An Influencing Factor to Predict Plasma Valproate Concentrations: Circadian Stage-Dependent Kinetics

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This study was designed to examine how the dosing time of the day influenced the accuracy in predicting plasma valproate (VPA) concentrations at steady state. Eight healthy male volunteers took 400-mg doses of VPA for 9 days on a twice-daily basis (08:30 and 20:30). The circadian changes in VPA kinetics occurred at the absorption phase. The prediction of plasma VPA concentrations at 2hr (around $C_{\max}$) and at 12hr after both the morning and the evening dose on the ninth day was performed using the individual subject's pharmacokinetic parameters and population pharmacokinetic parameters (Bayesian method) obtained from the morning trial on the eighth day. The predictive accuracy for VPA concentration around $C_{\max}$ after the morning dose was better, but that for VPA concentration after the evening dose was significantly biased toward overestimation. The individual pharmacokinetic parameters obtained from the morning trial became better sources for the prediction of VPA concentrations around $C_{\max}$ after the morning dose, but worse sources for that after the evening dose. The predictive performance based on the Bayesian approach also showed the similar finding to that based on individual pharmacokinetic parameters. The overestimation of the target points around $C_{\max}$ after the evening dose is closely related to that of K_a value produced by using population parameters obtained from morning trial. Therefore, these results suggest that the time in the circadian stage at which VPA is administered is important for evaluating exactly the predictive accuracy.

Key words: prediction, sodium valproate, Bayesian approach, circadian change

Introduction

Recently determination of plasma drug concentrations has been widely used for monitoring drug therapy, because many drugs have a well defined therapeutic window of drug concentration in plasma and show a large interindividual variation

of plasma drug concentrations. Equally, some approaches have been developed to assist the dosage optimisation for individual patient. The Bayesian approach proposed by Sheiner et al.¹⁻⁴⁾ is the most attractive from the clinical point of view. This approach needs prior information on interindividual variability. Consequently many reports have been

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published on the interindividual variation in dose-concentration relationship of drugs in dosage adjustment. However little attention has been paid, to date, to the intraindividual variation, including the circadian rhythm of pharmacokinetics, in dosage adjustment.

The circadian stage-dependent changes in kinetic aspects of drugs have been reported for many drugs as a function of the time of day of administration. These drugs include sodium valproate,⁵⁻⁷⁾ theophylline,⁸⁾ amitriptyline,⁹⁾ diazepam,¹⁰⁾ acetaminophen,¹¹⁾ phenacetin,¹¹⁾ salicylate¹²⁾ and ethanol.¹³⁾ However, the relationship between the circadian stage-dependent kinetics of these drugs and the accuracy in predicting plasma drug concentration is not clear at present, although the dosage optimisation using limited number of plasma concentrations is reported to require an appropriate knowledge of the time of sampling.^{14,15)}

This study was designed to examine how the dosing time of the day influences the accuracy in predicting plasma VPA concentrations at steady state by using VPA, a widely used antiepileptic drug.

Methods

Eight male Japanese medical students (age; mean $\pm$ S. D. = 24.0 ± 2.3 years, body weight; 62.5 ± 6.9 kg) participated in this study. None had evidence of identifiable medical or psychiatric disease or was taking any drugs. Informed consent for the study was obtained. Meals before drug administration on each study day were controlled to fit the subject's usual food contents and amount. They took breakfast between 08:00 and 08:15 in the morning trial and supper between 18:00 and 18:30 in the evening trial. Subjects ingested no other food or liquid for 4 hr after each dose. VPA (Depakene®, Kyowa Hakko Kogyo Co. Ltd., Japan), 400 mg in tablet form, was orally administered to each subject for 9 days on the twice-daily basis (08:30 and 20:30). Venous blood samples were drawn immediately before drug administration and 0.5, 1, 2, 3, 4, 6, 8 and 12 hr after morning and evening doses on the eighth day and then 2 and 12 hr after morning and evening doses on ninth day of repeated administration. Plasma VPA concentrations were measured by a homogeneous enzyme immunoassay technique

(EMIT®, SYVA).

