

A Model-Informed Evaluation of Three-Times-Daily Levetiracetam Dosing in Epilepsy: A Population Pharmacokinetic and Simulation Study

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Abstract

We aimed to explore the adequacy of levetiracetam three times daily dosing in patients with epilepsy by pharmacokinetic modeling and simulation. In this prospective cohort, 27 adult patients diagnosed with epilepsy, who had been on an oral levetiracetam regimen, were included. A population pharmacokinetic model was developed, followed by Monte Carlo simulations to compare the plasma profiles using different doses ranging from 500 to 1500 mg at twice time (BID) and three times daily (TID) frequencies. The final model for levetiracetam concentration was a one-compartment model with linear elimination. The estimated values of the absorption rate (K_a), apparent clearance (CL/F), and apparent volume of distribution (V/F) were 1 hr^{-1} , 0.64 L/h, and 2.51 L, respectively. Body weight and concomitant antiseizure medications use significantly influenced CL/F, and body weight also significantly influenced V/F. A clinical trial simulation of 1,000 virtual subjects was generated for each regimen using the final population pharmacokinetic model. The BID regimen produced higher peak and lower trough concentrations, whereas the TID regimen maintained more stable plasma levels throughout the dosing interval. These findings suggest the TID dosing regimen of levetiracetam is expected to provide more sustained plasma concentrations, which may be associated with longer seizure-free periods in patients with epilepsy.

Introduction

Epilepsy is a chronic neurological disorder defined by recurrent seizure episodes. [1, 2] A seizure is a brain abnormal electrical activity that causes a behavioral alteration. An uncontrolled seizure is a life-threatening condition that leads to stroke and permanent disability. Epilepsy affects around 50 million people worldwide [3]. Its prevalence rate in Saudi Arabia is approximately 6.54 per 1,000 individuals [4]. The risk of epilepsy-related mortality has diminished due to the availability of potent antiseizure medications [5, 6], the efficacy and safety of which antiseizure medications vary according to their mechanisms of action [7, 8].

Levetiracetam is a broad-spectrum antiseizure medication that has demonstrated efficacy in the treatment of multiple forms of epilepsy. It also has a favorable safety profile with fewer adverse events. It has no drug interactions with other antiseizure medications, making it the preferred adjunct antiseizure medications for resistant seizures. Its efficacy in managing long-life seizure episodes in patients with Juvenile myoclonic epilepsy (JME) is promising [9].

Levetiracetam demonstrates linear and predictable pharmacokinetics, with rapid and nearly complete absorption following oral administration. Peak plasma concentrations are reached within 1–2 hours, with bioavailability exceeding 95%. Levetiracetam demonstrates a volume of distribution of 0.5–0.7 L/kg and minimal protein binding (< 3%). It is primarily eliminated through renal excretion, with about two-thirds excreted unchanged and 27% as inactive metabolites. Because this metabolic pathway is minor and independent of CYP enzymes, levetiracetam presents minimal risk for clinically significant drug–drug interactions. [10, 11] Levetiracetam half-life in adults is approximately 6 to 8 hours .

Despite the favorable characteristics, levetiracetam pharmacokinetics vary among individual in terms of targeted therapeutic concentration and optimal dosing regimens. Levetiracetam has a broad serum concentration range. Although no universally accepted target level has been established.

A commonly used reference range for treatment of epilepsy trough concentration is 12–46 mg/L, with alternative lower ranges suggested for perioperative or post-traumatic seizure prophylaxis trough concentration as low as 6–20 mg/L have been proposed, and even narrower targets of 6–12 mg/L are suggested in another study. [12, 13] However, the correlation between serum levetiracetam concentration and the efficacy of seizure control has not been confirmed. Levetiracetam remains well tolerated even at concentrations above the doubled upper reference, with no clearly defined toxic threshold. [14]

Levetiracetam's standard dosing ranges from 500 to 1500 mg twice daily (BID). The maximum dose of the levetiracetam oral regimen is 3000 mg per day. However, recent meta-analyses suggest that higher doses may be required in patients with augmented renal clearance to maintain therapeutic concentrations and seizure control. [15] Two clinical trials evaluated the efficacy of oral levetiracetam at 4000 mg per day in two divided doses. The findings highlight the robust effectiveness of the 4000 mg daily dose in reducing seizure frequency and improving patient outcomes despite increasing the risk of somnolence and asthenia [16, 17].

