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AN EVALUATION ON PHARMACOKINETICS PARAMETERS OF PHENYTOIN IN ADULT EPILEPTIC PATIENTS: A SINGLE CENTRE STUDY FROM MALAYSIA

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Phenytoin follows Michaelis-Menten, a non-linear pharmacokinetics that occurs when drug molecules saturates the enzymes ability to metabolise the drug. When this occurs, steady state phenytoin serum concentration increases in a disproportionate manner after a dosage increase. General population data are usually used for the phenytoin dose calculation. However, many studies show that population pharmacokinetic parameters of phenytoin have high variations. Thus, use of specific local pharmacokinetic parameters for each population group in estimating individualised phenytoin dose can reduce phenytoin toxicity cases. This prospective, observational study was conducted to estimate a local V_{max} and K_m of phenytoin for adult epileptic patients in neurological ward and clinic at Hospital Pulau Pinang, Malaysia. All therapeutic drug monitoring of oral capsule phenytoin were studied in a three-month data collection period. Out of the 17 subjects in our study, there are 13 male subjects (76.47%) and 4 female subjects (23.53%). A total 11 Malay subjects (64.71%), 4 Chinese subjects (23.53%) and 2 Indian subjects (11.76%) were included. Median V_{max} and K_m were found to be 8.25 mg/kg/day and 3.80 mg/l. Male subjects have a higher V_{max} (8.30 mg/kg/day) but a lower K_m (3.3 mg/l). Chinese population has the highest V_{max} (8.80 mg/kg/day). For K_m, Indian population is the highest, with a value of 5.5 mg/l. From our study, gender does not correlate with V_{max} and K_m of phenytoin (p-value > 0.05). Ethnicity was also found to have no association with V_{max} and K_m (p-value > 0.05). Local V_{max} (8.25 mg/kg/day) is higher and K_m (3.8 mg/l) is lower when compared with standard V_{max} (7 mg/kg/day) and K_m (4 mg/l) obtained from Caucasian population.

***Keywords*:** Phenytoin, Pharmacokinetic parameters, V_{max}, K_m

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INTRODUCTION

In Hospital Pulau Pinang, Malaysia, anti-epileptics available are sodium valproate, carbamazepine, phenobarbitone, phenytoin, clonazepam, clobazam, primidone (first generation of antiepileptic drugs [AEDs]) and zonisamide, gabapentin, levetiracetam, topiramate, lamotrigine, locasamide, vigabatrin (second generation AEDs). Among these drugs, only sodium valproate, carbamazepine, phenobarbitone and phenytoin are available for therapeutic drug monitoring. Monitoring of phenytoin concentrations is required due to the narrow therapeutic range of phenytoin, in order to optimise therapy and to avoid intoxication or inadequate treatment of seizures (Omer *et al.* 2010). Phenytoin is chosen instead of other antiepileptics because pharmacokinetics variability of phenytoin is common among different patients (Bauer 2006).

Phenytoin is one of the first generation anti-epileptic drugs used for management of generalised status epilepticus and chronic treatment of tonic-clonic or partial seizure (Bauer 2006). The hydrotoin compound found in phenytoin is related to barbiturates which act by inhibiting sodium dependent channel, stabilising neuronal membranes, blocking repetitive firing of action potential and inhibiting prolonged depolarisation of neurons (Morita and Glauser 2011; Bauer 2006).

Since phenytoin follows Michaelis-Menten pharmacokinetics, it does not have true half-life due to variation with serum concentration. Once phenytoin was given as maintenance therapy, the half-life for oral phenytoin is approximately 22 hours in adult. Estimation of suitable dose (D) can be done based on Michaelis-Menten equation, which is ($D = V_{max}C_{ss}/K_m + C_{ss}$). The parameters of phenytoin are V_{max} (maximum rate of metabolism (mg/d)), K_m (the serum concentration (ug/ml) when the rate of metabolism is half. General population data of V_{max} (7 mg/kg/day) and K_m (4 mg/L) are usually use for the calculation of the phenytoin dose. However, there are many studies show that population pharmacokinetic parameters of phenytoin have high variations (Vozeh *et al*. 1981; Grasela *et al*. 1983).

The pharmacokinetics parameters varied from patient to patient, depending on factors such as age, weight, sex, race, renal function, hepatic function, pregnancy, trauma or burns, dialysis, hypoalbuminemia and hyperbilirubinemia (Omer *et al.* 2010; Bauer 2006). Several factors that might influence phenytoin kinetic parameters include sex, age and race (Grasela *et al*. 1983). 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).

According to Kapetanovic and Kupferberg (1985), approximately 90% of phenytoin is bound to albumin in healthy adults. The phenytoin levels must be corrected according to albumin levels before the pharmacokinetics parameter could be identified. Study conducted by Omer *et al*. (2010) found that V_{max} values demonstrated a correlation with albumin level and age but the relationship was non-linear. K_m was not affected by age, albumin levels and gender but it was influenced by ethnicity. V_{max} values are not influenced by gender.

