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A Feasibility Study of the Multiple-peak Approach for Pharmacokinetic Screening: Population-based Investigation of Valproic Acid Relative Clearance Using Routine Clinical Pharmacokinetic Data

EIJI YUKAWA

Division of Pharmaceutical Sciences, Graduate School, Kyushu University, 3-1-1 Maidashi, Higashi-Ku, Fukuoka 812, Japan

Abstract

The multiple-peak approach was used to evaluate the effect of age, body mass, dose and gender on the population estimates of valproic acid relative clearance.

Routine clinical pharmacokinetic data (n = 474) was collected from 250 patients receiving valproic acid and no other drug. The data was analysed according to a simple steady-state pharmacokinetic model using NONMEM, a computer program designed for population pharmacokinetic analysis allowing pooling of data.

The final regression model for relative clearance (CL, mL kg^{-1} h^{-1}) was:

$$CL = 18{\cdot}9 \times \text{body weight}^{-0{\cdot}276} \cdot \text{daily dose}^{0{\cdot}142} \cdot \text{gender}$$

where gender = 1 for males, 0·877 for females.

NONMEM estimates suggested that the rate of valproic acid clearance decreased nonlinearly with increasing body weight in the maturation process, and increased nonlinearly with increasing valproic acid dose (mg kg^{-1} day^{-1}). The clearance in females was about 11% less than in males. These estimates were similar to those detected from previous studies.

The major strength of the population analysis approach is that useful information can be extracted from sparse data collected during routine clinical care. Sheiner & Benet (1985) have provided an excellent summary of various approaches that can be used to conduct a pharmacokinetic screen and they discuss the costs, benefits and problems surrounding its implementation. I undertook a feasibility study of the multiple-peak approach for pharmacokinetic screening. The multiple-peak approach was then used to evaluate the effect of age, body mass, dose and gender on the population estimates of valproic acid relative clearance.

Valproic acid is a simple 8-carbon branched-chain fatty acid, which is structurally unrelated to any other marketed antiepileptic drug. Valproic acid is an important drug in the treatment of childhood epilepsy because of its wide spectrum of antiepileptic activity. It has been suggested that the therapeutic serum concentration range for the drug is 50–100 $\mu g\,mL^{-1}$ in epileptic seizures (Schobben et al 1975). However, the use of valproic acid in patients is complicated by marked variability in the ratio of serum concentration to dose, and this has been attributed to interpatient differences. Interindividual variability in drug disposition and response is a therapeutic premise, thus evaluation and management of such variability are the basis for individualized pharmacotherapy.

Optimal use of valproic acid in 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 patients. This study examined the population-based investigation of valproic acid relative clearance with the computer program NONMEM (Beal & Sheiner 1992). With this approach it is possible to estimate the pharmacokinetic parameters of a population by using sparse data collected during routine clinical care (Yukawa et al 1992a, b, 1993). In addition, one can establish to what degree patient characteristics influence pharmacokinetics of the drug.

Correspondence: E. Yukawa, Division of Pharmaceutica, Higashi-Ku, Fukuoka 812, Japan.

Materials and Methods

Data sources

The study used 250 patients (474 observations) from Kyushu University Hospital who had reliable measurements of the steady-state concentration of valproic acid in serum. Compliance was assessed by the determination of several steady-state serum levels of valproic acid before the study as well as by interview with the attending physician, although the degree of consistent compliance of patients included for analysis cannot be absolutely guaranteed. Patients in whom concurrent therapy was altered were excluded from the study. All patients had normal renal and hepatic function, and valproic acid was administered as a tablet or syrup (Depakene, Kyowa Hakko Co. Ltd, Tokyo) two to three times a day. All patients had been taking valproic acid alone for more than one month, and at the same dose for at least two weeks when selected for study. All blood samples were drawn 2–6 h after the morning dose. The serum concentration of

Table 1. Summary of patient data.