Although the half-life of levetiracetam is approximately 6 hours, it has been used as a twice-daily regimen. Emerging evidence from pharmacokinetic simulations suggests that more frequent dosing (e.g., three times daily) may improve concentration stability and reduce peak–trough fluctuations. Bilbao-Meseguer et al. recommended levetiracetam dosing three times daily for critically ill patients with normal or augmented renal clearance. [18]. Harlan et al. suggested three- and four-times daily levetiracetam regimens among critically ill individuals diagnosed with severe traumatic brain injury [19]. Determining the optimal levetiracetam dosages will help optimize the consistency of the therapeutic serum concentration during the day to avoid drug resistance in patients with epilepsy.

This study is a preclinical simulation-based study that aims to investigate the targeted levetiracetam concentration range in the Saudi population, and to design an optimal dose regimen. It assesses the feasibility and potential impact of a TID levetiracetam regimen in patients with epilepsy, and provide preliminary evidence to support future clinical trials.

Materials and Methods

Study Design, Setting, and Subjects

A prospective cohort study was conducted in the inpatient wards of King Saud University Medical City (KSUMC), Riyadh, Saudi Arabia. Patients were recruited between May 2024 and May 2025. The study inclusion criteria included patients diagnosed with epilepsy, aged 18 years or older, who have been on an oral levetiracetam regimen with a dose of 500 mg per day or higher for the last 24 hours. The exclusion

criteria include patients younger than 18 years, patients who received intravenous levetiracetam within the last 24 hours, patients on a levetiracetam dose of less than 500 mg per day, patients admitted to intensive care units within the last 24 hours, or patients who missed a dose of oral levetiracetam within the previous 24 hours.

Ethical Approval

Ethical approval was obtained from the Institutional Review Board (IRB) of King Saud University Medical City (KSUMC) (IRB No. E-24-8806). All research activities were conducted in compliance with the IRB's fundamental ethical principles and policies. Clinical trial number: not applicable.

Data Source and Procedure

A daily Electronic Medical Record (EMR) (Esihi™) report was generated to identify patients on levetiracetam orally in the inpatient setting. The primary investigator assessed patients' eligibility for the study inclusion and exclusion criteria. Eligible patients were approached, and the study was explained to them. Only patients who provided informed consent were enrolled.

After written informed consent was obtained, the investigator (Physician or Clinical pharmacist) ordered to draw five blood samples for each patient, a 2 ml sample collected at 1, 2, 4, 6, and 12 hours post oral levetiracetam dose. The nurse collected the blood samples as instructed and then sent them to the KSU kinetics laboratory. Samples were collected and stored at the kinetics laboratory until analysis. Each sample was centrifuged at 3000 rpm for 30 minutes to separate the plasma, which was then frozen at -80°C. The plasma concentrations of levetiracetam were quantified using a high-performance liquid chromatography (HPLC) assay with ultraviolet detection at a wavelength of 205 nm. The method was validated following the guidelines established by the US Food and Drug Administration (FDA, 2018) and the European Medicines Agency (EMA, 2012). The separation process utilized a Symmetry® C18 column (4.6 mm × 150 mm, 5 µm) from Waters (Milford, Massachusetts, USA), with a mobile phase consisting of ammonium phosphate and acetonitrile (95:5, v/v) delivered at a flow rate of 1.2 mL/min. Sample preparation involved protein precipitation using acetonitrile and centrifugation at 15,000 × g for 10 minutes. The supernatant was subsequently injected into the HPLC system for analysis. The data was extracted from the Esihi database at KSUMC based on a data collection sheet and then exported to Excel. The Data collection sheet information includes: 1) Patient demographic: age, gender, weight, Height, and BMI. 2) Indication for levetiracetam use. 3) Smoking status. 4) levetiracetam drug: dosage form, Brand name, dose, frequency, duration. 5) Concomitant Antiseizure medications (ASMs): dosage form, dose, frequency, duration. 6) Serum creatinine. Finally, the levetiracetam plasma concentration at 1, 2, 4, 6, and 12 posts of the levetiracetam dose, and its date & time.

Model Development

A population pharmacokinetic model was developed using Monolix version 4.4 (Lixoft, France) [20], which estimates pharmacokinetic parameters using the stochastic approximation expectation–maximization (SAEM) algorithm [21]. Structural model development was initiated by fitting several candidate compartmental models to the observed plasma levetiracetam concentrations, including one- and two-compartment models. The optimal structural model was selected based on multiple criteria: (a) a reduction in the objective function value (OFV; $-2 \log$ -likelihood); (b) precision of parameter estimates expressed as the relative standard error (RSE%), calculated as the ratio of the standard error to the final parameter estimate; (c) physiological plausibility; and (d) goodness-of-fit diagnostics, including observed versus predicted concentrations, residual plots, and visual predictive checks (VPC). For nested models, a decrease in OFV of 3.84 was considered statistically significant at $P < 0.05$ for one degree of freedom.

