Original article

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THERAPEUTIC DRUG MONITORING OF NEW-GENERATION ANTIEPILEPTICS IN PEDIATRIC PATIENTS: A FOCUS ON FACTORS INFLUENCING THE PLASMA CONCENTRATION

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Monitoring the concentrations of antiepileptic drugs (AEDs) in the pediatric population represents an important step in the vast variety of decisions related to the optimization of new-generation epilepsy therapy. The primary objective of this research was to determine the concentrations of lamotrigine (LTG) and levitiracetam (LEV) in the plasma of children and adolescents receiving combined antiepileptic therapy. Secondly, we examined the influence of demographic factors and co-therapy on the measured concentrations of AEDs. The prospective study included 71 subjects diagnosed with epilepsy, aged 2−18 years, receiving combined antiepileptic therapy, which included the following therapeutic regimens/modalities: valproic acid (VA)/LTG, VA/LEV and LTG/LEV. The results indicated that 86.27% of LTG concentrations and 68.97% of LEV concentrations were within the reference range. No statistically significant influence of co-medication on the concentrations of the tested AEDs was recorded. Additionally, the obtained results confirmed that LTG dose was the most significant predictor for LTG concentrations. The results of the conducted research indicated that only LEV dose corrected by body weight could potentially affect LEV concentrations. Although the therapeutic monitoring of new-generation AEDs is not commonly imposed in daily clinical practice, the results of the conducted research indicate that monitoring the concentrations of LTG and LEV can be of great benefit in the pediatric population receiving combined antiepileptic therapy due to the very nature of the disease and the potential pharmacokinetic variability of the investigated antiepileptics.

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Introduction

Epilepsy treatment often requires lifelong use of antiepileptic drugs (AEDs). Effectiveness and safety have been recognized as key issues in the successful treatment of epilepsy, and still represent a difficult goal to achieve in each daily clinical practice (1). Although most patients may be successfully managed with monotherapy, polytherapy remains the reality for more than 30% of patients with epilepsy (2, 3). In the pediatric population, new challenges in AED therapy management include the wide range of combinations of AEDs available, the lack of information regarding optimal dose regimen, unpredictable drug efficacy and changes in pharmacokinetics due to physiological changes during maturation and development (4).

Due to unfavourable pharmacokinetic properties, a high risk of drug–drug interactions and a narrow range of therapeutic options, therapeutic drug monitoring (TDM) of AEDs has traditionally been used to support and optimize epilepsy management (5). Therapeutic drug monitoring of the first-generation AEDs has been commonly performed for decades. Nowadays, the use of old-generation AEDs is decreasing as new-generation AEDs are being increasingly prescribed, mostly due to more predictable kinetics and fewer risks of drug interaction (6). Although new-generation AEDs have lower pharmacokinetic variability, they still show significant changes in

their bioavailability with certain comedications or under specific physiological conditions (7). A routine therapeutic monitoring for most new AEDs is not common in clinical practice. On the other hand, due to the presence of unexpectedly high interindividual variability, TDM is still the focus of investigation, especially in the vulnerable pediatric population (8).

The main aim of the study was to determine the concentrations of lamotrigine (LTG) and levitiracetam (LEV) in children and adolescents receiving combined antiepileptic therapy. The second aim was to examine the influence of demographic factors and co-therapy on the AED concentrations.

Materials and Methods

The research in the form of a prospective study was conducted at the Pediatric Internal Medicine Clinic, Department of Pediatric Neurology, University Clinical Centre of Niš, Serbia and Research Centre for Biomedicine, Faculty of Medicine, University of Niš. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committees and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The protocols were approved by the Ethics Committee of the Faculty of Medicine, University of Niš (Decision No. 12-3782/4). The collection of data was performed over 12 month from May 2020 in the presence of parents or guardians who provided written informed consent.

