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Phenobarbitone Population Pharmacokinetics from Routine Clinical Data: Role of Patient Characteristics for Estimating Dosing Regimens

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Abstract—Routine clinical pharmacokinetic data collected from patients receiving phenobarbitone have been analysed to evaluate the role of patient characteristics for estimating dosing regimens. The data were analysed using NONMEM, a computer program designed for population pharmacokinetic analysis that allows pooling of data. The pharmacokinetic model of phenobarbitone was described using a one-compartment steady-state model. The effect of a variety of developmental and demographic factors on clearance was investigated. NONMEM estimates indicated a nonlinear function of total body weight as the optimum adjustment of phenobarbitone clearance. Concomitant administration of phenobarbitone and other antiepileptic drugs showed a decrease of phenobarbitone clearance in young children. The dosing method based on clearance values obtained by NONMEM analysis allowed the prediction of the steady-state concentration as a function of maintenance dose with acceptable error for therapeutic drug monitoring.

Phenobarbitone is a widely used antiepileptic drug. It has been suggested that the therapeutic serum concentration range for this drug is 10–30 $\mu g\ mL^{-1}$ in epileptic seizures (Buchthal et al 1968). Several investigators have described the pharmacokinetics of phenobarbitone in children and adults (Hvidberg & Dam 1976). Svensmark & Buchthal (1964) evaluated the ratio of the serum phenobarbitone concentration to dose per kilogram body weight (L/D ratio) in paediatric patients and they found that young patients exhibited a small L/D ratio. Heimann & Gladtke (1977) also emphasized that phenobarbitone exhibited age-dependent changes in elimination. Guelen et al (1975) indicated that the relative clearance declined from about 12·0 $mL\ kg^{-1}\ h^{-1}$ in young children to about 4·0 $mL\ kg^{-1}\ h^{-1}$ by the age of 12–15 years, but thereafter did not change with age. Other published clearance values for adults include 0·4 $L\ h^{-1}$ (Martin et al 1979), 3·0 $mL\ kg^{-1}\ h^{-1}$ (Nelson et al 1982) and 3·8 $mL\ kg^{-1}\ h^{-1}$ (Wilensky et al 1982). In neonates the clearance was 6·4 $mL\ kg^{-1}\ h^{-1}$ (Fischer et al 1981), and in infants 8·2 $mL\ kg^{-1}\ h^{-1}$ (Minagawa et al 1981).

Optimal use of phenobarbitone in paediatric patients requires information regarding the drug's pharmacokinetics. However, because of sampling restrictions, it is often difficult to perform traditional pharmacokinetic studies in a large group of paediatric patients. As a result, information obtained from adults, along with limited experience in paediatric patients, is often extrapolated to the paediatric population.

Beal & Sheiner (1980, 1985, 1986) have proposed a nonlinear mixed-effects model (NONMEM) method for estimating population pharmacokinetic parameters from routine clinical data—data generated during the usual course of patient care. We have examined the population pharmacokinetics of phenobarbitone with this method. The purpose of this investigation was to evaluate interpatient variation in individual pharmacokinetic variables and multiple potential interactions with other anticonvulsants by using this approach on data collected from patients receiving phenobarbitone. There are no studies in the literature evaluating the application of these pharmacokinetic values to the design of a phenobarbitone dosage regimen. We also evaluated the accuracy of pharmacokinetic values obtained with the software system NONMEM for predicting steady-state serum concentrations in patients who were taking phenobarbitone chronically.

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Materials and Methods

Data sources

We studied 539 patients (286 males and 253 females) from Kyushu University Hospital who had stable steady-state serum phenobarbitone measurements. Patients who had their concurrent therapy altered were excluded from the study. All patients had normal renal and hepatic function, and phenobarbitone was prescribed two to three times a day as a powder preparation. All blood samples were drawn at approximately 2 to 6 h after the morning dose. The serum concentration of phenobarbitone was determined by a fluorescence polarization immunoassay method (Abbott TDx analyser). The coefficient of variation of this assay was less than 10%. The clinical characteristics of the patients studied are given in Table 1.

Population pharmacokinetics of phenobarbitone

Data analysis was performed with the NONMEM program developed by Beal & Sheiner (1980, 1985, 1986) on the computer at Kyushu University (FACOM M-780). The statistical model used in this program is based on the premise that particular pharmacokinetic parameters of a patient population arise from a distribution which could be de-

Table 1. Summary of data from three groups of patients treated with phenobarbitone.