Covariate model

Covariate model development was performed in a stepwise manner using forward inclusion and backward elimination procedures. Initially, empirical Bayes estimates of individual pharmacokinetic parameters were plotted against candidate covariates to screen for potential relationships. Subsequently, covariates identified during this screening step were formally tested using a stepwise regression approach based on the $-2 \log$ -likelihood ratio test. During model building, a covariate was retained in the model if its inclusion resulted in a statistically significant reduction in the objective function value at $P < 0.05$ during forward inclusion, and it was removed if its exclusion did not produce a significant increase in the objective function value at $P < 0.001$ during backward elimination. The following covariates: age, body weight, height, BMI, sex, CLCr, smoking status, and concomitant AEDs were tested as covariates.

Model evaluation

Model goodness-of-fit was evaluated using the log-likelihood criterion throughout the model development process. Diagnostic plots of model-based individual predictions (IPRED) and population predictions (PRED) versus the observed levetiracetam concentrations were generated to assess model performance. A prediction-corrected visual predictive check (pcVPC) based on 1,000 simulations was constructed to further evaluate the adequacy of the final model. Both the base and final models were assessed using these diagnostic criteria. The 10th, 50th, and 90th prediction intervals derived from simulations of the final model were overlaid with the corresponding percentiles of the observed data. Adequate model performance was indicated when the observed percentiles were contained within and aligned with the simulated prediction intervals. A statistically significant improvement in the log-likelihood value ($P < 0.05$) was required to justify the selection of a more complex model.

Clinical Trial Dosing Simulation

Simulations were performed using Simulx (version 4.4, Lixoft, a Simulations Plus) to compare the plasma profiles of three different dosing regimens [22]. The population pharmacokinetic parameters generated from the initial clinical trial data were exported from Monolix and used as inputs for the scenario analysis. The trough concentration of levetiracetam was reported following different dosing regimens. These dosing regimens include different doses ranging from 500 to 1500 mg, and they were given at different dose frequencies (twice daily and three times daily). For each dosing regimen, 1000 virtual subjects were simulated using a 1:1 ratio of males to females and assuming average body weight.

Results

Patient Demographics

Twenty-seven adult patients participated in the study. The baseline characteristics are presented in Table 1. A total of 135 plasma samples (5 per patient) were collected. levetiracetam was effective for one week post the dose, based on free seizure days, with no treatment-related adverse events observed. The main indications for receiving oral levetiracetam were 14 (51.85%) Generalized epilepsy, followed by 9 (33.33%) Seizure prophylaxis. The majority of the levetiracetam dose was 500 mg, 19 (70.37%). Patients were non-smokers in 19 (70.37%). Two dosage forms were used in this cohort: tablets (n = 20, 74.07%) and 7 (25.93%) patients received syrup. Only 5 patients received other antiseizure medications as co-administered with levetiracetam.

Population pharmacokinetic modeling

The plasma concentrations of levetiracetam were obtained from five samples per subjects, yielding a total of 135 observations. Several base models were initially explored (i.e. one- and two-compartment models). The final model was a one-compartment model with linear elimination from the central compartment. A combined error model best described the residual unexplained variability. The pharmacokinetic model was parameterized in terms of the absorption rate (K_a), apparent clearance (CL/F), and apparent volume of distribution (V/F). The parameter estimates of the model are shown in Table 2. The estimated values of K_a , CL/F , and V/F were 1 hr^{-1} , 0.64 L/h , and 2.51 L , respectively. The interindividual variability was 11%, 22%, and 21% for K_a , CL/F , and V/F , respectively. Among the investigated covariates, weight and concomitant AEDs were found to significantly influence the CL of levetiracetam. While, weight was found to significantly influence the V of levetiracetam. The inclusion of these covariates statistically improved the base model by decreasing the OFV by 34 points and decreasing the between-subject variability of CL and V by approximately 50%. The values of the parameters for the final models are summarized in Table 2.

