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Validation of Population Pharmacokinetic Parameters of Phenytoin Using the Parallel Michaelis-Menten and First-Order Elimination Model

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Summary: This study was conducted to assess whether the parallel Michaelis-Menten and first-order elimination (MM+FO) model fitted the data better than the Michaelis-Menten (MM) model, and to validate the MM+FO model and its parameter estimates. The models were fitted to 853 steady state dose : serum concentration pairs obtained in 332 adults with epilepsy using nonlinear mixed-effects modeling (NONMEM). The MM+FO model fitted the data better than the MM model. The validity of the pharmacokinetic models and the estimated population parameter values was tested using the naive prediction method. The estimation and validation of the pharmacokinetic parameters were undertaken in two separate patient groups (cross-validation) obtained by splitting the data set. Patients were randomly allocated to two equally matched groups (groups 1 and 2). The predictive performance was assessed using 770 paired predicted versus actual dose or measured serum concentrations. The population pharmacokinetic parameters estimated by NONMEM in group 1 were validated in group 2 and vice versa. When predicting steady state serum concentration, the MM+FO model was clearly superior to the MM model (mean bias of 0.91 and 8.13 mg/L, respectively).
Key Words: Phenytoin—Population pharmacokinetic parameters—Validation—Linear clearance.

The pharmacokinetics of phenytoin are complicated by the nonlinearity in the dose–serum concentration relationship, which is a consequence of capacity-limited metabolism. A small increase in dose can result in a disproportionate increase in serum phenytoin concentration and vice versa (1). Drugs exhibiting nonlinear kinetics are likely to have at least a small parallel first-order pathway. An appropriate expression for the rate of phenytoin elimination should therefore also include clearance for the first-order (linear) pathway (2). An equation which takes parallel Michaelis-Menten metabolism and first-order kinetics of phenytoin into account has been described (2,3).

A first-order pathway which is only 1% to 2% of the maximum clearance at low concentrations can significantly influence steady state concentration when serum concentrations are high (2). At rates of administration approaching the maximum metabolic rate (Vm), renal elimination of unchanged phenytoin can significantly influence the steady state serum phenytoin concentration (3). Although the population pharmacokinetic parameters for the parallel Michaelis-Menten and first-order elimination (MM+FO) model have recently been reported (4), to our knowledge, this model has not been validated in patients taking phenytoin routinely. Most methods that have been used to predict phenytoin dose or serum concentration have traditionally taken into ac-

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count Vm and K_m values only. Therefore a model which includes linear clearance should predict phenytoin dose or serum concentration more accurately.

This study was conducted to assess whether the MM+FO model provides a better fit to the phenytoin data than the Michaelis-Menten (MM) model (i.e., whether a linear pathway is present in parallel to a nonlinear pathway in the elimination of phenytoin). The second objective was to ascertain whether including a linear pathway results in a meaningful improvement in the prediction of the dose–concentration relationship.

Black refers to indigenous people of South Africa who speak one of the Bantu languages as their home language. Colored refers to people considered to be of mixed race, classified as such by the previous apartheid government of South Africa.

METHODS

Patients

The study population comprised 332 (149 black and 183 colored) adults with epilepsy residing in the Western Cape, South Africa. Of these, 226 were male and 106 female. The mean age was 36.4 ± 14.1 years (range, 15–82 years). All patients were receiving phenytoin monotherapy for epilepsy. The total daily dose of phenytoin was 310 ± 64.9 mg/d (range 100 to 500 mg/d). Phenytoin was prescribed in 91.0%, 7.1%, and 1.9% of patients once, twice, or thrice daily, respectively. Of the patients, 37.3% were taking other medicines concurrently with phenytoin. None of these medicines taken concurrently are known to interfere with phenytoin pharmacokinetics. Of the patients taking other medicines, the most frequently prescribed was paracetamol in 38%. Of the patients, 49.7% smoked cigarettes. There was no hepatic or renal disease or history of alcohol or drug abuse. Informed written consent was obtained from each patient. Patients were recruited at 9 epilepsy clinics. Compliance was assessed by patient interview, tablet counts, correct completion of the patient's diary, and variation between two measured serial serum phenytoin concentrations taken at different times on the same dose. A variation of 20% or less was regarded as acceptable.

Serum Phenytoin Samples

If the patient was compliant and the serum phenytoin concentration was assumed to be at steady state, a request form for blood collection was completed. Steady state was assumed 1 month after dosing was started or after a change in dose (5). Total serum phenytoin concentrations were measured with a fluorescence polarization immunoassay using an automated TDxFLx system (Abbott Laboratories, Diagnostic Division, Chicago, IL, USA).

