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Predictive Performance of Population Pharmacokinetic Models of Levetiracetam in Children and Evaluation of Dosing Regimen

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Abstract

Levetiracetam is a broad-spectrum antiepileptic drug that exhibits high interindividual variability in serum concentrations in children. A population pharmacokinetic approach can be used to explain this variability and optimize dosing schemes. The objectives are to identify the best predictive population pharmacokinetic model for children and to evaluate recommended doses using simulations and Bayesian forecasting. A validation cohort included children treated with levetiracetam who had a serum drug concentration assayed during therapeutic drug monitoring. We assessed the predictive performance of all the population pharmacokinetic models published in the literature using mean prediction errors, root mean squared errors, and visual predictive checks. A population model was finally constructed on the data, and dose simulations were performed to evaluate doses. We included 267 levetiracetam concentrations ranging from 2 to 69 mg/L from 194 children in the validation cohort. Six published models were externally evaluated. Most of the models underestimated the variability of our population. A 1-compartment model with first-order absorption and elimination with allometric scaling was finally fitted on our data. In our cohort, 57% of patients had a trough concentration <12 mg/L and 12% <5 mg/L. To reach a trough concentration >5 mg/L, doses ≥30 mg/kg/d for patients ≤50 kg and ≥2000 mg/d for patients >50 kg are required. In our population, a high percentage of children had low trough concentrations. Our population pharmacokinetic model could be used for therapeutic drug monitoring of levetiracetam in children.

Keywords

epilepsy, neurology, pediatrics, pharmacokinetics, therapeutic drug monitoring

Levetiracetam is a new generation antiepileptic drug (AED) frequently used to treat children with epilepsy. It has a broad-spectrum activity on focal and generalized seizures as first-line treatment or adjunctive therapy.[1] Levetiracetam exhibits a good tolerability profile. Some adverse effects are reported: behavioral abnormalities such as aggression, irritability, or psychotic symptoms; headache; somnolence; ataxia; and seizures.[2]

Levetiracetam demonstrates linear pharmacokinetics with high interindividual variability in serum concentrations with same doses.[2] It is rapidly absorbed (time to maximum concentration, 1-2 hours) and has very low protein binding (<10%).[3,4] Half-life for pediatric patients is estimated between 4 and 6 hours,[5–7] and clearance per kilogram decreases with increasing age. Levetiracetam is mainly excreted unmetabolized by the kidney (70%), explaining that glomerular filtration rate is often included in pharmacokinetic models and that dose adjustments are needed for patients with renal impairment; only one-third of levetiracetam undergoes hepatic metabolism by hydrolysis. Clearance per kilogram in children is 30% to 40% higher than in adults, so children necessitate higher doses in milligrams per kilogram per day.[6,7] Drug-drug interactions between

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levetiracetam and other AEDs seem to be minor because of its minimal hepatic metabolism. However, lower concentrations and exposure to levetiracetam are reported by several studies for patients treated concomitantly with an enzyme inducer (carbamazepine, phenobarbital, or phenytoin). Studies do not report any effect of enzyme inhibitors such as valproate on levetiracetam clearance.[2,8,9]

One-third of patients with epilepsy remain nonresponsive to antiepileptic therapy.[10] To deal with those patients, we need to rationalize AED use, and a population pharmacokinetic approach might be a key to manage it. Model-based dosing algorithms have been proven effective to reduce the variability of concentrations and to individualize treatments with therapeutic drug monitoring (TDM) of AEDs.[10] However, several population pharmacokinetic models for levetiracetam on different populations have been published in the literature. The issue is to choose the appropriate model to use on our pediatric population to optimize dosing schemes. External validation of population pharmacokinetic models is the most robust form of evaluation of predictive performance of models and will be used in our study.[11]

This study reviews all population pharmacokinetic models of levetiracetam in children and assesses their predictive performance on an external validation cohort. The objectives were (1) to externally evaluate the predictive performance of published population pharmacokinetic models, (2) to construct a model with our monitoring data, and (3) to evaluate doses using simulations.

Methods

Population and Treatment

We extracted data for the validation data set from the pharmacology laboratory database of Hôpital Cochin, Paris, France. We included all patients ≤18 years old who had at least 1 levetiracetam serum concentration assay at steady state for routine therapeutic monitoring between 2007 and 2019. The ethics committee of Hôpital Necker Enfants-Malades approved the anonymous use of these data and their publication. Levetiracetam treatment and doses were conducted according to clinicians' expertise. We collected data on dosing regimen, time of last intake, sampling time, age, weight, serum creatinine (SCr), and comedication by valproate or an enzyme-inducing AED (phenobarbital, phenytoin, or carbamazepine). SCr was measured by the enzymatic method. We treated missing data for weight and height by taking the median weight or height for age and sex according to the Centers for Disease Control and Prevention clinical growth charts for the pediatric population. Missing SCr values were calculated according to age with the following formula[12]: mean creatinine (μmol/L) = –2.37330 – 12.91367 × ln(age) + 23.93581 × (age)$^{0.5}$. Glomerular filtration rate was calculated using the Schwartz formula.[13] We excluded patients with missing comedication data, unknown dosing regimen, or unclear delay between dose and sampling and patients for whom a lack of compliance was clearly suspected.

Levetiracetam Serum Concentration Assay

Levetiracetam serum concentrations were measured in the pharmacology laboratory of Hôpital Cochin, Paris, France, by high-pressure liquid chromatography with ultraviolet detection, with a calibration range from 2 to 80 mg/L. Coefficients of variation of intra- and interassay for this method were <15%. The lower limit of quantification (LLOQ) was 2 mg/L.

