

Original Article

Population pharmacokinetics modeling of levetiracetam in Chinese children with epilepsy

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Aim: To establish a population pharmacokinetics (PPK) model of levetiracetam in Chinese children with epilepsy.

Methods: A total of 418 samples from 361 epileptic children in Peking University First Hospital were analyzed. These patients were divided into two groups: the PPK model group ($n=311$) and the PPK validation group ($n=50$). Levetiracetam concentrations were determined by HPLC. The PPK model of levetiracetam was established using NONMEM, according to a one-compartment model with first-order absorption and elimination. To validate the model, the mean prediction error (MPE), mean squared prediction error (MSPE), root mean-squared prediction error (RMSPE), weight residues (WRES), and the 95% confidence intervals (95% CI) were calculated.

Results: A regression equation of the basic model of levetiracetam was obtained, with clearance (CL/F)=0.988 L/h, volume of distribution (V/F)=12.3 L, and $K_a=1.95\text{ h}^{-1}$. The final model was as follows: $K_a=1.56\text{ h}^{-1}$, $V/F=12.1\text{ (L)}$, $CL/F=1.04\times(\text{WEIG}/25)^{0.563}\text{ (L/h)}$. For the basic model, the MPE, MSPE, RMSPE, WRES, and the 95%CI were 9.834 (-0.587–197.720), 50.919 (0.012–1286.429), 1.680 (0.021–34.184), and 0.0621 (-1.100–1.980). For the final model, the MPE, MSPE, RMSPE, WRES, and the 95% CI were 0.199 (-0.369–0.563), 0.002082 (0.00001–0.01054), 0.0293 (0.001–0.110), and 0.153 (-0.030–1.950).

Conclusion: A one-compartment model with first-order absorption adequately described the levetiracetam concentrations. Body weight was identified as a significant covariate for levetiracetam clearance in this study. This model will be valuable to facilitate individualized dosage regimens.

Keywords: levetiracetam; epilepsy; population pharmacokinetics; pediatric; Chinese children

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Introduction

Levetiracetam (LEV; (S)-ethyl-2-oxo-pyrrolidine acetamide (Keppra[®]), UCB Pharma, Braine-l'Alleud, Belgium) is a new antiepileptic drug. It is mainly used for the adjunctive treatment of partial-onset seizures in adults and children, as well as myoclonic and primary generalized tonic-clonic seizures in patients with idiopathic generalized epilepsy^[1–3]. The primary mechanism of action of LEV relates to its binding to synaptic vesicle proteins^[4]. The results of clinical trials in a Chinese population have demonstrated that LEV is effective and well tolerated in adults with inadequately controlled partial-onset seizures^[5].

LEV shows linear pharmacokinetics, and its major route of elimination is through the kidneys, with approximately 66% of a dose eliminated unchanged and 27% as inactive metabolites^[6–9]. Renal function determines the rate of elimination of LEV. The half-life is 6–8 h in healthy adults, and 5–7 h in

children aged 6–12 years. However, the apparent clearance is 30%–40% higher in children than in adults^[10]. The initial daily dose is $20\text{ mg}^{-1}\cdot\text{kg}^{-1}\cdot\text{d}^{-1}$ (10 mg/kg twice daily) and can go up to $60\text{ mg}^{-1}\cdot\text{kg}^{-1}\cdot\text{d}^{-1}$. Even higher doses ($>60\text{ mg}^{-1}\cdot\text{kg}^{-1}\cdot\text{d}^{-1}$) have also been reported^[11].

Measuring the serum concentration (SC) of LEV can be useful in assessing compliance and managing patients in situations associated with pharmacokinetic (PK) alterations in pathological states such as renal impairment, as well as in specific age groups such as children and the elderly^[12,13]. Numerous chromatographic methods for the quantification of LEV in serum have been described. These include high performance liquid chromatography (HPLC) with ultraviolet (UV) detection and gas chromatography (GC) with various detection systems^[14–16].

