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SHORT COMMUNICATION

Influence of enzyme inducing antiepileptic drugs on the pharmacokinetics of levetiracetam in patients with epilepsy

Priscila Freitas-Lima[a,*], Veriano Alexandre Jr.[a], Leonardo Regis Leira Pereira[b,c], Fausto Feletti[c], Emilio Perucca[c,d], Americo Ceiki Sakamoto[a]

[a] *Ribeirão Preto School of Medicine, University of São Paulo, Av. Bandeirantes 3900, 14049-900 Ribeirão Preto, Brazil*
[b] *Faculty of Pharmaceutical Sciences of Ribeirão Preto, University of São Paulo, Av. do Café s/n°, Campus Universitário USP, 14040-903 Ribeirão Preto, Brazil*
[c] *Department of Internal Medicine and Therapeutics, Clinical Pharmacology Unit, University of Pavia, Via Ferrata 1, 27100 Pavia, Italy*
[d] *Clinical Trial Center, National Institute of Neurology, IRCCS C. Mondino Foundation, Via Mondino 2, 27100 Pavia, Italy*

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Summary To assess whether levetiracetam elimination is influenced by enzyme inducing antiepileptic drugs (EIAEDs), serum levetiracetam levels were determined at frequent intervals after a single oral 1000 mg dose in 15 subjects co-medicated with EIAEDs and 15 matched controls. The EIAED group showed a higher levetiracetam oral clearance ($p = 0.01$) and a shorter half-life ($p = 0.02$) than controls. Although the magnitude of interaction is relatively modest, it could have clinical significance for some patients.

Introduction

The antiepileptic drug (AED) levetiracetam (Keppra, UCB Pharma) shows virtually complete oral bioavailability, elimination primarily by renal excretion in unchanged form, and a linear relationship between plasma concentration and dose (Patsalos, 2004). In healthy volunteers, 66% of a single oral dose is recovered unchanged in urine, and an additional 34% is hydrolyzed to the pharmacologically inactive metabolite ucb LO57 (Strolin Benedetti et al., 2003; Patsalos, 2004). Two additional inactive metabolites are produced through oxidation, but together they account for ≤2.5% of total urinary recovery (Strolin Benedetti et al., 2003).

Because the primary route of levetiracetam metabolism does not involve microsomal enzymes, pharmacokinetic interactions between levetiracetam and other AEDs have not been anticipated (Patsalos, 2004). However, compar-

* Corresponding author at: HCFMRP-CIREP, 3900 Av. Bandeirantes, Ribeirão Preto/SP 14048-900, Brazil. Tel.: +55 16 3602 2613; fax: +55 16 3633 0760.
E-mail addresses: priscilalima@usp.br, priscilalima_12@hotmail.com (P. Freitas-Lima).

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Table 1 Demographic and treatment characteristics of the subjects included in the study.

Group	Gender	Age (years)	Weight (kg)	Drug treatment (dose)
EIAED group ($n = 15$)	8M/7F	39.4 ± 9.8 (19—52)	64.8 ± 11.7 (39—82)	Carbamazepine ($n = 13$),[a] 1153 ± 457 mg/day Phenobarbital ($n = 2$),[b] 150 ± 70 mg/day Phenytoin ($n = 1$), 200 mg/day
Control group ($n = 15$)	8M/7F	39.3 ± 10.1 (19—51)	64.5 ± 9.2 (49—82)	No treatment ($n = 4$) Lamotrigine ($n = 9$),[c] 488 ± 92 mg/day Clobazam ($n = 7$),[d] 37 ± 17 mg/day

Data are expressed as mean ± SD [range]. EIAED, enzyme inducing antiepileptic drugs; F, female, M, male.
[a] As monotherapy ($n = 6$) and in combination with clobazam ($n = 6$) and phenobarbital ($n = 1$).
[b] In combination with carbamazepine ($n = 1$) and oxcarbazepine ($n = 1$).
[c] As monotherapy ($n = 2$) and in combination with clobazam ($n = 5$), clonazepam ($n = 1$) and gabapentin ($n = 1$).
[d] As monotherapy ($n = 1$) and in combination with lamotrigine ($n = 5$) and ethosuximide ($n = 1$).

isons of steady-state plasma concentration data in patients with epilepsy provided suggestive evidence that levetiracetam clearance is higher in subjects receiving concomitant enzyme inducing AEDs (EIAEDs) than in those not receiving enzyme inducers, with the magnitude of differences being variable across studies (May et al., 2003; Perucca et al., 2003; Contin et al., 2004; Hirsch et al., 2007; Dahlin et al., 2010). To date, however, no formal pharmacokinetic study has investigated the influence of EIAEDs on levetiracetam disposition in humans.

