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Factors Influencing the Population Pharmacokinetic Parameters of Phenytoin in Adult Epileptic Patients in South Africa

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Summary: The influence of various covariates (including weight, race, smoking, gender, age, mild-to-moderate alcohol intake, and body surface area) on the population pharmacokinetic parameters of phenytoin in adult epileptic patients in South Africa was investigated. The parameters were the maximum metabolic rate (Vm) and the Michaelis-Menten (MM) constant (Km) of phenytoin. The study population comprised 332 black and colored epileptic patients (note: "black" refers to indigenous people of South Africa, who speak one of the Bantu languages as their native language; "colored" refers to people considered to be of mixed race, classified as such by the apartheid former government of South Africa). The influence of covariates on Vm and Km estimates was determined using nonlinear mixed-effects modeling (NONMEM). Parameter models describing the factors that could potentially influence Vm and Km were tested using the Michaelis-Menten parallel MM and first-order elimination models, to which 853 steady state dose-to-serum concentration pairs were fitted. The results indicated that body weight, smoking, race, and age (65 years or older), in descending order of importance, significantly influenced Vm ($p < 0.05$). Although a significant difference ($p = 0.03$) in Km was found between black and colored patients, incorporating the influence of race in Km in the final regression model did not improve the fit of the model to the data, which indicated that the variability in Km was accounted for by Vm. The scaling factors for smoking, colored patients and age (65 years or older) in Vm were 1.16, 1.10, and 0.88, respectively. These factors should be taken into account when adjusting phenytoin dose. **Key Words:** Patient factors—Phenytoin—Population pharmacokinetic parameters.

The influence of various covariates (including weight, race, gender, and body surface area) on the pharmacokinetic parameters of phenytoin has been previously investigated (1–3) in adults. The parameters were the maximum metabolic rate (Vm) and the Michaelis-Menten constant (Km). Interpretation and comparison of earlier studies were difficult because of their retrospective study design (questionable compliance), small sample sizes, multiple drug therapy, different analytic techniques, different methods of data analysis, and other noncontrolled factors. The use of multiple regression analysis and the calculation of correlation coefficients to determine the effect of patient attributes on the pharmacokinetic parameters have been demonstrated by Sheiner and Beal (4) to be inappropriate methods. It is also possible that the relationship between phenytoin dose and patient attributes in many studies was influenced by the presence of other anticonvulsants (5).

Phenytoin, a drug with a narrow therapeutic range, displays zero-order kinetics in the therapeutic range and significant interpatient variability in pharmacokinetic parameters. Use of therapeutic drug monitoring is thus indispensible in optimizing dose (6). In the individualization of phenytoin dosage, it is important to use estimates of Vm and of Km that are representative of the population concerned (7). Knowledge of factors influencing Vm and Km in a population should allow for an appropriate dose to have been determined earlier in the course of therapy (8,9). Miller and colleagues (7) demonstrated

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in a retrospective study that the mean Vm and Km values representative of the black population attending Baragwanath Hospital (Johannesburg, South Africa) were lower than those reported in most other studies. This finding implied that race may be an important covariate of Vm and Km.

The nonlinear mixed-effects modeling (NONMEM) computer program was ideal for the estimation of population pharmacokinetic parameters, their variability, and the influence of demographic and clinical factors on this variability. A number of studies have used this method for estimating population pharmacokinetic parameters for phenytoin (2,3,7,9).

This study involved careful prospective data collection from a large sample of adult South African patients receiving phenytoin monotherapy for epilepsy. The NONMEM approach was used to evaluate the influence on patients of weight, race, gender, age, body surface area, smoking status, and mild-to-moderate alcohol consumption on Vm and Km.

PATIENTS AND METHODS

Patients

Patients for this study were recruited from nine epilepsy clinics at which clinical pharmacokinetic dosing services were offered on a weekly basis during a 2-year period. The pharmacokinetic service entailed a patient interview, a chart review, drug analysis, and provision of either a written or a verbal consultation report. Informed, written consent was obtained from each patient in the study.

Particular attention was given to the collection of reliable steady state serum phenytoin concentrations from patients. Compliance was assessed by extensive patient interviews, tablet counts, correct completion of the patient diaries, verification of hospital prescription cards, and a variation between two measured, serial serum phenytoin concentrations taken at different times at the same dose. A variation of 20% or less was considered acceptable. Steady state was assumed a month after dosing was initiated or changed.