Characteristic	Population study			
	Group I	Group II	Group III	Prospective study
Number of patients	222	136	181	82
Number of observations	371	241	390	82
Proportion of data from males	0·52	0·50	0·48	0·49
Means ± s.d.				
Age (years)	8·67 ± 5·60	12·63 ± 6·65	11·88 ± 5·78	11·69 ± 7·57
Weight (kg)	27·98 ± 16·17	36·36 ± 16·55	34·33 ± 17·29	34·73 ± 19·82
Dose (mg kg^{-1} day^{-1})	2·93 ± 1·01	2·59 ± 0·96	2·42 ± 1·03	2·76 ± 1·37
Steady-state concentration ($\mu g\ mL^{-1}$)	13·68 ± 5·75	17·62 ± 6·50	20·49 ± 8·23	15·91 ± 6·01

Group I = phenobarbitone only. Group II = phenobarbitone + other antiepileptic drugs, excluding valproic acid. Group III = phenobarbitone + other antiepileptic drugs, including valproic acid.

scribed by the population mean and interindividual variation.

The following one-compartment steady-state pharmacokinetic model fitted the data:

$$Css_{ij} = D_{ij}/(CL_{ij} \cdot \tau_{ij}) \quad (1)$$

where D_{ij} is the dosage of phenobarbitone for the ith Css in the jth patient ($\mu g\ kg^{-1}$); Css_{ij} is the steady-state serum concentration ($\mu g\ mL^{-1}$) measured in the jth patient while he received the ith dosage; CL_{ij} is the ith total body clearance ($mL\ kg^{-1}\ h^{-1}$) for phenobarbitone in the jth patient; and τ_{ij} is the dosing interval (h) for the ith dosage in the jth patient. Bioavailability is not assumed; if it is assumed, CL_{ij} must be regarded as $(CL/F)_{ij}$, in which F is the bioavailability of phenobarbitone.

We examined the influence of age and body weight on the population mean value for total body clearance of phenobarbitone. Thus the models tested were:

model 1: $$\widehat{CL}_{ij} = \theta_1 \cdot TBW_{ij}^{\theta_2} \quad (2)$$

model 2: $$\widehat{CL}_{ij} = \theta_3 \cdot AGE_{ij}^{\theta_4} \quad (3)$$

model 3: $$\widehat{CL}_{ij} = \theta_1 \cdot TBW_{ij}^{\theta_2} \cdot AGE_{ij}^{\theta_4} \quad (4)$$

model 4: $$\widehat{CL}_{ij} = \theta_1 \cdot TBW_{ij}^{\theta_2} + \theta_3 \cdot AGE_{ij}^{\theta_4} \quad (5)$$

where TBW_{ij} represent the ith total body weight of the jth individual in kg and AGE_{ij} represent the ith age of the jth individual in years. The remaining θs represent the fractional increase or decrease in phenobarbitone clearance associated with the presence of patient variables.

In modelling the uncertainty between observed and predicted values we assume

$$\ln(Css_{ij}) = \ln(\widehat{Css}_{ij}) + \varepsilon_{ij} \quad (6)$$

where Css_{ij} is the predicted steady-state serum concentration for ith dosage in the jth patients, and ε_{ij} are independent identically distributed statistical errors with mean zero and variance σ_E^2.

For interindividual variation, we assume

$$\ln(CL_{ij}) = \ln(\widehat{CL}_{ij}) + \eta_j \quad (7)$$

where CL_{ij} are from equations 2–5, and η_j are independently distributed statistical errors with mean zero and variances ω_{CL}^2.

To test the significance of various factors that influence CL_{ij}, we used the value of the objective function determined in the NONMEM fitting routine. The difference in objective function values obtained by comparing each model is asymptotically distributed as chi-square with degree of freedom equal to the difference in the number of parameters between the two models. In order to identify potentially significant factors, the difference in the objective function associated with a P value of $< 0{\cdot}005$ was required.

Results

Individual data treatment

Scatter plots of total body clearance against age, total body weight and daily dose are shown in Fig. 1.

The phenobarbitone clearance reduced exponentially with an increase of age and total body weight. However, the drug clearance increased with dosage increase, possibly due to the use of higher doses in young children, who exhibit high biotransforming capacity. The scatter plots for the individual clearances against daily dose also show the wide scatter of phenobarbitone clearance.

