Population Pharmacokinetics of Phenytoin in Thai Epileptic Patients

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ABSTRACT

The study determined the population estimates for K_m and V_{max} of phenytoin in Thai patients. The serum phenytoin concentrations collected prospectively from outpatients who received phenytoin were analyzed to estimate population pharmacokinetic parameters. There were 197 steady-state concentrations and associated dosage rates (mg/day) from 167 outpatients. The data were analyzed using NONMEM, a computer program designed for population pharmacokinetic analysis that allows pooling of data from many individuals. The maximum elimination rate (V_{max}) was estimated to be 690 mg/d, based on the assumption that the bioavailability of orally-administered phenytoin was 100%. The Michaelis-Menten constant (K_m) value was 16.10 mg/L. The volume of distribution (Vd) was estimated to be 81.90 L. The interindividual variability of V_{max}, K_m, and Vd was estimated to be 87.46%, 0.15% and 23.96% respectively. The intraindividual (residual) random variability of serum phenytoin concentration was 27.55%. It appears as a linear function of weight on K_m (0.265*Wt). Vmax was significantly reduced in patients who consumed alcohol ($p<0.01$). Vmax of patients who did not consume alcohol was 649 mg/d (SD=135) while V_{max} of patients who consumed alcohol was 260 mg/d (SD=63.8). Km was significantly increased in patients who consumed alcohol ($p<0.01$). K_m of patients who did not consume alcohol was 16.1 mg/L (SD=3.49) whereas K_m of patients who consumed alcohol was 23.6 mg/L (SD=5.89). The population pharmacokinetic parameters of phenytoin for Thai epileptic patients were different and higher than the parameters obtained in previous studies. The population pharmacokinetic parameters of phenytoin will be useful for designing dosage regimens in Thai epileptic patients. The dosage regimens for patients who consume alcohol should be initiated at lower dose than the standard dose and gradually increased to the maintenance dose.

Key words: Population pharmacokinetics, Phenytoin, Michaelis-Menten, Thai, K_m, V_{max}

INTRODUCTION

Approximately 1% of the general Thai population has epilepsy. Thus it is estimated that there are more than 600,000 epileptic patients in Thailand (Chulalongkorn Comprehensive Epilepsy Program, 2001). Phenytoin is an anticonvulsant drug, frequently prescribed in adults and children. Present approved uses of phenytoin include: primary or secondary generalized tonic-clonic seizures, simple and complex partial seizures, mixed seizure types which include partial or generalized tonic-clonic seizures and tonic-clonic status epilepticus.

Dosage adjustment of phenytoin is complicated because of the nonlinear (Michaelis-Menten) pharmacokinetics exhibited by this drug (Thomson and Whiting, 1992). A small increase in dose can result in a disproportionate increase in serum phenytoin concentration

and vice versa (Valodia et al., 2000). There are many factors which alter the metabolism of phenytoin and this accounts for the tremendous variability in handling of this drug among patients. Thus empirical dosing of phenytoin is extremely difficult, even with the use of serum drug concentrations (Burton et al., 1985). Several methods using measured serum concentrations have been proposed for phenytoin dosing (Bauer, 2001). Because phenytoin follows saturable pharmacokinetics, these methods are based on derivation of values for Km and Vmax rather than the traditional pharmacokinetic parameters of clearance and volume of distribution.

Many studies show that population pharmacokinetic parameters of phenytoin have high variations (K_m: CV 50%–73%, V_{max}: CV 11%–24%) (Vozeh et al., 1981; Grasela et al., 1983; Rheeders, 1985). A number of factors which influence phenytoin kinetic parameters include sex, age, body size and race (Grasela et al., 1983). Genetic variability of cytochrome P450 (CYP) 2C19 and CYP2C9 affects drug metabolism and pharmacokinetic parameters. Consequently the use of specific pharmacokinetic parameters of the population group will enable the prediction of the serum concentration more accurately than using general population pharmacokinetic parameters (Odani et al., 1997; Mamiya et al., 1998).

