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Original Article

Different Pharmacokinetic Parameters of Phenytoin in Iranian Outpatients: Need to Optimize the Current Dosage Administration

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Abstract

Dose-dependent pharmacokinetic of phenytoin necessitates the estimation of the maximum rate of metabolism (Vm) and the Michaelis-Menten constant (Km) in a concerned population. The aim of this study was to determine the pharmacokinetic parameters of phenytoin in a sample of Iranian patients to optimize the antiepileptic pharmacotherapy. Fourty patients who received a constant dose of phenytoin for at least three weeks were included in the study. Steady-state trough serum concentration has been used to determine the Vm and Km by Vozeh-Sheiner (orbit-graph) method. Mann-Whitney U-test and chi-square test have been used to compare the quantitative and qualitative variables respectively. Only half of the patients were in the therapeutic range. Mean Vm and mean Km were 6.12±1.01 mg/kg/day and 5.90±1.26 mg/l respectivly with significant differences [95% confidence interval of difference with the reported to mean values of 7 mg/Kg/day for Vm and 4 mg/l for Km interval -0.88 (-1.2 to 0.55) and +1.9 (1.49 to 2.31) respectively]. A trend towards higher clearance (CL) and intrinsic clearance (CL_{int}) were observed in patients on polytherapy with phenobarbital compared to those on phenytoin monotherapy. Advanced age was inversely associated with the values of Vm and CL_{int} in the group on monotherapy. Considering the observed lower Vm and higher Km, our population may have a lower metabolic capacity for metabolism of phenytoin, and using the estimates of Vm and Km obtained this study could help the clinicians to individualize antiepileptic therapy. In addition, the results of this study may propose that the expression of CYP2C9 and CYP2C19, as two main pathways of phenytoin metabolism, may be lower in iranians than the other populations, and phenotyping/genotyping studies of these pathways are recommended.

Keywords: Phenytoin; Pharmacokinetics; Maximum rate of metabolism (Vm); Michaelis-Menten constant (Km); Clearance.

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Introduction

Phenytoin, an effective antiepileptic drug, has been used for a long time to treat many types of seizures. It differs from the other antiepileptic drugs in that its kinetic properties are known to be dose-dependent. Due to zero-order kinetics of phenytoin with in the therapeutic range, a small increase in dose may result in a disproportionate increase in serum phenytoin serum concentration (1). considerable inter-individual variation in steady-state concentrations observed with standardized dosing, due to significant interpatient variability in pharmacokinetic parameters (1). The clearance-dependent half-life of phenytoin has made it challenging to adjust the dose individually to attain optimal steady-state concentration (2). To individualize phenytoin doses, it is important to have phenytoin pharmacokinetic parameters including the maximum metabolic rate (Vm) and the Michaelis-Menten constant (Km) (3) which are involved in determmation of the intrinsic clearance of the patient (CL_{int}). CL_{int} is a representative of the metabolic activity in the absence of liver blood flow limitations and could be calculated by dividing Vm by Km (CL_{int}=Vm/Km). In other words, it would be inferable that patients who have a lower Vm or a higher Km may be at increased risk of phenytoin toxicity (4).

Although a great variation has been reported for the amounts of Vm and Km from 100 to 1000 mg/day and 1-15 mg/l respectively (5, 6), but the estimated average values for adults are 500 mg/day or, expressed relative to body weight, 7 mg/kg/day and 4 mg/l for Vm and Km, respectively (2).

Phenytoin is mainly metabolized by cytochrome P4502C9 (CYP2C9) and cytochrome P4502C19 (CYP2C19) (7). Both of these pathways are known to exhibit polymorphism in terms of genetic sequences and metabolic activities in other populations (8-11), leading to considerable different pharmacokinetic parameters and hence dosage requirements.

In addition to genotyping differences, knowledge of various covariates that may influence the Vm and Km (e.g.: gender, weight, body mass index, co-administration of other antiepileptics, and duration of treatment) could be helpful in determining the most appropriate dose for a patient.

