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

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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 seizures[6] in patients with juvenile myoclonic epilepsy and generalized tonic-clonic seizures[7] 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.[4–8]

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 ($t_{1/2}$) 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

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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 N165[21] (ClinicalTrials.gov NCT00600509) and its open label extension N01020[22] (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 population pharmacokinetic analysis; therefore, data from this study were included up to the clinical cut-off date of 14 June 2011, when 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).

Software and data analysis: Nonlinear mixed-effects modelling 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 2.10.1[25] 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 $\pm$ 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 (k_a), 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_a, CL/F and V/F) as an exponential term and was assumed to be normally distributed. The magnitude of inter-

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

Study	N165[21]	N01020[22]	N01223
Study type	Therapeutic, confirmatory, placebo-controlled	Long-term, open follow-up to N165	Therapeutic confirmatory + follow-up
Number of patients included in the dataset	216	154	73
Population	Adults	Adults	Children
Age range	16 to 55 years	16 to 55 years	4 to 16 years
Formulation	Tablet	Tablet	Dry syrup, tablet
Dose	1,000 and 3,000 mg/day	1,000 to 3,000 mg/day	20 to 60 mg/kg/day, capped to adult doses
PK sampling	1 sample at any time at selection visit, end of baseline visit, all evaluation visits and final visit	1 sample at any time every 3 months	Treatment period: 2 samples × 2 visits during up-titration, 2 samples × 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 × 2 visits
PK samples per patient	Approximately 5	Approximately 2 to 3	>12
Maximum number of concomitant AEDs	3	3	2

AED, antiepileptic drug; PK, pharmacokinetic.