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Title:

Influence of comedication on levetiracetam pharmacokinetics.

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Abstract:

Background:

Evaluate the effect of concomitant antiepileptic therapy on levetiracetam (LEV) pharmacokinetics.

Methods:

A 6-year retrospective observational study. Patients were grouped according to the antiepileptic drug (AED) used as concomitant medication: **Group A,** LEV in monotherapy; **Group B,** LEV + enzyme-inducing antiepileptic drugs (EIAEDs) and **Group C,** LEV + non-enzyme-inducing antiepileptic drugs (NEIAEDs). Apparent oral LEV clearance (LEV CL/F) and basal serum LEV concentrations (LEV C_0) were compared among the different groups by analysis of variance (ANOVA).

Results:

A total of 330 LEV C_0 corresponding to 205 patients (56% men) were identified. The mean (± SD) of LEV CL/F in group A (n=180), B (n=92) and C (n=58) were 4.41±2.06 L/h, 7.23±3.72 L/h and 4.87±1.65 L/h, respectively. EIAEDs increased LEV CL/F (L/h) by 64% compared to the monotherapy group and by 48% compared to the NEIAEDs group. The greatest induction in LEV CL/F, compared to the LEV monotherapy group,

was observed with carbamazepine (CBZ), followed by oxcarbazepine (OXC) and phenobarbital (PB) and was increased by 81%, 64% and 44%, respectively. LEV C_0 values were significantly lower in the EIAEDs group than in the monotherapy group (17.30±7.77 vs. 20.08±9.69 μg/mL; p=0.038) or indeed the NEIAEDs group (17.30±7.77 vs. 20.49±9.46 μg/mL; p=0.027).

Conclusions:

Comedication with EIAEDs increased LEV CL/F by more than 40% whilst CBZ had the greatest inducing potency with LEV CL/F being 81% higher than that of the monotherapy group. These data suggest that monitoring LEV serum concentration during polytherapy with EIAEDs is indicated.

Key words: Levetiracetam; Pharmacokinetics; Interactions; Comedication.

Introduction:

Levetiracetam (LEV) is a newer-generation antiepileptic drug (AED) extensively used over the past ten years due to its wide range of action, few adverse effects, and good tolerance.

LEV was introduced in clinical practice and referred to as an “ideal antiepileptic drug” (1) because according to pivotal studies, and other previously published studies related to the development of this drug, it presented a favorable pharmacokinetic/pharmacodynamic (PK/PD) profile compared to older AEDs (2).

Its broad spectrum of action has been evidenced in many clinical trials, showing its efficacy and safety as add-on therapy in the treatment of generalized and focal epilepsies (3), myoclonic seizures (4), clonic-tonic seizures (5), and it has also been used in monotherapy (6,7).

LEV presents a predominantly renal elimination and therefore, its plasma clearance mostly depends on renal function as well as the age of the patient. This type of dependence, in contrast to classical AEDs, decreases the probability of pharmacological interactions given its minimal hepatic metabolism and low protein binding (<10%). However, some recent studies (8,9) show that the LEV serum concentration and its half-life elimination can be affected by concomitant drugs.

The aim of this study was to evaluate the effect of concomitant AEDs on LEV pharmacokinetics.

Materials and methods

This retrospective observational study was carried out between June 2007 and December 2013. Study participants were diagnosed with epilepsy and under treatment with oral LEV. The inclusion criteria were as follows: providing one or more basal serum LEV concentrations (LEV C_0), age >16 years old and treatment with LEV for at least one month. Patients considered as "not adhering to and/or doubtfully adhering" to treatment were excluded from the study.

The following data were collected: age, sex, height, weight, serum creatinine and creatinine clearance (CCr) estimated by the Cockcroft-Gault equation using actual weight (10), LEV daily dose (mg), date of regimen initiation, date and hour of serum sampling, basal serum LEV concentrations (μg/mL), diagnosis, type and frequency of seizure, concomitant AEDs and their dosage (mg/day). The AEDs were classified as enzyme-inducing antiepileptic drugs (EIAEDs) or non-enzyme-inducing antiepileptic drugs (NEIAEDs).

Apparent oral clearance of LEV (LEV CL/F) was calculated using equations 1 and 2, depending on whether it was expressed in L/h or mL/h/Kg, respectively.