Levetiracetam has been used in the treatment of children with epilepsy in China since 2007; however, the PK parameters in Chinese children are not known. Therefore, the aims of the present study were to develop a population pharmacokinetics (PPK) model of levetiracetam in Chinese children with epilepsy.

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Materials and methods

Patients

Children with epilepsy aged 0.5–14 years were recruited by pediatricians at outpatient clinics in Peking University First Hospital. They were treated with LEV monotherapy or adjunctive therapy for 1 week at least on a stable LEV dose treatment. They presented with various types of epilepsy syndromes, including partial, generalized and undetermined. For each patient, the time between dosing and sampling, gender, age, weight, serum concentration, and co-administered medications were recorded. LEV tablets were administered in daily doses of 20–60 mg/kg. The LEV dose regimen could be adjusted in cases of inadequate seizure control or side effects.

Sample collection

The sampling times to last LEV intake were generally between 1 h and 13 h (Figure 1). Blood samples were kept at room temperature for 30 min before they were centrifuged, and the separated serum was preserved at -20°C in our laboratory for less than a week before analysis.

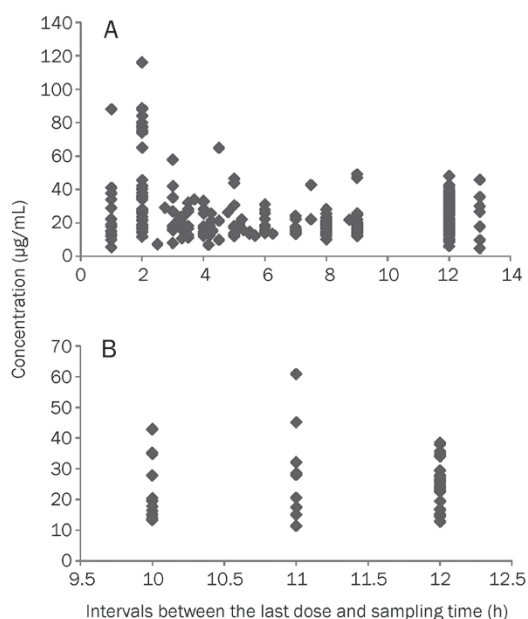


Figure 1. Scattergram of concentrations and intervals between the last dosage time and the sampling time of patients. (A) the PPK model group. (B) the PPK validation group.

Analytical method

This method has already been successfully established in China^[17]. Briefly, the HPLC system consists of a Waters 1525 (Waters company), including a manual sampler, a degasser, a quaternary pump, a thermostatted column compartment and a variable wavelength detector. The chromatographic separation of the analyte is done on an Alltima C18 (Grace Davison Discovery Sciences Company, Deerfield, IL, USA, 150 mm \times 4.6 mm, 5 mm particle size) analytical column protected with a

pre-filter. Data were collected and analyzed using a Breeze software package, version 3.03. LEV and an internal standard UCB17025 were provided by UCB Pharma (Brain-l'Alleud, Belgium). By spiking drug-free human serum with a working solution, calibration samples between 160 and 1.25 mg/L were obtained. A linear regression was performed from chromatographic data that allowed us to extrapolate the LEV concentration in each patient sample. Quality control samples were prepared at three concentration levels, with target values of 2, 16, and 80 mg/mL. An internal standard (100 μL of a 40 $\mu\text{g/mL}$ solution) and 1 mL dichloromethane were added to 100 μL serum sample. After vortexing for 1 min, ultrasonication for 10 min and centrifuging at $4000\times g$ for 10 min, the upper layer was removed and evaporated to dryness under a nitrogen stream at room temperature. The residue was reconstituted in 100 μL methanol, of which 20 μL was injected into the chromatographic system. The flow rate was 1 mL/min and the column temperature was 37°C . The wavelength detection was set at 210 nm. The retention time of LEV and UCB17025 was 5.45 ± 0.10 and 7.50 ± 0.20 min under the described conditions, respectively.

