POPULATION PHARMACOKINETICS OF VALPROATE IN CHILDREN: THE IMPORTANCE OF TOTAL DAILY DOSE, COMPLIANCE AND CO-TREATMENT

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ABSTRACT

Valproate represents one of the most commonly used anticonvulsants worldwide, whose narrow therapeutic range and high potential for drug-drug interactions leads to pronounced intra- and inter-individual variability in plasma concentration and response. The aim of our study was to apply population pharmacokinetics analysis to comprehensively investigate and detect the most important factors affecting pharmacokinetics of valproate in Serbian children with epilepsy. This retrospective observational study was based on demographic and medical data retrieved from the medical records on epileptic patients treated with valproate at the pediatric department of the Clinical Centre, Kragujevac, Serbia. Valproate serum concentrations were obtained as a part of routine medical practice. Population pharmacokinetics analysis was performed by MonolixSuite 2019R1 (Lixoft, Antony, France) software, using one-compartment model with first order absorption and linear elimination. The study included 1642 valproate concentrations obtained from 232 patients, of which 201 (1420 concentrations) were included in the index set used for the modelling, while the other 31 (222 concentrations) were the validation set used for external validation of the final model. Covariate testing based on the whole index set revealed that only total daily valproate dose significanly affected the clearance of valproate: $Cl\ (l/h) = 0.135 \times 1.002^{DD}$. When only compliant patients were included, co-treatment with carbamazepine was shown to be of significance as well: $Cl(l/h) = 0.121 \times 1.002^{DD} \times 1.2^{CBZ}$. Our study demonstrated that valproate clearance correlates with total valproate daily dose. The influence of co-treatment with carbamazepine on valproate pharmacokinetics can be observed and used for clearance estimation only in compliant patients.

Keywords: *Valproate, children, population pharmacokinetics, total daily dose, carbamazepine.*

INTRODUCTION

Epilepsy is a chronic disease characterized by simultaneous irregular discharge of neurons in the brain. The goal of anticolvusive therapy is to achieve complete control of the onset of seizures, with as little side effects as possible (1). Choosing appropriate medication for each individual patient is a hard task, which neurologists are facing in everyday clinical practice. The decision is influenced by many factors, including the type of epilepsy, age of the patient, concomitant therapy, pharmacological drug profile, as well as the pharmacoeconomic aspects (2). The treatment should start with a single drug, which can be later replaced or combined with another, if it turns out to be insufficient to control seizures (1, 3).

Based on the available literature, valproate (VPA) represents one of the most commonly used anticonvulsants worldwide (4). It's narrow therapeutic range and high potential for drug-drug interactions at several pharmacokinetics levels often leads to pronounced intra- and inter-individual variability in VPA plasma concentration and response (5). Polytherapy that combines VPA with other anticonvulsants, such as carbamazepine (CBZ), phenytoin or barbiturates, usually results in increased VPA clearance in both adults and children, mostly due to induction of drug metabolizing enzymes (6). The effect on VPA pharmacokinetics of newer anticonvulsants, such as clobazam, ethosucimide, levetiracetam, or topiramate, has been investigated too, yet with limited or inconclusive results (6-8).

It has been reported that the pharmacokinetics of VPA also strongly depends on age, especially during the infant period and in childhood, and even more if used in children in combination with other anticonvulsants (9). In Tunisia, Ben-Mahmoud et al. showed that the frequency of subtherapeutic serum VPA levels increased significantly at younger age, as well as in the presence of several enzyme inducing anticonvulsants (10, 4). In Mexico, Correa et al. found that body weight, total daily dose and concomitant use of phenobarbital, but not CBZ, were of greatest importance for the disposition of VPA in children (11, 6). The study by Jankovic et al., as the only one available in the literature that included Serbian pediatric population treated with VPA, demonstrated that body weight and concomitant administration of CBZ may have significant effect on VPA clearance (12, 2). However, this study did not examine the possible effect of concomitant use of drugs other than CBZ or lamotrigine.

Besides age and concomitant use of other drugs, it has been observed that patients prescribed with anticonvulsants frequently fail to comply with drug regimen, which often reduces treatment efficacy. Factors that can increase noncompliance could be adverse reactions to drug and inconvenient drug regimens affecting everyday life, as well as the lack of family support, or inadequate relationship with the clinician [13]. In addition, VPA pharmacokinetic profile may be affected by various other demographic and medical factors, such as total daily dose, body weight, and comorbidities (14).

Having in mind that highly variable response to VPA among pediatric epileptic patients has been frequently met in routine practice in Serbia, and that the available literature does not clarify the role of many of the proposed VPA-affecting factors in this population, the aim of our study was to apply population pharmacokinetics (PPK) analysis to comprehensively investigate and detect the most important factors affecting pharmacokinetics of VPA in Serbian children diagnosed with and treated for epilepsy.

