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Population pharmacokinetics of topiramate in Japanese pediatric and adult patients with epilepsy using routinely monitored data

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Short title: Population pharmacokinetics of topiramate

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Abstract

Background: Topiramate is a second-generation antiepileptic drug used as monotherapy and adjunctive therapy in adults and children with partial seizures. A population pharmacokinetic analysis was performed to improve the topiramate dosage adjustment for individualized treatment.

Methods: Patients whose steady-state serum concentration of topiramate was routinely monitored at Kyoto University Hospital from April 2012 to March 2013 were included in the model-building data. A nonlinear mixed effects modeling program (NONMEM) was used to evaluate the influence of covariates on topiramate pharmacokinetics. The obtained population pharmacokinetic model was evaluated by internal model validations, including goodness-of-fit plots and prediction-corrected visual predictive checks, and was externally confirmed using the validation data from January 2015 to December 2015.

Results: A total of 177 steady-state serum concentrations from 93 patients were used for the model-building analysis. The patients' age ranged from 2 to 68 years, and body weight ranged from 8.6 to 105 kg. The median serum concentration of topiramate was 1.7 μg/mL, and half of the patients received carbamazepine co-administration. Based on a one-compartment model with first order absorption and elimination, the apparent volume of distribution was 105 L/70 kg, and the apparent clearance was allometrically related to the body weight as 2.25 L/h/70 kg without carbamazepine or phenytoin. Combination treatment with carbamazepine or phenytoin increased the apparent clearance to 3.51 L/h/70 kg. Goodness-of-fit plots, prediction corrected visual predictive check, and external validation using the validation data from 43 patients confirmed an appropriateness of the final model. Simulations based on the final model showed

that dosage adjustments allometrically scaling to body weight can equalize the serum concentrations in children of various ages as well as adults.

Conclusion: The population pharmacokinetic model, using the power scaling of body weight, effectively elucidated the topiramate serum concentration profile ranging from pediatric to adult patients. Dosage adjustments based on body weight and concomitant antiepileptic drug help obtain the dosage of topiramate necessary to reach an effective concentration in each individual.

Keywords: topiramate; epilepsy; population pharmacokinetics; allometric scaling; CYP inducer

Topiramate is a second-generation antiepileptic drug (AED) that has been approved for the treatment of both adults and children with partial seizures as mono- or adjunctive therapy.[1, 2] Since topiramate is reported to have multiple mechanisms of action,[1, 3, 4] it is expected to have a therapeutic effect on different types of epileptic seizures for which previous treatment had no effect. The package information recommends that the daily dosage of topiramate is 200 - 400 mg for adults and 6 mg/kg for children, and is administered orally twice a day. According to the therapeutic drug monitoring (TDM) guidelines of the International League Against Epilepsy (ILAE),[5] the effective serum topiramate concentration is considered to be between 5 and 20 μg/mL, which is slightly higher than that reported in a previous study;[6] however, the usefulness of topiramate TDM has not been established.

Topiramate is metabolized by cytochrome P450 (CYP) 3A4, and half of the dose is excreted unaltered by the kidneys.[7] Topiramate exhibits a relatively long plasma half-life (20 - 30 h), and in patients co-medicated with enzyme-inducing AEDs (e.g., carbamazepine, phenytoin, and phenobarbital), the half-life becomes reduced by as much as 50%.[1, 8] A pharmacokinetic linearity is reported over the dose range of 100 - 800 mg.[4, 8, 9] To date, several population pharmacokinetic (PPK) analyses of topiramate have reported some significant covariates of topiramate apparent clearance (CL/F), such as age, body weight, renal function, and concomitant AEDs.[10-12] However, previous PPK studies have been performed primarily on only pediatric or adult populations.

In this study, we aimed to identify potential covariates and to develop a PPK model of topiramate using routinely monitored serum concentration data from patients with epilepsy of different ages (including pediatric and adult patients). In addition, to improve the individualized

dose regimen of topiramate, a simulation study based on the obtained PPK model was conducted.

