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RESEARCH ARTICLE

Estimation of apparent clearance of valproic acid in adult Saudi patients

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Abstract

Background Valproic acid is one of several antiepileptic medications requiring therapeutic drug monitoring due to its complex and wide pharmacokinetic interindividual variability. *Objective* The objective of this study was to determine the population pharmacokinetics of valproic acid in adult Saudi patients and to identify factors that explain its pharmacokinetic variability. *Setting* Tertiary referral teaching hospital, Riyadh, Saudi Arabia. *Method* A retrospective chart review was performed at King Saud University Medical City of patients who received oral valproic acid. The population pharmacokinetic models were developed using Monolix 4.4. After development of the base model, we investigated several covariates including age, sex, weight, total daily dose, and cotherapy with carbamazepine and phenytoin. Main outcome measures the pharmacokinetic parameters of valproic acid and the variables that contributing towards its inter-individual variability. *Results* The analysis included a total of 54 valproic acid plasma concentrations from 54 patients (42.5% male). The data were sufficiently described by a one-compartment model with linear absorption and elimination processes. Average parameter estimates for valproic acid apparent clearance (CL/F) and apparent volume of distribution (V/F) were 0.14 L/h and 37.7 L (fixed), respectively. The inter-individual variability (coefficients of variation) in CL/F was 12%. The most significant covariates for valproic acid CL/F were age, body weight, total daily dose, and cotherapy with carbamazepine and phenytoin. *Conclusion* This model showed significant inter-individual variability between subjects. Our findings showed that patient age, body weight, total daily dose, and cotherapy with carbamazepine and phenytoin are the most significant covariates of valproic acid clearance. Collectively, healthcare providers should take these factors in consideration for optimal valproic acid dosage regimen.

Keywords Dose individualization · Pharmacokinetic modelling · Pharmacokinetics · Saudi Arabia · Valproic acid

Impacts on practice

- The inter-individual variability in the kinetics of valproic acid in the Saudi population can be explained by a number of factors including age, bodyweight, dose and cotherapy with other anti-epileptics.
- Clinicians should be aware of the need to dose valproic acid based on more factors than age or body weight alone.

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Introduction

Antiepileptic drugs have complicated pharmacokinetics as well as narrow therapeutic ranges that cause significant differences in individual therapeutic dosages [1]. Valproic acid is one of several antiepileptic medications requiring therapeutic drug monitoring (TDM) due to its complex and wide pharmacokinetic inter-individual variability [2]. Owing to its broad-spectrum activity against seizures, valproic acid is the most widely prescribed antiepileptic, which is also used to treat several psychiatric disorders and migraine [3–5]. However, its use is limited by rare but potentially life-threatening side effects, including teratogenicity, hepatotoxicity, and pancreatitis [6]. Valproic acid is almost completely absorbed following oral administration with high plasma protein binding that shows a small volume of distribution (V) and follows nonlinear pharmacokinetics [2, 7, 8]. It undergoes

complex hepatic metabolism resulting in minimal excretion of unchanged drug in the urine [7–9].

Population pharmacokinetics best represents the variability in valproic acid concentrations of different patient populations [10–12]. In 1997, Yukawa et al. [13] found that the clearance (CL) of valproic acid was decreased in a weight related fashion in children, with minimal changes observed in adults. In addition, Smith et al. [9] found that females and elderly patients have significant variability in valproic acid serum concentration compared to that in male and adult patients. Another study showed valproic acid CL was affected by total body weight proportionally and inversely with an increasing valproic acid daily dose [14]. In 1978, Klotz et al. [15] found that the elimination of valproic acid slightly impaired with liver dysfunction. In addition, studies have shown several drug and food interactions which may introduce a variation in valproic acid plasma concentration [16, 17]. Thus, close monitoring of valproic acid concentration is required to achieve optimal efficiency, and thus minimize the risk of sub-therapeutic or toxic blood concentrations. To the best of our knowledge, a detailed study of valproic acid concentrations using a population pharmacokinetics approach has not yet been performed in Saudi Arabia.