Model evaluation

Diagnostic goodness-of-fit plots for the final levetiracetam covariate model are presented in Figure 1 and demonstrate no substantial systematic bias. The relative standard errors (RSE%), presented in Table 2, indicate that all model parameters were estimated with acceptable precision. The prediction-corrected visual predictive check (pcVPC) (Figure 2) demonstrated that the simulated concentration profiles adequately captured the observed data, supporting the robustness and validity of the final model. Collectively, these diagnostics indicate that the developed pharmacokinetic model provides an appropriate description of the levetiracetam concentration–time data.

Clinical Trial Dosing Simulation

Clinical trial simulations were performed to compare the pharmacokinetic performance of BID and TID levetiracetam dosing regimens. A total of 1,000 virtual subjects were generated for each regimen using the final population pharmacokinetic model. Simulated concentration–time profiles demonstrated that the TID regimen resulted in lower peak-to-trough fluctuations compared with the BID regimen. The BID dosing produced higher peak concentrations and lower trough concentrations, whereas the TID regimen maintained more stable plasma levels across the dosing interval (Figure 3).

Discussion

Understanding how levetiracetam behaves pharmacokinetically in a specific patient population is essential before drawing conclusions about optimal dosing. In this study, we developed a population pharmacokinetic model using data collected prospectively from adult Saudi patients with epilepsy and subsequently used that model to compare the plasma concentration profiles of BID and TID oral levetiracetam regimens through simulation. Saudi adults were included to assess whether levetiracetam pharmacokinetics in this population are comparable to those reported in other ethnic groups, or whether population-specific differences may influence dosing. The final model that best described our data was a one-compartment model with linear elimination from the central compartment - a finding that is in keeping with what others have reported for this drug. Body weight emerged as an important determinant of both clearance and volume of distribution, while co-administration of other AEDs additionally influenced clearance. Together, these covariate relationships are physiologically plausible and consistent with levetiracetam's known pharmacology. Saudi ethnicity does not appear to confer a distinct effect relative to other ethnic groups. Similar to a population pharmacokinetic analysis of Japanese and Western adults found no significant ethnic effect after adjustment for major covariates.[23]

When we compared our parameter estimates to those in the published literature, some differences were apparent. Our estimates for CL/F (0.64 L/h) and V/F (2.51 L) were lower than those reported by Karatza et al. and Ito et al., whose models yielded a CL/F of approximately 3.26 L/h and a V/F of 34.7 L [24, 25, 26]. These discrepancies likely reflect differences in study design and sampling strategy rather than deficiencies in our model. In our study, each patient contributed five samples drawn at 1, 2, 4, 6, and 12 hours post-dose, capturing the full arc of drug absorption, distribution, and elimination phases [27]. This

richer sampling design allowed K_a and V/F to be informed more directly by the observed data. Many published models, by contrast, were built on trough-heavy TDM datasets, where information about the absorptive and distributive phases is sparse, and model assumptions carry more weight in shaping the final estimates. Differences in patient characteristics - particularly renal function and body weight, which are the primary drivers of levetiracetam clearance - and in which covariates were included, also contribute to the variability seen across studies. These are well-recognized sources of heterogeneity in population pharmacokinetic modelling, which interpreted our findings.

The clinical simulation was, in many ways, the central question of this work: does a TID regimen actually perform better than BID from a pharmacokinetic standpoint? Our results suggest it does. Across 1,000 virtual subjects generated for each regimen, the TID dosing produced noticeably smaller peak-to-trough swings in plasma concentration compared to BID, which was associated with higher peaks and lower troughs over the dosing interval. This matters clinically because levetiracetam, like most immediate-release antiseizure medication, is susceptible to the practical consequences of concentration fluctuation. When trough levels dip below the therapeutic range, even transiently, patients may lose adequate seizure protection during that window - an issue that has been linked to breakthrough seizures in antiseizure medication therapy more broadly [28, 29]. On the other end, disproportionately high peak concentrations may increase the likelihood of dose-dependent side effects. The carbamazepine literature has illustrated this relationship well, demonstrating that interdose plasma fluctuations correlate with intermittent adverse effects, even when average drug exposure remains acceptable [30, 31]. Regulatory perspectives on extended-release antiseizure medication formulations echo the same concern, noting that smoothing the concentration–time profile is a meaningful clinical goal in epilepsy management [32]. Against this backdrop, the pharmacokinetic stability offered by TID levetiracetam dosing seems worth pursuing, particularly in patients who continue to experience breakthrough seizures despite adequate BID dosing.

