Majalah Farmaseutik
ISSN-e: 2614-0064 | ISSN-p: 1410-590x
Volume 20(4), 605-612

Valproic acid Population Pharmacokinetics in Asian Pediatric Epileptics: A Systematic Review

Muh. Faris Hidayat[1], Purwantiningsih[2]*, Rizaldi T. Pinzon[3]
[1] Master of Clinical Pharmacy, Faculty of Pharmacy, Universitas Gadjah Mada
[2] Department of Pharmacology and Clinical Pharmacy, Faculty of Pharmacy, Universitas Gadjah Mada
[3] Neurology Department, Bethesda Hospital, Yogyakarta
Corresponding author: Purwantiningsih; Email: purwanti_n004@yahoo.com
Submitted: 17-05-2024 *Revised: 13-06-2024* *Accepted: 13-06-2024*

ABSTRACT

The pharmacokinetic profile of valproic acid in pediatric subjects in Asian populations is lacking. One of the most useful ways to develop a personalized dosing strategy is to use population pharmacokinetics. The focus of this systematic review is to describe the population pharmacokinetic profile of valproic acid (VPA) and determine the variables influencing pharmacokinetic models of the drug in children with epilepsy that have been published in Asian journals. A comprehensive literature search was carried out from 2014 to 2024 on Science Direct and PubMed. Keywords used *valproic acid, valproic, VPA, sodium valproate and population pharmacokinetic, pharmacokinetic model.* In this review, four studies were considered. The pharmacokinetic model was developed by looking at several covariates that significantly affect the population pharmacokinetics of VPA using TDM data from pediatric epilepsy patients. The clearance value and volume of distribution of VPA can be seen to be in the range of 0.148 - 3.19 L/h, and 0.317 - 24 L/KgBB. In addition, subjects with SCN1A A/A genotype showed a decreased therapeutic effect of VPA. Significant covariates affecting the pharmacokinetics of VPA were age, dose, and the use of comedication with other anti-seizure drugs.
Keywords: Epilepsy; Pediatric; population pharmacokinetics; valproic acid

INTRODUCTION

Valproic acid (VPA) has broad potential as an antiepileptic therapy to treat partial and generalized seizures (Methaneethorn, 2018). The regulation of glutamate and GABA formation pathways and the neuroprotective ability of valproic acid are important modulations in epileptogenesis. In particular, epileptic seizures, in this case status epilepticus events can cause damage to the nerves and then cause spontaneous recurrence of seizures (Romoli et al., 2019). Valproic acid is highly bound to plasma proteins by about 90-95%. The binding of valproic acid to plasma proteins reaches a saturation state within the therapeutic range, indicating nonlinear protein binding (Bauer, 2008).

There are various challenges to doing therapeutic drug monitoring (TDM) on pediatric patients, including reduced blood volume, technical limitations with pediatric venous access, and patient discomfort. Ideal TDM is expensive, making it impossible to use in daily practice. One approach to overcoming this issue is to forecast individual blood concentrations using equations derived from population pharmacokinetic data. Previous research Teixeira-da-Silva dkk., 2022 conducted studies on populations with Caucasians, but there are very few studies focusing on pediatric epilepsy patients in Asia.

All of these studies were conducted in Asia with the hope of providing an overview of the pharmacokinetic profile of VPA in its clinical application in the pediatric epilepsy patient population in Asian populations. The aim of this review is to describe the population pharmacokinetic profile of valproic acid (VPA) and determine the variables influencing pharmacokinetic models of the drug in children with epilepsy that have been published in Asian journals that will be beneficial in therapeutic settings and future study.

METHODS

The literature was searched by selecting studies based on quality evaluation, synthesizing data, then extracting data from PubMed and Science direct databases with a time range of 2014 -

2024 were the steps in this research process. The keywords used: ((*'Sodium valproate' OR 'valproic acid' OR 'VPA') AND '(population pharmacokinetic' OR 'pharmacokinetics model')*). Selection was based on a population of pediatric epilepsy patients.