Number of patients	250
Number of observations	474
Proportion of data from males	0·50
Age (years)	
Mean ± s.d.	10·1 ± 5·6
Range	0·3 ~ 32·6
Body weight (kg)	
Mean ± s.d.	31·7 ± 15·3
Range	5·2 ~ 90·0
Dose (mg kg^{-1} day^{-1})	
Mean ± s.d.	15·89 ± 5·38
Range	2·38 ~ 46·78
Css (μg mL^{-1})	
Mean ± s.d.	62·3 ± 20·7
Range	6·5 ~ 159·4
CL (mL kg^{-1} h^{-1})	
Mean ± s.d.	11·2 ± 4·0
Range	4·6 ~ 34·6

Css: serum valproic acid concentration; CL = total body clearance; s.d. = standard deviation.

valproic acid was determined by fluorescence polarization immunoassay (FPIA). The coefficient of variation of this assay was less than 10%.

The clinical characteristics of the patients studied are given in Table 1. The frequency distribution within the data set of their demographic factors, age, body weight, serum concentration and daily dose are displayed in Fig. 1. Fig. 2 shows the serum concentration of valproic acid as a function of the daily valproic acid dose.

Data analysis

Computation was carried out using the NONMEM program (version III, level 1.2) developed by Beal & Sheiner (1992), on the computer of Kyushu University (FACOM M-1800). 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 described by the population mean and interpatient variation. The pharmacokinetics of valproic acid were described by the following steady-state pharmacokinetic model:

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

where D_{ij} is the dosage of valproic acid for the ith Css in the jth patient (μg kg^{-1}); Css_{ij} is the steady-state serum concentration (μg mL^{-1}) measured in the jth patient while he or she received the ith dosage; CL_{ij} is the ith total body clearance (mL kg^{-1} h^{-1}) for valproic acid in the jth patient; and τ_{ij} is the dosing interval (h) for the ith dosage in the jth patient. Bioavailability was assumed to be 100%. All blood samples were drawn 2–6 h after the morning dose. Therefore, the total body clearance estimated is not average, but is a relative clearance.

The influence of several factors for the relative clearance of valproic acid was examined. Thus, the models tested were:

$$\text{Model 1 } \tilde{C}L_{ij} = \theta_1 \cdot W_{ij}^{\theta_2} \quad (2)$$

$$\text{Model 2 } \tilde{C}L_{ij} = \theta_3 \cdot A_{ij}^{\theta_4} \quad (3)$$

$$\text{Model 3 } \tilde{C}L_{ij} = \theta_5 \cdot D_{oij}^{\theta_6} \quad (4)$$

$$\text{Model 4 } \tilde{C}L_{ij} = \theta_7 \cdot G_j \quad (5)$$

where W_{ij} represents the ith total body weight of the jth individual in kg, A_{ij} represents the ith age of the jth individual in years, D_{oij} is the ith dose of jth individual in