MATERIALS AND METHODS

Patients and data collection

This was a retrospective observational study based on the data retrieved from the medical records on epileptic patients treated with VPA at the pediatric department of the Clinical Centre, Kragujevac, Serbia, between March 1st 2010 and March 30th 2020. To be included, patients had to meet the following criteria: 1) age between 1 and 18 years, 2) confirmed diagnosis of epilepsy, 3) VPA treatment lasting for at least 12 months, and 4) availability of relevant demographic and medical data, including at least 3 steady-state VPA serum concentrations. The exclusion criteria were: 1) any concomitant non-anticonvulsive therapy that could significantly affect pharmacokinetics of VPA, and 2) pregnancy or breastfeeding. For each patient, the following information was collected: age, sex, weight, the data on VPA treatment, including drug formulation, total daily dose, compliance with the recommendations on VPA treatment (routinely obtained from patients and/or their parents as a part of anamnesis), and available steady-state serum concentrations, as well as the information on concomitant use of other anticonvulsants, including their total daily dose. VPA steady-state serum concentrations were obtained at least 2 weeks[15] after beginning of the treatment or adjustment of the dose, as a part of routine medical practice. In brief, 3ml blood samples were taken half an hour before the morning dose, and the trough valproate concentrations[15] were determined using the immunoassay technique (Emit® 2000 Valproic Acid Assay, Beckman Coulter, Brea, California), with the linear range between 3.98 and 150 μg/mL, limit of quantification of 3.98 μg/mL, and an assay precision defined by ≤ 5% total coefficient of variation. The study was approved by the ethics committee at the Clinical Centre, Kragujevac, Serbia (approval No 01/20-402, obtained on April 3rd 2020), and conducted in accordance with the Declaration of Helsinki and its subsequent revisions. Given the record-based type of the study, the anonimization of the data, and the risk of authorisation bias, written information consent has not been obtained from the patients[16].

PPK modelling

PPK analysis was performed using MonolixSuite 2019R1 (Lixoft, Antony, France) software, which combines stochastic approximation expectation maximization with a Markov chain Monte Carlo procedure for maximum likelihood

estimation of the pharmacokinetic (PK) parameters in non-linear mixed effect model.

To determine the structural model, one- and two- compartment PPK models with first order absorption and linear elimination were compared (15), and the selection was made based on the precision of the parameter estimation expressed as the relative standard error (RSE), correlation between parameters from the correlation matrix of the estimates, collinearity between parameters expressed as the condition number, as well as on goodness of fit (GOF) plots, including observations vs. predictions plot, distribution of the population- and individual-weighted residuals (PWRES and IWRES, respectively), and the visual predictive check (VPC) plot (17, 18). For the residual variability, combined, proportional and constant error models were assessed, and the selection was based on the estimate for the combined residual error and the value of corrected Bayesian information criteria (BICc) (17). PK parameters were assumed to be lognormally distributed.

To determine the statistical model, covariates that were tested included age, sex, weight, compliance, VPA formulation, VPA total daily dose, as well as concurrent use and total daily dose of other anticonvulsants. To select the informative covariates, all were screened by Pearson's correlation test (for continuous covariates) or ANOVA (for categorical covariates) vs individual parameters and random effects, and those deemed to be potentially significant were assessed by addition to the structural model in order of significance. The covariates were considered relevant and kept as a part of the final model if they decreased the interindividual variability of the affected parameter (expressed as standard deviation of the inter-individual variability i.e. ω), and decreased the values of −2 log-likelihood (−2LL) and BICc. Similarly, correlations between random effects that were screened for using the Pearson correlation tests were selected and added to the final model if they decreased the values of -2LL and BICc (17).

The ability of the final model to capture the data was evaluated by assessing GOF plots, especially observation vs individual and population predictions, and VPC plot. The predictive performance of the final model was tested externally using a validation set, which consisted of data on pediatric epileptic patients that were subsequently collected and not included in the index set used for PK modelling (19). Bias, expressed as mean prediction error (MPE), and precision, expressed as mean absolute prediction error (MAPE), mean squared prediction error (MSE) and root mean squared prediction error (RMSE), were calculated with 95%CI based on the observed VPA concentrations and the mode of the predicted VPA concentrations for each individual (19, 20).