Individual pharmacokinetic parameters were determined separately for morning and evening trials from the time-course of 9 plasma VPA concentrations after dosing on the eighth day of repeated administration. The pharmacokinetic parameters (K_a , V_d and CL etc.) obtained using one-compartment model were compared between morning and evening trials. Then, the effect of the dosing time of day on the accuracy to predict plasma VPA concentrations was examined by using individual pharmacokinetic parameters. Target points for prediction were plasma VPA concentrations at 2 hr (around C_{max}) and at 12 hr (around C_{min}) after morning and evening doses on the ninth day of repeated administration. The accuracy to predict these target points was compared by using the individual pharmacokinetic parameters obtained from morning trial on the eighth day.

After that, the effects of the dosing time of day and sampling time on the predictive accuracy were examined by Bayesian approach. The sources of population pharmacokinetic parameters for Bayesian approach were means and variances of pharmacokinetic parameters obtained from the morning trial on the eighth day. The source of one plasma VPA concentration was plasma VPA concentration at 0.5, 1, 2, 3, 4, 6, 8 or 12 hr after morning dose on the eighth day. Target points for prediction were plasma VPA concentrations at 2 and 12 hr after morning and evening doses on ninth day. The accuracy to predict these target points was compared by using the population pharmacokinetic parameters and one plasma VPA concentration obtained from morning trial on the eighth day. Additionally, individual pharmacokinetic parameters obtained from Bayesian approach were compared with the actual individual pharmacokinetic parameters obtained using all 9 plasma samples in the morning or in the evening trial on the eighth day. The effect of sampling time on the predictive accuracy of plasma VPA concentrations and pharmacokinetic parameters was then examined through all the sampling points described above.

Pharmacokinetic models

All data were analyzed using the program for one-compartment model implemented on NEC PC-9801 microcomputer. Bayesian approach was carried out using a modification of the program

"PEDA (parameter estimation and dosage adjustment)" with high flexibility and stability in clinical practice.¹⁶⁾ The objective function is minimized with a Gauss-Newton method with a damping factor.¹⁷⁾ The population pharmacokinetic parameters are shown in Tab. 1. The weight of concentration was set to 15% of the measured concentrations with consideration of both a measurement error and a degree of model misspecification.

Statistical analysis

Differences in pharmacokinetic parameters between morning and evening trials except observed $t_{\max}$ were assessed by the paired t-test. Difference in observed $t_{\max}$ between two trials were evaluated by the Wilcoxon matched-pairs signed-ranks test. Significance was defined as $P < 0.05$.

The following errors suggested by Sheiner and Beal¹⁸⁾ were used for an evaluation of predictive

accuracy.

$$ME = \frac{1}{n} \sum_{i=1}^n P_e \quad (1)$$

$$RMSE = \left\{ \frac{1}{n} \sum_{i=1}^n P_e^2 \right\}^{1/2} \quad (2)$$

In the equations, prediction error (P_e) means the difference between the predicted value and the actual value; mean prediction error (ME) means an index of bias; root mean squared error (RMSE) means a composite index of bias and precision; and n is the number of predictions. To express relative prediction errors (%ME and %RMSE), P_e was substituted with (predicted value - actual value)/(actual value) in equation (1) and (2). Significance is defined as $P < 0.05$ and was determined by the 95% confidence intervals (C.I.) of the ME, %ME, RMSE and %RMSE.

Results

The plasma VPA concentration-time profiles and VPA pharmacokinetic parameters are shown in Fig. 1 and Tab. 2. $C_{\max}$ was higher ($P < 0.01$), K_a was larger ($P < 0.05$) and $t_{\max}$ was shorter ($P < 0.05$) in the morning trial than in the evening trial. There was no significant difference between any other pharmacokinetic parameters in morning and evening trials.

Tab. 1 Summary of Population Pharmacokinetic Parameters

	K_a (1/hr)	V_d (L)	CL (L/hr)
Mean	1.57	7.16	0.397
CV (%)	(26.8)	(18.0)	(10.6)

These values were obtained from the morning trial on the eighth day of repeated doses.