The study population comprised 332 (149 black, 183 colored) adult epileptic patients residing in the Western Cape, South Africa, from whom 853 reliable phenytoin dose-to-serum concentration pairs were obtained. Of these patients, 226 were men and 106 were women. The mean age was 36.4 ± 14.1 years (range, 15–82 years), with only 17 patients between 65 and 82 years. All patients were receiving phenytoin monotherapy for the management of epilepsy. Patients were concurrently taking no drugs known to interfere with phenytoin pharmacokinetics, and there was no laboratory evidence of hepatic or renal disease or of a history of alcohol or drug abuse; 49.7% of the patients smoked cigarettes and 27% reported mild-to-moderate alcohol consumption.

Phenytoin Analysis and Data Analysis

Total serum phenytoin concentrations were measured with a fluorescent polarization immunoassay (FPIA) using an automated TDxFLx system (Abbott Laboratories: Chicago, IL, U.S.A.).

Double-precision NONMEM, version IV, level 1.0 (NONMEM Project Group [University of California: San Francisco, CA, U.S.A.]) was used in this study (10)

Pharmacokinetic Models

A one-compartment model with either Michaelis-Menten (MM) or parallel MM and first-order elimination (MM + FO) was used. In the MM model, dose rather than steady state serum concentration was chosen as the dependent variable to ensure stability during data fitting (9). This model was represented as follows:

$$R_{ij} = \frac{Vm_j \times Cp_{ssij}}{Km_j + Cp_{ssij}}$$

where R*ij* is the *i*th dosing rate of phenytoin (mg/day) predicted to achieve the *i*th steady state serum concentration in the *j*th patient (Cp_{ssij}); Vm*j* and Km*j* are the maximum metabolic rate (mg/day) and MM constant (mg/L) of phenytoin, respectively, in the *j*th patient. Vm*j* and Km*j* are assumed to be constant over time within a patient but may differ between patients (2,11,12).

The MM + FO model was represented as follows (13,14):

$$Cp_{ssij} = -\frac{1}{2}\left[\left(\frac{Vm_j}{Cl_j} + Km_j - \frac{R_{ij}}{Cl_j}\right) - \sqrt{\left(\frac{Vm_j}{Cl_j} + Km_j - \frac{R_{ij}}{Cl_j}\right)^2 + \frac{4 \cdot R_{ij} \cdot Km_j}{Cl_j}}\right]$$

The derivation of this equation has been described by Ludden and colleagues (13), although the parameterization differs in that linear clearance (Cl) was substituted for the product of Vd (volume of distribution) and K_{el} (first-order elimination rate constant). This model was used to verify the results obtained with the MM model and has been shown to fit the data better than the MM model (unpublished data, P. Valodia).

Development of the Regression Model

The covariates (weight, body surface area, age, race, smoking, gender, and mild-to-moderate alcohol consumption) were tested for their influence on Vm and Km for both the MM and the MM + FO models. The continuous covariate (i.e., weight) was introduced in a linear form or as a power model:

$$Vm = \theta_1 WT + \theta_2$$

or

$$Vm = \theta_1 WT^{\theta_2}$$

When quantifying the influence of a discontinuous variable such as smoking status, the model was of the type:

$$Vm = [\theta_1 WT + \theta_2] * SMK$$

where SMK equals 1 for nonsmokers and Θ_{SMK} for smokers. Therefore, for colored smokers who were men and 65 years or older and had mild-to-moderate alcohol consumption, the value of Θ represented the fractional increase or decrease in Vm as compared with a value of unity for the patient if a black nonsmoker younger than 65 years and a woman who abstained from alcohol. A cut-off point of 65 years was chosen because changes in the renal excretion of drugs were expected to occur at this age.