Population Pharmacokinetic Models Used

A literature review was performed using the PubMed database to identify all published population pharmacokinetic models of levetiracetam. The search was conducted in April 2020 with associations of the following terms ("levetiracetam" AND ("children" OR "infants" OR "pediatric") AND ("population pharmacokinetic" OR "nonlinear mixed effects" OR "NONMEM"). The studies were included if they fulfilled the following criteria: (1) They were in the English language, (2) they contained data on pediatric patients, and (3) a population pharmacokinetic model was developed on oral levetiracetam.

Five studies presenting six different population pharmacokinetic models were published between 2008 and 2016.[14–18] A summary of the main characteristics of those studies is presented in Table 1. A 1-compartment model and a first-order absorption described levetiracetam pharmacokinetics in all studies. Only model 2 described a lag time.[15] Models 4 and 5 were developed on both child and adult data.[17,18] Models 1a, 1b, and 2 were developed with data from trials.[14,15] The covariates explaining interindividual variability were body weight (all models), comedication by an inducer (3 models), glomerular filtration rate (GFR; 2 models), dose (2 models), and age (1 model). In model 1, two different models were proposed: a full model (1a) including weight, inducer comedication, GFR, and dose as covariates of clearance; and a reduced model (1b) with only body weight and inducer comedication as covariates of clearance. Validation methods varied between articles: Goodness-of-fit plots were used for all the models; model 1 used the jackknife method; model 2 used normalized predictive distribution errors; models 2, 4, and 5 used visual predictive checks; and models 3 and 4 used an external validation.

Q4

Table 1. Summary of Key Information of Published Population Pharmacokinetic Models of Levetiracetam in Children

Author (year) N° model	N patients (Samples) Location of the study	Age, y	BW (kg)	Dose (mg/kg/d)	Comedication	Parameters	IIV	Proportional RV
Toublanc (2008) 1a 1b	228 (2319) *Data from trials* North America	9.8 (0.2–18)	32 (6–89)	10–60	Neutral: 44 INH: 75 IND: 86 INH + IND: 23	Full model: $ka = 1.46 \times (AGE/10)^{0.27}$ $CL = 2.17 \times 1.22^{IND} \times (BW/30)^{0.64} \times (DOSE/500)^{0.0443} \times (GFR/100)^{0.111}$ $V = 21.5 \times (BW/30)^{0.901}$ Reduced model: $ka = 1.48 \times (AGE/10)^{0.277}$ $CL = 2.18 \times 1.21^{IND} \times (BW/30)^{0.753}$ $V = 21.4 \times (BW/30)^{0.898}$	$\omega ka = 1.0$ $IOVka = 1.12$ $\omega CL = 0.19$ $\omega V = 0.19$	$\sigma = 0.3$
Chuun (2009) 2	44 (170) *Data from trials* France	11 (4.6-16.6)	33 (16-65)	10-40	Adjunctive therapy	$ka = 3.83$ $ALAG = 0.283$ $CL = 2.47 \times (BW/33)^{0.89}$ $V = 21.9 \times (BW/33)^{0.93}$	$\omega ka = 1.17$ $\omega CL = 0.243$ $\omega V = 0.163$ covCL-V = 0.167	$\sigma = 0.189$
Wang (2012) 3	311 (368) China	6.34 (0.5-14)	25.17 (5-70)	35.7 (5.1-62.5)	Adjunctive therapy: VPA, LAMO, TOPI, CBZ, MHD	$ka = 1.56$ $CL = 1.04 \times (BW/25)^{0.563}$ $V = 12.1$	$\omega CL = 0.442$ $\omega V = 0.404$	$\sigma = 0.167$
Toublanc (2014) 4	186 adults 73 children (1816) Japan and North America		13-90		50% IND 33% IND + INH	$ka = 2.56$ $CL = 2.1 \times (BW/32)^{0.75} \times 1.22^{IND}$ $V = 20.4 \times (BW/32)$	$\omega ka = 0.858$ $\omega CL = 0.199$ $\omega V = 0.122$ covCL-V = 0.135	$\sigma = 0.189$
Ito (2016) 5	225 (583) Adults and children Japan	38 (1-89)	53.8 (9.5-109)	21.4 (1.2-76.7)	None: 57 IND: 298 INH:89 IND + INH: 116 Neutral: 80 VPA: 51	$ka = 0.464$ $CL = 4.33 \times (BW/70)^{0.75} \times (GFR/100)^{0.638} \times (1 + 0.175 \times ((DD/(BW^{0.75}))/59.3))$ $V = 0.753 \times BW$	$\omega ka = 0.638$ $\omega CL = 0.244$	$\sigma = 0.306$
Our model	171 (267) France	8.9 (0.04-18.9)	26.8 (2.8-95)	35.1 (5-66.7)	None or neutral: 171 IND: 28 INH:89 IND + INH: 3 VPA: 65	$ka = 2.56$ (fixed) $CL = 2.4 \times (BW/26.8)^{0.75}$ $V = 80 \times (BW/26.8)$	$\omega CL = 0.434$ $\omega V = 0.758$	$\sigma = 0.43$

ALAG, lag-time (h); BW, body weight (kg); CBZ, carbamazepine; CL, clearance (L/h); covCL-V, covariance between clearance and volume; DD, total daily dose; DOSE, dose of last intake; GFR, glomerular filtration rate (mL/min/1,73m^2); IIV, interindividual variability expressed as the square root of the variance of the eta-distribution (ω); IND, enzyme inducer; INH, enzyme inhibitor; IOVka, interoccasion variability on ka; ka, absorption constant (h^{-1}); LAMO, lamotrigine; MHD, oxcarbazepine; proportional RV, proportional residual variability expressed as square root of the variance of the epsilon-distribution (σ); TOPI, topiramate; V, volume of distribution (L); VPA, valproic acid .