MATERIALS AND METHODS

Patients and Data Collection

Japanese inpatients and outpatients with epilepsy whose steady-state serum topiramate concentrations were measured at Kyoto University Hospital from April 2012 to March 2013 were included in the model-building data used to develop a PPK model of topiramate. In addition, the patients whose steady-state serum concentrations of topiramate were measured from January 2015 to December 2015 were included in the validation data, which were used to evaluate the obtained PPK model. The patients included in the model-building data were excluded from the validation data. For each patient, the following data were retrospectively collected from the electronic medical records: topiramate serum concentration, dosage, time of dosing and sampling, body weight, height (for patients aged less than 16 years), gender, age, concomitant AEDs, and clinical laboratory data (e.g., aspartate aminotransferase [AST], alanine aminotransferase [ALT], and estimated glomerular filtration rate [eGFR]). For patients aged younger than 16 years, the eGFR was calculated using the Schwartz formula,[13] and patients whose height or body weight were missing were excluded from the dataset. The serum topiramate concentrations were routinely determined by the previously reported method of high-performance liquid chromatography with tandem mass spectrometry (LC-MS/MS),[14] which had a lower limit of quantification of 0.2 μg/mL. The measurements under the lower limit of quantification were fixed to 0.1 μg/mL in accordance with the previous report.[15] This

study was performed in accordance with the Declaration of Helsinki and its amendments, and was approved by the Ethics Committee of Kyoto University Graduate School and School of Medicine and Kyoto University Hospital.

PPK modeling

The PPK analysis was undertaken using the nonlinear mixed-effects modeling program (NONMEM) version 7.2.0 (ICON, Ellicott City, MD) with the first-order conditional estimation method with interaction. The structural model used was a one-compartment model, and the interindividual variability (IIV) of the pharmacokinetic parameters was estimated with the proportional error model. The residual variability of the topiramate concentration was selected according to the comparison between additive, proportional, and mixed (additive and proportional) error models. Due to the lack of data in the absorption phase, only the CL/F and V/F were estimated, and the absorption rate constant (Ka) was fixed to 2 h^{-1} of the literature value.[10]

The influence of each covariate on CL/F was evaluated based on the change in the objective function value (OFV) between the previous model and the model including the covariate. The OFV changes were considered significant at a minimum value of 3.84 (chi-square test; $P < 0.05$), and 7.88 (chi-square test; $P < 0.005$) per one additional parameter via the stepwise forward inclusion and the stepwise backward elimination method, respectively. The model including all covariates that were considered statistically significant by these stepwise methods was defined as the final model.

For the scale parameter, the effect of body weight was analyzed using the following

allometric model:

$$CL/F = \theta_1 \times (\mathrm{BW}/70)^{\theta_2}$$

where θ_1 and θ_2 are the mean parameter to be estimated. BW indicates the body weight of each patient and 70 kg is an ideal standard body weight. Covariates, such as gender, age, dose, AST, ALT, eGFR, and concomitant AEDs (e.g., phenytoin, phenobarbital, carbamazepine, levetiracetam, valproic acid, and gabapentin) were tested in the covariate model. For the categorical covariates (e.g., gender and existence of each concomitant AED), a covariate analysis was performed using the following model:

$$CL/F = \theta_1 \times \theta_3{}^{COV}$$

where COV is 1 for patients who are co-treated with each AED, and otherwise 0 when evaluating the influence of concomitant AED, and COV is 1 in male patients, or 0 for females when evaluating the influence of gender; $\theta_1$and θ_3 are the mean parameters to be estimated. Regarding the other continuous covariates, a covariate analysis was performed using the following model:

$$CL/F = \theta_1 \times \left(\frac{COV}{COV_{medain}}\right)^{\theta_4}$$

where $\theta_1$and θ_4 are the mean parameter to be estimated. COV indicates the value of each patient and COV_{median} is the median value of the model-building data, which are 31, 18, 14, 95.6, and 2.31 for age, AST, ALT, eGFR, and dose (mg/kg/day), respectively.