Statistic Analysis

To test the hypothesis of whether the fit of the model to the data was significantly different, the value of the minimum objective function (MOF) determined was used. Assuming that inter- and intraindividual variances were normally distributed, a difference in the minimum objective function (DOBF) of more than 3.8 indicated statistic significance ($p < 0.05$, assuming chi-square distribution) in the improvement or worsening of the fit of the model to the data when the restricted model had 1 regression parameter less than the full model (i.e., 1 degree of freedom). To identify potentially significant factors, a DOBF of > 7.9 for 1 degree of freedom associated with a p value of 0.005 was required (15). This approach was only used when comparing nested models. When two models that were not restricted in terms of each other (i.e., 0 degree of freedom) were compared, the goodness-of-fit was judged by comparing the scatterplots of weighted residuals versus predicted dose or serum concentration, weight, age, race, alcohol intake, sex, body surface area, or smoking status. If the DOBF was not sufficiently decisive to select the most appropriate model to describe the data, other criteria in addition to the DOBF were used (10): Inspection of the correlation matrix of the parameter estimates to indicate whether a minimal correlation between the parameters existed; whether the scatterplot of weighted residuals versus predicted concentration was randomly scattered around zero; whether smaller standard errors for the estimates were obtained; and whether a decrease in the size of the interindividual variance of the pharmacokinetic parameters and residual error were obtained.

All patient variables showing possible evidence of influence on Vm and Km were re-evaluated using the MM + FO model. The influence of the following patient characteristics was re-evaluated: Race, smoking, mild-to-moderate alcohol intake, gender, age less than 65 years, and age of 65 years or older in Vm; and race, age less than 65 years, and age older than 65 years in Km. This was performed by comparing the full model with all the patient factors included with a regression model from which one of the covariates was independently removed stepwise (16).

RESULTS

Nonlinear Mixed-Effects Modeling Analysis

The results of this study are reported as two sets of analyses: Set 1 for the MM model and Set 2 for the MM + FO model.

Set 1 Analysis

The results obtained with the MM model are summarized in Table 1. A multiplicative error model for intersubject variability in Vm and Km did not improve the fit of the model to the data when compared with the additive error model. The latter model was thus used. An additive error model was used for intrasubject variability. A stepwise procedure was used to find the final model that fitted the data the best. The covariate tested, the resulting DOBF, and the associated p value obtained are presented in Table 1.

Incorporation of weight, race (black or colored), and smoking status (smoker or nonsmoker) in Vm indicated that these factors significantly influenced Vm. Gender and mild-to-moderate alcohol intake were not found to influence Vm. Incorporating race in Km when the patients were classified as either black or colored indicated that race significantly influenced Km. When patients were separated into two groups (patient subjects younger than 65 years and those 65 years of age or older), no significant improvement in fit was obtained when age was included in Vm or Km. A continuous effect of age could not be detected, and thus discontinuity at 65 years of age was tested.

TABLE 1. *Models tested for factors influencing Vm and Km values of phenytoin (set 1 and set 2 analyses)*

Test	MM model		MM + FO model		Comments
	DOBF	*p*-Value	DOBF	*p*-Value	
Weight in Vm	58.3	< 0.0005*	63.847	< 0.0005*	Vm is related to weight
Weight raised to a power	0.762	0.385			No improvement in fit
Body surface area in Vm	56.087	< 0.0005*	55.724	< 0.0005*	Body surface area provided no advantage over weight
Race in Km	4.787	0.03*	7.417	0.0233*	Km related to race
Race in Vm	9.486	0.003*	12.421	< 0.0005*	Vm related to race
Gender in Vm	1.485	0.228	0.467	0.495	Vm not related to gender
Smoking in Vm	11.773	< 0.0007*	34.821	< 0.0005*	Vm influenced by smoking
Smoking in Vm (< 10 versus ≥ 10 cigarettes/day)					No improvement in fit
Smoking in Vm (< 20 versus ≥ 20 cigarettes/day)					No improvement in fit
Mild-to-moderate alcohol consumption in Vm	2.923	0.09	0.471	0.494	Vm not influenced by mild-to-moderate alcohol consumption
Age in Vm (< 65 versus ≥ 65 years)	1.735	0.1877	5.496	0.021*	Conflicting results obtained for models S1 and S2
Age in Km (< 65 versus ≥ 65 years)	0.521	0.488	1.29	0.262	Km not influenced by a discontinuity at 65 years of age
Race and smoking in Vm	10.621	0.001*	9.951	0.0175	Influence of race and smoking combined in Vm provided a better fit than race alone in Vm

* Indicates statistical significance ($p \leq 0.05$) and improvement in fit of the model to the data.
DOBF, difference in objective function.

