Development of an Integrated Population Pharmacokinetic Model for Oral Levetiracetam in Populations of Various Ages and Ethnicities

Nathalie Toublanc1,†,*, Brigitte D. Lacroix1,† and Junichi Yamamoto2
1Modeling and Simulation, GED, UCB Pharma, Braine-l’Alleud, Belgium
2Clinical Pharmacology, UCB Pharma, Tokyo, Japan

Summary: Levetiracetam [E Keppra®] is a second generation antiepileptic drug for different types of epilepsy in adults and children ≥1 month. The objective is to develop a population pharmacokinetic model to describe the pharmacokinetics of levetiracetam in Japanese children and adults as well as North American children, the purpose being to explore potential dosing recommendations in Japanese children. Levetiracetam plasma concentration-time data were obtained from Japanese adult and pediatric clinical studies. The data were analyzed through non-linear mixed effects modelling. The model was used to perform simulations and compare the exposure in Japanese children and adults. It was subsequently extended to North American children through an external validation. A one-compartment model with first-order absorption and first-order elimination adequately described the data. The exposure parameters determined based on the simulations in children were well within the adult range. The external validation against historical data from North American children was successful. The integrated population pharmacokinetic model provided a good description of the data, confirming the similarity of levetiracetam pharmacokinetics in these various populations. In Japanese children, a target dose of 10 to 30 mg/kg twice daily ensures the same exposure as the recommended dose in Japanese adults of 500 to 1,500 mg twice daily.

Keywords: levetiracetam; anti-epileptic; population pharmacokinetics; pediatric; epilepsy; Japanese; ethnicity; Keppra; E Keppra

Introduction

Levetiracetam [E Keppra®; (−)-(S)-α-ethyl-2-oxo-1-pyrrolidine acetamide] is a second-generation antiepileptic drug (AED) indicated as an adjunctive therapy for partial-onset seizures in adults and children ≥1 month.1–5 Myoclonic seizures6 in patients with juvenile myoclonic epilepsy and generalized tonic-clonic seizures7 in patients with idiopathic generalized epilepsy. Studies have shown that levetiracetam has a rapid onset of action, and the recommended starting dose for adjunctive therapy (500 mg twice daily in adults, 10 mg/kg twice daily in children ≥4 years) is effective in controlling seizures.4,6

To date, the pharmacokinetic characteristics of the drug have been established from studies conducted mainly in Caucasian adults and children and Japanese adults.9 In adults, levetiracetam is rapidly and completely (>95%) absorbed, with proportional and time-independent pharmacokinetics and a low potential for clinically relevant drug-drug interactions.10–15 Levetiracetam is excreted in the urine, mainly unchanged (two thirds of the dose) and as a pharmacologically inactive metabolite (ucb L057; one third of the dose) formed by serine esterase hydrolysis of the acetamide group.16

In children, as in adults, levetiracetam is rapidly absorbed, with peak plasma concentrations being achieved within 0.5–2.3 h after dosing, and it has also shown linear pharmacokinetics.17–19 The terminal elimination half-life (t1/2) in children is 5–6 h, slightly shorter than in adults, and steady state is reached rapidly, which is consistent with findings in adults, where steady state is achieved after 2 days.18,20 A population pharmacokinetic analysis of five studies in children from North America (the United States, Mexico and Canada) showed that a one-compartment open model with first-order absorption and elimination adequately described the data and that the pharmacokinetics in children is very similar to that in adults.15

In order to establish whether the pharmacokinetics of levetiracetam is similar between Japanese and Caucasian adults, a population pharmacokinetic meta-analysis was conducted on data from Japanese adults including healthy volunteers and patients. It...
confirmed there was no significant difference in pharmacokinetics between Japanese and Caucasian adults.14)

This paper reports a population pharmacokinetic analysis conducted on pharmacokinetic data from Japanese patients, including both adult and pediatric epileptic patients. The objectives of the analysis were to characterize the pharmacokinetics of oral levetiracetam in Japanese children, to assess dose recommendations for Japanese children by comparing the pharmacokinetics in Japanese adults and children and to compare levetiracetam pharmacokinetics in Japanese and North American children. This work was conducted to provide support for a pediatric submission in Japan.