To evaluate the influence of associated therapy, patients were divided into three groups according to their associated therapy. Group I was administered phenobarbitone only; group II received phenobarbitone plus other antiepileptic drugs excluding valproic acid; and group III received phenobarbitone plus other antiepileptic drugs including valproic acid. The scatter plots for phenobarbitone clearance against total body weight are shown in Fig. 2. Drug clearance was greatly influenced by associated therapy in lower body mass patients (young children).

NONMEM estimates

The combined effect of patient features and associated therapy on phenobarbitone clearance was evaluated by dividing patients into subgroups homogeneous for their associated therapy. The results of the NONMEM analysis in each group are summarized in Tables 2, 3 and 4.

We required a change in the objective function of more than 7·9 (associated with $P < 0{\cdot}005$) to indicate significant variables for phenobarbitone clearance with these associated therapy groups. It is apparent that total body weight represents an important determinant of phenobarbitone clearance in these patients. For each group, the model of best fit for phenobarbitone clearance was model 1, which retained only the total body weight of the patient as the determinant.

Table 2. Population mean parameter values and their variances obtained using NONMEM for group I data.

	Model 1	Model 2	Model 3	Model 4
θ_1	61·0	—	55·6	68·1
(95%CI)	(54·7,67·3)		(50·1,61·1)	(57·8,78·4)
θ_2	−0·613	—	−0·556	−0·720
(95%CI)	(−0·647,−0·579)		(−0·617,−0·495)	(−0·766,−0·674)
θ_3	—	17·5	—	2·3
(95%CI)		(9·7,25·3)		(2·2,2·5)
θ_4	—	−0·370	−0·045	−0·159
(95%CI)		(−0·556,−0·184)	(−0·111,0·021)	(−0·200,−0·118)
ω_{CL}(%)	17·64	24·27	17·64	17·65
(95%CI)	(13·50,20·97)	(17·74,29·38)	(13·49,20·98)	(13·69,20·89)
σ_E(%)	20·40	20·81	20·35	20·32
(95%CI)	(17·84,22·67)	(16·87,24·12)	(17·83,22·59)	(17·83,22·54)
OBJ	1270·241	1368·766	1268·823	1268·878

95%CI = 95% confidence intervals of the mean.
OBJ = value of the objective function calculated by NONMEM program.

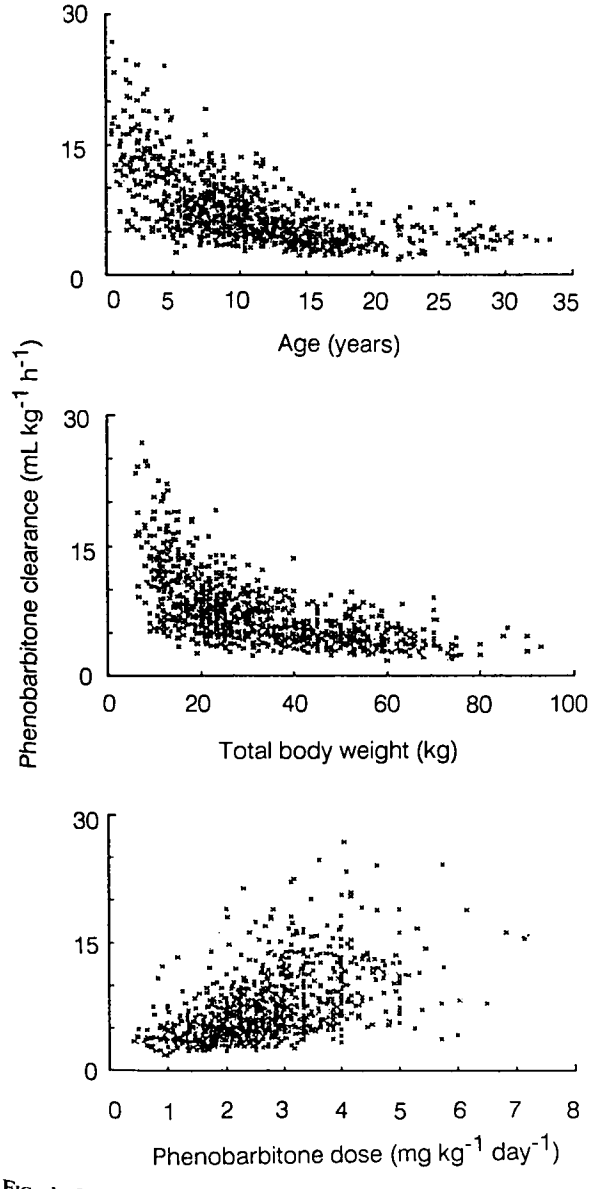

FIG. 1. Scatter plots of total body clearance of phenobarbitone against age, total body weight and daily dose.

