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Short Communication

DETERMINATION OF PHARMACOKINETIC PARAMETERS AND FACTORS INFLUENCING THE PHARMACOKINETIC PARAMETERS OF PHENYTOIN IN THAI CHILDREN WITH EPILEPSY

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ABSTRACT

Objective: Phenytoin displays nonlinear pharmacokinetics due to the saturation of its' metabolizing enzymes, thus making dosing adjustments a challenge in clinical practice. However, data on the pharmacokinetic parameters of phenytoin in pediatric patients with epilepsy in Thailand remain lacking. This study aimed to determine the pharmacokinetic parameters of phenytoin, and the factors influencing them in epileptic Thai children using therapeutic drug monitoring data.

Methods: Steady state phenytoin plasma concentrations were collected from 96 Thai children with epilepsy aged ≤ 15 y. For individuals having a single steady-state concentration (Css) on one dosage, the Vmax was determined by fixing Km = 4.5 mg/l. For patients with two values for Css with different dosages, the Ludden method was used to determine Vmax and Km. Influences on Vmax and Km by demographic factors including age, sex, weight, serum albumin, and the use of CYP2C9 inducers (carbamazepine, phenobarbital, folic acid, and vigabatrin) and inhibitors (valproic acid and topiramate) were determined by linear mixed-effects regression.

Results: The majority of patients had sub-therapeutic plasma concentrations of phenytoin. The Vmax and Km were estimated to be 9.84 mg/kg/d and 2.32 mg/l, respectively. Age and weight significantly influenced Vmax, whereas Km had no significant influencing factors.

Conclusion: The Vmax estimated in this study is different from other populations previously reported. Our results suggest that increased phenytoin dosages may be required to achieve optimal concentrations due to the sub-therapeutic concentrations reported here. The results from this study are beneficial for phenytoin dosage individualization in Thai children.

Keywords: Pharmacokinetic, Factors Influencing, Phenytoin, Epilepsy

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Phenytoin is the anti-epileptic drug of choice for both generalized and partial seizures in children [1]. Phenytoin is known to have a narrow therapeutic range of 10-20 mg/l and exhibit nonlinear pharmacokinetics with a wide inter-individual variability in plasma concentrations. Thus, small changes in the dosing of phenytoin may result in disproportionately large changes in plasma concentrations. Plasma concentrations below the therapeutic window may lead to treatment failure, while concentrations above may result in toxicity. Therefore, dosage adjustments to maintain plasma concentrations within the therapeutic range are necessary. Phenytoin pharmacokinetics follow Michaelis-Menten kinetics in the therapeutic dose range [2]. To individualize a phenytoin dosage regimen, it is important to know certain pharmacokinetic parameters of phenytoin, including the maximum rate of metabolism (Vmax) and the Michaelis-Menten constant (Km). High variability in the values of Vmax and Km has been reported among populations [3-10]. Several factors have been identified to impact the variability of these parameters, including age, sex, weight, serum albumin, and drugs that either induce or inhibit the activity of the enzyme CYP2C9 [3-10]. However, the values of Vmax and Km, as well as any factors influencing them, have never been studied in a population of Thai children.

Therefore, this study aimed to determine Vmax and Km in Thai children with epilepsy and identify the impact of factors on these pharmacokinetic parameters.

A cross-sectional analytical study was performed at Maharaj Nakorn Chiang Mai hospital from January 2015 to December 2018. Therapeutic drug monitoring data from 96 Thai children aged ≤ 15 y and diagnosed with epilepsy was collected from the Therapeutic Drug Monitoring unit. All the patients had been receiving phenytoin treatment for at least 7 d before the blood collection. Phenytoin was given as monotherapy or concomitant with other antiepileptic drugs serving as either CYP2C9 inducers (carbamazepine, phenobarbital, folic acid, and vigabatrin) or CYP2C9 inhibitors (valproic acid and topiramate). A total of 76 patients had a single steady-state concentration (Css) on a single dosage, whereas 20 patients had two Css values with two different dosages. Patients with laboratory evidence of renal or hepatic disease, as well as patients with incomplete information regarding phenytoin dosing, sampling history, or laboratory data were excluded. Data collection included phenytoin dosing history (dosage regimen and dosing schedule), total phenytoin concentration, co-medications and demographic data including age, gender, body weight and laboratory data (i.e., AST, ALT, serum albumin, total bilirubin and serum creatinine). The study was approved by the Research Ethics Committee Faculty of Medicine Chiang Mai University, Chiang Mai, Thailand (NONE-2561-05300).