Pharmacokinetic Models

A one-compartment model with either Michaelis-Menten or parallel Michaelis-Menten and first-order elimination was used.

Structural Model S1 (Michaelis-Menten Model With Dose as the Dependent Variable)

In this model, dose rather than steady state serum phenytoin concentration was chosen as the dependent variable to ensure stability during data fitting (6). This model was represented as follows:

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

where R_{ij} (mg/day) is the $_i$th dosing rate of phenytoin predicted to achieve the $_i$th Cp_{ss} (mg/L) in the $_j$th patient; Vm_j and Km_j are the maximum metabolic rate (mg/day) and Michaelis-Menten constant (mg/L) of phenytoin, respectively, in the $_j$th patient and Cp_{ssij} is the steady state serum phenytoin concentration measured in the $_j$th patient receiving dosage R_{ij}. Vm_j and Km_j are assumed to be constant over time for an individual patient, but may differ between patients (7–9). The MM model was used for comparison with the MM+FO model.

Structural Model S2 (Michaelis-Menten and First-Order Elimination Model With Dose as the Dependent Variable)

This model was represented as follows (2):

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

where Cl_j is the linear clearance (L/d) of phenytoin for the $_j$th patient.

Structural Model S3 (Michaelis-Menten and First-Order Elimination Model With Steady State Serum Concentration as the Dependent Variable)

This model was represented as follows (2,3):

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

The derivation of this equation has been described (3). Our equation differed from that of Ludden et al (3) in that linear clearance (Cl) was substituted for the product of Vd (volume of distribution) and K_{el} (first-order elimination rate constant).

Structural Model S4 (Michaelis-Menten Model With Steady State Serum Concentration as the Dependent Variable)

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

The predictive performance of model S4 was compared with that of S3 to indicate the importance of Cl in the latter.

Parameter Models

The parameter models applied with the structural models were as follows:

$$Vm = (\theta_1 * WT + \theta_3)RACE*SMK*AGE*EXP\eta_1$$
$$Km = \theta_2 * EXP\eta_2$$
$$Cl = \theta_6 * EXP\eta_3$$

where

$$RACE = \theta_4 \text{ if colored, otherwise } = 1$$
$$SMK = \theta_5 \text{ if smoker, otherwise } = 1$$
$$AGE = \theta_7 \text{ if } \geq 65 \text{ years, otherwise } = 1$$

where η_1, η_2, and η_3 were assumed to represent random normally distributed terms with zero means and variances (ω^2_1, ω^2_2, ω^2_3 respectively). The development of the models and the influence of covariates have been described (4). An additive error model was used for the residual variability.

NONMEM Data Analysis

Double precision NONMEM version III level 1.2 and version IV level 1.0 (NONMEM Project Group, University of California, San Francisco, CA, USA) were used in this study.

The MM and the MM+FO models were fitted to 853 steady state dose : serum concentration pairs. When comparing models S1 and S2, a difference in the minimum objective function (DOBF) of more than 3.8 indicated statistical significance ($p < 0.05$, assuming χ^2 distribution) in the improvement or worsening of the fit of the model to the data when the restricted model had one regression parameter less than the full model, i.e., one degree of freedom (10). Model S3 predicted steady state serum concentration and therefore the minimum objective function (MOF) values obtained with models S1 and S2 that predicted dose could not be compared with those obtained with model S3. The importance of Cl in model S3 was evaluated using a variation of a method described by Sheiner et al (11).

The first-order conditional estimation (FOCE) method was used to obtain population parameter estimates for the validation procedure. It is expected that this approach would reduce bias in parameter estimates because the approximate marginal moments may be closer to the true moments (12). The FOCE method is an iterative procedure that involves multiple, sequential estimation of individual parameters, then population parameters, then individual parameters etc., until convergence is achieved for the population values.

Validation of Structural Models and Population Pharmacokinetic Parameters

The validity of the pharmacokinetic models and the estimated population parameter values was tested using the naive prediction method (13), which uses the mean population estimates of Vm, Km, and Cl but no patient-specific phenytoin concentration data. The covariates (race, smoking status, and age younger than 65 years or 65 years and older) previously found to influence Vm were included in the model (4). This allowed the testing of the best model that we have developed. The naive prediction method was used as it is a method one could most likely use in an outpatient practice prior to obtaining serum concentrations of a drug in the patient concerned. The predictions of dose or steady state serum concentrations obtained with the mean population estimates were compared. For models S1 and S2, the estimated population parameters (obtained from the NONMEM outputs and calculated from the parameter models) were used to predict the dose of phenytoin that would achieve the measured concentration. For models S3 and S4, the estimated population parameters were used to predict the steady state serum concentration that would be achieved when a particular dosing rate was administered. The estimates of Vm and Km obtained with model S1 were used in model S4 for predictions because NONMEM was unable to fit the latter model where Cp_{ss} is used as the dependent variable. A similar problem was experienced by Miller et al (14).