Since levetiracetam is often used in combination with EIAEDs (Alexandre et al., 2010), clarification of potential pharmacokinetic interactions with these agents can be important for rational prescribing. The purpose of the present study was to compare the plasma level profile and metabolic disposition of levetiracetam in patients comedicated with EIAEDs and in matched controls not receiving medications known to influence drug metabolizing activity.

Methods

Subjects and study design

Enrolled subjects were aged between 18 and 65 years and had to be healthy except for epilepsy. Pregnant women or at risk for pregnancy were excluded. The EIAED group ($n = 15$) comprised subjects on stable (>1 month) treatment with carbamazepine, phenytoin or phenobarbital alone or in combination. The control group ($n = 15$) included matched subjects not on pharmacological treatment or receiving AEDs not considered to affect drug metabolizing activity (e.g., gabapentin, lamotrigine, ethosuximide, benzodiazepines). Subjects on valproate or other drugs known to influence drug metabolism were excluded. Oxcarbazepine was allowed as comedication in the EIAED group only. All subjects gave their written consent, and the protocol was approved by the Ethics Committee of Hospital das Clínicas, Ribeirão Preto School of Medicine, Brazil.

Each subject received a single oral 1000 mg dose of levetiracetam (UCB Pharma, Italy) with 50 mL water. Blood samples were collected before dosing and 1, 3, 6, 9, 12 and 24 h after dosing. The plasma was separated immediately after sampling and stored at −20 °C until analysis. Urine was collected before dosing and for the 0—12 h and 12—24 h intervals after dosing. Urine volumes were recorded and a 20 mL aliquot of each sample was stored at −20 °C until analysis.

Assay methods

Plasma levetiracetam concentrations were determined by high performance liquid chromatography (HPLC) according to Ratnaraj et al. (1996), with minor modifications. The limit of quantification (LOQ) was 1 mg/L. Precision (% CV) at concentrations between 1 and 40 mg/L was better than 15% and accuracy was between 85 and 115%.

Levetiracetam and ucb LO57 were quantified in urine according to Isoherranen et al. (2003), with minor modifications. The LOQ was 25 mg/L for levetiracetam and 10 mg/L for ucb LO57. Precision (% CV) at concentrations from 25 to 600 mg/L (levetiracetam) and 10 to 240 mg/L (ucb LO57) was better than 15% and accuracy was between 85 and 115%.

Pharmacokinetics and statistical analysis

Peak plasma concentration (C_{max}) and time of peak (t_{max}) were obtained directly from the data. The rate constant of the terminal (elimination) phase (λ) was calculated as the slope of the log-linear plasma concentration-versus-time curve. Half-life was obtained as $0.693/\lambda$. The area under the plasma concentration-versus-time curve (AUC) was calculated by the trapezoidal rule with extrapolation to infinity. Apparent oral clearance (CL/F, where F is oral bioavailability) was calculated as dose/$AUC_{0-\infty}$, and apparent volume of distribution (Vd/F) as dose/($AUC_{0-\infty} \cdot \lambda$). Renal clearance ($CL_r$) was calculated as the amount excreted as unchanged drug in 24 h/$AUC_{0-24\,h}$. Non-renal CL/F was calculated as $CL/F - CL_r$.

Pharmacokinetic parameters were compared between groups by using, as appropriate, the Mann—Whitney test (t_{max}, $t_{1/2}$ and $AUC_{0-\infty}$) or paired two-tail Student's t-test (all other parameters). Mean, standard deviation (SD), median and range were calculated for all variables. Statistical significance was set at <0.05.