Aim of the study

Therefore, the primary objective of this study is to build a population pharmacokinetic model in adult Saudi patients. Secondary objectives are to estimate the percentage of patients that achieve therapeutic concentrations and to determine the factors that explain pharmacokinetic variability of valproic acid such as sex, age, body weight, comedications, and significant drug interactions; and to improve the efficacy and safety of dosing, which will benefit individual patients.

Ethics approval

Ethics approval for the study was obtained from the IRB committee at King Saud Medical City. Riyadh, Saudi Arabia (IRB no. E-17-2331).

Method

Patients and data collection

This was a retrospective chart review study based on data retrieved between January 2009 and March 2015 from the health information system at King Saud University Medical City on adult Saudi patients who were taking oral valproic acid. Patients visited the outpatient neurology clinics for follow-up while maintained on valproic acid. Dosing for these patients was based on the institution's standard of care for the treatment of seizure. Laboratory guidelines for monitoring valproic acid concentrations stated that blood samples be drawn after steady-state conditions had been reached; for patients receiving oral valproic acid, blood samples were drawn immediately before the next dose. The following information was collected for each patient: age, weight, sex, concurrent antiepileptics, aspartate amino transferase, alanine amino transferase, total albumin concentration, total bilirubin and serum creatinine concentration, total daily dose, and valproic acid trough concentration.

Analytical method

All blood samples were analyzed in the same laboratory. Serum concentrations of valproic acid were measured by fluorescence polarization immunoassay (TDx; Abbott Laboratories). The calibration curve range of this assay was between 12.5 and 150 mg/mL. The lowest measurable concentration was 0.7 mg/mL, and the coefficient of variation was $< 10\%$.

Population pharmacokinetic modelling

Pharmacokinetic analysis was carried out using Monolix 4.4 software. [18]. We developed the base structural model for valproic acid comparing one- and two- compartment pharmacokinetic models with first or zero order absorption. Pharmacokinetic parameters were assumed to follow a log-normal distribution. For the residual variability, the following error models were tested: combined, proportional, and constant error models. The structural models were selected according to the following: (a) the decrease in the minimum of the objective function value (Log-likelihood value); (b) the precision of the parameter estimation expressed as the relative standard error [RSE (%)] and calculated as the ratio between the standard error and the final parameter estimate; (c) physiological plausibility; and (d) goodness of fit (GOF) plots that included the observed versus predicted concentration, residuals plot, and the visual predictive check (VPC). The bioavailability (F), absorption with a lag time, and V could not be determined because valproic acid was orally administered and we had only trough levels. Additionally, the pharmacokinetic values of CL and V corresponded to the ratios of apparent clearance (CL/F) and apparent volume of distribution (V/F), respectively.

Covariate model

After the appropriate base model was established, covariates were tested, specifically age, sex, body weight, total daily dose, albumin concentration, and concurrent antiepileptics. Only carbamazepine, phenytoin, and topiramate, which were administered in $> 5\%$ of the population, were included in the

covariate testing. For covariate testing, we started by plotting the individual pharmacokinetic parameters vs covariates to screen for potentially significant correlations. Then, we performed a stepwise regression analysis to test the significant covariates identified in step 1 using the log-likelihood ratio test. If a trend between a covariate and pharmacokinetic parameter was found, it was considered for inclusion in the base model.

Model evaluation

GOF plots were used as the first indicator of suitability, including the representation of model-based individual predictions (IPRED) and population predictions (PRED) vs observed concentrations. VPC was constructed to study the performance of the final model. VPC was constructed with the 10th, 50th, and 90th percentiles of the observed data.

Results

Patients and data collection

The analysis included a total of 54 valproic acid plasma concentrations from 54 patients (42.5% male). Baseline demographic and clinical characteristics of the patients used for model building are shown in Table 1. The mean (± SD) age was 36.3 ± 13.5 years, and the mean body weight was 82.5 ± 26.8 kg. The patients received a valproic acid total daily dose of 867 ± 514.2 mg/day, which resulted in an average trough concentration of 69.5 ± 27.5 mg/L.