Inclusion criteria
This review contained articles that matched the following criteria: (1) Patients < 18 years of age; (2) Treatment: valproic acid as the investigational drug; (3) Research population on the Asian continent.

Exclusion criteria
Published in non-English articles

Data extraction
Each of the included articles provided the following information: (i) study characteristics (type of study, number of samples collected, dosing regimen and VPA formulation), population characteristics (age and weight, gender, comorbidities, concomitant medications), and (ii) information regarding the population pharmacokinetic analysis, such as the pharmacokinetic analysis model, the software used, the approach used for model evaluation (e.g. internal or external validation), parameter estimates, and statistical analysis (factors influencing the pharmacokinetics of valproic acid).

RESULTS AND DISCUSSION
Study Identification
A total of 192 and 88 publications were found on Science direct and PubMed. The result was four articles matching the inclusion and exclusion criteria. The PRISMA identification diagram is presented in Figure 1. Then the article conducted a validity test using a few questions from the JBI Checklist, 2020 for analytical cross sectional study. Questions 1 and 2 about the subject and background of the research, 3 and 4 about exposure and standard criteria for measurement, 5 and 6 about confounding variables and how to handle them, 7 and 8 about outcome measurements and statistical analysis used. All study can clearly answer the issue; however, research done by Gu dkk., 2021 does not properly define the statistical analysis employed. We conclude that the four articles are applicable to this review.

Study Characteristics
All studies published between 2014-2024 were conducted in Asia. Table I summarises various characteristics of the studies. There were two studies that addressed PKPD of VPA. One study conducted in Indonesia compared the results of pharmacokinetic population estimation with seizure frequency in patients receiving therapeutic drug monitoring (TDM). Another study done in Japan tried to create a PKPD model of the correlation between VPA concentration and seizure frequency. Two more research established pharmacokinetic models of VPA, and one study was undertaken to investigate the influence of daily dosage on the pharmacokinetic characteristics of VPA. One study was conducted to see the effect of protein bound and unbound VPA on the pharmacokinetic modeling of VPA. The sample sizes of the subjects used ranged from 38 to 902 subjects. The daily VPA doses in the studies involved varied from 19.55 - 1120.0 mg/kg/day. Three studies analyzed the effect of comedication with other seizure therapies while one study used only VPA monotherapy. The VPA formulations used in the pharmacokinetic model development research used syrup, tablets and sustained-release tablets, while the other two studies used one formulation, namely Nakashima's research, 2015 using sustained-release tablet preparations and Nugraha's research, 2021 using syrup preparations.

Population pharmacokinetics models of valproic acid
Two articles were found that aimed to describe the variability of VPA pharmacokinetics. This was shown by determining the amount of variability between individuals as well as the factors that influence the pharmacokinetics of VPA. One study was a multicenter study to look at the effect of