A data-splitting technique was used for validation (cross-validation). The full data set (332 patients) was used to develop the population models as described (4). To minimize possible bias in favor of the model by predicting dose or serum concentrations for patients whose data were used for the estimation of the population parameters, the estimation and validation of the pharmaco-

kinetic parameters were undertaken in two separate patient groups (cross-validation) obtained by splitting the data set. Eighty-one patients producing only one steady state serum concentration on a single dose of phenytoin were excluded from the analysis to rule out the possibility of noncompliance influencing the predictive performances of the models. The remaining 251 patients were randomly allocated to two equally matched groups (1 and 2), stratified according to the factors (race, smoking status, and age less than 65 years or 65 years and older) known to influence the pharmacokinetics of phenytoin (4). The predictive performance was assessed using 770 (388 and 382 in groups 1 and 2, respectively) paired predicted versus actual dose or measured serum concentrations obtained in the 251 (126 and 125 in groups 1 and 2 respectively) patients. The population pharmacokinetic parameters estimated by NONMEM in group 1 were validated in group 2 and vice versa. Prediction error analysis involved the calculation of the mean prediction error (MPE) and the root mean squared error (RMSE) (15). The MPE described the bias and RMSE the precision of the model with its associated population estimates in predicting the actual dose or serum phenytoin concentration. The 95% confidence intervals (CI) about the MPE and RMSE for each model were constructed (16). The predictive performance of our models and the associated parameters was compared with the MM model using the estimates (Vm = 7.22 mg/kg/d and Km = 4.44 mg/L) obtained by Vozeh et al (6). These estimates were previously widely used in our clinical practice for the calculation of phenytoin dose and prediction of steady state serum concentration.

Ranking the methods only on the basis of bias and precision does not always predict their ranking in respect of superiority of clinical use. For this reason, our study also examined the relative frequencies of satisfactory predictions. The ability to predict a dose or steady state serum concentration with precision within 10% of the actual dose or within 20% of measured serum concentration was tested for the various models. The percentage of underpredictions and overpredictions of dose or steady state serum concentrations was also assessed.

RESULTS

The MOF values obtained with model S1 were compared with those obtained with model S2. Model S2 fitted the data significantly better than model S1, as reflected by a decrease in the MOF and a DOBF of 2922.524 ($p < 0.0005$). The results suggest that linear clearance is important in model S2.

To illustrate the importance of Cl in model S3, the MOF was used to construct the 95% confidence interval for the Cl estimate by evaluating the MOF associated with a change in the Cl value. The value of Cl was fixed at values greater than or less than the mean population Cl value of 2.68 L/h derived from the model which fitted the data best. The Cl values were plotted against the corresponding MOF values. Where a horizontal line corresponding to a DOBF of 3.8 (measured from the lowest MOF value on the graph) intersects the graph the corresponding Cl values were read off. The Cl values of 1.49 and 3.89 L/d represent the approximate lower and upper limits of the 95% confidence interval of the Cl estimate, respectively. As the lower limit of the confidence interval was observed well before the Cl value approached zero, the importance of Cl in the model is confirmed.

The average parameter estimates for models S1, S2, and S3 obtained for groups 1 and 2 are presented in Table 1. The predictive performances of the 4 structural models using the mean population estimates were compared. Tables 2 and 3 present the MPE and RMSE obtained with each model and their associated population estimates. The combined results are reported for groups 1 and 2. A confidence interval (2.32–4.2 mg/day) for the difference in the predictions of S1 and S2 did not include the value zero, indicating that the two models behave differently. Similarly, the confidence interval (2.3–8.3 mg/L) for the difference in predictions comparing models S3 and S4 did not include zero, indicating that these two models also behaved differently from each other. The predictions of phenytoin dose or steady state serum phenytoin concentrations obtained with the MM model using the estimates obtained by Vozeh et al (6) are reported in Tables 4 and 5, respectively

DISCUSSION

Models S1 and S2 underpredicted the phenytoin dose by an average of 1.32 and 3.73 mg/d, respectively (Table 2), and model S3 was found to overpredict phenytoin concentration by an average of 0.91 mg/L (Table 3). This