Weight had a significant effect and thus was left in the model. When body surface area was incorporated in Vm, no additional information over weight when estimating Vm was obtained. Therefore, only the influence of weight in Vm was included in the model. When the smokers were separated into two groups (those who smoked less than 10 cigarettes and those who smoked 10 or more cigarettes daily, and those who smoked less than 20 cigarettes and those who smoked 20 or more cigarettes daily), no improvement in the fit of the model to the data was obtained. Accordingly, the patients were categorized as smokers or nonsmokers. Because of the homogeneity of the patient population in respect to alcohol consumption (abusers excluded), no effect of alcohol consumption on Vm was expected.

On investigating the influence of race alone on Vm, a DOBF of 9.486 ($p = 0.003$) was obtained, indicating that race produced a statistically significant influence on the variation in Vm. On investigating the influence of race alone on the variation in Km, a DOBF of 4.787 ($p = 0.03$) was obtained, indicating that race produced a statistically significant influence on the variation in Km. This finding indicated that the influence of race is greater on the variation in Vm than on Km. When race was incorporated in Km in a model that already included the influence of race in Vm, a DOBF of 0.052 ($p = 0.825$), which indicated virtually no improvement in the fit of the model to the data. This finding confirmed that race has a greater influence on the variation in Vm. However, when race was incorporated in Vm in a model that only included the influence of race in Km, a DOBF of 4.751 ($p = 0.031$) was obtained. We concluded that the final model only needed to account for the influence of race on the variation in Vm. In the final model, Vm was expressed as a function of race, weight, and smoking. A DOBF of 10.621 ($p = 0.001$) indicated that the combined influence of race and smoking on the variation in Vm was more significant than race in Vm alone (see Table 1).

Set 2 Analysis

In Set 2 analysis, the MM + FO model was used. The additive error model for inter- and intraindividual variability was used. The same factors shown to influence Vm and Km in Set 1 analysis using the MM model were found in this set of analysis. In this set of analysis, when age was categorized into two groups (younger than 65 years and 65 years or older) a DOBF of 5.315 ($p =$

TABLE 2. *Parameter estimates obtained for the MM + FO model*

Parameter	Parameter estimates	Standard error (%)
θ_1	3.86	10.72
θ_2	7.45	15.43
θ_3	112.0	40.55
θ_4	1.10	3.89
θ_5	1.16	4.11
θ_6	2.31	35.75
θ_7	0.88	8.72

0.022) was obtained, indicating statistic significance. A DOBF of 156.2 ($p < 0.0005$) was obtained when the simplest model with no covariates was compared with the model including all the covariates.

The final regression model obtained can be represented as follows:

$$Vm = (\Theta_1 * WT + \Theta_3)RACE*SMK*AGE+\eta_1$$
$$Km = \Theta_2+\eta_2$$
$$Cl = \Theta_6+\eta_3$$

where RACE $= \Theta_4$ if colored, otherwise $= 1$
SMK $= \Theta_5$ if smoker, otherwise $= 1$
AGE $= \Theta_7$ if ≥ 65 years, otherwise $= 1$

The parameter estimates and the percentage standard errors of the estimates are given in Table 2. The percentage of standard errors indicate a good fit with reliable parameter estimates. Vm, Km, and Cl showed interindividual variability of 12.5, 67.9, and 46.3% (expressed as a percentage coefficient of variation [CV]), respectively. An intraindividual variability of 20.1% was obtained. Scatterplots of the measured-versus-predicted serum phenytoin concentrations (853 data points) when no covariates were included (weight included in Vm) and all the factors (i.e., weight, race, smoking, and age) included in Vm are shown in Figure 1. A comparison of the scatterplots indicate that less scatter is obtained when weight was included in Vm. When all the covariates were included and compared with weight alone, a decrease in scatter of the predicted-to-measured serum concentration pairs was found. It is clear that weight was the most important covariate. Because of the large interindividual variablilty in the pharmacokinetic parameters, minor differences in the influence of covariates in Vm cannot be observed from scatterplots.

DISCUSSION

This study demonstrated that estimates of Vm improved when weight, race, smoking, and age were taken into account. Other than weight, the most influential factor related to Vm was smoking, which significantly increased Vm ($p < 0.0007$), on average by a factor of 16%.