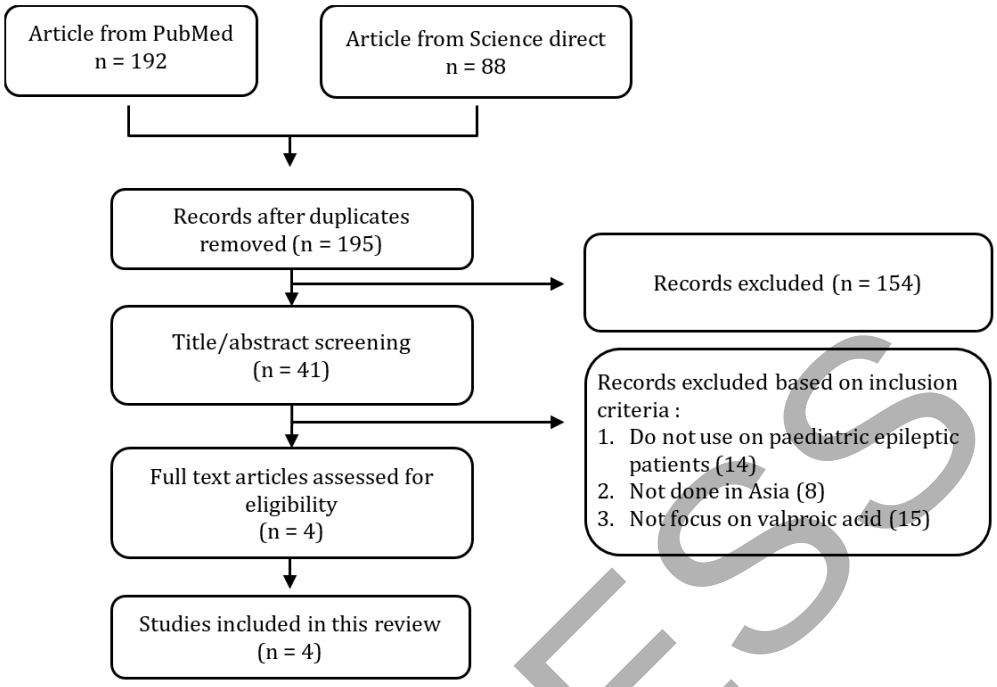

Figure 1. PRISMA flowchart of research identification

daily dosing on the pharmacokinetics of VPA (Ding et al., 2015)Another study characterized the relationship between total serum VPA concentration and unbound VPA based on the Langmuir equation (Gu et al., 2021). (Gu et al., 2021). Two other studies used population pharmacokinetic modeling and looked at the effect on seizure reduction frequency. One study showed the effect of VPA concentration and SCN1A genotype on reducing seizure frequency (Nakashima et al., 2015). Another study proposed the use of population pharmacokinetic equations to describe the pharmacokinetic profile of VPA in pediatric patients (Nugraha et al., 2021). All studies used TDM research. All described the pharmacokinetics of VPA as a one-compartment model, the study conducted by Nugraha, 2021 used the population pharmacokinetic equation from a previous study (Yukawa, 2011). NONMEM software is the most commonly used software for developing population pharmacokinetic models. Table II summarizes information on population pharmacokinetic models with respect to the type of study, pharmacokinetic model and model validation.

Several covariates were tested for model development. Age, weight, gender, additional medications, and daily dose of VPA were the most frequently tested covariates. Age was a significant covariate affecting VPA pharmacokinetics in 2 studies. Three studies looked at the effect of comedication from other anti-seizure therapies on the pharmacokinetic profile of VPA. CBZ affected the CL/F of VPA while LMT increased the serum concentration of unbound VPA. Another study showed that concomitant use with PHT, TPM, affected the slope of the curve relating VPA concentration to 50% seizure reduction effect. Only one study related genotype to VPA PKPD, where it was found that SCN1A G/A genotype, SCN1A A/A genotype had an effect on the slope of the curve relating VPA concentration to the effect of 50% seizure reduction. The covariates used and their significance are shown in Table II.

Pharmacokinetically VPA has high bioavailability, this is due to its high absorption in the gastrointestinal tract. Ka values were presented by 3 studies, with a range of 0.46 for SR tablets, 1.57 for tablets and 2.12 - 2.64 for syrup formulations. Nugraha et al. showed the results of TDM conducted on 5 subjects who received VPA syrup preparation, the estimated population ka value (VPA absorption rate) was 6.25 / hour with a random effect standard deviation value of 1.03. The estimated ka value compared with the TDM results obtained results that were not clinically different (bias < 20%). The study conducted by Nakashima, 2015 used a slow-release tablet formulation, but

le I. Characteristics of population pharmacokinetics studies considered in the systematic review

