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Population Estimation of Valproic Acid Clearance in Adult Patients using Routine Clinical Pharmacokinetic Data

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ABSTRACT: The aim of the present study was to estimate valproic acid (VPA) clearance values for adult patients with epilepsy, using serum concentrations gathered during their routine clinical care. Retrospective steady state serum concentrations data ($n = 534$) collected from 208 adult patients receiving VPA were studied. Data were analysed according to a one-compartment model using the NONMEM program. The influence of VPA daily dose (Dose), gender, age, total body weight (TBW), and comedication with carbamazepine (CBZ), phenytoin (PHT) and phenobarbital (PB) were investigated. The results of the population pharmacokinetics analysis were validated in a group of 30 epileptic patients. The final regression model for VPA clearance (Cl) was:

$$Cl(L/h) = 0.004 \times TBW \times Dose^{0.304} \times 1.363\ CBZ \times 1.541\ PHT \times 1.397\ PB$$

The inter-individual variability in VPA clearance, described by a proportional error model, had a variation coefficient (CV) of 23.4% and the residual variability, described using an additive model, was 11.4 mg/L. These results show that VPA clearance increased linearly with TBW, but increases nonlinearly with increasing VPA daily dose. Concomitant administration of CBZ, PHT and PB led to a significant increase in VPA clearance. The model predictions in the validation group were found to have satisfactory precision and bias. In conclusion, inter-individual variability in VPA clearance can be partly explained by TBW, daily dose and bitherapy with CBZ, DPH or PB. Inclusion of these factors allows this variability to be reduced by 37.23% which may be very useful for clinicians when establishing the initial VPA dosage regimen. However, the magnitude of inter-individual plus residual variabilities, remaining in the final model, render these dosage predictions imprecise and justify the need for VPA serum level monitoring in order to individualize dosage regimens more accurately.

Key words: valproic acid; population pharmacokinetics; NONMEM; therapeutic drug monitoring; drug interactions

Introduction

During the past 30 years, the monitoring of serum concentrations of anticonvulsant drugs has markedly improved the treatment given to patients with epilepsy. This kind of control has led to a more rational use of this group of therapeutic agents, focused on optimizing therapy by integrating drug concentration measurements with clinical observations. Additionally, the use of therapeutic drug monitoring (TDM) has become more efficient because clinicians have become more familiar with the pharmacokinetic properties of the standard antiepileptic drugs and have learned to use TDM in an appropriate way. This is why the need for serum level monitoring has probably decreased in recent years [1,2].

The widespread use of TDM has generated a huge body of data on the serum concentrations of antiepileptic drugs in populations of patients with different physiopathological and clinical characteristics. Such data are a potentially useful source of information for characterizing the kinetic profile of theses drugs in specific populations of interest by applying mixed-effect models [3,4].

Valproic acid (VPA) is an important drug in the treatment of epilepsy because of its broad therapeutic spectrum. This agent is one of the drugs of choice in primarily generalized seizures (absence, tonic–clonic and myoclonic), and is also effective in the treatment of partial seizures [5].

We have investigated the influence of the VPA dose, gender, age, weight, and concomitant treatment with carbamazepine (CBZ), phenytoin (PHT) and phenobarbital (PB) on VPA clearance in a large number of adult outpatients using VPA serum data gathered during routine clinical care. Data analysis was performed with the NONMEM program.

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Materials and Methods

Study Design

Retrospective data from 208 compliant adult epileptic patients, with a total of 534 steady state serum concentrations obtained in routine monitoring of VPA therapy at the University Hospital of Salamanca, were analysed. All patients had normal renal and hepatic function. Table 1 describes the demographic characteristics of patients included in the study.

The patients had been receiving sodium valproate as enteric-coated tablets or oral solution (Depakine®) two to three times a day for more than 1 month at the same dose. Patients on concomitant anticonvulsant drugs were included if all medication was at steady state. Samples were obtained at steady state at the end of the dose interval, before the morning dose, in order to minimize diurnal variations in serum protein binding. Individual information was carefully collected at the moment of obtaining blood samples and included: dosing history, sampling time, gender, age, weight, height, main diagnosis and concomitant pathologies, and complete drug history. Patients taking more than two standard antiepileptic drugs were excluded. Compliance was assessed by the examination of at least two steady state serum VPA serum concentrations. A patient was considered to be complying with the treatment when the CV of the level/dose ratio was less than 20%.

