I Komang Prawira Nata Nugraha, Anita Purnamayanti*, I Gusti Ngurah Made Suwarba and Nani Parfati

Developing pharmacokinetics–pharmacodynamics model of valproic acid syrup based on prediction of population pharmacokinetics parameter and seizure frequency in Indonesian pediatric epilepsy outpatients

https://doi.org/10.1515/jbcpp-2020-0488
Received November 29, 2020; accepted April 1, 2021

Abstract

Objectives: Valproic acid (VPA) is a broad-spectrum antiepileptic drug with known efficacy profile in pediatric patients, despite of its narrow therapeutic index. There is lack of VPA's pharmacokinetics profile in Indonesian pediatric subjects, partly due to limited pediatric blood volume taken for conducting therapeutic drug monitoring. This study aimed to determine the correlation between VPA pharmacokinetics parameters based on population data and seizure frequency in pediatric epilepsy outpatients.

Methods: This observational study was conducted at Sanglah General Hospital during June–December 2019. The subjects of this research were 38 pediatric epilepsy patients who adhered to VPA syrup monotherapy for at least 3 weeks. Five subjects randomly selected for blood sample collection. Thus, VPA concentration level in the blood being analysed as a comparison to its concentration predicted from Yukawa's steady state equation. Monolix2019R2® software was used to identify VPA population pharmacokinetics–pharmacodynamics (PK–PD) parameters at steady state level.

Results: Population PK–PD of VPA syrup at steady state level were ka_pop = 6.25/h, Vd_pop = 3.36 L, Cl_pop = $3.17 \cdot e^{-11}$ mL/min, IC_{50}_pop = $1.85 \cdot e^{-6}$, correlation of Vd_pop and Cl_pop = 0.966. Kendall Tau Correlation of predicted VPA steady state concentration and frequency of seizure was –0.66. Mean prediction error between predicted steady state concentration of five subjects and their related blood levels was ≤25% and considered as within clinically acceptable limit.

Conclusions: It needs further study to develop best matched PK–PD model of VPA syrup at steady state condition in pediatric epilepsy.

Keywords: pediatric; population pharmacokinetics; prediction of concentration; seizure frequency; valproic acid.

Introduction

According to International League Against Epilepsy (ILAE), Commission on Therapeutic Strategies, situations in which anti epilepsy drug (AED) measurements are most likely to be of benefit include to guide dosage adjustment in situations associated with increased pharmacokinetic variability (e.g., children, the elderly, patients with liver or renal impairment, and drug formulation changes) [1].

Pediatric is a special population group associated with increased pharmacokinetics variability, as well as drug toxicities due to limited capability of the developing physiological system. Pediatric epilepsy patients rely on their parents in administering the medicines for treating their disease. Valproic acid (VPA) is a broad-spectrum first line antiepileptic therapy in pediatric which means it can be used in almost all type of epileptic seizures due to its well establish efficacy. Indeed, VPA has a narrow therapeutic

***Corresponding author: Anita Purnamayanti**, Department of Clinical Pharmacy, Faculty of Pharmacy, University of Surabaya, Surabaya, Indonesia, Phone: +62 81336444888,
E-mail: anita_p_rahman@yahoo.com. https://orcid.org/0000-0003-4544-7052
I Komang Prawira Nata Nugraha, Faculty of Pharmacy, University of Surabaya, Surabaya, Indonesia
I Gusti Ngurah Made Suwarba, Department of Paediatric Health, Sanglah General Hospital, Denpasar, Indonesia
Nani Parfati, Department of Pharmaceutics, Faculty of Pharmacy, University of Surabaya, Surabaya, Indonesia

index and high protein binding, which means discrepancies between the minimum concentration of VPA to be able to effectively act as AED with its minimum toxic concentration level is relatively near. Thus pediatric patients have increased risk of sub- or supra-optimal VPA therapy [2, 3].