RESULTS

Patients and data collection

The study was based on a total of 1642 VPA concentrations (observations) obtained from 232 patients, of which 201 (1420 observations) were included in the index set used for PPK modelling, while the other 31 (222 observations) were the validation set used for external validation of the final model. Demographic and medication characteristics of the patients are presented in Table 1. Of them, all patiens from the index set and 30 from the validation set were deemed to be compliant with the recommendations on VPA treatment in 1273 and 177 occasions (observations), respectively, and their characteristics are presented separately in Table 2.

PPK modelling

The fitting of the compared structural models without covariates suggested that one-compartment PPK model with first order absorption and linear elimination adequatelly described the available VPA data, and it was subsequently applied as a base model. The constant error model was the most accurate for assessment of inter-individual and inter-occasion variability.

Covariate testing based on the whole index set revealed that only total daily VPA dose significanly affected the clearance (Cl) of VPA, decreasing -2LL and BICc each by approximately 15%, i.e. from 13209.47 to 11252.13, and from 13283.45 to 11333.37, respectively. There was no significant correlations observed between random effects. GOF plots of observed vs. population predicted VPA concentrations by the base and the final model in the whole index set (presented in Figure 1) reveals that the final model improves the data fitting and adequately describes the obtained VPA concentrations, with the proportion of outliers of 5.28%. The values of the PPK final model estimates for VPA Cl in all patients included in the modelling are summarized in Table 3, and the model based on the data from the whole index set can be described as follows:

$$Cl\ (l/h) = 0.135 \times 1.002^{DD}$$

where DD represents the total VPA daily dose in mg. Based on the equation, VPA Cl ranged from 0.201 l/h in patients daily receiving the minimal 200mg VPA dose to 7.341 l/h in those receiving maximal, i.e. 10 times higher dose, with the Cl of 0.604 l/h corresponding to the 750mg VPA daily dose, i.e. the median VPA daily dose in our index set. External validation of the predictive performance of the final model was carried out using a validation set, and the prediction errors of validation set are presented in Table 4. GOF plots of observed vs. population predicted VPA concentrations by the base and the final model in the validation set are presented in Figure 2.

Stratification of the GOF plot of observed vs. population predicted VPA concentrations in the whole index set according to compliance with the recommendations on VPA treatment revelaed that the data fit better for the group of patients/observations that were compliant (Figure 3). Therefore, the data were split by compliance, and only compliant patients/observations were included in the index subset used for additional PPK modelling. One-compartment PPK model with first order absorption and linear elimination and the constant error model were used as a base for covariate testing.

In the index subset consisted of compliant patients/observations, in addition to daily VPA dose that was confirmed to significantly affect VPA PK (decreasing -2LL and BICc each by approximately 18%, i.e. from 13995.27 to 11480.31, and from 11553.38 to 14061.20, respectively), co-treatment with carbamazepine (CBZ) was shown to be of significance as well: it additionally decreased -2LL and BICc to 10082.79 (approx. 13%) and 10163.02 (approx.12%), respectively. There was no significant correlations between random effects. GOF plots of observed vs. population predicted VPA concentrations for comparison of the base and the final model in the index subset of compliant patients/observations (Figure 4) confirmed the suitability and accuracy of the final model, with the proportion of outliers decreased to 4.63%.

The values of the PPK final model estimates for VPA Cl in compliant patients/observations included in the modelling are summarized in Table 3, and the model based on the data from the index subset of compliant patients/observations can be described by the following equation:

$$Cl(l/h) = 0.121 \times 1.002^{DD} \times 1.2^{CBZ}$$

where DD represents the total VPA daily dose in mg, and CBZ has a value of 1 if a patient is co-treated with CBZ, and 0 if not.

Based on the equation, a) if CBZ is not used, VPA Cl values correspond to those obtained by the PPK model based on the whole index set and range from 0.201 l/h to 7.341 l/h, depending on the VPA daily dose; b) if CBZ is used, VPA Cl range from 0.216 l/h to 7.896 l/h in patients daily receiving 200mg to 2000mg VPA, respectively, with the value of 0.650 l/h associated with the median VPA daily dose of 750mg. External validation of the predictive performance of the final model was carried out using a validation subset of compliant patients/observations, and the corresponding prediction errors are presented in Table 4. The corresponding GOF plots of observed vs. population predicted VPA concentrations by the base and the final model in the validation set are presented in Figure 5.