The study involved 71 patients with diagnosed epilepsy (31 males and 40 females). Inclusion criteria were: diagnosed epilepsy based on criteria of the International Classification of Diseases (G40); patients of both genders aged 2−18 years on combined antiepileptic therapy which included the following therapeutic regimens/modalities: valproic acid (VA)/LTG, VA/LEV and LTG/LEV. The data were collected from medical records and during face-to-face interviews which were performed at the clinic during the control visit, with the patient himself or his parents/guardians. In order to protect patient data, each patient was assigned a code at the beginning of the study, which was used in statistical analysis instead of the patient's name. For the purpose of analysis, the following data were collected: demographic characteristics (gender, age, body weight (BW)), therapy characteristics (drug formulation, administered, dose, dosing interval, plasma drug concentration, and adverse drug effects). Patients included in the study had been on a specific drug dosing regimen for at least 3 weeks to ensure that the steady-state condition had been reached for each of the AEDs included in the therapy. All blood samples were collected in the morning before the next dose of AEDs. Hence, all blood samples corresponded to trough levels.

For the purpose of control and optimization of therapy, blood samples are taken from patients at the request of the doctor. Blood was taken by venipuncture, and sterile disposable vacuum tubes were used for sampling. From the whole blood sample, 200 ml of blood was separated and used to determine the concentration of LTG and LEV. The VA concentrations were routinely determined in the Central Biochemical Laboratory in the University Clinical Centre of Niš and collected from medical records, while the LTG and LEV concentrations were determined using the high-performance liquid chromatography (HPLC) at the Research Centre for Biomedicine in the Medical Faculty, Niš. The blood samples were collected and stored at −80 °C until further analysis. This analysis was performed on an Agilent 1200 HPLC system (Agilent Technologies, Palo Alto, CA., USA) with a diode array detector (DAD). An analytical column C18 Zorbax Eclipse AAA, 150 x 4.6 mm, with a particle size of 3.5 µm manufactured by Agilent was used (Supplementary Information). Lamotrigine and levetiracetam as solid standard compounds were kindly provided by pharmaceutical company Hemofarm AD (Vršac, Serbia).

Lamotrigine and levetiracetam were extracted from 200 µl of plasma by adding 400 µl of a solution of 0.1% trifluoroacetic acid in methanol. After vortexing (1 min) and centrifugation (10 min at 12000 rpm and 4 °C), a volume of 200 µl of the supernatant was transferred to a clean vial with an insert and 10 µl was injected onto a column whose temperature was maintained at 30 °C at a flow rate of 1 ml/min. Compounds were identified and quantified based on UV-Vis signal response compared to standards. Detection of LTG was performed at a wavelength of 240 nm, and LEV at 205 nm. When determining LTG, the mobile phase consisted of a mixture of 0.1% aqueous solution of triethanolamine (TEA) pH 6.5 (A) and acetonitrile (B) with a linear gradient. The proportion of acetonitrile at the beginning of the linear gradient was 23% and was maintained at that level for the next 5 minutes. In 0.5 minutes, the percentage of B rose to 80% and was maintained at that value for the next 3 minutes. After that, in 0.5 minutes, the percentage of component B was returned to the initial 23% and this value remained for 1 minute until the end of the analysis. The total duration of the analysis was 10 minutes. For the determination of LEV, the mobile phase consisted of a 0.1% aqueous solution of TEA (A) and acetonitrile (B). The pH value of the TEA solution was adjusted to 3.9 by adding phosphoric acid. Optimal separation of LEV was achieved by establishing a gradient with the following composition: 0−3.8 min 10−10% B; 3.8−4.3 min 10−80% B; 4.3−7.3 min 80−80% B; 7.3-8.5 min 80−10% B; 8.5−10 min 10% B.