TABLE 1. *Average parameter estimates for Groups 1 and 2 obtained for models S1, S2 and S3*

Parameter	Parameter estimates (% SE)		
	S1	S2	S3
θ_1	2.56 (13.4)	1.88 (13.68)	2.91 (11.15)
θ_2	4.72 (6.96)	1.96 (19.4)	7.31 (10.08)
θ_3	238 (8.8)	194 (15.1)	228 (24.83)
θ_4	1.05 (1.81)	1.07 (2.15)	1.07 (2.84)
θ_5	1.09 (1.80)	1.06 (2.08)	1.09 (2.94)
θ_6	—	2.07 (13.4)	2.14 (31.07)
θ_7	0.83 (1.76)	0.81 (1.96)	0.96 (7.95)

TABLE 2. *Predictive performance evaluation of models S1 and S2*

	Models	
	S1	S2
n	770	770
MPE (mg/day)	−1.32	−3.73
MPE (%)	−0.43	−1.2
RMSE (%)	17.58	16.86
95% CI of BIAS (mg/day)	−5.26–2.6	−7.33—0.11
Does the 95% CI of BIAS include zero?	Yes	No
95% CI of RMSE	53.96–55.52	51.75–53.25

MPE, mean prediction error; RMSE, root mean squared error; CI, confidence interval; dose, steady-state serum phenytoin concentration pairs.

was remarkable for a pharmacokinetic analysis where a number of variables can influence the results and where a naive feedback method is used. The MPEs obtained with models S1, S2, and S3 were all considered acceptable (Tables 2 and 3). The predictions obtained with model S1 were unbiased, as reflected by the 95% confidence interval, which included zero (Table 2). Predictions with model S2 were biased. However, when the groups were analyzed separately, groups 1 and 2 for models S1 and S2 were unbiased. Only group 1 predictions obtained with model S3 were unbiased. This is possible because the width of the CI decreases as the sample size increases. The width of the 95% CI for MPE did not differ much between models S1 and S2 (Table 2). All predictions lacked precision as the 95% CI for RMSE did not include zero.

No significant difference between the frequency of underprediction and overprediction of dose was found when comparing models S1 and S2. There was a trend towards conservative predictions, i.e., underpredictions

TABLE 3. *Predictive performance evaluation of models S3 and S4*

	Models	
	S3	S4
n	770	750
MPE (mg/L)	0.91	8.13
MPE (%)	5.67	52
RMSE (%)	64.78	338.5
95% CI of BIAS (mg/L)	0.27–1.55	4.39–11.87
Does the 95% CI of BIAS include zero?	No	No
95% CI of RMSE	10.23–10.52	52.14–53.62
No. of predictions excluded		20
No. of unrealistic predictions >75 mg/l		25

MPE, mean prediction error; RMSE, root mean squared error; CI, confidence interval.

TABLE 4. *Performance evaluation of the Michaelis-Menten model (S1) to predict phenytoin dose*

n	770
MPE (mg/day)	35.15
MPE (%)	11.4
RMSE (%)	26.05
95% CI of BIAS (mg/day)	30.33–40.67
Does the 95% CI of BIAS include zero?	No
95% CI of RMSE	79.56–82.28

MPE, mean prediction of error; RMSE, root mean squared error; CI, confidence interval.

* Using the estimates of Vm and Km obtained by Vozeh et al. (1981)

of dose. This is an important attribute for a phenytoin dosing method because even a small overdosage may lead to substantial toxicity. The percentage of prediction errors greater than 10% did not differ substantially between models S1 and S2. Using the latter models, on average 43.7% of predictions had errors less than 10%. Although model S2 fitted the data better than model S1, the results showed that Cl was unimportant when predicting the dose, as the percentage bias (% MPE) did not improve when Cl was incorporated in the model (Table 2). No significant difference was found between the actual and predicted doses for models S1 ($p = 0.64$) and S2 ($p = 0.153$).

Model S4 was used in this study so that the prediction performance of model S3 could be compared. Model S4 tended to overpredict the steady state serum concentration—a % MPE of 52%. When linear clearance was taken into account (model S3), the % MPE decreased to 5.67% (Table 3), reflecting an 89.1% reduction. The precision of the prediction improved markedly when Cl was included, from 338.5% for model S4 to 64.78% for model S3 (Table 3). Model S3 tended to overpredict the Cp_{ss} (54.3%) more than model S4 (49.5%). This was considered satisfactory. When model S4 was used, 20 patients were excluded (Table 3) because predictions could not be made as the predicted Vm value for the population was probably too low in relation to the dose

TABLE 5. *Performance evaluation of the Michaelis-Menten model (S4) to predict serum phenytoin concentration*

n	753
MPE (mg/L)	3.78
MPE (%)	23.88
RMSE (%)	457.53
95% CI of BIAS (mg/L)	−2.05–9.61
Does the 95% CI of BIAS include zero?	Yes
95% CI of RMSE	80.78–83.17

MPE, mean prediction of error; RMSE, root mean squared error; CI, confidence interval.