Population pharmacokinetics

We first fitted the one- and two-compartment models without any covariates; the results of this fitting suggested that the valproic acid data were adequately described by a one-compartment open model with linear absorption and elimination. The pharmacokinetic model was parameterized in terms of CL/F and V/F. A proportional error model was the most accurate for residual and interpatient variability. After covariate testing, age, body weight, total daily dose of valproic acid, and combined therapy with carbamazepine and phenytoin were shown to significantly influence the CL/F of valproic acid; whereas, sex, albumin concentration, and cotherapy with topiramate were not notable factors related to the valproic acid CL/F. Age, body weight, total daily dose of valproic acid, and combined therapy with carbamazepine and phenytoin statistically improved the base model by decreasing the OFV by 65 points and decreasing the between-subject variability of CL by approximately 46%. Therefore, these covariates were included in the model; whereas other covariates, which displayed no correlation with the pharmacokinetic parameters, were not investigated further. Due to single point sparse data, not all parameters and their inter-individual variability could be determined. Thus, valproic acid CL/F and its inter-individual variability were determined while Ka and V/F were fixed without variability using available literature [11, 19, 20]. The values of the parameters for the final model are summarized in Table 2.

Model evaluation

Diagnostic GOF plots for the valproic acid final covariate model are shown in Fig. 1. The values of RSE (%) that are shown in Table 2 reveal that CL/F was precisely estimated. Additionally, inspection of the VPC (Fig. 2) revealed a correlation between the percentile intervals obtained by simulation in the final model with those of the observed data. Both figures show that the final pharmacokinetic model describes the measured concentrations adequately.

Table 1 Summary of patient characteristics

Characteristics	Mean (SD)	Range
Age (year)	36.3 (13.5)	18–72
Sex, % male/%female	42.5/57.5	
Weight (kg)	82.5 (26.8)	34–146
Valproic acid dose (mg)	867 (514.2)	200–2500
Valproic acid serum concentration (mmol/L)	69.5 (27.5)	20–132
Concurrent antiepileptics, n (%)		
Carbamazepine	10 (18.51)	
Phenytoin	5 (9.25)	
Topiramate	3 (5.5)	

Table 2 Population pharmacokinetic model estimates for valproic acid following oral administration

Parameter	Population estimate	RSE (%)
CL/F (L/h)	0.14	12
Ka (h^{-1})	0.7	Fixed
V/F (L)	37.7	Fixed
IIV for CL (%)	12	18
Residual errors		
b	0.1	16

IIV inter-individual variability expressed as the coefficient of variation, RSE % relative standard error

CL (L/h) = $0.14 \times (\text{Age}/36.3)^{-0.84} \times [\text{body weight (kg)}/82.5]^{0.36} \times [\text{total daily dose (mg/d)}/867]^{2.13} \times 1.42$ (if cotherapy with carbamazepine) × 1.11 (if cotherapy with phenytoin)

