REVIEW ARTICLE

Population-based investigations of drug relative clearance using nonlinear mixed-effect modelling from information generated during the routine clinical care of patients

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SUMMARY

Interpatient variability in drug disposition and response is a therapeutic premise, and thus evaluation and management of such variability are the basis for individualized pharmacotherapy. If the mathematical approach to determining drug doses were accurate and practical, the use of calculated doses could reduce the potential for toxicity and decrease the need for repetitious drug assays. The major strength of the population pharmacokinetics approach is that useful information can be extracted from sparse data collected during routine clinical care. Population pharmacokinetics can be defined as the study of the variability in serum drug concentrations between individuals when standard dosage regimens are administered. An approach to population pharmacokinetic data analysis has been implemented in the Nonlinear Mixed Effects Model (NONMEM) computer program. This report shows the feasibility of using a simple pharmacokinetic screen approach to estimate the population mean relative drug clearance and detecting drug–drug interaction by use of NONMEM. In clinical application of multiple trough screen or multiple peak screen, the variability of drug relative clearance within the population is assessed and a mathematical relationship between drug relative clearance and individual patient characteristics, such as age, body weight, gender, disease state or drug interaction with concomitant drug is

derived. In this report I describe this approach and its application using several examples previously reported by us and others.

INTRODUCTION

Pharmacokinetic studies are important for optimizing drug therapy. They are essential to dosage determination, efficacy studies and toxicology studies. Pharmacokinetic studies may generally be categorized into two types: (a) population-based investigations, (b) individual-based investigations. The former studies pool samples from more than one subject to obtain the pharmacokinetic estimates, while the latter studies develop estimates from each individual subject using a sequence of samples. The major strength of population pharmacokinetics is that useful information can be extracted from sparse data collected during routine clinical care. Population pharmacokinetics can be defined as the study of the variability in serum drug concentrations between individuals when standard dosage regimens are administered. It is of interest both to measure this variability within the population and to account for it in terms of patient variables, such as age, body weight, gender, disease state or drug interaction with concomitant drug. One major aim of these studies has been to establish guidelines for adjustment of dosage regimens to be used together with Therapeutic Drug Monitoring and a Bayesian feedback algorithm. Sheiner & Benet (1) have provided an excellent summary of various population approaches that can be used to conduct a pharmacokinetic screen and they discuss the costs, benefits and problems surrounding its implementation. We

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examined the feasibility of using the multiple trough approach or multiple peak approach for pharmacokinetic screening of the effects of patient variables on the population estimates of a drug's relative clearance. A method of population pharmacokinetic data analysis has been implemented in the Nonlinear Mixed Effects Model (NONMEM) computer program, developed by Beal & Sheiner (2).

THEORY

Multiple trough screen or multiple peak screen

In this design, an attempt is made to obtain more than one steady-state trough (or peak) concentration from each patient. Although single trough (or peak) data need not be discarded, two or more trough (or peak) values obtained on separate occasions will allow the variance components to be estimated. These screenings provide a reasonable approach to the assessment of pharmacokinetic variability in a large, heterogeneous patient population. However, this approach for pharmacokinetic screening is more qualitative than quantitative, and cannot be expected to provide reliable quantification of the magnitude of pathophysiological effects due to uncertainties in the data (e.g. compliance, timing) and pharmacokinetic model misspecification.

Pharmacokinetic model to estimate drug relative clearance

The pharmacokinetics of a drug can be described by the following steady-state pharmacokinetic model:

$$Css_{ij} = D_{ij}/(CL_{ij} \times \tau_{ij}) \qquad (1)$$

where D_{ij} is the dosage of drug for the ith Css in the jth patient; Css_{ij} is the steady-state serum concentration measured in the jth patient while he or she received the ith dosage; CL_{ij} is the ith total body clearance in the jth patient; and τ_{ij} is the dosing interval for the ith dosage in the jth patient. A bioavailability (F) of unity is assumed for this model; if it is not, CL_{ij} must be regarded as $(CL/F)_{ij}$.