Statistical Analysis

Descriptive data are presented as absolute numbers, percentages, mean values ± standard deviations (SD), centre (median) values and interquartile difference. Data are presented in tables or graphically. In order to estimate the influence of demographic factors, dosage regimens and co-therapy on LTG and LEV concentration, univariate and multivariate regressions were performed. Also, the comparison of antiepileptics dosage regimen and concentration between defined patient groups (sex, age, BW and co-therapy) was done by ANOVA and Student's t-test (normally distributed data) and Kruskal–Wallis and Mann–Whitney U test (not normally distributed data). The significance level was set at 5% in all analyses. All analyses were performed using SPSS statistical analysis software, version 20.0 (SPSS, Chicago, IL, United States).

Results

The study included 71 patients. During the investigation period, we did not record exclusions from the study because there was no expression of serious side effects. The demographic characteristics of the study population are given in Table 1.

The median age was 10.9 years (interquartile range 11 years), with female gender accounting for 56.3% (N = 40) and male contributing for the remaining 43.7% (N = 31). The median BW was 37.1 kilograms (interquartile range: 21 kg).

All respondents were on dual antiepileptic therapy (VA/LTG, VA/LEV and LTG/LEV). A total of 59.1% of respondents received the combination of VA/LTG.

Table 1. Demographic characteristics of respondents

Gender	**Number (%)**	
Male	31 (43.7%)	
Female	40 (56.3%)	
Age (years)	**Number (%)**	Mean: 10.9 Median: 11 Interquartile range: 7
2–12	43 (60.6%)	
> 12	28 (39.4%)	
BW (kg)	**Number (%)**	Mean: 37.1 Median: 35 Interquartile range: 21
< 20	11 (15.5%)	
20–40	38 (53.5%)	
> 40	22 (31%)	

Table 2. Pharmacotherapy characteristics and antiepileptic drug concentrations of the children participating in the study

Therapeutic modalities	**Male (%)**	**Female (%)**	**Total**
VA/LTG	19 (45.24%)	23 (54.76 %)	42 (59.16%)
VA/LEV	8 (40%)	12 (60%)	20 (28.17%)
LTG/LEV	4 (44.44%)	5 (55.56%)	9 (12.67%)
AEL concentration	**Below range (%)**	**In range (%)**	**Above range (%)**
LTG (N = 51)	6 (11.77%)	44 (86.27%)	1 (1.96%)
LEV (N = 29)	8 (27.59%)	20 (68.97%)	1 (3.45)

The therapeutic modalities VA/LEV was administered to 28.2% of respondents. Finally, 12.7% of the respondents participating in the study received the LTG/LEV combination. In the conducted study, it was observed that 86.27% of LTG and 68.97% of LEV measured concentrations during combined antiepileptic therapy were in the reference range. The highest number of concentrations below the reference range was recorded in the group of patients who used LEV as part of combined therapy (27.59%).

The further focus of the research was the factors that influence the pharmacokinetic variability of the selected AEDs, which are considered to contribute to concentrations outside the therapeutic range.

Figure 1 shows the dose and concentration of LTG in relation to gender, age, body weight and co-medication.

In the conducted research, DLTG were higher in the group of female respondents with a statistically significant difference p = 0.049 (1.62 ± 1.14 mg/kg vs. 2.63 ± 1.90 mg/kg) (Figure 1a). The measured CLTG in the group of female respondents were statistically significantly higher compared to the male (5.35 ± 2.70 μg/ml vs. 7.91 ± 4.10 μg/ml; p = 0.018) (Figure 1b). The dose and concentration of LTG in relation to the age of the respondents did not statistically differ within the studied groups. Analyzing the obtained results, it can be seen that higher DLTG were applied (71.34 ± 58.28 mg vs. 108.75 ± 82.23 mg) and higher CLTG were measured (6.33 ± 3.22 μg/ml vs. 7.41 ± 4.40 μg/ml) in the group of respondents with BW > 40kg, but statistical significance was not found between the studied groups.

The dose and concentration of LEV in relation to gender, age, body weight and co-medication are shown in Figure 2.

