Original Articles

Population pharmacokinetic model of valproate and prediction of valproate serum concentrations in children with epilepsy[1]

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KEY WORDS pharmacokinetics; valproic acid; epilepsy; Bayes theorem; USC*PACK software

ABSTRACT

AIM: Using sparse data of valproate (VPA) serum concentrations to build a population pharmacokinetic (PPK) model of VPA in Chinese children with epilepsy and to predict serum concentrations for new patients using a Bayesian approach. **METHODS:** Two hundred epileptic children, whose VPA serum concentrations were collected, were divided randomly into two groups (A and B, n=100 each). The PPK parameter values of group A were calculated to establish a PPK Model by using the NPEM Program of USC*PACK software. Based on it, VPA serum concentrations of group B were predicted with the Bayesian Fitting Program of the USC*PACK software. To assess the accuracy and precision of prediction, a paired-comparisons t-test was run between predicted and observed concentrations, and then the mean prediction error (MPE), mean square prediction error (MSPE), root mean square prediction error (RMSPE), and coincidence rates for different percentages of prediction error were all calculated. **RESULTS:** Optimum PPK parameters were: Ka, 2.522±2.743 h^{-1}; Vs, 0.329±0.496 L/kg; and Kel, 0.0438±0.0384 h^{-1}. For group B, there was no significant difference between predicted and observed concentrations. MPE was -0.43 mg/L, MSPE was 115.40 $(mg/L)^2$, and RMSPE was 5.47 mg/L. The coincidence rates for percentages of prediction error, which were less than 5 %, 10 %, 15 %, 20 %, 25 %, and 30 %, were 62 %, 74 %, 82 %, 85 %, 89 %, and 93 %, respectively. **CONCLUSION:** A PPK model of VPA in epileptic children was successfully established. Based on it, VPA serum concentrations can be predicted accurately with a Bayesian approach.

INTRODUCTION

Valproate (VPA) is an important drug in the treatment of childhood epilepsy because of its broad therapeutic spectrum[1-3]. For most antiepileptic drugs (AEDs), drug concentration (blood) should be monitored during epilepsy treatment. Since the drug concentration in serum or plasma is better at predicting concentration at the site of action than the orally administered dose, those levels correlate better with clinical response than the dosage. So does VPA[4,5]. It is therefore important to understand, and if possibly predict, the relationship between the drug dose and the resulting drug plasma levels.

The use of VPA in children is complicated by marked variability in the relationship between serum concentrations and dose that can be attributed to interpatient differences in drug clearance[6]. Effective VPA concentrations also show interpatient variability. In order to use VPA more effectively, individualized VPA dosage regimens must be used. This can be most effectively

[1] Project supported by the National Natural Science Foundation of China (No 30170994).
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Received 2004-03-01 Accepted 2004-04-29

done when individual pharmacokinetic (PK) parameter values are known.

The traditional method of calculating individual PK parameters was to collect multiple (up to 7-10) blood samples from a single patient at different time after single dose; then individual PK parameters' values were calculated using PK professional software. This method was not always accepted by patients (especially children) because of pain, inconvenience, and heavy economic burden it produced. A new way of determining individual doses uses Population Pharmacokinetics (PPK) and Maximum Aposteriori Probability (MAP) Bayesian method to obtain individual PK parameter values.

Many successful uses of PPK have been described. However, to our knowledge, at the time of this study, no detailed study of VPA concentrations using PPK and a Bayesian approach had been performed in China, and did not know whether there is ethnicity variability for PPK parameter values of VPA between Occidental and Chinese. We used VPA concentrations from a group of Chinese children with epilepsy to set up a PPK model and then used this model to see how well could VPA serum concentrations be predicted in another group of similar children.

MATERIALS AND METHODS

Patients information This study was carried out at the pediatric clinics and wards of Peking University First Hospital in China. The protocol for this study was approved by the Regional Ethics Committee, and assent and consent were obtained from all patients or their parents. We collected sparse therapeutic drug monitoring (TDM) data for VPA serum concentrations from 200 pediatric patients with epilepsy. All were taking VPA, either alone or concomitant with other AEDs, such as phenobarbital, phenytoin, carbamazepine, clonazepam, topiramate and lamotrigine. These VPA concentrations were steady state serum concentrations and included peaks and troughs. All patients or their parents recorded all dosage administered, as well as times of dosage taking and blood sampling. They were all judged to have had good compliance and known the importance of good records emphasized by their treating physicians.

