Effect of Valproic Acid Daily Dose on its Clearance in Adult Patients with Epilepsy – Population Analysis of TDM Data

K. Vučićević (1), B. Miljković (1), M. Pokrajac (1), M. Prostran (2), Ž. Martinović (3), R. Veličković (4), I. Grabnar (5)*

(1) Department of Pharmacokinetics, Faculty of Pharmacy, University of Belgrade, Serbia
(2) Department of Pharmacology, Clinical Pharmacology and Toxicology, School of Medicine, University of Belgrade, Serbia
(3) School of Medicine, University of Belgrade, Institute of Mental Health, Department of Epilepsy and Clinical Neurophysiology, Belgrade, Serbia
(4) Institute of Mental Health, Belgrade, Serbia
(5) The Chair of Biopharmaceutics and Pharmacokinetics, Faculty of Pharmacy, University of Ljubljana, Slovenia

Objective: To investigate the influence of valproic acid daily dose (DVPA) on its oral clearance (CL/F) using therapeutic drug monitoring (TDM) data in adult patients diagnosed with epilepsy.

Methods:

Study design

- Retrospective routine clinical data from 2003-2005 period from Institute of Mental Health, Belgrade, Serbia.
- VPA was administered 1-3 times per day in the form of film tablets containing 333 mg of sodium VPA and 145 mg of VPA (Eftil®retard 500, Hemofarm, Serbia) either as monotherapy or in combination with other antiepileptic drugs.
- 1-2 mainly trough concentrations were available per patient.
- Assay: EMIT® - Cobas Mira (Roche Diagnostics, Basel, Switzerland). Inter- and intra- CVs <10%. Total VPA concentrations were measured.
- Covariates available from patients' chart whose effect was co-examined as well: age, gender, smoking status, co-therapy (phenobarbitone, carbamazepine, lamotrigine, topiramate, benzodiazepines).

Pharmacokinetic analysis

- NONMEM (ver. 6, level 2, GloboMax LLC, Ellicott City, MD, USA) and Perl speaks NONMEM (Version 2.3.0, http://psn.sourceforge.net).
- A one compartment model with first order absorption and elimination (ADVAN2/TRANS2 PREDPP subroutine), FOCE estimation.
- ka and V/F were fixed at the literature values: ka=0,67h^{-1}, V/F=0.14 L/kg. Oral clearance (CL/F) was estimated.
- Analysis was performed by forward inclusion of covariates into the base model: minimum decrease in objective function value (OFV) of 3.84 ($p < 0.05$).
- A bootstrap sampling method with replacement using 2000 replications was applied to calculate 95% confidence intervals (95% CI) of the final model parameter values.
- Validation of the final model was performed.

Results: Inclusion of DVPA greater than 1000 mg/day into the base model, resulted in the highest decrease in OFV of 16.809 ($p < 0.0001$) and reduced interindividual variability. With the final model for a typical patient of 70 kg, CL/F was estimated at 0.517 L/h. If DVPA was greater than 1000 mg/day CL/F was found to increase by 43%. Interindividual variability of VPA CL/F (95% CI) was 31.9% (22.4–37.9%), while residual variability was 23.8% (15.4–32.4%) for the proportional and 13.2 mg/L (3.17–18.8 mg/L) for the additive component. In the validation set predictive performance indicated no bias since 95% CI of mean prediction error included zero, and it was smaller than the model's residual error.

Table 1. Patients' characteristics

CHARACTRISTICS	LEARNING SET	VALIDATION SET
Number of patients	129	24
Number of steady-state samples	200	40
Patients' weight [kg], *mean* ± *Sd*	72.10 ± 14.19	70.96 ± 11.04
VPA dose [mg/day],	1107.75 ± 412.05	1031.25 ± 306.74
VPA concentration [mg/L] , *mean* ± *Sd*	72.32 ± 35.70	70.80 ± 32.38

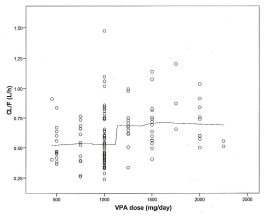

Figure 1. Influence of daily dose of valproic acid, on its oral clearance

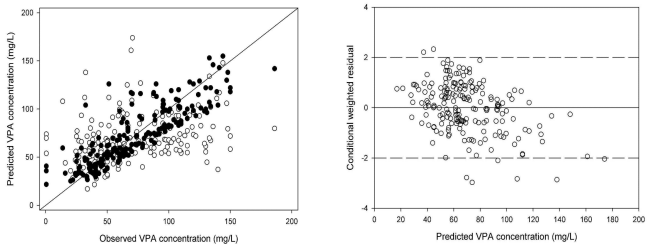

Figure 2. Diagnostic plots of the final model (filled circles-individual predictions, open circles-population predictions)

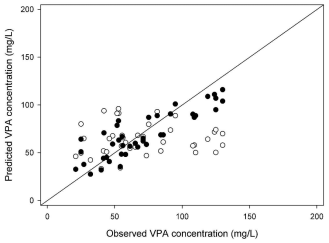

Figure 3. Diagnostic plot of the final model validation set for the final model (filled circles-posterior Bayesian predictions, open circles-*a priori* predictions)

Conclusion: In the present study, CL/F was found to increase significantly with DVPA greater than 1000 mg/day in a step-like manner. The relationship between DVPA and CL/F may be associated with the so-called TDM-effect. This implies the use of higher doses of VPA in patients with higher elimination rates, or in patients who are insensitive to lower VPA doses.

Reference: Bondareva IB, Jelliffe RW, Sokolov AV, Tischenkova IF. Nonparametric population modeling of valproate pharmacokinetics in epileptic patients using routine serum monitoring data: implication for dosage. J Clin Pharm Ther 2004; 29:105-20.

* kacav@pharmacy.bg.ac.rs