This study has a number of features that we believe strengthen its findings. Collecting five timed samples from each participant - rather than relying on opportunistic trough levels — gave us a much clearer picture of individual pharmacokinetic behavior and improved the reliability of our parameter estimates. The Monte Carlo simulation approach then allowed us to stress-test our model across a large and diverse virtual population, something that would not have been feasible within our real-world cohort alone. It is also worth emphasizing that this work was never intended to be the final word on TID levetiracetam dosing. Rather, it is a model-informed, preclinical step - designed to build the pharmacokinetic case and provide preliminary evidence before committing patients to a prospective trial comparing the two regimens on clinical outcomes.

That said, we are under no illusion that this study is without limitations. The most obvious is the sample size: 27 patients is modest for a population pharmacokinetic analysis, and while simulation mitigates some of the downstream consequences of this, it cannot fully substitute for a larger and more diverse real-world dataset. The covariate finding related to co-administered antiseizure medications is particularly sensitive to this constraint, given that only five patients in the cohort were receiving

combination therapy. Beyond sample size, the entire analysis rests on pharmacokinetic endpoints - plasma concentrations and derived parameters - without any direct measurement of clinical outcomes. Whether a more stable plasma profile actually translates into fewer seizures, better tolerability, or improved quality of life remains an open question that only a prospective clinical trial can answer. Finally, the simulations assume perfect adherence to a TID schedule, which may not reflect real-world patient behavior; adherence to three-times-daily regimens is generally lower than to twice-daily ones, and this could attenuate the benefits we have modelled. f. These important caveats underscore that the present work should be viewed as a foundation for further clinical investigation rather than a definitive recommendation. This is the first study, to our knowledge, to examine the

population pharmacokinetics of levetiracetam in Saudi adults, providing novel insights while recognizing that observed differences may reflect underlying ethnic, demographic, and regional variability.

Conclusion

Our population pharmacokinetic modeling and simulation study suggests that TID dosing of oral levetiracetam results in more stable plasma concentrations than BID dosing in patients with epilepsy. These findings support consideration of TID regimens for selected patients, particularly those who experience inadequate seizure control with the maximum levetiracetam dose and who cannot tolerate other antiseizure medications. Further clinical studies are warranted to confirm the impact of the TID dosing strategy on long-term seizure outcomes.

Declarations

Authors' contributions

WHA and SAA conceived and designed the study. WHA developed the study protocol, conducted data collection, performed the primary analysis, and prepared the first draft of the manuscript. SAA conducted the PK/PD simulation model analysis and contributed to the interpretation of the modeling results. AA performed the laboratory HPLC analysis. SAA, BSB, and BNA critically reviewed the manuscript for important intellectual content. All authors contributed to the revision of the manuscript, approved the final version, and agree to be accountable for all aspects of the work.

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Conflict of Interest Statement

The authors declare no conflicts of interest related to this study.

Ethics approval

Ethical approval was obtained from the Institutional Review Board (IRB) of King Saud University Medical City (KSUMC) (IRB No. E-24-8806). All research activities were conducted in compliance with the IRB's fundamental ethical principles and policies.

Consent to participate

Written informed consent was obtained from all individual participants before blood extraction and inclusion in the study.

Availability of data and material

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Tables

Table 1: Patient demographic characteristics

		N (27)	%	Mean	SD
Age				48.93	15.17
Gender	Male	11	40.74		
	Female	16	59.26		
Weight (kg)				70.22	16.57
Height (cm)				162.52	8.55
BMI				26.56	61.30
Scr				79.04	85.20
CrCl				123.71	61.30
Dosage Form	Tablet	20	74.07		
	Syrup	7	25.93		
Dose	500	19	70.37		
	750	2	7.41		
	1000	3	11.11		
	1250	1	3.70		
	1500	2	7.41		
Smoking	Smoker	8	29.63		
Status	Non-smoker	19	70.37		
Indication	Seizure prophylaxis	9	33.33		
	Focal	1	3.70		
	Generalized	14	51.85		
	Unclassified Epilepsy	3	11.11		
Concomitant ASMs	0	22	81.48		
	1	5	18.52		
SD; standard deviation, BMI; body mass index, Scr; serum creatinine, CrCl; creatinine clearance, ASMs; Antiseizure medications.					

Table 2: Population pharmacokinetic parameter estimates of levetiracetam following oral administration.