Results in Suzuki *et al*. (1994) showed that there is no significant difference in either V_{max} or K_m between patients receiving phenytoin as single therapy and patients receiving combination anticonvulsant therapy. Patsalos *et al*. (2002) stated that the probability of epileptic patient experiencing drug interaction is high when treated with combination first generation antiepileptics. Antiepileptics often interfere with disposition of another drug, alter the drug concentration at site of action and change the plasma concentration of drug and its metabolites. Enzymes-inducing drugs such as phenytoin will also augment the metabolism of other AEDs.

From the pharmacokinetics characteristic, individualised dosage adjustment can be catered to each and every patient in order to control seizure and avoid toxicity of phenytoin (Mahmoudian, Abbasi and Jamshidi 1995). However, there is lack of study on phenytoin prescribing in Malaysia to control seizure. This study was conducted to estimate local pharmacokinetic parameters of phenytoin for adult epileptic patients in neurological ward. We also aim to identify the influence of gender and race on the pharmacokinetic parameters of phenytoin. All therapeutic drug monitoring of oral capsule phenytoin was studied to obtain V_{max} and K_m value.

METHODS

Study Location

This study was carried out in neurological ward and clinic of Hospital Pulau Pinang, Malaysia.

Data Collection

This is a prospective study of adult epileptic patient started with oral capsule phenytoin from 15 December 2017 to 15 March 2018. All samples that are available within six months of study period were recruited to our study. Screening and selection of patients were done in neurological ward and clinic. Adult epileptic patient (19 years old and above) started with oral capsule phenytoin in the neurological ward and clinic at Hospital Pulau Pinang were selected to undergo therapeutic drug monitoring (TDM). Patients with laboratory evidence of end stage renal failure (EGFR < 15 ml/min), chronic liver disease (Child-Pugh score B and C), pregnant ladies and patients who are taking medications that have established interactions with phenytoin concurrently such as atorvastatin, carbamazepine, dexamethasone and voriconazole were excluded from this study.

Patients shall be informed of the study during their stay in neurological ward or during their follow up in neurological clinic. An appointment will be made where the patient information sheet will be provided and explained to them. If they are willing to participate, the consent forms will be signed and dated. Since TDM is not a routine investigation for patient started with oral phenytoin in Hospital Pulau Pinang, 3 ml to 5 ml of blood sample was taken using plain tube at least after five days from administration of oral capsule phenytoin for TDM purpose.

The sampling time of phenytoin must be after the steady state of phenytoin is achieved, which is at least five days after the first administration dose of phenytoin (Bauer 2006). If patient was discharged within five days period, they were given an appointment date (at least five days from administration of oral phenytoin) for blood sample taking in neurological clinic. A data collection form was used to collect the required data. Pharmacokinetics parameters (V_{max} and K_m) of phenytoin in epileptic patient were estimated by using Orbit Vozeh Sheiner method.

Subjects will be withdrawn from the study if they do not show up for the blood sampling session based on the appointment date given, have transportation problem to come back for blood sampling session after consent forms are signed or there is communication barrier between the investigator and the subjects during the recruiting process.

Research proposal was submitted to Medical Research Ethics Committee (MREC) with approval letter number: KKM.NIHSEC.P17-1956(12) and trial was conducted in compliance with Good Clinical Practice requirements.

Data Analysis

All collected data was entered in Microsoft Excel spreadsheet and analysed using SPSS version 21 with Kruskal-Wallis and Mann-Whitney statistical analysis with 95% confidence interval. Statistics was performed to compare the medians and interquartile range of V_{max} and K_m between adult epileptic patient of different race and gender to determine if there is any significant differences ($p < 0.05$).

RESULTS

Twenty-one subjects were recruited in this study. However, four subjects dropped out from our study as they were unable to attend for the blood taking session on the appointment date given, leading to a dropout rate of 19.05%. Referring to Table 1, average age of the subjects is 47.3 years. Thirteen male subjects (76.47%) and four female subjects (23.53%) were included in our research study. A total of 11 Malay subjects (64.71%), 4 Chinese subjects (23.53%) and 2 Indian subjects (11.76%) were included among ethnicity groups.

Referring to Table 2, the median V_{max} and K_m were found to be 8.25 mg/kg/day and 3.80 mg/l, respectively, among patients in Hospital Pulau Pinang. Male subjects have a higher V_{max} (8.30 mg/kg/day) but a lower K_m (3.3 mg/l) as compared to the female group as shown in Table 2. Chinese population was found to be having the highest V_{max} (8.80 mg/kg/day), followed by Malay (8.10 mg/kg/day) and Indian (6.80 mg/kg/day). As for K_m, Indian population appeared to be the highest with a value of 5.5 mg/l and Chinese population appeared to be the lowest with a value of 4.3 mg/l. From our study, gender does not correlate with V_{max} and K_m of phenytoin (p-value > 0.05). On the other hand, ethnicity was also found to have no correlation with V_{max} and K_m from our research (p-value > 0.05).