Clinical factors were then included in the model according to the following general approaches:

(i) Linear model: $CL = \theta_1 + \theta_2 \times factor\ 1 + \theta_3 \times factor\ 2$

(ii) Nonlinear model: $CL = \theta_1 \times factor\ 1^{\theta_2}$

where the factors are continuous variables such as age or body weight, and $\theta_1, \ldots, \theta_k$ are the parameters to be estimated.

(iii) Step model: $CL = \theta_1$

If factor present, $CL = \theta_1 \times \theta_2$ factor where factor is a discrete variable such as female gender.

The following models were used to describe the intersubject variability in clearance:

$$CL_{ij} = \tilde{C}L_{ij} + \eta_j \text{ Additive model}$$

$$CL_{ij} = \tilde{C}L_{ij}(1 + \eta_j) \text{ Proportional model}$$

where CL_{ij} is the ith true clearance for the jth individual, $\tilde{C}L_{ij}$ is the ith clearance predicted for the jth individual with the regression model, and η_j is an independently distributed random variable with mean zero and variances ω_{CL}^2.

Residual variability on the concentration was modelled in two ways:

$$Css_{ij} = \tilde{C}ss_{ij} + \varepsilon_{ij} \text{ Additive model}$$

$$Css_{ij} = \tilde{C}ss_{ij} (1 + \varepsilon_{ij}) \text{ Proportional model}$$

where Css_{ij} is the ith measured steady-state serum concentration in the jth patient, $\tilde{C}ss_{ij}$ is the corresponding predicted steady-state serum concentration, and ε_{ij} is the residual intrasubject variability term, representing independent identically distributed statistical error with mean zero and variance σ_E^2.

Data analysis

In the data studies undertaken by us, data analysis was performed with NONMEM (2) (Version III, level 1·2 or Version IV, level 1·1) on the Kyushu University computer (FACOM M-1800) or the Hewlett Packard computer (HP Apollo 9000 model 712/60).

Minimizing the objective function provided by each NONMEM fitting routine is equivalent to maximizing the likelihood of the data. Hypothesis testing can be performed by monitoring changes in the objective function when one or more parameters in the model are first estimated iteratively and then restricting each to a fixed value. The difference in the values of the

objective function is asymptotically distributed between two competitive models according to the chi-square distribution with degree of freedom equal to the difference in the number of parameters between the two models.

The first stage in the model-building phase is to use a minimum number of parameters that are thought to influence clearance. Alternative statistical models are then tested to determine which model would afford the best fit of the data. Additional parameters can be incorporated into the initial regression model in a stepwise fashion to develop the full regression model. Any fixed effect that reduced the objective function by more than 3·841 (χ^2, $P < 0.05$; 1 degree of freedom) is considered to be significant and added to the model.

After all statistically significant parameters are added to the full regression model, each parameter is eliminated from the model one at a time to identify those factors that contribute unique information. If the objective function does not increase by more than 3·841 (χ^2, $P < 0.05$; 1 degree of freedom), the parameter is excluded from the final model. The final regression model includes all parameters that cannot be eliminated from the full regression model during this restriction process.

CLINICAL APPLICATION

Drug relative clearance using steady-state trough concentrations measured before the morning oral dose

Digoxin

Digoxin is a cardiac glycoside that is widely prescribed for the treatment of congestive heart failure and atrial fibrillation. It is well known that digoxin is a difficult drug to dose because of a lack of a good relationship between the dose and the desired effect, its narrow therapeutic range reported to be 0·5–2·0 ng/ml, and the variation in the pharmacokinetic characteristics of the drug (3). Knowledge of the pharmacokinetics of digoxin is essential in optimizing the safety and efficacy of this drug (4, 5). The variability in this drug's clearance creates difficulty for the clinician in choosing the drug dosage. For a given daily dosage, steady-state serum digoxin concentrations vary greatly from patient to patient (6). Because of this large interpatient variability, the clinician needs an appropriate dosage

regimen for individual patients. NONMEM estimates using the multiple trough approach suggest that this digoxin's clearance is influenced by the age (years), total body weight (kg), serum creatinine (mg/dL), gender, the coadministration of spilonolactone, the presence or absence of congestive heart failure and the dose (7).