uthor	Country	Sample size	Gender (%)	Age (Mean)	Weight (Mean)	Formulation	Dose (mg/kgBB)	Css (Mean)	Pharmacokinetic Model	Model validation	Softv
ng et 2015	China	902	Female 39,3 %	5.7 (3-14 years)	21,6 (2,6-70)	Syrups, Tablets, and sustained-release tablets	27,1 (5,1-63,2)	67,5 (15-149)	1 compartment (first-order absorption, first-order elimination)	Bootstrap and NDPE simulation	Nonr
kashi et al., 15	Japan	77	Female 37,7 %	15.2 (0-18 years)	NR	Slow-release tablets	15-40	69,3 (11,8-130,1)	1 compartment (first-order absorption, first-order elimination)	Bootstrap	Nonr
et al., 21	China	313	Female 33,2 %	5,96 (0,31-15,89)	21,2 (7-94)	Syrups, Tablets, and Slow-release tablets	412,66 (80-1250)	52,31 (11,19-162,12)	1 compartment (first-order absorption, first-order elimination)	Botstrap with	Nonr
graha al., 21	Indonesia	38	NR	NR	32,32 (14-76)	Syrup	19,55 (8-37)	74,87 (43,89-121,51)	NR	Based on PE and WPE values	Mon

lot reported; NDPE, Normalized prediction distribution error; NR, Not reported; PE, Prediction error; TDM, Therapeutic drug monitoring; WPE, Weighted prediction error.

le II. Covariates used and their significance to the pharmacokinetic model

udy	Covariate tested	Covariate selection	Significant covariates
ng et al., 2015	Age, gender, formulation, VPA dose and comedication (CBZ, CZP, TPM)	P value < 0.001	Age, dose and CBZ co-administration on clear
kashima et al., 15	Patient age, gender, seizure locus, seizure type, intellectual disability complications, co-administered AED drugs (CBZ, CZP, CLB, GBP, LTG, PB, PHT, TPM and ZNS).	P value < 0.05	Age, CZP, SCN1A A/A genotype, SCN1A G/A genotype to intercept TPM, SCN1A G/A genotype, SCN1A A/A genot on Slope (decrease in therapeutic effect of VP
et al., 2021	Height, weight, sex, age, albumin, total bilirubin, ALT, AST, Scr, and comedications (CBZ, LTG, LVT, OCZ and TPM)	Decrease in function >3.84 (A = 0.05, df =1)	BW, PMA affect CL/F LTG increases CL/F of unbound VPA by 27%
graha et al., 2021	NR	NR	NR

Clobazam; CZP, clonazepam, GBP, gabapentin; LTG, lamotrigine; LVT , Levetiracetam; OCZ, Oxcarbazepin; PB Phenobarbital; PHT, Phenytoin; TPM, Topiramat; ZNS, Zonisamide ne transferase; AST Aspartate transferase; PMA, Post menstrual age; NR, Not reported.

did not include ka or CL estimation data. The variability of ka values in syrup dosage formulations did not differ much from the other 3 studies.

Three studies showed the estimated volume of distribution (Vd). The Vd values obtained were 0.317 L/KgBB (22.2 L/70kgBB); 3.78 L/KgBB, and 24 L/KgBB (1680 L/70 KgBB). Research conducted by Gu, 2021 showed an unbound VPA Vd value of 1680 but it cannot be explained the cause of the high Vd value in this study, most likely due to the sample collected and the lack of information to accurately estimate the Vd value. Of the 3 studies that provided Vd values, only the studies of Ding, 2015 and Gu, 2021 provided equations for estimating Vd values. Whereas in the study of Nugraha, 2021, the correlation value of Vd and CL from the estimation results showed a low correlation value (0.23), but the correlation of Vd and CL from the TDM results showed a high correlation value (0.97). The distribution volume of VPA increases with body weight and VPA dose, this can be explained by saturated protein binding (Cohen 2014). From the covariate examination, no covariates were found that significantly affected the Vd of VPA.