Model evaluation

The final model was extensively evaluated using internal model validations, including

goodness-of-fit plots and prediction-corrected visual predictive checks (pcVPC),[16] and was externally confirmed using the validation data. The goodness-of-fit plots were as follows: observed concentration (OBS) *vs.* population-predicted value (PRED) or individual predicted value (IPRED), and conditional weighted residuals (CWRES) *vs.* PRED, time after dosing, body weight, and eGFR to identify any bias corresponding to model miss-specification. To assess the predictive ability of the model, pcVPC was performed by using the simulation of 200 data sets from the final model. The 5th, 50th, 95th percentile curves of the observed data were overlaid on the 90% confidence interval (CI) of the 5th, 50th, and 95th simulated percentiles, and evaluated visually.

For the external validation, pcVPC was performed (200 data sets) against the new data set (validation data), and the predictive ability of the final model was graphically evaluated once again. In addition, to quantitatively assess the bias and precision, the prediction error (PE%), mean prediction error (MPE%), and the root mean squared prediction error (RMSE%) were calculated as described below:[17, 18]

$$PE_i\% = \frac{IPRED_i - OBS_i}{IPRED_i} \times 100$$

$$MPE\% = \frac{1}{N}\sum_{i=1}^{N} PE_i\%$$

$$RMSE\% = \left(\frac{1}{N}\sum_{i=1}^{N} PE_i\%^2\right)^{1/2}$$

where OBS_i is the observed concentration of topiramate for the *i*th patient and $IPRED_i$ is the individually predicted concentration of topiramate corresponding to the observed data. N

denotes the number of blood samples. Each 95% confidence interval was estimated using the bootstrap method (N = 1000).

Finally, to assess the stability and robustness of the final model, the model-building and validation data were combined into the integrated data, and the PPK parameters were estimated. The results were compared with the PPK parameters using the model-building data.

Simulation

The simulation for serum topiramate concentration was performed using the final PPK model and parameters using the model-building data. We assumed typical patients weighing 10, 20, 50, or 70 kg, who were not co-administered with the AED inducer (carbamazepine or phenytoin). In the first simulation, the dose of topiramate was fixed to 6 mg/kg/day, in accordance with the package information for the children, and 200 simulations were performed. Subsequently, the dose was corrected via allometric scaling based on the final PPK model in this study, and the simulation was performed again.

RESULTS

Patient Characteristics

The patient characteristics are summarized in Table 1. A total of 177 steady-state concentrations from 93 patients were included in the model-building analysis, and a total of 94 steady-state concentrations from 43 patients were used to validate the model. The age of the patients ranged from 2 to 76 years, and the body weight ranged from 8.6 to 130 kg. In the model-building data, the numbers (% of total patients) of patients 2 to 6 years, 7 to 12 years, adults (12 to 59 years), and elderly aged 60 or more were 6 (6.5%), 9 (9.7%), 70 (75.2%), and 8 (8.6%) respectively. The median serum topiramate concentration was 1.7 and 1.8 μg/mL for the model-building data and validation data, respectively, which was lower than the value recommended in the TDM guidelines.[5] Half of the patients included in the model-building data received a co-administration of carbamazepine. There was no significant difference between these two groups except ALT, which was significantly different ($P < 0.01$; Mann-Whitney test), but the values in most of the patients were within the normal values.

PPK Modeling

A one-compartment model described the topiramate concentration-time profiles reasonably well. For the IIV, the inclusion of an exponential error model for the CL/F improved the model fitting (OFV: 105 *vs.* 234); however, the inclusion of IIV for the V/F and absorption rate constant did not decrease the OFV, and therefore, these IIV parameters were excluded from the base model. For the residual variability, since the mixed error model exhibited the smallest

OFV (149, 108, and 105 for additive, proportional, and mixed error model, respectively), this model was selected. For the allometric factors of body weight in the CL/F model, the model for which CL/F was proportional to the 0.75 power of the body weight revealed a superior model fitting compared with the power of 0 or 1 (OFV: 56.5, 105, and 65.8, respectively).