$$CL\ (L/day) = 106.0 \times (1 - 0.00475 \times age) \times$$
$$body\ weight^{0.310} \times Serum\ creatinine^{-0.569} \times$$
$$0.858^{GEN} \times 0.895^{SPI} \times 0.813^{CHF} \times 0.824^{DFAC}$$

GEN = 1 for female
GEN = 0 for male
SPI = 1 for combination of spironolactone
SPI = 0 for otherwise
CHF = 1 for presence of congestive heart failure
CHF = 0 for otherwise
DFAC = 1 for 1/2 tablet
DFAC = 0 for 1 tablet

The retention of serum creatinine in the model for drug clearance supports the view that the principal elimination of digoxin takes place via renal excretion. Digoxin clearance increases non-linearly with an increasing total body weight. The inclusion of age in the model also indicates that an elderly patient is expected to have a lower clearance than a young patient of equal body weight and serum creatinine. The clearance in females was on average 14·2% less than in males. There is a great deal of similarity with the differences between males and females obtained using the prediction formulae of creatinine clearance proposed by Jelliffe (8) and Cockroft & Gault (9), and which were 10 and 15%, respectively.

Using the approach adopted in this study, the effects on bioavailability and clearance cannot be separated, as only their ratio (CL/F) was estimated. The oral bioavailability of digoxin, although somewhat variable, has been reported to be ≈70% from tablets (4). The bioavailability of orally administered digoxin tablets in healthy volunteers has been shown to be dose-independent over the range of doses of one to eight tablets (10). However, the regression model for clearance suggests that clearance increases by about 20% with an increase in dose from half a tablet to one tablet as the daily dose of digoxin. The decreased clearance with the half tablet dosage may reflect changes in bioavailability or renal and non-renal excretion activity, or both.

The clearance of digoxin decreased by about 10% with spironolactone administration, an effect which is comparable to values previously reported for renal clearance of digoxin in earlier sutdies (24%, 18%, 13% and 12·2%, respectively) (11–14). The effects of gender and spironolactone on glycoside clearance were also observed in patients who received metildigoxin (15). This effect may reflect decreased renal excretion due to inhibition of p-glycoprotein transport of digoxin by spironolactone (16), or cross reactivity with the assay antibody used in the FPIA method, due to the structural similarity between spironolactone metabolites and digoxin (17) or both.

Several investigators found that congestive heart failure was an important factor in estimating digoxin clearance (18, 19). Sheiner *et al.* (18) found that the digoxin clearance was significantly lower in patients with congestive heart failure than in patients without congestive heart failure [clearance (L/h) = 0·06 × creatinine clearance (ml/min) + 0·05 × body weight (kg) for without congestive heart failure; clearance (L/h) = 0·053 × creatinine clearance (ml/min) + 0·02 × body weight (kg) for with congestive heart failure]. Naafs *et al.* (19) found that digoxin's clearance was significantly lower in patients with congestive heart failure than in patients with atrial fibrillation (2·88 ± 1·26 vs. 4·26 ± 2·16 L/h). In this study, digoxin clearance decreased by about 19% in the presence of congestive heart failure.

Metildigoxin

Metildigoxin is designed to reduce the polarity of digoxin and to enhance intestinal absorption by substituting a methyl group for the hydroxyl group on the tridigitoxose residue of digoxin (3, 6). It has positive inotropic effects equal to digoxin (20, 21) slowing heart rate in patients with atrial fibrillation (22). It is virtually completely absorbed with an absorption rate of more than 90% (23), and its elimination half-life is about the same as that of digoxin (24). Metildigoxin is first metabolized to digoxin and then hydrolysed to the sugar residue-free metabolites; digoxigenin bisdigitoxoside, digoxigenin monodigotoxoside and digoxigenin. After a single oral administration of metildigoxin, about 55% of the dose is excreted in urine over 156 h as metildigoxin (53·7%) and digoxin (42·6%) (25). Knowledge of the pharmacokinetics of metildigoxin is essential in optimizing the safety and efficacy of this drug. The variability in this drug's

clearance creates difficulty for the clinician in choosing the correct dosage. The pharmacokinetics of digitalis glycosides were studied using routine therapeutic drug monitoring data to evaluate the role of patient characteristics for estimating metildigoxin dosing regimens. NONMEM estimates using the multiple trough approach indicated that the clearance of this digitalis glycoside was influenced by the subject's age (years), total body weight (kg), serum creatinine (mg/dL), gender, daily dose (μg/kg/day) and the co-administration of spilonolactone as shown in the following formulae (15).