Age, BW, and dose are expressed as median (range).

External Validation

We applied each population pharmacokinetic model to our validation cohort by implementing them one by one into Monolix software version 2018R1 (Lixoft, Antony, France) with the parameters described in the original article. We used R software version 3.3.2 (R Foundation for Statistical Computing, Vienna, Austria) for statistics and graphics. Population predictions were made according to dose, sampling time, and covariate characteristics of our validation data set.

To assess predictive performance of each model, we first compared goodness-of-fit plots of the population predicted concentrations and the observed concentrations. To assess bias and precision of the models, we calculated mean prediction error (MPE) (1) and root mean squared prediction error (2) between population

predicted concentrations of each model and observed concentrations of the validation data set.[19]

$$MPE = \frac{1}{n}\sum_{i=1}^{n}(Cpred_i - Cobs_i) \quad (1)$$

$$MPE = \frac{1}{n}\sum_{i=1}^{n}(Cpred_i - Cobs_i) \quad (2)$$

Predictive performance was also assessed with prediction corrected–visual predictive check (pc-VPC) on 1000 simulations. We plotted observed concentrations of the validation data set along with the 5th, 50th, and 95th percentiles of the simulated concentrations to evaluate population predictions visually.

Modeling of the Data With a New Model

Data were analyzed using the nonlinear mixed effect modelling software Monolix. A 1-compartment model with first-order absorption and elimination best described the data. Several error models were investigated (ie, proportional, additive, or combined error models) to describe residual variability. Interindividual variability was defined by an exponential error model. Continuous covariates were integrated as follows: $\theta_i = \theta_{pop} \times (\frac{Cov_i}{median(Cov)})^{\beta}$ where θ_{pop} is the typical value of clearance for a patient with the median covariate value and β is the estimated influential factor for the continuous covariate estimated by the modeling software. For body weight, according to the allometric rule, the power was fixed at 0.75 for clearance parameters and 1 for volume of distribution parameters. Categorical covariates were tested as follows: $\theta_i = \theta_{pop} \times \beta^{COV_i}$, $\mathrm{COV_i}$ equals 0 or 1.

A covariate was finally retained in the model if its effect was biologically plausible, if it produced a reduction in the variability of the pharmacokinetic parameter interindividual variability, and if the OFV was decreased by at least 3.84 (χ^2 with 1 df; $P < .05$) in the upward phase and was increased by >6.63 (χ^2 with 1 df; $P < .01$) in the backward phase.

For evaluation of the goodness-of-fit, the following graphs were performed: observed concentrations vs population predictions and vs individual predictions, and normalized predictive distribution errors vs time and vs predictions.

From the final model, Monte Carlo simulations were performed to compute the pc-VPC. The 5th, 50th, and 95th percentiles of the simulated concentrations at each time were then overlaid on the observed concentration data, and a visual inspection was performed.

Evaluation of Dose Recommendations

Using our final model, we estimated trough levels for our patients. We determined the proportion of patients reaching target concentrations (between 12 and 46 mg/L according to the International League Against Epilepsy)[20] and the proportion of trough concentrations <5 mg/L.[21] Doses simulations were conducted using our final model. For each patient, 1000 simulations were made for each following dose: 20, 30, 40, 50, and 60 mg/kg/d for patients ≤10, 10 to 30, and 30 to 50 kg, and 1000, 1500, 2000, 2500, and 3000 mg/d for patients >50 kg (daily dose divided equally in 2 intakes a day).

Table 2. Demographic and Treatment Characteristics of the Validation Cohort

Number of patients	194
Number of concentrations	267
Number of male/female subjects	109/85
Age, N (%)	
0-1 y	13 (6.7)
1-2 y	8 (4.1)
2-6 y	41 (21.1)
6-10 y	49 (25.3)
10-18 y	83 (42.8)
Median (range)	8.9 (0.04-18.9)
Body weight, kg,[a]	26.8 (2.8-95)
Serum creatinine, μmol/L[a]	37 (13-99)
Glomerular filtration rate, mL/min/1.73m^2[a]	123 (53-350)
Daily dose, mg/d[a]	900 (100-3000)
Daily dose, mg/kg/d[a]	35.1 (5-66.7)
Comedication, N (%)	
Monotherapy or neutral comedication	171 (64.0)
Valproate	65 (24.3)
Inducer	28 (10.5)
Inducer + valproate	3 (1.2)

[a] Median (range)

Results

Population and Treatment

We included data from 194 patients and 267 levetiracetam serum concentrations. The median age was 8.9 years (range, 0.04-18.9 years), and the median weight was 26.8 kg (range, 2.8-95 kg). The main characteristics of the validation data set are described in Table 2. Serum concentrations ranged from the LLOQ (2 mg/L) to 69 mg/L. We had 9 concentrations (3.4%) under the LLOQ for which we used the LLOQ/2. Covariates were missing in 9% of the patients and replaced as indicated in the method. To avoid imprecision in the data, we excluded patients with missing comedication data, unknown dosing regimen, or unclear delay between dose and sampling and patients for whom a lack of compliance was clearly suspected. Since we did not have that much missing data, we did not try to use only complete cases for the external validation.