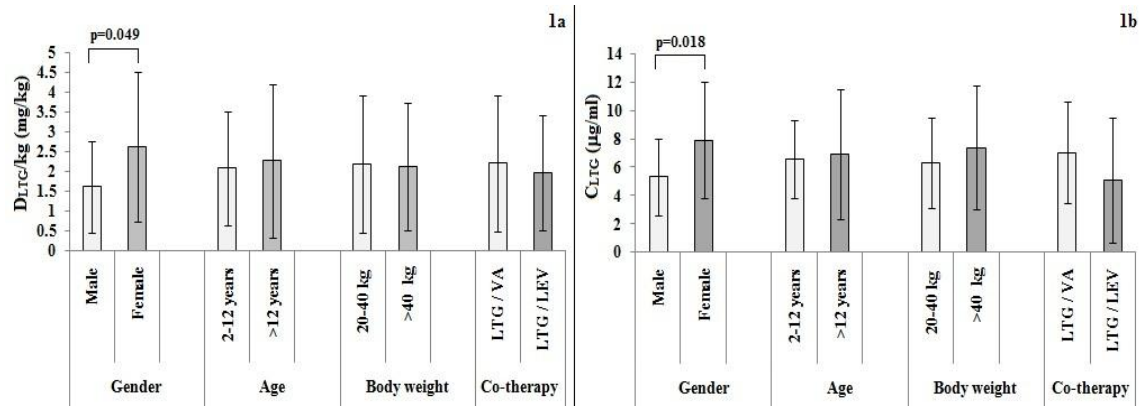

Figure 1. Dose (1a) and concentration (1b) of LTG in relation to gender, age, body weight and co-medication

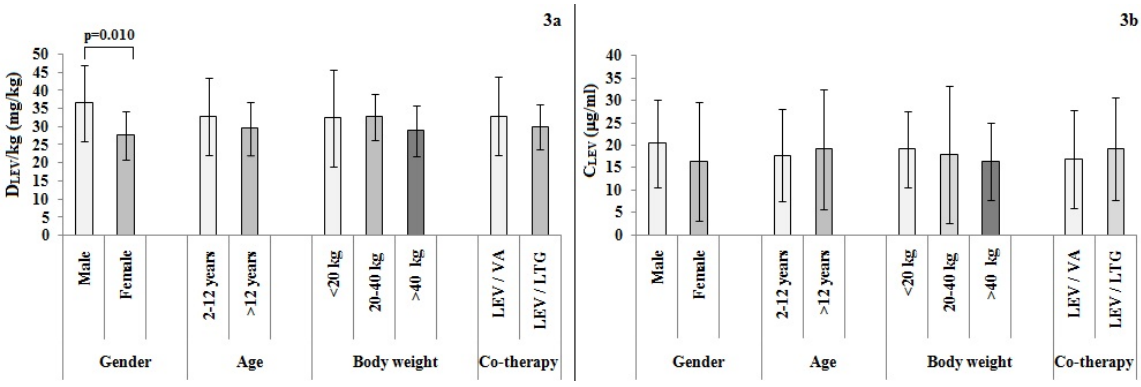

Figure 2. Dose (2a) and concentration (2b) of LEV in relation to gender, age, body weight and co-medication

