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Detection of Carbamazepine-induced Changes in Valproic Acid Relative Clearance in Man by Simple Pharmacokinetic Screening

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Abstract

Selecting the optimum dose of valproic acid is difficult because the pharmacokinetics are complicated by inter-patient variability and by effects arising as a result of co-administration with other antiepileptic drugs. The multiple peak approach has been used to evaluate the effect of age, total body weight, dose, gender and co-medication (carbamazepine-induced change) on population estimates of valproic acid relative clearance.

Routine clinical pharmacokinetic data (n = 479) were collected from 207 epilepsy patients on combination therapy. The data were analysed by a simple steady-state pharmacokinetic model with the use of NONMEM, a computer program designed for population pharmacokinetic analysis that enables pooling of data. NONMEM estimates suggested that the rate of valproic acid clearance in patients receiving concomitant administration of valproic acid and carbamazepine decreased non-linearly with increasing total body weight in the maturation process, and increased non-linearly with increasing valproic acid dose. The clearance in females was 5.7% less than in males. NONMEM estimates also suggested that the rate of valproic acid clearance increased non-linearly with increasing carbamazepine dose. Concomitant administration of valproic acid and carbamazepine with other antiepileptic drugs resulted in an increase in valproic acid clearance of 10%. The final regression model of valproic acid relative clearance was $CL = 6{\cdot}06TBW^{-0{\cdot}168} \times DOSE^{0{\cdot}414} \times CBZDOSE^{0{\cdot}095} \times 0{\cdot}943^{GEN} \times 1{\cdot}10^{CO}$, where CL is the clearance (mL kg^{-1} h^{-1}), TBW is the total body weight (kg), DOSE is the dose of valproic acid, CBZDOSE is the dose of carbamazepine, GEN = 0 for males and 1 for females and CO = 0 for concomitant administration of valproic acid and carbamazepine and 1 for concomitant administration of valproic acid and carbamazepine with other antiepileptic drugs.

This technique can be used to estimate the pharmacokinetic parameters of a population from sparse data collected during routine clinical care and to determine the extent to which patient characteristics influence drug pharmacokinetics.

Valproic acid is a branched-chain fatty acid structurally unrelated to other commercial antiepileptic drugs. It is an important drug in the treatment of childhood epilepsy because of its wide spectrum of activity. It has been suggested that the therapeutic serum concentration range of the drug is approximately 50–100 $\mu g\ mL^{-1}$ in epileptic seizures (Schobben et al 1975). Valproic acid is often administered with other antiepileptic drugs, a practice that can lead to clinically significant pharmacological interactions (Bourgeois 1988). Concomitant administration of such enzyme-inducing antiepileptic drugs as carbamazepine, phenobarbital, primidone or phenytoin markedly accelerates the metabolic conversion of valproic acid, particularly in children (Chiba et al 1985; Hall et al 1985; Yukawa et al 1991; Cloyd et al 1993). Accordingly, the use of valproic acid in patients is complicated by marked variability in the ratio of serum concentration to dose owing to inter-patient differences. Because inter-individual variability in drug disposition and response is a therapeutic premise, evaluation and management of such variability are the basis for individual pharmacotherapy.

Optimum use of valproic acid in patients requires information about the pharmacokinetics of the drug. However, because of sampling restrictions, it is often difficult to perform traditional pharmacokinetic studies of a large group of patients. Sheiner & Benet (1985), in an excellent summary of various approaches that can be used to conduct pharmacokinetic screening, discuss the costs, benefits and problems of its implementation.

In this study the multiple peak approach (Yukawa 1995a, b) that can be used to conduct pharmacokinetic screening was used to evaluate the effect of age, total body weight, dose, gender and co-medication (carbamazepine-induced change) on population estimates of valproic acid relative clearance in associated therapy. The study was performed 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. It can also be used to establish the extent to which patient characteristics influence the pharmacokinetics of the drug.

Materials and Methods

Data sources

207 patients (479 observations) in Kyushu University Hospital for whom reliable measurements of the steady-state concentration of valproic acid in serum were available were retrospectively selected. Compliance was assessed by determination of several steady-state serum levels of valproic acid before the study and by interviewing the attending physician, but the extent of consistent compliance of the patients

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selected cannot be absolutely guaranteed. Patients for whom concurrent therapy was altered were excluded from the study. All patients had normal renal and hepatic function. Valproic acid was administered as a tablet or syrup (Depakene, Kyowa Hakko, Tokyo) twice or three times a day. All patients had been taking valproic acid 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 valproic acid was determined by fluorescence-polarization immunoassay (FPIA); the coefficient of variation of the assay was <10%.

