International Journal of Pharmacy and Pharmaceutical Sciences
Vol 2, Suppl 1, 2010

Research Article

PHARMACOKINETIC STUDY OF PHENYTOIN IN MALAYSIAN PEDIATRIC PATIENTS AT PENANG HOSPITAL

OMER Q. B. AL-LELA*[1], YAHAYA HASSAN[1], NOORIZAN ABD. AZIZ[1], MOHAMED R. ABD. RASHID[2], LAW CHUAN LIN[2]

[1] School of Pharmaceutical Sciences, Universiti Sains Malaysia, 11800 Pinang, Malaysia. [2] Department of Pharmacy, Pinang Hospital, 10450 Pinang, Malaysia. Email: omarallela@yahoo.com

ABSTRACT

Pharmacokinetic variability of phenytoin is a well known phenomenon among pediatric patients. However, data on pharmacokinetic parameters of phenytoin in a pediatric patient with epilepsy in Malaysia are still lacking. This study is to estimate the pharmacokinetic parameters (*Vmax* and *Km*) and to determine the effect of age, ethnic, gender and serum albumin levels on pharmacokinetic parameters. There were 102 steady-state phenytoin concentrations and associated dosage rates (mg/day) from 75 pediatric patients. Phenytoin pharmacokinetic parameters (*Vmax* and *Km*) were estimated using Ludden graph or Vozeh-Sheiner graph method. The Mean ±SD for *Km* and *Vmax* in 75 pediatric patients were 4.402±3.09mg/L and 9.66±6.15mg/kg/day respectively. *Km* did not correlate with age (R^2=0.03), albumin levels (R^2=0.001) and gender (P=0.651), however, *Km* correlated with Indian race (Indian = 7.083±5.485, Malay= 3.765±1.868, Chinese= 4.30±2.622) but the *Vmax* didn't effect by race (Indian= 7.378±3.893, Malay= 9.045±4.812, Chinese=10.554±7.622). *Vmax* showed a correlation with albumin levels (R^2=0.118). In our study, we found that *Vmax* had a good relation with age but this relation is nonlinear. This study similar to other studies that *Vmax* and *Km* are independent on the sex. Indian ethnic groups were difference from Malay and Chinese for the *Km* value. Albumin levels influence the value of *Vmax*.

Key word: Phenytoin, *Vmax, Km*, pediatric, malaysian.

INTRODUCTION

The pharmacokinetics of antiepileptic drugs largely determines their ability to achieve and maintain concentrations that maximize their efficacy and safety (1). Phenytoin is an anti-epileptic drug used widely in the management of partial and generalized seizure disorders in the pediatric unit (2, 3). Michealis and Menten in the 1900s demonstrated that enzyme have affinity capacity to metabolize substrate. When saturation occurs, change in metabolism of phenytoin will be occur from first-order (linear) process to a zero-order (non linear) process (4). When a concentration steady-state of phenytoin (Css) is available, methods based on the Michaelis-Menten equation (D = *Vmax*. Css /*Km* + Css) can be used to estimate the suitable dose (D) (5). The pharmacokinetic parameters of phenytoin *Km* (the serum concentration at which the rate of metabolism is half-maximal (ug/ml)) and *Vmax* (maximum rate of metabolism (mg/d)) are variable from patient to the other patient depend on many factors (age, weight, sex, race, renal function, liver function…….). Careful monitoring of phenytoin concentrations is necessitated Because of the narrow therapeutic index of phenytoin to prevent intoxication or insufficient treatment of seizures. However, small change in phenytoin dose may greatly disproportionate change in serum (6). The aim of this retrospective data collection was to estimate the phenytoin pharmacokinetic parameters (*Vmax* and *Km*) and to describe the effect of (Age, Ethnics grope, Serum albumin levels and Gender) on pharmacokinetic parameters of phenytoin.