The results of the covariate analyses are presented in Table 2. Using the forward inclusion step followed by the backward elimination step, the co-administration of carbamazepine or phenytoin was included as significant covariates for the CL/F of topiramate. For further analysis, we compared model 1 (additive effect model) with model 2 (integrated effect model) for the minimum OFV:

$$\text{Model 1: } {}^{CL}/_{F} = \theta_1 \times \theta_2^{PHT} \times \theta_3^{CBZ}$$

$$\text{Model 2: } {}^{CL}/_{F} = \theta_1 \times \theta_2^{IND}$$

in Model 2, the IND was 1 if the patient received a co-administration of phenytoin or carbamazepine, or 0 if the patient did not receive phenytoin or carbamazepine. As a result, model 2 provides superior model fitting, because the OFV are virtually the same values; although the number of parameters in the model 2 is less than that in the model 1. (OFV: Model 1 *vs.* Model 2 = 29.4 *vs.* 29.7).

The final estimates of the topiramate PPK parameters with a 95% confidence interval are presented in Table 3. The CL/F of topiramate in patients who were co-administered carbamazepine or phenytoin exhibited a value 1.56 times higher than that in patients that did not receive carbamazepine or phenytoin. Including the co-medication covariates improved the

model fitting, because the difference in the OFV between the base model and the final model was -26.8 and the IIV for CL/F also decreased from 35.6% to 28.3% in the final model. In the final check after the inclusion of the covariates, the residual error model was revised from the mixed error model to the proportional error model, since the deletion of an additive part had no significant impact (OFV: mixed *vs.* proportional = 29.7 *vs.* 30.8).

Model evaluation

Goodness-of-fit plots for the final model are shown in Fig. 1. The plots of OBS *vs.* PRED and IPRED revealed a favorable agreement between the model predictions and observations. Moreover, CWRES were evenly distributed around zero against PRED, the time after dosing, body weight, and eGFR.

Figure 2 presents the individually predicted body weight normalized CL/F (L/h/70 kg) in five groups classified by concomitant AED. The CL/F for the group co-administered with carbamazepine or phenytoin was significantly greater than that for the group without carbamazepine or phenytoin (Non; $P < 0.001$). However, the CL/F in the groups co-administered with only phenytoin or phenytoin plus carbamazepine were not significantly different compared to the group that received only carbamazepine. The CL/F of the patients co-administered with phenobarbital or phenobarbital plus carbamazepine or phenytoin showed that phenobarbital had no significant influence on the CL/F of topiramate.

The pcVPC results for the final model and external validation are presented in Fig. 3. The pcVPC plots demonstrated that the final model had a reasonably good predictive ability. The MPE value for the validation data was -1.12% (95% confidence interval (CI): -6.01% to 3.82%)

of the individual prediction, indicating no significant bias. The value of RMSE was 23.9% (95%CI: 20.7% to 27.2%) of the individual prediction.

The estimated PPK parameters of the integrated data are shown in Table 3, which are moderately similar to the final PPK parameters obtained by the model-building data.

Simulation

Figure 4 presents the simulated serum concentration of topiramate obtained by the final PPK model and parameters using the model-building data. The serum concentrations of topiramate in patients weighing 50 or 70 kg were significantly higher compared with those of patients weighing 10 kg in the case of fixed dose of 6 mg/kg/day ($P < 0.001$).

To equalize the serum concentrations regardless of body weight, the dose was adjusted based on the final PPK model that was allometrically scaled to the body weight as 60 mg/day/10 kg (i.e., 60 mg for 10 kg, 101 mg for 20 kg, 201 mg for 50 kg, and 258 mg for 70 kg), and the simulations were performed again. No significant differences were observed for the serum concentrations among the different body weight groups. In addition, the concentrations in the groups of 50 kg and 70 kg were significantly lower in the allometrically scaled dose compared with the fixed dose ($P < 0.001$).

DISCUSSION

In this study, a topiramate PPK model, including both adults and children, was established using routinely obtained clinical data through various evaluation models. Moreover, the topiramate CL/F was proportional to the power of 0.75 of the body weight, and the CL/F for the

patients that received a co-administration of phenytoin or carbamazepine was 1.56 times higher than that of the patients who were not treated with these drugs. Dosage adjustments based on the allometric scaling of body weight and concomitant AEDs are helpful for determining the concentration required to reach the effective range of topiramate for each individual.