Ideally it is necessary to apply AED measurement, also known as therapeutic drug monitoring (TDM). Blood samples should be taken from the subjects to identify AED concentration, as well as pharmacokinetics parameter in specific clinical conditions; in order to analyzed inter- and intra-subject variability that could lead to sub- or supratherapeutic concentration of AED. Subtherapeutic concentration means that there was no or minimal effect of the drug, while supratherapeutic one means that there was increased risk of toxicity of AED therapy. The main objective of pharmacokinetic monitoring of antiepileptic drugs is to optimize treatment by studying drug levels in biological matrices. Inter- and intra-subject variability in blood VPA concentration is not uncommon in pediatric epilepsy. Adapting individual doses is complicated, due to the presence of factors including: (a) the considerable interindividual pharmacokinetic variability of antiepileptic drugs; (b) the use of these drugs as prophylactics for long-term epileptic seizure control, and (c) having no defined correlation between efficacy and a biological marker that could help with decision-making [3, 4].

Incidence epilepsy in pediatric patients remains high in Sanglah General Hospital Bali, Indonesia. There were 276 incidences of epilepsy with average of 69 cases per year, mostly in age group less than one year (46.0%) during period of January 2007–December 2010 [5]. There is lack of pharmacokinetics data population for AEDs in Indonesian pediatric epilepsy as guidance in individualizing dosage regimens. There are several obstacles in performing TDM to pediatric patients, for example limited blood volume, technically difficult in accessing the pediatric vein, and patient discomfort. One of the strategies to overcome these limitations is to calculate the individual blood concentration prediction from the equation derived from population pharmacokinetics data [6–9]. Yukawa et al. conducted pharmacokinetics–pharmacodynamics (PK–PD) study of VPA administered to pediatric patients and developed an equation for calculating the clearance of VPA from population data [7]. In this research, we used Yukawa's equation for calculating VPA clearance, due to similarities in research design which is conducted for assessing VPA syrup in its steady state condition among pediatric epilepsy patients. Aim of this research was to analyze the estimated concentration of VPA and its correlation with seizures frequency in pediatric outpatients. This research was aimed to determine the correlation between VPA pharmacokinetics parameters based on population data and seizure frequency in order to develop PK–PD analysis in the future research. As far as our knowledge, this is the first PK–PD study of VPA syrup in the steady state condition in Indonesian pediatric epilepsy subjects.

Materials and methods

The design of this research was as an observational study conducted prospectively. All patient were treated in Sanglah General Hospital – Bali, Indonesia from June to December 2019, and fulfilled all of the following inclusion criteria: (1) aged 6–18 years, (2) had been receiving VPA syrup monotherapy for at least 3 weeks before the research, (3) had not discontinued administration of VPA because of the side effect, (4) were not take any drugs that might alter clearance of VPA, and (5) patients and their family was willing to be involved in this research. We excluded pediatric patients with abnormal liver and renal function tests. This research complies with all national relevant regulations and had been given ethical clearance from Ethics Committee of Faculty Medic and Health Sciences, Udayana University/Sanglah General Hospital.

Recruited subjects were followed every 2 weeks on their visit schedule to Outpatient Department. We performed twice weekly oral and written education session starting on the day of recruitment up to one month in order to improve concordance between subject's parents and health professionals, thus to maintain VPA monotherapy adherence. We supplemented written education material (booklet) for each subjects. Subjects had been asked to bring their VPA syrup bottle in every visit, and its volume measurement conducted by comparing the volume left in the subject's bottle to a standardized scaled VPA syrup bottle. All of the subjects included in this research had 100% VPA syrup adherence during this stage of research, so that drug adherence was not the confounding factor.