METHODS

Data collection

The study depends on Retrospective Cross-sectional data for 75 pediatric patients (age <17 years) with documented epilepsy diagnosis, one steady-state serum concentration at one dose was determined in 48 patients and two steady-state serum concentrations at different doses were determined in 27 patients. The data obtained from Therapeutic Drug Monitoring (TDM) service in Penang General Hospital-Malaysia, collected data for three years (2006-2007-2008). Briefly, exclusion criteria were patients with laboratory evidence of renal or hepatic disease, patients taking any concurrent medication known to interfere with phenytoin pharmacokinetics, and those patients with inaccurately documented dosage and sampling histories. Data collection included demographic data (age, gender, race and total body

weight), phenytoin dosing history (total daily phenytoin dose, time of last phenytoin dose intake and dosing schedule), total phenytoin serum concentration, sampling time and Laboratory data (potassium level, sodium level, serum creatinine and serum albumin). The Clinical Research Committee (CRC) and National Institutes of Health (NIH) approved the study.

Pharmacokinetic Analysis

Estimated the phenytoin pharmacokinetic parameters (*Vmax* and *Km*) in the pediatric patients by two methods: If we have two different dose and two Css we used Ludden method, but if we have one dose and one Css we used Orbit Vozeh-Sheiner method.

Statistical analysis

Data are expressed as means ± standard deviation (SD). We used (SPSS) version 15 to describe the factors effect on (*Vmax* and *Km*).

RESULTS

We identified 75 patients in whom total phenytoin concentrations were simultaneously measured. The age of the patients averaged 8.5±5.39 yrs (range 6 months to 16.6 yrs), Race (44 Malay, 22 Chinese, and 9 Indian) and Gender (35 male / 40 female). The mean serum albumin concentration was 5.05±4.8 g/dl. Hypoalbuminemia (<3.5 g/dl) was present in 43 patients (57%), normal albumin level (3.5–5 g/dl) in 25 patients (33%), hyperalbuminemia (>5 g/dl) in one patient (2%), and six patients (8%) without albumin level (Table1).

Table 1: Demographic information, findings, and laboratory measures for the sample patients

No. of patients	75 patients	
Gender (Male/Female)	(35/40)	(47.2% / 52.8%)
Age (years)	(98.5±5.39 yr)	[a](6monthes-16.6yr)[b]
6months-3years	20pts	(26%)
>3years-<7years	12pts	(16%)
7years-<10years	10pts	(14%)
10years-<17years	33pts	(44%)
Race Malay	44pts	(58.4%)
Chinese	22pts	(29.2%)
Indian	9pts	(12.4%)
Serum albumin concentration (g/dl)	(5.05±4.8 g/dl)[a]	(1.4-12.1 g/dl)[b]
Serum albumin <3.5 g/dl	43pts	(57%)
Serum albumin 3.5–5 g/dl	25pts	(33%)
Serum albumin >5 g/dl	1pt	(2%)
Without albumin level	6pts	(8%)

The Mean ± SD for *Km* and *Vmax* in 75 pediatric patients were 4.402±3.09mg/L and 9.66±6.15mg/kg/day respectively (Table2). *Km* did not correlate with age (R^2 =0.03) (Fig.1), albumin levels (R^2=0.001) (Fig.2), and gender (P =0.651), however, *Km* correlated with Indian race (P = 0.002) but the *Vmax* didn't effect by race (P =0.606), gender (P=0.426), and age (R^2 = 0.001) (Fig.3). *Vmax* showed a correlation with albumin levels (R^2 =0.118) (Fig.4).

Table 2: Vmax and Km value of phenytoin in pediatric patients in 75patients.