Methods

Data: Data from three clinical trials were included in the population pharmacokinetic analysis (Table 1). All patients were Japanese and had epilepsy with partial-onset seizures. Study N16521) (ClinicalTrials.gov NCT00600509) and its open label extension N0102022) (ClinicalTrials.gov NCT00160615) were conducted in adults and Study N01223 (ClinicalTrials.gov NCT01063764) was conducted in children between 4 and 16 years old. Dosing was twice daily for at least 10 weeks in all three studies. Adults were treated with levetiracetam 250 mg and 500 mg tablets while children were treated with either dry syrup or 250 mg tablets. The research followed the ethical principles for medical research in the Declaration of Helsinki 1964 as modified by subsequent revisions. Approval was obtained for all trials from Independent Review Boards and informed consent was obtained from each patient/guardian.

Any patient who received levetiracetam and provided at least one plasma concentration with a valid dosing record and time was included in the analysis. Study N01223 was ongoing at the time of the last child had completed at least 6 months of treatment. Only sparse data were available from the adult patients (between 2 and 5 samples per patient). The pediatric study was prospectively designed to perform a population pharmacokinetic analysis; therefore, the pediatric data were more comprehensive (more than 12 samples planned per patient).

Table 1. Summary of the design, dosing and sampling for the three trials included in the levetiracetam population pharmacokinetic analysis of Japanese patients with partial-onset seizures

<table>
<thead>
<tr>
<th>Study</th>
<th>N165 21)</th>
<th>N0102022)</th>
<th>N01223</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study type</td>
<td>Therapeutic, confirmatory, placebo-controlled</td>
<td>Long-term, open follow-up to N165</td>
<td>Therapeutic confirmatory + follow-up</td>
</tr>
<tr>
<td>Number of patients included in the dataset</td>
<td>216</td>
<td>154</td>
<td>73</td>
</tr>
<tr>
<td>Population</td>
<td>Adults</td>
<td>Adults</td>
<td>Children</td>
</tr>
<tr>
<td>Age range</td>
<td>16 to 55 years</td>
<td>16 to 55 years</td>
<td>4 to 16 years</td>
</tr>
<tr>
<td>Formulation</td>
<td>Tablet</td>
<td>Tablet</td>
<td>Dry syrup, tablet</td>
</tr>
<tr>
<td>Dose</td>
<td>1,000 and 3,000 mg/day</td>
<td>1,000 to 3,000 mg/day</td>
<td>20 to 60 mg/kg/day, capped to adult doses</td>
</tr>
<tr>
<td>PK sampling</td>
<td>1 sample at any time at selection visit, end of baseline visit, all evaluation visits and final visit</td>
<td>1 sample at any time every 3 months</td>
<td>Treatment period: 2 samples x 2 visits during up-titration, 2 samples x 3 visits during evaluation Follow-up period: 1 sample per visit at any time every 12 weeks Following down-titration: 1 sample at any time x 2 visits</td>
</tr>
<tr>
<td>PK samples per patient</td>
<td>Approximately 5</td>
<td>Approximately 2 to 3</td>
<td>&gt;12</td>
</tr>
<tr>
<td>Maximum number of concomitant AEDs</td>
<td>3</td>
<td>3</td>
<td>2</td>
</tr>
</tbody>
</table>

AED, antiepileptic drug; PK, pharmacokinetic.

Software and data analysis: Nonlinear mixed-effects modeling was performed using the computer program NONMEM version 7.1.2 (ICON Development Solutions, Ellicott City, MD)23) launched using the PsN version 3.2.12 interface (Uppsala University).24) The first-order conditional estimation with interaction (FOCE I) method was used as the estimation algorithm. Model selection was based on changes in the NONMEM objective function value, the goodness-of-fit plots, and clinical significance. SAS 9.2 and R 2.10.125) were used for graphic outputs. Simulations were performed with NONMEM and R.

Handling of outliers: Before starting the analysis, the levetiracetam plasma concentration-time dataset was examined to detect outliers. The dose-normalized concentrations were transformed to the log domain and the lower and upper bounds of the range (defined by mean ± 3 standard deviations) were computed. Concentrations outside this range were considered absolute outliers and were excluded from the model building after checking for explanatory covariates. Furthermore, based on the results of the first runs, points with conditional weighted residuals (CWRES) greater than 6 were considered as suspected outliers. These outliers were excluded from the initial model building; however, the final model was rerun with re-inclusion of the suspected outliers but not the absolute outliers that remained commented out.