PPK modeling

After parameterization according to previous studies^[11, 18], the LEV concentrations were suited to using a one-compartment model and a first-order absorption process. The PPK modeling included the base model and final model.

PPK model of LEV

The PK data were analyzed with the use of nonlinear mixed effects modeling (NONMEM, version 7, level 1.2). To describe the PK of LEV, the PK disposition model was tested using a standard one-compartment model with subroutine ADVAN2 TRANS2. The first order conditional estimation (FOCE) was used to develop the model. Firstly, the basic model with inter-individual variability was set up. The model was parameterized for apparent clearance (CL/F), the apparent volumes of distribution of the central compartment (V/F), and the absorption rate constant (K_a). $CL/F = \theta_{CL/F} \exp(\eta_{CL/F})$; $V/F = \theta_{V/F} \exp(\eta_{V/F})$; $K_a = \theta_{K_a} \exp(\eta_{K_a})$. Secondly, the covariate variability was added step by step and the full PPK model was set as follows:

$$P_i = \theta_i \times (\text{COV}/\text{mCOV})^{\theta_j} \times e^{\eta_i}$$

where P_i is the individual predicted parameter value, θ_i is the typical population estimate of P_i , η_i is the proportional difference, COV and mCOV are the individual and median covariate values, and θ_j is the power factor for the effect of the covariate on P_i . The effects of categorical covariates on the structural parameters were modeled as follows:

$$P_j = [\theta_{1j} \times N_{1j} + \theta_{2j} \times N_{2j} + \dots] \times e^{\eta_j}$$

where P_j is the individual predicted parameter value, θ_{1j} is the typical population value of P_j for category 1 of the covariate, and N_{1j} is an indicator variable that has a value of 1 when the covariate is present and 0 when the covariate is absent. The covariates of this study included: age (year), weight (WEIG), dose [the dosage of whole day (mg) before sampling] and co-administered medications (CO)].

Data analysis

When the important covariates were selected, a stepwise forward and backward approach was used and each covariate was added or deleted individually. Sex and CO were the categorical covariates. These categorical covariates were modeled by the use of indicator variables. The influences of continuous covariates, such as age, weight, dosage, were also explored. The likelihood ratio test was used to determine the appropriateness of a selected covariate. A decrease in the objective function values (OFV) (-2 log-likelihood) of 7.88 units was considered significant ($\chi^2 P < 0.005$, $df = 1$). Throughout the process of model development, graphic methods were also used to judge the general goodness of fit.

Statistical model

When an influence of the fixed effect was not considered, individual PK parameters were typical population values plus the random deviation. According to the experiential formulations, inter-individual and intra-individual deviations (residual deviation) were presented as follows:

$$P_j = P_{TV} \times e^{\eta^p}$$

$$E_{ij}^0 = E_{ij} + \varepsilon_{ij}$$

where P_j is the j th patient PK parameter; P_{TV} is the typical value of P for the population, η^p is inter-individual deviation (a mean of 0 and variance ω_p), E_{ij}^0 is the observation value, E_{ij} is the prediction value of E_{ij}^0 , and ε_{ij} is the intra-individual deviation (its mean is 0 and variance is σ_E^2).

Model validation

To validate the basic and the final model, concentrations from 50 patients in the valid group were predicted by the two models. These patients were enrolled at random. To assess the accuracy and precision of the concentration prediction, the mean prediction error (MPE), mean squared prediction error (MSPE), root mean-squared prediction error (RMSPE), weight residues (WRES), and the 95% confidence intervals (95% CI) were calculated. Then, the values of the two models were compared^[19]. The shrinkage for each of the parameters in the model was evaluated using the method described by

Karlsson^[20].

Results

Patient demographics

A total of 418 samples obtained from 361 patients aged from 0.5–14 years were available for PK modeling. The characteristics of the studied population are summarized in Table 1. The intervals between the last dosage time and sampling time were distributed over 1–13 h (Figure 1). The distributions of the intervals between the last dosage time and sampling time in the model group are shown in the Figure 2. All of the patients had normal renal and hepatic function. In this population, 40% and 60% used one or two concomitant anti-epileptic drugs (AEDs), respectively. The most frequently used concomitant AEDs were valproic acid (VPA), lamotrigine (LTG), carbamazepine (CBZ), oxcarbazepine (OXC), and topiramate (TPM).