Drug analysis of VPA serum concentrations was carried out using a fluorescence polarization immunoassay (FPIA; Abbott TDx analyser), with inter- and intra-assay CVs of less than 10%.

Table 1. Demographic and treatment characteristics of the patients included in the population study and in the validation analysis

	Index set	Validation set
Observations (n)	534	30
Patients (n)	208	30
Age (years)	27.3 (14–95)[a]	29.4 (14–67)[a]
TBW (kg)	64.1 (27–100)[a]	63.6 (36–88)[a]
Sex (M/F)	276/258	19/11
Dose (mg/kg/day)	17.2 (5.03–50.0)[a]	18.6 (8.0–40.0)[a]
Concentration (mg/L)	56.6 (21.0–123.0)[a]	56.1 (24.2–83.5)[a]
CBZ (Yes/No)	97/437	4/26
PHT (Yes/No)	34/500	2/28
PB (Yes/No)	45/489	6/24

Values are refered to the observations.
[a] Mean value (range).
TBW: total body weight; CBZ: carbamazepine; PHT: phenytoin; FB: phenobarbital.

Population Pharmacokinetic Analysis

Data analysis was performed using the NONMEM computer program (version IV, level 2.0), with double precision and first order estimation [6]. A one-compartment open kinetic model with first order absorption and elimination was assumed according to the available bibliographic information [7]. Because previous studies had shown that VPA bioavailability (F) after oral administration is nearly 100% [8–10], and since Perucca *et al*. [11] found that this parameter is not modified in patients taking other antiepileptic drugs, F was fixed at 1. Since collected VPA steady state trough serum concentration data did not provide information about the volume of distribution (V_d) or the absorption rate constant (K_a) they were fixed to 0.2 L/kg and 1.2/h, respectively [9]. Accordingly, only clearance (Cl) was estimated.

The program subroutines ADVAN 2, TRANS 2 and SS2 from the PREDDPP library were selected to define the chosen pharmacokinetic model. Proportional and additive error models were used to characterize inter-individual and residual variabilities, respectively.

The regression model was developed by use of the forward inclusion–backward elimination method. Total body weight (TBW), age and VPA daily dose were included in the model as continuous covariates in a linear and nonlinear way. Discrete covariates (gender and concomitant medication with CBZ, PHT or PB) were evaluated by stepwise inclusion of scaling factors. Thus, the parameters of these covariates show the extent by which factor VPA clearance is raised or lowered when these variables are present.

In recent years, Bayesian estimation has been proposed to provide individual estimates of pharmacokinetic parameters and to facilitate population model building [12,13]. Therefore, we previously computed empirical Bayesian estimates of individual VPA clearances, using the '*posthoc*' option of the NONMEM program. The plots of these values versus each covariate were analysed in order to ascertain their effect on VPA clearance.

During the forward inclusion, a difference of 3.85 ($p < 0.05$) in the objective functions (D_{obj}) between compared models was required for statistical significance. In addition, the improvement in the fitting by adding a parameter to the model was examined by inspection of weighted residuals errors plots versus predicted concentrations, the precision of the parameter estimate (% S.E.M. and 95% confidence interval (C.I.)) and reductions in inter-individual and residual variabilities. Last, the final model was elaborated, from the full model, by backward one-by-one elimination of each covariate previously selected, using a more restrictive statistical criterion ($D_{obj} = 6.6$, $p < 0.01$).

Validation with a Test Group

To evaluate the results of the population pharmacokinetic analysis, a second group of 30 epileptic patients receiving VPA therapy was studied. The demographic and treatment characteristics of this validation group are shown in Table 1. We compared the VPA concentrations measured in these patients with the corresponding concentrations predicted at the same sampling times by the basic and the final models.

Predictive performance was assessed in terms of precision (root mean square prediction error) and bias (mean prediction error) [14]. The weighted residual errors in VPA concentrations, which were expressed as population S.D. units, were examined to evaluate whether the error size was in accordance with that described by the population model.

Results

The estimates of the population mean VPA clearance, its inter-individual coefficient of variation and the residual variability in the population model without covariates (basic model) were 0.653 L/h, 37.3% and 12.8 mg/L, respectively. The graphic exploratory analysis of the relationship between the individual Bayesian clearances and the covariates analysed revealed that TBW and the VPA daily dose were clearly correlated with the individual estimates for clearance (Figure 1). However, there was no obvious pattern in the plots versus age. Regarding the discrete variables analysed, the effect of combined treatment with PHT, PB and CBZ on VPA clearance was evident, while no differences attributable to gender were observed.

