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Original Article

Levetiracetam Serum Concentrations in Pediatric Patients: Is There a Role in Clinical Decision Making?

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Abstract

Objective: Monitoring levetiracetam plasma concentration is not frequently used in clinical practice due to the linear pharmacokinetics of the drug and the absence of drug interactions. Nonetheless, some studies mention pharmacokinetic interactions of the drug and suggest drug level monitoring. This study was conducted to evaluate the effect of concomitant antiepileptics on levetiracetam plasma concentration in children and to determine the importance of drug plasma concentration in clinical follow-up.

Methods: One hundred and forty patients with epileptic seizures on levetiracetam therapy, aged between 1 month and 18 years, were enrolled in this retrospective study. We evaluated gender, age, body weight, daily drug dose, comedication with enzyme inducers and inhibitors, and levetiracetam serum trough concentration records of patients admitted to Pediatric Neurology Clinic between 2018 and 2020.

Results: In this study, 57.9% of 140 patients were on monotherapy. The mean dose of levetiracetam was 35.40 mg/kg/day, while the mean drug concentration was 14.06 μg/mL. The correlation between the dose and the serum concentration in the polytherapy group was poor (P =.024), whereas it was positive and highly significant in the monotherapy group (P < .001). The plasma concentration of the drug was not affected by the enzyme inhibitors and inducers, as there was no significant difference between the groups.

Conclusion: Monitoring is not necessary for patients on levetiracetam, even in polypharmacy. The clinical decision is not affected by plasma drug concentration as drug has linear pharmacokinetics and the drug concentration is not affected by concomitant drugs, and age has no significant impact on plasma concentrations.

Keywords: drug monitoring, epilepsy, levetiracetam, pediatric

INTRODUCTION

The treatment of epilepsy in clinical practice is based on effectiveness of the drug and its tolerability by the patient. However, measuring antiseizure drug (ASD) serum concentrations can anticipate clinical effects.[1] Drug monitoring is often recommended in pediatric patients for certain ASDs due to significant interindividual differences and unpredictable drug disposition.[2] Levetiracetam (LEV) is a second-generation broad-spectrum ASD effective in treating multiple seizure types in children. The lack of effect on cytochrome P450 and its minimal protein binding reduce its pharmacokinetic interactions. In patients receiving LEV, blood level monitoring is not frequently done in clinical follow-up due to its favorable pharmacokinetics.[3-5] Still, the dosing of LEV may be more complicated in the presence of polypharmacy. Some studies mentioning pharmacokinetic drug interactions suggest therapeutic drug monitoring.[6-8] This study evaluated the LEV blood level concentrations, correlation with dose, and enzyme-inducing and enzyme-inhibiting antiepileptic comedication effect to decide the need for monitoring blood concentrations in pediatric patients' follow-up.

METHODS

We retrospectively searched the database of Süleyman Demirel University Faculty of Medicine for children with epileptic seizures on LEV treatment between January 2018 and January 2020. All patients for whom LEV serum trough concentration was requested were included. We did not assess patients with insufficient data regarding age, weight, serum concentrations, dosage, or the time of intake of the last dose. One hundred and forty children with epilepsy aged between 1 month and 18 years were enrolled in the study. They presented different types of epilepsy/epileptic syndromes. Levetiracetam serum concentrations were determined using a kit with high-performance liquid chromatography in a single laboratory.

In the management of epileptic patients, the trough drug serum concentration is determined a month after the initiation of treatment or a month following a change in dosage. Patients are instructed to have blood drawn just before taking a usually scheduled dose. All the patients were anonymized, only data regarding the gender, age, body weight, daily drug dose, comedication, and trough drug blood level records were collected. Patients on LEV were divided into 2 groups: monotherapy and polytherapy groups. We further divided the polytherapy group into 4 subgroups: patients

on enzyme inducers, enzyme inhibitors, enzyme inducers+inhibitors, and those on neutral drugs, and evaluated the realtionship between dose and plasma concentration in these groups. The institutional Süleyman Demirel University Faculty of Medicine Ethics Committee approved this retrospective study (Date: May 22, 2020, Decision no: 159).

Statistical Analysis

Descriptive statistics were presented as frequency (percentage) for categorical variables and as mean ± SD (median, min, max where necessary) for numerical variables. The chi-squared test with Monte Carlo exact method was used to determine the relationship between the categorical variables. Mann–Whitney *U* test was used to compare drug groups since the distribution of the continuous variables was not normal by the Shapiro–Wilk test. Spearman's Rho correlation coefficients were calculated to determine the correlation between the dose and the drug's serum level. The associations were presented as scatter plots. A value of $P < .05$ was considered a statistically significant result for 5% type I error in all analyses. The analysis was carried out using Statistical Package for the Social Sciences software 20.0 (IBM Inc, Chicago, Ill, USA) software.

Power Analysis

The priori power analysis was performed using GPower 9.1.2 software. The effect size was calculated as 0.58 using the dose level of LEV in a pilot study. Using a 1-tailed *t*-test for the Mann–Whitney *U* test for independent samples, the resulting sample size was 54 and 76 for each group (total 130). Therefore, we considered the power as 0.80, the error as 5%, and the allocation ratio as 1.5.