Malaysian pediatric patients	Vmax (mg/kg/day)	Km (mg/L)
75 pediatric patients	9.66±6.15	4.402±3.09
Malay	9.045±4.812	3.765±1.868
Chinese	10.554±7.622	4.30±2.622
Indian	7.378±3.893	7.083±5.485

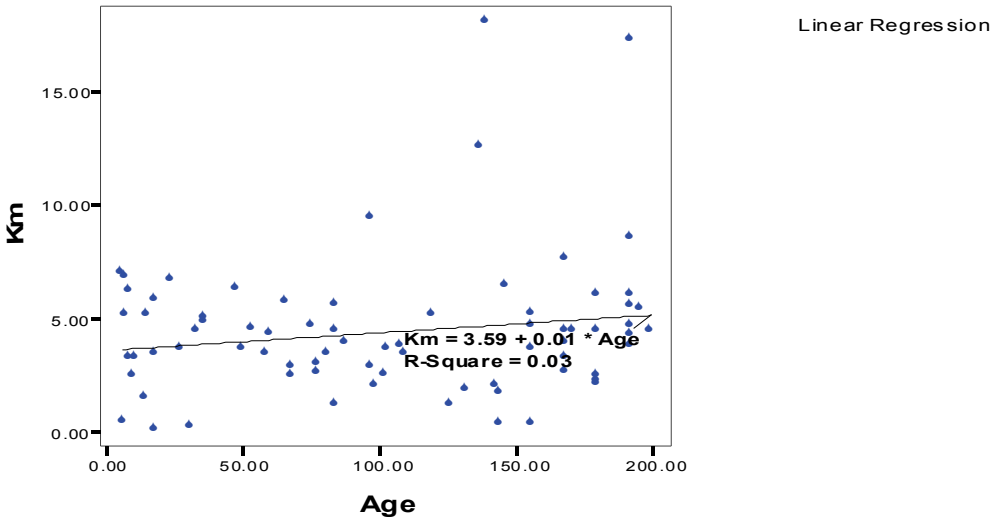

Fig 1: Scatter plot of *Km* vs. Age in 75 patients.

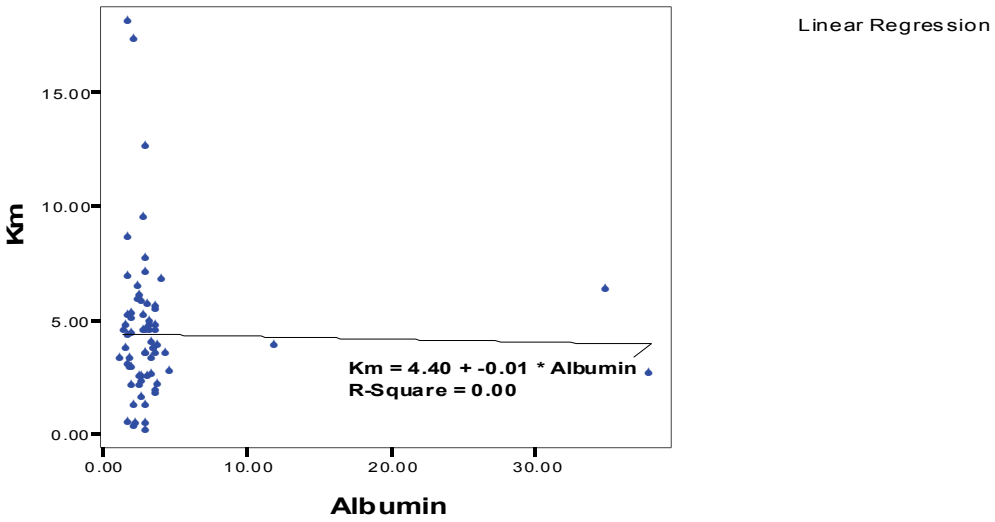

Fig 2: Scatter plot of *Km* vs. Albumin level in 75 patients.

DISCUSSION

The values of *Vmax* and *Km* that this study obtained were in good agreement with those found by other workers (7) in Malaysia also. Average *Vmax* was 9.66 mg/kg/day, a value comparable to previous study (8, 9). The average *Km* was 4.402 mg/L, higher than previous study results in Japan (10) but consistent with those in other reports (9, 11-12). The difference could be due to the change in the race or age.