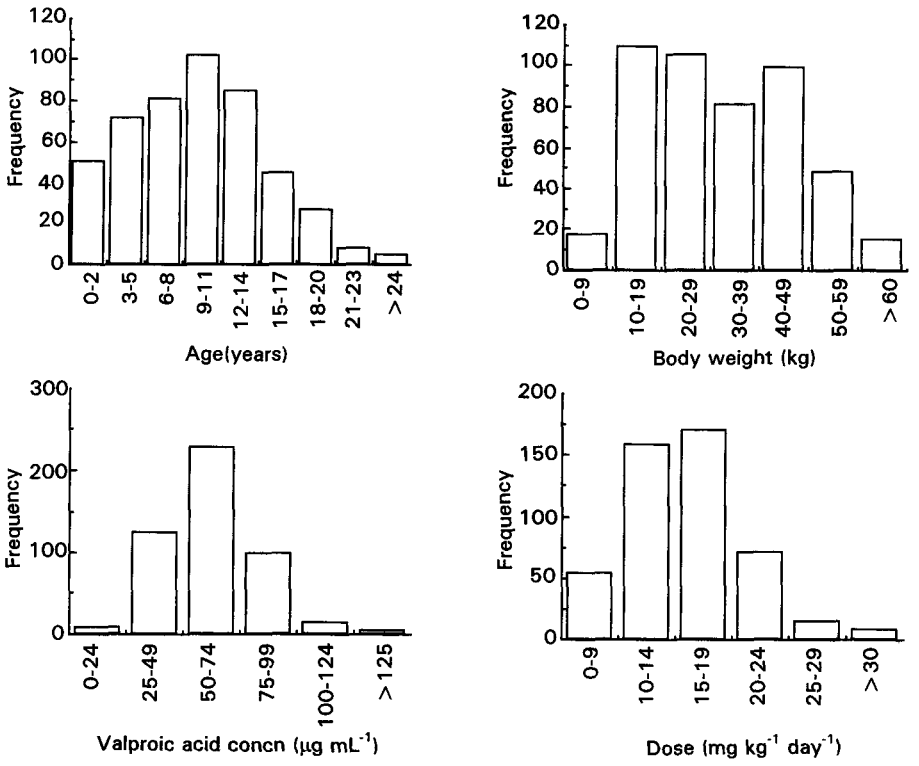

FIG. 1. The frequency distribution within the data set of demographic factors, age, body weight, serum concentration and daily dose.

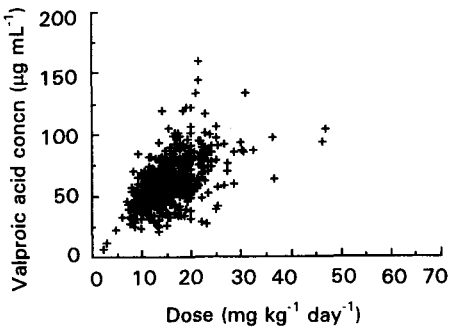

FIG. 2. Correlation between valproic acid dose and serum concentration.

$mg\,kg^{-1}\,day^{-1}$, and G_j is an indicator variable which has a value of unity if the jth patient is male, θ_8 otherwise. The remaining θ values represent the fractional increase or decrease in valproic acid relative clearance associated with the presence of patient variables.

The interpatient variability in relative clearance was modelled with proportional error according to the following equation:

$$CL_{ij} = \tilde{C}L_{ij}(1 + \eta_j) \quad (6)$$

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 independently distributed random variables with mean zero and variances ω^2_{CL}.

The intrapatient residual variability was also modelled with proportional error according to the following equation:

$$Css_{ij} = \tilde{C}ss_{ij}(1 + \varepsilon_{ij}) \quad (7)$$

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 intrapatient variability term, representing independent identically distributed statistical error with mean zero and variance σ^2_E.

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. To identify potentially significant factors, the difference in the objective function associated with a P value of $<0{\cdot}05$ was required.

Results

Individual data treatment

It was at first intended to calculate individual relative clearance from equation 1. Scatterplots of relative clearance against patient characteristics such as age, total body weight and daily dose are shown in Fig. 3.

The valproic acid relative clearance reduced curvilinearly with an increase of age and body weight. However, the drug clearance increased with increasing dosage, possibly due to the use of higher doses in young children, who exhibit a higher biotransforming capacity.