The effect of TBW on VPA clearance was adequately described by a direct proportional relationship; however, the VPA daily dose (mg/kg) was best modelled in an exponential way. Additionally, the presence of other antiepileptic drugs (CBZ, PHT or PB) in the treatment, modelled as corrections factors, was associated with an increase in VPA clearance. According to the graphic exploratory analysis, no other covariate (gender and age) was found to significantly improve the NONMEM fit.

Table 2 shows the differences in the objective function between the full model and the models from which each factor was deleted one by one. All of these factors appeared to significantly contribute to the goodness of fit and were, therefore, conserved in the final model. Thus the final regression model for VPA clearance (L/h) was as follows:

$$\mathrm{Cl} = 0.004 \times \mathrm{TBW} \times \mathrm{Dose}^{0.304} \times 1.363\ \mathrm{CBZ} \times 1.541\ \mathrm{PHT} \times 1.397\ \mathrm{PB}$$

The estimate of the variation coefficient of inter-individual variability in VPA clearance, described using a proportional error model, was 23.39%, with a 95% C.I. from 4.04 to 42.70%. An additive error model for VPA concentrations best described the residual variability over the whole range observed. The S.D. of the additive residual error in the predicted concentrations was 11.36 mg/L, with a 95% C.I. from 1.1 to 21.5 mg/L.

Fixed effect parameters were estimated with a similar degree of precision as the random effects, the values of the percentage relative S.E. of these parameters in all cases being less than 22%.

Table 3 summarizes the prediction errors established by the basic and final models, and shows an important improvement in the predictive performance of the final model as compared to the basic one. Weighted residual errors in the predicted VPA concentrations with the final model, expressed in population S.D. units, versus patient identification number are shown in Figure 2. Although there are some marked absolute differences between the observed and predicted concentrations, more than 90% of the observed concentrations were between -1 and $+1$ S.D.s of the mean population predicted values, indicating that they were in accordance with the range of variability described by the population model proposed. Figure 3 shows the plot of predicted versus observed concentrations, confirming the good predictive capacity of the final model.

Discussion and Conclusions

The data from TDM are collected according to a sparse strategy designed to assess the goodness of the recommended dosage regimen, with practically no variation in sampling times across patients. However, these data are representative of the population receiving the drug for therapeutic purposes. From these kinds of data, our study has identified some of the factors that may result in serum level variations of VPA in adult epileptic patients.

According to our results, the important factors that appear to influence the clearance of VPA are TBW, the VPA daily dose and bitherapy with CBZ, PHT and PB, which were included in the final model as the main predictors of this pharmacokinetic parameter. Among these factors, TBW and daily dose (mg/kg) seemed to be the main determinants of the variability of VPA clearance within the adult population, their introduction leading to decreases in the objective function of 474.06 and 271.93, respectively.

Regarding the daily dose, this showed a nonlinear relationship with VPA clearance that was statistically superior to the linear one and that was in agreement with the results reported by other