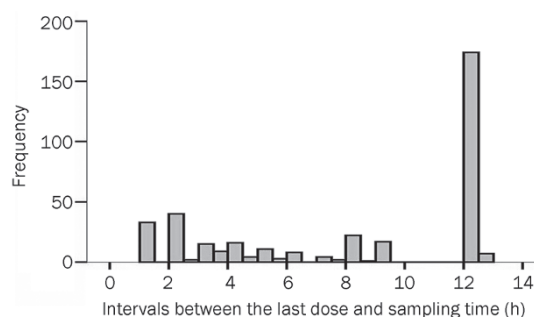


Figure 2. Frequency of intervals between the last dose and sampling time in the model group.

PPK modeling

A classical one-compartment model with first-order absorption, and linear elimination (ADVAN2 and TRANS2) best described the data. The distributions of concentration data and sampling times in the PPK model and PPK valid groups are shown in Figure 1. In the basic model, $K_a = 1.95$ (h^{-1}),

Table 1. Baseline characteristics of patients included in this study.

Characteristics	PPK model group	PPK validation group
Patient data		
No patients	311	50
Gender (male: female)	160:151	27:23
Mean age (years) (range)	6.34 (0.5–14)	5.78 (1.5–13)
Mean weight (kg) (range)	25.17 (5–70)	21.77 (11–35)
Mean dosage (mg/d) (range)	655.17 (250–2000)	529.17 (250–1000)
Sample data		
Mean sampling time (h) (range)	7.35 (0.1–13)	11.01 (10–12)
Total no. concentration-time points	368	50
Mean dose ($mg \cdot kg^{-1} \cdot d^{-1}$) (range)	35.7 (5.1–62.5)	31.4 (10–50.7)
Mean LEV concentration ($\mu g/mL$) (range)	27.99 (4.85–116.11)	25.11 (11.27–60.88)

$V/F=12.3$ (L), and $CL/F=0.988$ (L/h). In the full regressive model, the results of all the covariates were validated by a hypothesis test (Table 2). The parameters of the final model are shown in Table 3, and the final model was as follows: $K_a=1.56$ (h^{-1}), $V/F=12.1$ (L), $CL/F=1.04 \times (WEIG/25)^{0.563}$ (L/h). No significant interaction with the concomitant AEDs was found. The estimated levetiracetam CL/F was 1.04 L/h and the corresponding half-life estimate in these subpopulations was 8.13 h.

Table 2. Results of the hypothesis validation for the full regression model.

Parameter	Covariate	Δ OFV	P-value
CL/F	Age	-6.714	$P>0.005$
	Weight	-128.412	$P<0.005$
	CO	-0.431	$P>0.005$
	Dose	-3.242	$P>0.005$
	Gender	-1.105	$P>0.005$
V/F	Age	-0.154	$P>0.005$
	Weight	-0.528	$P>0.005$
	CO	-3.644	$P>0.005$
	Dose	-2.145	$P>0.005$
	Gender	-2.233	$P>0.005$
K_a	Age	-2.550	$P>0.005$
	Weight	-1.476	$P>0.005$
	CO	-1.560	$P>0.005$
	Dose	-2.279	$P>0.005$
	Gender	-2.410	$P>0.005$

Model validation

Comparison between scattergrams of basic and final model

Diagnostic plots are shown in Figure 3, including Dependent Variable (DV) versus Prediction (PRED), DV versus Individual Prediction (IPRED), weighted residual error (CWRES) versus PRED, and CWRES versus TIME.