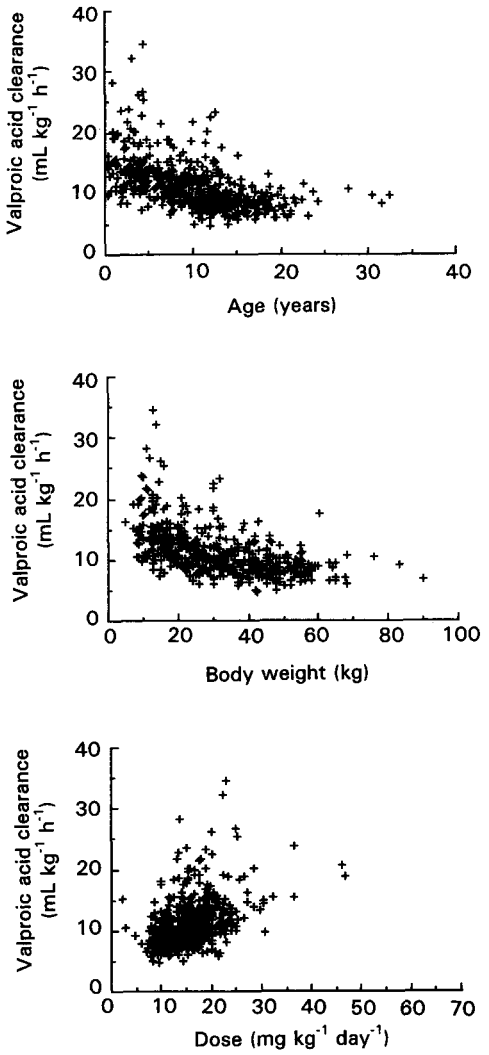

FIG. 3. Scatterplots of valproic acid clearance against age, body weight and daily dose.

NONMEM estimates

In the preliminary analyses, the modelling of clearance with age, body weight and daily dose improved the estimate of valproic acid relative clearance (Table 2). The nonlinear relationships between clearance and patient characteristics were superior to the linear relationships. Females had lower valproic acid relative clearance than males. Body weight was the most important determination of clearance, and it was superior to age and daily dose. The combinations of age and other factors (e.g. body weight and daily dose) did not significantly improve the description of the data.

The final regression model for clearance in $mL\,kg^{-1}\,h^{-1}$ was:

$$CL = 18{\cdot}9 \cdot W^{-0{\cdot}276} \cdot D_o^{0{\cdot}142} \cdot G \quad (8)$$

with G = 1 for male and 0·887 for female

The 95% confidence intervals of each θ value (18·9, −0·276, 0·142 and 0·887) were 14·7–23·1, −0·319–−0·233, 0·082–0·202 and 0·844–0·930, respectively. The estimate of coefficient of variation for interpatient variability in clearance was 13·4%, with a 95% confidence interval of 8·3–17·1%. The interpatient variability of clearance increased to

Table 2. Population mean parameter values and their variances obtained using NONMEM.