Many researchers (13, 14) have shown that age played an important role in determining phenytoin dosage requirement both in adults and in children and *Vmax* was shown to decline with age, but in the other studies (7, 15) shown that *Vmax* and *Km* aren't depended on the age. In our study, we identified a good relation between (*Vmax*, *Km*) with age (Eta^2=0.61, 0.68) but this relation is nonlinear (R^2=0.001, 0.027).

Based on our results, *Vmax* depend on the albumin factor (R^2=0.118, *P*= 0.004) and change according to the albumin value, but the second phenytoin pharmacokinetic parameters *Km* isn't depend on the albumin value (R^2=0.001, *P*= 0.855).

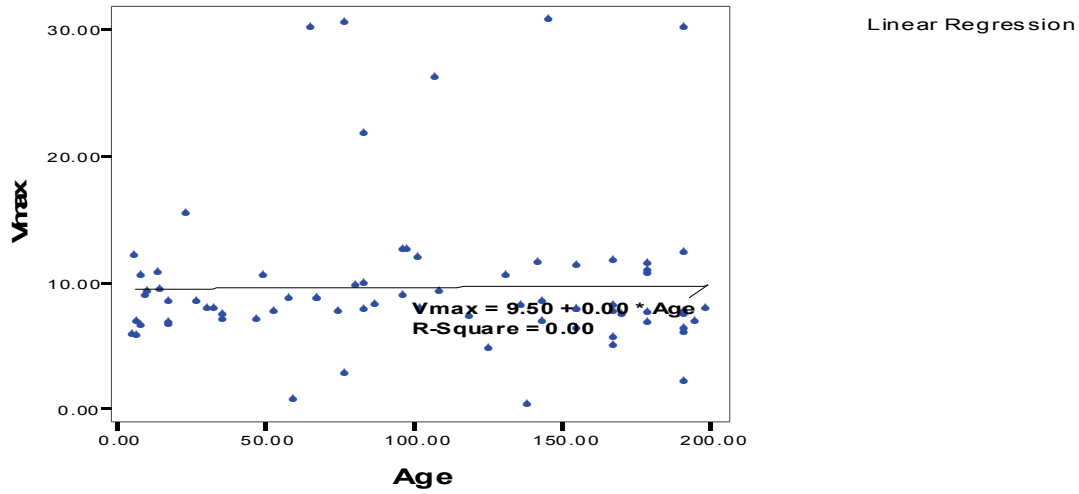

Fig 3: Scatter plot of *Vmax* vs. Age in 75 patients.

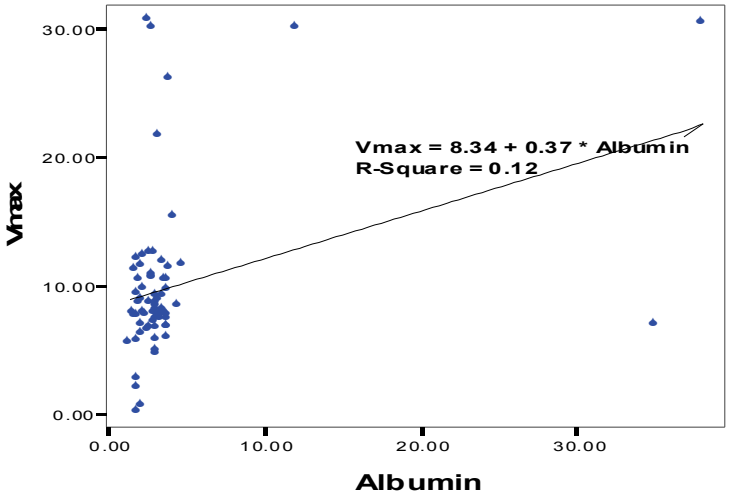

Fig 4: Scatter plot of *Vmax* vs. Albumin level in 75 patients.