The primary aim of this study was to determine the Vm and Km values of phenytoin in an outpatient sample of our province, mazandaran In addition, comparison of these values with the mean reported values in other populations and the effects of various covariates on the pharmacokinetic parameters of phenytoin have been addressed.

Experimental

Patients

The sample population comprised 40 Mazandaranian patients with a history of head trauma or epilepsy who needed phenytoin for prophylaxis of seizures. Inclusion criterion was receiving phenytoin on fixed regular daily doses for at least three weeks. Exclusion criteria were pregnancy, and evidence of hepatic or renal insufficiency (based on history, clinical examination and/or laboratory data). All patients had signed informed consent forms and understood the aim of the study and the procedures. Patients' demographic data, cigarette smoking and alcohol-drinking state, had been asked and collected in the study form.

Compliance with the treatment was classified as good, moderate or poor according to the patients' declarations and count of the remained drugs when applicable. Good compliance was defined as taking nearly all doses of drugs on a regular made, moderate compliance as taking most of the doses in most of the days in a week (missed dose$\leq$3 doses/week) and poor compliance as forgetting to take more than three doses per week.

Date and setting

This research has been conducted in an outpatient neurosurgery office in Sari, the center of Mazandaran province of Iran, December 2006 until September 2007.

Sample collection and analysis

Blood samples (5 ml) were drawn just before the next dose to monitor trough phenytoin concentration. Each sample centrifuged at 2000

rpm for 5 minutes in a clinical laboratory located beside the office. The serum was removed and stored in -20 °C. Sample was transferred to the faculty of pharmacy for assay of phenytoin. Total serum phenytoin concentrations were measured with high performance liquid chromatography (HPLC) system (Knuaver) with a C_8 column (5 µm, 15×4.6 mm), a UV-detector (K-2600) and Eurochrome 2000 software (12, 13).

Pharmacokinetic analysis

The main pharmacokinetic parameters of phenytoin, Vm and Km, were determined by Vozeh-Sheiner (orbit-graph) method based on the measured steady-state serum concentrations (Cpss) for each patient (14).

Clearance of phenytoin (CL) were calculated with the following equation using Vm, Km and Cpss (4):

$$CL = Vm/Km + Cpss \qquad \text{Equation (1)}$$

Where Vm represents the theoretical maximum rate of the process (mg/kg/day), Km represents the Michaelis-Menten constant (mg/L) and Cpss represents steady-state serum concentration (mg/L).

An estimation of the intrinsic ability of the liver to eliminate a drug in the absence of limitations imposed by blood flow is the intrinsic clearance. In biochemical terms and under first order conditions, intrinsic clearance is a measure of the ratio of Michaelis-Menten parameters for the elimination process, and the following Equation was used to calculate the intrinsic clearance (CL int) of subjects (4):

$$CL_{int} = Vm/Km \qquad \text{Equation (2)}$$

Where CL int is Intrinsic clearance (L/kg/day), Vm is maximum metabolic rate and Km is Michaelis-Menten constant.

Phenytoin doses were individually adjusted based on the patients weights to calculate the adjusted doses (Equation 3).

$$Dose_{adj} = Dose/Wt \qquad \text{Equation (3)}$$

Where $Dose_{adj}$ represents the adjusted dose (mg/kg/day), Dose is the rate of phenytoin administration (mg/day) and Wt is the weight of the patient (kg).

Considering weight of the patient,the adjusted steady-state serum concentration was calculated (Equation 4).

$$Cpss_{adj} = Cpss/Wt \qquad \text{Equation (4)}$$

Where $Cpss_{adj}$ is the adjusted steady-state concentration, Cpss is the steady-state serum concentration (mg/L), and Wt is the weight of the patient (kg).