Table 3. Analysis of the influence of factors on LTG and LEV concentration

Univariate model for LTG				
Parameter	Beta	B, IP-95%	R^2	Significance
Age	0.178	0.182 (0.119−0.483)	3.2%	0.230
Body weight	0.081	0.022 (-0.059−0.104)	0.7%	0.587
Gender	**0.344**	**2.559 (0.465−4.653)**	**11.9%**	**0.018***
D_{LTG}	**0.607**	**0.031 (0.019−0.044)**	**36.8%**	**P < 0,001***
D_{LTG} / kg	**0.453**	**0.992 (0.398−1.586)**	**20.5**	**P = 0,002***
C_{VA}	0.101	0.029 (-0.064−1.21)	1.0%	0.535
C_{LEV}	-0.606	-0.209 (-0.525−0.107)	36.7%	0.150
Multivariate model for LTG				
Parameter	Beta	B, IP-95%	Significance[1]	Significance[2]
Gender	**0.156**	**1.154 (0.712−3.021)**	**0.219**	**39% (< 0.001)**
D_{LTG}	**0.560**	**0.29 (0.16−0.42)**	**P < 0.001***	
Univariate model for LEV				
Parameter	Beta	B, IP-95%	R^2	Significance
Gender	-0.180	-3.960(-12.897−4.977)	3.2%	0.370
Body weight	-0.072	-0.047(-0.311−0.218)	0.5%	0.720
Age	0.098	0.205(-0.653−1.064)	1%	0.627
D_{LEV}	0.032	0.001(-0.007−0.008)	0.1%	0.872
D_{LEV} / kg	0.386	0.353(-0.045−0.816)	12.5%	0.077
C_{LTG}	-0.485	-1.313 (-4.603−1.977)	23.5%	0.330
C_{VA}	0.130	0.067(-0.214−0.347)	1.7%	0.620

B-unstandardized regression coefficient; IP-95 % confidence interval; Beta-standardized regression coefficient; R^2-the proportion of variance around the mean value of C_{LTG} that is explained by the appropriate model; Significance$^{1-1}$ Significance of the predictor within the model, Significance$^{2-2}$ Significance of the model itself

In relation to the gender of the respondents in the conducted study, a statistically significant difference was recorded only for parameter DLEV/kg (36.58 ± 10.58 mg/kg vs. 27.71 ± 6.63 mg/kg, p = 0.010) (Figure 2a). The values of DLEV/kg and CLEV did not differ statistically significantly compared to other analyzed parameters (Figures 2a and 2b).

Univariate regression showed that gender, DLTG, and DLTG/kg were significant predictors of LTG concentration values, while the results of multivariate analysis confirmed that DLTG, but not gender, was a significant predictor of CLTG. Based on the previously obtained results, a univariate linear regression was conducted in order to assess the factors that could potentially affect the CLEV. Subject-related factors (gender, age, BW) and drug-related factors (DLEV, DLEV/kg, CVA, CLTG) were included in the regression model. Univariate regression indicated that the analysed parameters did not represent significant predictors for LEV concentration values, however, the parameter DLEV/kg showed a trend towards statistical significance with a value of p = 0.077.

Discussion

The fundamental objectives of epilepsy treatment are reflected in the optimal control and reduction of the number of seizures, with the minimal risk of side effects (9). From the clinical aspect, it is a real challenge to set up an adequate therapeutic regimen, which would enable a long-term safe and effective therapeutic response. The rational aspect of the application of TDM in epilepsy therapy has been clearly described in recent years (10), and the ultimate goal of its implementation is reflected in the improvement of therapeutic outcomes (11). Therapeutic drug monitoring contributes to and facilitates the work of clinicians in daily practice, due to the fact that reference ranges of AED concentrations can be used as a measure of the effectiveness and safety of antiepileptic therapy (8).

In the conducted research, LTG was present in 71.83% of respondents (Table 2). The dose of LTG (p=0.049) and measured concentrations of LTG (p = 0.018) in the group of female subjects were statistically significantly increased (Figures