Model development:

Model structure

In previous population analyses following oral administration of levetiracetam,14,15) data were adequately described by a one-compartment linear model with first-order absorption and first-order elimination. The same structural model was assumed and evaluated for this analysis. The model was expressed in terms of the absorption rate constant (ka), apparent clearance (CL/F) and volume of distribution (V/F). As the analysis included pediatric patients, body weight was incorporated in the structural model on both CL/F and V/F. The exponents for body weight were estimated on CL/F and V/F. They were fixed to the accepted allometric values if supported by the data (0.75 on CL/F and 1 on V/F).26,27)

Random effects models

The inter-individual variability (η) was assessed on each fixed effects parameter (k<sub>a</sub>, CL/F and V/F) as an exponential term and was assumed to be normally distributed. The magnitude of inter-
individual variability in each parameter was approximated as the square root of the variance, expressed as a coefficient of variation (CV).

Given that concentrations were available on multiple occasions during the pediatric study, an intra-occasion variability was evaluated on the fixed effects parameter, \( k_a \).

A combined additive and constant CV error model was initially tested for the residual error. The relative merits of each component were evaluated.

**Covariate model**

Based on previous knowledge,\(^5\) the following covariates were deemed to be of potential clinical relevance or are known factors in the pharmacokinetics of levetiracetam: age on CL/F and V/F, formulation (tablet or dry syrup) on \( k_a \) and concomitant AEDs by category (neutral, enzyme inducer, enzyme inhibitor, or mixed, i.e., a combination of inducer and inhibitor) on CL/F. Further analyses were conducted on the effect of specific inducing AEDs on CL/F. The covariates were tested for statistical significance and for the relevance of their influence on drug exposure. Only the covariates that fulfilled both criteria were kept in the final model. The need for any dose adjustment based on the magnitude of the clinical effect was discussed subsequently.

The covariate selection, based on the likelihood ratio test, began with the testing of individual covariate effects. All statistically significant covariates at the \( p = 0.05 \) level were included in a full model. A backward elimination procedure was then implemented during which the covariates were removed one at a time until all remaining covariates in the model were statistically significant at the \( p = 0.001 \) level.

Steady-state Monte-Carlo simulations were performed from the model, including and excluding the statistically significant covariates. The maximum plasma concentration (\( C_{\text{max}} \)) area under the plasma concentration-time curve during a dosing interval (AUC\( \text{tr} \)) and minimum plasma concentration (\( C_{\text{min}} \)) were calculated in each case. Clinical relevance was assessed based on calculated ratios for the 3 parameters: ratios of the values for the model including the covariate and the reference for categorical covariates, and ratios of the values for models with extreme values for continuous covariates. If the ratios were >1.20 or <0.80, the covariate was kept in the model. If the ratios were >0.90 and <1.10, the covariate was not kept in the model and the model was reduced.

In all other cases, the decision was made on a case-by-case basis, taking into account the potential influence that the covariate might have on later simulations.

**Final model**

The model, including all covariates that were both statistically significant and clinically relevant, was tested for inclusion of a covariance between the inter-individual variability on CL/F and V/F. The decision to estimate or fix the allometric scaling power exponents on CL/F and V/F was made based on this model. The resulting model was defined as the final model.

**Model evaluation/validation**

To ensure that the final model predicted both the central tendency and the variability in the observed data, a visual predictive check (VPC) was performed overall and with age stratification. Five hundred replicates of the original dataset were simulated, and the simulated concentrations were summarized by computing the 95% confidence interval (CI) of the 5th, 50th (median), and 95th percentiles. The percentiles of the simulated data were then compared to the 5th, 50th and 95th percentiles of the observed data.

**Comparison between Japanese children and adults:** The steady-state plasma concentration-time data simulated with the final model were compared between Japanese children and adults. Concentrations were simulated for two adults, one weighing 40 kg and one weighing 80 kg. This weight range covers the majority of the Japanese adult population in this study (Table 2). Dosing regimens were simulated with low dose (10 mg/kg bid, 500 mg bid) and high dose (30 mg/kg bid, 1,500 mg bid) for children and adults to cover the approved dosing range, even though the pharmacokinetics of levetiracetam is dose proportional. The relevant parameters (\( C_{\text{max}}, C_{\text{min}} \) and AUC\( \text{tr} \)) were derived from simulated concentration vs. time profiles.