Parameter	Base Model		Final Model	
	Estimates	RSE (%)	Estimates	RSE (%)
Ka (hr ⁻¹)	1	14	1	10
CL/F (L/h)	0.57	23	0.64	13
V/F (L)	3.4	22	2.51	16
IIV for Ka (%)	27	22	11	9
IIV for CL/F (%)	38	31	22	18
IIV for V/F (%)	39	29	21	16
Residual errors				
A	8.4	14	8.4	14
B	0.11	25	0.11	25
**IIV Interindividual variability is expressed as the coefficient of variation; RSE% is the relative standard error; σ_{sh} : shrinkage value for a parameter; σ_{sh} : shrinkage value for the residual error; Ka: absorption rate constant; CL/F: apparent clearance; V/F: apparent volume of distribution.				

Figures

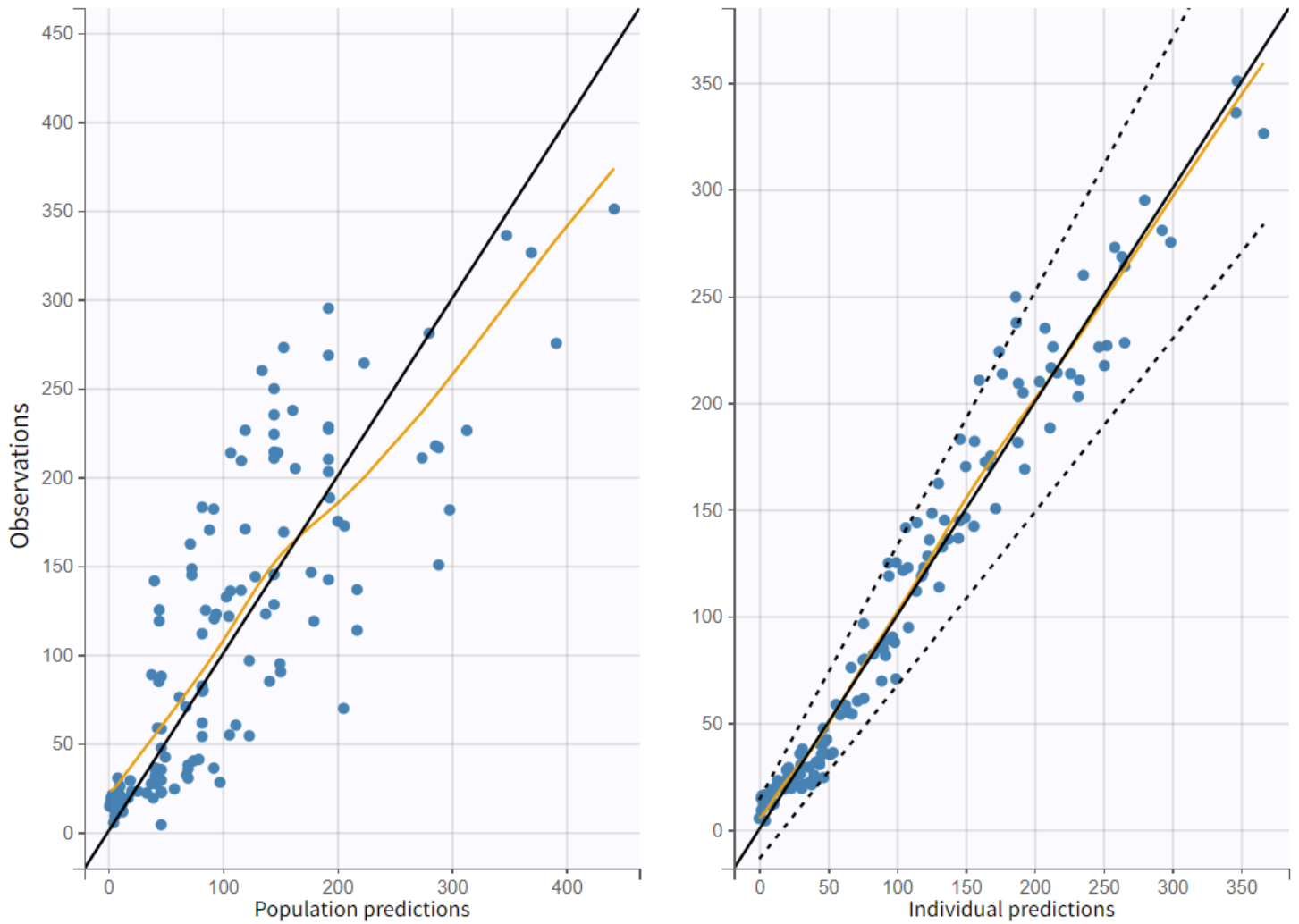


Figure 1

Goodness-of-fit (GOF) plots obtained from the final model for levetiracetam. (A) The population predictions of levetiracetam vs. observed concentrations. (B) The individual predictions of levetiracetam vs. observed concentrations. (C) The conditional weighted residuals vs. population predicted concentrations. (D) The conditional weighted residuals vs. time. Blue circles are the observed data points, the solid black line is the line of identity, the orange line is the trendline, and the dotted line is the 90% prediction interval.