Fig. 1 Mean ($\pm$ SE) total plasma VPA concentrations after repeated, oral, 400-mg doses in the morning ($\bullet$) or in the evening ($\circ$).

Tab. 2 VPA Pharmacokinetic Parameters after Repeated, Oral, 400-mg Doses in the Morning or in the Evening

Time of drug administration	K_a (1/hr)	C_{max} (μ g/ml)	t_{max} (hr)	AUC (μ g·hr/ml)	V_d (l/kg)	CL (ml/kg/hr)	K_e (1/hr)	$t_{(1/2)}$ (hr)
Morning Mean (08 : 30) (SD)	1.57 (0.42)	99.7 (8.8)	1.50 (0.53)	882 (92)	0.117 (0.025)	6.40 (0.80)	0.057 (0.011)	12.6 (2.7)
Evening Mean (20 : 30) (SD)	0.74 (0.49)	88.8 (7.9)	2.88 (0.64)	841 (103)	0.112 (0.033)	6.74 (0.96)	0.064 (0.020)	11.6 (3.0)
Statistical significance	$P < 0.05$	$P < 0.01$	$P < 0.05$	NS	NS	NS	NS	NS

$P < 0.01$, $P < 0.05$; when compared between morning and evening by paired t-test or Wilcoxon matched pairs signed-ranks test (two-tailed). C_{max} and t_{max} are presented in the observed values.

Tab. 3 Comparison of Accuracy in Prediction of Plasma VPA Concentration (C_p) after Morning and Evening Doses by Using Individual Pharmacokinetic Parameters Obtained from Morning Trial

Target C_p (μ g/ml)	ME (95% C.I.)	%ME (95% C.I.)	RMSE (95% C.I.)	%RMSE (95% C.I.)
C_p at 2 hr after morning dose	-2.83 (-9.56, 3.89)	-2.4 (-9.1, 4.3)	8.04 (0, 12.60)	7.9 (0, 12.0)
C_p at 2 hr after evening dose	9.61 (1.50, 17.70) ^{a)}	12.8 (2.6, 23.1) ^{a)}	13.19 (2.75, 18.50)	17.2 (5.6, 23.7)
C_p at 12 hr after morning dose	-1.51 (-4.45, 1.43)	-2.9 (-8.6, 2.8)	3.62 (0, 5.61)	7.0 (0, 11.0)
C_p at 12 hr after evening dose	-2.39 (-6.25, 1.48)	-4.1 (-11.1, 3.0)	4.94 (0, 7.15)	8.9 (0, 12.9)

^{a)} Significantly overestimated the true concentrations, $P < 0.05$.

Tab. 4 Comparison of Accuracy in Prediction of Plasma VPA Concentration (C_p) after Morning and Evening Doses by Using Population Parameters and One C_p Obtained from Morning Trial