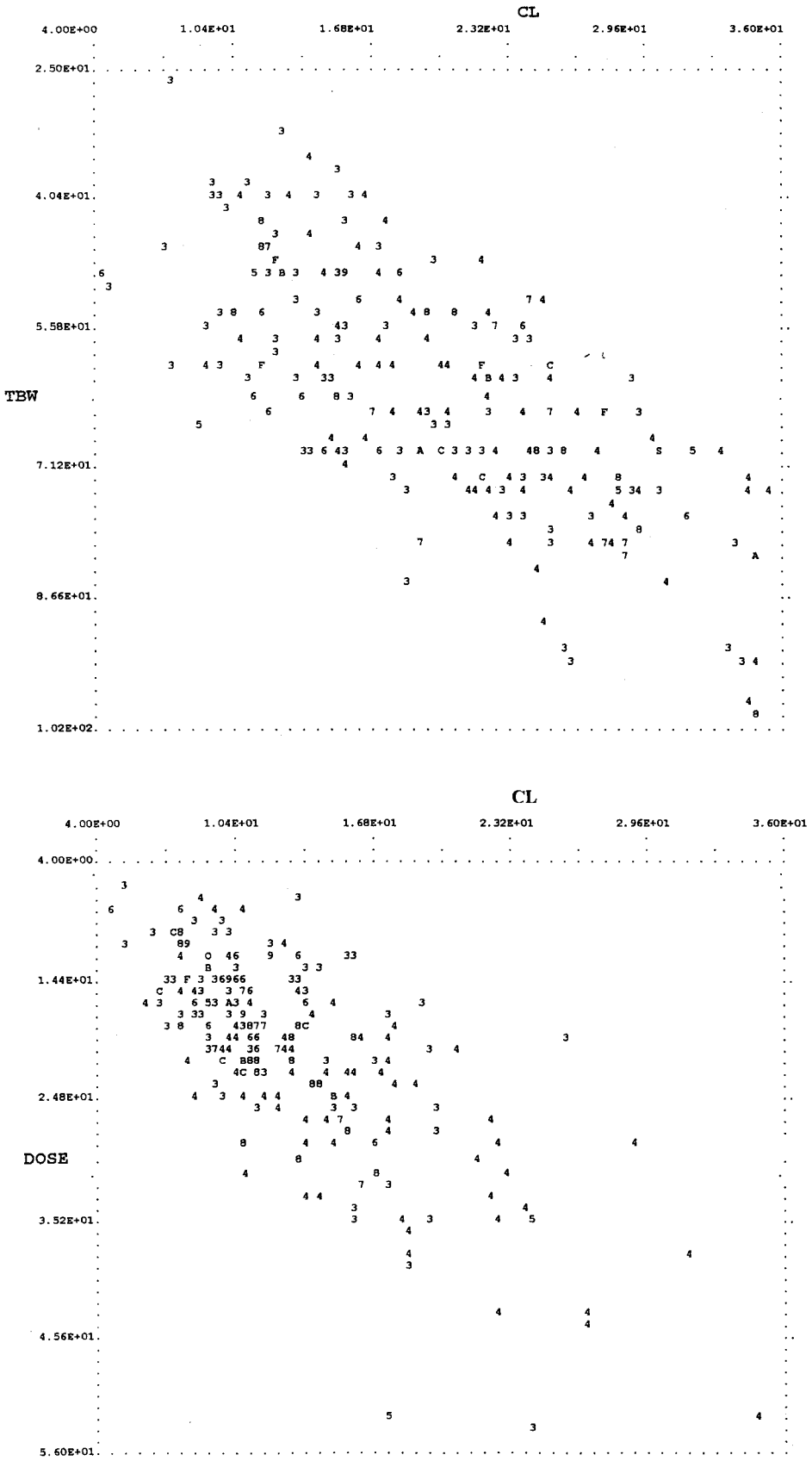

Figure 1. Relationship between individual estimates for clearance (L/h) and total body weight (kg; top panel) and daily dose (mg/kg/day; bottom panel)

Table 2. Differences in the objective function minimum value between the full model and the models from which one of the covariates was deleted in the clearance model

Deleted covariate or fixed parameter	Change in the objective function	p value
TBW	474.06	<0.001
Dose	50.08	<0.001
θ_2 fixed to 1	271.93	<0.001
CBZ fixed to 0[a]	54.55	<0.001
PHT fixed to 0[a]	33.53	<0.001
PB fixed to 0[a]	39.95	<0.001

Cl: clearance; θ_{1-5}: regression parameters; TBW: total body weight; Dose: daily dose (mg/kg); CBZ: 1 if the patient received carbamazepine and 0 otherwise; PHT: 1 if the patient received phenytoin and 0 otherwise; PB: 1 if the patient received phenobarbital and 0 otherwise.

[a] $Cl = \theta_1 \times TBW \times Dose^{\theta_2}[(1+\theta_3) \times CBZ][(1+\theta_4) \times PHT][(1+\theta_5) \times PB]$

Table 3. Prediction errors established in the validation set by the basic and final models.