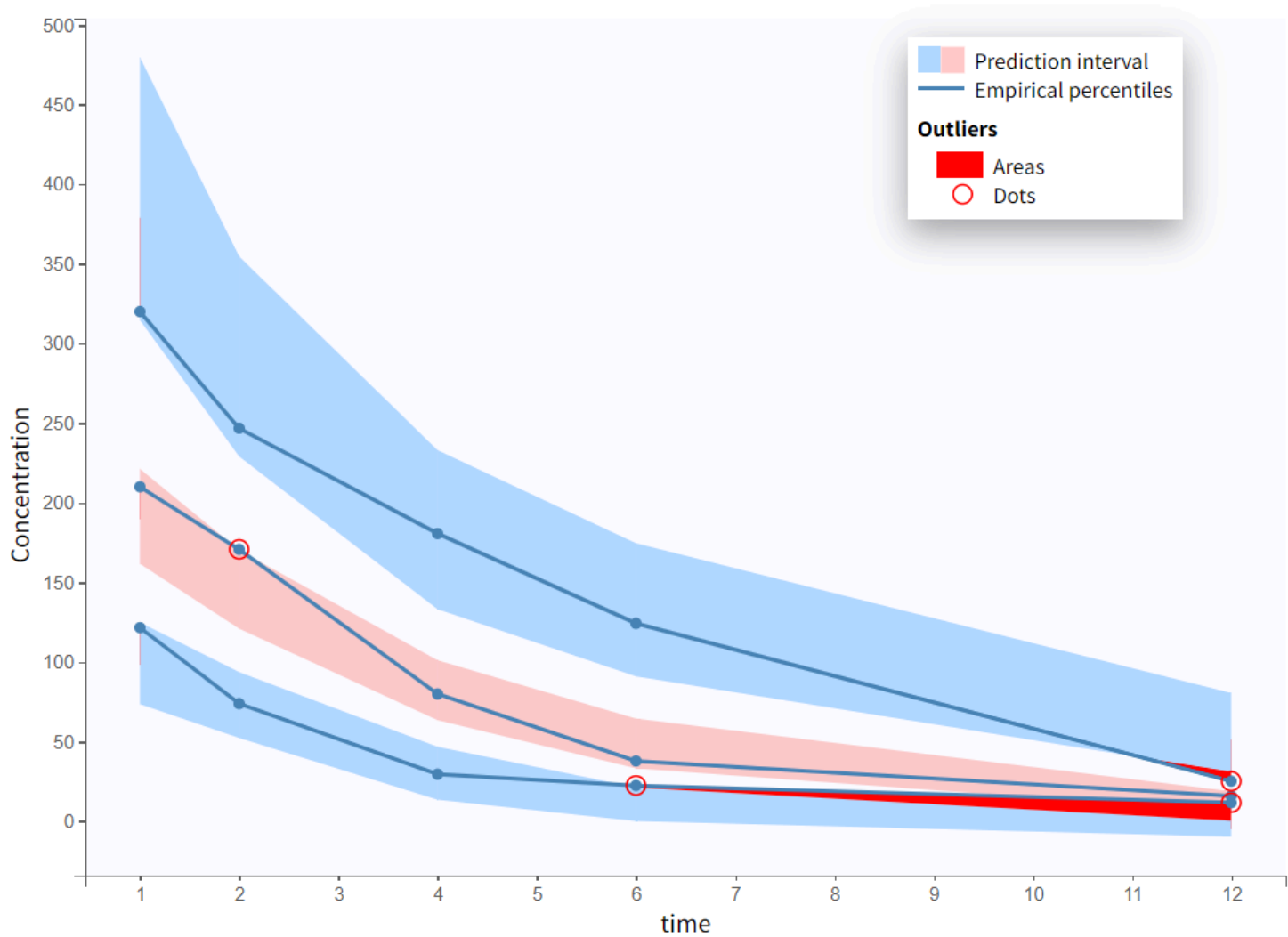


Figure 2

Visual predictive check (VPC) for levetiracetam concentration vs. time based on 1000 Monte Carlo simulations. The solid blue line represents the 10th, 50th, and 90th percentiles of the observed data. The shaded regions represent the 90% CI around the 10th, 50th, and 90th percentiles of the simulated data. The observed plasma concentrations are represented by blue circles.