Equation 1: LEV CL/F (L/h) = [Dose/day (mg/day) x 1 day / 24h] / [LEV C_0 (μg/mL)]

Equation 2: LEV CL/F (mL/h/Kg) = [Dose/day (mg/Kg/day) x 1 day / 24h] / [LEV C_0 (μg/mL) x 1L/1000mL

Patients were grouped according to the concomitant AEDs:

Group A: LEV monotherapy.

Group B: LEV + EIAEAD (phenobarbital: PB; oxcarbazepine: OXC; or carbamazepine: CBZ)

Group C: LEV + NEIAED (pregabalin, gabapentin, topiramate (dose< 200 mg/day), lacosamide, lamotrigine, valproic acid or zonisamide)

Quantification of LEV C_0 was performed using high performance liquid chromatography following the technique described and validated by our Pharmacokinetics Unit (11).

Statistical analysis was carried out using the program Stata®. The quantitative variables were described as mean (□) ± standard deviation (SD) in the cases of normal distribution and as median and 25^{th}-75^{th} percentiles when deviation from a normal distribution was found. The qualitative variables were described as percentages.

The differences between LEV CL/F among the different groups were analysed using the Student t test or by analysis of variance (ANOVA), depending on whether two or more groups were analyzed when the variables followed a normal distribution. If normal

distribution was not followed, analysis was carried out using the Kruskal – Wallis test for multiple comparisons (more than two groups) and the Mann Whitney test for comparisons between two groups. Differences of qualitative variables between groups were analyzed using the Chi-square test. The correlation between continuous variables was measured with the Pearson or Spearman correlation coefficient, depending on the parametric or non-parametric behaviour. Significance was set at $p < 0.05$.

A stepwise multiple linear regression model was used for determining the effect of the different variables on LEV CL/F, with a level of significance of 0.05 for introducing variables in the model.

Results

A total of 330 LEV C_0, corresponding to 205 patients (56% men), were studied.

The principal diagnostics were generalised idiopathic epilepsy (38%), symptomatic focal epilepsy (49%) and cryptogenic focal epilepsy (14%). In each case, LEV was administered in tablet form by oral route.

Table 1 summarizes the demographic and anthropometric characteristics of the patients studied.

Table 2 summarizes the data corresponding to mean ± SD of dose, LEV C_0, LEV CL/F and CCr of the different groups.

The LEV CL/F data are shown in table 2. It can be seen that there was a statistically significant difference in LEV CL/F between the group with EIAEDs and the other groups, expressed in either L/h or mL/h/Kg. No statistically significant difference in LEV CL/F was found between the monotherapy group and the NEIAEDs group (p=0.356).

In table 2, it can be observed that the mean of LEV C_0 was less in the patients of the EIAEDs group compared to the monotherapy group (p=0.038), or compared to the NEIAEDs group (p=0.027). There was no difference between monotherapy group and NEIAEDs group (p=0.478). All the concentrations were within the reference range (12-46 μg/mL) quoted by Leppik et al. (12), and also within the range (20-40 μg/mL) quoted by Stepanova & Beran (13).

In EIAEDs group, the highest LEV CL/F corresponded to patients undergoing combined therapy with carbamazepine (CBZ), followed by oxcarbazepine (OXC), and phenobarbital (PB) (table 3), but these differences were not statistically significant. Twenty-two patients were treated with LEV+CBZ; twelve with LEV+OXC, and sixteen with LEV+PB. Statistically significant differences were observed in LEV C_0 obtained between patients treated with PB vs. OXC (p=0.015) and with PB vs. CBZ (p=0.033).

A linear regression analysis was performed using LEV CL/F as a dependent variable. The significant variables in the statistical model were: dose (mg), CCr (mL/min), gender, and weight (Kg).

The regression resulting equation was:

Equation 3: LEV CL/F (L/h) = 0.001 x dose + 0.023 x CCr – 0.914 x gender + 0.036 x weight + 3.844

p=0.000 R^2= 0.361 R^2 adjusted= 0.349

(men=0; women=1)

The model did not possess good predictive capacity but it allowed identifying and adjusting the variables that exert significant influence on LEV CL/F.

Discussion

Due to the fact that there is a general perception that LEV is safe, Spanish clinicians rarely undertake dose adjustments based on renal function or concomitant medication. Therefore, the practice of routine monitoring of LEV levels is quite unusual in Spanish hospitals (14,15).

Initial data regarding the pharmacokinetics of LEV suggested minimal metabolism via microsomal enzymes, and therefore a priori interactions between LEV and other drugs were not expected (1,2). However, after licensing and wide-spread use of LEV, clinical cases of pharmacokinetic interactions were reported with significant clinical consequence on the response to LEV (9,16).