The CL/F and V/F of topiramate for a typical patient with a body weight of 70 kg receiving monotherapy were calculated to be 2.25 L/h and 105 L, respectively, based on the final PPK parameters. For the CL/F, this value was moderately higher, but is comparable with the findings of previous studies.[10, 19, 20] For the Vd/F, this value is partly consistent with some previous studies,[12] but is higher compared to other studies.[3, 21] The PK parameters of topiramate previously reported are summarized in Table 4.

In a previous study, the co-administration of carbamazepine or phenytoin were significant independent covariates,[12] but in our study, the integrated effect model (Model 2) provided a better model fitting than the additive effect model (Model 1). Indeed, the CL/F of topiramate for patients receiving the co-administration of both carbamazepine and phenytoin were not significantly different from that of patients receiving the co-administration of either carbamazepine or phenytoin alone (Fig. 2). Phenobarbital is a well-known enzyme inducer; however, the effects of phenobarbital on the CL/F of topiramate are controversial.[10, 19] In our study, the CL/F of topiramate in patients receiving a co-administration with phenobarbital was the same as in patients with no inducers (Fig. 2). This result was not surprising because there were only five patients co-administered with phenobarbital in our study, and phenobarbital is not considered to be as strong enzyme inducer as phenytoin and carbamazepine.[10] However, the dose or concentrations of phenobarbital might affect the inducing ability against the

CYP3A4-mediated metabolism of topiramate.

Approximately half of topiramate in the body is excreted unaltered by the kidneys,[7, 21] and eGFR was reported to be a significant covariate for the CL/F of topiramate.[4, 12, 22, 23] In the present study, since only five patients with a moderate-to-severe renal impairment (eGFR of 55–60 mL/min/1.73 m^2) were included in the model-building data, we could not evaluate the effect of renal function on the topiramate CL/F. We also examined the effects of age especially for young children (2 to 6 years) and elderly people (60 years or more) on the CL/F in the final model. However, no significant age effects were observed, due to the limited number of young children or elderly. The present PPK analysis of topiramate was performed by using routinely monitored data, and therefore included some limitations. The number of patients and blood sampling points per patients were small and the sampling design was unbalanced. If the distribution of age or renal function were uniform and more rich data were obtained, the effect of age or renal function on the CL/F might be proven to be significant covariates in addition to the co-medication effects and body weight. Therefore, the present findings should be regarded as preliminary pending on larger trials and with different populations.

The simulation of serum concentrations using the final PPK model demonstrated that if the dose per body weight (mg/kg/day) is kept constant among children with various ages based on the package information, the concentrations of patients weighing 70 kg exhibited 1.4-fold higher value than that of patients weighing 10 kg (Fig. 4); this is consistent with previous studies showing that when corrected for body weight, the CL/F of topiramate (L/h/kg) is higher in children than in adults[24-27]. After an adjustment of the dose according to the final PPK model based on allometric scaling was performed, almost the same concentration was obtained in

children of various ages, as well as adults (Fig. 4). Therefore, we recommend that the dose be normalized by a 0.75-power of body weight, not the typical per kg for consistent concentrations regardless of the body weight in children of various ages. The present PPK model could predict the clearance of the different age of patients more precisely because it is approximately approaching the clearance calculated by using the body surface area, which more accurately reflects the actual clearance of the young children.[28]

CONCLUSION

A population pharmacokinetic analysis using routinely monitored data clarified the CL/F of topiramate by power scaling to the patients' body weight and the significant effect of the co-administration of carbamazepine or phenytoin. Dosage adjustments based on body weight and concomitant AEDs in this model are helpful for determining the individual concentration required to achieve optimal effects of topiramate.

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FIGURE LEGENDS

FIGURE 1. Goodness-of-fit plots for the final model of topiramate. The observed concentrations (OBS) *vs.* population predictions (PRED) (A) and individual predictions (IPRED) (B). CWRES *vs.* PRED (C), time after dosing (D), body weight (BW; E), and estimated glomerular filtration ratio (eGFR; F). Each line in (A) and (B) represent a line of unity.

