearly proportional to the body weight. θ_{ZNS} was estimated to be 1.16, assuming that zonisamide inhibits the phenytoin metabolism competitively. The interindividual variability of V_{\max_i} , K_{m_i} , and V_i (*i.e.*, $\omega_{V_{\max}}^2$, $\omega_{K_m}^2$, and ω_V^2) was estimated to be 15.1%, 31.3%, and 45.4%, respectively. The intraindividual (residual) random vari-

Table 2. Population Pharmacokinetic Parameters of Phenytoin

Parameter	Estimate	95% CI
V_{\max} (mg/d/kg)	9.80	8.81–10.8
K_m ($\mu\text{g/ml}$)	9.19	7.05–11.3
V (l/kg)	1.23	0.32–2.15
θ_{WT}	0.463	0.399–0.527
θ_{ZNS}	1.16	1.07–1.25
$\omega_{V_{\max}}$ (%)	15.1	10.8–18.4
ω_{K_m} (%)	31.3	22.2–38.3
ω_V (%)	45.4	14.6–62.5
σ (%)	18.2	16.3–19.9

ability of serum phenytoin concentrations was 18.2%.

DISCUSSION

The general solution for the population analysis with the TRUE model has been available with ADVAN10 in the PREDPP library of NONMEM software.^{9,14)} However, analysis with the TRUE model requires an approximately 50-fold longer computational (CPU) time than that with the MM model. Moreover, because the first-order method is not adequate for the TRUE model which is highly nonlinear in its parameters, the population analysis with the TRUE model requires the precise analysis method (*e.g.* first-order conditional estimation method) which demands an approximately 15-fold longer CPU time than the first-order method.⁴⁾ Perhaps mainly for these reasons, the population pharmacokinetic parameters of phenytoin have not been estimated using the TRUE model. On the other hand, the DDCL model was shown to be a very precise approximate solution for the TRUE model,¹⁶⁾ and was first applied for the estimation of population pharmacokinetic parameters of an antiepileptic drug, zonisamide.¹⁵⁾ The DDCL model in conjunction with precise analysis methods gives accurate population parameters as well as the TRUE model, but runs much faster than the TRUE model.⁴⁾ In the present study, we applied the DDCL model for the estimation of population pharmacokinetic parameters of phenytoin. The CPU time required for the estimation of final parameters and their standard errors was approximately 200 s on our 276-MIPS (40-MFLOPS) mainframe machine.

The MM model gives the downwardly biased estimates of V_{\max} and K_m for the TRUE model, especially when the pharmacokinetic data are analyzed by the first-order method.⁴⁾ The V_{\max} and K_m values of phenytoin estimated here using the DDCL model were significantly larger (as expected) than those estimated previously using the MM model or its variant (Table 2).^{5–8)} The estimated value of V was 1.23 l/kg in a typical 42-kg patient, which may be consistent with the previously reported value, 1.01 l/kg in a typical 70-kg patient.¹⁷⁾ However, the 95% CI for the estimated V was relatively large compared with those for V_{\max} and K_m (Table 2). This may be due to the limited information on an elimination half-life of phenytoin in the pharmacokinetic data used. In the present study, most of the samples were obtained at 2 to 6 h after the dosing, and only 54 samples were obtained for the measurement of trough levels.

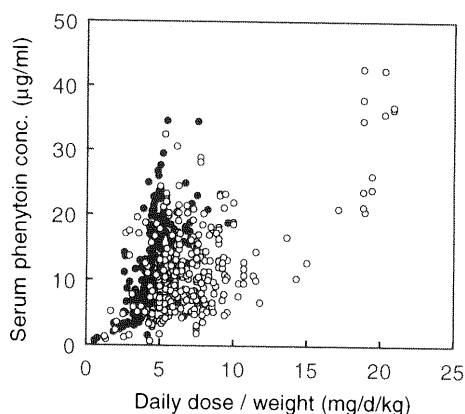


Fig. 2. Serum Concentration vs. Weight-Corrected Daily Dose of Phenytoin in Younger (Less than 15 Years Old, Open Circles) and Older Patients (More than and Equal to 15 Years Old, Closed Circles)