Statistical analysis

Data analysis was performed with SPSS 16 software package. To compare quantitative and qualitative variables between male and females, Mann-Whitney U-test and chi-square test have been used respectively. Correlations between pharmacokinetic parameters with the other variables (e.g.: age, weight, dose, adjusted dose, steady-state concentration, adjusted steady-state concentration, and duration of therapy) were evaluated with Spearman correlation test. A P value less then 0.05 was considered to be the limit of statistical significance.

Results

The demographic information and antiepileptic regimens are presented in Table 1. Although the height and body mass indices of males were more than females, but the age and the weight of the two genders were not significantly different. Monotherapy with phenytoin had been prescribed for 9 patients (22.5%) while the others received polytherapy of phenytoin and other antiepileptics including phenobarbital, carbamazepine and sodium valproate. The most common regimen was the combination of phenytoin and phenobarbital (57.5% of patients) (Table 1).

The mean length of treatment with a constant dose was more than 1 year with a great deviation ranging from less than 1 month in (6 patients) to more than 3 years (in 5 patients).

39 patients (97.5%) had good compliance and just one patient had a moderate compliance (Table 1).

Values of the administered doses, steady-

Table 1. Demographic data, antiepileptic regimens and compliance of patients (mean ±SD).

Items	Total (n=40)	Male (n=29)	Female (n=11)	P value*
Age (years)	37.6±18.2	34.5±17.3	45.9±18.9	0.08
Weight (Kg)	69.1±9.3	69.6±8.9	67.8±10.5	0.72
Height (cm)	172.9±8.7	176.4±7	163.6±5.1	<0.001
Body mass index (kg/m²)	23.2±3.4	22.4±2.9	25.3±3.6	0.49
Antiepileptic regimen (n)				0.29
PHT	9	8	1	
PHT+PHB	23	15	8	
PHT+CBZ	1	0	1	
PHT+VAL	5	4	1	
PHT+PHB+VAL	2	2	0	
Days on a constant dose	407±691	399±723	427±633	0.84
Compliance (n)				0.53
Good	32	21	9	
Moderate	8	6	2	
Poor	0	0	0	

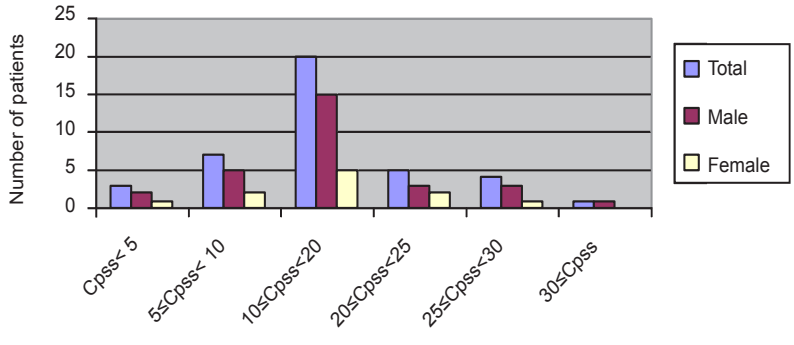
PHT: Phenytoin; PHB: Phenobarbital; CBZ: Carbamazepine; VAL: Valproate Na
* Mann-Whitney U test was used to compare the numerical data and chi-square to compare the string data between males and females. P<0.05 was considered as significant difference.

state serum concentrations and, pharmacokinetic parameters of subjects are presented in Table 2.

It is notable that although the mean steady-state serum concentration of phenytoin in patients was in the therapeutic range (15.36±7.67 mg/L), but 20 of patients (50%) had concentrations less than the lower limit or higher than the upper limit of therapeutic range (Figure 1).

To evaluate the effects of phenobarbital on the pharmacokinetic characteristics of phenytoin, a set of non-parametrical statistical analysis was performed to compare theses parameters in patients undergoing phenytoin monotherapy whit these in patients on polytherapy with phenobarbital. Other combination therapies were ignored because of relatively low sample sizes (Table 3).

The correlation between demographic characteristics of patients and dosages of phenytoin with steady-state serum concentrations and pharmacokinetic variables



Cpss: Steady-state serum concentrations

Figure 1. Steady-state serum concentrations of patients.