Comparison of prediction errors between the final model and basic model

MPE, MSPE, RMSPE, WRES and 95% CI in the basic model and final model are defined in Table 3. The indicators in the final model, such as MPE, MSPE, and RMSPE, decreased and showed more accurate predictions. The shrinkage for each of the parameters in the model is shown in Table 4.

Discussion

In this study, a one-compartment model with first-order absorption and elimination best characterized the data. The model describes the data adequately. The mean CL/F , V/F , and K_a were 1.04 L/h ($0.69 \text{ mL} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$), 12.1 L and 1.56 h^{-1} , respectively. No drug-drug interaction was observed in this study. In this model, the median WEIG in our population was 25 kg. Weight was identified as the most important covariate that explained the inter-individual variability of the apparent serum clearance of LEV.

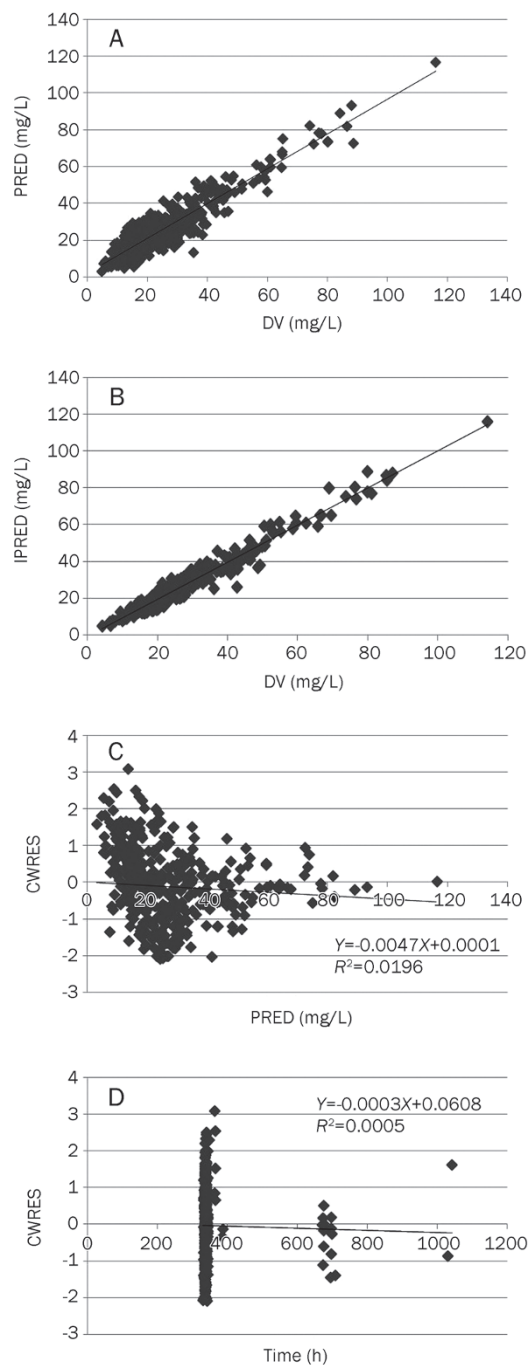


Figure 3. Diagnostic plots of the final PK model. (A) Plot of the observed concentrations versus population predicted levetiracetam concentrations (PRED). (B) Plot of the observed concentrations versus individual population predicted levetiracetam concentrations (IPRED). (C) Plot of population predicted levetiracetam concentrations (PRED) versus CWRES. (D) Plot of CWRES versus TIME. DV: Dependent Variable.

Patient data

There are very sparse PK samples for modeling. There were not enough points in the absorption phase (Figures 1 & 2); therefore, the ωK_a was fixed at 0. There was insufficient information about the absorption and distribution phases, which

Table 3. Comparison of the prediction accuracy between the basic and the final models.

Error	Basic model	Final model
MPE (95% CI)	9.834 (-0.587-197.720)	0.199 (-0.369-0.563)
MSPE (95% CI)	50.919 (0.012-1286.429)	0.002082 (0.00001-0.01054)
RMSPE (95% CI)	1.680 (0.021-34.184)	0.0293 (0.001-0.110)
WRES (95% CI)	0.0621 (-1.100-1.980)	0.153 (-0.030-1.950)

Table 4. Population parameter values for the final model.