Hypothesis	Equation	OBJ[a]	LLD[b]	*P* value	Conclusion
	$CL = \theta_1$ $\theta_1 = 10{\cdot}4$ $\omega_{CL} = 23{\cdot}1\%$, $\sigma_E = 19{\cdot}9\%$	3120·955			
Did weight influence CL?	$CL = \theta_1 \cdot W^{\theta_2}$ $\theta_1 = 30{\cdot}1$, $\theta_2 = -0{\cdot}319$ $\omega_{CL} = 16{\cdot}2\%$, $\sigma_E = 18{\cdot}5\%$	2966·737	154·218	<0·001	Yes
Did age influence CL?	$CL = \theta_3 \cdot A^{\theta_4}$ $\theta_3 = 15{\cdot}1$, $\theta_4 = -0{\cdot}180$ $\omega_{CL} = 17{\cdot}8\%$, $\sigma_E = 19{\cdot}0\%$	3014·661	106·294	<0·001	Yes
Did dose influence CL?	$CL = \theta_5 \cdot D_o^{\theta_6}$ $\theta_5 = 4{\cdot}08$, $\theta_6 = 0{\cdot}347$ $\omega_{CL} = 19{\cdot}1\%$, $\sigma_E = 19{\cdot}5\%$	3046·648	74·307	<0·001	Yes
Did gender influence CL?	$CL = \theta_7 \cdot G$ G = 1 for male $G = \theta_8$ for female $\theta_7 = 11{\cdot}3$, $\theta_8 = 0{\cdot}860$ $\omega_{CL} = 22{\cdot}2\%$, $\sigma_E = 19{\cdot}6\%$	3097·045	23·91	<0·001	Yes
	$CL = \theta_1 \cdot W^{\theta_2} \cdot G$ G = 1 for male $G = \theta_8$ for female $\theta_1 = 31{\cdot}6$, $\theta_2 = -0{\cdot}313$, $\theta_8 = 0{\cdot}870$ $\omega_{CL} = 14{\cdot}5\%$, $\sigma_E = 18{\cdot}5\%$	2935·594			
	$CL = \theta_1 \cdot W^{\theta_2} \cdot A^{\theta_4}$ $\theta_1 = 34{\cdot}5$, $\theta_2 = -0{\cdot}394$, $\theta_4 = 0{\cdot}054$ $\omega_{CL} = 16{\cdot}2\%$, $\sigma_E = 18{\cdot}4\%$	2964·545			
	$CL = \theta_1 \cdot W^{\theta_2} \cdot D_o^{\theta_6}$ $\theta_1 = 15{\cdot}9$, $\theta_2 = -0{\cdot}272$, $\theta_6 = 0{\cdot}178$ $\omega_{CL} = 14{\cdot}6\%$, $\sigma_E = 18{\cdot}7\%$	2944·455	15·237	<0·001	Yes
	$CL = \theta_3 \cdot A^{\theta_4} \cdot D_o^{\theta_6}$ $\theta_3 = 7{\cdot}48$, $\theta_4 = -0{\cdot}144$, $\theta_6 = 0{\cdot}233$ $\omega_{CL} = 15{\cdot}6\%$, $\sigma_E = 19{\cdot}1\%$	2977·422	24·098	<0·001	Yes
	$CL = \theta_1 \cdot W^{\theta_2} \cdot D_o^{\theta_6} \cdot G$ G = 1 for male $G = \theta_8$ for female $\theta_1 = 18{\cdot}9$, $\theta_2 = -0{\cdot}276$, $\theta_6 = 0{\cdot}142$, $\theta_8 = 0{\cdot}887$ $\omega_{CL} = 13{\cdot}4\%$, $\sigma_E = 18{\cdot}6\%$	2920·357			

[a]The minimum value of objective function (−2 log likelihood) in each NONMEM run. [b]−2 log likelihood difference from the value for basic clearance equation.

23·1% if the patient characteristics were not incorporated into the model. The coefficient of variation for residual variability was 18·6%, with a 95% confidence interval of 16·3–20·6%. Clearance for females was about 11% less than that for males.

The clearance in $mL\,h^{-1}$ was:

$$CL = 18{\cdot}9 \cdot W^{0{\cdot}724} \cdot D_o^{0{\cdot}142} \cdot G \qquad (9)$$

when the dose was measured in $mg\,kg^{-1}\,day^{-1}$, and

$$CL = 18{\cdot}9 \cdot W^{0{\cdot}582} \cdot D_o^{0{\cdot}142} \cdot G \qquad (10)$$

when the dose was measured in $mg\,day^{-1}$.

Discussion

The maturation process is a significant confounding factor in predicting drug dosages using pharmacokinetic data, particularly for antiepileptic drugs. One would like to understand the effect of several developmental and demographic factors on pharmacokinetic parameters and the observed patient variables on valproic acid disposition. Several studies have noted age-related changes in valproic acid pharmacokinetics of paediatric patients (Chiba et al 1985; Hall et al 1985; Cloyd et al 1993). Valproic acid clearance is relatively large in young children but decreases with maturation, reaching adult values around age 14–16 years. Recently, Cloyd et al (1993) show that valproic acid clearance varies from 19·9 to $7{\cdot}6\,mL\,kg^{-1}\,h^{-1}$ in the age range 2–14 years ($CL = 23{\cdot}3\ e^{-0.08A}$).