Sampling time: Time after morning dose (hr)	Target C_p :		Target C_p :	
	C_p (μ g/ml) at 2 hr after morning dose		C_p (μ g/ml) at 2 hr after evening dose	
	ME (95% C.I.)	RMSE (95% C.I.)	ME (95% C.I.)	RMSE (95% C.I.)
0.5	-5.08 (-13.10, 2.92)	10.30 (0, 15.10)	7.36 (-0.63, 15.40)	11.58 (6.30, 15.10)
1	-2.49 (-11.70, 6.69)	10.58 (3.32, 14.60)	9.95 (0.97, 18.90) ^{a)}	14.14 (6.00, 19.10)
2	-1.51 (-10.00, 6.97)	9.61 (0, 13.90)	10.90 (2.84, 19.00) ^{a)}	14.18 (5.40, 19.30)
3	-2.62 (-11.50, 6.22)	10.25 (0, 15.60)	9.82 (1.72, 17.90) ^{a)}	13.34 (4.56, 18.30)
4	-4.59 (-14.00, 4.86)	11.53 (0, 17.40)	7.85 (0.40, 15.30) ^{a)}	11.45 (4.23, 15.60)
6	-4.54 (-12.70, 3.62)	10.20 (0, 15.50)	7.90 (0.90, 14.90) ^{a)}	11.09 (3.52, 15.30)
8	-4.52 (-12.30, 3.27)	9.81 (0, 14.70)	7.92 (0.82, 15.00) ^{a)}	11.22 (5.80, 14.80)
12	-2.60 (-11.70, 6.54)	10.54 (0, 15.80)	9.83 (2.77, 16.90) ^{a)}	12.61 (3.95, 17.40)
Sampling time: Time after morning dose (hr)	Target C_p :		Target C_p :	
	C_p (μ g/ml) at 12 hr after morning dose		C_p (μ g/ml) at 12 hr after evening dose	
	ME (95% C.I.)	RMSE (95% C.I.)	ME (95% C.I.)	RMSE (95% C.I.)
0.5	-3.28 (-7.69, 1.12)	5.92 (0, 8.53)	-4.16 (-9.79, 1.47)	7.55 (0, 11.00)
1	-1.46 (-6.48, 3.55)	5.80 (2.05, 7.94)	-2.34 (-8.58, 3.90)	7.37 (0, 10.60)
2	-0.80 (-5.67, 4.07)	5.50 (2.68, 7.31)	-1.68 (-7.70, 4.35)	6.95 (2.85, 9.41)
3	-1.47 (-6.36, 3.42)	5.67 (2.87, 7.48)	-2.35 (-8.25, 3.56)	7.01 (2.78, 9.52)
4	-3.02 (-6.78, 0.75)	5.18 (1.92, 7.07)	-3.89 (-8.63, 0.85)	6.57 (1.30, 9.21)
6	-3.22 (-6.97, 0.53)	5.29 (1.50, 7.32)	-4.09 (-8.83, 0.64)	6.69 (1.79, 9.29)
8	-3.57 (-6.96, -0.19) ^{b)}	5.21 (0.79, 7.32)	-4.45 (-9.17, 0.27)	6.91 (0, 10.10)
12	-1.19 (-3.94, 1.56)	3.30 (1.47, 4.42)	-2.07 (-6.17, 2.04)	5.04 (0.72, 7.09)

^{a)} Significantly overestimated the true concentrations, $P < 0.05$

^{b)} Significantly underestimated the true concentrations, $P < 0.05$

Table 3 shows prediction errors for VPA target concentrations by using individual pharmacokinetic parameters. The individual pharmacokinetic parameters obtained from the morning trial were better sources for the prediction of VPA concentrations at 2 hr after morning dose. However, the prediction of VPA concentrations at 2 hr after evening dose produced about one and half times larger RMSE and more than two times larger %RMSE than that after morning dose. The ME and %ME were significantly biased toward overestimating the target concentration; i.e., the 95% confidence

interval of the ME and %ME did not include zero. On the other hand, the prediction of VPA concentrations at 12 hr after dosing showed no statistical difference between both predictive performances.

Table 4 shows prediction errors for VPA target concentrations by Bayesian approach. The pharmacokinetic parameters obtained from morning trial were better sources for the prediction of VPA concentrations at 2 hr after morning dose. However, they were worse sources for that after evening dose. That is, the RMSE tended to be larger, when the concentration values at 1, 2 and 3 hr

Tab. 5 Comparison of Accuracy in Prediction of Pharmacokinetic Parameters after Morning and Evening Doses by Using Population Parameters and One C_p Obtained from Morning Trial