Genetically determined polymorphism in drug metabolism is an important factor affecting drug disposition, thus interest has developed in the individualization of dose to account for racial differences (17). In this study, clearly discernible differences have been found between South African blacks and coloreds in the kinetics of phenytoin, which may be related to genetic as well as environmental factors (e.g., diet and alcohol intake [18]). Our results conflict with those of Grasela and coworkers (2); our study showed that race influenced Vm and Km whereas theirs showed an influence on Km only. However, our final model did not include the influence of race in Km for the reasons discussed previously.

Similar to the study by Grasela and coworkers (2), our study did not detect a continuous effect of age on Vm. Grasela and coworkers (2) reported that discontinuity at 15 years of age provided the best fit of the model to their data; their patient population differed from ours in that it included children. Our study in adults showed that discontinuity at 65 years of age in Vm provided a marginal improvement in fit ($p < 0.021$) when the MM + FO model was used. On the contrary, discontinuity at 65

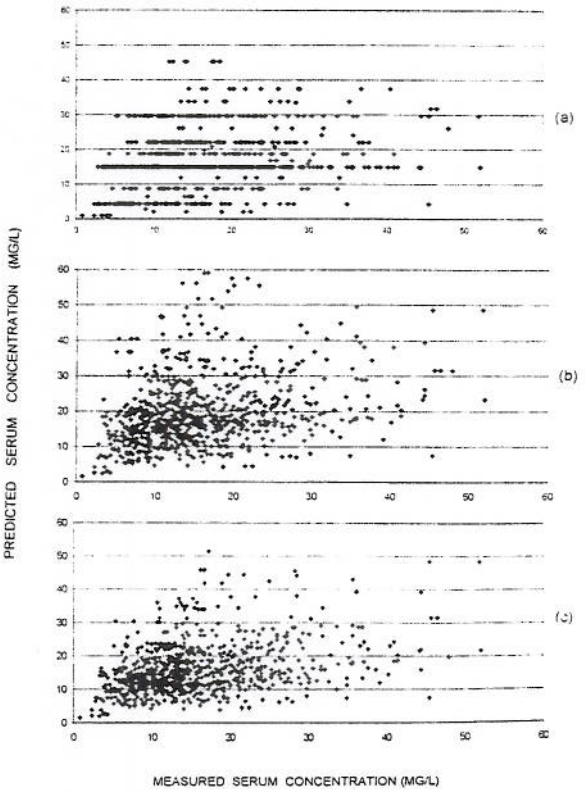

Figure 1. Scatter plots of measured serum phenytoin concentration (x axis) versus predicted serum phenytoin concentration (y axis) when: (a) no covariates were included, (b) weight included in Vm and (c) all the factors (i.e., weight, race, smoking, and age) were included in Vm.

years of age in Vm was not significant ($p = 0.188$) when the MM model was used. This finding indicated that a relationship existed between Vm, linear clearance of phenytoin, and age older than 65 years. Our results agree with those of a prospective study performed by Bauer and Blouin (19), who showed that Vm values for geriatric patients were lower than those for younger adults and that age did not influence Km. The decline in Vm value for patients 65 years of age or older implied a decreased phenytoin metabolizing capacity in this age group. Therefore, caution should be used when prescribing phenytoin in patients 65 years of age or older. We found, as did others (2,3), that gender did not influence Vm and Km.

It is important to understand why variation in pharmacokinetic parameters occurs so that the dose can be tailored to achieve an optimal response in each patient. The estimates of this variability should be obtained in a patient population in whom the drug is used clinically (20). Although nomograms (predictive algorithms) are useful to initiate drug therapy, most are based on invalid assumptions of either a constant Vm or Km, and their error in achieving target concentration is considerable. More appropriate initial estimates of population pharmacokinetic parameters may greatly improve the prediction of phenytoin dose or serum concentration (21). Application of a model to a diverse patient population requires that the mean values for pharmacokinetic variables be defined appropriately for various subpopulations.

The implications of the present results are that if colored patients are to achieve the same serum level of total phenytoin as black patients, they should receive a higher dose because their Vm is higher. Although a specific ethnic group of patients (colored) and a smoking history correlated with an increase in Vm (10% and 16%, respectively), none of these correlations alone may require an altered dosage policy. An age of 65 years or older was associated with a decrease in Vm of 12.0%. These increases or decreases of percentages in Vm were obtained when the MM + FO model was used. Therefore, in a patient who is colored, nonsmoking, and 65 years of age or older, the overall effect on Vm may be minimal because the factors increasing or decreasing Vm may counterbalance each other. However, multiple factors, each of which is relatively minor, may together produce a significant contribution to the Vm value.

