Epilepsy Research 132 (2017) 8–14

Contents lists available at www.sciencedirect.com

Epilepsy Research

journal homepage: www.elsevier.com/locate/epilepsyres

Population pharmacokinetics and dose-response relationship of levetiracetam in adult patients with epilepsy

Su-jin Rhee[a,1], Jung-Won Shin[b,1], SeungHwan Lee[a], Jangsup Moon[c], Tae-Joon Kim[c], Ki-Young Jung[c], Kyung-Il Park[c,d], Soon-Tae Lee[c], Keun-Hwa Jung[c], Kyung-Sang Yu[a], In-Jin Jang[a], Kon Chu[c,*], Sang Kun Lee[c,*]

[a] Department of Clinical Pharmacology and Therapeutics, Seoul National University College of Medicine and Hospital, Seoul, Republic of Korea
[b] Department of Neurology, CHA Bundang Medical Center, CHA University, Seongnam, Republic of Korea
[c] Department of Neurology, Laboratory for Neurotherapeutics, Comprehensive Epilepsy Center, Biomedical Research Institute, Seoul National University College of Medicine and Hospital, Seoul, Republic of Korea
[d] Department of Neurology, Seoul National University Hospital Healthcare System Gangnam Center, Seoul, Republic of Korea

ARTICLE INFO

Article history:
Received 16 December 2016
Received in revised form 15 February 2017
Accepted 23 February 2017
Available online 27 February 2017

Keywords:
Levetiracetam
Population pharmacokinetics
Non-linear mixed effect model
Seizure control
Dose titration

ABSTRACT

Levetiracetam (LEV) is commonly used as a mono- or adjunctive therapy for treating patients with partial and generalized epilepsy. This study aimed to develop a population pharmacokinetic (PK) model of LEV, based on sparse data, and to explore LEV efficacy relative to its PK properties in patients with epilepsy. We included 483 LEV concentrations from 425 patients with epilepsy that received multiple oral LEV doses. We performed a population PK analysis, implemented in NONMEM (version 7.2). In addition, we explored the relationships between seizure control and PK variables (i.e., LEV dose, trough concentration, and the number of concomitant anti-epileptic drugs). LEV concentration–time profiles were adequately described with a one-compartment, open linear model, with first-order absorption, and additive residual error. The typical population estimates of the apparent clearance (CL/F) and the volume of distribution (V/F) were 3.9 L/h and 65.3 L, respectively. Body weight was a significant covariate for CL/F and V/F; the estimated glomerular filtration rate only significantly affected CL/F; and concomitant intake of other anti-epileptic drugs did not significantly affect either parameter. A cumulative percentage analysis revealed that over 95% of patients that remained seizure-free received LEV doses of 2000 mg/day or lower. LEV trough concentrations were not significantly different between seizure-free and seizure groups, for each LEV dose. In conclusion, we successfully developed a population PK model of LEV, which enabled investigation of LEV efficacy, relative to its PK properties. The findings in this study can be utilized to optimize LEV dosing regimens in clinical practice.

1. Introduction

Levetiracetam (LEV) is a second-generation, anti-epileptic drug, which is commonly used as a mono- or adjunctive therapy for treating patients with partial and generalized epilepsy. LEV is known to be well tolerated, with a low frequency of side-effects, although there is some remaining concern over behavioral side effects (French et al., 2001; Weintraub et al., 2007). In addition, the favorable pharmacokinetic characteristics of LEV have facilitated clinical use and patient compliance (Rossetti and Bromfield, 2005).

Oral LEV is rapidly and nearly completely (>95%) absorbed. It has displayed dose-proportional pharmacokinetics, with low intra- and inter-subject variability. About 70% of the LEV administered is excreted renally, and the remaining portion undergoes enzymatic hydrolysis of the acetamide group by a plasma hydroxylase. Furthermore, LEV does not bind to plasma proteins, and it is not metabolized in the liver (Patsalos, 2000; Patsalos, 2004). Consequently, LEV is unlikely to participate in clinically significant pharmacokinetic or pharmacological interactions (Otoul et al., 2007; Gidal et al., 2005), although several studies have reported potential drug–drug interactions between LEV and other concomitant drugs (Hirsch et al., 2007; Pigeolet et al., 2007).

* Corresponding authors.
E-mail addresses: stemcell.snu@gmail.com (K. Chu), sangkun2923@gmail.com (S.K. Lee).
[1] These authors contributed equally to this work.

http://dx.doi.org/10.1016/j.eplepsyres.2017.02.011
0920-1211/

For optimum seizure control with LEV monotherapy, serum LEV levels of 12–46 mg/L (6–20 mg/L for trough level) have been suggested as the recommended therapeutic range (Krasowski, 2010; Spencer et al., 2011). Furthermore, in General, the efficacy and adverse effect profile of a drug are dependent on, and mediated by, its pharmacokinetics. Therefore, optimization of systemic LEV exposure is important to achieve a desirable clinical outcome. This optimization requires identification of the population pharmacokinetics and its significant covariates.

The present study investigated determinants of LEV pharmacokinetics in a large population of patients with epilepsy. In addition, we conducted an exploratory assessment of LEV efficacy, relative to its pharmacokinetic characteristics in adult patients with epilepsy to elucidate potential clinical implications.