Sampling time: Time after morning dose (hr)	Target parameter:		Target parameter:	
	K_a (1/hr) after morning dose		K_a (1/hr) after evening dose	
	ME (95% C.I.)	RMSE (95% C.I.)	ME (95% C.I.)	RMSE (95% C.I.)
0.5	-0.055 (-0.373, 0.263)	0.361 (0, 0.543)	0.771 (0.292, 1.250) ^{a)}	0.939 (0.554, 1.210)
1	0.019 (-0.310, 0.348)	0.369 (0, 0.544)	0.845 (0.413, 1.280) ^{a)}	0.974 (0.578, 1.250)
2	0.013 (-0.336, 0.362)	0.391 (0, 0.590)	0.839 (0.423, 1.260) ^{a)}	0.960 (0.587, 1.220)
3	0.003 (-0.349, 0.354)	0.394 (0, 0.599)	0.829 (0.417, 1.240) ^{a)}	0.948 (0.576, 1.210)
4	0.010 (-0.343, 0.364)	0.396 (0, 0.602)	0.837 (0.428, 1.250) ^{a)}	0.953 (0.582, 1.220)
6	0.012 (-0.341, 0.365)	0.395 (0, 0.606)	0.838 (0.428, 1.250) ^{a)}	0.956 (0.586, 1.220)
8	0.014 (-0.342, 0.369)	0.397 (0, 0.609)	0.840 (0.432, 1.250) ^{a)}	0.956 (0.591, 1.220)
12	0.002 (-0.349, 0.353)	0.392 (0, 0.600)	0.828 (0.414, 1.240) ^{a)}	0.949 (0.577, 1.210)
Sampling time: Time after morning dose (hr)	Target parameter:		Target parameter:	
	V_d (l) after morning dose		V_d (l) after evening dose	
	ME (95% C.I.)	RMSE (95% C.I.)	ME (95% C.I.)	RMSE (95% C.I.)
0.5	0.037 (-1.020, 1.100)	1.183 (0, 1.730)	0.241 (-1.400, 1.880)	1.847 (0.546, 2.550)
1	-0.045 (-1.100, 1.010)	1.183 (0, 1.750)	0.159 (-1.460, 1.780)	1.822 (0.489, 2.530)
2	-0.107 (-1.180, 0.970)	1.208 (0, 1.820)	0.097 (-1.560, 1.760)	1.860 (0.390, 2.600)
3	-0.033 (-1.110, 1.050)	1.208 (0, 1.750)	0.171 (-1.440, 1.780)	1.811 (0.498, 2.510)
4	0.050 (-1.020, 1.120)	1.196 (0, 1.740)	0.254 (-1.370, 1.880)	1.836 (0.568, 2.530)
6	0.000 (-1.080, 1.080)	1.208 (0, 1.780)	0.203 (-1.460, 1.870)	1.873 (0.619, 2.580)
8	-0.072 (-1.140, 0.992)	1.192 (0, 1.760)	0.131 (-1.620, 1.880)	1.960 (0.612, 2.700)
12	0.024 (-0.963, 1.010)	1.105 (0, 1.620)	0.227 (-1.470, 1.920)	1.913 (0.752, 2.600)
Sampling time: Time after morning dose (hr)	Target parameter:		Target parameter:	
	CL (l/hr) after morning dose		CL (l/hr) after evening dose	
	ME (95% C.I.)	RMSE (95% C.I.)	ME (95% C.I.)	RMSE (95% C.I.)
0.5	0.008 (-0.016, 0.033)	0.029 (0.016, 0.038)	-0.013 (-0.051, 0.026)	0.045 (0, 0.065)
1	-0.004 (-0.034, 0.026)	0.034 (0.012, 0.047)	-0.025 (-0.067, 0.017)	0.054 (0, 0.078)
2	-0.008 (-0.039, 0.022)	0.035 (0.013, 0.048)	-0.030 (-0.071, 0.012)	0.055 (0, 0.081)
3	-0.004 (-0.034, 0.027)	0.034 (0.017, 0.045)	-0.025 (-0.065, 0.015)	0.051 (0, 0.073)
4	0.007 (-0.018, 0.031)	0.028 (0.017, 0.037)	-0.014 (-0.051, 0.022)	0.043 (0, 0.064)
6	0.007 (-0.012, 0.027)	0.023 (0.012, 0.031)	-0.014 (-0.044, 0.017)	0.037 (0.013, 0.051)
8	0.009 (-0.008, 0.025)	0.021 (0, 0.030)	-0.012 (-0.040, 0.016)	0.034 (0.016, 0.045)
12	-0.004 (-0.028, 0.020)	0.027 (0.007, 0.038)	-0.025 (-0.056, 0.006)	0.042 (0, 0.065)

^{a)} Significantly overestimated the true value, $P < 0.05$

after morning dose were used. The ME was consistently and significantly biased toward overestimating the target VPA concentrations through all the sampling points evaluated except at 0.5 hr after morning dose. On the other hand, the prediction of VPA concentrations at 12 hr after morning and evening doses showed no significant difference between the two target points. The prediction using one plasma VPA concentration at 12 hr after morning dose tended to show smaller RMSE for both target points as compared with that using any other plasma VPA concentration than 12 hr. The ME was significantly biased toward underestimating the target VPA concentration after morning dose, when the concentration values at 8 hr after morning dose were used.