Table 1. Demographic and medication characteristics of all patients included in the study: index set included in PPK modelling and the corresponding validation set

		All patients/observations	
		Index set	Validation set
Demographic data			
No of patients		201	31
Sex (male/female)		84/117	16/15
No of observations		1420	222
Age (years)	range	1 - 17	1 - 17
	median (IQR)	8 (5 - 11)	7 (4 - 11)
Weight (kg)	range	4 - 94	10 - 88
	median (IQR)	29 (20 - 42)	28 (18 - 43)
Medication data			
Valproate			
Daily dose (mg)	range	200.0 - 2000.0	200.0 - 1500.0
	median (IQR)	750.0 (550.0 - 1000.0)	700.0 (500.0 - 1000.0)
Weight-adjusted daily dose (mg/kg)	range	0.3 – 79.6	14.3 - 50.0
	median (IQR)	27.3 (23.1 - 33.3)	27.8 (23.6 – 31.6)
Drug formulation (syrup/retard tbl.)		604/816	119/106
Serum concentration (mg/l)	range	3.7 - 128.0	18.9 - 120.0
	median (IQR)	76.8 (64.0 - 87.0)	75.6 (62.8 - 87.6)
Co-treatment			
Carbamazepine	yes/no	57/1363	11/211
daily dose (mg)	range	100.0 - 800.0	100.0 - 800.0
	median (IQR)	400.0 (300.0 - 600.0)	360.0 (270.0 - 540.0)
Clobazam	yes/no	104/1316	12/210
	range	5.0 - 20.0	10.0 - 20.0

		All patients/observations	
		Index set	Validation set
daily dose (mg)	median (IQR)	15.0 (10.0 - 15.0)	17.5 (15.0 - 20.0)
Ethosuximide	yes/no	69/1351	7/215
daily dose (mg)	range	500.0 - 1000.0	600.0 - 900.0
	median (IQR)	700.0 (600.0 - 800.0)	600.0 (600.0 - 800.0)
Levetiracetam	yes/no	116/1304	10/212
daily dose (mg)	range	300.0 - 1500.0	300.0 - 1000.0
	median (IQR)	1000.0 (675.0 - 1000.0)	750.0 (600.0 - 1000.0)
Topiramate	yes/no	37/1383	7/215
daily dose (mg)	range	50.0 - 200.0	75.0 - 150.0
	median (IQR)	75.0 (60.0 - 100.0)	100.0 (100.0 - 100.0)
Lamotrigine	yes/no	14/1406	5/217
daily dose (mg)	range	50.0 - 75.0	50.0 - 1500.0
	median (IQR)	50.0 (50.0 - 50.0)	50.0 (50.0 - 100.0)

Table 2. Demographic and medication characteristics of compliant patients included in the study: index set included in PPK modelling and the corresponding validation set

		All patients/observations	
		Index set	Validation set
Demographic data			
No of patients		201	30
Sex (male/female)		84/117	16/14
No of observations		1273	177
Age (years)	range	1 - 17	1 - 17
	median (IQR)	8 (5 - 11)	7 (5 - 11)
Weight (kg)	range	4 - 94	10 - 88
	median (IQR)	29 (20 – 42)	30 (20 – 44)
Medication data			
Valproate			
Daily dose (mg)	range	200.0 - 2000.0	200.0 - 1500.0
	median (IQR)	750.0 (600.0 - 1000.0)	700.0 (600.0 - 1000.0)
Drug formulation (syrup/retard tbl.)		518/754	85/92
Serum concentration (mg/l)	range	8.0 - 128.0	55.3 - 120.0
	median (IQR)	79.0 (68.9 - 88.0)	80.0 (70.6 - 91.0)
Co-treatment			
Carbamazepine	yes/no	47/1226	6/171
daily dose (mg)	range	100.0 - 800.0	300.0 - 800.0
	median (IQR)	400.0 (360.0 - 600.0)	500.0 (325.0 - 750.0)
Clobazam	yes/no	96/1177	11/166
daily dose (mg)	range	5.0 - 20.0	10.0 - 20.0
	median (IQR)	15.0 (10.0 - 15.0)	20.0 (15.0 - 20.0)
Ethosuximide	yes/no	55/1218	7/170

		All patients/observations	
		Index set	Validation set
daily dose (mg)	range	500.0 - 1000.0	600.0 - 900.0
	median (IQR)	800.0 (600.0 - 800.0)	600.0 (600.0 - 800.0)
Levetiracetam	yes/no	110/1163	8/169
daily dose (mg)	range	300.0 - 1500.0	300.0 - 1000.0
	median (IQR)	1000.0 (625.0 - 1000.0)	750.0 (675.0 - 1000.0)
Topiramate	yes/no	33/1240	4/173
daily dose (mg)	range	50.0 - 200.0	100.0 - 150.0
	median (IQR)	100.0 (60.0 - 100.0)	100.0 (100.0 - 112.5)
Lamotrigine	yes/no	12/1261	5/172
daily dose (mg)	range	50.0 - 75.0	50.0 - 150.0
	median (IQR)	50.0 (50.0 - 50.0)	50.0 (50.0 - 100.0)