The cause of the large clearance of valproic acid in younger children is unknown. Rylance et al (1982) showed that there is a linear decrease in liver volume per unit body weight with increased age throughout childhood. One possible explanation proposed for this finding is that younger children may have a higher metabolic capacity for valproic acid. Several authors have also observed that the valproic acid concentration shows a nonlinear relationship with the dose (Vajda et al 1978; Gram et al 1979; Bowdle et al 1980);

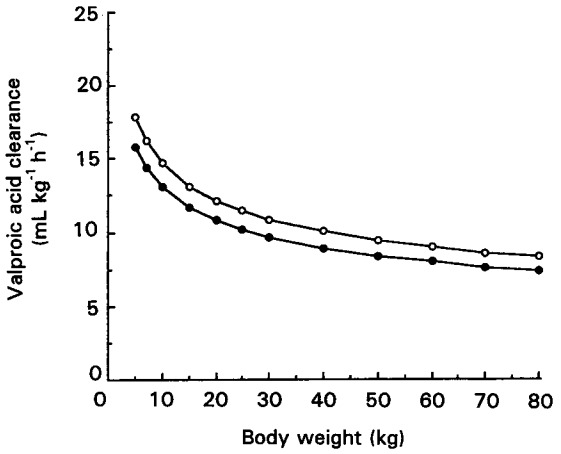

FIG. 4. Effects of body weight on valproic acid clearance. ○ Male, ● female.

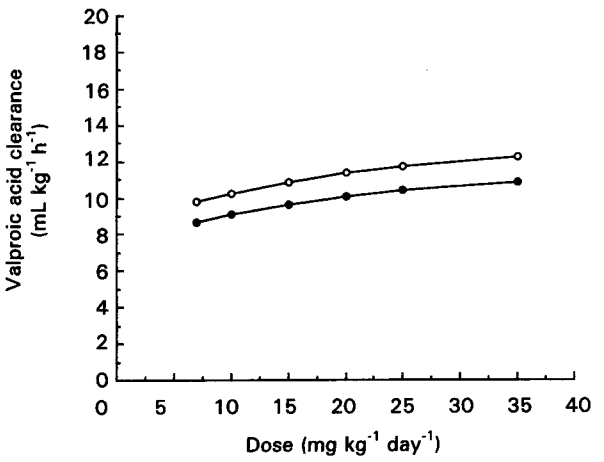

FIG. 5. Effects of daily dose on valproic acid clearance. ○ Male, ● female.

however, it is not known if the increased valproic acid clearance at higher dosages is caused by changes in bioavailability, hepatic enzyme activity, or both.

In our study, the mean relative clearance values of patients weighing 10–80 kg and given a dose of 15 mg kg^{-1} day^{-1} were from 8·3 to 14·7 mL kg^{-1} h^{-1} for males, and from 7·3 to 13·0 mL kg^{-1} h^{-1} for females (Fig. 4). The mean relative clearance values in patients receiving 7–35 mg kg^{-1} day^{-1} and weighing 30 kg were from 9·7 to 12·2 mL kg^{-1} h^{-1} for males, and from 8·6 to 10·9 mL kg^{-1} h^{-1} for females (Fig. 5). The clearance in females was about 11% less than in males.

The final regression model for clearance suggests that the rate of valproic acid clearance decreases nonlinearly with increasing total body weight in the maturation process. The improvement in fit obtained with the inclusion of valproic acid dose also shows that a patient receiving a higher dose has a higher rate of clearance than a patient receiving a lower dose. These estimates were similar to those from previous studies. For a drug with a narrow therapeutic range, some factors affecting pharmacokinetics observed in this study could very well merit precautionary statements or warnings regarding the initial dose or the suggested frequency of patient monitoring.

The findings of this study show the feasibility of using a multiple-peak approach and estimating population mean relative clearance by use of NONMEM. This multiple-peak screen represents a reasonable approach to assessment of pharmacokinetic variability in a large, heterogeneous population. However, this multiple-peak approach for pharmacokinetic screening is more qualitative than quantitative and cannot be expected to provide reliable quantitation of the magnitude of pathophysiologic effects due to uncertainties in the data (compliance, timing) and use of an inappropriate pharmacokinetic model.

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