POPULATION PHARMACOKINETICS OF VALPROIC ACID, LAMOTRIGINE AND LEVETIRACETAM IN PEDIATRIC POPULATION

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INTRODUCTION

Managing epilepsy in pediatric patients through combined pharmacotherapy is a challenging task for clinicians. This is due to the unpredictable efficacy of drugs, adverse effects and a lack of knowledge about optimal dosage regimens. Therapeutic drug monitoring (TDM) is a common practice as part of personalized epilepsy management, which has several clinical benefits [1]. However, there are limitations to TDM, as drug concentrations often do not correlate with improved clinical outcomes. Therefore, there is a need for practical decision-making tools to assist clinicians in providing personalized treatment. Pharmacometrics and mathematical simulation tools can be crucial in improving personalized epilepsy management for vulnerable pediatric populations [2].

OBJECTIVES

- To describe the population pharmacokinetics (PopPK) of valproic acid (VA), lamotrigine (LTG), and levetiracetam (LEV) through non-linear mixed effects modeling in a pediatric population.
- To uncover the potential effect of covariates on the model parameters. The latter included demographic factors such as body weight (BW), age (in years), additional antiepileptic medications co-administered (therapeutic regimen), daily dose of the drug, and the presence or absence of epileptic seizures.

METHODS

A 12-month prospective study was carried out at the Clinic of Pediatric Internal Medicine, Department of Pediatric Neurology, including 71 patients aged 2-18 years with diagnosed epilepsy. These patients were undergoing dual antiepileptic therapy modalities: VA/LTG, VA/LEV, and LTG/LEV. Demographic and therapy characteristics, along with seizure control data, were documented. Blood samples were collected in the morning before the next dose. Pharmacokinetic analysis of the concentration-time data for LEV, LTG, and VA was performed using nonlinear mixed-effects modeling in Monolix™ 2021R2. Initially, the number of compartments describing the disposition of LEV, LTG, and VA was determined. Various error models of residual variability, including constant, proportional, and combined error models, were evaluated. Additionally, the effect of several covariates on the model parameters was explored, including demographic factors such as BW, age, co-administered additional antiepileptic medications, daily drug dose, and the presence or absence of epileptic seizures. The final model was selected based on statistical and graphical goodness-of-fit criteria. The precision of parameter estimates was assessed using relative standard errors (RSE%).

RESULTS

TDM of antiepileptic drugs is essential for optimizing epilepsy treatment, particularly in pediatric patients. PopPK modeling indicated that a one-compartment model with first-order absorption and elimination best describes the pharmacokinetics of LEV, LTG, and VA (**Figure 1**). For levetiracetam, two statistically significant covariates were identified during stepwise covariate modeling: body weight (BW) on volume (V) and clearance (Cl). For lamotrigine, three statistically significant covariates were identified: body weight on the apparent volume of distribution (using a weight-centered individual model), daily dose on apparent clearance, and coadministration of LTG and VA on clearance. In the case of valproate, three statistically significant covariates were found: BW on apparent volume (with an allometric exponent of 0.75), daily dose on clearance, and age, which had a significant positive impact on distribution volume.

Our study revealed that most measured drug concentrations in pediatric patients were within the recommended range (**Figure 2**). However, over 30% of LEV concentrations were outside the therapeutic range, highlighting the necessity of TDM. VA had the highest percentage of concentrations within the reference range, as it is the most frequently monitored antiepileptic drug, unlike LTG and LEV.

A.Levetiracetam

1. $V/F= 25.01*\exp(BW/26.7)*\exp(n_v)$
2. $Cl/F=1.51*\exp(0.75*(BW/26.7)*\exp(n_{Cl})$

B.Lamotrigine

1. $V/F=5.15*\exp(2.83*BW/39.5)*\exp(n_v)$
2. $Cl/F=0.15*\exp(0.0056*\text{daily dose})*\exp((-0.61)*1\text{comed. with VA})*\exp(nCl)$

C. Valproic acid

1. $V/F=15.61*\exp(BW/32)*\exp(0.07*age)*\exp(n_v)$
2. $Cl/F=0.12*\exp(0.0012*\text{daily dose})*\exp(ncl)$

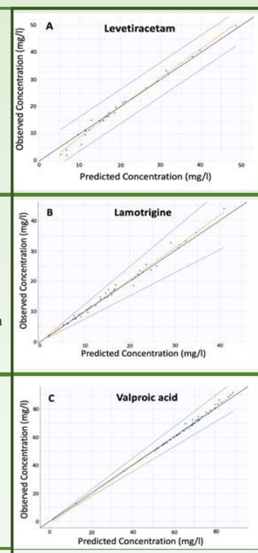

Figure 1. Individual predicted versus observed concentration data for the models of the three drugs: (a) levetiracetam, (b) lamotrigine, and (c) valproic acid.

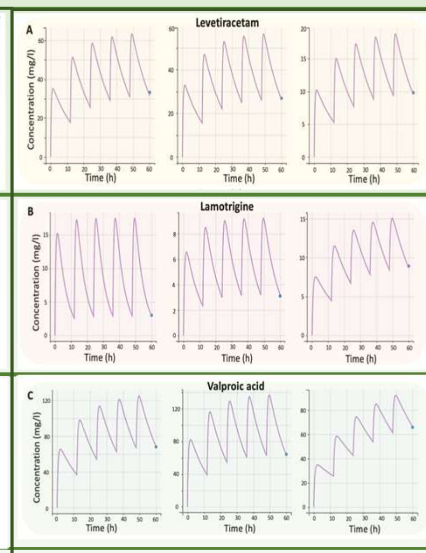

Figure 2. Individual fittings to the experimental concentration–time data of the three drugs: (a) levetiracetam, (b) lamotrigine, and (c) valproic acid. Due to space limitations, three random subjects were chosen for each drug.

Joint use of population pharmacokinetics and machine learning for optimizing antiepileptic treatment in pediatric population

CONCLUSIONS

- The weight and age of children are negatively associated with LTG, LEV and VA levels.
- Concomitant administration of VA and LTG leads to increased LTG levels.
- An increase in the total daily dose of VA leads to an increase in the Cl of the drug.
- The main factor that may influence antiepileptic activity in children is the levels of antiepileptic drugs, followed by BW and age.
- Gender demonstrates no effect on epileptic activity.
- The application of popPK and machine learning models in therapeutics may lead to improved control of seizures and management of seizure risk through optimization of individualized dosing regimens.

REFERENCES

[1] Oliva CF, Gangi G, Marino S, et al. Single and in combination antiepileptic drug therapy in children with epilepsy: how to use it. AIMS Med Sci 2021; 8: 138–146.

[2] Lebedev G, Fartushnyi E, Fartushnyi I, et al. Technology of supporting medical decision-making using evidence-based medicine and artificial intelligence. Procedia Comput Sci 2020; 176: 1703–1712.

[3]Patsalos PN, Spencer EP, Berry DJ. Therapeutic drug monitoring of antiepileptic drugs in Epilepsy: a 2018 Update. Ther Drug Monit 2018; 40: 526–548.

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