Error	Basic model	Final model
MPE (95% C.I.)	−3.75 (−15.85; 8.36)	3.63 (−2.10; 9.36)
MSPE (95% C.I.)	1030.13 (78.70; 1981.56)	240.79 (108.81; 372.77)
RMSPE (95% C.I.)	32.10 (8.87; 44.51)	15.52 (10.43; 18.10)
SPE		
Mean value (95% C.I.)	—	0.22 (−0.07; 0.51)
S.D.	—	0.77

MPE: mean prediction error; MSPE: mean squared prediction error. RMSE: root mean squared prediction error; SPE: standardized prediction error.

authors [15–18]. This can be attributed to the fact that VPA is highly bound to albumin and displays saturable protein binding within the recommended serum concentration range [19], and also that only unbound drug is cleared (*kinetic effect*) [5]. Further, TDM may also be responsible for the nonlinear relationship found between VPA clearance and dose, since individuals with higher VPA clearances were given higher doses (*TDM effect*) [20]. Thus, the correlation between VPA clearance and daily dose is at most only partially due to VPA saturable protein binding and both types of effects—kinetic and TDM—may be confused. Nevertheless, the amount and nature of data afforded by TDM does not permit the use of an appropriate kinetic model that properly reflects this nonlinearity and expresses the effect of saturable binding, such that the only way of suitably fitting the model is to introduce dose as an inter-individually varying parameter, which includes both effects and hence does not permit their differentiation.

Figure 4 shows the relationship found, on applying the final model parameters, between VPA clearance and daily dose (mg/kg) for patients on a monotherapy regimen with VPA and a TBW ranging from 50 to 80 kg. As predicted by the proposed model, a moderate increase in VPA clearance is observed with an increase in dose and weight.

It is important to have knowledge of possible interactions in order to anticipate their clinical effects and to reduce the risk of both toxicity and seizures worsening when a drug is added to, or withdrawn from, the patient's antiepileptic drug regimen [21]. Several studies have shown considerable evidence that concomitant therapy with classic antiepileptic drugs increases VPA clearance in both adults and children as a consequence of their enzyme induction capacity [5,7,11,22–28]. It was observed that patients receiving enzymatic inducers undergo decreases of between 30 and 40% in VPA concentrations in the case

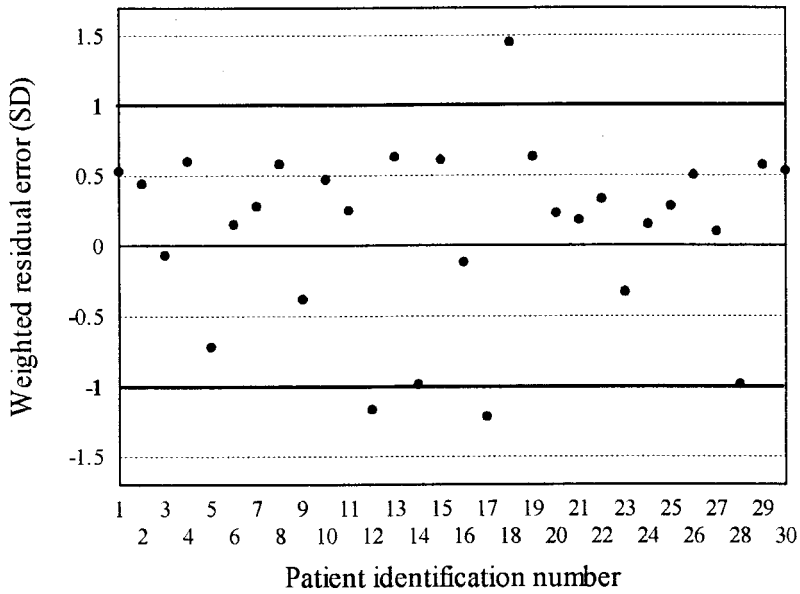

Figure 2. Plot of weighted residual errors in the predicted VPA concentrations with the final model in the validation group

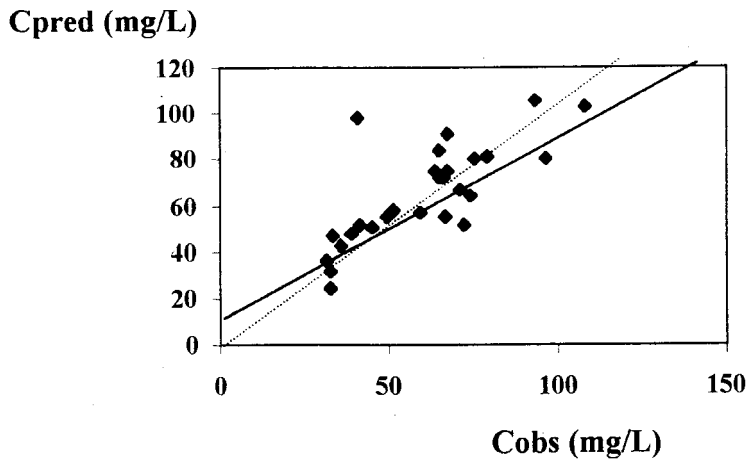

Figure 3. Plot of valproic acid concentrations predicted by the final population model versus the corresponding observed concentrations (solid line) and unit line (dashed line) in the validation group