**Comparison between Japanese and North American children:** The model developed from the Japanese data was tested for its ability to predict the concentration-time data in North American children. This was performed through an external

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**Table 2. Demographic data and number of concomitant antiepileptic medications for patients included in the levetiracetam population pharmacokinetic analysis of Japanese patients**

<table>
<thead>
<tr>
<th>Study variables</th>
<th>Statistics</th>
<th>N165 (n = 137)</th>
<th>N01020* (n = 152)</th>
<th>N01223 (n = 73)</th>
<th>Overall (n = 259)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>n (%)</td>
<td>74 (54.0)</td>
<td>77 (50.7)</td>
<td>41 (56.2)</td>
<td>137 (52.9)</td>
</tr>
<tr>
<td>Female</td>
<td>n (%)</td>
<td>63 (46.0)</td>
<td>75 (49.3)</td>
<td>32 (43.8)</td>
<td>122 (47.1)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>Mean (SD)</td>
<td>32.8 (10.6)</td>
<td>32.9 (10.1)</td>
<td>10.8 (3.5)</td>
<td>26.8 (13.5)</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>31.0</td>
<td>31.9</td>
<td>11.2</td>
<td>25.6</td>
</tr>
<tr>
<td></td>
<td>Min-Max</td>
<td>16.3–55.4</td>
<td>16.7–54.9</td>
<td>4.3–16.2</td>
<td>43.3–55.4</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>Mean (SD)</td>
<td>59.8 (12.6)</td>
<td>58.7 (12.5)</td>
<td>33.1 (13.7)</td>
<td>51.6 (17.2)</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>58.0</td>
<td>56.9</td>
<td>32.2</td>
<td>51.5</td>
</tr>
<tr>
<td></td>
<td>Min-Max</td>
<td>40.0–107</td>
<td>39.0–96.0</td>
<td>13.8–69.4</td>
<td>13.8–107</td>
</tr>
<tr>
<td>Concomitant AEDs</td>
<td>n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1 Patients in N01020 came from N165. Differences come from N165 patients not going into N01020 and patients who were on placebo during N165.

2 Some patients changed AED during the study; hence, the percentage can be greater than 100%.

AED, antiepileptic drug; SD, standard deviation.
validation using the dataset from a historical, retrospective North American pediatric population pharmacokinetic analysis.\textsuperscript{13} The North American dataset included patients from the United States, Mexico and Canada, with a range of ethnic backgrounds: Caucasian (68.9%), Hispanic (12.3%), Black (11.1%), Asian (1.3%) and Other (5.7%). All the parameters from the final population pharmacokinetic model developed in Japanese patients (fixed and random) were fixed to the values determined for the Japanese patients. The model was first used to predict the North American pediatric data without re-optimizing model parameters. By doing so, the model predicted the concentrations in the North American children using the parameters determined from the Japanese patients. Subsequently, the model developed for the Japanese patients was used to perform a VPC to verify that the model predicted both the central tendency and the variability in the observed data for the North American children. As for the internal validation, 500 replications of the original North American dataset were simulated using the model developed in Japanese patients, and the simulated concentrations were summarized by computing the 95% CI of the 5th, 50th, and 95th percentiles and comparing them to the 5th, 50th and 95th percentiles of the observed North American concentrations.

Results

Data and demographics: Data were available from a total of 259 unique Japanese patients with at least one plasma concentration with a dosing record (186 adults and 73 children). In the pediatric population, each age group (4–8, 8–12 and 12–16 years) was represented by at least 20 patients (Table 2). The majority of adult patients (84%) were between 20 and 50 years old. Due to the combination of pediatric and adult patients, body weight ranged from 13 kg to 90 kg. Over 80% of patients were classified as having received enzyme-inducing AEDs, either alone (50%) or in combination with enzyme-inhibiting AEDs (33%). At the cut-off date of 14 June 2011 for the pediatric study, 21 patients had switched from the dry syrup to the tablet during the follow-up period as permitted by the protocol.