Parameter	Estimate	RSE (%)	95% CI	Shrinkage
CL/F (L/h)	1.04	1.4	1.011-1.069	
V/F (L)	12.1	5.6	10.767-13.433	
K_a (h^{-1})	1.56	14.3	1.230-1.997	
Weight (kg)	0.567	6.7	0.489-0.637	
$\omega_{CL/F}$	0.195	7.0	0.106-0.141	20%
$\omega_{V/F}$	0.163	45.5	0.127-0.175	44.9%
ϵ	0.028	18.6	0.018-0.035	31%

RSE (%), percentage of relative standard error ($100\% \times SE/EST$); $\omega_{CL/F}$, $\omega_{V/F}$, variance of the CL/F, V/F, parameters, respectively; ϵ , variance of intra-individual deviation of fitted concentration. The ω_{K_a} was fixed at 0, as there were not enough points in the absorption phase.

may have resulted in potential bias and imprecision regarding the parameter estimates. More attention should be paid to the distribution of the blood sampling time.

Comparison with similar domestic research

Zhao *et al*^[21] studied healthy Chinese male subjects following a single-dose of either 500 mg and 1500 mg of levetiracetam, the median t_{max} was 0.5 h; $t_{1/2}$ was 7.3 ± 0.8 and 7.3 ± 0.7 h. The pharmacokinetic data obtained in these Chinese subjects were similar to the historical data from a matched group of white subjects. There are no related studies of PPK of LEV in Chinese adults with epilepsy.

Comparison with similar overseas studies

Pigeole *et al*^[22] found the following parameters in Japanese and Western adults: K_a (h^{-1})=2.44 (fed intake) or 4.80 (fasted intake), L/F (L/h)= $4.02 \times (WT/70)^{0.268} \times (CL_{CR}/110)^{0.122} \times S \times M$, $F(L)$ = $52.7 \times (WT/70)^{0.952} \times P \times VA$, where WT is the bodyweight in kg; CL_{CR} is creatinine clearance in mL/min; $S=1$ for males and 0.896 for females; $M=1.09$ for enzyme-inducing AEDs, 0.812 for valproic acid and 1 for other AEDs; $P=1$ for epileptic subjects and 0.861 for healthy subjects, and $VA=0.776$ for valproic acid and 1 for other AEDs. Glauser *et al*^[23] found that CL/F was 1.46 ± 0.42 mL·min⁻¹·kg⁻¹ in patients aged from 2.3 to 46.2 months. Toublanc *et al*^[17] found in children aged between 3 months and 18 years, CL/F (L/h)= $2.18 \times K \times (WEIG/30)^{0.753}$, $K=1$ for children not receiving enzyme-inducing AEDs and $K=1.22$ in the presence of enzyme-inducing AEDs. K corresponds to

the typical fold increase in LEV clearance by enzyme inducers. V/F (L/h)= $21.4 \times (WEIG/30)^{0.898}$, K_a (h^{-1})= $1.48 \times (Age/10)^{0.277}$. Chhun *et al*^[18] found that, from 4 to 16 years, CL/F (L/h)= $2.47 \times (BW/33)^{0.89}$, V/F (L)= $21.9 \times (BW/33)^{0.93}$, and K_a (h^{-1})=3.83. The CL/F of this study was lower than in the children in the studies by Toublanc and Chhun^[17, 18]. In Merhar's study of neonates^[24], clearance was 1.21 mL·min⁻¹·kg⁻¹. In Pellock's study^[12] of 6-12 years old, CL/F was 1.43 mL·min⁻¹·kg⁻¹, which was higher than that in adults (0.96 mL·min⁻¹·kg⁻¹) and than the 0.69 mL·min⁻¹·kg⁻¹ observed in the current study. It appears that the CL/F of Chinese children is lower than that of white Caucasian children. The trough serum concentration was also higher than in the white children (Table 5).