External Validation

Graphically in Figure 1, models 1a, 1b, 2, and 4 seemed to have the best adequacy between predicted and

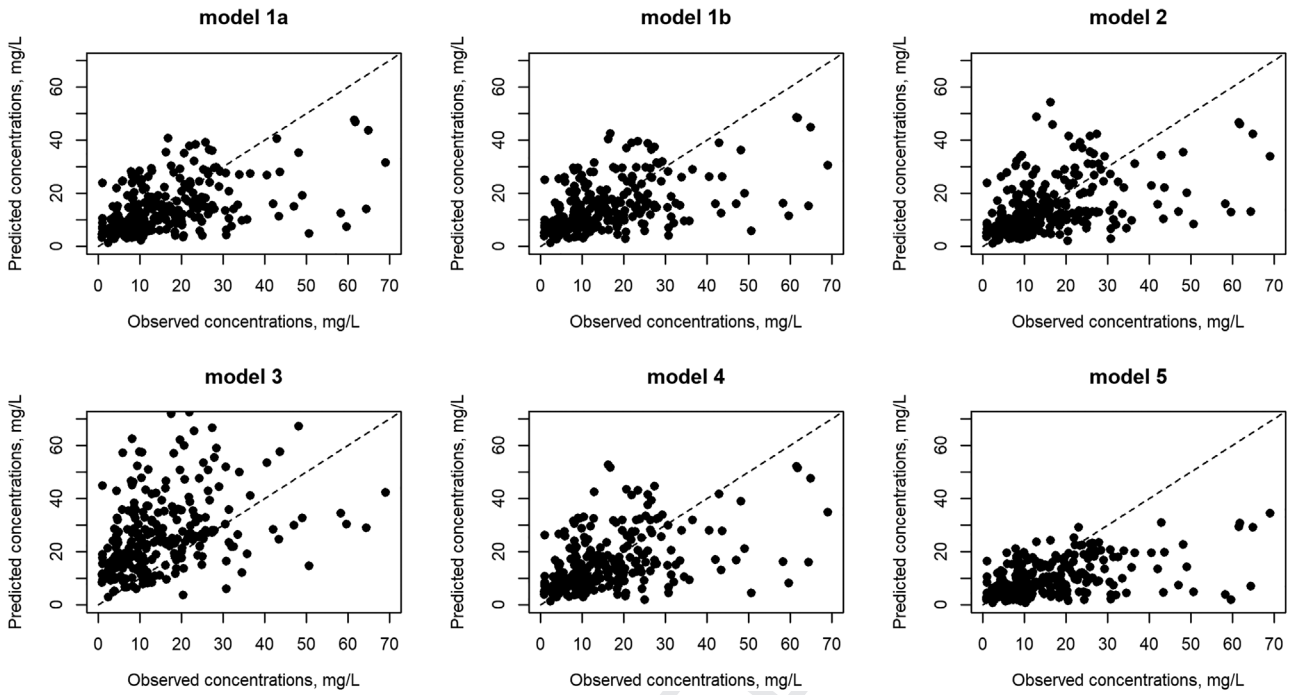

Figure 1. Population predicted concentrations (milligrams per liter) vs observed levetiracetam serum concentrations (milligrams per liter) for the 6 population pharmacokinetic models evaluated. Identity line is represented as a dashed line.

Table 3. Results of Assessment of Predictive Performance for the 6 Levetiracetam Models: Evaluation of Prediction Error

	Bias and Precision	
Model	Mean Prediction Error (mg/L)	Root Mean Squared Prediction Error (mg/L)
1a	−1.6	11.7
1b	−1.0	11.6
2	−−1.1	12.3
3	12.8	20.9
4	−0.14	12.3
5	−5.9	12.8

observed concentrations. These 4 models showed the least bias, with an MPE between –0.14 and 1.6 mg/L, and the highest precision, with a root mean squared prediction error between 11.6 and 12.3 mg/L. Models 3 and 5, respectively, largely overpredicted and underpredicted our observed concentrations. The results of the external validation are presented in Table 3.

On the pc-VPC (Figure 2), most of the models seemed to underestimate the variability observed in our population, for example, lines representing the 5th and 95th percentiles of the observations are often outside the blue areas representing 95% confidence intervals of the 5th and 95th simulated percentiles. Models 1a and 1b seemed to best represent our population with very similar predictive performance graphically and numerically. Because model 1b was a reduced version of model 1a, it appeared to be easier to apply in clinical practice, particularly because no GFR calculation is needed.

Modeling of the Data With a New Model

A 1-compartment model with first-order absorption and elimination, with an allometric model, best described the data. Due to the lack of samples in the first hour after drug intake, the absorption constant rate could not be estimated and was fixed to a value of the literature. The median value of 2.56/h was chosen, although all the other values produced similar estimates for apparent clearance and volume. A proportional error model was used to describe residual variability. Final pharmacokinetic parameter estimates are summarized in Table 4 and diagnostic graphs are shown in Figure 3.

Evaluation of Dose Recommendations

We used our pharmacokinetic model to predict trough concentrations using Bayesian forecasting. The median predicted trough concentration was 11.0 mg/L (range, 0.2-44.1 mg/L). In our population, 146 predicted trough concentrations (55%) were <12 mg/L (lower limit of the reference range), 34 values (13%) <5 mg/L, and none were >46 mg/L (higher limit of the reference range). Predicted trough concentrations according to daily dose, weight, and comedications for our patients are represented in Figure 4.