A variety of methods are used to estimate the serum concentration and the dose of phenytoin (Richens and Dunlop, 1975a, 1975b; Ludden et al., 1977; Martin et al., 1977; Mullen, 1978; Rambeck et al., 1979; Chiba et al., 1980). They consist of a single total phenytoin steady-state serum concentration method, two or more steady-state level method and an orbit graph method. The two or more steady-state level method is most accurate but the calculation must be based on at least two blood samples. The orbit graph method is convenient but may not be accurate for Thai patients because it was developed from foreign population data (Winter and Tozer, 1986; Winter, 1994; Bauer, 2001).

A new method which helps reduce the problems experienced with these old methods is population pharmacokinetics. Population kinetic studies generate population pharmacokinetic parameters from routine clinical pharmacokinetic data by applying statistical principles. Population pharmacokinetics has increased the efficiency in designing individual dosage regimens and making dosage adjustments (Whiting et al., 1986; Rosenbaum et al., 1995). This method can be used to study a distinct sub-set of the population such as Thai patients.

PATIENTS AND METHODS

Patients

The study population comprised 167 outpatients residing in Thailand from 2 epilepsy clinics. Of these outpatients, 84 were male and 83 were female. The mean age was 33.40 years (range, 4–74 years). One-hundred-and-ninety-seven serum concentration values were used for the pharmacokinetic analysis. The average total daily dose of phenytoin was 277.92 mg/d (range, 100–500 mg/d). Phenytoin was prescribed in doses of one (77.16%), two (8.12%), three (14.21%) and four (0.51%) times per day. Of these patients, 41.12% were taking other antiepileptic drugs concurrently with phenytoin. In addition, 20.30% smoked cigarettes and 16.20% consumed alcohol. There was no patient with hepatic or renal failure or a history of drug abuse. Table 1 depicts the patient characteristics. Informed written consent was obtained from each patient. Compliance was assessed by patient interview. The study was approved by the Ethical Committee of the Faculty of Pharmacy, Chiang Mai University.

Table 1. Patient description used in population analysis of phenytoin pharmacokinetics in epileptic patients.

Number of patients	167
Number of males	84
Age (years)	33.40±13.21
Weight (kg)	55.19±12.70
Height (cm)	158.81±10.99
Daily dose of phenytoin	227.92±62.94
Number of measurements	197
Number of patients taking phenytoin alone	116 (58.88%)
+ Phenobarbital	64 (32.49%)
+ Carbamazepine	5 (2.54%)
+ Valproic acid	5 (2.54%)
+ Phenobarbital + Valproic acid	6 (3.04%)
+ Phenobarbital + Carbamazepine + Valproic acid	1 (0.51%)
Cigarette smoking	40 (20.30%)
Alcohol consuming	32 (16.20%)

Serum Phenytoin Samples

Total serum phenytoin concentrations were measured by fluorescence polarization immunoassay, using an automated TDxFLx system (Abbott Laboratories).

Pharmacokinetic Models

A one-compartment model with the Michaelis-Menten equation was used. It was available with ADVAN10 in the PREDPP library of NONMEM software.

Structural Model:

$$Rij = \frac{Vmj * Cssij}{Kmj + Cssij}$$

Rij (mg/d) = dosing rate of phenytoin predicted
Cssij (mg/L) = plasma concentration
Vmj (mg/d) = the maximum metabolic rate
Kmj (mg/L) = Michaelis-Menten constant of phenytoin

Statistical Models:
For interindividual variation:

$$Km = BW * \theta 1 * (1+\eta 1)$$

If (ALC.EQ.0) Then
TVVM = θ2
ELSE
TVVM = θ4

ENDIF

Or

If (SMOK.EQ.0) Then
TVVM = θ2
ELSE
TVVM = θ4
ENDIF

V_{max} = TVVM * (1+η2)

Vd = θ3 * (1+η3)

θ1 for K_m, θ2 and θ4 for V_{max}, and θ3 for Vd are fixed effect parameters.

η1 for K_m, η2 for V_{max}, and η3 for Vd are random variables describing interindividual variabilities with zero mean and variances equal to $\omega^2 V_{max}$, $\omega^2 K_m$ and ω^2_{Vd}, respectively.