$$CL \ (L/day) = (13\cdot4 - 0\cdot0589 \times age) \times \\ body \ weight^{0\cdot661} \times serum \ creatinine^{-0\cdot506} \times \\ daily \ dose^{0\cdot163} \times 0\cdot89^{GEN-SPI}$$

GEN–SPI = 1 for female or combination of spironolactone

GEN–SPI = 0 for otherwise

The effects of gender and spironolactone administration on clearance cannot be separated (log-likelihood difference of 2·391, *P* > 0·05). Despite the confounding, the effect of gender on clearance appears to be similar to that reported in a previous digoxin study (7). This effect of spironolactone administration may reflect decreased renal and nonrenal elimination (11), or cross-reactivity with the assay antibody (17) or both.

Using the approach used in this study, the effects on bioavailavility and clearance cannot be separated, as only their ratio (CL/F) is estimated. The final regression model for clearance suggests that the rate of clearance increases nonlinearly with increasing daily dose of metildigoxin. This factor was significant with a log-likelihood difference of 7·083 (*P* < 0·01), but was of minor significance with a 95% confidence interval value which included zero. It is not known if the increased clearance at higher dosages is caused by changes in bioavailavility or renal and nonrenal excretion activity, or both.

Lithium

Lithium is the primary treatment for long-term prophylaxis of recurrent bipolar (manic-depressive) disorders and for short-term treatment of mania. The efficacy and toxicity of lithium in patients with bipolar disorder are claimed to be closely related to serum

lithium concentration, with the therapeutic range reported to be 0·6–1·2 mEq/L (26, 27). The therapeutic range for lithium was established based on concentrations drawn 12 h after the dosage, regardless of the dosing interval. The narrow therapeutic range and the large intersubject differences in lithium disposition (28, 29) have led to the development of several dosing strategies (30–38). The large degree of variability observed in lithium pharmacokinetics makes it difficult to predict a priori the optimal dosing regimen for an individual subject. NONMEM estimates using the multiple trough approach suggest that lithium clearance was influenced by the demographic variables age (years), total body weight (kg), and serum creatinine (mg/dL) (39).

CL (L/day) = 31·6 − 0·634 × (age−50) ×
  H + (−7·79 + 0·225 × body weight)/serum creatinine

H = 0 for age <50
H = 1 for age ⩾50

Jermain *et al.* (40) suggested that lean body weight (LBW) and creatinine clearance (Clcr) estimated with the Cockcroft–Gault equation are important predictors of lithium clearance [CL (L/h) = 0·0093 (L/kg/h) × LBW (kg) + 0·0885 × Clcr (L/h)] using the NONMEM method. Taright *et al.* (41) performed a population analysis by the nonparametric maximum likelihood method to provide an estimate of the distribution of five kinetic parameters and covariates. Mean lithium clearance was 1·5 L/h with a coefficient of variation of 38%, and was found to increase with body weight.

Drug relative clearance using steady-state concentrations measured at any time after morning oral dose

Phenobarbital

Phenobarbital is the oldest, and one of the most widely used of the modern antiepileptic drugs. It has been suggested that the therapeutic serum concentration range for this drug is 10–40 µg/ml in epileptic seizures (42). Optimal use of phenobarbital 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. Until our recent publication of a large population study from Japanese patients, comprising both adults and children (43), pharmacokinetic information for phenobarbital in epileptic patients has been limited (44–53).

There are several important findings in this retrospective analysis of effects of the maturation process and drug–drug interaction on phenobarbital clearance (43). First, NONMEM analysis suggests that total body weight was superior to age as an index of the maturation process. Second, phenobarbital clearance was highest in the very young and decreased in a weight-related fashion in children (0·4–14 years), with minimal changes observed in adults (15–33·4 years). This pattern was consistent whether phenobarbital was administered alone or coadministered with other antiepileptic drugs. Third, when phenobarbital was coadministered with other antiepileptic drugs, phenobarbital clearance decreased as compared with that in monotherapy.