LEV is mainly eliminated by renal excretion. Approximately 66% of the dose administered is excreted unchanged in the urine while 34% of the drug is metabolized (1). Therfore, in patients aged> 65 years, with renal dysfunction or in those patients in whom renal assessment is not reliable from serum creatinine, such as patients who are malnourished or bed bound, routine LEV monitoring may help guide LEV treatment.

The main metabolic route, resulting in the formation of three pharmacologically inactive metabolites, is enzymatic hydrolysis of the acetamide group. The three aforementioned metabolites are as follows: a primary metabolite derived from carboxylic acid (L057 which corresponds to 24% of the dose); and two minor metabolites (3% of the dose), one formed by hydroxylation of the pyrrolidone ring (1.6% of the dose) and another formed by the opening of the pyrrolidone ring (0.9% of the dose). Other unknown compounds represent 0.6% of the dose. The exact metabolic process of LEV has yet to be determined and therefore none of the theories proposed in terms of explaining cases of pharmacokinetic interactions have been proven, with each theory differing from the

others. One of the theories, reported by Patsalos (2), involves the participation of hydrolase enzymes because there is existing evidence about their ability to interfere with the metabolism of other AEDs via their induction (17,18). One of the studies attempting to analyze the metabolic process of LEV was developed by Freitas-Lima et al. (19). Their study compared two groups of treated patients. The first group was administered a single dose of LEV together with an inducer AED while the second group received LEV alone. The results showed that there were no differences between the two groups in terms of L057 metabolite concentration. This allowed the first hypothesis regarding hydrolase participation to be rejected and subsequently led these authors to support the hypothesis proposed by Strolin et al. (20), which involved the participation of cytochrome P450 in the mechanism of LEV metabolic induction, although no family or subfamily of cytochrome P450 was specified.

The present study found that comedication with EIAEDs increased LEV CL/F (L/h) by 64% in comparison with the monotherapy group and by 49% with respect to the NEIAEDs group. These results are similar to those reported by Contin et al. (8), who observed a 30% increase in clearance in the EIAEDs group. Similar findings have been reported by other authors such as Hirsch et al. (9), who found an increase of LEV CL/F between 24% and 37% or Dahlin et al. (21), who reported clearance values that were 30% higher in their EIAEDs group. This latter study entailed pediatric patients.

More than 40% increase in LEV CL/F would be expected to be of clinical significance and therefore LEV should not be considered to be a drug that is devoid of pharmacokinetic interactions.

The EIAEDs analyzed in this study entailed CBZ (n=42), PB (n=34) and OXC (n=16). The greatest inducing potency exerted on LEV CL/F was observed with CBZ, followed by OXC and PB. In fact, when comparing the results of these subgroups with the patients who received LEV in monotherapy, LEV CL/F was 80.72%, 63.94% and 43.99% greater, respectively.

PB is often considered a more potent inducer of hepatic metabolism than CBZ. Indeed, Hirsch et al. (9) observed a greater induction of LEV CL/F by PB than by CBZ. Nevertheless, this study has important limitations, such as a small sample size and lack of analysis of possible confounding by patient age.

However, our results contradict this idea, and are supported by data obtained by some authors with other AEDs. Bae et al. (22) observed a greater increase of topiramate clearance in patients in comedication with CBZ versus PB (2.17 L/h vs 1.64 L/h). Other authors, such as May et al. (23), determined the effect of hepatic enzyme induction on LEV C_0. Curiously, these researchers could not find a PB-inducing effect on LEV C_0 and they reported that this was due to the small number of patients on comedication with PB, a similar limitation commented on by Hirsch´s study (9). In our research, a lower inducing effect on LEV C_0 with PB, compared with the other AEDs, was observed. In our study, the PB group is also smaller than CBZ group. Studies with larger sample sizes are necessary to confirm these results.

Included variables, regression coefficients and independent term of the LEV clearance model in EIAEDs group were similar to those in the regression model for the entire patient population. Consequently, LEV seems to have similar behaviour in all groups.

A great inducing effect of OXC was observed, with a 12% lower mean LEV C_0 value than that obtained in the CBZ group (Table 3). In addition, 38% of the patients of OXC group had basal concentrations below the reference range (12-46 μg/mL) (12) and

significantly lower concentrations than those proposed by Stepanova & Beran (20-40 μg/mL) (13).