VPA clearance estimates ranged from 0.148 to 3.19 with inter-individual variability of 13.5 to 43%. Body weight, VPA dosage, concurrent use of other anti-seizure medications, gender, and age are frequently found as significant variables of CL VPA. Some studies have indicated an increase in CL VPA when body weight increases. This might be related to the link between body weight and the development of organs involved in drug clearance. However, research by Yukawa et al. has shown that CL VPA in pediatric patients decreases with increasing body weight during the maturation process (Eiji Yukawa et al., 1997; Yukawa, 2011). In considering the age impact, it was shown that young children had greater CL VPA than adults. On the other hand, there is disagreement over how age affects CL VPA in children. Gu, 2021 study showed that total and unbound VPA concentrations decreased from 40 weeks PMA (*post menstrual age)* (0 years), reached a peak at 92 weeks PMA (1 year), and then increased thereafter. It appears that for children under the age of two, maturity is determined by both age and BW, whereas for children above the age of two, BW is the primary factor influencing CL/F, which can be explained by the mechanism of maturation of drug-metabolizing enzymes in the liver. Uridine Diphosphate Glucuronosyltransferase/UGT1A9 and UGT1A6, the enzymes that mediate the liver's clearance of VPA, attain adult levels at two years of age (Gu et al., 2021). These elimination enzymes are also lower in number in females compared to males (Methaneethorn, 2018)

An increase in CL VPA due to an increase in VPA dose was also reported. One probable explanation for this is protein binding saturation, which causes more free VPA to be removed (Ding et al., 2015). Researchers examined three pharmacokinetic models (i.e. power exponent model, dose-dependent maximum effect (DDE) model and protein binding model). Based on conventional evaluation criteria, the DDE model best describes the VPA pharmacokinetics profile. Concomitant anti-seizure medications commonly found to affect CL VPA include carbamazepine, phenobarbital, and phenytoin which are enzyme inducers (Methaneethorn, 2018) This causes an increase in the CL of VPA when taken concurrently with VPA. Concomitant use with clozepam showed its effect on the PKPD curve, so further investigation is needed.

The relationship of concentration to therapeutic effect was described by 2 studies, Nakashima, 2015 and Nugraha 2021. Nakashima (2015) investigated the relationship between VPA exposure and seizure control, using a logistic regression model to assess the likelihood of achieving at least a 50% reduction in seizure frequency. Furthermore, the authors used receiver operating characteristic (ROC) curves to calculate the best cut-off point for that probability. Age, seizure type, SCN1A polymorphism, and Clozepam co-administration were significant predictors of 50% decrease in seizure frequency. This study offers a Logit (pr) equation of the pharmacokinetic pharmacodynamic model for achieving 50% seizure reduction using estimated drug levels in the steady state. This study explains that certain individuals with the SCN1A A/A genotype are discovered to be medication resistant and may require VPA doses larger than the typical therapeutic range of 50-100 mg/L. This could be explained by the effect of changes in the Nav1.1 alpha subunit of the voltage-gated Na+ channel encoded by the SCN1A gene, this sub unit is thought to play an important role in the pathogenesis of several epileptic syndromes (Heinzen et al., 2007). Research conducted by Nugraha, 2021 compared the results of estimation using the population pharmacokinetic equation to estimate drug concentrations in the steady state compared to the results of TDM in 5 randomly selected