Table 5 shows prediction errors for individual pharmacokinetic parameters (K_a , V_d and CL) by Bayesian approach. The pharmacokinetic parameters obtained from morning trial were better sources for the prediction of K_a value after morning dose. However, they were worse sources for that after evening dose. The mean RMSE in the prediction of K_a value after evening dose was about three times larger than that after morning dose. The ME was consistently and significantly biased toward overestimating the K_a value through all the sampling points evaluated. The predictions of V_d and CL values after morning dose showed smaller RMSE as compared with those after evening dose. Estimates in K_a and V_d values were not influenced by the choice of sampling time. However, predictive accuracy in CL value tended to be improved slightly when one plasma VPA concentration was obtained during elimination phase irrespective of the source of target pharmacokinetic parameters.

Discussion

The present findings of higher C_{max} , larger K_a and shorter t_{max} after morning dose reflecting circadian changes in VPA absorption are similar to that previously reported,^{5,6)} but these results are in contrast to an increase in VPA clearance after evening dose found by other.⁷⁾ The discrepancy may be due to the different experimental design, because VPA has the different kinetics depending on the dose^{19,20)} or the duration of drug administration.²¹⁾ However, consistent circadian changes in VPA absorption were found in these studies.

In the predictive performance based on the individual pharmacokinetic parameters obtained from morning trial, the predictive accuracy of the VPA concentrations around C_{min} did not differ irrespective of the source of target points. The predictive accuracy for VPA concentration around C_{max} after morning dose was better, but that for VPA concentration after evening dose was significantly biased toward overestimation. The reason for overestimation seems to be closely related to the larger K_a value used for the prediction. Namely the K_a obtained from morning trial was significantly larger than that obtained from evening trial. Also, target points around C_{max} are significantly lower after evening dose than after morning dose (mean $\pm$ S.D. = 81.4 ± 10.5 and 93.8 ± 11.8 , $P < 0.05$), although no difference was demonstrated in those around C_{min} . Certainly an improvement in bias and precision must be found, if the pharmacokinetic parameters obtained from the evening trial are used for the prediction. These results suggest that the predictive accuracy of VPA concentration is improved when the time-of-day matched pharmacokinetic parameters are used.

The predictive performance based on the Bayesian approach also showed close similarity to that based on individual pharmacokinetic parameter. That is, population pharmacokinetic parameters and one plasma sample obtained from morning trial were better source for the prediction of VPA concentrations around C_{max} after morning dose, but worse sources for that after evening dose. Similarly, they could predict exactly the K_a value after morning dose, but overestimated significantly that after evening dose and produced larger RMSE. Therefore the overestimation of the target points around C_{max} after evening dose is clearly influenced by that of K_a value produced by using population parameters obtained from morning trial.

Accurate initial population parameter selections are essential in Bayesian approach. For this purpose, programs such as NONMEM have been successfully applied to phenytoin,²⁾ digoxin,²²⁾ gentamicin,²²⁾ theophylline²³⁾ and procainamide²⁴⁾ etc. For example, the CL values are expressed as linear model of renal function via creatinine clearance and body weight. The V_d values are closely related to body weight and/or creatinine clearance. However the values of K_a are usually obtained from the literature. The trial of dividing the

population into subpopulations has not been examined. The report published by Higuchi et al.²⁵⁾ indicated that K_a is insensitive in the optimisation process using less informative samples. Therefore, K_a value might be fixed at population mean in the dosage adjustment based on the Bayesian approach. In fact K_a value did not change largely through all the sampling points evaluated in the present study. But the predictive accuracy in K_a value will be improved, if the time-of-day matched population parameters and one plasma concentration value are used. Therefore, more appropriate estimates in K_a value can be obtained if the population are divided into subpopulations on the basis of variables such as the time of drug administration.