In South African children, the (final) model describing clearance included total body weight, the parameter which was also the most important fixed effect parameter, ahead of age (CL (L/h) = Exp [0·0288 × body weight (kg) − 2·53] for phenobarbital monotherapy, where Exp = the base of natural logarithm) (54). The effect of carbamazepine on phenobarbital disposition is variable. Cereghino *et al.* (55) showed no effect of carbamazepine on phenobarbital concentrations for adult. Guelen & van der Kleijn (56) showed that concomitant administration of phenobarbital and carbamazepine resulted in a 15% decrease on phenobarbital clearance for children. Botha *et al.* (54) showed that concomitant administration of phenobarbital and carbamazepine or phenytoin resulted in a 13% decrease on phenobarbital clearance for South African children.

The effects of drug–drug interaction on phenobarbital clearance were examined through a retrospective analysis of serum concentration data from 349 paediatric and adult epileptic patients (age range, 0·4–33·3 years) (57). Patients received phenobarbital as monotherapy or in combination with either the antiepileptic drugs carbamazepine or valproic acid. The final regression model for clearance using NONMEM was:

CL (ml/kg/hr) = 52·3 × body weight$^{-0.567}$ × CO

where CO equals $46.4^{(-1/\text{body weight})}$ if the patient took carbamazepine, 0.642 if the patient took valproic acid, or 1 if the patient took neither. The regression analysis for clearance suggested that the effects of carbamazepine on phenobarbital clearance are maximal in early childhood (about 54%), and decreased in a weight-related fashion in children, with minimal changes observed in adults.

The drug interaction between phenobarbital and valproic acid is probably one of the clinically most important interactions, as it occurs predictably in the majority of patients taking these two drugs together. The mechanism by which valproic acid causes phenobarbital accumulation is thought to involve inhibition of phenobarbital metabolism (58). Subsequent clinical trials confirmed that serum phenobarbital levels rose when valproic acid therapy was initiated. The increases usually have ranged from 15% to 70%, but at times have been much higher (59). Botha *et al.* (54) showed that concomitant administration of phenobarbital and valproic acid resulted in a 38% decrease on phenobarbital clearance for South African children. Using our approach, concomitant administration of phenobarbital and valproic acid resulted in a 35.8% decrease on phenobarbital clearance.

Carbamazepine

Carbamazepine is currently considered the drug of choice for the treatment of partial seizures, generalized tonic-clonic seizures, and other minor or partial seizure disorders. Carbamazepine is also approved as the drug of choice for treatment of the pain associated with trigeminal neuralgia. It is well known that carbamazepine is a difficult drug to dose because of a lack of a good relationship between dose and desired effect, its narrow therapeutic range reported to be 4–12 µg/ml in epileptic seizures, and the variation in the pharmacokinetic characteristics of the drug (60, 61). It has become apparent that the variation in the pharmacokinetics of carbamazepine is affected primarily by age (62–65), dose (65–67) and comedication (68–72). The concomitant use of enzyme-inducing antiepileptics such as phenytoin, phenobarbital and primidone decreases average serum carbamazepine concentrations. There are a number of conflicting reports on the effect of valproic acid on carbamazepine disposition. Thus, evaluation and management of such variability form the basis for optimizing therapy at the level of the individual.

The final regression model for clearance by NONMEM analysis using the multiple peak approach (73) was:

$$CL\ (ml/kg/h) = 64.9 \times \text{body weight (kg)}^{-0.336} \times \text{daily dose (mg/kg/day)}^{0.465} \times 1.07^{VPA} \times 1.16^{PB} \times 1.27^{POLY}$$

Carbamazepine clearance is relatively high in young children but decreases with maturation, reaching adult values around age 14–16 years (62–65). The final regression model for clearance suggests that carbamazepine clearance decreases nonlinearly with increasing total body weight in the maturation process. Total body weight was superior to age as an index of the maturation process (an age range of 5 months to 15 years) in NONMEM analysis. One possible explanation proposed for those findings is that younger children may have a higher metabolic capacity for carbamazepine.