Table 2. Doses, steady-state serum concentrations and pharmacokinetic characteristics of patients (mean±SD).

Items	Total (n=40)	Male (n=29)	Female (n=11)	P value*
Dose (mg/day)	278.90±51.51	283.14±48.98	267.73±58.69	0.94
$Dose_{adj}$ (mg/Kg/day)	4.12±1.02	4.16±1.05	3.99±0.98	0.88
Cpss (mg/L)	15.36±7.67	15.77±7.99	14.26±6.96	0.61
$Cpss_{wt\ adj}$ (mg/Kg/L)	0.23±0.14	0.24±0.14	0.22±0.14	0.61
$Cpss_{dose\ adi}$ (day/L)	0.055±0.028	0.056±0.026	0.055±0.03	0.53
Vm (mg/Kg/day)	6.12±1.01	6.17±1.04	5.98±0.96	0.59
Km (mg/L)	5.90±1.26	5.84±1.34	6.06±1.08	0.45
CL (L/Kg/day)	0.36±0.25	0.37±0.29	0.34±0.15	0.44
CL_{int} (L/Kg/day)	1.12±0.46	1.15±0.49	1.04±0.35	0. 46

$Dose_{adj}$: adjusted dose; Cpss: steady-state serum concentration; $Cpss_{adj}$: adjusted steady-state serum concentration; Vm: maximum metabolic rate; Km: Michaelis-Menten constant; CL: clearance of phenytoin; CL_{int}: intrinsic clearance of patient.
*Mann-Whitney U test was used to compare the variables between males and females. $p<0.05$ was considered as significant difference.

have been assessed with Spearman correlation test for all patients and the two subgroups including those who were on phenytoin monotherapy and those who received phenytoin with phenobarbital (Table 4).

Age was inversely correlated with Vm and CL_{int} in patients receiving phenytoin as monotherapy. Considering all patients, weight correlated negatively with Vm and positively with Km. Correlations between BMI and pharmacokinetic parameters were similar to those between weight and pharmaceokinetic in most subjects. There were positive correlations between the dose (and also adjusted dose) with Cpss, Vm and CL_{int} in whole patients analysis. The dose and the adjusted dose had a negative correlation with Km in whole patients analysis, in patients under monotherapy of phenytoin and also in patients receiving phenytoin with phenobarbital (Table 4).

Comparison of Vm and Km in of our patients with the reported mean value in other populations (3) demonstrated that the mean Vm in our sample was significantly lower than 7 mg/kg/day (mean difference: -0.88, 95% confidence interval: -1.2 to -0.55) and the mean of Km was significantly higher than 4 mg/L (mean difference: +1.9, 95% confidence interval: 1.49 to 2.31). This comparison was made for subgroups receiving phenytoin alone or phenytoin and phenobarbital. In combination both groups had a lower Vm in comparison to the whole sample (Table 5).

Discussion

This study demonstrated that in our sample, the Vm was lower and the Km was higher as compared to the reported mean values. In addition, only half of our patients had the steady-state concentrations within the therapeutic range, i.e. 10-20 mg/L, where 25% had lower and the remaining had upper concentrations.

More or less, most of the drugs may display pharmacokinetic variations that cause some degree of difficulty in accurate dosing. This problem is more prominent (and most of the times clinically significant) for drugs with a narrow therapeutic window and non-linear pharmacokinetic like phenytoin.

Due to non-linear pharmacokinetic behavior, phenytoin represents a dose-dependent (or concentration dependent) clearance, which means that the limited metabolic capacity may lead to a disproportionate increase in serum concentration following a small increment in dosage.

Vm and Km as two major pharmacokinetic parameters, have a critical impact on determining the clearance and intrinsic clearance of phenytoin in patients hence it would be difficult to predict the dosage requirement to establish a given serum concentration without considering these parameters (4).