There are reports concerning significance of the choice of sampling time on the predictive accuracy of plasma drug concentrations.^{14,15)} In the present study, the accuracy in predicting plasma VPA concentration around C_{max} did not differ irrespective of the choice of sampling time. On the other hand, as for the prediction of plasma VPA concentration around C_{min} , smaller RMSE is associated with the use of plasma concentration values obtained during elimination phase. Although estimates in K_a and V_d values were not largely influenced by the choice of sampling time, predictive accuracy in CL value tended to be improved when one plasma concentration value during elimination phase was used. These results suggest that sampling time may become an important factor as far as the prediction of CL value and that of plasma VPA concentration around C_{min} at steady state are concerned. However, the effect of circadian dependent changes in VPA kinetics on the prediction of VPA concentration around C_{max} after dose seems to be more important at least in predictive performance as evidenced by larger prediction error.

In this study, the effect of circadian stage-dependent VPA kinetics on the predictive accuracy was investigated especially in relation to VPA absorption phase. Generally, drug concentrations are influenced by the rate of four pharmacokinetic factors including absorption, distribution, metabolism and excretion of drug. Also, the circadian rhythm in pharmacokinetics of drugs has been reported to be affected by the rhythm in the rates of absorption,⁵⁻¹⁰⁾ distribution,^{10,11)} metabolism¹¹⁾ and excretion^{12,13)} of drugs. It might be important to investigate the effect of circadian stage-dependent

kinetics on the predictive accuracy of the concentrations of theophylline,⁸⁾ amitriptyline,⁹⁾ diazepam,¹⁰⁾ acetaminophen,¹¹⁾ phenacetin,¹¹⁾ salicylate¹²⁾ and ethanol.¹³⁾ Especially, further studies on drugs with a more narrow therapeutic range like theophylline⁸⁾ are necessary.

In one limitation on present Bayesian approach, since population parameters were selected from the same population as subjects used for predictive performance, the present finding may differ from that found in clinical practice. However, the importance of the circadian stage-dependent kinetics of VPA in predictive performance must also be reproduced in routine therapeutic drug monitoring, if appropriate estimate of population parameters is done. Because the importance of time in the circadian stage at which the target points are used for the prediction were found in the approach based on individual pharmacokinetics and the usefulness of Bayesian approach has been found for monitoring drug therapy.¹⁻⁴⁾ The present results suggest that the intraindividual variability, such as circadian rhythm, as well as interindividual variability become influencing factors to predict plasma drug concentrations.

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References

- 1) Sheiner, L. B., Beal, S. L., Rosenberg, B. et al.: Forecasting individual pharmacokinetics. *Clin. Pharmacol. Ther.*, **26**: 294-305 (1979).
- 2) Sheiner, L. B. and Beal, S. L.: Evaluation of methods for estimating population pharmacokinetic parameters. I. Michaelis-menten model: routine clinical pharmacokinetic data. *J. Pharmacokinet. Biopharm.*, **8**: 553-571 (1980).
- 3) Sheiner, L. B., Rosenberg, B. and Marathe, V. V.: Estimation of population characteristics of pharmacokinetic parameters from routine clinical data. *J. Pharmacokinet. Biopharm.*, **5**: 445-479 (1977).
- 4) Sheiner, L. B. and Beal, S. L.: Bayesian individualization of pharmacokinetics: Simple implementation and comparison with non-Bayesian methods. *J. Pharm. Sci.*, **71**: 1344-1348 (1982).
- 5) Nakano, S., Watanabe, H., Ohdo, S. et al.: Circadian stage-dependent changes in diazepam and valproate kinetics in man: a single and