2. Methods

2.1. Patients

We obtained 483 LEV concentrations from 425 patients with epilepsy who received multiple doses of immediate-release LEV (Keppra®, UCB Pharma, Belgium), administered orally. Patients had visited the epilepsy center, Seoul National University Hospital, Seoul, Korea, from February 2011 to January 2014. Blood samples were drawn from each patient, once the drug had reached a steady state level in the circulation. We extracted data from patient medical records, including LEV dosing histories, times of blood sampling, demographic characteristics, seizure frequency, concomitant drug therapy, and routine laboratory results. Approval for the use of these data was obtained from the institutional review board of Seoul National University Hospital (No. H-1010-042-335).

2.2. Population pharmacokinetic analysis

We analyzed logarithmically-transformed plasma concentration data with a nonlinear mixed-effects modeling approach. We employed the First-Order Conditional Estimation with Interaction method, implemented in NONMEM, version 7.2. The data comprised mostly one sample per patient; therefore, we assumed that the structural model of LEV followed a one-compartment model with first-order absorption and elimination processes. We fixed the absorption rate constant (ka) to a value of 2.44 h^{-1}, based on the literature (Pigeolet et al., 2007). The apparent clearance (CL/F) and the apparent volume of distribution (V/F) were estimated in the model development process. We tested the possibility of estimating inter-individual variability (IIV) for each pharmacokinetic parameter with an exponential error model. To describe intra-individual variability, we tested several residual error models, including additive, proportional, and combined additive and proportional error models, and finally chose an additive error model based on the comparison of goodness-of-fit plots or objective function value (OFV).

The potential influence of covariates was explored graphically and statistically. We evaluated several types of variables, including demographic data: sex, age, body weight, and height; laboratory measurements: serum creatinine, estimated glomerular filtration rate (eGFR), calculated with the modification of diet in renal disease (MDRD) equation (Levey et al., 1999), total bilirubin, albumin, AST, and ALT; and concomitant drugs: phenytoin, valproic acid, carbamazepine, phenobarbital, lamotrigine, oxcarbazepine, pregabalin, topiramate, zonisamide, and clobazam. Each covariate was added to the model, one at a time, and the effect was considered significant, when the OFV decreased by at least 3.84 (χ^2, $P \leq 0.05$ with 1° of freedom). The full model was developed by incorporating all significant covariates. After we constructed the multivariate intermediate model, with all the significant covariates, we assessed the final model by independently deleting each covariate from the model, and we retained only the covariates that changed the OFV by more than 6.63 (χ^2, $P \leq 0.01$ with 1° of freedom).

2.3. Model evaluation

Throughout the model-building process, the adequacy of the model was evaluated by visually inspecting the generated goodness-of-fit plots. A plot of observed vs. population predicted values and a plot of observed vs. individual predicted values were evaluated for randomness around the line of unity. Plots of the conditional weighted residual (CWRES) vs. the individual predicted values and the CWRES vs. time were evaluated for randomness around the zero line. The bootstrap resampling method was used to evaluate the stability of the final model. The final population pharmacokinetic model was fitted repeatedly to 1000 additional bootstrap data sets. The obtained medians of parameter estimates were compared to the final parameter estimates from the original data set. We constructed empirical 95% confidence intervals by observing the 2.5 and 97.5 quartiles of the resulting parameter distributions for those bootstrap runs. In addition, we performed visual predictive checks by overlaying the observed concentrations, classified by LEV dose, onto the median and 90% interpercentile range curves of the steady state concentrations simulated with the final model.

2.4. Exploratory assessment of LEV efficacy

All patients were divided into two groups: the seizure-free and the seizure groups. Patients in the seizure-free group had displayed a seizure-free response to LEV for at least 3 months before the blood sample was taken for pharmacokinetic analysis. Patients in the seizure group had experienced at least one episode of epileptic seizure. The correlation between LEV dosage and seizure occurrence was explored in each dose group. In addition, we also investigated two factors that could potentially influence seizure occurrence: the trough plasma LEV level, predicted from the final model, and the number of concomitant antiepileptic drugs.

3. Results

3.1. Patient characteristics

We enrolled 425 patients into the study, including 206 males (48.5%) and 219 females (51.5%), with a mean age of 37.9 years (range 16–85), and a mean body weight of 65.0 kg (range 40.0–123.6). The daily LEV dose ranged from 125 to 4000 mg/day. The most frequently used concomitant anti-epileptic drugs were oxcarbazepine (33.6%), topiramate (26.4%), and valproic acid (25.4%) (Table 1).

3.2. Population pharmacokinetics

A one-compartment linear model with additive residual error adequately described the concentration–time profiles of LEV. The final model equations for CL/F and V/F were as follows: $CL/F\ (L/h) = 3.9 \times (WT/70)^{0.70} \times (eGFR/90)^{0.44}$; and $V/F\ (L) = 65.3 \times (WT/70)$, where WT = body weight. For CL/F and V/F, IIVs were included in the final model and estimated as 19.9% and 60.8%, respectively, and a significant covariance term was found between the IIVs of CL/F and V/F. Based on all goodness-of-fit plots of the final model, we observed no pronounced bias, which confirmed an adequate model fit (Fig. 1).

The significant covariates of CL/F in the final model were body weight and eGFR. Body weight positively affected LEV CL/F, and it was incorporated into the final model with a power term (Fig. 2A).