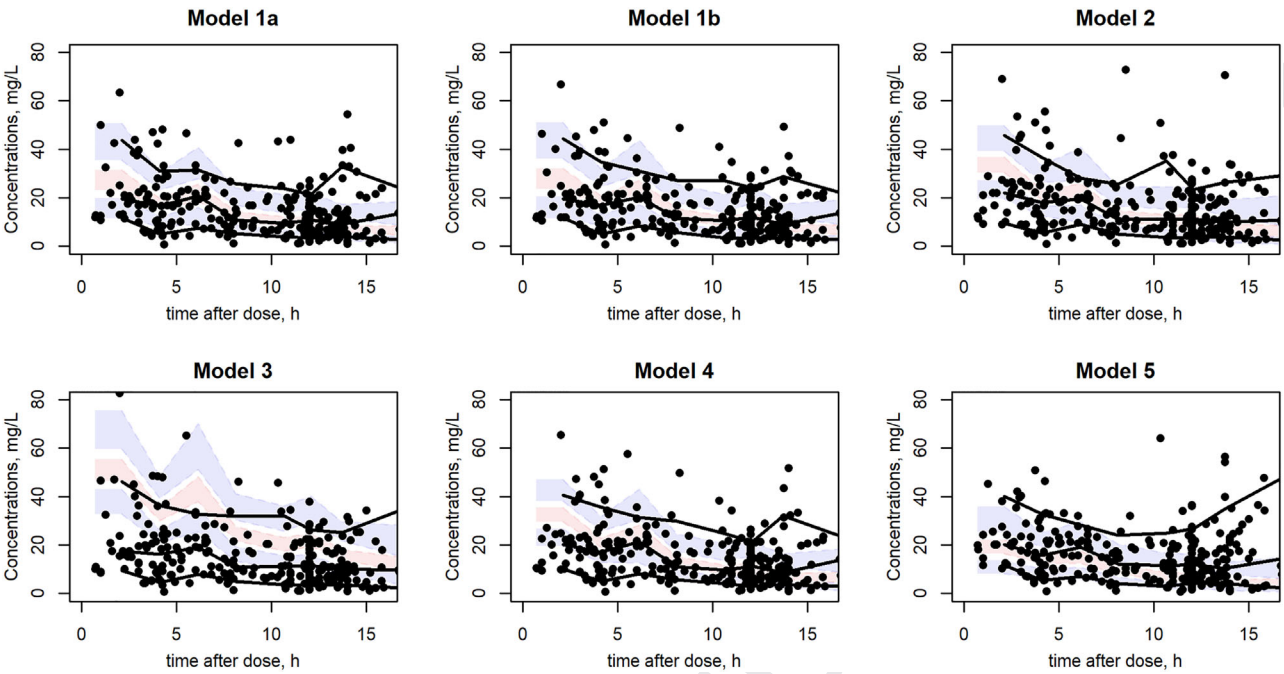

Figure 2. Prediction-corrected visual predictive checks for the 6 levetiracetam models. Colored areas represent 95% confidence intervals of 5th, 50th, and 95th simulated percentiles. Lines are empirical (observed) 5th, 50th, and 95th percentiles. Dots are observed data.

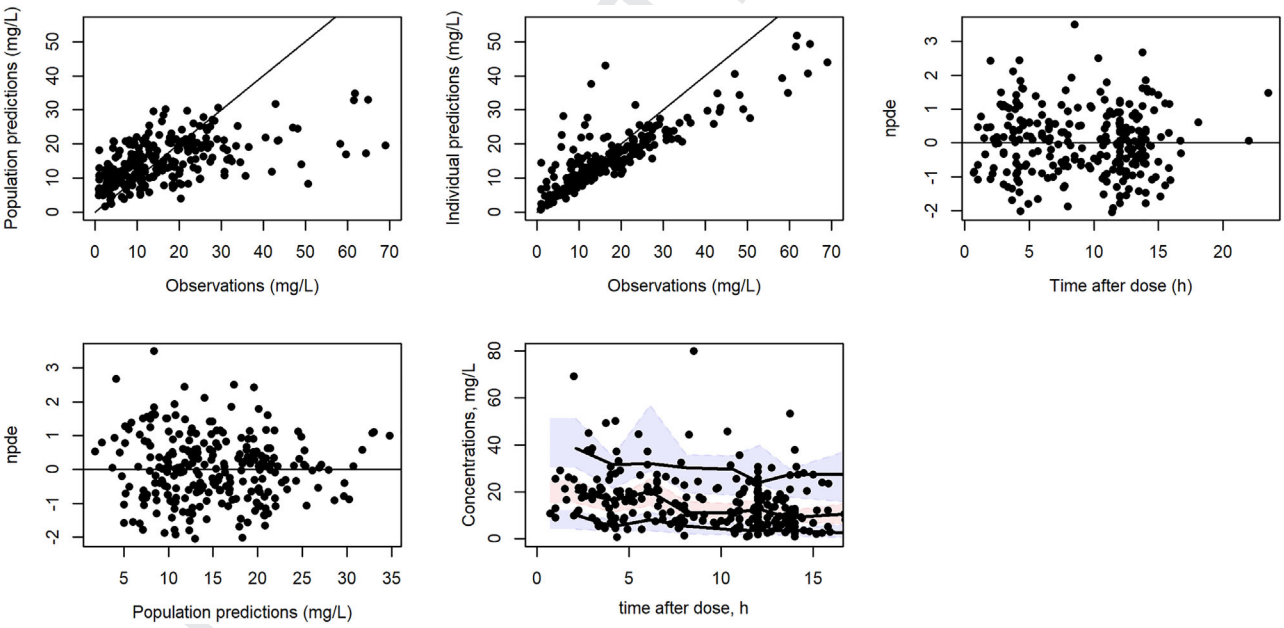

Figure 3. Performance of our model: Population (upper left) and individual (upper middle) predicted concentrations (milligrams per liter) vs observed levetiracetam serum concentrations (milligrams per liter), normalized prediction distribution error metrics vs time after dose (upper right) and vs predictions (lower left) and predicted-corrected visual predictive check (lower middle).