FIGURE 2. Comparison of individually predicted body weight normalized apparent clearance (CL/F, L/h/70 kg) between the five groups classified by the concomitant antiepileptic drug (AED). Each open symbol represents a patient, and the bar of each group represents the mean of the normalized clearance. Non, carbamazepine (CBZ), phenytoin (PHT), phenobarbital (PB), and PHT plus CBZ along the x-axis show the group of patients with each concomitant AED. *Non*, without CBZ and PHT. Each closed symbol represents a patient co-administered with either CBZ or PHT plus PB. ***$P < 0.001$ by the Kruskal-Wallis test followed by the Dunn test between the Non and each concomitant AED groups.

FIGURE 3. Prediction corrected visual predictive check (pcVPC) plots for topiramate using the model-building (A) and validation (B) data. Each open symbol represents the observed concentration in the model-building group and validation group, respectively. The solid lines in each graph denote the 5th, 50th, and 95th percentiles of the observed concentrations. The dotted lines in each graph show the 5th, 50th, and 95th percentiles of the predicted concentrations. The

shaded areas indicate the simulation-based 95% confidence interval for the 95th, 50th, and 5th percentiles.

FIGURE 4. Simulation of topiramate concentration in the 200-replication datasets in a typical patient classified by body weight. The number along the x-axis represents the patient weight, and each patient did not receive an enzyme inducer (carbamazepine or phenytoin). In the white box plot, the dose was 6 mg/kg, and in the grey box plot, each dose was allometrically corrected by the body weight in reference to the final population model (i.e., 60 mg for 10 kg, 101 mg for 20 kg, 201 mg for 50 kg, and 258 mg for 70 kg). ***$P < 0.001$ by the Kruskal-Wallis test followed by the Dunn test, in the comparison between the patients shown as the white box plot and the gray box plot in the same body weight. †††$P < 0.001$ by the Kruskal-Wallis test followed by the Dunn test, in the comparison between the patients weighting 10 kg and other patients weighting 20, 50, and 70 kg in the white box plot.

TABLE 1. Patient Characteristics

Characteristic	Model-building data	Validation data	*P*
Male/Female	40/53	24/19	0.16
Total number of blood samples	177	94	-
Age (year)	31 (2–68)	30 (2–76)	0.67
Body weight (kg)	54.1 (8.6–105)	53.8 (8.8–130)	0.65
AST (IU/L)	18 (8–167)	19 (11–56)	0.35
ALT (IU/L)	14 (4–316)	19 (6–79)	< 0.01
eGFR (mL/min/1.73 m^2)	95.6 (55.2–200)	98.2 (62.7–178)	0.30
Observed concentration (μg/mL)	1.7 (0.1–8.65)	1.8 (0.3–10.6)	0.23
Dose (mg/kg/day)	2.31 (0.13–11.4)	1.92 (0.32–8.77)	0.43
Concomitant AED (n)			
CBZ	48 (51.6%)	17 (39.5%)	0.19
PHT	22 (23.7%)	7 (16.3%)	0.33
PB	10 (10.8%)	5 (11.8%)	0.88

Each value shows the number or median (range).

AST, aspartate aminotransferase; *ALT*, alanine aminotransferase; *eGFR*, estimated glomerular filtration; *AED*, antiepileptic drug; *CBZ*, carbamazepine; *PHT*, phenytoin; *PB*, phenobarbital.

The *P* value was obtained by performing a Mann-Whitney test and chi-square test for the continuous and categorical values, respectively.

TABLE 2. Effect of the Tested Covariates on the Difference in Objective Function Values (ΔOFV)

	Forward Step		Backward Step
Covariates	**ΔOFV1**	**ΔOFV2**	**ΔOFV3**
Concomitant AED			
CBZ	–14.1	–12.8	
PHT	–14.3	Included	+13.0
PB	–0.18		
LEV	–0.00		
LTG	–1.28		
VPA	–0.37		
AST	–0.81		
ALT	–2.26		
eGFR	–3.42		
Age	–0.39		
Gender	–0.37		
Dose (mg/kg/day)	–2.35		
Model 2	-	–26.8	

AED, antiepileptic drug; *CBZ*, carbamazepine; *PHT*, phenytoin; *PB*, phenobarbital; *LEV*, levetiracetam; *LTG*, lamotrigine; *VPA*, valproic acid; *AST*, aspartate aminotransferase; *ALT*, alanine aminotransferase; *eGFR*, estimated glomerular filtration.