Table 3. PPK model estimates for valproate clearance in patient included in the final PPK model**

	All patients/observations		Compliant patients/observations	
	Estimated value	RSE(%)	Estimated value	RSE(%)
Pop. estimate*	0.135	6.47	0.121	4.9
β_Cl_DD	0.000794	4.66	0.000861	3.72
β_Cl_CBZ	/	/	0.0792	28.5
ω_Cl*	0.059	13	0.046	21.5
γ_Cl*	0.019	26.3	0.022	24.5

RSE(%) – relative standard error; * - l/h; CBZ - carbamazepine co-treatment; DD - daily dose of VPA; ω - standard deviation of the inter-individual variability; γ - standard deviation of the inter-occasion variability; ** - in the base model, parameters of variability, i.e. ω_Cl and γ_Cl, were estimated to 0.317 and 0.130, respectively, in the whole index set, and to 0.304 and 0.133, respectively, among compliant subjects

Table 4. Prediction errors of the final PPK models in validation sets

	All patients/observations		Compliant patients/observations	
	Error	95% CI	Error	95% CI
MPE	-0.098	-1.037, 0.841	-0.185	-1.121, 0.751
MAPE	5.429	4.822, 6.037	5.036	4.468, 5.605
MSE	50.737	37.481, 63.994	40.157	32.285, 48.029
RMSE	7.123	6.122, 8.000	6.337	5.682, 6.930

MPE - mean prediction error; MAPE - mean absolute prediction error;
MSE - mean squared prediction error; RMSE - root mean squared prediction error

Figure 1. Goodness-of-fit plots of observed vs. population predicted VPA concentrations by the base (a) and final (b) models in all patients and observations included in the index set

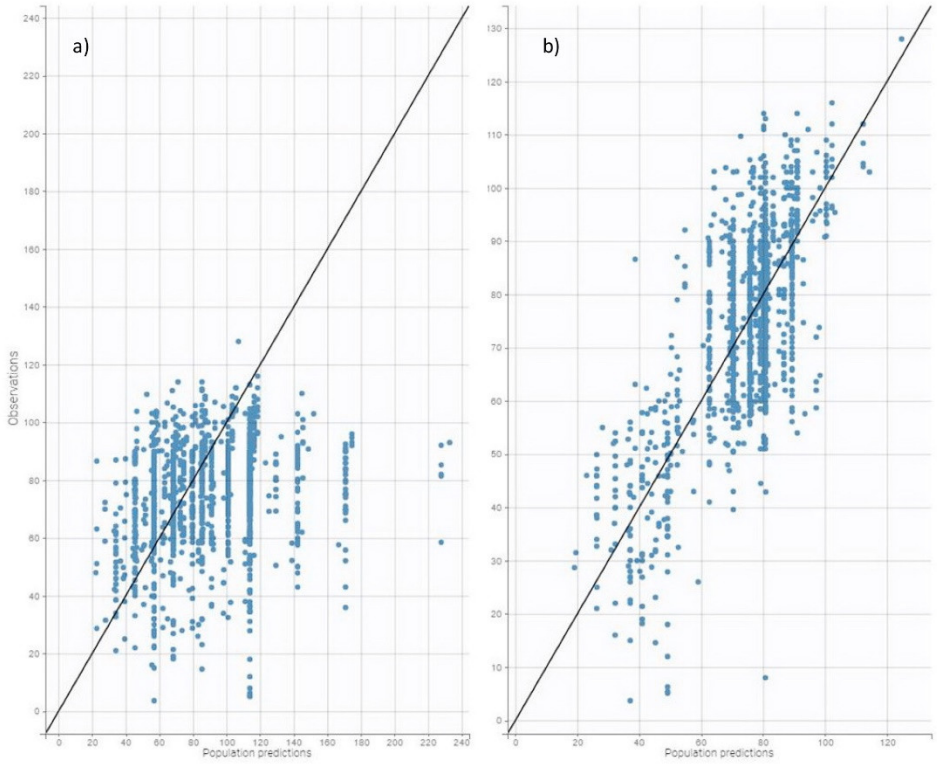


Figure 2. Goodness-of-fit plots of observed vs. population predicted VPA concentrations by the base (a) and final (b) models in all patients and observations included in the validation set