For intraindividual variation:

$$C_{ssij}^{\circ} = C_{ssij} * (1 + \varepsilon_{ij})$$

C_{ssij}° = the observed serum phenytoin concentration for the i^{th} pair in the j^{th} patient
C_{ssij} = the adjusted serum phenytoin concentration for the i^{th} pair in the j^{th} patient
ε_{ij} is a random variable describing intraindividual (residual) variability with zero mean and variance equal to σ^2.

Data Analysis

Data analysis was performed with the NONMEM version V. NONMEM pools data from all individuals but explicitly models and handles the complicated error structure arising from a proper accounting of the interindividual and intraindividual random effects; it gives an estimate of the population mean parameters, V_{max}, K_m, Vd, and the interindividual variabilities, ($\omega^2 V_{max}$, $\omega^2 K_m$ and ω^2Vd), and also the intraindividual variability, (σ^2), simultaneously. NONMEM provides estimates of the standard errors for all the parameters, and the standard errors can be used to define confidence intervals. The statistical significance of the parameters was also evaluated for the objective function produced by NONMEM. When the difference of -2 log likelihood between two models allowing a parameter of interest freely estimated and fixed to a hypothetical value was greater than 6.60, the parameter value was considered to be statistically significant ($p<0.01$). The influence of weight, height, age, gender, co-anticonvulsants, alcohol, cigarettes, renal and hepatic function and albumin level on V_{max} and K_m were investigated.

RESULTS

Table 2 shows the estimates of the population pharmacokinetic parameters and their 95% confidence interval (CI). V_{max} was estimated to be 690 mg/d (12.50 mg/kg/d), based on the assumption that the bioavailability of orally-administered phenytoin is 100%. The estimated K_m value was 16.10 mg/L. Vd was estimated to be 81.90 L. The interindividual variability of V_{max}, K_m, and Vd was estimated to be 87.46%, 0.15%, and 23.96%, respec-

tively. The intraindividual (residual) random variability of serum phenytoin concentration was 27.55%.

Table 2. Population pharmacokinetic parameters of phenytoin.

Parameers	Estimates	SE	95% CI
V_{max} (mg/d)	690.00	333.00	37.30–1342.70
K_m (mg/L)	16.10	0.54	15.04–17.16
Vd (L)	81.90	24.10	40.22–129.14
ω_{Vmax} (%)	87.46	0.84	85.81–89.11
ω_{Km} (%)	0.15	0.23	-0.30–0.60
ω_{Vd} (%)	23.96	0.14	23.69–24.23
σ (%)	27.55	0.023	27.50–27.60

Many factors tended to influence the pharmacokinetic parameters of phenytoin as shown in Table 3. Alcohol consumption, cigarette smoking and gender influence V_{max}. Weight, alcohol consumption, height, creatinine level and cigarette smoking influence K_m.

Table 3. Factors influencing the pharmacokinetic parameters of phenytoin.

Factors	Vmax (Objectives Function)	Factors	Km (Objectives Function)
None	992.685	None	992.685
Alcohol	969.636	Weight	958.343
Smoking	981.526	Alcohol	971.302
Sex	985.724	Height	976.196
		Creatinine level	981.914
		Smoking	982.386

There appears to be a linear function of weight on K_m (=0.265*Wt). Vmax was significantly reduced in patients who consumed alcohol ($p<0.01$). V_{max} of patients who did not consume alcohol was 649 mg/d (SD=135) while V_{max} of patients who consumed alcohol was 260 mg/d (SD=63.8). K_m was significantly increased in patients who consumed alcohol ($p<0.01$). K_m of patients who did not consume alcohol was 16.1 mg/L (SD=3.49), and K_m of patients who consumed alcohol was 23.6 mg/L (SD=5.89). Smoking and gender did not influence V_{max}; and height, creatinine level and smoking did not show a significant difference on K_m when these factors were added to the model.

DISCUSSION

Population pharmacokinetics has an important role in current therapeutic drug monitoring. To adjust phenytoin dosage for individual patients, one must know the accurate and precise estimates of phenytoin population pharmacokinetic parameters. In this study, an

attempt was made to estimate phenytoin population pharmacokinetic parameters in Thai epileptic patients so as to be able to predict differences from Caucasian people.