ΔOFV1-3 is the difference in the objective function value (OFV) induced by the corresponding covariate after its addition to the previous model (ΔOFV1 and 2) or its deletion from the intermediate model (ΔOFV3).

Model 2 was the integrated effect model of carbamazepine and phenytoin: $CL/F = \theta_1 \times \theta_2^{IND}$,

where IND is 1 if a patient received a co-administration with PHT or CBZ, or 0 if a patient did

TABLE 3. Population Pharmacokinetic Parameters of Topiramate

	Model-building data		Integrated data	
Parameter	**Estimate**	**95 % CI**	**Estimate**	**95 % CI**
θ_{CL} (L/h)	2.25	1.95–2.55	2.15	1.91–2.39
$\theta_{PHT\ or\ CBZ}$	1.56	1.3–1.82	1.54	1.33–1.75
Vd/F (L)	105	58.7–151	108	65.5–151
Ka (h^{-1})	2 (FIX)	-	2 (FIX)	-
IIV for CL/F (CV%)	28.3	21.9–33.5	30.0	24.1–34.9
Residual variability (CV%)				

not receive such combination treatment.

Proportional error	31.1	24.1–36.7	29.3	24.1–33.6

$$CL/F = \theta_{CL} \times \left(\frac{BW}{70}\right)^{0.75} \times \theta_{PHT\ or\ CBZ}^{IND}$$

$$V/_F = \theta_v \times \left(\frac{BW}{70}\right)$$

CL/F, apparent clearance; *V/F*, apparent volume of distribution; *Ka*, absorption rate constant; *IIV*, interindividual variability; *CV*, coefficient of variation; *CI*, confidence interval.

IND is 1 if a patient received the co-administration of carbamazepine or phenytoin, or 0 if a patient did not receive a co-administration of carbamazepine or phenytoin. Ka was fixed to the literature value (2 h^{-1}).[10]

TABLE 4. Previously Reported Pharmacokinetic Parameters of Topiramate

PK parameter	Value
Apparent clearance (*CL/F*)	1.2–1.8 (L/h) [10,19,20]
Apparent volume of distribution (*Vd/F*)	0.6–1.0 (L/kg) [3,21]
Absorption rate constant (*Ka*)	2 (h^{-1}) [10]
Half-life ($T_{1/2}$)	20–30 (h) [1,8]
Time to reach peak concentration (T_{max})	1–4 (h) [3,21]
Binding to blood protein	9–17 (%) [3,21]

Bioavailability (*F*)	81–95 (%) [3,21]