1a and 1b). The obtained results can potentially be explained by the influence of hormonal factors; however, further research in this field is still needed. Concerning the subjects' age, the dose and concentration of LTG did not show a statistically significant difference, which is in accordance with the previous research (12, 13). Although BW is often considered a potential factor in the pharmacokinetic variability of LTG, the results of available studies provide inconsistent results (12, 14–16). By analyzing the obtained results, it was observed that BW did not significantly affect DLTG and CLTG. In children, BW does not represent an independent variable, because it is in most cases directly dependent on age. This is why the focus should be primarily aimed at the subject's age as a factor that could potentially affect the pharmacokinetic variability of LTG (17). Lamotrigine has more predictable pharmacokinetics than classic AELs and it attains less potential for interactions (18). It obtains a minor effect on CYP450 isoenzymes and does not displace other drugs from their binding to plasma proteins (19). According to the guidelines, the reference range for monitoring LTG concentrations is 3–15 μg/ml (20). By analyzing the obtained data, it was observed that 86.27% of the measured LTG concentrations were within the reference range, while 13.73% of the concentrations were out of the range (11.77% below and 1.96% above) (Table 2). A statistically significant effect of co-therapy on LTG concentration was not recorded. The increased concentration of LTG in the LTG/VAL group of subjects (Figure 1b) is potentially the result of the inhibition of the UGT 2B7 isoform. The obtained results are in accordance with the research results of Reimers et al. (21). On the other hand, the simultaneous administration of LTG and LEV is considered much simpler, due to the absence of recorded interactions between these two drugs (22). However, more than 40% of the measured LTG concentrations in the co-medication with LEV were in the subtherapeutic range, which might be associated with inadequate seizure control. Univariate regression showed that gender, DLTG, and DLTG/kg are significant predictors for LTG concentration values (Table 3). A multivariate analysis confirmed that DLTG emerged as the most significant predictor for LTG concentration. The obtained results of the multivariate analysis are in accordance with the research conducted by Weintraub et al. demonstrating that DLTG is an important factor for predicting the concentration of LTG (18).

Levetiracetam belongs to the group of new-generation AELs that have been approved for use in the pediatric population since 2004 (23). Its mechanism of action is specific and differs from other AELs. It is characterized by a very favourable pharmacokinetic profile, so the routine administration of TDM of this antiepileptic drug is not recommended. However, there is a growing body of evidence indicating that changes in pharmacokinetics may occur in special populations, specifying the need for monitoring LEV concentrations (24, 25). In the conducted research, LEV was represented in therapy by 40.85% of respondents (Table 2). In relation to the gender of the respondents, a statistically significant difference was recorded in the parameter DLEV/kg ($p = 0.010$, Figure 2a). The results of existing studies indicate that gender does not have a significant effect on the concentration of LEV, which is in accordance with the results of the conducted research (Figure 2b) (24, 26, 27). Literature data suggest that the clearance of LEV is significantly higher in children under the age of 10 compared to the older population (28). One of the explanations is based on the fact that normal values of glomerular filtration as in adults are reached only after the age of 6 (29). Available literature data show that children under 10 years of age have 30–40% higher clearance and therefore require higher doses to achieve optimal concentrations (30). In the conducted research, a statistically significant difference was observed for the DLEV/kg parameter, which was higher in the group of examinees under the age of 12 ($p = 0.003$, Figure 2a). This result is in accordance with the previously mentioned studies. The analysis of the influence of age on CLEV indicated no significant difference and similar results were obtained in the research conducted by Dahlin and associates (31). The subject's BW is an important factor that can affect LEV concentration (25, 30). The results of the conducted research indicate that the values of DLEV/kg and CLEV parameters were not statistically significantly different in relation to the respondents' BW. Currently, only few studies with a relatively small number of subjects are available, which significantly prevents the identification of the influence of important demographic and physiological determinants on the pharmacokinetics of LEV. Further research focused on the concentration-to-dose ratio (C/D ratio) may be useful to evaluate LEV pharmacokinetic variability. Due to its favourable pharmacokinetic profile, LEV is often combined with other AELs (32). The optimal serum/plasma concentration of LEV should be in the interval of 12–46 μg/ml (33). Analyzing the obtained data, it was observed that 68.97% of the total concentrations of LEV were in the reference range, while 27.59% of the measured concentrations were below the defined reference range (Table 2). A statistically significant difference in the distribution of measured LEV concentrations depending on the applied cotherapy (VA/LTG) was not found. The obtained results are in accordance with the results of other available studies which indicate that the simultaneous administration of VPA or LTG does not significantly affect the concentration of LEV (28). The subtherapeutic concentrations of LEV that were recorded in the research, provide the possibility of correction of the dose of LEV within the combined therapy in order to obtain an optimum seizure control. Based on the previously obtained results, a univariate linear regression was conducted in order to assess the factors that might affect the concentration of LEV. Univariate