e III. A summary of models and estimated population pharmacokinetics

Study	Fixed Model	Estimate parameters	Variability
Ding et al., 2015	DDE Model $\frac{Cl}{F} = 0{,}3\ x\ 1{,}43^{CBZ} x \left(\frac{BW\ (kg)}{70}\right)^{0{,}791 \frac{0{,}96\ x\ Age^{8{,}63}}{0{,}802^{8{,}63} + Age^{8{,}63}}} x\left(1 + \frac{2{,}8\ x\ TDD^{1{,}68}}{3{,}74^{1{,}68} + TDD^{1{,}68}}\right.$ $\mathrm{Vd/F} = 22{,}2\ x\left(\frac{BW}{70}\right)$ CBZ = 1, if the patient is using CBZ, 0 otherwise.	CL/F 1.43 (2.7) Ka (/Hour) syrup 2.64; Tablet 1.57; 0.46 SR tablet Vp (BW/70) 22.2 (8.6)	Individual variability (ωCL/F) 0.195 (9.4)
Nakashima et al., 2015	$CL = 0{,}577\ x\ \left(\frac{dose}{1000}\right) 0{,}535\ x\ 0{,}875\ gender$ $x\ 1{,}22\ CBZ\ x\ 1{,}10\ PB\ x\ 1{,}40\ PHT\ x\ 0{,}915\ CLB$ $\mathrm{VD} = 110\ \mathrm{x}\ \left(\frac{\mathrm{dose}}{1000}\right)^{1{,}51}$ Dose = daily dose of VPA, female = 1, male = 0, CBZ, PB, PHT, CLB = 1 if comedicated, and 0 if not.	NR	NR
Gu et al., 2021	$CL/F\ =\ 10{,}4\ x \left(\frac{\mathrm{BW}}{70}\right)^{0{,}75}\ x\ \left(\frac{\mathrm{PMA}^{4{,}17}}{33{,}7^{4{,}17} + PMA^{4{,}17}}\right) x1{,}25^{LGT}$ $\mathrm{V/F} = 1680\mathrm{x}\ \left(\frac{\mathrm{BW}}{70}\right)$ PMA =post menstrual age (weeks), LTG = 1 if comedicated with Lamotrigine, 0 otherwise	CL (L/h/70 kg) 10.40 K_d (mg/L) 2.12 V_u (L/70kg) 1680	Individual variability (ωCL/F) 0.43, (ωV/F) 0.928
Nugraha et al., 2021	$CL(ml.kg^{-1}h^{-1}) =\ 18{,}9\ xBW\ (kg)^{-0{,}276} x\ VPA\ daily\ dose^{0{,}142}\ x\ gender$ Gender = 1 for male and 0.887 for female	CL 3.19 ± 1.55 Ka 2.18 ± 2.32 V 3,78 ± 0,30	Mean PE 5.11 (95% C 11.1173-21.3414; p=0.431) Mean WPE 8.20 (95% -17.46837-338637; p=0.425)

ody weight; CL, Clearance; V, Volume of distribution; Ka, Absorption constant; CBZ, Clobazam; LTG, lamotrigine; PB Phenobarbital; PHT, Phenytoin;

patients, found that the average bias effect of PE and WPE values was at a low level of 5.11 and 8.20 respectively. These values are acceptable and have no clinically significant effect (≤25% is considered clinically favorable) (Bondareva et al., 2011).

This is the only paper we are aware of that provides information on population models of pharmacokinetics in pediatric patients for Asian populations. The studies presented in this article cover a wide range of Asian pediatric populations. However, the published predictive models should be applied to the target population before being used in clinical applications.

The limitation of this study is the lack of population pharmacokinetic studies in several countries in Asia so that it does not cover the entire population in Asia. In addition, there are no studies that focus on the toxicity of valproate acid included in this review. So, it is also recommended that further research be carried out on monitoring side effects that can occur using population pharmacokinetic data.

CONCLUSION

Significant covariates affecting the pharmacokinetics of VPA have been discussed and summarized in this article. Weight, gender, age, VPA dose, and other anti-seizure medications taken are frequent factors influencing the pharmacokinetic model of VPA. The clearance and volume of distribution of valproic acid in Asian populations have also been presented above. Further research is needed to be able to apply parameters and population models of VPA pharmacokinetics according to the characteristics of the target population.

ACKNOWLEDGMENT

This systematic review is supported by the Master of Clinical Pharmacy, Faculty of Pharmacy, Gadjah Mada University.

CONFLICT OF INTEREST

There are no conflicts of interest in this journal.

REFFERENCES

Bauer, L. A. (2008). *Applied clinical pharmacokinetics* (2nd ed). McGraw-Hill Medical.