The final regression model suggests that carbamazepine clearance increases nonlinearly with increasing daily dose of carbamazepine. It is not known if the increased carbamazepine clearance at higher dosages is caused by changes in bioavailability, hepatic enzyme activity, or both. However, absorption of carbamazepine from the gastrointestinal tract is slow and extremely variable. It is most plausible that the fractional absorption of carbamazepine decreases with higher doses because of its low aqueous solubility and the limiting effects of dissolution on the rate of absorption (74).

In the approach adopted, the effects on bioavailability and clearance cannot be separated, as only their ratio (CL/F) is estimated. A further complicating factor is the question of whether the increase in carbamazepine clearance with increasing dose is in fact due to an increased clearance in younger children or to a decrease in drug absorption. However, the improvement in fit obtained with the inclusions of total body weight and carbamazepine dose indicates that it may be due to incomplete or very slow dissolution of high doses of carbamazepine in the gastrointestinal fluid.

The following model describing carbamazepine clearance in Portuguese epileptic children included total body weight and carbamazepine dose, the parameters which were also the important fixed effect parameters, as well as age ([CL (L/h) = (0.0122 × body weight (kg) + 0.0467 × daily dose (mg/kg/day)) × age (years)$^{0.331}$] for carbamazepine monotherapy) (75).

Several studies have noted the induction of carbamazepine clearance by the concomitant administration of other antiepileptic drugs (68–72). Drug interactions with carbamazepine include its increased enzymatic biotransformation by phenobarbital, phenytoin and primidone. Valproic acid increases the unbound fractions of both carbamazepine and carbamazepine epoxide and inhibits the metabolism of the latter through hepatic microsomal epoxide hydrolase. Using the present approach, concomitant administration of carbamazepine and valproic acid led to an increase in carbamazepine clearance of 7%. However, there are a number of conflicting reports on the effect of valproic acid on carbamazepine disposition. Both increases and decreases in carbamazepine concentrations have been observed following the addition of valproic acid (71). In addition, elevation of carbamazepine epoxide concentration has been reported after the addition of valproic acid (74). Since the interaction between valproic acid and carbamazepine may involve both displacements from protein binding and metabolic inhibition, carbamazepine concentrations may increase, decrease, or remain unchanged where the drugs are co-administered, depending on which effect prevails. The addition of valproic acid to carbamazepine regimens should be accompanied by careful monitoring of serum drug concentrations.

Optimizing carbamazepine therapy for patients receiving enzyme-inducing antiepileptic drugs will be more difficult because of the significantly greater interpatient variability in clearance that was observed among patients receiving these drugs. Concomitant administration of carbamazepine and phenobarbital showed an increase in carbamazepine clearance of 16%, possibly due to hepatic microsomal enzyme induction. Coadministration with more than one enzyme inducer generally results in a greater decrease in carbamazepine concentrations. Concomitant administration of carbamazepine and two or more antiepileptic drugs showed an increase in carbamazepine clearance of 27%. Delgado Iribarnegaray *et al.* (75) showed that concomitant administration of carbamazepine and phenobarbital resulted in a 28·9% increase in carbamazepine clearance in Portuguese children with epilepsy.

Valproic acid

Valproic acid is a branched-chained fatty acid, structurally unrelated to any other antiepileptic drug. It has a broad spectrum of activity against both the convulsive and nonconvulsive generalized epilepsies. It has been suggested that the therapeutic serum concentration range for this drug is 50–100 µg/ml in epileptic seizures (76). Optimal use of valproic acid in paediatric patients requires information regarding the drug's pharmacokinetics.

Valproic acid is often administered with other antiepileptic drugs, a practice that can lead to clinically significant pharmacologic interactions. Concomitant administration of such enzyme-inducing antiepileptic drugs as carbamazepine, phenobarbital, primidone or phenytoin will markedly accelerate the metabolic conversion of valproic acid, particularly in children (77–82).