For patients from 10 to 30 kg, 76% (55/72) of patients treated with a dose <40 mg/kg/d had a trough concentration below 12 mg/L vs 35% (17/49) for patients with a dose ≥40 mg/kg/d. For patients from 30 to 50 kg, 76% (29/38) of patients treated with a dose <40 mg/kg/d had a trough concentration <12 mg/L vs 12% (3/25) for patients with a dose ≥40 mg/kg/d. For patients >50 kg, 86% (18/21) of patients treated with a dose <2000 mg/d had a trough concentration <12 mg/L vs 17% (4/24) for patients with a dose ≥2000 mg/d. When looking at trough concentrations with a lower threshold at 5 mg/L, for patients from 10 to 30 kg, 40% (14/35) of

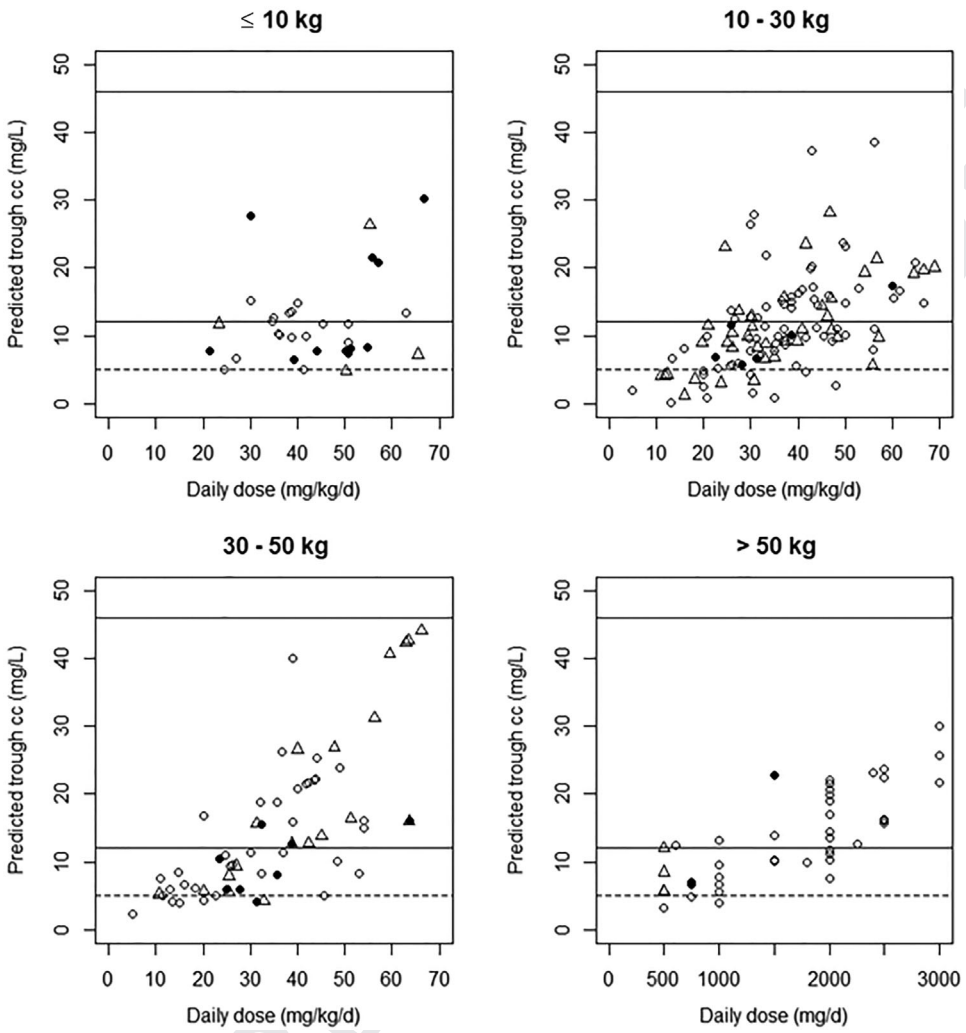

Figure 4. Predicted trough concentrations (cc) in our population (milligrams per liter) according to recommended daily dose in milligrams per kilogram per day for patients ≤10 kg (upper left), patients from 10 to 30 kg (upper right), patients from 30 to 50 kg (lower left) and recommended daily dose in milligrams per day for patients >50 kg (lower right). Monotherapy and neutral comedication are represented with circles (○), enzyme inducer comedication with dots (●), and valproate comedication with triangles (△).

patients treated with a dose <30 mg/kg/d had a trough concentration <5 mg/L vs 7% (6/86) for patients with a dose ≥30 mg/kg/d. For patients from 30 to 50 kg, 21% (5/24) of patients treated with a dose <30 mg/kg/d had a trough concentration below 5 mg/L vs 8% (3/39) for patients with a dose ≥30 mg/kg/d. For patients >50 kg, 14% (3/21) of patients treated with a dose <2000 mg/d had a trough concentration <5 mg/L vs 0% (0/24) for patients with a dose ≥2000 mg/d.