The clinical characteristics of the patients studied are given in Table 1. Fig. 1 shows the serum concentration of valproic acid as a function of the daily dose.

Data analysis

Computation of the results was performed with the NONMEM program (version VI, level 1·0), 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 inter-patient variation. The pharmacokinetics of valproic acid were described by the steady-state pharmacokinetic model:

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

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

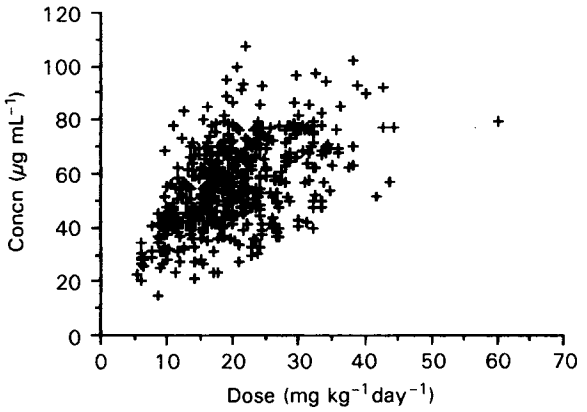

FIG. 1. Scatter plot of valproic acid serum concentration against daily dose.

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

$$\text{Model 1} \quad \text{'C'}L_{ij} = \theta_1 TBW_{ij}^{\theta 2} \quad (2)$$

$$\text{Model 2} \quad \text{'C'}L_{ij} = \theta_3 AGE_{ij}^{\theta 4} \quad (3)$$

$$\text{Model 3} \quad \text{'C'}L_{ij} = \theta_5 DOSE_{ij}^{\theta 6} \quad (4)$$

$$\text{Model 4} \quad \text{'C'}L_{ij} = \theta_7 CBZDOSE_{ij}^{\theta 8} \quad (5)$$

$$\text{Model 5} \quad \text{'C'}L_{ij} = \theta_9 \theta_{10}^{GEN} \quad (6)$$

$$\text{Model 6} \quad \text{'C'}L_{ij} = \theta_{11} \theta_{12}^{CO} \quad (7)$$

where TBW_{ij} is the ith total body weight of the jth individual (kg), AGE_{ij} is the ith age of the jth individual (years), $DOSE_{ij}$ is the ith dose of jth individual (mg kg^{-1} day^{-1}); $CBZDOSE_{ij}$ is the ith carbamazepine dose of the jth individual (mg kg^{-1} day^{-1}); GEN is an indicator variable which has a value of unity if the patient is female, zero otherwise and CO is an indicator variable which has a value of unity if the patient is administered valproic acid and carbamazepine with other

Table 1. Summary of patient data.

Characteristic	Group I*	Group II†	Total
Number of patients	84	123	207
Number of observations	178	301	479
Proportion of data from males	0·52	0·53	0·53
Age (years)			
Mean ± s.d.	15·9 ± 10·2	15·6 ± 6·6	15·7 ± 8·2
Range	0·3–54·8	0·4–35·5	0·3–54·8
Total body weight (kg)			
Mean ± s.d.	43·4 ± 17·6	42·2 ± 18·3	42·6 ± 18·0
Range	5·8–83·0	4·5–86·0	4·5–86·0
Valproic acid dose (mg kg^{-1} day^{-1})			
Mean ± s.d.	16·73 ± 5·97	22·15 ± 7·83	20·14 ± 7·66
Range	5·56–38·1	5·97–60·0	5·56–60·0
Carbamazepine dose (mg kg^{-1} day^{-1})			
Mean ± s.d.	8·70 ± 2·87	11·00 ± 3·82	10·14 ± 3·66
Range	3·08–19·23	2·99–22·22	2·99–22·22
Serum valproic acid concn (μg mL^{-1})			
Mean ± s.d.	55·5 ± 15·5	56·3 ± 16·5	56·0 ± 16·1
Range	22·3–107·7	14·7–97·3	14·7–107·7
Total body clearance (mL kg^{-1} h^{-1})			
Mean ± s.d.	12·8 ± 3·8	17·0 ± 5·8	15·4 ± 5·6
Range	5·8–26·1	7·3–33·9	5·8–33·9

*Valproic acid + carbamazepine. †Valproic acid + carbamazepine + one or more other antiepileptic drugs (phenobarbitone, primidone, phenytoin or clonazepam).

antiepileptic drugs, zero otherwise. The remaining θ values represent the fractional increase or decrease in valproic acid relative clearance associated with the presence of patient variables.

