Medical Journal of the
Islamic Republic of Iran

Volume 9
Number 3
Fall 1374
November 1995

DETERMINATION OF PHARMACOKINETIC PARAMETERS OF PHENYTOIN IN IRANIAN EPILEPTIC PATIENTS

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ABSTRACT

Adjustment of phenytoin dosage in patients is very difficult due to its non-linear metabolism and patient to patient variation in its kinetics. It has been recommended that the dosage of phenytoin should be adjusted according to its plasma concentration and requirements of the patients. Therefore, the present study was carried out to identify the various factors which may influence the plasma level of this drug. The phenytoin plasma concentration was determined in 91 patients with steady-state concentrations according to the ***EMIT*** method. In a further 14 patients, who had recieved at least two different doses of phenytoin, the K_m and V_{max} of phenytoin metabolism were determined according to Mullen's direct linear plot. The results of this study showed that the plasma level of phenytoin was below the therapeutic level in 62 (68.2%) of the patients and above the therapeutic level in 8 (8.8%). Statistical analysis did not show any correlation between plasma level and factors such as sex, age, or type of drug administered. Only a small correlation was found between dosage and plasma level. The K_m of phenytoin metabolism in the group studied was found to be in the range of 1.8-26μg/ml and that of V_{max} in the range of 5.33-13.88 mg/kg/day. The mean values of K_m (8.4±1.7 μg/ml) and V_{max} (7.3±0.58 mg/kg/day) were slightly higher than reported values in the literature (5.7±2.9 μg/ml and 5.9±1.2 mg/kg/day, respectively). However, this difference was not statistically significant.
MJIRI, Vol. 9, No. 3, 227-231, 1995.

INTRODUCTION

Since there is a very good correlation between the therapeutic effects of phenytoin and its serum concentration, determination of serum levels of this drug is recommended for the control of seizures and in order to prevent its toxic effects.[1-3] The anti-convulsive effects of phenytoin appear at serum concentrations of 10-20 μg/ml. This drug is not active at lower concentrations and will be toxic at higher levels.[1-4,8] This drug also shows special pharmacokinetic characteristics, such as nonlinear metabolism. Therefore, the clinical response will be specific in every individual patient. It is thus of great importance to measure its plasma level and determine its pharmacokinetic characteristics in every patient to be able to individualize the dosage.[1-3,9] The present study was carried out to determine the pharmacokinetic characteristics of phenytoin in Iranian patients and investigate the effect of various factors which may influence the serum level of this drug.

MATERIAL AND METHODS

The influence of various factors on the serum concentration of phenytoin was investigated in 91 epileptic patients (59 males and 32 females) aged from 4 to 80 years. All patients had a history of using phenytoin for more than one month. They did not have any kind of renal, hepatic or heart disease. Various biochemical parameters (including serum albumin concentrations) were examined and found to be normal. Blood samples were collected in the morning just before the next dose. At this time, the concentration of drug will be at trough level of the steady state condition. The serum was separated quickly and stored at -20°C prior to assay. Determination of phenytoin serum concentration was carried out according to the EMIT method[9] in duplicate samples and the mean value was reported as the drug concentration. In 14 patients, who had received at least two different dosage regimens of phenytoin, individual metabolic parameters (K_m and V_{max}) were determined using Mullen's direct linear plot method.[5,6] Statistical analysis of data has been carried out according to the ANOVA method using the SPSS-PC package.

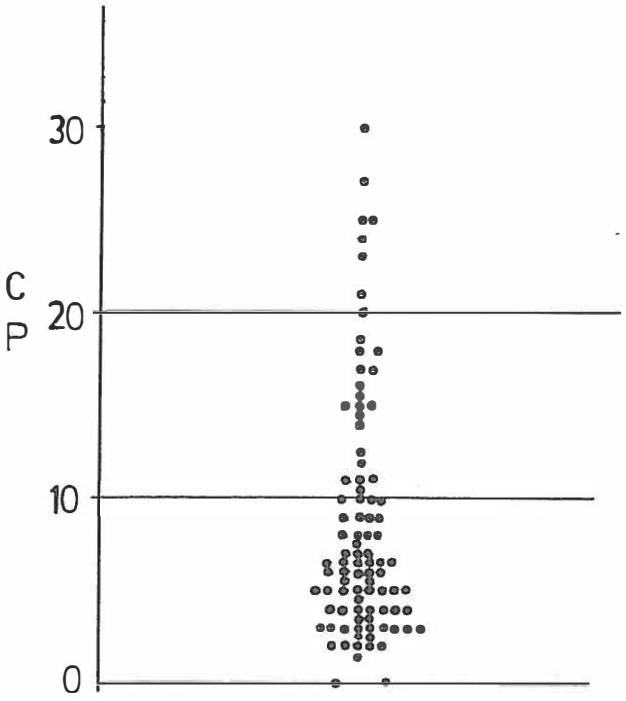

Fig. 1. The distribution of serum phenytoin concentrations among the patients under study.