It appears that the CL/F in Chinese children was approximately 50% lower than in Western children based on the published data (eg, 0.69 mL·min⁻¹·kg⁻¹ vs 1.21-1.46 mL·min⁻¹·kg⁻¹). LEV was mainly eliminated by the kidneys, and significant ethnic differences were not expected in previous studies; however, racial differences are likely to be at least partly responsible for the difference in CL/F that we observed, and these differences will be the subject of future studies. Our study has a good representation of Chinese children with epilepsy with ages that ranged from 0.5 to 14 years.

Validation of the PPK model

The final model contained covariates, such as age, weight, concomitant medication, and different formulations, and it was more accurate in predicting the patients' blood concentrations than the basic model that had no covariates. For the basic model, the MPE, MSPE, RMSPE, WRES, and their 95% CIs were 9.834 (-0.587-197.720), 50.919 (0.012-1286.429), 1.680 (0.021-34.184), and 0.0621 (-1.100-1.980), respectively. For the final model, the MPE, MSPE, RMSPE, WRES, and their 95% CIs were 0.199 (-0.369-0.563), 0.002082 (0.00001-0.01054), 0.0293 (0.001-0.110), and 0.153 (-0.030-1.950). Furthermore, the RMSPE (95% CI) of 0.0293 (0.001-0.110) in the final model outweighed the basic model's value of 1.680 (0.021-34.184). Therefore, the final model had a better accuracy and precision than the basic model. The shrinkage values of $\omega_{CL/F}$, $\omega_{V/F}$ and ϵ were 20%, 44.9%, and 31%, respectively. The shrinkage of $\omega_{V/F}$ (44.9%) was caused by insufficient information regarding the distribution phase (Figure 2). Based on this final PPK model, individual PK parameters will be estimated by the Bayesian approach in the near future, which will facilitate individualized dosage regimens.

Table 5. Levetiracetam pharmacokinetic parameters from the published literature and from our study.

Dose	Parameters	Fountain ^[25]	Pellock ^[42]	Chhun ^[18]	Our study
10 mg/kg, bid	$C_{12\text{h}}$ (mg/L)	8.4±3.8	-	6.4±2.7	11.25±3.10
	$t_{1/2}$ (h)	4.9±0.6	-	6.8±1.5	8.13±0.3
	CL/F (mgkg ⁻¹ min ⁻¹)	1.14±0.18	-	1.24±0.29	0.69±0.1
20 mg/kg, bid	$C_{12\text{h}}$ (mg/L)	15.6±5.3	-	12.7±4.7	17.5±2.63
	$t_{1/2}$ (h)	4.9±0.4	6.0±1.1	6.8±1.5	8.13±0.22
	CL/F (mgkg ⁻¹ min ⁻¹)	1.10±0.16	1.43±0.36	1.24±0.29	0.69±0.13
30 mg/kg, bid	$C_{12\text{h}}$ (mg/L)	20.6±5.8	-	19.1±7.2	31.25±3.8
	$t_{1/2}$ (h)	4.9±0.7	-	6.8±1.5	8.13±0.35
	CL/F (mgkg ⁻¹ min ⁻¹)	1.12±0.119	-	1.24±0.29	0.69±0.09

CL/F, apparent oral clearance; $t_{1/2}$, elimination half-life.

Conclusion

The population analysis has been successful in describing the pharmacokinetics of LEV in children aged 0.5–14 years. A one-compartment model with first-order absorption adequately described the LEV concentrations. The findings indicate that weight was the most influential factor for the CL/F of LEV in children with normal renal function. This will be invaluable for the development of individualized dosage regimens.

Acknowledgements

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Author contribution

Li WANG designed research; Ye WU and Min-ji WEI performed research; Wei LU and De-wei SHANG contributed new analytical tools and reagents; De-wei SHANG and Ying-hui WANG analyzed data; Ying-hui WANG wrote the paper.

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