The pharmacokinetic parameters (Vmax and Km) of each patient were determined by two methods: for patients having two Css values with different dosages, Vmax and Km were determined by Ludden's method [11]. Using Ludden's method, on the graph of daily dose vs. daily dose/Css, Vmax and–Km are calculated as the intercept and slope, respectively. For patients with one Css on one dosage, Vmax was determined using the following equation and fixing Km to 4.5 mg/l:

$$V_{max}=MD+K_m\left(\frac{MD}{C_{ss}}\right)$$

Where Vmax is the maximum rate of metabolism, Km is the Michaelis-Menten constant, MD is the maintenance dose, and Css is the steady-state concentration.

Descriptive data were presented as the mean±standard deviation (SD) or as the median±interquartile range (IQR) depending on the

data distribution. The comparison of Vmax and Km between age groups (1 mo–6 y and 7–15 y) was performed using ANOVA or the Wilcoxon rank-sum test depending on the normality of the data. The influence of demographic factors including age, sex, weight, serum albumin, CYP2C9 inducers (carbamazepine, phenobarbital, folic acid, and vigabatrin) and CYP2C9 inhibitors (valproic acid and topiramate) on Vmax and Km were determined using linear mixed-effects regression. Data analysis was performed using STATA version 14.0 (Stata Statistical Software: Release 14. College Station, TX: StataCorp LP.)

A total of 158 blood samples from 96 Thai children with epilepsy were included in the analysis. This included 20 patients with two Css values on two dosages and 76 patients with a total of 118 Css values collected on a single dosage. Fifty-nine of the patients (61.46%) were male. The medians for age and weight were 7 y and 20.9 kg, respectively. The mean serum albumin collected from 28 patients was 4.43 g/dl. The median phenytoin concentration was 2.88 mg/l. approximately 33.5% of the patients were receiving phenytoin along with CYP2C9 inducers and 24% were receiving co-treatment with CYP2C9 inhibitors. A summary of the demographic information is represented in table 1.

Table 1: Summary of patient demographics (N=96 patients)

	Frequency (%)
Female, n (%)	37 (38.5)
Inhibitors, n (%):	33 (34.38)
Valproic acid	23 (23.96)
Topiramate	13 (13.54)
Inducers, n (%):	21 (21.88)
Carbamazepine	5 (5.21)
Phenobarbital	7 (7.29)
Folic acid	11 (11.46)
Vigabatrin	1 (1.04)
	Mean/median (SD/IQR)
Age (y), mean (SD)	7 (8)
PHT serum concentration (mg/l), mean (SD)	2.88 (1.48)
Dose of PHT (mg/kg/d), median (IQR)	4.86 (1.72)
Serum albumin (g/dl)‡, median (IQR)	4.43 (0.48)

‡ Serum albumin was obtained from 28 patients

Using a therapeutic index for phenytoin of 10-20 mg/l, our data shows that only 12 blood samples (7.6%) from 9 patients had phenytoin concentrations within the therapeutic range. Sub-therapeutic concentrations were found in 141 blood samples (from 89 patients) and supra-therapeutic concentrations in 5 blood samples (from 5 patients) (table 2).

Table 2: Serum phenytoin concentration range

	Blood samples (n=158)	**(%)**
Sub-therapeutic range (<10 mg/l)	141	(89.2%)
Therapeutic range (10-20 mg/l)	12	(7.6%)
Supra-therapeutic range (>20 mg/l)	5	(3.2%)

The median for Vmax and Km from 96 patients was 2.32 mg/l and 9.84 mg/kg/d, respectively. When the median Vmax or Km was compared between age groups (1 mo–6 y vs. 7–15 y), the Km of the younger group was significantly lower than that of the older age group (1.21 vs 3.42 mg/l, p<0.001). Meanwhile, the Vmax of the younger age group was significantly higher than the Vmax of the older age group (14.65 vs 8.21 mg/kg/d, p<0.001) (table 3).

Table 3: Pharmacokinetic parameters of phenytoin according to age group

Parameters	**Median (IQR)**	**p-value[a]**
Km (mg/l) (n=40)	2.32 (3.65)	
1 mo–6 y (n=16)	1.21 (1.61)	<0.001
7–15 y (n=24)	3.42 (4.30)	
Vmax (mg/kg/d) (n=158)	9.84 (8.28)	
1 mo–6 y (n=70)	14.65 (13.78)	<0.001
7–15 y (n=88)	8.21 (4.11)	

[a] P-value was calculated using wilcoxon rank-sum test.