Data description and handling of outliers: Levetiracetam plasma concentration-time data were available from 259 Japanese epileptic patients (186 adults and 73 children), resulting in 1,840 plasma concentration-time points, of which 1,833 were above the limit of quantification (Fig. 1). From the 1,833 quantifiable concentrations, following the initial checks, 15 absolute outliers and 2 suspected outliers (representing less than 1% of the concentrations) were excluded from the dataset. All excluded data were from adult patients who participated in the two older studies (N165 and N01020) which were not prospectively designed to perform a population pharmacokinetic analysis.

Model development: Consistent with previous evaluations of the pharmacokinetics of levetiracetam after oral administration, the plasma concentration-time profile was adequately described by a one-compartment model, with body weight on both CL/F and V/F (base model). Testing of covariates in the univariate analysis revealed there was no significant effect of the formulation on \( k_{a} \), or of age on CL/F or V/F. The only statistically significant covariate with a clinically relevant impact was the effect of inducing AEDs on CL/F. Its effect on drug exposure was close to 20% on AUCr, 10% on \( C_{\text{max}} \) and 30% on \( C_{\text{min}} \). Although the effect was limited, it was still considered sufficiently influential to be retained in the model. The model with body weight on CL/F and V/F and inducing concomitant AED on CL/F was close to the final model. A covariance term between the inter-individual variability on CL/F (\( \eta_{\text{CL}} \)) and V/F (\( \eta_{V} \)) was then introduced, that led to a significant decrease (10.4) in the objective function value (\( p = 0.05, \Delta \text{OBJ} = 3.84 \)). The correlation coefficient between \( \eta_{\text{CL}} \) and \( \eta_{V} \) was high at 74.5%. All the parameters were predicted at least as accurately as when the omega block was not in the model; hence, the omega block between \( \eta_{\text{CL}} \) and \( \eta_{V} \) was kept in the model.

The exponents for body weight on both CL/F and V/F were not significantly different from their allometric values (typical value [95% CI]: 0.758 [0.70–0.81] vs. 0.75 and 0.928 [0.83–1.02] vs. 1, respectively). Hence, they were fixed to their respective allometric values. Although the objective function increased by 3.672, the parameters for the model with fixed allometric exponents for body weight on CL/F and V/F had plausible values and were accurately determined, and the goodness-of-fit plots were good. This model, including inducing AED on CL/F and a covariance term between the inter-individual variability on CL/F and V/F, was declared the final model.

In the final model (Table 3), CL/F (L/h) was expressed by the following equation:

\[
CL = 2.10 \times \left( \frac{BW}{32} \right)^{0.75} \times \theta_{\text{IND.CL}}
\]

where \( \theta_{\text{IND.CL}} \) is a multiplicative factor for the influence of the inducing AEDs on CL/F. It is equal to 1 for patients not taking inducing AEDs and to 1.22 for patients receiving at least one inducing AED. BW is body weight.

Volume of distribution, V/F (L) was expressed by the following equation:

\[
V = 20.4 \times \left( \frac{BW}{32} \right) = 0.6375 \times BW
\]

The overall VPC and the VPC stratified by age (Fig. 2) confirmed that the model could predict both the central tendency and the variability of the plasma concentrations observed during the Japanese studies. The variability may be slightly overestimated by the model as only a very limited number of the observed concentrations were either above the 95th percentile or below the 5th percentile.

Fig. 1. Levetiracetam (LEV) concentration vs. time after last dose in Japanese adults and Japanese children in semi-logarithmic scale

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Comparison between Japanese children and adults: The comparison of the simulated concentrations between Japanese children receiving 10 mg/kg bid and adults receiving 500 mg bid confirmed that the levetiracetam concentrations that would be achieved in Japanese children would be in the ranges of those predicted in Japanese adults. Given the dose proportionality of levetiracetam pharmacokinetics, the results are only presented for the low dose (Table 4 and Fig. 3).

The predicted C_max and AUCr in children were within the predicted C_max and AUCr for adults. The predicted C_min in children was within the predicted C_min in adults for the 12 and 16 year old simulations (median body weight 43 kg and 57 kg, respectively), and slightly below the predicted C_min in adults for the 4 and 8 year old simulations (median body weight 15 kg and 26 kg, respectively). However, the 95% prediction interval (PI) for the C_min of the younger children largely overlapped that of the adults (Table 4).