With the PASTRX program of USC*PACK software[7], patient information were stored in files. Each file contained subject treatment data such as doses, times of administration and blood sampling, and corresponding VPA level measurements; and covariates such as sex, age, weight, height, serum creatinine levels and corresponding estimates of creatinine clearance[8].

These 200 patients were randomly divided into two groups (A and B Group, n=100 each). Group A was used to calculate PPK parameter values by the nonparametric expectation maximization program (NPEM)[9] of USC*PACK software and to set up the PPK model by using median of PPK parameter values. Group B was used to estimate individual PK parameter values and to predict concentrations by the MAP Bayesian Fitting Program of USC*PACK software so as to verify this PPK model[10,11].

Serum concentration assay VPA serum concentrations were assayed by a fluorescence polarization immunoassay (FPIA) (TDx; Abbott Laboratories, Abbott Park, IL, USA). The mean and standard deviation (SD) of the assay at standard concentration points of 25 mg/L, 50 mg/L, 100 mg/L, and 125 mg/L were (25.33±0.91) mg/L, (50.14±0.77) mg/L, (101.04±0.56) mg/L, and (122.67±1.69) mg/L, respectively. Typical intraday and day-to-day coefficients of variation for the assay were less than 4 %.

By using the "Determine Assay Error Polynomial" Program of the USC*PACK software to describe the assay error pattern, the relationship between the assay standard deviation (SD) and the serum concentration (C) was fit to a third order polynomial equation and its R^2 (coefficient of determination) was 1[12]. The polynomial equation was:

$$SD\ (mg/L)=0.2803+0.04849C-0.001093C^2+0.000006357C^3$$

PPK model parameterization VPA concentrations can be fit using a one-compartment model and a first order kinetic process[13]. VPA is largely metabolized by the liver and a little is excreted by the kidney. Therefore, we selected 3 parameters: the Ka or absorption rate constant, expressed in h^{-1}; the Kel or elimination rate constant, expressed in h^{-1}; and the Vs or slope of the volume of distribution to body weight relationship, expressed in L/kg. Initial ranges were 0-0.8 h^{-1} for Ka, 0-0.3 L/kg for Vs, and 0-0.08 h^{-1} for Kel[14]. FA (bioavailability) was fixed for 1 because actual bioavailability could not be calculated from only oral dosing data and previous studies have shown that VPA bioavailability after oral administration was nearly 100 %[2,6].

NPEM program was used to obtain the parameter distributions and values for a one-compartment model. The run was set for a maximum of 4000 iterative cycles.

The convergence criterion chosen was that the likelihood value must have proceeded at least 99.999 % of the way from that found with a prior uninformed joint density to that found for the true maximum likelihood joint density. The number of grid points used was 20011[12].

Evaluation of PPK parameter values Using the NPEM program of USC*PACK software to calculate parameter values, the maximum likelihood is the best criterion to choose the optimal PPK parameter values from several successful runs with different initial ranges. The AKAIKE Information Criterion (AIC) and SCHWARTZ (BAYESIAN) Information Criterion (BIC) are related to the most efficient parameter values, and were used to choose the efficient model parameters while not being constrained by those results. The goodness of fit (correlation coefficient, bias, precision) for VPA serum concentrations determined for 100 patients in A group, using the median population parameter values and the MAP Bayesian method to fit the model to the data of the doses and of the VPA serum concentrations[15]. Mean prediction error (MPE), a measure of accuracy; mean squared prediction error (MSPE), representing precision; and root mean squared prediction error (RMSPE), a measure of both accuracy and precision were calculate[16].

Bayesian prediction A PPK model was set up by using medians of optimal PPK parameter values, then was used in the MAP Bayesian Fitting Program of USC*PACK software to predict individual PK parameter values and concentrations of patients in B group to verify this PPK model.