DISCUSSION

The median V_{max} and K_m of phenytoin obtained from present study were 8.25 mg/kg/d and 3.8 mg/l, respectively, at a daily oral phenytoin dose of 300 mg, with the targeted serum concentration of phenytoin at 15 mg/l. Similar study done by Ismail and Rahman (1990) in Malaysia reported that the average V_{max} and K_m were 8.45 ± 1.39 mg/kg/d and 6.72 ± 5.31 mg/l, respectively. The median V_{max}, 8.25 mg/kg/d obtained through our study is similar to average V_{max} of 8.45 ± 1.39 mg/kg/d in Ismail and Rahman's study. However, the K_m is not comparable as the average K_m reported by Ismail and Rahman (1990) has large standard deviations. In Ismail and Rahman (1990), a total of 11 Malay subjects, 4 Chinese subjects and 2 Indian subjects were included, while in our study there are a total of 14 Malay subjects, with only 1 Chinese subject and 0 Indian subjects. The difference in demographic characteristics might also be the cause of the non-consistent K_m value.

By comparing with the current practice of using population data of V_{max} = 7 mg/kg/d and K_m = 4 mg/l in estimating the maintenance dose of phenytoin by Winter (2003), our V_{max} is slightly higher than the population V_{max} whereas our K_m is slightly lower than the population K_m. This is probably due to genetic variations between locals and Caucasians. The effect of genetic variations is further shown in the study conducted by Martin *et al*. (1977) in Switzerland with a higher average of V_{max} and K_m, that is, 10.3 mg/kg/day and 11.54 mg/l, respectively, as compared to our study.

In the present study, influence of gender on V_{max} and K_m was observed. It is found out that gender does not correlate with V_{max} and K_m of phenytoin. Similar results were observed in the study by Omer *et al*. (2010), which also shown that V_{max} values are not influenced by gender; and K_m is not affected by age, albumin levels and gender. Thus, same V_{max} and K_m of phenytoin can be used to estimate the individualised phenytoin dose for both male and female subjects. Another study done in Thailand by Kanjanaslip *et al*. (2005) also find out that there is no correlation between gender and V_{max}. Similar study done by Chanawong (2002) in Thailand also stated that K_m value appeared to be have no correlation to gender. To sum it up, other studies done in Asian country also showed no correlation of gender with phenytoin pharmacokinetic parameters. This might indicate no significant genetic variances among Asians.

Besides, correlation of race with V_{max} and K_m was observed. There were no significant difference between race in V_{max} and K_m. Similar results were observed in the study done by Grasela *et al*. (1983), which showed that V_{max} was not influenced by ethnicity and gender. On the contrary, ethnicity was shown to influence the K_m value, as the K_m for Japanese patients was 23% lower than for European patients. The results of Bauer and Blouin (1983), in comparison with those of Grasela *et al*. (1983), showed that for each age group, the K_m values (mg/ml) were higher in Caucasian children than in Japanese children but the V_{max} values did not differ. By comparing with our present study, opposite results were reported by Kromann *et al*. (1981), a study done in Greenland Eskimos and Caucasian Danes regarding phenytoin disposition and found out that ethnic differences in pharmacokinetics can be of significance, especially on K_m values.

By calculating estimated maintanence dose calculated using Michaelis-Menten equation ($D = V_{max}.C_{ss}/K_m + C_{ss}$), we found that the pharmacokinetic paramaters obtained from our study (V_{max} = 8.25 mg/kg/day and K_m = 3.80 mg/l) will produce higher maintanence dose compared to using standard population data (V_{max} = 7 mg/kg/d and K_m = 4 mg/l). This is because our study K_m is almost similar to the population data but our V_{max} is higher than the population data.

Due to the limitations imposed by the short study duration and the patient groups recruited for the study being registered in only one hospital, the results may not be applicable to the general population.

A larger sample size of patients can be recruited for future studies to better elucidate the average mean ± standard deviation of V_{max} and K_m of phenytoin. The average mean value of V_{max} and K_m obtained from the first blood sample can then be used to estimate the individualised dosage of phenytoin for patients. To ensure plasma phenytoin level reaches the desired therapeutic range, the patients can be given another appointment date for second blood sampling.

CONCLUSION

The local V_{max} and K_m of phenytoin for adult epileptic patients from the present study in neurological ward and clinic at Hospital Pulau Pinang are 8.25 mg/kg/d and 3.8 mg/l, respectively. In this study, gender and race factors do not significantly influence the V_{max} and K_m of phenytoin among the patients.

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