In conclusion, the factors of weight, smoking, race, and age (65 years or older) significantly influenced the Vm of phenytoin in descending order of importance. The scaling factors for smoking, colored patients aged 65 years or older in Vm were 1.16, 1.10, and 0.88, respectively, when the MM + FO model was used. These factors should be taken into account when adjusting phenytoin dose. Our study confirmed that different populations have differences in phenytoin disposition.

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REFERENCES

1. Rambeck B. Boenigk HE. Dunlop A. et al. Predicting phenytoin dose: A revised nomogram. *Ther Drug Monit* 1979:1:325–33.
2. Grasela TH. Sheiner LB. Rambeck B. et al. Steady-state pharmacokinetics of phenytoin from routinely collected patient data. *Clin Pharmacokinet* 1983:8:355–64.
3. Chan E. Ti TY. Lee HS. Population pharmacokinetics of phenytoin in Singapore Chinese. *Eur J Clin Pharmacol* 1990:39:177–81.
4. Sheiner LB. Beal SL. Some suggestions for measuring predictive performance. *J Pharm Biopharm* 1981:94:503–12.
5. Barot MH. Grant RHE. Maheendran KK. et al. Individual variation in daily dosage requirements for phenytoin sodium in patients with epilepsy. *Br J Clin Pharmacol* 1978:6:267–71.
6. Winter ME. Tozer TN. Phenytoin. In: Evans WE. Schentag JJ. Jusko WJ. eds. *Applied pharmacokinetics. Principles of therapeutic drug monitoring*. Spokane. WA: Applied Therapeutics. 1987: 493–539.
7. Miller R. Rheeders M. Klein C. et al. Population pharmacokinetics of phenytoin in South African black patients. *S Afr Med J* 1987: 72:188–90.
8. Sheiner LB. Beal SL. Bayesian individualization of pharmacokinetics: Simple implementation and comparison with non-Bayesian methods. *J Pharm Sci* 1982:7112:1344–8.
9. Vozeh S. Miur KT. Sheiner LB. et al. Predicting individual phenytoin dosage. *J Pharmacokinet Biopharm* 1981:92:131–46.
10. Beal SL. Sheiner LB. Boeckmann AJ. *NONMEM users guide*. San Francisco. CA: NONMEM Project Group. University of California. 1988.
11. Sheiner LB. Beal SL. Evaluation of methods for estimating population pharmacokinetic parameters. I. Michaelis-Menten model: Routine clinical pharmacokinetic data. *J Pharmacokinet Biopharm* 1980:86:553–71.
12. Yukawa E. Higuchi S. Aoyama T. Population pharmacokinetics of phenytoin from routine clinical data in Japan: An update. *Chem Pharm Bull* 1990:387:1973–6.
13. Ludden TM. Allen JP. Schneider LW. et al. Rate of phenytoin accumulation in man: A simulation study. *J Pharm Biopharm* 1978:65:399–415.
14. Ludden TM. Nonlinear pharmacokinetics. Clinical implications. *Clin Pharmacokinet* 1991:206:429–46.
15. Sheiner LB. Rosenberg B. Marathe VV. Estimation of population characteristics of pharmacokinetic parameters from routine clinical data. *J Pharmacokinet Biopharm* 1977:55:445–79.
16. Fattinger K. Vozeh S. Ha HR. et al. Population pharmacokinetics of quinidine. *Br J Clin Pharmac* 1991:31:279–86.
17. Wood AJJ. Zhou HH. Ethnic differences in drug disposition and responsiveness. *Clin Pharmacokinet* 1991:205:350–73.
18. Kalow W. Ethnic differences in drug metabolism. *Clin Pharmacokinet* 1982:7:373–400.
19. Bauer LA. Blouin RA. Age and phenytoin kinetics in adult epileptics. *Clin Pharmacol Ther* 1982:313:301–4.
20. Vozeh S. Katz G. Steiner V. et al. Population pharmacokinetic parameters in patients treated with oral mexiletine. *Eur J Clin Pharmacol* 1982:23:445–51.
21. Burton ME. Vasko MR. Brater DC. Comparison of drug dosing methods. *Clin Pharmacokinet* 1985:10:1–37.