The validation of this PPK Model was performed by concentration prediction through a Bayesian approach. The model was used to predict each group B patient's VPA serum concentration by estimating individual PK parameters with the Bayesian maximum a posterior probability (MAP), using the optimal median PPK parameters as the Bayesian prior probability. Prediction of subsequent drug concentrations is usually more precise with MAP Bayesian methods than with other methods[17-20]. Moreover, the technique has the advantage of requiring fewer (as few as one) serum concentration measurements[21]. The MAP Bayesian approach is a good method to predict drug concentrations and has significantly improved TDM for a variety of drugs.

The accuracy and precision of the Bayesian prediction was assessed by two steps. First, with SPSS Software (10.0 version, Microsoft Company, USA), a paired-comparisons *t*-test was run between predicted and observed concentrations to evaluate any possible significant difference between the predicted and the measured values. Second, the relationship between predicted and measured serum concentrations was then examined by calculating MPE, MSPE, RMSPE, percentage of prediction error (the percentage of prediction error divided by corresponding observed concentration), coincidence rates (the percentage of sample numbers, which having same percent range of prediction error, divided by total concentration points, it becomes bigger as percent range of prediction error increasing, and in total more than 100 %) and their 95 % confidence intervals (CI) for various percentages of prediction error, and proportions (the percentage of sample numbers, which having different range of percentage of prediction error, divided by total concentration points, and in total is 100 %) for different ranges of percentage of prediction error[15-17].

RESULTS

A total of 485 steady state concentrations from 200 patients were collected in routine monitoring of VPA therapy, 257 concentrations were from patients in group A and 228 from group B. The intervals between the last dose time and sampling time were distributed over 0-36 h, mostly within 0-24 h. Renal and hepatic function kept normal in all patients. Demographic features of the patients were shown in Tab 1. The distributions of concentration data and sampling times for patients in A and B groups were shown in Fig 1.

For one of the several successful runs of the NPEM program, the greatest log-likelihood was -1191.90; the AIC was 1201.90; the BIC was 1219.65. Median of this run's population parameters were used to estimate median of individual parameters. Then to fit the 257 concentrations in A group by each subject's individual MAP Bayesian posterior individual model. For the Goodness-of-Fit, r (correlation coefficient) was 0.93; the best least square line for regression function was Y_{OBS}= -0.03+1.03*Y_{PRED}, R^2 (coefficient of determination) was 0.90, P<0.05; MPE was -1.74 mg/L; and MSPE was 53.32 $(mg/L)^2$. Results revealed that the PPK parameter values of this run were optimum. The optimum Mean, Median, SD, % CV, 2.5 %, 97.5 % of PPK parameters of VPA were given in Tab 2.

The plot of predicted and observed concentrations for group B was shown in Fig 2. For the paired-com-

Tab1. Demographic features of the patients.

Characteristic	Group A	Group B
Patient data:		
No of subjects	100	100
Gender (male: female)	64:36	58:42
Mean age (years) (range)	5.82 (0.28-16)	6.25 (0.17-16)
Mean weight (kg) (range)	22.49 (6-73)	25.87 (4-73)
Mean height (cm) (range)	109.77 (63-172)	113.85 (55-172)
Sample data:		
Mean sampling time (hour) (range)	10.22 (0-36)	7.41 (0-34)
Total No of concentration-time points collected	257	228
No of observations per subject (sparse data range)	1-7	1-6
No of observations per subject (rich data range)	10	10
Mean dose ($mg \cdot kg^{-1} \cdot d^{-1}$) (range)	23.1 (15.7-50.0)	26.2 (10.0-49.0)
Mean VPA concentration (mg/L) (range)	56 (13-163)	63 (11-160)