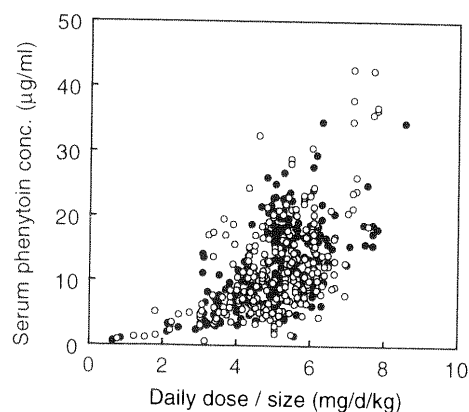


Fig. 3. Serum Concentration vs. Size-Corrected Daily Dose of Phenytoin in Younger (Less than 15 Years Old, Open Circles) and Older Patients (More than and Equal to 15 Years Old, Closed Circles)

The estimated θ_{WT} value, 0.463, suggested that the metabolic activity (V_{max_i}) and the distribution volume (V_i) for phenytoin are not simply proportional to body weight. Figure 2 shows the routinely collected drug monitoring data of phenytoin, where the 531 serum phenytoin concentration values are plotted vs. the weight-corrected daily dose. A significant interindividual difference was observed in the relationship between the daily dose and the serum phenytoin concentration. In addition, the serum phenytoin concentrations at a given dose were much lower in the younger (less than 15 years old) patients than in the older (equal to and more than 15 years old) patients. On the other hand, Fig. 3 shows the relationship between serum phenytoin concentration and size-corrected daily dose, assuming that V_{max_i} and V_i were adjusted by using weight to the power 0.463 ($\theta_{WT} \neq 1$). The large interindividual difference in serum phenytoin concentration in Fig. 2 was significantly converged in Fig. 3. Furthermore, the relationship between the serum phenytoin concentration and size-corrected daily dose in the younger patients was almost identical to that in the older patients. These findings suggested that the correction of dose by weight results in a considerable misconception for predicting phenytoin levels especially in pediatric patients, and that the effect of age on the pharmacokinetics of phenytoin can be adjusted by use of a power function of body weight. In addition, the NONMEM analysis, in which the θ_{WT} value for V_i was different from that for V_{max_i} , did not significantly improve the model fit ($l.l.d. \approx 0$).

Various drug interactions with phenytoin have been reported.^{18,19} However, the detection of the effect of concurrently administered drugs on phenytoin disposition was complicated by the large interindividual variability in pharmacokinetics of phenytoin in routine therapeutic monitoring data.⁸ In the present study, we observed only a significant effect of zonisamide on the disposition of phenytoin. Figure 4 shows the effect of the concomitantly administered zonisamide on the relationship between the serum concentration and the size-corrected daily dose of phenytoin. Slight but significant increases in the serum phenytoin concentration were observed in patients receiving zonisamide. We modeled K_m , so that the con-

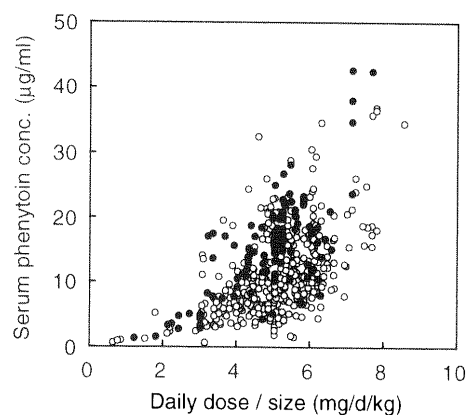


Fig. 4. Serum Concentration vs. Size-Corrected Daily Dose of Phenytoin in Patients Taking Phenytoin without (Open Circles) or with (Closed Circles) Coadministration of Zonisamide

currently administered zonisamide may inhibit the phenytoin metabolism competitively (Eq. 6). The estimated θ_{ZNS} value, 1.16, means that the apparent clearance of phenytoin at a given dose was 14% (on the average) decreased by zonisamide, and that the serum phenytoin concentration was 16% increased in patients receiving zonisamide. In addition, this effect of zonisamide was considered to be statistically significant ($p < 0.01$): the NONMEM analysis, in which the θ_{ZNS} value was assumed to be 1.0, revealed a decreased model fit ($l.l.d. = 15.8$).

In conclusion, the population pharmacokinetics of phenytoin was studied using routine therapeutic drug monitoring data from 116 epileptic patients. The 531 serum concentration values at steady-state after repetitive oral administration were analyzed using a one-compartment model with dose-dependent clearance (Michaelis-Menten elimination). The values of V , V_{max} , and K_m , and also the effect of body weight and concurrently administered zonisamide on the parameters were estimated simultaneously with a NONMEM program. The population pharmacokinetic parameters of phenytoin will be useful for designing dosage regimens in epileptic patients.

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