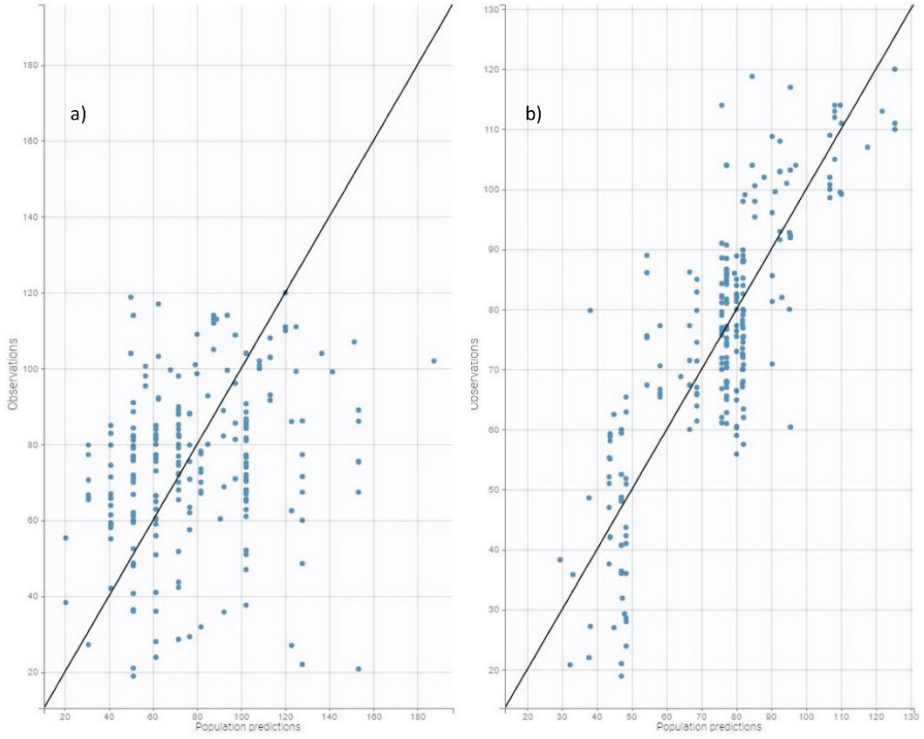
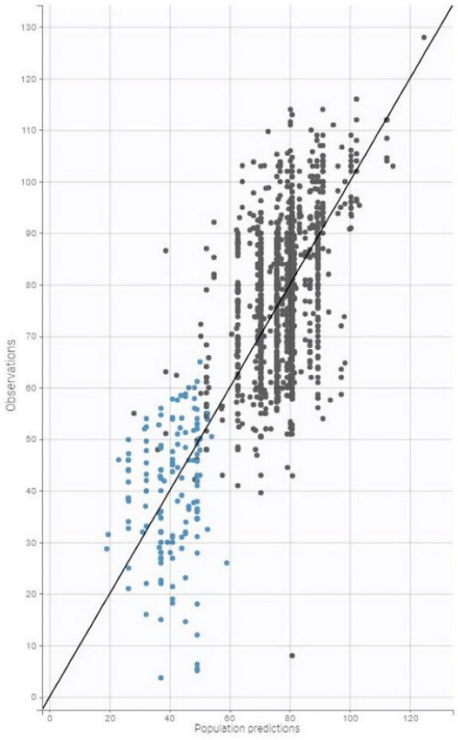


Figure 3. Goodness-of-fit plot of observed vs. population predicted VPA concentrations by the final models in all patients and observations included in the index set, stratified by compliance



compliant patients are marked with black, and non-compliant with blue dots

Figure 4. Goodness-of-fit plots of observed vs. population predicted VPA concentrations by the base (a) and final (b) models in compliant patients and observations included in the index set