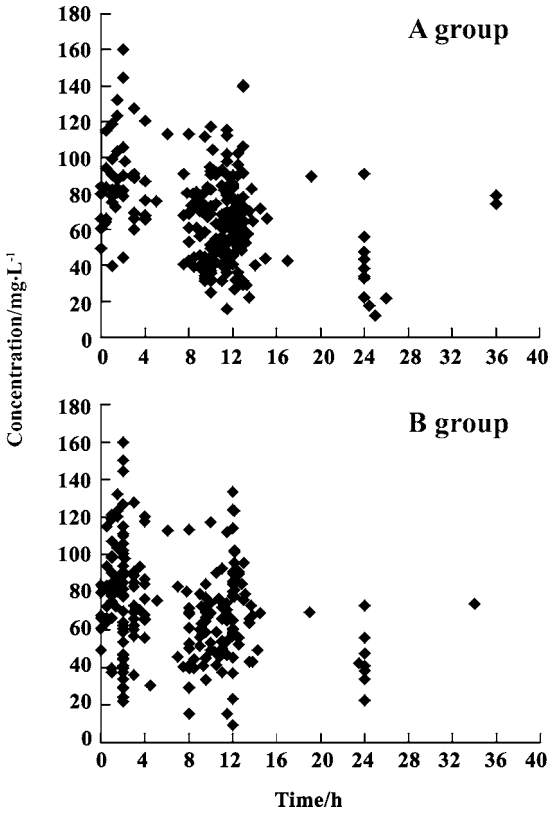

Fig 1. Scattergram of concentrations and intervals between last dose time and sampling time of patients in A group and B group.

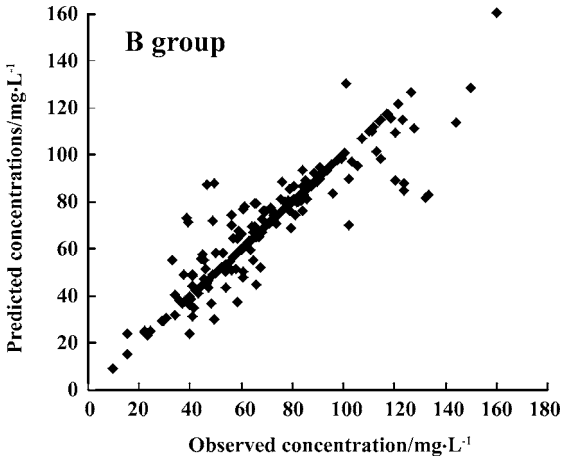

Fig 2. The Scattergram of predicted and observed concentrations of patients in B group.

parisons *t*-test, there was no statistically significant difference ($P>0.05$). MPE was -0.43 mg/L, the MSPE was 115.40 $(mg/L)^2$, and RMSPE was 5.47 mg/L. The smaller the MPE, the MSPE, and the RMSPE, the less biased and the more precise the results were expected to be [16].

The coincidence rates and their 95 % CI for different percentages of prediction error for total concentration range in this study, which were less than 5 %, 10 %, 15 %, 20 %, 25 %, and 30 %, were 62 % (56 %, 69 %), 74 % (68 %, 79 %), 82 % (77 %, 87 %), 85 % (80 %, 90 %), 89 % (85 %, 93 %) and 93 % (89 %, 96 %) respectively, and those for therapy window range (50-100 mg/L) were 71 % (64 %, 79 %), 83 % (77 %, 89 %), 90 % (85 %, 95 %), 93 % (89 %, 97 %), 96 % (93 %, 100 %), and 98 % (96 %, 100 %), respectively (Tab 3). The specimen number and proportions for different ranges of percentage of prediction error in group B for total concentration range in this study and therapy window range (50-100 mg/L) were illustrated in Tab 4.

Tab 2. Optimum parameter values found in the population pharmacokinetic analysis of 100 patients in A group.

Parameter	Mean	Median	SD %	CV	2.5 %	97.5 %
*K*el (h^{-1})	0.050	0.044	0.038	71.97	0.004	0.149
*K*a (h^{-1})	3.544	2.522	2.743	87.06	0.016	10.657
*V*s (L/kg)	0.554	0.329	0.496	103.64	0.028	2.276

CV, coefficient of variation for mean; 2.5 %, 2.5th percentile; 97.5 %, 97.5th percentile; *K*el, elimination rate constant; *K*a, absorption rate constant; *V*s, slope of volume to body weight.

Tab 3A. The coincidence rates and their 95 % confident intervals (CI) for different percentages of prediction error of patients in B group for total concentration range.

Percentage of prediction error/%	Sample numbers (total 228)	Coincidence rate/%	Lower limit of 95 % CI/%	Upper limit of 95 % CI/%
<5	142	62	56	69
<10	168	74	68	79
<15	187	82	77	87
<20	194	85	80	90
<25	204	89	85	93
<30	211	93	89	96
<35	216	95	92	98
<40	221	97	95	99
<45	221	97	95	99
<50	222	97	95	99

Tab 3B. The coincidence rates and their 95 % confident intervals (CI) for different percentages of prediction error of patients in B group for therapy window range (50-100 mg/L).