Comparison between Japanese and North American children: The model for Japanese patients predicted the data for North American children well, indicating that the pharmacokinetics was similar in Japanese patients (4 to 55 years old) and North American children (3 months to 18 years) and that the same model was applicable for both Japanese patients and North American children.

The loess and identity lines were confounded, both in the goodness-of-fit plot representing the population and individual predictions vs. observed concentrations, and in the CWRES. Furthermore, the VPC confirmed that the model developed for the Japanese patients could predict both the central tendency and the variability of the plasma concentrations observed in North American patients (Fig. 4). In this VPC, 7.6% of the concentrations were below the 5th percentile and 8.3% were above the 95th percentile, i.e., slightly greater than the expected 5%. The residual variability determined for the retrospective population pharmacokinetic model developed previously in North American children was higher than that determined during the current model building (30.5 vs. 18.9%).

Discussion

A population pharmacokinetic model was developed based on Japanese pediatric and adult data, which adequately described the pharmacokinetics of levetiracetam in the various groups tested: Japanese children, Japanese adults and North American children. This provided strong evidence for the similarity in pharmacokinetics across different age groups, down to 4 years old, and in different ethnic populations.
conventional effective and safe doses should be evaluated in children. Food and Drug Administration requirements for pediatric label-

Table 4. Pharmacokinetic parameters predicted from the final model in Japanese children and adults for the low dose treatment: 10 mg/kg for children and 500 mg for adults

<table>
<thead>
<tr>
<th>Dose bid</th>
<th>Body weight (kg)</th>
<th>C_max (µg/mL)</th>
<th>C_min (µg/mL)</th>
<th>AUC(0-24h) (µg h/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 mg/kg</td>
<td>15</td>
<td>17.4</td>
<td>4.87</td>
<td>125</td>
</tr>
<tr>
<td></td>
<td>26</td>
<td>18.6</td>
<td>6.30</td>
<td>144</td>
</tr>
<tr>
<td></td>
<td>43</td>
<td>20.4</td>
<td>7.71</td>
<td>164</td>
</tr>
<tr>
<td></td>
<td>57</td>
<td>[14.2–28.8]</td>
<td>[4.51–13.2]</td>
<td>[112–248]</td>
</tr>
<tr>
<td>500 mg</td>
<td>10 mg/kg</td>
<td>[13.0–26.0]</td>
<td>[4.48–12.7]</td>
<td>[106–227]</td>
</tr>
<tr>
<td></td>
<td>26</td>
<td>18.4</td>
<td>7.57</td>
<td>153</td>
</tr>
<tr>
<td></td>
<td>43</td>
<td>[17.2–35.4]</td>
<td>[5.36–16.2]</td>
<td>[137–300]</td>
</tr>
<tr>
<td></td>
<td>57</td>
<td>18.4</td>
<td>7.57</td>
<td>153</td>
</tr>
<tr>
<td></td>
<td>80</td>
<td>14.1</td>
<td>6.08</td>
<td>119</td>
</tr>
<tr>
<td></td>
<td></td>
<td>[9.82–19.8]</td>
<td>[3.65–10]</td>
<td>[83.6–174]</td>
</tr>
</tbody>
</table>

This analysis was consistent with previous findings that the pharmacokinetics of oral levetiracetam is close to ideal characteristics. In summary, the following favourable characteristics were confirmed in this analysis:

- Levetiracetam oral pharmacokinetics can be described by a simple one-compartment model with first-order absorption and first-order elimination.14,15
- Levetiracetam distributes in total body water (0.6–0.7 L/kg), reinforced by the volume of distribution in this analysis (0.6375 L/kg).
- The commonly accepted allometric scaling exponents of 0.75 for the body weight and 1 for the volume of distribution were corroborated based on the levetiracetam data, as discussed below.
- Levetiracetam behaves in a consistent manner irrespective of age or ethnicity.

In accordance with current European Medicines Agency and US Food and Drug Administration requirements for pediatric labeling, effective and safe doses should be evaluated in children.