RESULTS

This study included 140 epilepsy patients aged between 1 month and 18 years and 53.6% of the patients were girls, and the mean age was 9.45 ± 4.91 years. The number of patients on monotherapy was 81 (57.9%) and the others were on polytherapy. The most commonly used concomitant drugs were valproate, clobazam, and carbamazepine. We found that the mean dose of LEV was 35.40 ± 16.53 (10.2-77.0) mg/kg/day, while the mean drug level in blood was 14.06 ± 11.14 (0.1-55.3) µg/mL. A significant and positive correlation was found between the drug dose and the drug level in the blood (R=0.484; $P < .001$) (Table 1).

We compared the correlation of the dose and the serum level of the drug in the monotherapy and polytherapy groups. The patients' age and gender did not differ significantly between monotherapy and polytherapy. We found the drug dose to be considerably higher in the patients with comedication ($P = .001$). The mean dose was calculated as 31.51 ± 15.62 mg/kg/day in the monotherapy group, while it was 40.76 ± 16.38 mg/kg/day in the polytherapy group. The serum level was higher in the polytherapy group (18.08 ± 12.01 µg/mL), but the difference was not significant ($P = .485$). The correlation value between the daily dose and the serum level in the patients with comedication was poorly significant (R=0.293; $P = .024$), whereas the correlation between the dose and serum level in the monotherapy group was positive and highly significant (R=0.619; $P < .001$) (Table 2).

We compared LEV plasma level and LEV dose values according to age groups. The drug dose differed significantly among age groups ($P < .001$). The dose was relatively high in patients aged 0-1 year and moderate in the 7-12 age group. We observed that the dose decreased significantly as the age increased (>12 years old). Serum drug levels did not differ significantly by age group (Table 3).

Anticonvulsant inducer comedication group included carbamazepine, oxcarbazepine, phenobarbital, or their polytherapy. Inhibitor comedications included valproate only. Neutral drugs were clobazam, lacozamide, lamotrigine, clonazepam, and topiramate.

Table 1. General Characteristics of the Patients

Characteristics	Categories	n (%)		
Gender	Female	75 (53.6)		
	Male	65 (46.4)		
Comedication	Polytherapy	59 (42.1)		
	Monotherapy	81 (57.9)		
		Mean ± SD	**median, min-max**	**Correlation, R (*P*)**
Age	year	9.45 ± 4.91	9.5, 1.0-18.0	
LEV dose	mg/kg/day	35.40 ± 16.53	31.1, 10.20-77.0	0.484 ($P < .001$)
LEV PC	µg/mL	14.06 ± 11.14	10.29, 0.11-55.31	

PC, plasma concentration.

Table 2. The Characteristics of the Patients in Monotheray and Polytherapy Groups

	Polytherapy (n=59)	Monotherapy (n=81)	
Comedication	**Mean ± SD (median, min-max)**		***P***
Age (year)	9.27 ± 4.60 (10.0, 1.0-18.0)	9.58 ± 5.14 (9.0, 1.0-18.0)	.775
LEV dose (mg/kg/day)	40.76 ± 16.38 (40.0, 12.0-70.5)	31.51 ± 15.62 (27.7, 10.2-77.0)	.001*
LEV PC (µg/mL)	18.08 ± 12.01 (12.04, 0.53-50.64)	13.32 ± 10.46 (9.32, 0.10-55.31)	.485
Correlation, R (*P*)	0.293 ($P = .024$)	0.619 ($P < .001$)	
Gender, n (%)			
Female	33 (55.9)	42 (51.9)	.634
Male	26 (44.1)	39 (48.1)	

*Significant at $P < .05$ level according to Mann–Whitney *U* test.

PC, plasma concentration.

Table 3. Drug Dose-Drug Plasma Concentration Values According to the Age Groups

	LEV Dose	LEV PC
Age, n (%)	**Mean ± SD**	
0-1 year[b,c], 6 (4.3)	55.82 ± 14.10	17.35 ± 10.93
2-6 years[c], 44 (31.4)	32.85 ± 16.06	11.51 ± 11.70
7-12 years[a], 48 (34.3)	40.51 ± 15.16	15.11 ± 11.10
>12 years[a,b], 42 (30.0)	29.33 ± 15.24	15.06 ± 10.50
P	<.001*	.053

*significant at .05 level according to Kruskal–Wallis test.

[a, b, c]Same superscript letters denote the significant pairwise groups.

PC, plasma concentration.

Table 4. Comedication Effect on Drug Dose and Plasma Concentration

	LEV Dose	LEV PC
Drug Subclasses	**Mean ± SD**	
Enzyme inducers (n=14)	33.37 ± 17.53	12.52 ± 10.45
Enzyme inhibitors (n=29)	33.02 ± 15.16	14.16 ± 9.87
Enzyme inducers+inhibitors (n=11)	29.39 ± 14.53	11.46 ± 9.79
Neutral (n=4)	36.70 ± 9.97	19.95 ± 11.86
Monotherapy (n=82)	37.34 ± 17.29	14.35 ± 11.89
P	.561	.640

PC, plasma concentration.