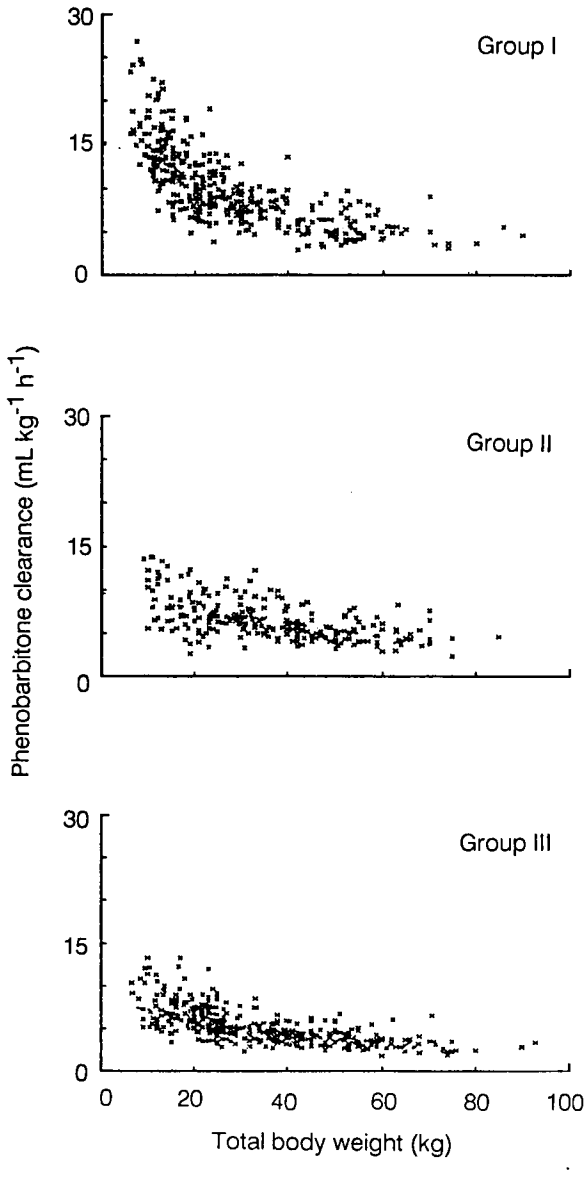

FIG. 2. Scatter plots of total body clearance of phenobarbitone against total body weight in groups I, II and III.

Table 3. Population mean parameter values and their variances obtained using NONMEM for group II data.

	Model 1	Model 2	Model 3	Model 4
θ_1	19·4	—	21·0	26·0
(95%CI)	(15·0,23·8)		(16·9,25·1)	(25·3,26·7)
θ_2	−0·345	—	−0·434	−0·407
(95%CI)	(−0·410,−0·280)		(−0·585,−0·283)	(−0·428,−0·386)
θ_3	—	10·7	—	−6·0
(95%CI)		(7·5,13·9)		(−13·9,1·9)
θ_4	—	−0·254	0·095	−1·110
(95%CI)		(−0·371,−0·137)	(−0·086,0·276)	(−0·520,−0·700)
ω_{CL}(%)	22·20	24·88	22·18	21·98
(95%CI)	(18·12,25·65)	(20·52,28·58)	(18·52,25·32)	(17·83,25·46)
σ_E(%)	18·65	19·03	18·55	18·60
(95%CI)	(14·02,22·35)	(14·19,22·86)	(14·11,22·11)	(14·23,22·12)
OBJ	958·986	988·408	957·049	956·136

95%CI = 95% confidence intervals of the mean.
OBJ = value of the objective function calculated by NONMEM program.

Table 4. Population mean parameter values and their variances obtained using NONMEM for group III data.