The effects of drug–drug interaction on valproic acid clearance were examined through a retrospective analysis of serum concentration data from paediatric and adult epileptic patients (83). Patients received valproic acid as monotherapy or in combination with either the antiepileptic drugs carbamazepine or phenobarbital. The final regression model for clearance by NONMEM was:

$$CL \ (ml/kg/h) = 15{\cdot}6 \times \text{body weight (kg)}^{-0{\cdot}252} \times \text{daily dose (mg/kg/day)}^{0{\cdot}183} \times 0{\cdot}898^{GEN} \times CO^{PB} \times CO^{CBZ}$$

where CO^{PB} equals 1·10 if the patient was treated with phenobarbital, a value of unity otherwise, and CO^{CBZ} equals $0{\cdot}769 \times \text{daily dose (mg/kg/day)}^{0{\cdot}179}$ if the patient was treated with carbamazepine, a value of unity otherwise. Botha *et al.* (84) suggested that total body weight and concomitant carbamazepine are important predictive factors of valproic acid clearance [CL (L/h) = Exp (0·022 × body weight (kg) –1·38] for valproic acid monotherapy, where Exp = the base of natural logarithm) using the NONMEM method. Botha *et al.* showed that carbamazepine produced an increase of 61% in valproic acid clearance. The clearance of valproic acid is profoundly affected by the concurrent administration of other antiepileptic drugs (85). The mechanism(s) by which valproic acid interacts with other antiepileptic drugs has not been definitely established (86, 87). However, the induction of drug metabolizing enzymes in the liver by other antiepileptic drugs is the most likely explanation (88). Our results also show that the relative clearance of valproic acid is clearly larger when valproic acid is given in combination with carbamazepine or phenobarbital than when valproic acid is given alone. The additional

influence of phenobarbital was relatively slight (10%). Sackellares *et al*. (89) found that, in children, phenobarbital reduced the valproate level:dose ratio by 45%. May & Rambeck (90) found that the concentration of valproic acid was lower when the drug was given in combination with phenobarbital (76·3%) than when given alone (100%). A similar effect has been noted with carbamazepine (66·2%). Carbamazepine has been reported to increase the metabolic clearance and decrease the plasma concentration of valproic acid (81, 82, 91, 92). The specific metabolic pathways induced by carbamazepine include glucuronidation, ω oxidation, and ω-1 oxidation (93). Using the present approach, the concomitant administration of carbamazepine led to induction of clearance of valproic acid higher than is seen with phenobarbital.

Clinically important drug interactions between valproic acid and carbamazepine or phenobarbital may occur not only when one drug is added but also when it is withdrawn from therapy. Withdrawal of carbamazepine or phenobarbital alters valproic acid concentrations to a lesser degree, the average increase being 50% and 67%, respectively (94). For example, increased valproate serum concentrations were reported in six patients following carbamazepine discontinuation, associated with signs of valproate toxicity in one of the patients (95).

CONCLUSIONS AND THERAPEUTIC IMPLICATIONS

Interpatient variability in drug disposition and response is commonly observed in therapeutics, and thus evaluation and management of such variability form the basis for individualized pharmacotherapy. If the mathematical approach to determining drug doses were accurate and practical, the use of calculated doses could reduce the potential for toxicity and decrease the need for repetitious drug assays. This report shows the feasibility of using a simple pharmacokinetic screening approach to estimating population mean relative drug clearance and detecting drug–drug interaction through use of the program NONMEM. In clinical application of multiple trough screen or multiple peak screen, the variability of drug relative clearance within the population was assessed and a mathematical relationship between drug relative clearance and individual patient characteristics, such as age, body weight, gender, disease state or drug interaction with concomitant drug was derived. These methods provide qualitatively correct predictions about whether a drug concentration is subtherapeutic, therapeutic, or toxic given a dosage regimen. Further, the addition or withdrawal of associated antiepileptic drugs may change antiepileptic drug dosage requirements. Therefore, routine monitoring of antiepileptic drug serum levels would be extremely useful, especially in the paediatric age group, and in patients requiring associated antiepileptic medication.

This simple pharmacokinetic screen represents a reasonable approach to the assessment of pharmacokinetic variability in a large, heterogeneous patient population. However, it should be kept in mind that this approach is more qualitative than quantitative and may not be expected to provide reliable quantification of the magnitude of pathophysiologic effects due to pharmacokinetic model mis-specification.

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