The results were similar to the population values reported by Odani et al., (1990) and Chanawong (2002) that the K_m trend was higher in Caucasians. Odani et al., (1990) estimated V_{max}, K_m, and Vd to be 9.80 mg/d/kg, 9.19 mg/L, and 1.23 L/kg in a typical 42-kg Japanese patient by NONMEM. In addition, they found an influence of weight on V_{max} and Vd and these values were not linearly proportional to the body weight (θWT, 0.265). However, we didn't find an influence of weight on V_{max}, but only on K_m. Chanawong (2002) determined the values of Michaelis-Menten parameters of phenytoin in 42 Thai epileptic patients who used phenytoin monotherapy by calculating from two steady-state serum phenytoin concentrations derived from two maintenance doses, using the Michaelis-Menten equation and assessed the influence of body weight, age, gender and duration of phenytoin usage. A mean ± SD of Km was 9.28 ± 5.42 mg/L (CV 58.40%). A mean ± SD of Vmax and the values adjusted by actual body weight were 466.45 ± 140.79 mg/d (CV 30.18%) and 7.80 ± 1.93 mg/kg/d (CV 24.74%), respectively. The influence of age on Vmax was obvious in the 60–79-year-old patients. No correlation between Vmax and gender or duration of phenytoin usage was demonstrated. The Km value appeared to have no correlation to actual body weight, age, gender and duration of phenytoin usage.

The population pharmacokinetic parameters of phenytoin in Asian patients were also reported by Yukawa et al., (1989) and Ismail et al., (1994). It was shown that the V_{max} and K_m values in this study were higher than those obtained in their studies. Yukawa et al., (1989) retrospectively collected 550 steady-state phenytoin concentrations from 220 Japanese epileptic patients to estimate population pharmacokinetic parameters by NONMEM. They reported V_{max} and K_m for a 60-kg adult to be 369 mg/d (6.15 mg/kg/d) and 3.67 mg/L. The interindividual variability was 18.6% for the V_{max} and 57.4% for the K_m. The intraindividual variability was 11.4%. They also reported the influence of weight on the V_{max} and age on the K_m. In 1990, they studied more factors and reported the co-anticonvulsants influence on V_{max} and K_m. The V_{max} and K_m for a 60-kg adult outpatient treated with phenytoin alone were estimated to be 325 mg/d and 2.41 mg/L respectively while for the same-sized individual taking phenytoin with co-anticonvulsants, the estimates were 351 mg/d (8% higher) and 3.18 mg/L (32% higher), respectively. Ismail et al., (1994) used OPT® to estimate Michaelis-Menten parameters for phenytoin in 58 routine Malaysian epileptic patients. The average K_m was 3.7 (16.3-5.18) mg/L and the average V_{max} was 7.32 (4.56–9.57) mg/kg/d. The K_m was independent of age, weight and gender but there was a weak correlation between V_{max} and body weight. They could not define the extent of genetic influence on K_m and V_{max} with regard to differences between Caucasian and Asian patients.

Sheiner and Beal (1980) reported V_{max} 7.22 mg/kg/d (interindividual SD 1.72, CV 24%) and K_m 4.44 mg/L (interindividual SD 2.4, CV 54%) for serum concentrations collected from epileptic Caucasian patients. Grasela et al., (1983) presented a more comprehensive analysis of routine phenytoin data collected from a number of different sources. The V_{max} and K_m for a 70-kg adult male European were estimated to be 415 mg/d (5.93 mg/kg/d) and 5.7 mg/L, respectively. V_{max} was not influenced by gender, age or data source. K_m was not influenced by gender. The K_m for patients less than 15 years old was 43% less than that of older patients. The K_m of Japanese patients appeared to be 23% less than that for European patients. Rheeders (1985) investigated steady-state phenytoin samples from 37 black epileptic patients and reported the results as: V_{max} 6.5 mg/kg/d (interindividual SD 1.3, CV 20%) and K_m 3.4 mg/L (interindividual SD 2.47, CV 73%).

Table 4 shows the population pharmacokinetic parameters of phenytoin in Asian and Caucasian epileptic patients and presents the factors which influence V_{max} and K_m compared between several studies.