RESULTS

Examination of 91 Iranian epileptic patients who had been referred to the TDM center has shown that in the majority of cases (77%) the serum level of phenytoin was outside of the therapeutic range (68.2% were below and 8.8% above the 10-20 μg/ml range). It is interesting to note that more than half of the patients had serum concentrations below 10 μg/ml (Fig. 1). Statistical analysis of the variance showed no correlation between various factors such as sex, age group, manufacturing company or co-administration with other anti-epileptic drugs (Table I). Only a small correlation was found between the dose of the drug and its serum level. This indicates that the observed low concentration value is a patient-dependent factor and is not related to other parameters.

To further investigate this problem, the phenytoin metabolic parameters (K_m and V_{max}) of 14 patients who had received at least two different doses of this drug were determined according to Mullen's direct linear plot. The results are presented in Table II and Figs. 2 and 3. The range of half-saturation concentration (K_m) in this group was found to be 1.8 to 26 μg/ml with a mean value of 8.4 and standard error of 1.7 μg/ml. The maximum metabolic capacity (V_{max}) was in the range of 5.35-13.88 mg/kg/day with a mean and standard error of 7.3 ± 0.58 mg/kg/day. The values of K_m and V_{max} are

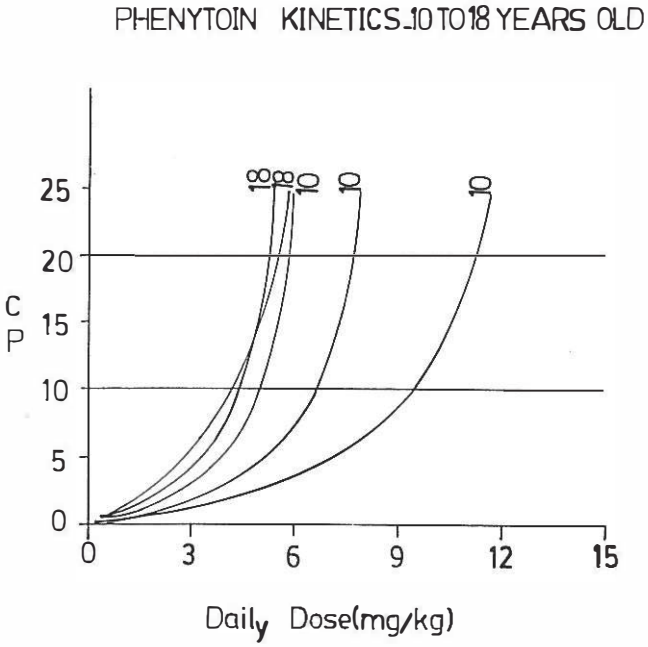

Fig. 2. The dose-serum level relationship curves of phenytoin metabolism in Iranian epileptic children.

Table I: Statistical analysis of phenytoin plasma concentration with respect to various factors.

Variables		No. of Cases	Mean Plasma Concentration	F Value	P Value
Sex	male	59	8.7	0.16	0.69
	female	32	9.36		
Age	0-4	1	12.60	0.18	0.95 N.S.
	4.1-12	8	10.64		
	12.1-19	18	8.64		
	19.1-50	57	8.78		
	50.1-80	7	8.43		
Drugs†	PHN	11	8.28	0.20	0.95 N.S.
	PHNcomp	24	10.12		
	PHN + PHB	14	8.94		
	PHNcomp+PHB	30	8.58		
	PHN + CBZ	7	7.30		
	PHN+PHB+CBZ	5	9.04		
Manuf.	ALHAVY	29	8.0	0.30	0.73 N.S.
	LOGHMAN	58	9.35		
	IMPORTED	4	9.5		
Dose mg/day	50	3	6.23	1.72	0.126*
	100	5	5.22		
	150	6	7.57		
	200	26	6.16		
	250	1	15.0		
	300	48	10.99		
	400	2	9.85		

†PHN: Phenytoin alone. PHNcomp: Phenytoin-phenobarbital compound. PHB: phenobarbital. CBZ: carbamazepine.
* nearly significant at 0.10 probability. N.S.: not significant.