Percentage of prediction error/%	Sample numbers (total 142)	Coincidence rate/%	Lower limit of 95 % CI/%	Upper limit of 95 % CI/%
<5	101	71	64	79
<10	118	83	77	89
<15	128	90	85	95
<20	132	93	89	97
<25	137	96	93	1.00
<30	139	98	96	1.00
<35	141	99	98	1.00
<40	142	1.00	1.00	1.00
<45	142	1.00	1.00	1.00
<50	142	1.00	1.00	1.00

Tab 4A. The sample numbers and their proportions for different percentage ranges of prediction error of patients in B group for total concentration range.

Percentage ranges of prediction error/%	Sample numbers (total 228)	Proportion/%
<5	142	62.3
5-10	26	11.4
10-15	19	8.3
15-20	7	3.1
20-25	10	4.4
25-30	7	3.1
30-35	5	2.2
35-40	5	2.2
40-45	0	0.0
45-50	1	0.4
>50	6	2.6

Tab 4B. The sample numbers and their proportions for different percentage ranges of prediction error of patients in B group for therapy window range (50-100 mg/L).

Percentage ranges of prediction error/%	Sample numbers (total 142)	Proportion/%
<5	101	71.1
5-10	17	12.0
10-15	10	7.0
15-20	4	2.8
20-25	5	3.5
25-30	2	1.4
30-35	2	1.4
35-40	1	0.7
40-45	0	0.0
45-50	0	0.0
>50	0	0.0

DISCUSSION

Data collection For a one-compartment model, the mean population parameter values begin to stabilize after about 25-30 subjects, but that is clearly not enough to be able to see any subpopulations. This may well require at least 100 subjects[18]. The NPEM program, like the NPML method, is able to operate with only single datum point per patient[19, 20]. However, the traditional strategy of obtaining only trough whole blood levels does not provide enough dynamic information. Modifying the blood concentration-monitoring scheme to add at least one other concentration measured during the absorptive or distribution phase generates much more information about the behavior of the drug[15]. In our study, data from 100 compliant epileptic children, with 257 steady state concentrations obtained during routine monitoring of VPA therapy, were enough to generate predictive PPK parameters. Commonly used VPA formulations need to be taken 2-3 times per day, while sustained release formulations can be given once per day. The intervals between the last dose time and blood sampling time in our study were distributed over 0-36 h, but most were 0-24 h, especially 0-15 h. Therefore, the sampling time intervals covered the whole range of possible drug administration intervals. Such data should reflect the characteristics of absorption, distribution and excretion and be useful to predict all necessary PPK parameters for VPA.

PPK parameter values We are unaware of any prior report of PPK parameter values for VPA in China, only some individual PK parameter values for taking different formulations of VPA, such as a traditional tablet, an enteric-coated tablet, a syrup. The values from various reports were different. For example: *K*a was 0.46±0.25 h^{-1}, 1.19±0.13 h^{-1}, 2.53±2.43 h^{-1}, 4.10±1.57 h^{-1}; *K*el was 0.015-0.02 h^{-1}, 0.0455±0.0082 h^{-1}, 0.08±0.01 h^{-1}; *V*s was 0.156±0.026 L/kg, 0.15-0.4 L/kg[5,21-24]. The PPK parameter values calculated in this report encompassed those individual PK parameters, reported for patients coinciding with the characteristics of our population.

The PPK parameter values for VPA, reported in American populations were: *K*a 1.13±0.587 h^{-1}; *CL* 0.731±0.197 h^{-1}; *V*s 0.268±0.148 L/kg[25]. The values for Ka reported abroad were also different, such as: Ka 1.2 h^{-1} [26] and 1.9 h^{-1} [27]. There was no apparent racial difference since the values reported for other populations were in the same range as ours.

The range of PPK parameter values in our study were very large: the 2.5th and 97.5th percentiles for *K*el, *K*a, and *V*s were: (0.004, 0.149), (0.016, 10.657), (0.028, 2.276), respectively.