Table 4. The population pharmacokinetic parameters of phenytoin in Asian and Caucasian patients.

Parameters	Asian					Caycasian		
	Thai (this study)	Thai (Chanawong, 2002)	Japan (Yukawa et al., 1989)	Japan (Odani et al., 1977)	Malasian (Ismail et al., 1994)	Black (Rheeders, 1985)	Switzerland (Sheiner and Beal, 1980)	European (Grasela et al., 1983)
V_{max} (mg/kg/d)	12.50 (690.00 mg/d)	7.80 (466.45 mg/d)	6.15 (369 mg/d)	9.80	7.32	6.5	7.22	5.93 (415 mg/d)
K_m (mg/L	16.10	9.28	3.67	9.19	3.7	3.4	4.44	5.7
Vd (L)	81.90			1.23 L/kg				
ω_{Vmax} (%)	87.46	30.18	18.6	15.1		20	23.8	20
ω_{Km} (%)	0.15	58.40	57.4	31.3		73	54.1	50
ω_{Vd} (%)	23.96			45.4				
σ (%)	27.55		11.4	18.2			0.250 mg/kg/d	8.6
Factors influence: V_{max}	Alcohol Smoking		Weight Co-anticon--vulsants	Weight				Weight
K_m	Weight Alcohol Height		Age Co-anticon--vulsants					Age Race

Genetic characteristics, environmental factors such as diet, alcohol consumption, smoking, concomitant use of other medications, over-the-counter (OTC) drugs or products and herbal preparations, as well as physiological variables such as age, gender and pregnancy can affect the disposition of medications and modify the intricate balance between medication dose and serum concentration. A major factor contributing to interindividual differences in the pharmacokinetics of medications is the distinct variation in the capacity of individuals to metabolize drugs. In addition to more familiar influences such as environmental and nutritional factors, age, coadministration of other medications and underlying disease processes, genetic factors have been found to be important determinants of drug metabolizing activity (Sinclair and Jessen, 2002).

The differences of population pharmacokinetic parameters are shown between Asian and Caucasian patients. Phenytoin is metabolized in the liver principally by CYP2C9 to form (S)-4'-hydroxyphenytoin and also to a minor extent by CYP2C19 to form R-4'-hydroxyphenytoin. Polymorphically-expressed human CYP2C subfamily are CYP2C9 and CYP2C19 (Odani et al., 1997; Mamiya et al., 1998; Mary et al., 2001; Shintani et al., 2001). Site-directed mutagenesis studies have led to the isolation and subsequent characterization of 6 allelic variants of CYP2C9. However, only two of these synthetic variants, CYP2C9*2 (Arg144Cys) and CYP2C9*3 (Ile359Leu), have been found to occur in human.

The CYP2C9*2 and CYP2C9*3 alleles are expressed at a greater frequency in Caucasians (7%-10%) compared to Asians (<3%). Individuals heterozygous for the CYP2C9*3 allele have an estimated Vmax for phenytoin hydroxylation that is 33 to 42% lower than that of individuals homozygous for the wild type CYP2C9*1. The CYP2C9 slow metabolisers (the CYP2C9*2/*3 or the CYP2C9*3/*3 genotype) requiring phenytoin therapy may be initiated at 50% of the standard 300 mg daily dose. While CYP2C19*2 and CYP2C19*3 are the best characterized among 8 alleles, the CYP2C19*2 allele is expressed at a greater frequency in Asians (25%) than in Caucasians (13%). However, a report has indicated that poor metabolizers (PMs) of CYP2C19 represent approximately 3–5% of Caucasian, a similar percentage of African-American and 12–100% of Asian groups (Goldstein, 2001). The CYP2C19*3 is 8% in Asians, but <1% in Caucasians. CYP2C19 also catalyses phenytoin 4' hydroxylation but with a higher K_m when compared with CYP2C9. The elimination of phenytoin is impaired in poor metabolisers of CYP2C19 when a high dose of phenytoin is administered. In addition, we also found differences in population pharmacokinetic parameters between Thai and Japanese patients. Another variant of CYP2C9 has been identified in Japanese patients with epilepsy. The isoleucine at amino acid residue 359 has been replaced by threonine (CYP2C9-Thr^{359}). The occurrence of CYP2C9-Thr^{359} appears to result in a reduced capacity to metabolise phenytoin. Besides CYP2C9, CYP2C19 and CYP2C18 were reported to contribute to the hydroxylation of phenytoin and there are reports of genetic polymorphisms. Another study presented genetic links between the CYP2C18 gene and the CYP2C19 gene in Japanese patients with epilepsy and speculated that the polymorphisms of CYP2C19 might also be the polymorphisms of CYP2C18 (Mamiya et al., 1998).