In individualizing phenytoin dosage, it is important to use estimates that are representative of the population concerned. Vozeh et al. reported the following estimates of Vm and

Table 3. Comparison of demographic and pharmacokinetic characteristics between patients undergoing phenytoin monotherapy and combination therapy with Phenobarbital.

Parameters	Phenytoin monotherapy (n=9)	Phenytoin + Phenobarbital (n=23)	Monte Carlo 95% confidence interval		P v.alue*
			Lower	Upper	
Age (years)	44.78±22.34	34.61±16.78	0.023	0.227	0.17
Weight (Kg)	70.56±10.63	69.52±9.50	0.3	0.6	0.79
Height (cm)	170.78±12.21	172.83±8.03	0.77	0.97	0.58
BMI (Kg/m²)	24.24±3.58	23.33±3.42	0.47	0.77	0.63
Dose (mg/day)	265.44±54.45	272.26±47.38	0.47	0.77	0.72
$Dose_{adj}$ (mg/Kg/day)	3.79±0.77	3.98±0.88	0.22	0.52	0.57
Cpss (mg/L)	16.75±6.90	14.15±7.76	0.12	0.38	0.38
$Cpss_{wt\ adj}$ (mg/Kg/L)	0.25±0.14	0.21±0.13	0.10	0.35	0.17
$Cpss_{dose\ adi}$ (day/L)	0.066±0.035	0.0515±0.026	0.20	0.50	0.20
Vm	5.69±0.65	6.09±1.05	0.35	0.66	0.32
Km	6.41±1.14	5.94±1.42	0.16	0.44	0.40
CL	0.28±0.11	0.40±0.31	0.37	0.68	0.50
CL_{int}	0.93±0.27	1.13±0.52	0.30	0.60	0.31

Dose $_{adj}$: adjusted dose; Cpss: steady-state serum concentration; $Cpss_{adj}$: adjusted steady-state serum concentration; Vm: maximum metabolic rate; Km: Michaelis-Menten constant; CL: clearance of phenytoin; CL_{int}: intrinsic clearance of patient.
There was no significant differences between two groups regarding the demographic and pharmacokinetic characteristics.
*Mann-Whitney U test was used to compare the variables between "Phenytoin monotherapy" and "Phenytoin + Phenobarbital" groups. $p<0.05$ was consideredas significant difference.

Km: mean Vm=7.22 mg/kg/day (interindividual SD=1.72, and CV, 24%) and mean Km=4.44 mg/L (interindividual SD=2.4, and CV=24%) (14). similar values have been reported by others proposing an average value of 7 mg/kg/day for Vm and 4 mg/L for Km (2, 3). Considering the mean from Vm and Km of our study (6.12±1.01and 5.9±1.26, respectively), the intrinsic clearance would be 1.12±0.46 L/kg/day (Table 2), which is much lower than the estimated intrinsic clearance in other populations that it would be 1.75 L/kg/day.

It would be inferable that using the preceding estimates would overdose our patients and prone them to the adverse reactions of phenytoin especially neurotoxicities (e.g.: nystagmus, ataxia, dysarthria, diplopia) wich are dose-related toxicities (15). Similar differences of Vm and Km with general estimates have been reported in black population,which implied that the race may be an important covariate for estimation of Vm and Km (16).

Several factors including age, weight, smoking, and race may influence the pharmacokinetic characteristics of phenytoin. In our study, age was inversely correlated with the Vm and CL_{int} in patients treated with phenytoin alone, where this correlation was not confirmed in the group receiving phenytoin and phenobarbital or in whole patient analysis. These findings may be explained by at least two reasons.

First, the patients receiving phenytoin monotherapy were relatively older than those receiving phenytoin and phenobarbital (Table 3); i.e. that the patients in phenytoin combination therapy were not that old to reflect the limiting capacity of hepatic metabolic activity with age advancing.