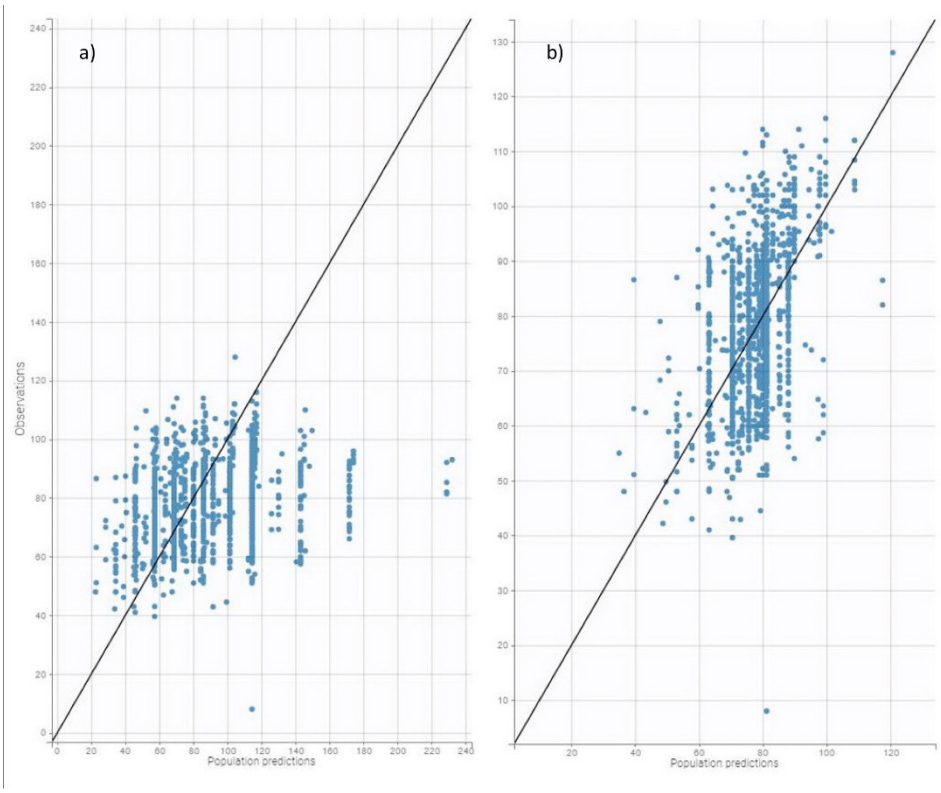
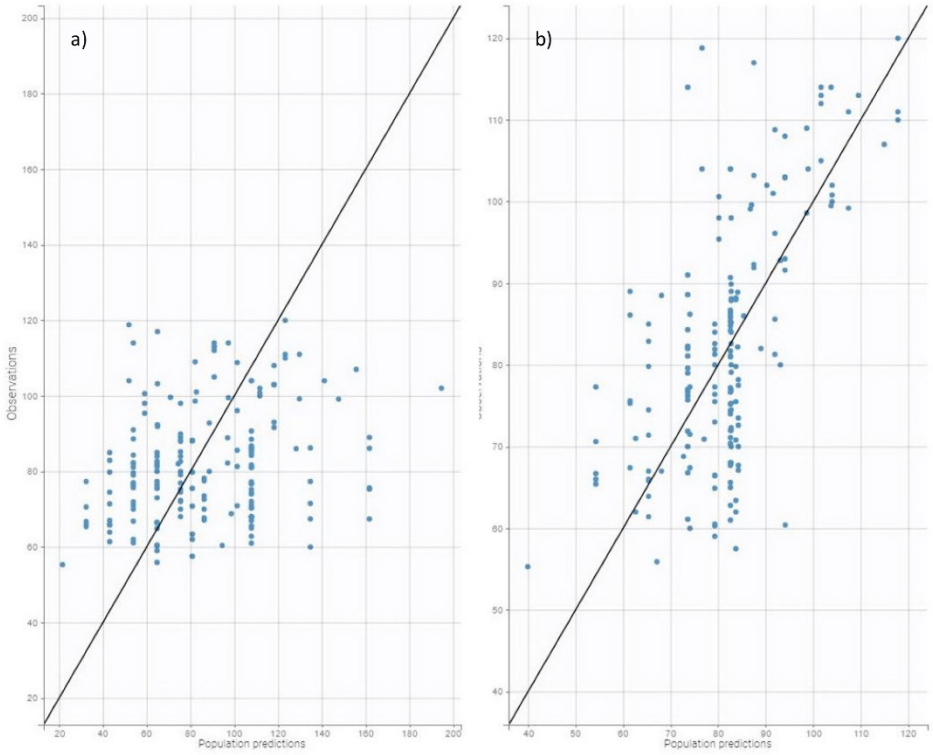


Figure 5. Goodness-of-fit plots of observed vs. population predicted VPA concentrations by the base (a) and final (b) models in compliant patients and observations included in the validation set



DISCUSSION

In the present study, we investigated the influence of several demographic and drug-related factors on VPA pharmacokinetics in Serbian pediatric epileptic patients. PPK analysis revealed that VPA Cl depends on total VPA daily dose, while co-treatment with CBZ exhibits additional effect that can be detected only in compliant patients. Given the pronounced variability in response to VPA observed among pediatric epileptic patients in Serbia that renders the need for better and more informative drug dosing decisions, we hope our findings will add to clinicians' considerations related to VPA-based anticonvulsive treatment.

The total daily dose is generally recognized as an important factor affecting drug pharmacokinetics. In both adults and children, VPA is usually administrated at a low starting dose, which is thereafter increased slowly until the optimal clinical response is achieved, or a maximum tolerated dose reached [1]. Serum drug levels, which serve as a reliable indirect indicator of VPA efficcacy, can be assessed by therapeutic drug monitoring (TDM), which is widely recommended and used as a guide for drug dose adjustment (21, 5). The reference range for the total serum VPA concentration has been set between 50 mg/L and 100 mg/L (350 μmol/L to 700 μmol/L) [6], although seizure control has been reported at concentrations as low as 8.7 mg/L (22). In our study, both the daily dose (total and weight-adjusted) and the observed VPA serum concentrations varied considerably, and spanned the range much wider than the recommended. While the administered dose was usually higher than recommended for pediatric population (9), serum drug concentrations mainly corresponded well to the previous reports (23, 24). Although the difference in age could be at least partly responsible for these findings, the observed variability clearly suggests the presence of other factors that could affect drug concentration and response.