The inter-patient variability in relative clearance was modelled with proportional error according to the equation:

$$CL_{ij} = \text{'C'}L_{ij}(1 + \eta_j) \quad (8)$$

where CL_{ij} is the ith true clearance for the jth individual, $\text{'C'}L_{ij}$ is the ith clearance predicted for the jth individual with the regression model, and η_j is an independently distributed random variable with a mean value of zero and variance ω_{CL}^2. The intra-patient residual variability was also modelled with proportional error according to the equation:

$$Css_{ij} = \text{'C'}ss_{ij}(1 + \varepsilon_{ij}) \quad (9)$$

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

To test the significance of the 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-squared with the number of degrees of freedom equal to the difference between the number of parameters of the two models. In order 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

We had intended to calculate individual relative clearance from equation 1. Scatter plots of relative clearance against patient characteristics such as age, total body weight and daily dose are shown in Fig. 2.

The valproic acid relative clearance decreased curvilinearly with increasing age and total body weight. However, the drug clearance increased with increasing dosage, possibly because of the use of higher doses for young children, who have high biotransforming capacity.

NONMEM estimates

In the preliminary analyses, the modelling of clearance with age, total body weight and daily dose improved estimates of valproic acid relative clearance (Table 2). The non-linear relationships between clearance and patient characteristics were superior to the linear relationships. Females had lower valproic acid relative clearance than males.

Daily dose was the most important factor influencing clearance, and it was superior to age and total body weight. The combinations of age and other factors (e.g. total body weight and daily dose) did not significantly improve the description of the data.

The final regression model for clearance was:

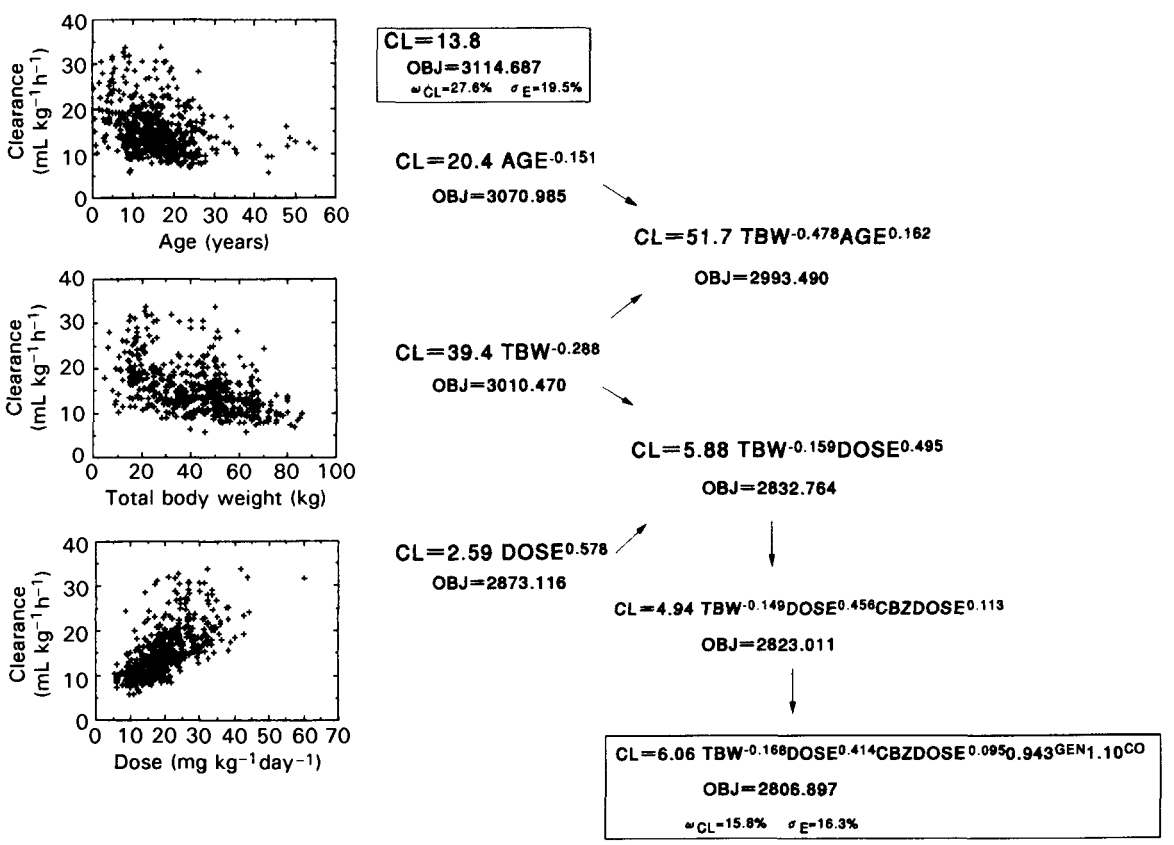

FIG. 2. Scatter plots of relative clearance against patient characteristics such as age, total body weight and daily dose and the final regression model for clearance.

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

Hypothesis	Equation	OBJ[a]	LLD[b]	P value	Conclusion
	$CL = \theta_1$ $\theta_1 = 13{\cdot}8$ $\omega_{CL} = 27{\cdot}6\%$, $\sigma_E = 19{\cdot}5\%$,	3114·687			
Did weight influence CL?	$CL = \theta_1 \cdot TBW^{\theta 2}$ $\theta_1 = 39{\cdot}4$, $\theta_2 = -0{\cdot}288$ $\omega_{CL} = 23{\cdot}4\%$, $\sigma_E = 17{\cdot}9\%$,	3010·470	104·217	< 0·001	yes
Did age influence CL?	$CL = \theta_3 \cdot AGE^{\theta 4}$ $\theta_3 = 20{\cdot}4$, $\theta_4 = -0{\cdot}151$ $\omega_{CL} = 25{\cdot}6\%$, $\sigma_E = 18{\cdot}8\%$,	3070·985	43·702	< 0·001	yes
Did valproic acid dose influence CL?	$CL = \theta_5 \cdot DOSE^{\theta 6}$ $\theta_5 = 2{\cdot}59$, $\theta_6 = 0{\cdot}578$ $\omega_{CL} = 18{\cdot}4\%$, $\sigma_E = 16{\cdot}8\%$,	2873·116	241·571	< 0·001	yes
Did carbamazepine dose influence CL?	$CL = \theta_7 \cdot CBZDOSE^{\theta 8}$ $\theta_7 = 6{\cdot}13$, $\theta_8 = 0{\cdot}366$ $\omega_{CL} = 25{\cdot}0\%$, $\sigma_E = 18{\cdot}6\%$,	3041·198	73·489	< 0·001	yes
Did female gender influence CL?	$CL = \theta_9 \cdot \theta_{10}^{GEN}$ GEN = 0 for male GEN = 1 for female $\theta_9 = 14{\cdot}4$, $\theta_{10} = 0{\cdot}918$ $\omega_{CL} = 27{\cdot}4\%$, $\sigma_E = 19{\cdot}3\%$,	3108·990	5·697	< 0·05	yes
Did co-medication influence CL?	$CL = \theta_{11} \cdot \theta_{12}^{CO}$ CO = 0 for concomitant administration of carbamazepine alone CO = 1 for otherwise $\theta_{11} = 12{\cdot}3$, $\theta_{12} = 1{\cdot}22$ $\omega_{CL} = 25{\cdot}4\%$, $\sigma_E = 19{\cdot}6\%$,	3082·591	32·096	< 0·001	yes

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

$$CL(mL\ kg^{-1}h^{-1}) = 6{\cdot}06TBW(kg)^{-0{\cdot}168} \times DOSE(mg\ kg^{-1}\ day^{-1})^{0{\cdot}414} \times CBZDOSE(mg\ kg^{-1}\ day^{-1})^{0{\cdot}095} \times 0{\cdot}943^{GEN} \times 1{\cdot}10^{CO} \quad (10)$$

The results of hypothesis testing are summarized in Table 3. When each factor was eliminated successively from the full regression model as described above, all factors were found to influence the objective function value significantly.