* Using estimates of Vm and Km obtained by Vozeh et al. (1981).

administered to the individual patient. This resulted in unrealistic predicted steady state serum concentration values. In this case, the equation yielded a negative value for the steady state concentration. This would have affected the analyses of bias and precision (17). Given that there is an interindividual variability in Vm, some patients may require doses that exceed the mean value for Vm in the population. A statistical difference between the measured and predicted concentrations was found with model S4 ($p = 3.06 \times 10^{-5}$). With model S3, a statistical difference was not found ($p = 0.0502$). When interpreting the results, one should take into consideration that 20 dose : serum concentration pairs had to be removed from the data set when model S4 was used. The results clearly indicate that Cl in model S3 was important when predicting steady state serum concentrations, because the % MPE was much lower when clearance was incorporated in the model. Model S3 should therefore be used in preference to model S4.

Despite the acceptable MPEs, the precision of the predictions was poor. Whereas this is trivial for most other drugs, it may be significant in the case of phenytoin because of the Michaelis-Menten characteristics of the drug (18). The majority of the predictions of dose were underpredictions, which minimized the risk of potentially toxic dosages. Because of the poor precision, the 3 models (S1, S2, and S3) evaluated in this study should be applied with caution when predicting dose or serum concentration. Such a finding is not surprising in view of the considerable variability associated with the clearance of phenytoin. The greater the number of feedback serum concentrations available, the more the precision of the predictions can be expected to improve (16). However, the accuracy of the predictions cannot improve indefinitely because some factors cannot be completely controlled. Inappropriate specification of the pharmacokinetic model may be partly responsible for the difference in prediction accuracy (19). In our study, the naive prediction method was used and therefore high prediction errors were expected. The bias and precision of our predictions would undoubtedly have improved if one or more feedback serum concentrations had been used. The degree of improvement in the predictive performance of the MM+FO model with one or more feedback serum phenytoin concentrations needs to be assessed.

Our results are compared with the predictions of dose and steady state serum concentration using estimates obtained in the study of Vozeh et al (6). They reported the following parameter estimates: mean Vm = 7.22 mg/kg/d (interindividual SD, 1.72; CV, 24%) and mean Km = 4.44 mg/L (interindividual SD, 2.4; CV, 54%). The Michaelis-Menten model and the NONMEM method were used in this study. When using model S1, the % MPE of −1.32% obtained with our estimates was much lower than that of 11.4% obtained with the estimates of Vozeh et al (6). The estimates of Vozeh et al (6) also tended to overpredict the dose in 69% of cases, and this may be problematic with phenytoin considering its nonlinear pharmacokinetics. When our estimates were used the dose was overpredicted in 48.8% of cases. The precision of the prediction was superior with our estimates of Vm and Km (17.58% versus 26.05%). The width of the 95% CI for MPE was narrower with our estimates (−5.26–2.6 mg/d) of Vm and Km than with that obtained with the estimates of Vozeh et al (6) (30.33–40.67 mg/d) (Tables 2 and 4). The frequency of PE greater than 10% for dose was 58.2% for our estimates, and 70.1% when the estimates of Vozeh et al (6) were used.

When using model S3, the % MPE of 5.67% obtained with our estimates was much lower than that of 23.88% obtained with the estimates of Vozeh et al (6). When our estimates were used, model S3 overpredicted steady state serum phenytoin concentration in 54.3% of cases, in comparison with 30.7% with the estimates of Vozeh et al (6). The precision of the prediction was superior with our estimates (64.78% versus 457.53%) (Tables 3 and 5). The frequency of prediction errors greater than 20% for serum concentration was 75.3% for our estimates, and 85.5% when the estimates of Vozeh et al (6) were used. This analysis indicated that predictive performance improved when population estimates representative of a specific population were used.

In contrast to previous studies that have not taken into account the contribution of a parallel first-order elimination pathway, our study showed that the parallel Michaelis-Menten and first-order elimination model fitted the data better than the Michaelis-Menten model considered alone. Such a model provides predictions that are less biased when predicting serum phenytoin concentrations.

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