Second, the inducing activity of phenobarbital on the metabolic pathways of phenytoin may overcome the decreasing effect of aging in the rate of phenytoin metabolism. Comparison of Vm values in monotherapy and polytherapy groups, i.e. 5.69 mg/kg/day and 6.09 mg/kg/day respectively, also confirms these explanations (Table 3). Unlike our findings and the results by some other studies (17, 18), Aarons et al did not find any influence of age on Vm in patients receiving phenytoin as monotherapy (19).There

Table 4. Correlation of patients' demographic and doses with steady-state serum concentrations and pharmacokinetic variables.

Groups	Cpss	$Cpss_{adj}$	Vm	Km	CL	CL_{int}
All Patients (n=40)						
Age (years)	+0.11	+0.04	+0.11	-0.05	-0.09	+0.10
Weight (Kg)	-0.3	-0.26	-0.50**	+0.62**	-0.59**	-0.58**
Height (cm)	-0.14	-0.13	-0.03	+0.06	+0.05	+0.05
BMI (Kg/m^2)	-0.27	-0.22	-0.54**	+0.65**	-0.62**	-0.62**
Dose	+0.31*	+0.012	+0.36*	-0.40*	-0.4*	+0.39*
$Dose_{adj}$	+0.4*	+0.21	+0.61**	-0.78**	-0.75	+0.73**
Days on a constant dose	-0.26	-0.22	-0.20	+0.30	+0.28	-0.27
Phenytoin alone (n=9)						
Age (years)	+0.17	+0.39	-0.82*	+0.63	-0.59	-0.67*
Weight (Kg)	-0.23	-0.25	-0.14	+0.68	-0.62	-0.70
Height (cm)	-0.32	-0.35	+0.14	+0.39	+0.29	-0.31
BMI (Kg/m^2)	-0.17	-0.13	-0.23	+0.7	-0.70	-0.75*
Dose	+0.02	-0.4	+0.7*	-0.53	-0.44	+0.36
$Dose_{adj}$	+0.13	-0.18	+0.59	-0.98**	-0.85**	+0.83*
Days on a constant dose	+0.88**	-0.31	+0.69	-0.34	-0.40	+0.40
Phenytoin with phenobarbital (n=23)						
Age (years)	-0.13	-0.27	+0.38	-0.31	-0.38	+0.37
Weight (Kg)	-0.19	-0.16	-0.46	+0.53**	-0.54**	-0.54**
Height (cm)	-0.03	+0.02	-0.02	-0.001	+0.01	-0.01
BMI (Kg/m^2)	-0.16	-0.15	-0.47*	+0.55**	-0.55**	-0.56
Dose	+0.33	+0.02	+0.06	-0.14	-0.14	+0.13
$Dose_{adj}$	+0.39	+0.21	+0.49*	-0.68**	-0.67**	+0.64**
Days on a constant dose	-0.15	-0.1	-0.27	+0.42*	-0.43*	-0.4

* Correlation is significant at the 0.05 level (Spearman correlation).
** Correlation is significant at the 0.01 level (Spearman correlation). BMI: body mass index; $Dose_{adj}$: adjusted dose; Cpss: steady-state serum concentration; $Cpss_{adj}$: adjusted steady-state serum concentration based on the dose; Vm: the maximum metabolic rate; Km: Michaelis-Menten constant; CL: clearance of phenytoin; CL_{int}: intrinsic clearance of patient.

was not any correlation between Km and the age of patients in our study, the same as previous studies (17, 19). Considering the effects of age on pharmacokinetic parameters of phenytoin, in spite of the lower age of our sample, our findings are in agreement with the results of the most other studies that the Vm values for older patients are lower than those for younger adults and age does not influence Km (17-19). Therefore, special caution should be applied when phenytoin is prescribed in old patients.

The mechanism responsible for the effect of aging on pharmacokinetic parameters of phenytoin is likely the decrease in metabolization capacity which in turn, could be related to a physiological decrease in liver volume in aging (20) and possibly, a decline in the activity of CYP2C9 and CYP2C19, the two main isoenzymes responsible for phenytoin metabolism (21).