Many studies on the Gender factors affecting on phenytoin pharmacokinetic parameters, that isn't correlation between *Vmax* and sex, and also we aren't saw any correlation between *Km* and sex, our study results similar to other studies (7, 15) that *Km* isn't depended on the sex, but differ from same study (7) that *Vmax* depended on sex.

In Malaysia, many races detected in this area (Malay, chains and Indian), that stimulate us to see the effect of race on the phenytoin pharmacokinetic parameters, according to this reason, the study results *Vmax* isn't significant (*P*= 0.271), and *Km* have a good correlation and significant with race only between Indian race and chains or Malay (*P*=0.017, 0.002 respectively).

ACKNOWLEDGEMENT

I would like to thank Mr. Abdlullah Aldahbali for his un-ending support and everyone who helped me to finish this study.

REFERENCE

1. Ferrendelli JA. Concerns with Antiepileptic Drug Initiation: Safety, Tolerability, and Efficacy. Epilepsia 2001; 42 :28-38.
2. Tozer TN, Winter ME Phenytoin. In**:** Evans WE, Schentag JJ, Jusko WJ. Applied Therapeutic. San Francisco; 1980. p. 279-314.
3. Richens A. Clinical pharmacokinetics of phenytoin. Clinical Pharmacokinetics. 1979; **4:** 153-169.
4. Tozer TN, Winter ME. phenytoin. In: Evans WE, Schentag JJ, Jusko WJ. applied pharmacokinetics: principle of therapeutic drug monitering . 3rd ed. Vancouver: 1992. p. 26-29.
5. Martin E, Tozer TN, Sheiner LB, Sidney R. The clinical pharmacokinetics of phenytoin. J Pharmacokinet Biopharm 1977; 5:579–96.
6. Richens A, Dunlop A. Serum-phenytoin levels in management of epilepsy. Lancet. 1975; 2:247–248.
7. Ismail R, Rahman AF, Chand P. Pharmacokinetics of phenytoin in routine clinic patients in Malaysia. J Clin Pharm Ther 1994; 19:245–248.
8. Abduljabbar M, Al-Khamis K, Ogunniyi A, Daif AK, Al-Yamani M. Phenytoin dosage adjustment in Saudi epileptics: utilization of steadystate pharmacokinetic parameters. Eur J Neurol 1999; 6:331–334.
9. Bauer LA, Blouin RA. Phenytoin Michaelis-Menten pharmacokinetics in Caucasian paediatric patients. Clin Pharmacokinet.1983; 8:545-549.
10. Yukawa E, Higuchi S, Aoyama T. Population pharmacokinetics of phenytoin from routine clinical data in Japan: an update. Chem Pharm Bull 1990; 38:1973–1976.
11. Grasela, T.H., Sheiner, L.B., Rambeck, B., Boenigk HE, Dunlop A, Mullen PW. et al. Steady-state pharmacokinetics of phenytoin from routinely collected patient data. Clinical Pharmacokinetics 1983; 8:355-364.
12. Chiba, K., Ishizaki, T., Miura, H. & Minagawa, K. Michaelis-Menten pharmacokinetics of diphenylhydantoin and application in the pediatric age patient. Journal of Pediatrics 1980; 96:479-484.
13. Bauer LA, Blouin RA. Age and phenytoin kinetics in adult epileptics. Clin Pharmacol Ther. 1982; 31(3):301-4.
14. El-sayed YM, Islam SI. Phenytoin Michaelis-Menten pharmacokinetics in Saudi patients. Int J Clin Pharmacol Ther Toxicol1989; 27(4):173-8.
15. Chan E, Ti TY, Lee HS. Population pharmacokinetics of phenytoin in Singapore Chinese. European Journal of Clinical Pharmacology. 1990; 39: 177-181.