regression indicated that the analyzed parameters do not represent significant predictors for LEV concentration values, noting that the parameter DLEV/kg was the closest to statistical significance with a value of p = 0.077.

Conclusion

Antiepileptics represent a specific group of drugs characterized by a narrow-range therapeutic index and great variability in pharmacokinetics and therapeutic response, which is especially pronounced in the pediatric population. In the conducted study, it was observed that 86.27% of LTG and 68.97% of LEV measured concentrations during combined antiepileptic therapy were in the reference range. No statistically significant influence of co-medication on the concentrations of the tested AEDs was recorded. The results of multivariate analysis confirm that DLTG is the most significant predictor for LTG concentration. Concerning the LEV concentration, the obtained results indicate that DLEV/kg is an important factor. Although routine monitoring of new-generation antiepileptic drugs is not commonly imposed in daily clinical practice, the results of the conducted research indicate that monitoring the concentrations of LTG and LEV can be of great benefit in children and adolescents who receive combined antiepileptic therapy due to the nature of the disease itself and the possible pharmacokinetic variability of the tested antiepileptics.

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TERAPIJSKI MONITORING ANTIEPILEPTIKA NOVIJE GENERACIJE KOD PEDIJATRIJSKIH BOLESNIKA: FOKUS NA FAKTORE KOJI UTIČU NA KONCENTRACIJU U PLAZMI

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Monitoring koncentracije antiepileptičnih lekova (AEL) u pedijatrijskoj populaciji predstavlja važan korak u donošenju odluka vezanih za optimizaciju savremene terapije epilepsije. Primarni cilj ovog istraživanja bilo je određivanje koncentracija lamotrigina (LTG) i levetiracetama (LEV) u plazmi dece i adolescenata na kombinovanoj antiepileptičnoj terapiji. Sekundarni cilj bio je ispitati uticaj demografskih faktora i koterapije na izmerene koncentracije AEL-a. Prospektivna studija obuhvatila je sedamdeset jednog ispitanika sa dijagnozom epilepsije, starosti od dve godine do osamnaest godina, na kombinovanoj antiepileptičnoj terapiji koja je uključivala sledeće terapijske modalitete: valproinsku kiselinu (engl. *valporic acid* – VA) / LTG, VA/LEV i LTG/LEV. Rezultati sprovedenog istraživanja pokazali su da je 86,27% LTG koncentracija i 68,97% LEV koncentracija bilo u referentnom opsegu. Nije zabeležen statistički značajan uticaj komedikacije na koncentracije ispitivanih antiepileptika. Takođe, dobijeni rezultati potvrdili su da je doza LTG-a bila najznačajniji prediktor za koncentracije LTG-a. Rezultati ovog istraživanja ukazali su na to da jedino doza LEV-a prilagođena telesnoj masi može uticati na LEV koncentracije. Iako se terapijski monitoring antiepileptika novije generacije ne sprovodi rutinski u svakodnevnoj kliničkoj praksi, rezultati našeg istraživanja predočili su da monitoring koncentracija LTG-a i LEV-a može biti od velike koristi u pedijatrijskoj populaciji tokom primene kombinovane antiepileptične terapije, kako zbog same prirode bolesti, tako i zbog potencijalne farmakokinetičke varijabilnosti ispitivanih antiepileptika.

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***Ključne reči**: pedijatrijska populacija, terapijski monitoring leka, lamotrigin, levetiracetam*