- repetitive administration study. *Annu. Rev. Chronopharmacol.*, **3**: 421-424 (1986).
- 6) Loiseau, P., Cenraud, B., Levy, R.H. et al.: Diurnal variations in steady-state plasma concentrations of valproic acid in epileptic patients. *Clin. Pharmacokinet.*, **7**: 544-552 (1982).
 - 7) Bauer, L.A., Davis, R., Wilensky, A. et al.: Diurnal variation in valproic acid clearance. *Clin. Pharmacol. Ther.*, **35**: 505-509 (1984).
 - 8) Watanabe, H., Nakano, S., Nagai, K. et al.: Time-dependent absorption of theophylline in man. *J. Clin. Pharmacol.*, **24**: 509-514 (1984).
 - 9) Nakano, S. and Hollister, L.E.: Chronopharmacology of amitriptyline. *Clin. Pharmacol. Ther.*, **33**: 453-459 (1983).
 - 10) Nakano, S., Watanabe, H., Nagai, K. et al.: Circadian stage-dependent changes in diazepam kinetics. *Clin. Pharmacol. Ther.*, **36**: 271-277 (1984).
 - 11) Shively, C.A. and Vesell, E.S.: Temporal variations in acetaminophen and phenacetin half-life in man. *Clin. Pharmacol. Ther.*, **18**: 413-424 (1975).
 - 12) Reinberg, A., Zagula-Mally, Z., Ghata, J. et al.: Circadian rhythms in duration of salicylate excretion referred to phase of excretory rhythm and routine. *Proc. Soc. Exp. Biol. Med.*, **124**: 826-832 (1967).
 - 13) Minors, D.S. and Waterhouse, J.M.: Aspects of chronopharmacokinetics and chronergy of ethanol in healthy man. *Chronobiologia*, **7**: 465-480 (1980).
 - 14) May, C.A. and Garnett, W.R.: Prediction of steady-state concentrations of valproic acid as determined from single plasma concentrations after the first dose. *Clin. Pharm.*, **2**: 143-147 (1983).
 - 15) Wilkens, J.H., Neuenkirchen, H., Sybrecht, G. W. et al.: Individualizing theophylline dosage: evaluation of a single-point maintenance dose prediction method. *Eur. J. Clin. Pharmacol.*, **26**: 491-498 (1984).
 - 16) Higuchi, S., Aoyama, T. and Horioka, M.: PEDDA: a microcomputer program for parameter estimation and dosage adjustment in clinical practice. *J. Pharmacobio-Dyn.*, **10**: 703-718 (1987).
 - 17) Hartley, H.O.: The modified Gauss-Newton method for the fitting of non-linear regression functions by least squares. *Technometrics*, **3**: 269-280 (1961).
 - 18) Sheiner, L.B. and Beal, S.L.: Some suggestions for measuring predictive performance. *J. Pharmacokinet. Biopharm.*, **9**: 503-512 (1981).
 - 19) Turnbull, D.M., Rawlins, M.D., Weightman, D. et al.: Plasma concentrations of sodium valproate: their clinical value. *Ann. Neurol.*, **14**: 38-42 (1983).
 - 20) May, T. and Rambeck, B.: Serum concentrations of valproic acid: influence of dose and comedication. *Ther. Drug Monit.*, **7**: 387-390 (1985).
 - 21) Hall, K., Otten, N., Irvine-Meek, J. et al.: First-dose and steady-state pharmacokinetics of valproic acid in children with seizures. *Clin. Pharmacokinet.*, **8**: 447-455 (1983).
 - 22) Benet, L.Z. and Sheiner, L.B.: Design and optimization of dosage regimens; pharmacokinetic data. Gilman, A.G., Goodman, L.S., Rall, T.W., Murad, F. (Eds.): *The Pharmacological Basis of Therapeutics*, 7th ed., Macmillan, New York, pp. 1663-1733 (1985).
 - 23) Jusko, W.J., Gardner, M.J., Mangione, A. et al.: Factors affecting theophylline clearances. *J. Pharm. Sci.*, **68**: 1358-1366 (1979).
 - 24) Grasela, T.H. and Sheiner, L.B.: Population pharmacokinetics of procainamide from routine clinical data. *Clin. Pharmacokinet.*, **9**: 545-554 (1984).
 - 25) Higuchi, S., Ieiri, I. and Aoyama, T.: Predictive performance of Bayesian method in a simulation work: one-compartment open linear model containing an oral route. *Jpn. J. Clin. Pharmacol. Ther.*, **19**: 597-606 (1988).