The 95% confidence intervals of each θ value (6·06, −0·168, 0·414, 0·095, 0·943 and 1·10) were, respectively, 4·95–7·17, −0·211– − 0·125, 0·333–0·495, −0·003–0·192, 0·891–0·995 and 1·037–1·163. The estimate of the coefficient of variation for inter-patient variability in clearance was 15·8%, with a 95% confidence interval of 13·2–18·1%. The inter-patient variability of clearance increased to 27·6% if the patient characteristics were not incorporated into the model. This proportional error model for residual variability yielded 16·3% with a 95% confidence interval of 14·4–17·9%. Clearance for females was approximately 5·7% less than that for males. The clearance in mL h^{-1} was:

$$CL(mL\ h^{-1}) = 6{\cdot}06TBW(kg)^{-0{\cdot}832} \times DOSE(mg\ kg^{-1}\ day^{-1})^{0{\cdot}414} \times CBZDOSE(mg\ kg^{-1}\ day^{-1})^{0{\cdot}095} \times 0{\cdot}943^{GEN} \times 1{\cdot}10^{CO} \quad (11)$$

Discussion

Aging is a significant confounding factor in predicting drug dosages using pharmacokinetic data. The age-related variability of pharmacokinetic parameters might require individualization of therapy, with subsequent re-evaluation as the child grows older. One would like to understand the effect of several developmental and demographic factors on pharmacokinetic parameters and observed patient variables in valproic acid disposition.

Factors that determine the relationship between dose and serum concentration of valproic acid are: age—the increase in

Table 3. Hypothesis tested using restricted models from the full model.

Hypothesis	Reduced model	LLD[a]	P value	Conclusion
Did total body weight influence clearance?	$TBW^{\theta=0}$	44·950	< 0·001	yes
Did valproic acid dose influence clearance?	$DOSE^{\theta=0}$	121·684	< 0·001	yes
Did carbamazepine dose influence clearance?	$CBZDOSE^{\theta=0}$	7·092	< 0·01	yes
Did gender influence clearance?	$\theta^{GEN=0}$	5·157	< 0·05	yes
Did co-medication influence clearance?	$\theta^{CO=0}$	10·613	< 0·01	yes

[a] −2 log likelihood difference from the value for full model equation.

the ratio with age in children corresponds to a progressive decrease in biotransformation capacity; dose—the relationship between valproic acid serum concentration and dose is non-linear because bioavailability varies, because the elimination constant is increased at high dosages, because protein binding is reduced at increasing levels of valproic acid; and simultaneous administration of other antiepileptic drugs (e.g. phenytoin, phenobarbital, primidone and carbamazepine)—these reduce valproic acid serum concentrations. Thus, there is a poor correlation between valproic acid dose and serum concentration.

Several studies have noted age-related changes in valproic acid pharmacokinetics of paediatric patients (Chiba et al 1985; Hall et al 1985; Yukawa et al 1991; Cloyd et al 1993). Valproic acid clearance is relatively large in young children but decreases with maturation, reaching adult values at an age of approximately 14 to 16 years. The final regression model for clearance suggests that the rate of valproic acid clearance decreases non-linearly with increasing total body weight during maturation (Fig. 2). Total body weight was superior to age as an index of maturation (between the ages of five months and 15 years) in NONMEM analysis (Table 2). In this study of polypharmacy, the mean relative clearance for patients weighing 10 to 80 kg and given a valproic acid dose of 15 mg kg^{-1} day^{-1} and a carbamazepine dose of 10 mg kg^{-1} day^{-1} varied from 17·3 to 12·2 mL kg^{-1} h^{-1} for males. Cloyd et al (1993) recently showed that valproic acid clearance varied from 38·2 to 14·6 mL kg^{-1} h^{-1} for patients between 2 and 14 years receiving polypharmacy (CL = 44·8EXP(−0·08 Age)). It is not known if the large clearance of valproic acid in younger children is caused by changes in protein binding, hepatic enzyme activity, or both. One possible explanation is that younger children might have a higher metabolic capacity for valproic acid, because Rylance et al (1982) show that there is a linear decrease in liver volume per unit body weight with increased age throughout childhood. Cloyd et al. (1993) conclude that age and enzyme-inducing antiepileptic drugs affect valproic acid clearance in children by altering hepatic metabolism rather than protein binding.