There was no significant difference between the dose (P =.561) and plasma concentration (P =.640) in patients on enzyme inducers, enzyme inhibitors, enzyme inducers+inhibitors, and those on neutral drugs (Table 4).

We divided the patients into 3 groups based on the plasma level as <12, 12–46, and >46 µg/mL according to the established reference range. Gender, age, and the presence of concomitant drugs did not differ significantly according to plasma level groups. However, we found that the drug dose was significantly lower in the patient group with plasma levels <12 µg/mL than the other groups (P < .001) (Table 5).

No adverse effects were found leading to a change in dose or discontinuation. Only 7% of the patients had adverse effects like irritability and nervousness.

DISCUSSION

Levetiracetam displays linear elimination kinetics; therefore, dose changes produce predictable changes in serum concentrations,[9-12] but some studies could not find a correlation between the administered dose and the serum drug level.[11,13]

In our study, different from those reports, we have found a strong correlation between the LEV dose and blood concentrations. However, some variation has been found among patients receiving the exact dosage for body weight. May et al[11] explained such variation by the effects of age and comedication.

Pharmacokinetic drug interactions must be carefully considered when multidrug therapies are prescribed. To investigate the comedication effect on LEV, we divided patients into 2 groups: monotherapy and polytherapy groups. We realized that the correlation was positive and highly significant, especially in the monotherapy group. However, the correlation between the daily dose and the serum level in the patients with comedication was poor. This may explain the possibility of alteration in LEV concentration when concomitant antiepileptic medications are used.[14]

Levetiracetam is not implicated in any drug interactions due to low hepatic metabolism, and previous studies have reported no significant interactions between LEV and other ASDs.[15,16] While some studies found that drug interactions may still occur, the mechanisms are not well understood. Data suggest that concomitant ASD, especially enzyme-inducing ASD, has a moderate effect on the LEV kinetics by the possible increase of clearance of LEV.[6,7,11,14,17]

Mathew et al[7] found that patients receiving concomitant enzyme-inducing ASD had drug serum concentrations lower than enzyme-inhibiting ASD or no interfering ASDs. Also, Stepanova et al[8] suggested interaction between LEV and concomitant ASDs as patients on polytherapy required a higher dose of LEV to achieve similar blood levels and therefore recommended the use of drug level determination.[8]

In our study, the dose was significantly higher in the polytherapy group, but plasma concentration did not differ sigificantly between the 2 groups. Therefore, the results of our study may indicate a modest effect of comedication on the LEV kinetics, supporting the theory that patients on polytherapy require higher doses of LEV to achieve similar blood levels.

In our study, serum concentration and drug dose of the patients on monotherapy were not significantly different from patients on concomitant enzyme inhibitors, enzyme inducers, and those drugs that do not interfere. These results were in agreement with the observation made by previous studies.[11]

Several age-related physiological changes can potentially affect drug pharmacokinetics and efficacy. According to the age group classification used in our study, serum drug concentration was not different, but the dose was higher in the 0-1 years group and moderate in the 7-12 age group. Pharmacokinetic differences for the drug between age groups have been described. Thus, children aged between 0 and 12 years should receive 30% higher LEV dosages to achieve comparable serum drug concentration.[6,18] May et al[11] found similar results and concluded that LEV dose was significantly dependant on age.

The International League Against Epilepsy (ILAE) committee set the LEV reference range between 12 and 46 µg/mL.[19] A reference serum range of 0.11-55.31 µg/mL was perceived for the LEV daily dosing of 10.20-77.0 mg/kg in our study. The mean drug concentration in our patients was within the reference range established by ILAE, but monitoring of concentrations revealed children with serum concentrations below (56.4%) and above (2.1%) the therapeutic range. All cases in our study had the typical range of drug dose per body weight with no adverse effects found leading to a change in dose or discontinuation of the drug.

Table 5. Drug Dose Distribution According to the Therapeutic Range

LEV PC, n (%)	LEV Dose (mean ± SD)	*P*
<12 µg/mL, 79(56.4%)	29.77 ± 14.26[+,ǂ]	< .001*
12-46 µg/mL, 58 (41.4%)	41.88 ± 16.37[+]	
>46 µg/mL, 3 (2.1%)	58.69 ± 11.94[ǂ]	

*Significant at .05 level according to 1-way ANOVA.

[+,ǂ]Same superscript symbols denote the significant pairwise groups according to Tukey's honest significance test with *P*-values < .001 and .004, respectively.

PC, plasma concentration.

Because of the wide therapeutic range, predictable changes in serum concentrations, possible minimal drug interactions that do not typically require adjustments to dosage, and low prevalence of side effects, LEV monitoring is not essential to optimizing drug therapy even in specific age groups, such as infants and children and those patients on polypharmacy. Instead, LEV dosing can be determined based on clinical efficacy and adverse effects, making LEV easier to use in pediatric patients.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Süleyman Demirel University (Date: May 5, 2020, Decision no: 159).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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