	Model 1	Model 2	Model 3	Model 4
θ_1	22·9	—	20·2	17·4
(95%CI)	(19·9,25·9)		(14·2,26·2)	(8·8,26·0)
θ_2	−0·467	—	−0·349	−0·481
(95%CI)	(−0·507,−0·427)		(−0·502,−0·196)	(−0·569,−0·393)
θ_3	—	11·2	—	3·4
(95%CI)		(5·2,17·2)		(2·4,4·5)
θ_4	—	−0·376	−0·118	−0·425
(95%CI)		(−0·578,−0·174)	(−0·243,0·007)	(−0·502,−0·348)
ω_{CL}(%)	20·37	23·24	20·59	20·57
(95%CI)	(16·60,23·55)	(19·00,26·81)	(16·70,23·86)	(16·86,23·70)
σ_E(%)	17·80	17·52	17·46	17·46
(95%CI)	(15·58,19·78)	(15·11,19·64)	(15·26,19·42)	(15·25,19·43)
OBJ	1583·830	1614·475	1578·138	1577·644

95%CI = 95% confidence intervals of the mean.
OBJ = value of the objective function calculated by NONMEM program.

NONMEM estimates indicated a nonlinear function of total body weight as the optimum adjustment of phenobarbitone clearance. No influence was found for gender. For group I, the typical magnitude of the interindividual variability, as expressed by the coefficient of variation, was 17·64%, and the intraindividual variability was 20·4%. The interindividual variability indicated that for groups II and III intersubject variations were greater than those for group I. However, residual error variance appeared to be larger for group I data.

Evaluation of predicted phenobarbitone concentrations

Model 1 needs to be validated in a separate patient population, and additional studies comparing it with other predictive methods are necessary to further elucidate its clinical utility. To assess the utility of these pharmacokinetic values for predicting steady-state phenobarbitone concentration in 82 patients (Table 1), we compared the proposed method with the method of Guelen & van der Kleijn (1978) incorporating the total body clearance of phenobarbitone (see Appendix). The precision and bias of each method were evaluated using the mean prediction error (m.e.) and mean absolute prediction error (m.a.e.) according to methods outlined by Sheiner & Beal (1981).

The m.e., m.a.e. and their respective 95% confidence limits for predicted concentration are shown in Table 5. The m.e. values were similar in magnitude, and the confidence intervals included zero and overlapped with each other. The

Table 5. Predicted performance evaluation.

Method	No. in prediction	Bias (m.e., $\mu g\ mL^{-1}$)	Precision (m.a.e., $\mu g\ mL^{-1}$)
Proposed method	82	0·10 (−0·71, 0·92)	2·81 (2·29, 3·33)
Guelen & van der Kleijn method	82	0·09 (−0·91, 1·10)	3·46 (2·81, 4·11)

m.e. = mean prediction error; prediction error = predicted value − actual value.
m.a.e. = mean absolute prediction error.
Parentheses are the 95% confidence intervals of the mean.

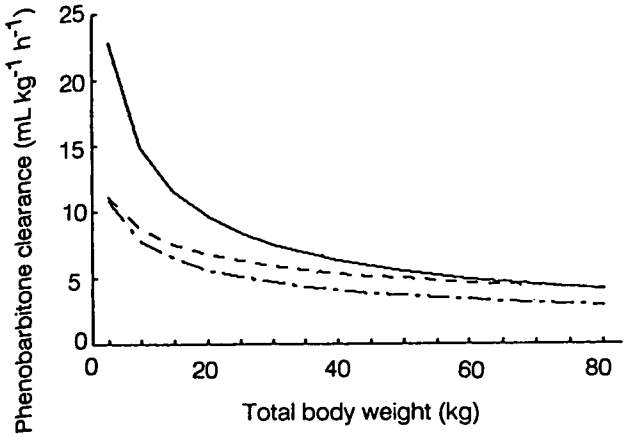

FIG. 3. Relationship between total body clearance of phenobarbitone and total body weight by NONMEM analysis. Group I —, group II – – – –, group III – · – · – ·.

m.a.e. values were also similar in magnitude and overlapped with each other. The proposed method was superior in precision to the Guelen & van der Kleijn method.

Discussion

Ageing is a significant factor in effecting prediction of drug dosages using pharmacokinetic data, particularly for drugs which take a long time to reach steady-state. Several studies have noted age or weight-related changes in phenobarbitone pharmacokinetics in paediatric patients (Svensmark & Buchthal 1964; Suganuma et al 1981). Guelen & van der Kleijn (1978) have demonstrated that phenobarbitone relative clearance correlated to both age and a corresponding decrease in liver volume in the elderly. This change in the ratio of liver to body size and drug metabolism can occur during periods of growth seen in childhood, thereby altering dosage requirement.