Bondareva, I. B., Jelliffe, R. W., Andreeva, O. V., & Bondareva, K. I. (2011). Predictability of individualized dosage regimens of carbamazepine and valproate mono- and combination therapy: Carbamazepine and valproate therapies. *Journal of Clinical Pharmacy and Therapeutics*, *36*(5), 625–636. https://doi.org/10.1111/j.1365-2710.2010.01215.x

Ding, J., Wang, Y., Lin, W., Wang, C., Zhao, L., Li, X., Zhao, Z., Miao, L., & Jiao, Z. (2015). A Population Pharmacokinetic Model of Valproic Acid in Pediatric Patients with Epilepsy: A Non-Linear Pharmacokinetic Model Based on Protein-Binding Saturation. *Clinical Pharmacokinetics*, *54*(3), 305–317. https://doi.org/10.1007/s40262-014-0212-8

Eiji Yukawa, Yukawa, E., Hideto To, To, H., Shigehiro Ohdo, Ohdo, S., Shun Higuchi, Higuchi, S., Toshinobu Aoyama, & Aoyama, T. (1997). Population-based investigation of valproic acid relative clearance using nonlinear mixed effects modeling: Influence of drug-drug interaction and patient characteristics. *The Journal of Clinical Pharmacology*, *37*(12), 1160–1167. https://doi.org/10.1002/j.1552-4604.1997.tb04301.x

Gu, X., Zhu, M., Sheng, C., Yu, S., Peng, Q., Ma, M., Hu, Y., Li, Z., Jiao, Z., & Zhou, B. (2021). Population pharmacokinetics of unbound valproic acid in pediatric epilepsy patients in China: A protein binding model. *European Journal of Clinical Pharmacology*, *77*(7), 999–1009. https://doi.org/10.1007/s00228-020-03080-y

Heinzen, E. L., Yoon, W., Tate, S. K., Sen, A., Wood, N. W., Sisodiya, S. M., & Goldstein, D. B. (2007). Nova2 Interacts with a Cis-Acting Polymorphism to Influence the Proportions of Drug-Responsive Splice Variants of SCN1A. *The American Journal of Human Genetics*, *80*(5), 876–883. https://doi.org/10.1086/516650

Methaneethorn, J. (2018). A systematic review of population pharmacokinetics of valproic acid. *British Journal of Clinical Pharmacology*, *84*(5), 816–834. https://doi.org/10.1111/bcp.13510

Nakashima, H., Oniki, K., Nishimura, M., Ogusu, N., Shimomasuda, M., Ono, T., Matsuda, K., Yasui-Furukori, N., Nakagawa, K., Ishitsu, T., & Saruwatari, J. (2015). Determination of the Optimal Concentration of Valproic Acid in Patients with Epilepsy: A Population Pharmacokinetic-Pharmacodynamic Analysis. *PLOS ONE*, *10*(10), e0141266. https://doi.org/10.1371/journal.pone.0141266

Nugraha, I. K. P. N., Anita Purnamayanti, Purnamayanti, A., I Gusti Ngurah Made Suwarba, Suwarba, I. G. N. M., Nani Parfati, & Parfati, N. (2021). Developing pharmacokinetics-pharmacodynamics model of valproic acid syrup based on prediction of population pharmacokinetics parameter and seizure frequency in Indonesian pediatric epilepsy outpatients. *Journal of Basic and Clinical Physiology and Pharmacology*, *32*(4), 305–311. https://doi.org/10.1515/jbcpp-2020-0488

Romoli, M., Mazzocchetti, P., D'Alonzo, R., Siliquini, S., Rinaldi, V. E., Verrotti, A., Calabresi, P., & Costa, C. (2019). Valproic Acid and Epilepsy: From Molecular Mechanisms to Clinical Evidences. *Current Neuropharmacology*, *17*(10), 926–946. https://doi.org/10.2174/1570159X17666181227165722

Teixeira-da-Silva, P., Pérez-Blanco, J. S., Santos-Buelga, D., Otero, M. J., & García, M. J. (2022). Population Pharmacokinetics of Valproic Acid in Pediatric and Adult Caucasian Patients. *Pharmaceutics*, *14*(4), 811. https://doi.org/10.3390/pharmaceutics14040811

Yukawa, E. (2011). A Feasibility Study of the Multiple-peak Approach for Pharmacokinetic Screening: Population-based Investigation of Valproic Acid Relative Clearance Using Routine Clinical Pharmacokinetic Data. *Journal of Pharmacy and Pharmacology*, *47*(12A), 1048–1052. https://doi.org/10.1111/j.2042-7158.1995.tb03295