The final regression model for clearance suggests that the rate of valproic acid clearance increases non-linearly with increasing daily dose of valproic acid (Figs 3 and 4). Although several authors observe that there is a non-linear relationship between valproic acid concentration and dose (Vajda et al 1978; Gram et al 1979; Bowdle et al 1980; Yukawa et al 1991), it is not known if increased valproic acid clearance at higher dosages is caused by changes in bioavailability or changes in clearance and volume of distribution because of increases in free fraction with increasing dose, or both. In a previous study of monopharmacy (Yukawa 1995b), the mean relative clearance of patients receiving 7 to 35 mg kg^{-1} day^{-1} and weighing 30 kg were from 9·7 to 12·2 mL kg^{-1} h^{-1} for males. In this study of polypharmacy, it varied from 10·5 to 20·4 mL kg^{-1} h^{-1} for males receiving 10 mg kg^{-1} day^{-1} of carbamazepine. The effects on bioavailability and clearance in this study cannot be separated, as only their ratio (CL:F) is estimated. A further complicating factor is the question of whether the increase of valproic acid clearance with increasing dose is because of increased clearance in younger children or because of reduced absorption of the drug. However, a decrease in bioavailability on increasing the valproic acid dose might be unlikely because of the high water-solubility of the drug. The improvement in fit obtained by including total body weight and valproic acid dose indicates that it might not be because of higher doses of valproic acid kg^{-1} in younger children. The influence of valproic acid daily dose on clearance was also larger in polypharmacy than in monopharmacy ($DOSE^{0.142} \rightarrow DOSE^{0.414}$), but the cause is unknown.

The final regression model for clearance suggests that valproic acid clearance increases non-linearly with increasing daily dose of carbamazepine. This factor was significant, with a log-likelihood difference of 7·902 ($P<0.01$), but was of minor significance with a 95% confidence interval value (including zero). However, the relative clearance values increased by up to 14% on varying the carbamazepine dose from 5 to 20 mg kg^{-1} day^{-1}.

May & Rambeck (1985) showed that serum concentrations were 7·3% higher in females than in males. In a previous study of monopharmacy (Yukawa 1995b), clearance in females was about 11% less than in males. This study of associated therapy showed that the clearance in females was 5·7% less than in males.

Several studies have noted a marked increase in valproic acid clearance when other anticonvulsants such as carbama-

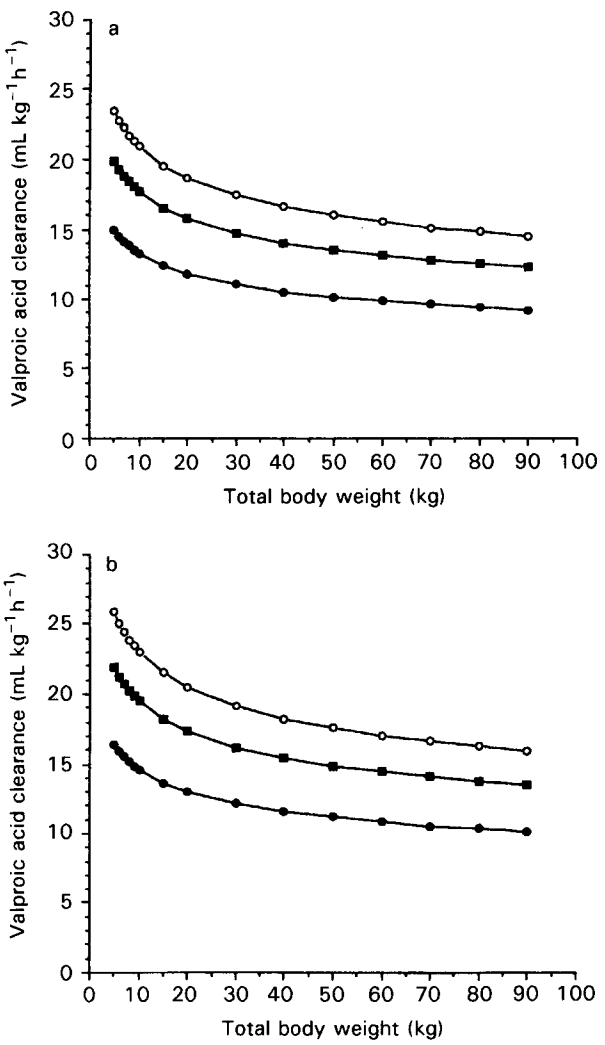

FIG. 3. Effects of total body weight on valproic acid clearance from males: (a) concomitant administration of carbamazepine alone; (b) concomitant administration of carbamazepine and other antiepileptic drugs. Dose: ●, 10 mg kg^{-1} day^{-1}; ■, 20 mg kg^{-1} day^{-1}; ○, 30 mg kg^{-1} day^{-1}. Carbamazepine dose: 10 mg kg^{-1} day^{-1}.