In childhood, VPA pharmacokinetics displays significant variations, one of the most important being related to gradual decrease of VPA Cl with age. Namely, it has been observed that infants may need a dose that is 2-3 times higher than recommended for older children, to achieve the same serum concentration (25, 10). However, our analysis revealed that the main determinant of VPA Cl in children was not the age, but the total daily dose. In spite of the opposite results described as well (12, 26), our finding complies with previous studies reporting higher VPA Cl rate in children treated with higher VPA doses (11, 15, 24). It seems there are two possible explanations for this finding: one related to VPA protein binding and the other to so-called "TDM effect" (15, 24). Namely, it is well known that VPA is up to 95% protein bound (17), with binding rate being concentration-dependent: higher VPA doses lead to binding saturation, resulting in higher unbound VPA fraction (6, 11), which is the only one that can undergo elimination processes and whose increase

accelerates dose-dependent drug Cl. On the other hand, "TDM effect" implies that patients having higher VPA Cl for other reasons will be, due to lower measured serum concentrations, prescribed with higher dose, thus the association between VPA dose and Cl might be easily misunderstood. While most probably both phenomena take a part in the observed (15, 24), inclusion of the total daily dose in the model certainly has a merit in estimating VPA clearance.

Another important feature of VPA is its susceptibility to drug-drug interactions, which usually take place during metabolism. VPA is metabolized through at least three different routes in humans, including glucuronidation, β oxidation, and cytochrome P450 (CYP)-mediated oxidation, responsible for biotransformation of approximatelly 50%, 40% and 10% of the administered dose, respectively (27). While any of the described pathways might endure alterations due to concomitant administration of other drugs, enzyme-inducing anticonvulsants, such as CBZ, phenytoine, or barbiturates, most probably affect VPA pharmacokinetics by inducing relevant UDP-glucuronosyltransferases (UGTs) and CYPs (6). Due to enzyme induction, anticonvulsive polytherapy has a potential to accelerate VPA Cl and the formation of its (frequently toxic) metabolites, decresing its half-life while at the same time increasing the risk of VPA-related adverse effects (6, 27). In the present study, concomitant therapy with CBZ was detected as another determinant of VPA pharmacokinetics, but the association became evident only after non-compliant patients were excluded from the analysis. Having in mind that most of the earlier studies based their analyses on the data from apparently compliant patients (4, 24, 28), our findings correspond well to the previosly published reports. It should be noted that the CBZ-related increase in VPA clearance, as both drugs are highly protein bound, could be at least partly also due to competition in protein binding (29). Namely, CBZ-driven displacement of VPA from protein binding sites will increase unbound VPA fraction and subseqeuntly its clearance. Since increased elimination of unbound fraction will return it to its previous level, the alteration of VPA unbound concentration, as well as the clinical consequences of this type of CBZ-VPA interaction, is expected to be transient. However, CBZ-dependent increase in VPA clearance, even if caused by disruption of VPA protein binding, is expected to last as long as both drugs are taken - not only concomitantly, but also in a regular manner. Regardless of the mechanism, our results imply that concomitant therapy with CBZ should be taken into account when assessing VPA pharmacokinetics, but only after compliance has been established.

It is worth noting that we did test for, but did not identified as important for VPA pharmacokinetics, the following: age, sex, weight, VPA formulation, and concomitant use of clobazam, ethosuximide, levetiracetam, topiramate and lamotrigine. All of the investigated factors were previously attended in VPA-related studies, and more or less frequently associated with at least one of the VPA pharmacokinetic parameters (15). We believe that the lack of significant associations in our study could be explained by the fact that we estimated only Cl, and not the absorption rate constant or volume of distribution, which were previously found to be affected by age, sex, weight, or formulation. In addition, some of the factors, such as co-treatment with anticonvulsants other than CBZ, were not very frequently observed in our study sample, thus there is a possibility that we were underpowered to detect their possible influence.

In conclusion, the present study demonstrated that VPA Cl correlates with total VPA daily dose. The influence of co-treatment with CBZ on VPA pharmacokinetics can be observed and used for Cl estimation only in compliant patients.

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CONFLICT OF INTEREST STATEMENT

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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