The results of doses simulations are presented in Figure 5 for patients ≤10, 10 to 30, 30 to 50 and >50 kg. To reach a trough concentration above 5 mg/L, simulations suggested the following dosing regimen: a dose between 30 and 60 mg/kg/d for patients ≤50 kg and between 2000 and 3000 mg/d for adolescents >50 kg.

Discussion

To our knowledge, this study is the first to review and assess all population pharmacokinetic models for levetiracetam in children. Our validation cohort was representative of the pediatric population treated by levetiracetam with large ranges of weights, ages, doses, and comedications. We identified suitable models to represent our population, but most of them could not describe the high variability of our patients. A new model was done that could be used for a personalized dosing regimen and dose individualization by Bayesian forecasting in clinical practice.

We conducted an external evaluation of predictive performance of all the population pharmacokinetic models of levetiracetam published for pediatric patients. Models 1a, 1b, 2, and 4 had good predictive

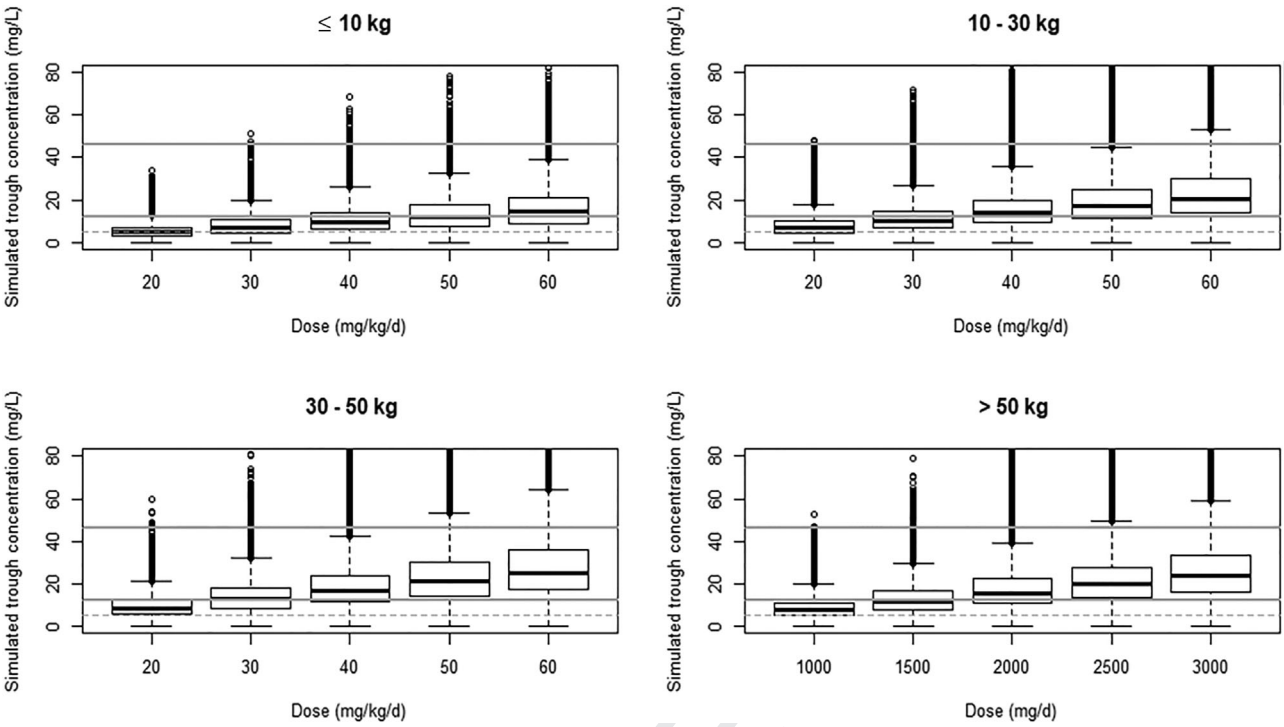

Figure 5. Boxplots of simulated trough concentrations according to daily dose for patients ≤10 kg (upper left), patients from 10 to 30 kg (upper right), patients from 30 to 50 kg (lower left), and patients >50 kg (lower right). Horizontal lines correspond to the target concentration range of 12 and 46 mg/L and dotted lines to a 5 mg/L trough concentration.

Table 4. Pharmacokinetic Parameter Estimates From the Final Model Built

Fixed Population Effects	Estimates	RSE (%)
$Ka(L.h^{-1})$	2.56	FIX
$CL = \theta_{CL} \times (BW/26.8)^{0.75}$		
θ_{CL} L/h	2.4	5
$V = \theta_V \times (BW/26.8)^1$		
θ_V L	80	21
Interindividual variability		
ω_{CL}	0.434	11
ω_V	0.758	34
Residual proportional variability	0.43	8
σ_{prop}		

ω_{CL}, ; ω_V, ; σ_{prop}, ; BW, body weight (kg); CL, clearance; ka, absorption constant; RSE, relative standard error; V, .