Tassaneeyakul et al., (2002) studied the pharmacogenomics of CYP2C19 in 107 Thai subjects and revealed that the allele frequencies for CYP2C19*1, CYP2C19*2 and CYP2C19*3 were 0.71 (95% CI 0.65–0.77), 0.27 (95% CI 0.21–0.33) and 0.02 (95% CI 0.01–0.05), respectively. The poor metabolizers phenotype and the frequencies of CYP2C19 defective alleles in Thais, particularly CYP2C19*3, were lower than those observed in other Oriental populations. Although there was not any study about pharmacogenetics of CYP2C9 and CYP2C18 in Thai patients, the proportion of genetic polymorphisms of these enzymes in Thai patients may be different from other populations. As Table 5 shows there is a high incidence of subtherapeutic responses (<10 mg/L, 57%) and about 16% incidence of toxic response concentrations (>20 mg/L) in the study of Winter and Tozer (1986), while in this present study we found 34% of subtherapeutic levels and 31% of toxic levels. Aberrations in the isoenzymes can cause clinical consequences, resulting in toxicity or altered efficacy of drugs. Signs of overdose are ataxia, disturbances of consciousness and mental confusion. The effects of genetics on the population pharmacokinetic of phenytoin in Thai patients need to be determined in future studies.

Table 5. Distribution of phenytoin concentrations in plasma among 100 ambulant patients chronically treated with 300 mg of phenytoin sodium daily.

Plasma phenytoin concentration (mg/L)	**Percent of patients** (Winter and Tozer, 1986)	**Percent of patients** (This study)
0–5	27	5
>5–10	30	29
>10–20	29	35
>20–30	10	23
>30	6	8

The influences of alcohol consumption and smoking on V_{max} and K_m were examined. It was found that only alcohol influenced V_{max} and K_m. This might be attributed to smoking having a lower effect on enzyme CYP450 than alcohol. The potential effect of tobacco smoking on the pharmacokinetics of phenytoin could be substantial, although it has not been found to significantly alter disposition of this drug. The pharmacokinetic parameters such as the mean body clearance, half-lives and the mean serum concentration compared between non-smoker and smoker were not found to be significantly different (Miller, 1989). The V_{max} of patients who consumed alcohol was significantly lower than patients who did not consume alcohol, so perhaps the initial daily dose of phenytoin in these patients who consumed alcohol should be lower than the standard dose. However, the K_m of patients who consumed alcohol was higher than patients who did not consume it, because alcohol competitively inhibits phenytoin metabolism, thus alcohol drinkers may be given a lower maintenance dose of phenytoin. The effect of alcohol on the metabolism of drugs was shown with antipsychotic drugs. Acute ingestion of alcohol (ethanol) together with tranquilizers or hypnotics (mainly governed by CYP2C19 and CYP2D6) is responsible for several pharmacokinetic interactions that can have significant clinical implications. In general, metabolism of these drugs is delayed when combined with alcohol, but some reports have suggested otherwise (Tanaka and Misawa, 1998).

CONCLUSION

In conclusion, the population pharmacokinetics of phenytoin was studied, using the data from 167 epileptic patients. The 197 serum concentration values were analyzed, using a one-compartment model. The values of Vd, V_{max} and K_m were estimated simultaneously with a NONMEM program. The population pharmacokinetic parameters of phenytoin in Thai epileptic patients were different and higher than the parameters found in previous studies. The population pharmacokinetic parameters of phenytoin will be useful for designing dosage regimens in Thai epileptic patients. The dosage regimens for patients who consume alcohol should be initiated at lower dose than the standard dose and increased gradually and carefully until the maintenance dose is reached.

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