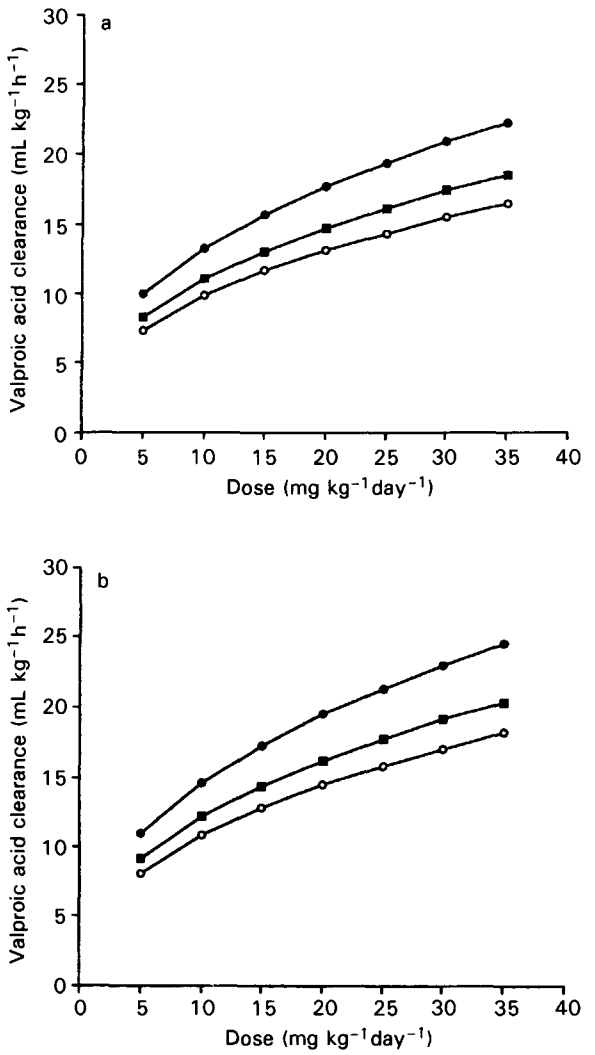

FIG. 4. Effects of daily dose on valproic acid clearance from males: (a) concomitant administration of carbamazepine alone; (b) concomitant administration of carbamazepine and other antiepileptic drugs. ●, Total body weight is 10 kg; ■, total body weight is 30 kg; ○, total body weight is 60 kg. Carbamazepine dose: 10 mg kg day^{-1}.

zepine, phenobarbital, primidone, and phenytoin were administered concomitantly (Chiba et al 1985; Hall et al 1985; Bourgeois 1988; Yukawa et al 1991; Cloyd et al 1993). Optimizing valproic acid therapy for patients receiving enzyme-inducing antiepileptic drugs will be more difficult because of the significantly greater inter-patient variability in clearance than was observed among patients receiving these drugs. In this study the concomitant administration of valproic acid and carbamazepine resulted in increased valproic acid clearance to different extents. The mean relative clearance values of patients weighing 10 to 80 kg and given a valproic acid dose of 15 mg kg^{-1} day^{-1} and a carbamazepine dose of 10 mg kg^{-1} day^{-1} varied from 15·7 to 11·1 mL kg^{-1} h^{-1} for males. The mean relative clearance values of patients weighing 30 kg receiving 7 to 35 mg kg^{-1} day^{-1} of valproic acid dose and 10 mg kg^{-1} day^{-1} carbamazepine varied from 9·5 to 18·6 mL kg^{-1} h^{-1} for males. Co-administration with more than one enzyme-inducer generally results in a greater decrease in valproic acid concentrations. Concomitant administration of valproic acid and two or more antiepileptic drugs resulted in a 10% increase in valproic acid clearance.

This multiple peak screening represents a reasonable approach to assessment of pharmacokinetic variability in a large, heterogeneous patient population. For a drug with a narrow therapeutic range, some factors (i.e. total body weight, daily dose of drug, gender, co-medication) affecting the pharmacokinetics observed in this study could very well merit precautionary statements or warnings about the initial dosage or the suggested frequency of patient monitoring. 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 pathophysiological effects because of uncertainties in the data (e.g. compliance, timing) and because the proportionality between peak level and steady-state average level will depend on clearance itself.

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