performance in our analysis.[14,15] All 4 models were developed on trial data, on a large number of children and samples. The reduced model from Toublanc et al[14] (1b) performed as well as the full model (1a) in our population. First, the coefficients on the covariates "DOSE" and "GFR" in model 1a are very low (0.0443 and 0.111, respectively), resulting in a small effect on clearance. Moreover, few patients had renal impairment (GFR <60 mL/min/1.73 m^2). Thus, the reduced model (1b) would be easier to apply in routine clinical practice. Graphically, both models 1a and 1b demonstrated good predictive performance in our analysis. Since models 1a and 1b had similar predictive performance as our model, we also conducted dose simulations with these models that confirmed our results. Model 5 also performed well but with less precision and more bias, probably because it was developed on both adults and children.[17,18] Indeed, their development data set contained a larger proportion of adults, and the calculation included an effect of the dose on clearance; children receive higher doses in milligrams per kilogram per day than adults, which might explain the lower performances of this model on our patients.[18] Model 3 reported a 50% lower clearance than the others, explaining the bias found with this model for our population.[16] In their article, the hypothesis for this difference was the existence of ethnical differences between White and Chinese children. This difference was not reported for other populations. For instance, in the study by Toublanc et al published in 2014,[17] there was no difference between a Japanese and a North American population of adults and children. Another study conducted on healthy Chinese adults reported similar pharmacokinetics as White subjects.[22] This difference of pharmacokinetics in Chinese children should be further studied. This raises the question of transferability of models. The studied models demonstrated little bias (as shown by small values of MPE). However, the evaluation by the

pc-VPC showed that none of the studied models were validated by our data because of underestimation of variability or due to structural model misspecification. The difference between data from trials and data from routine monitoring could explain these large differences in variability. Another hypothesis for this increased variability is that patients who need TDM during their levetiracetam treatment might have different underlying conditions or different characteristics or can have more severe forms of epilepsy. All this could induce bias in our data compared to trial data, for example. However, our study adds a "routine practice" point of view and exhibits the variability in concentrations experienced in clinical practice. For these reasons, we decided to build a new model to describe this variability.

In clinical practice, the first interest of a population pharmacokinetic model is to propose an initial dosing regimen knowing the patient's characteristics (weight and comedication): This estimation of doses is indicative for a population but is not as precise as individual predictions. Indeed, the second interest is at an individual level: A population pharmacokinetic model can be useful to individualize treatment using Bayesian forecasting when we have a serum concentration assayed during TDM.[23,24]

The reference range for levetiracetam serum concentrations relies on reported concentrations and retrospective database and is not consensual. Indeed, clear efficacy or toxicity thresholds have not been described yet. Different ranges of trough concentrations have been reported: 12 to 46 mg/L for the International League Against Epilepsy,[20] but other authors reported a lower threshold of 8, 6, or even 5 mg/L.[21,25,26] The target 12 to 46 mg/L is extracted from an abstract published in 2002 on 371 samples from adults and 29 children with no precision on the time of sampling.[25] In 2003, May et al[9] reported trough concentrations of 16 ± 9.7 mg/L for 363 adults and children. Similarly, Johannessen et al[27] proposed a target between 8 and 26 mg/L. In our study, 12% of our patients had a predicted trough concentration <5 mg/L and 57% were <12 mg/L. From these results, an efficacy threshold at 12 mg/L seems quite high, and an efficacy on seizures with lower trough concentrations is highly possible. A very high number of patients had predicted trough concentrations below the lower threshold. We can see in Figure 4 that these patients were mainly patients with low doses. According to our simulations, following doses would be required to reach a trough concentration >5 mg/L: ≥30 mg/kg/d for patients ≤50 kg and ≥2000 mg/d for patients >50 kg. Regarding the uncertainty of the efficacy threshold for levetiracetam, clinical evaluation should remain the major way to judge efficacy. Levetiracetam doses should be increased gradually to reach the lower efficient dose, and TDM could be useful in these cases to search for individual therapeutic levels. However, in case of nonresponse, our study suggests to increase doses to reach therapeutic levels before changing molecules. We could not evidence an effect of inducer comedications on levetiracetam pharmacokinetics, although several studies exhibit this effect. This might be due to a small proportion of patients with concomitant treatment by an inducer in our cohort (28/267; 10.5%). The mechanism of this induction on levetiracetam is not properly elucidated since levetiracetam is mainly excreted by the kidney and its hepatic metabolism is mainly due to non–cytochrome P–dependent hydrolysis.[2,6,28]

Since there is no clear target for serum concentrations, TDM of levetiracetam serum concentration is not currently conducted for all patients, and clinical evaluation remains the best way to judge the efficacy of this molecule. However, TDM might be beneficial, especially in some circumstances such as polytherapies, suspicion of toxicity, uncontrolled epilepsy with patients switching molecules, compliance assessment, or patient with an individual therapeutic concentration.[2–4]

This study presents some limitations. First, retrospective collection of routine data implies a degree of uncertainty. However, it reflects the use of population pharmacokinetics in clinical practice. Second, we had 9% of missing data on covariates that we imputed as described in the Methods section. Another way could have been to take only complete cases for the validation, but it would have reduced our population. Third, we did not have clinical data on the control of epilepsy and potential adverse events in our population. Hence, we could not conclude on a relationship between serum levetiracetam levels and the efficacy or toxicity of the molecule and on the relevance of the reference range used. Fourth, all our patients had normal renal function, probably preventing us from including the impact of GFR in our final model. However, impaired renal function is a rare condition in a pediatric population, and TDM should be carried out in those patients.

Conclusion

After a systematic evaluation of predictive performance of published population pharmacokinetic models of levetiracetam in children, we identified a model suitable for our population. Our population exhibits more variability than most of the models tested. This study highlights the need to evaluate population pharmacokinetic models published and raises the question of transferability of models and their utility in clinical practice. It also highlights the need to characterize more properly a reference range for levetiracetam to enable us to rationalize its use in children.

Conflicts of Interest

The authors declare no conflicts of interest.

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Data Availability

Data are available, upon reasonable request, by contacting the corresponding author (manon.tauzin@gmail.com).

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