Research in China and other countries have all indicated that the variability of PPK parameter values is large. That is associated with following factors: 1) Drug formulation. VPA can be administrated orally to children as a traditional tablet, an enteric-coated tablet, a syrup or as a sustained release tablet. PK theory predicts that various drug formulations will have different Ka values. Differences in Kel and Vd will be associated with characteristics of the drug itself and the patient but not the drug formulation. 2) Age. Variations in the different PK parameter values were related to differences in patient ages. Variability was especially large in 1-3 years old patients. There was distinction between 3-6 years and older than 6 years, but not as marked as in patients younger than 3 years. VPA is metabolized more quickly *in vivo* in younger children[6,28]. 3) Weight. The ranges of weight were large in this study. The lightest one was 6 kg, the heaviest was 73 kg, and the mean was 22.49 kg. PPK parameter values were influenced by bodyweight. This probably reflects the relationship between body surface area and liver size[29,30]. 4) Drug coadministration. In our study, some patients were given more than one AED. VPA was given in combination with AEDs such as phenobarbital, phenytoin, carbamazepine, clonazepam, topiramate and lamotrigine. There were interactions noted between AEDs. Phenobarbital, phenytoin, carbamazepine induced the metabolism of VPA, and VPA inhibited the metabolism of other AEDs[30-33].

As the above analysis indicates, the precision of the PPK parameter values could be enhanced through consideration of drug formulation used, separating monopharmacy from polypharmacy patients, and the age, weight and stature of patients. Finally, the quality of population data can greatly influence the precision of the model. All of these factors are being investigated in ongoing studies.

Evaluation of MAP Bayesian prediction The accuracy of this technique is dependent upon the accuracy of PPK parameter values used in the model, and also on the number of serum samples fitted in each patient's data, the assay error, the errors in preparing and giving the doses, the errors in recording when the dosed and the samples were given or taken, the model misspecification, and any changes in parameter values

during the period of the data taken.

We evaluated the accuracy of the obtained PPK parameter values by forecasting the serum VPA concentrations in a validation population (B group)[34], whose data were not used to calculated PPK parameter values. We are unaware of any literature on the degree of acceptable prediction accuracy or any recognized "gold standard" criterion for accuracy. Therefore, many indexes were used to evaluate prediction accuracy.

The paired-comparisons *t*-test found no statistically significant difference between predicted and observed concentrations (P=0.55). The MPE was -0.43 mg/L, used as a measure of bias; and the MSPE was 115.40 $(mg/L)^2$, used as a measure of precision; RMSE was 5.47 mg/L, used as a measure of both accuracy and precision. These values were so small and indicated that this prediction was reliable[16].

The accuracy of prediction was also evaluated with the coincidence rates and their 95 % CI for different percentages of prediction error. For 93 % of concentration predictions, prediction error was controlled below 30 %; and for 62 %, it was controlled below 5 % (Tab 3).

Some have suggested that one criterion is the percentage of measured serum levels accurately predicted (% SLAP), defined as being within 20 % of the predicted concentration[15,17]. According to this in our study, 85 % concentration predictions were within 20 %, and its 95 % CI was (80 %, 90 %). Furthermore, through analyzing specimen numbers and proportions for different ranges of percentage of prediction error, we found that specimen numbers decreased with increased ranges of percentage of prediction error, that mean proportion decreased gradually (as illustrated in Tab 4). It was concluded that most of the predicted concentrations were within a small range of percentage of prediction error and were accurate.

The data imply that the PPK model developed and its application in a MAP Bayesian approach to concentration prediction were successful. Simultaneously, it has provided a new way to obtain individual PK parameter values and to design individualized dosage regimens. This method could promote improvement of Evidence Based epilepsy treatment.

A PPK model for VPA dosing in children with epilepsy in China was successfully established using the USC*PACK software, and there was no ethnicity variability for PPK parameter values of VPA between Occidental and Chinese. Based on it, VPA concentrations could be predicted accurately with a Bayesian approach. It is potentially valuable resource for the use of VPA in clinical practice.

ACKNOWLEDGEMENTS The authors would like to thank Roger W Jelliffe, MD, Prof of Medicine, University of Southern California, for his generous donation of USC*PACK software and kind guidance.

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