Establishing such doses for pediatric studies is challenging, given the potential differences between adults and children in size, body composition, hepatic and renal function, and physiological and disease factors. One way of accounting for the size difference between children and adults is allometric scaling, which has been shown to produce accurate results in terms of drug exposure in children.26,27 However, the use of allometric scaling during pharmacokinetic model building, where the exponents are fixed directly to their allometric values, is still a subject of debate and we wanted to see whether our model supported the allometric values. When we left the exponent parameters unfixed, the estimates (0.76 on the CL/F and 0.93 on the V/F) were very close to the theoretical values of 0.75 for the clearance and 1 for the volume. This means that for levetiracetam, with its simple pharmacokinetics and mainly urinary excretion of the parent compound, the allometric scaling approach allows appropriate characterization of the pharmacokinetics down to the age of 4, without more complex methods to account for the other differences between children and adults. Interestingly, in the base model, before inclusion of the covariate “inducing AEDs” on CL/F, the exponent on CL/F was estimated at a value different from 0.75 (0.84 [0.78–0.90]).

The fact that, of the covariates tested in addition to body weight (age, formulation and concomitant AEDs), only the influence of inducing AEDs on CL/F was both statistically significant and had a relevant effect on drug exposure was in agreement with results of previous population analyses. The mechanism through which inducing AEDs increase levetiracetam clearance is still unexplained, given the metabolism of levetiracetam (two thirds urinary excretion of the parent compound and one third hydrolysis by a serine esterase).9,10 Even though inducing AEDs were found to increase the clearance of levetiracetam by 22%, this finding was
not deemed to require dosage adjustment, considering the broad efficacy and safety margin of levetiracetam and the therapeutic approach of individual up-titration. The influence of age on clearance and volume of the formulation on the rate of absorption was tested for completeness, although it was not expected to be significant. Its irrelevance in the current analysis was confirmed.

Age was expected to be clinically significant for levetiracetam only for children aged less than 2 years. When it comes to detecting a potential influence of the formulation (tablet vs. dry syrup) on the rate of absorption, levetiracetam is absorbed very quickly and completely in the fasted state (BCS class I drug) whatever the instant release formulation. Under fed conditions, the absorption is slower due to gastric emptying. The influence of food—uncontrolled in the studies included in the current analysis—would be more important than the potential influence of the formulation.

Overall, the secondary pharmacokinetic parameters (C\text{max}, C\text{min}, AUC, AUCr) predicted for the pediatric population with the dosing regimens used in the Japanese pediatric trial (N01223: 10 mg/kg bid to 30 mg/kg bid) for children up to 50 kg body weight, 500 mg bid to 1,500 mg bid for children over 50 kg) were well within those for adults (approved dose and regimen: 500 mg bid to 1,500 mg bid). Only the predicted C\text{min} for 4-year-old children was slightly lower than that predicted in the adults, probably due to faster clearance in the younger children. The dosing regimens recommended for children (10 mg/kg bid to 30 mg/kg bid) seem appropriate to reach concentrations similar to those predicted in adults.

As the dose recommendation for the trial conducted in Japanese children (N01223) was based on the assumption that the pharmacokinetics was the same as in North American children, it was important to confirm this hypothesis; this was done through the external validation. The Japanese model slightly under-predicted the North American variability, which could be due to the fact that the population pharmacokinetic analysis conducted in North Americans was purely retrospective, hence leading to slightly higher unexplained variability. Overall, however, there was strong evidence that the pharmacokinetics of levetiracetam is the same in Japanese and North American children and that the same dosing regimen can be used for both.

A population pharmacokinetic model was successfully developed, based on Japanese data, which provided a good description of levetiracetam concentration-time data in Japanese children and adults, as well as in North American children. This provided strong evidence for the similarity in pharmacokinetics across different age groups, down to 4 years old, and in different ethnic populations. There were two covariates explaining the inter-individual variability: body weight on CL/F and V/F, and inducing AEDs on CL/F. The model confirmed that the proposed pediatric dosing regimens that demonstrated efficacy and safety of levetiracetam in Japanese and also North American paediatric patients would produce levetiracetam concentrations in the range of those seen in adults. A suitable starting dose of levetiracetam in Japanese children ≥4 years old would be 10 mg/kg twice daily, followed by individualized tailoring of the dose, based on efficacy and tolerability. Levetiracetam confirmed its “toward-ideal” oral pharmacokinetic characteristics.

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