Among all demographic factors tested for influence on Vmax and Km, we found age and weight to significantly impact Vmax. None of the factors tested were found to significantly influence Km. Vmax can thus be described by the following equation:

$$V_{max}=173.32-11.95 \times(Age)+7.94\times(Weight)$$

The pharmacokinetics of phenytoin show high interindividual variability [3-10]; therefore individualizing a patient dosage regimen to obtain optimal plasma concentrations is crucial. Knowing the pharmacokinetic parameters of phenytoin, specifically, Vmax and Km, is important for optimizing phenytoin dosing. This study aimed to determine the Vmax and Km in Thai pediatric patients. Additionally, factors influencing these parameters were also investigated.

Sub-therapeutic concentrations of phenytoin are commonly observed in pediatric populations, although standard dosages of phenytoin are given [3, 12, 13]. A previous study found 43% of children studied had sub-therapeutic concentrations, this was

compared to 33% in adults and 10% in elderly subjects [13]. Another study showed 44% of phenytoin concentrations measured were below the therapeutic range [12]. In the current study, most of the patients (89%) had sub-therapeutic concentrations of phenytoin, while only 7.6% had phenytoin concentrations within the therapeutic range. A study by Suzuki Y. *et al.* recommended that phenytoin dosing in children be increased≥ 8 mg/kg/ d to obtain optimal phenytoin concentrations [3]. Therefore, increased phenytoin doses may also be required to achieve therapeutic concentrations in Thai children.

Our results calculated the median value of Km obtained from 20 patients to be 2.32 mg/l. This value is lower than a value for Km previously estimated for Thai children [14]. Of note, the previous study was performed in Thai children receiving phenytoin exclusively as monotherapy. Our reported value for Km is also lower than values previously estimated for Malaysian and Iranian populations but similar to a value reported for a Japanese population [4, 7, 8, 12]. The different values for Km seen in these studies could be due to the different baseline characteristics of the patients enrolled in those studies, as well as the different methods used for obtaining the pharmacokinetic parameters. Taken together, these results confirm that Km values vary among ethnicities.

When Km values were compared between age groups (1 mo-6 y vs. 7-15 y), Km was found to be statistically lower in the 1 mo-6 y group. This difference in Km between younger and older patients is in agreement with previous studies showing that Km tends to be lower in children, especially those aged between 6 and 11 y [15, 16].

The estimated Vmax in this study was 9.84 mg/kg/d. This Vmax is comparable to a previous report in Malaysian children but higher than that found previously in Thai patients [4, 14]. Compared between age groups, the Vmax in the the 1 mo-6 y group of patients was significantly higher than in the 7-15 y group (14.65 vs. 8.21 mg/kg/d, respectively). Significant differences in Vmax between age groups can be attributed to increased activity by CYP2C9, an enzyme responsible for the metabolism of phenytoin primarily in younger children compared to adolescents [10, 17].

Several factors may affect the pharmacokinetics of phenytoin including age, weight, race, albumin, and other co-medications. Our results show that advanced age is associated with a decreased Vmax, consistent with a previous study showing an inverse relationship between Vmax and age [3].

Among the factors we investigated for influence on Vmax, only age and weight were found to have a significant impact. Based on these results, we adjusted for weight and advanced age was shown to be associated with a decreasing Vmax. These results are in agreement with a previously published report by Suzuki Y. *et al.* demonstrating that Vmax, reflecting the activity of enzymes, decreases significantly with age [3, 15]. Even though the activity of CYP2C9 increases from the first week of life onwards, there is evidence that Vmax decreases from 14 mg/kg/d in infants to 8 mg/kg/d in adolescents [17]. As only a small number of infants were included in our study, any potential increase in Vmax during these ages could not be observed in our regression analysis. However, some evidence of increased activity by CYP2C9 in younger children is present when comparing Vmax values between children aged 1 mo-6 y vs. those aged 7-15 y. additionally, weight was found to impact Vmax in this study, as increased weight was associated with an increased Vmax. This positive relationship between Vmax and weight has been observed in previous studies [5, 6, 10, 18]. Although there is evidence of lower Km values in patients aged<15 y [10, 12], no factors investigated in this study were found to be associated with Km. This could be due to the small number of patients with two Css values and differing dosages from which the Km could be estimated.