Davis et al (1981) evaluated the use of once-daily dosing with phenobarbitone in nine children, who were taking no other anticonvulsants, and who were 8 months to 16·5 years of age. Those patients had a mean clearance of $8{\cdot}2 \pm 3{\cdot}1$ mL kg^{-1} h^{-1}. Jalling (1974) evaluated phenobarbitone pharmacokinetics in 33 infants aged 9–30 months who had an average clearance of $7{\cdot}9 \pm 2{\cdot}6$ mL kg^{-1} h^{-1} when weighing 10–20 kg. In our study, the mean clearance values of group I patients weighing 10–30 kg were from 7·6 to 14·9 mL kg^{-1} h^{-1}; for group II they were from 6·0 to 8·8 mL kg^{-1} h^{-1}; and for group III they were from 4·7 to 7·8 mL kg^{-1} h^{-1} (Fig. 3). The mean clearance values of group I patients weighing 30–50 kg were from 5·5 to 7·6 mL kg^{-1} h^{-1}, group II from 5·0 to 6·0 mL kg^{-1} h^{-1}, and group III from 3·7 to 4·7 mL kg^{-1} h^{-1}.

The reductions of total body clearance of phenobarbitone were greater for patients weighing 10–30 kg than for those weighing 30–50 kg, and for group III children than for children from group II.

Nelson et al (1982) reported a mean phenobarbitone clearance of 3·0 mL kg^{-1} h^{-1} in six adult subjects. Wilensky et al (1982) reported a mean phenobarbitone clearance of 3·8 mL kg^{-1} h^{-1} in six adult epileptic patients who were receiving concurrent treatment with phenytoin or carbamazepine, concluding that there was no major alteration in phenobarbitone metabolism. In our study, the mean clearance value of group I and II patients weighing 70 kg was 4·5 mL kg^{-1} h^{-1}, and for group III the value was 3·1 mL kg^{-1} h^{-1}. It also failed to find any significant reduction of total body clearance of phenobarbitone in adult group II patients.

The cause of the large clearance of phenobarbitone in young children is unknown. However, Rylance et al (1982) showed that there was a linear decrease in liver volume per unit body weight with increased age throughout childhood. One possible explanation is that there may be a higher metabolic capacity of phenobarbitone in the liver of young children (Chiba et al 1985). The cause of the large reduction of phenobarbitone clearance in children treated with other anticonvulsants is also unknown. However, the mechanism by which valproic acid causes phenobarbitone accumulation is thought to involve inhibition of phenobarbitone metabolism (Kapetanovic et al 1980).

A method that would provide correct predictions about whether a drug concentration is subtherapeutic, therapeutic, or toxic from a given dosage regimen would be valuable. In general, if the clinically acceptable variation of predicted serum values from actual serum concentrations ranges from ± 10 to $\pm 20\%$, the resultant acceptable range of predicted serum phenobarbitone concentration would be from ± 1 to ± 3 μg mL^{-1} and from ± 2 to ± 6 μg mL^{-1} for the therapeutic range of 10–30 μg mL^{-1}, respectively. With this range in mind, in this population, the precision of the proposed method (m.a.e. = 2·81 μg mL^{-1}) may be acceptable.

Some authors have recommended estimating paediatric dosages by adjusting the dosage based on body surface area (Rowland & Tozer 1989). We did not assess such a method in this study because we believed that using nomograms or other methods for determining body surface area would require additional time and would be impractical in our outpatient clinic.

In conclusion, the prediction method based on the estimated phenobarbitone clearance values as a function of total body weight allows the prediction of the maintenance dose needed to produce a desired steady-state concentration and also the prediction of the steady-state concentration as a function of maintenance dose with an acceptable error for therapeutic drug monitoring.

Appendix

Guelen & van der Kleijn (1978).

$CL = 5{\cdot}3 \times A^a \times M^b$ mL kg^{-1} h^{-1}

C_{ss} = (dose in mg day^{-1})/CL × (TBW in kg) × 24

(a) Age correction factor of clearance in children for phenobarbitone.

Age (years)	≦2	3	4	5	6	7	8	9	10	11	12	13	14≧
Correction factor (A)	3·50	2·70	2·15	1·82	1·60	1·45	1·30	1·25	1·18	1·08	1·05	1·02	1·00

(b) Co-medication correction factor for phenobarbitone.

Co-medication	PB only	PB+ PHT	PB+ CBZ	PB+ PRM	PB+PHT +CBZ	Random
Correction factor (M)	1·0	0·79	0·85	0·79	0·74	0·75

PB = phenobarbitone, PHT = phenytoin, CBZ = carbamazepine, PRM = primidone.

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