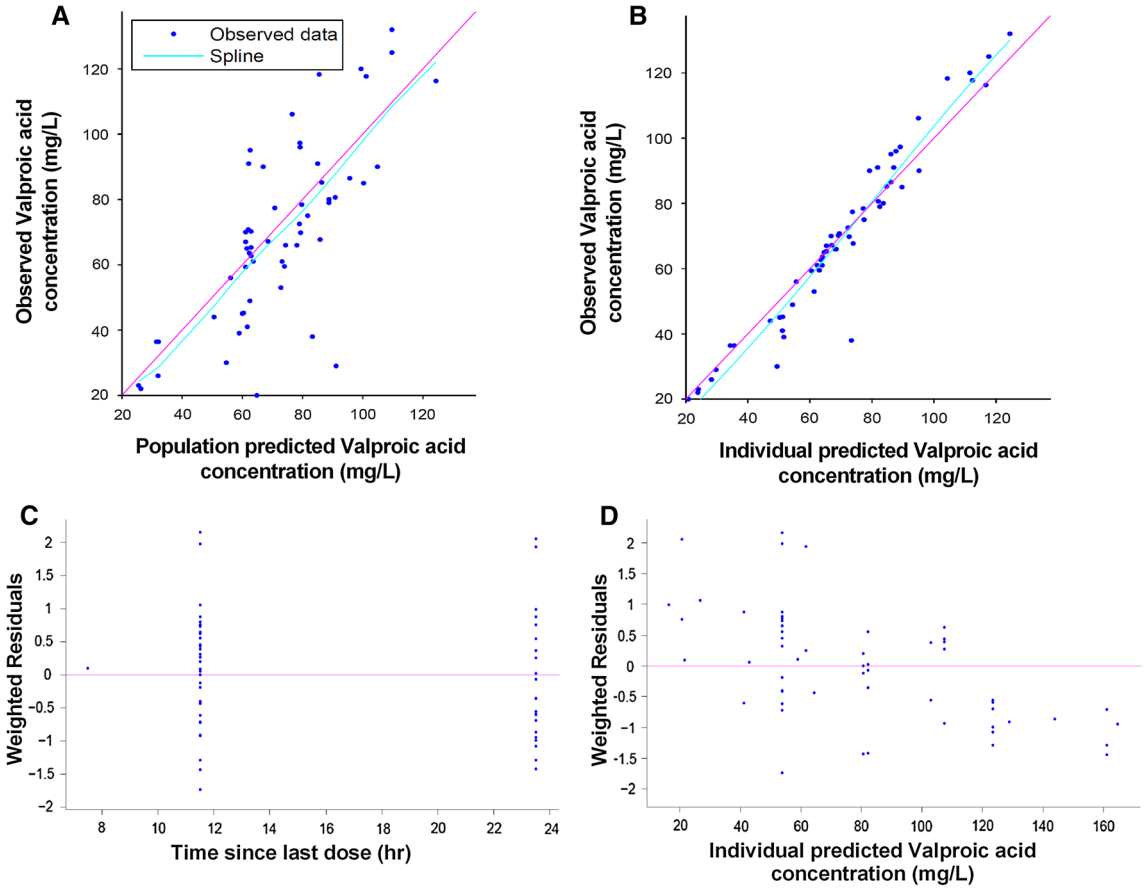

Fig. 1 Goodness-of-fit (GOF) plots obtained from the final model for valproic acid. **a** The individual predictions of valproic acid versus the observed concentrations. **b** The population predictions of valproic acid versus the observed concentrations. **c** The weighted residuals versus the time since last dose. **d** The weighted residuals versus the individual predicted concentrations

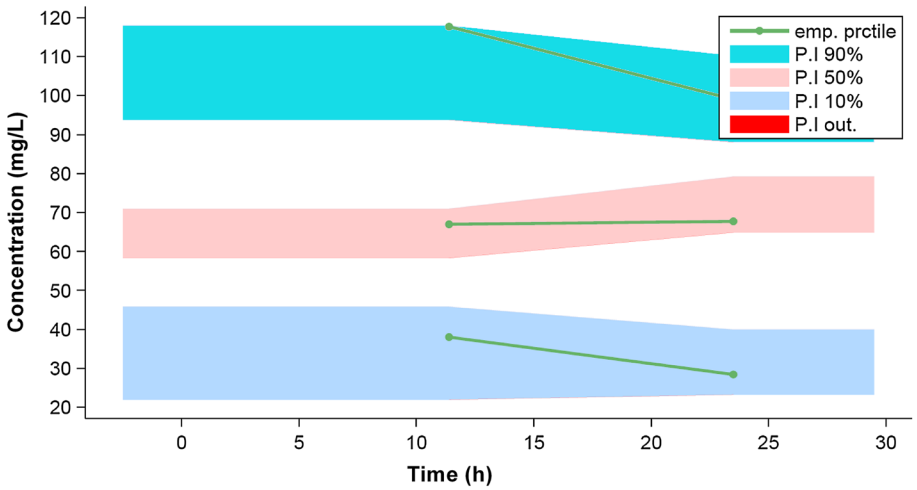

Fig. 2 Visual predictive check (VPC) for valproic acid concentration versus time based on 1000 Monte Carlo simulations. The solid green lines represent the 10th, 50th, and 90th percentiles of the observed data. The shaded regions represent the 90% CI around the 10th, 50th, and 90th percentiles of the simulated data. (Color figure online)

Discussion

Given its wide use in our clinical setting, the pharmacokinetic parameters of valproic acid and the factors affecting those parameters are important for us to know. In addition, there have been no studies until now evaluating those parameters and factors in our population. Thus, in this paper we used a population pharmacokinetics approach to estimate the pharmacokinetic parameters in Saudi patients. In addition, we identified the most significant covariates which are responsible for the high individual variability of valproic acid pharmacokinetic parameters, as the ultimate goal of this study is to optimize valproic acid treatment by individualization of valproic acid dosing.