Fig. 1

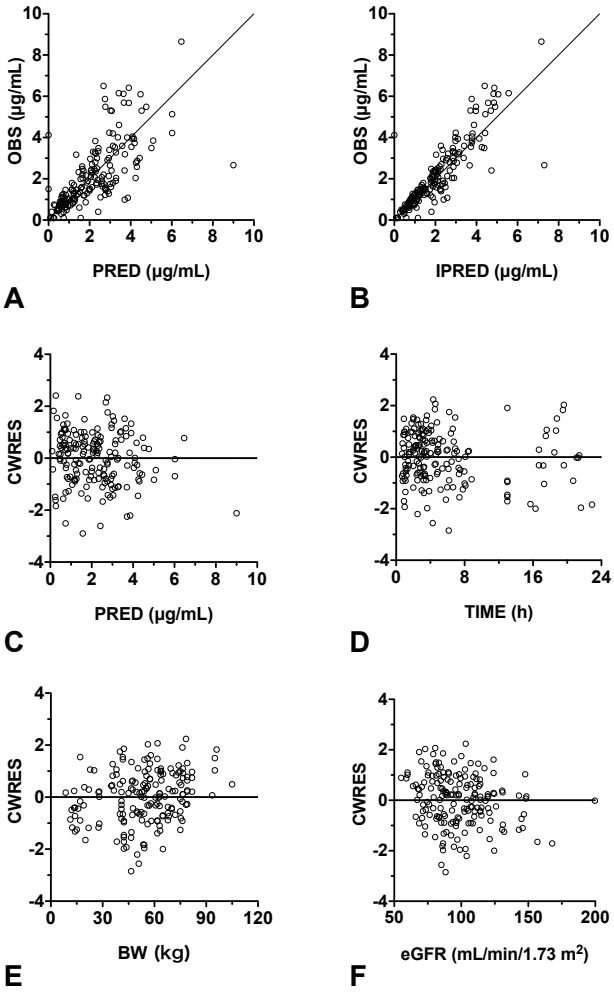

OBS (μg/mL)
PRED (μg/mL)
A
OBS (μg/mL)
IPRED (μg/mL)
B
CWRES
PRED (μg/mL)
C
CWRES
TIME (h)
D
CWRES
BW (kg)
E
CWRES
eGFR (mL/min/1.73 m2)
F

Fig. 2

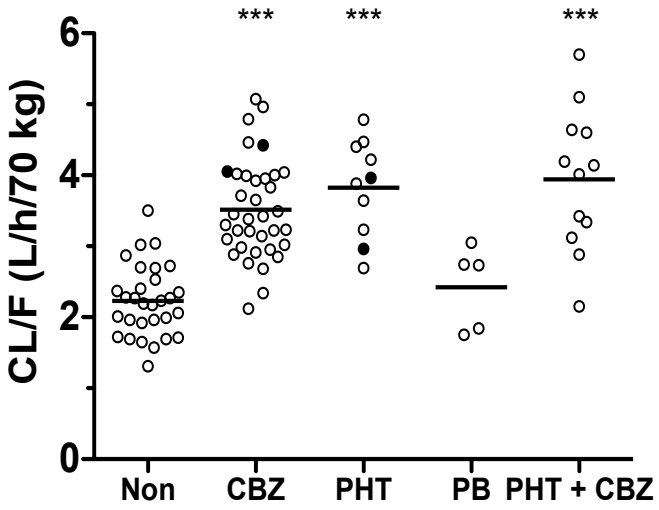
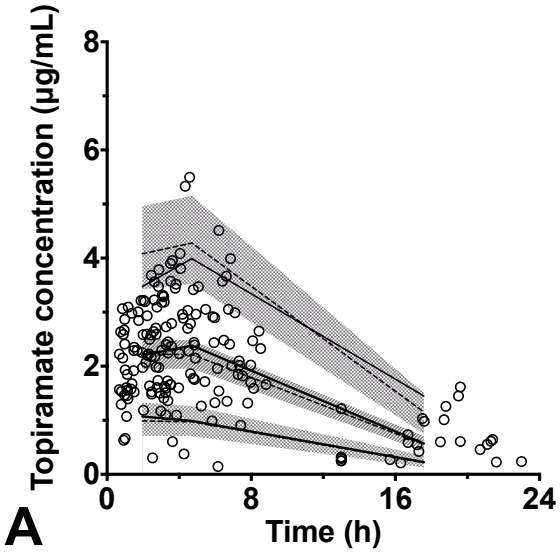


Fig. 3


Topiramate concentration (µg/mL)
0
2
4
6
8
0
8
16
24
Time (h)
A

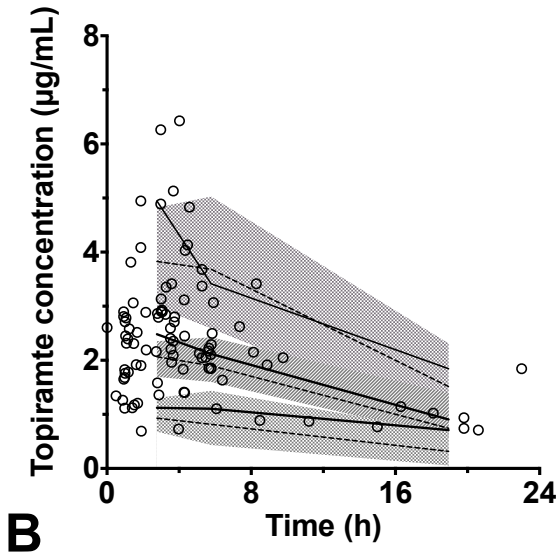

Topiramte concentration (µg/mL)
0
2
4
6
8
0
8
16
24
Time (h)
B

Fig. 4