One of the limitations of this study is its retrospective design, making it difficult to collect some relevant information, and some missing variables could contribute to explaining the variability in LEV clearance. Dosage and body weight were not available in some patients and had to be excluded from the analysis. Another limitation is the small sample size. Larger studies would be necessary to confirm our results. These limitations are frequent in naturalistic studies, however such studies provide invaluable information so as to guide clinical practice.

Conclusions

Our data shows that LEV CL/F is increased by more than 40% in patients prescribed concomitant EIAEDs. Such an increase would be expected to have clinical consequences and therefore confirming that LEV is not an inert drug and that potential interactions should be taken into consideration.

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Table 1: Demographic and anthropometric characteristics of the population.

	Sex (M/F)	Age (years) $\overline{X}$±SD	Weight (Kg) $\overline{X}$±SD	BMI (Kg/m^2) $\overline{X}$±SD
LEV monotherapy (n = 180)	95/85	49.96 ± 20.18	74.47 ± 13.81	26.41 ± 4.49
LEV + EIAED (n = 92)	65/27	47.89 ± 14.70	74.85 ± 13.05	25.56 ± 3.71
LEV + NEIAED (n = 58)	31/27	41.65 ± 16.28	72.84 ± 17.71	26.10 ± 5.54

LEV: Levetiracetam; EIAED: Enzyme-inducing antiepileptic drugs; NEIAED: Non-enzyme-inducing antiepileptic drugs; M: Male; F: Female; $\overline{X}$±SD: Mean ± Standard Deviation; BMI: Body mass index, n: number of concentrations.

Table 2: Levetiracetam (LEV) dose, basal serum concentration, apparent oral clearance and creatinine clearance (CCr) in the different groups.

	Dose LEV (mg/day) $\overline{X}$±SD	LEV C_0 (µg/mL) $\overline{X}$±SD	LEV CL/F (L/h) $\overline{X}$±SD	LEV CL/F (mL/h/Kg) $\overline{X}$±SD	CCr (mL/min) $\overline{X}$±SD
LEV monotherapy (n = 180)	1,891.66 ± 869.28	20.08 ± 9.69	4.41 ± 2.06	60.44 ± 28.86	102.81 ± 39.32
LEV + EIAED (n = 92)	2,559.78 ± 759.88*	17.30 ± 7.77*	7.23 ± 3.72*	98.25 ± 51.07*	111.42 ± 30.92
LEV + NEIAED (n = 58)	2,215.51 ± 788.41	20.49 ± 9.46	4.87± 1.65	69.73 ± 27.34	104.70 ± 30.67

EIAED: Enzyme-inducing antiepileptic drugs; NEIAED: Non-enzyme-inducing antiepileptic drugs; LEV C_0: Basal serum levetiracetam concentration; LEV CL/F: Apparent oral levetiracetam clearance; $\overline{X}$±SD: Mean ± Standard Deviation, n: number of concentrations.
*Statistically significant difference compared to monotherapy group and NEIAEDs group ($p<0.05$)

Table 3: Levetiracetam (LEV) dose, basal serum concentration, apparent oral clearance and creatinine clearance according to enzyme-inducing antiepileptic drug comedication.

	n	EIAED Dose (mg/day) $\overline{X}$±SD	LEV Dose (mg/day) $\overline{X}$±SD	LEV C_0 (µg/mL) $\overline{X}$±SD	LEV CL/F (L/h) $\overline{X}$±SD	LEV CL/F (mL/h/Kg) $\overline{X}$±SD	CCr (mL/min) $\overline{X}$±SD
PB	34	172.79 ± 55.85	2,676.47 ± 757.61	19.95 ± 8.97	6.35 ± 2.94	85.67 ± 40.45	96.49 ± 34.87
OXC	16	1,662.5 ± 532.44	2,218.75 ± 948.13	14.34 ± 4.71	7.23 ± 4.00	100.22 ± 55.03	105.10 ± 22.62
CBZ	42	983.59 ± 459.11	2,595.24 ± 657.86	16.28 ± 7.12	7.97 ± 4.09	107.88 ± 56.03	121.18 ± 31.32

EIAED: Enzyme-inducing antiepileptic drug; PB: Phenobarbital; OXC: Oxcarbazepine; CBZ: Carbamazepine; LEV C_0: Basal serum levetiracetam concentration; LEV CL/F: Apparent oral levetiracetam clearance; CCr: Creatinine clearance; $\overline{X}$±SD: Mean ± Standard Deviation, n: number of concentrations.