In this study, the plasma concentration–time curve for valproic acid was fitted by a one-compartment model, which was in agreement with other studies that used TDM routine data [11, 12, 19–26]. Owing to the small number of samples per subject which resulted in limited information during the absorption and distribution phase, we were able to estimate valproic acid CL only. Thus, the rate constant of absorption (Ka) and V were difficult to estimate and were fixed at 0.7 h^{-1} and 37.7 L, respectively, based on the literature [11, 19, 20]. The estimated valproic acid CL was 0.14 L/h, with inter-individual variability of 12%. This value was similar to that reported by previous studies [11, 12, 19–23, 25, 26]. One of the previous studies was conducted in a Middle Eastern population with similar characteristics to our population [11]. Eldesoky et al. developed a model to describe the pharmacokinetic parameters in Egyptian epileptic patients and estimated the CL value in Egyptian epileptic patients was 0.1 L/h, with an inter-individual variability of 23.6% [11]. These values were similar to our findings.

Our multivariate analyses revealed that age, body weight, total daily dose of valproic acid, and cotherapy with other antiepileptic medications were the main determinants of valproic acid CL in our population. These findings agreed with results of previous studies [11, 12, 19–23, 26]. In the present study we found that higher age negatively influenced valproic acid CL. Several previous studies reported age related changes in valproic acid CL between pediatrics and adults, with no changes in adult patients [11, 19, 22, 23]. Although the reason is not clear, we hypothesized that declining liver metabolism with aging and changes in protein binding might explain this observation. Moreover, our study indicated that valproic acid CL increased with increases in body weight. This factor has been reported by several previous studies as primarily resulting from the organ development responsible for drug elimination [12, 19–22, 25, 26]. Another important factor that affected the valproic acid CL in our population was the total daily dose of valproic acid, which was also reported in previous studies [11, 12, 19, 20, 26]. It is known that valproic acid has high protein binding with saturation occurring at high plasma levels, resulting in a higher free fraction available for metabolism. This could explain the relationship between high total daily dose and low valproic acid CL. In addition, our study indicated that cotherapy with other antiepileptic medications such as carbamazepine and phenytoin significantly affected valproic acid CL. These two drugs are enzyme inducers and lead to an increase in valproic acid CL when administered with valproic acid [27]. These findings were similar to previous studies [11, 12, 19, 22, 23, 26]. Unlike other studies that reported sex as one of the most significant factors that affect valproic acid CL [13, 28, 29], we could not find a relationship between valproic acid CL and sex in our study.

Although the findings of this study provide a tool for valproic acid treatment individualization, the study had some limitations including the retrospective collection of data; a limited number of samples per patients; availability of trough concentrations only for the modal analysis; and the effect of a variety of oral formulations of the valproic acid which include differences in enteric coating, extended release, and oral solutions was not included as well. In addition, the study did not investigate the role of genetic polymorphism on the pharmacokinetic viability of valproic acid because the absence of such information. The impact of genetic polymorphism on the pharmacokinetics of valproic acid and related variability is very well established and discussed in several studies [30–34]. However, this is the first study conducted in a Saudi population to provide the estimation of apparent CL of valproic acid for adult patients by using population pharmacokinetic modeling, which would be valuable for clinical practice. Although the data used in this study is considered locally, we believed the findings of this study will add to the whole region. Taken in consideration the wide use of valproic acid in the area population and lack of studies that touch upon the factors that affecting the clinical aspects of it. Thus, the findings of this study will provide a tool to optimize valproic acid therapy in our country and in the region.

Conclusion

A qualified population pharmacokinetic model was developed to optimize valproic acid therapy in adult Saudi patients. Using one trough concentration per subject only showed that one could adjust the individualization maintenance dose of valproic acid based on patient age, body weight, total daily dose, and co-therapy with carbamazepine and phenytoin as they significantly affect the CL of valproic

acid. Well-designed studies that investigate the influence of the other factors on the pharmacokinetics of valproic acid should be undertaken to assist in drug dosage decisions. They could be followed by a prospective study to evaluate the optimal dose.

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Conflicts of interests The author has no conflicts of interest to declare.

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