There were some limitations to our current study. First, due to the small number of patients having two Css values with different dosages, values for Km may not be estimated precisely. Also, no factors studied were found to significantly influence Km. Second, as the overall sample size was small, the equation developed for predicting Vmax could not be validated in this study and should be further studied. Third, as there was an insufficient number of patients receiving co-medication with either a CYP2C9 inducer or inhibitor, the influence of each individual inducer and inhibitor could not be quantified. Lastly, this was a retrospective study collected from data in patients' medical records; therefore some information may be missing. Previous studies have shown a positive correlation between Vmax and albumin, however, the influence of serum albumin was not investigated in our study due to the lack of serum albumin information for the majority of patients.

In conclusion, the pharmacokinetic parameters of phenytoin in epileptic Thai children differ from those of other ethnicities. Age was found to negatively affect the value of Vmax, whereas weight positively influenced the value of Vmax. The results from this study can be used to help individualize phenytoin dosage regimens in the pediatric Thai population.

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AUTHORS CONTRIBUTIONS

BP, AC, MR, and KD planned the study. AC, MR, and BP collected and analyzed data. All authors wrote and revised the manuscript.

CONFLICT OF INTERESTS

Declared none

REFERENCES

1. Prasat Neurological Institute. Thai clinical practice guidelines for epilepsy; 2016. p. 10-99.
2. Lineweaver H, Burk D. The determination of enzyme dissociation constants. J Am Chem Soc 1934;56:658-66.
3. Suzuki Y, Mimaki T, Cox S, Koepke J, Hayes J, Walson PD. Phenytoin age-dose-concentration relationship in children. Ther Drug Monit 1994;16:145-50.
4. Omer QB, Hassan Y, Aziz N, Rashid M, Lin LAW. Pharmacokinetic study of phenytoin in Malaysian pediatric patients at penang hospital. Int J Pharm Pharm Sci 2010;2:98-101.
5. Valodia P, Seymour M, Miller R, McFadyen ML, Folb PI. Factors influencing the population pharmacokinetic parameters of phenytoin in adult epileptic patients in South Africa. Ther Drug Monit 1999;21:57-62.
6. El-Sayed YM, Islam SI. Phenytoin michaelis-menten pharmacokinetics in Saudi patients. Int J Clin Pharmacol Ther Toxicol 1989;27:173-8.
7. Salehifar E, Zohrabi M, Eshghi S, Saeedi M, Ebrahimi P. Different pharmacokinetic parameters of phenytoin in iranian outpatients: need to optimize the current dosage administration. Iran J Pharm Res 2010;8:37-45.
8. Ismail R, Rahman AF, Chand P. Pharmacokinetics of phenytoin in routine clinic patients in Malaysia. J Clin Pharm Ther 1994;19:245-8.
9. Anderson GD. Children versus adults: pharmacokinetic and adverse-effect differences. Epilepsia 2002;Suppl 3:53-9.
10. Abduljabbar M, Al-Khamis K, Ogunniyi A, Daif AK, Al-Yamani M. Phenytoin dosage adjustment in Saudi epileptics: utilization of steady-state pharmacokinetic parameters. Eur J Neurol 1999;6:331-4.
11. Ludden TM, Allen JP, Valutsky WA, Vicuna AV, Nappi JM, Hoffman SF, *et al.* Individualization of phenytoin dosage regimens. Clin Pharmacol Ther 1977;21:287-93.
12. Yukawa E, Higuchi S, Aoyama T. Population pharmacokinetics of phenytoin from routine clinical data in Japan. J Clin Pharm Ther 1989;14:71-7.
13. Sharma S, Tabassum F, Dwivedi P, Agarwal R, Kushwaha S, Bala K, *et al.* Critical appraisal of serum phenytoin variation with patient characteristics in a North Indian population. Neurol India 2015;63:202-8.
14. Wisuttiwong P. Pharmacokinetic parameters of phenytoin in Thai epileptic children; 2007. p. 1-89.

15. Lietman PS, Chiba K, Ishizaki T, Miura H, Minagawa K. Michaelis-menten pharmacokinetics of diphenylhydantoin and application in the pediatric age patient. J Pediatr 1980;96:479-84.
16. Garrettson LK, Jusko WJ. Diphenylhydantoin elimination kinetics in overdosed children. Clin Pharmacol Ther 1975; 17:481-91.
17. Kearns GL. Impact of developmental pharmacology on pediatric study design: overcoming the challenges. J Allergy Clin Immunol 2000;Suppl 3:S128-38.
18. Houghton GF, Richens A, Leighton M. Effect of age, height, weight and sex on serum phenytoin concentration in epileptic patients. Br J Clin Pharmacol 1975;2:251-6.