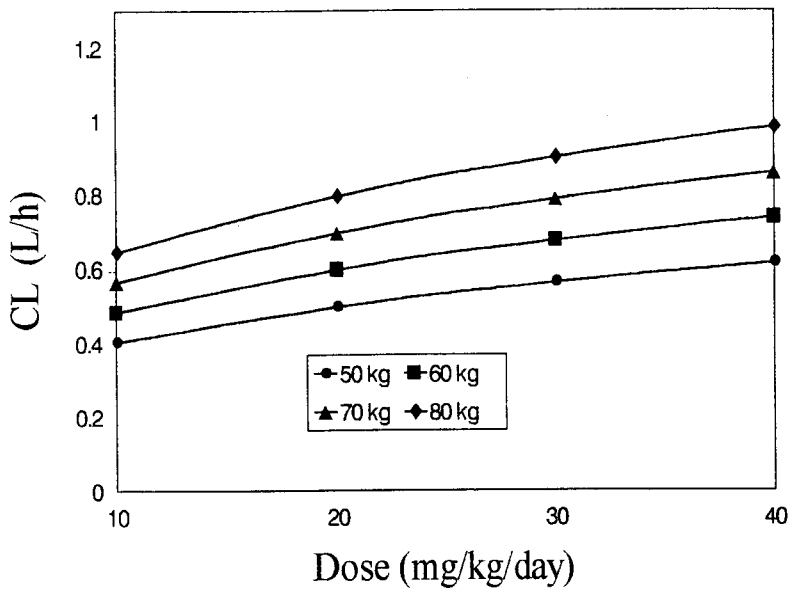

Figure 4. Relationship of VPA clearance and daily dose for patients with a TBW ranging between 50 and 80 kg

of adults, while such decreases are more pronounced (40–50%) in children [7,11,17,23,25–36].

In agreement with these studies, the proposed final model for VPA clearance showed that patients taking VPA on a bitherapy regimen with CBZ, PHT or PB had clearances 1.36, 1.54 and 1.40 times greater, respectively, than patients taking VPA alone. However, these results cannot applied to patients receiving three or more antiepileptics, in whom this relationship may be different.

As expected for an adult population, age did not appear to influence VPA clearance in this study (patients were aged between 14 and 95 years). Neither did the inclusion of gender in the initial model appear to improve the data fitting, in agreement with most studies in which no significant differences were seen in the serum concentrations of VPA between males and females. Despite this, Yukawa [18] did find a 12% reduction VPA clearance in females as compared with males.

The inter-individual variability in VPA clearance, with an initial value of 37.8% (basic model), was partly explained by the available covariates, a decrease of 23.32% being obtained in the final model. This relatively small coefficient of variation of VPA clearance obtained in our study suggests that consideration of TBW, the daily dose and bitherapy with CBZ, PHT or PB could be very useful to clinicians to establish initial VPA dosage regimens.

Regarding residual variability, modelled additively, a decrease by 11.32% with respect to the basic model (equivalent to a coefficient of variation of 18.93% for a concentration of 60 mg/L) was observed. Part of the unexplained variability may have been

attributable to the observational design of our study, data than experimental designs do.

The magnitude of the residual and inter-individual variabilities, remaining in the final model, render *a priori* dose predictions for patients imprecise and would justify the use of TDM and individual Bayesian dose adjustment.

The model predictions in the validation group were found to have satisfactory precision and bias, since the mean error 95% C.I. includes zero and plots of weighted residuals versus VPA serum concentrations produced a satisfactory degree of random scatter.

In conclusion, a population approach using NONMEM for the analysis of abundant of sparse VPA serum concentrations provides useful measures of the typical VPA clearance together with estimates of inter-individual and residual variability. The satisfactory predictive performance of the population regression model may prove valuable as a means of estimating *a priori* individual patient dosage schedules for VPA. Besides, the introduction of this pharmacostatistical model in computer programs will permit individual pharmacokinetic parameter determination, through Bayesian estimation, which may increase the predictive accuracy of dosage adjustment.

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