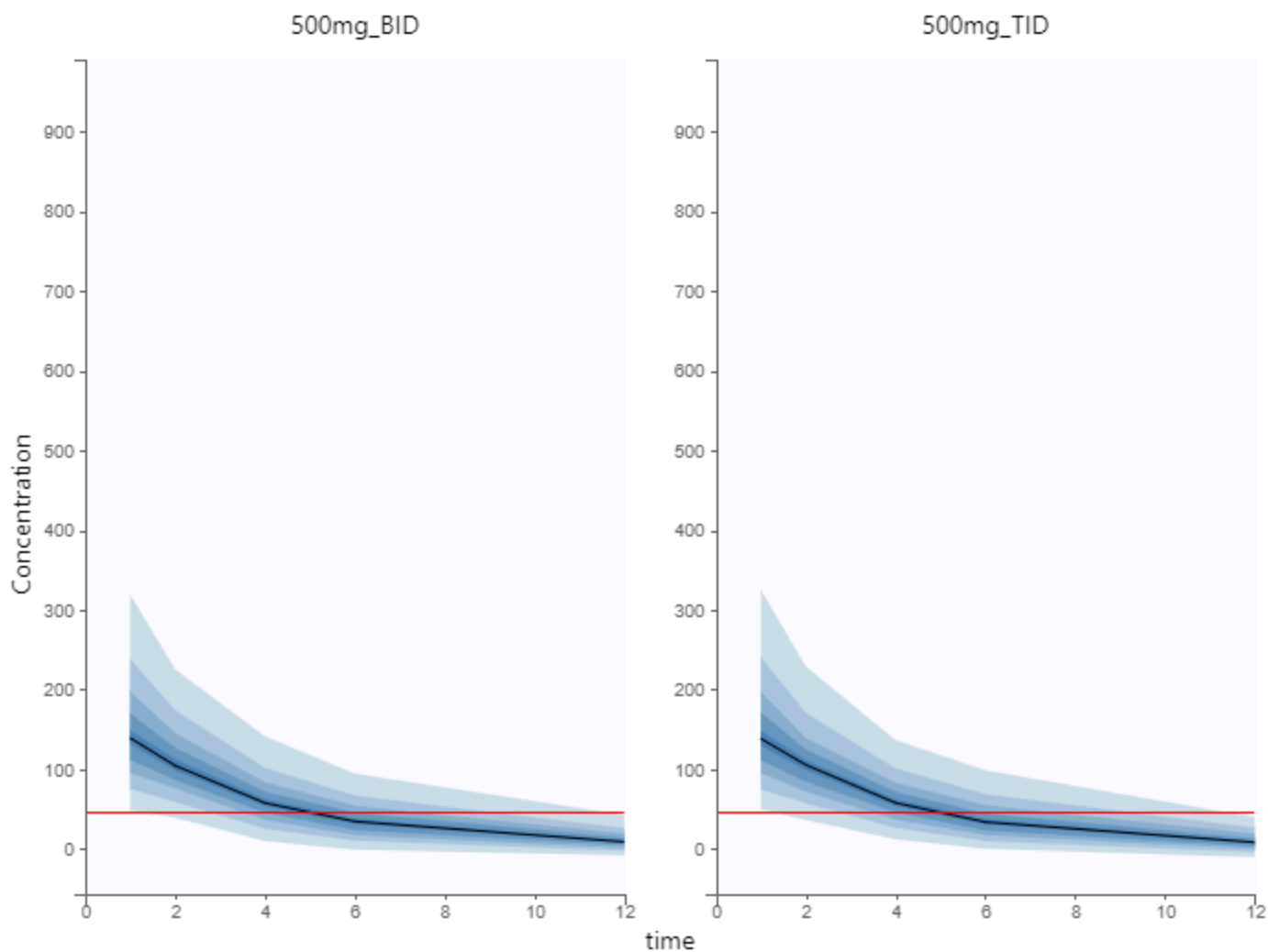


Figure 3

Simulated steady-state plasma concentration–time profiles of oral levetiracetam following BID and TID dosing regimens in 1,000 virtual subjects generated from the final population pharmacokinetic model. The solid lines represent the median predicted concentrations, and the shaded regions represent the 90% prediction intervals for each regimen. The horizontal red line indicates the suggested trough concentration of levetiracetam (46 mg/L).