In our study, as reported by others (3, 17, 19, 22, 23), gender did not influence the pharmacokinetic parameters of phenytoin.

The CL and CL_{int} in patients receiving phenobarbital comedication were higher compared to those in patients on phenytoin monotherapy, although these differences were not statistically significant (Table 3, Mann-Whitney U-test). This could be explained by inducing effects of phenobarbital on metabolization of phenytoin.

Table 5. Comparison of Vm and Km of patients with the mean reported value.

	Our sample	Mean differences with the mean reported values Ψ	95% Confidence interval of differences	P value*
All Patients (n=40)				
Vm	6.12	-0.88	-1.2 to -0.55	< 0.001
Km	5.90	+1.9	1.49 to 2.31	< 0.001
Phenytoin monotherapy (n=9)				
Vm	5.69	-1.31	-1.86 to -0.77	<0.01
Km	6.41	+2.41	1.46 to 3.37	<0. 01
Phenytoin + Phenobarbital (n=23)				
Vm	6.09	-0.91	-1.37 to -0.46	< 0.001
Km	5.94	+1.94	1.33 to 2.56	< 0.001

Ψ: Mean reported value for Vm and Km are 7 mg/Kg/day and 4 mg/L, respectively. Vm: maximum metabolic rate; Km: Michaelis-Menten constant. Vm and Km had a normal distribution according to Kolmogorov-Smirnov test (Z= 0.921 and P=0.365 for Vm and Z=0.917 and P=0.369 for Km; respectively).

*P value was derived from the comparison of Vm and Km with the mean reported values with one sample t-test. Both phenytoin and phenytoin plus phenobarbital groups had a statistically different Vm and Km with the mean reported values.

The dose and the adjusted dose based on weight ($Dose_{adj}$) had positive correlation with Vm, and inverse correlation with Km in all patients (Table 4).

Similar correlation were found between the adjusted dose, Vm and Km in combination therapy group. In phenytoin monotherapy group, the dose was positively correlated with Vm and the adjusted dose correlated inversely with Km.

In our study, the weight of patients correlated significantly with Vm and Km, as patients with a higher weight had a lower Vm and a higher Km. Adjustment of the weight considering the height and calculating the BMI was not associated with any difference in correlations with pharmacokinetic parameters, indicating that it would be unnecessary to consider the height and BMI of patients to individualize phenytoin dosage (Table 4).

In addition to age and weight, smoking and race are other covariates that may influence the Vm of phenytoin.Valodia et al demonstrated clearly discernible differences between South African blacks and colored in kinetics of phenytoin, and proposed that weight, smoking, race, and age significantly influence the Vm of phenytoin in descending order of importance (17). Our entire sample population were from Persian race and based on patients' declarations, only one of them was smoker, so that it was not possible to evaluate the effect of race races and smoking on pharmacokinetic parameters of phenytoin.

Different reported pharmacokinetic parameters of phenytoin among different populations may be related to genetic, as well as the environmental factors such as diet and alcohol intake (7, 24). Phenytoin is considered a low-extraction-ratio drug, and its metabolism is mainly dependent on metabolic activity. Genetically determined polymorphism in drug metabolism is an important factor affecting drug disposition. It has been reported that CYP2C9 and CYP2C19, the major microsomal metabolic pathways of phenytoin, may have completely different activities among the individuals and different populations due to genetic polymorphism (7, 9, 10).

Although genotyping is not currently performed in routine medical practice, due to the dramatic effects of CYP2C9 and CYP2C19 polymorphism on pharmacokinetic parameters of phenytoin, it could be recommended as a tool for optimization of phenytoin dosage regimen.

In conclusion, the pharmacokinetic parameters of outpatients in our sample were significantly different form the reported mean values in other populations and considering the lower Vm and higher Km in our patients, there may be an increased risk of adverse reactions

by calculation of the dosage based on the previously reported mean values of Vm and Km. In addition, the inverse correlation of Vm with age is implying that it would be prudent to utilize initially smaller phenytoin dosage in elderly.

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