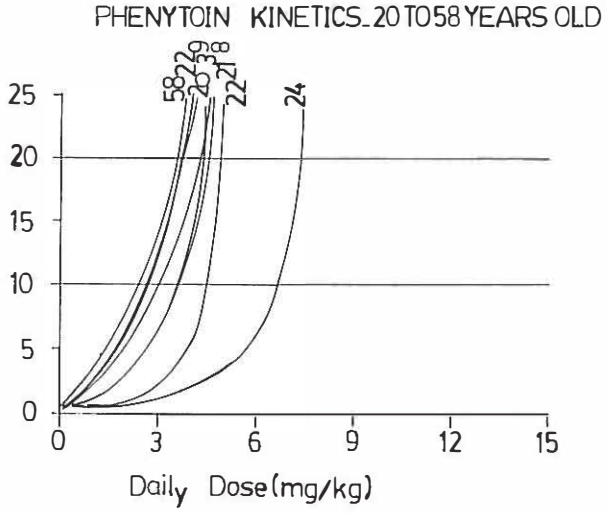

Fig. 3. The dose-serum level relationship curve of phenytoin metabolism in Iranian epileptic adult patents.

higher than reported values in the literature (K_m = 5.7±2.9 µg/ml and V_{max} = 5.9±1.2 mg/kg/day). However, these differences are not statistically significant.

DISCUSSION

It has been reported that there is considerable variation in the responsiveness of adult patients to phenytoin therapy, resulting in a poor correlation between dosage and serum concentration.[1] Individual differences in absorption, metabolism, compliance, disease states and concomitant medications combine to present a challenge to the clinician who aims for optimal phenytoin therapy. The rational use of serum concentration monitoring can help to overcome many of these problems. However, factors which may affect

Table II: Pharmacokinetic parameters of phenytoin in Iranian epileptic patients.

PATIENT	AGE (year)	WEIGHT (kg)	DOSE1 (mg)	C_p1 (μg/ml)	DOSE2 (mg)	C_p2 (μg/ml)	K_m (μg/ml)	V_{max} (mg/kg/day)
1	10	40	200	4.6	300	19.6	3.6	9.0
2	10	34	200	23.0	150	6.5	3.8	6.9
3	10	25	200	6.4	300	30.0	4.75	13.88
4	18	60	200	4.7	300	5.3	4.68	6.42
5	18	68	300	9.7	400	13.0	19.5	8.01
6	38	68	400	58.0	200	14.2	26.0	8.6
7	22	64	300	53.0	200	14.0	11.75	5.7
8	22	72	200	2.0	300	6.5	1.8	5.35
9	24	70	300	2.5	400	5.2	2.2	8.15
10	24	75	200	10.5	300	11.7	1.55	5.5
11	39	60	200	14.4	300	15.6	14.35	6.38
12	21	50	200	14.5	300	29.0	13.4	7.1
13	58	55	200	6.5	300	18.0	5.85	5.82

phenytoin serum concentration (such as source of drug used in each country, constitutional variations in drug metabolism, etc.) vary from one country to another. Therefore, it is necessary to carry out a systematic investigation of the effect of various factors in each country to be able to interpret the result of serum concentration assays and eliminate the troublesome factors. The present study was carried out to address this problem in Iranian epileptic patients. Our results showed a low serum level of phenytoin in epileptic patients who had referred to the TDM Center Reference Laboratory in a period between October 1990 to March 1992. Investigation of the effect of various factors failed to show any correlation between the plasma level of phenytoin and sex, age group, type of drug used or presence of other anti-epileptic drugs (Table I). In agreement with other reports[1-3] a poor correlation between phenytoin dosage and its plasma level was found which confirms that one can not predict clinical results on the basis of phenytoin dosage regimens alone. Therefore, it is of absolute necessity to measure its serum level in order to manage the patient properly. Stochastic simulation of phenytoin steady state concentrations have shown that the phenytoin serum level is very sensitive to change in dosage and the bioavailabilities of various products.[4] The simulation studies have illustrated the importance of product uniformity that must be maintained from lot to lot of the same product and from one manufacturer to another.[4] In the present study, while there is some difference in the mean serum phenytoin level of patients who have used different products, this difference is not statistically significant (Table I). A full-scale bioavailability study is needed to clarify the effect of the manufacturing process on the observed low serum concentrations of phenytoin in the patients under study. Another possible factor which may have resulted in low serum phenytoin levels is a higher rate of phenytoin metabolism in Iranian patients. In order to investigate this factor, we determined the K_m and V_{max} of phenytoin metabolism in some of our patients using Mullen's direct linear plot. Our results showed a higher metabolic capacity (higher V_{max}) in the patients under study compared to published values.[9] Whether this is a true constitutional difference or a characteristic of this group of patients, one cannot tell. It is possible that due to lack of clinical response in some patients, they may have been referred to the TDM center more often than those who have a normal metabolism and their phenytoin serum levels were in the clinical range.

In conclusion, our study points to a lower phenytoin serum level in Iranian epileptic patients and higher capacity for metabolism of this drug. Therefore, assessment of the bioavailability of phenytoin products manufactured in Iran and routine monitoring of phenytoin serum levels in all patients are highly recommended.

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