Estimated steady state concentrations of VPA was calculated based on pharmacokinetics population data using Yukawa's equation for VPA clearance as follow [7]:

$$\begin{aligned}\mathrm{Cl}\left(\mathrm{mL}\cdot\mathrm{kg}^{-1}\cdot\mathrm{h}^{-1}\right) = {} & 18.9\times\text{body weight (kg)}^{-0.276}\\ & \times\text{VPA daily dose}\left(\mathrm{mg}\cdot\mathrm{kg}^{-1}\cdot\mathrm{day}^{-1}\right)^{0.142}\\ & \times\text{gender (which is 1 for male, and 0.887 for female)}\end{aligned} \quad (1)$$

Predicted VPA steady state concentration of each subjects then was calculated from this estimated clearance, thus the results were so called "predicted VPA steady state concentrations based on population data". Correlation of the predicted valproic acid steady state concentration based on population data with the seizure frequency as a pharmacodynamics parameter of VPA's efficacy in seizure control was analyzed. Five subjects were then randomly selected to follow therapeutic drug monitoring procedure. Blood samples had been taken after the third visit to Outpatient Department and were analyzed as the subject's steady state plasma concentration of valproic acid and compared it to its predicted VPA steady state concentrations based on population data. The comparative results between predicted VPA steady state concentrations based on population data with the VPA plasma concentration of the five subjects randomly selected for blood sampling were further calculated as prediction error (PE) and weighted prediction error (WPE) thus tested

them for biases. Monolix2019R2® software was used to process pharmacokinetics and pharmacodynamics parameters based on population data as fixed effects. Parameters of PK–PD derived from fixed effects modelling using Monolix2019R2® software comprise of pharmacokinetics parameters of population clearance (Cl_pop), population volume of distribution (V_pop), population absorption rate constant (ka_pop); as well as pharmacodynamics parameter of 50% inhibition concentration (IC_{50}), and population inter individual deviation (lambda0pop).

Results

A total of 42 potential subjects (6–14 years old) in the September–December 2019 period were recruited; and 38 out of 42 subjects had been included in this research (Figure 1). The subjects came from difference tribes in around Indonesia, for example from Java, Bali, East Nusa Tenggara, as well as Chinese descent ethnicity. The average body weight of 38 subjects was 32.32 ± 16.05 (14–76 kg), the total dose of valproic acid syrup administered was 19.55 ± 6.19 (8–37 mg/kg body weight/day). There were a great intersubject variability in the mean predicted valproic acid steady state concentration of 38 subjects which was 74.87 ± 18.06 (43.89–121.51 mg/L); in comparing to serum valproic acid steady state concentration of five subjects which was 104.20 ± 36.05 (57.00–138.00 mg/L). Thirty six subjects had no seizure at all and one subject experienced one seizure per month at the end of research period, in comparing to 3–10 seizures per month at the baseline; another subject constantly had seizures as frequent as in the beginning of research. The subjects' characteristics at baseline and the end of the research period were presented in Table 1. The result of Wilcoxon sign rank test showed that there was statistically significant median differences between frequency of seizure per month at baseline form and at end of this research (p=0.04). The correlation between predicted valproic acid steady state concentration of 38 subjects and their frequency of seizures was calculated with Kendal Tau test. The results of the Kendall's Tau test was the predicted VPA steady state concentration of 38 subjects and their frequency of seizures had a very weak association (r=–0.067), in contrast to the correlation coefficient of five subjects and their frequency of seizures that had a strong association (r=–0.62).

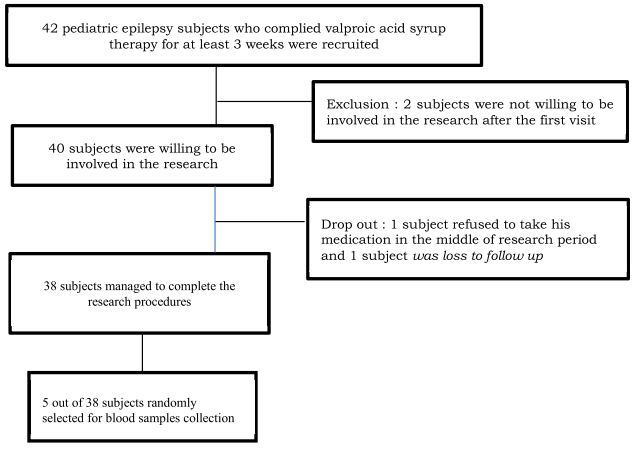


Figure 1: Patient selection process.

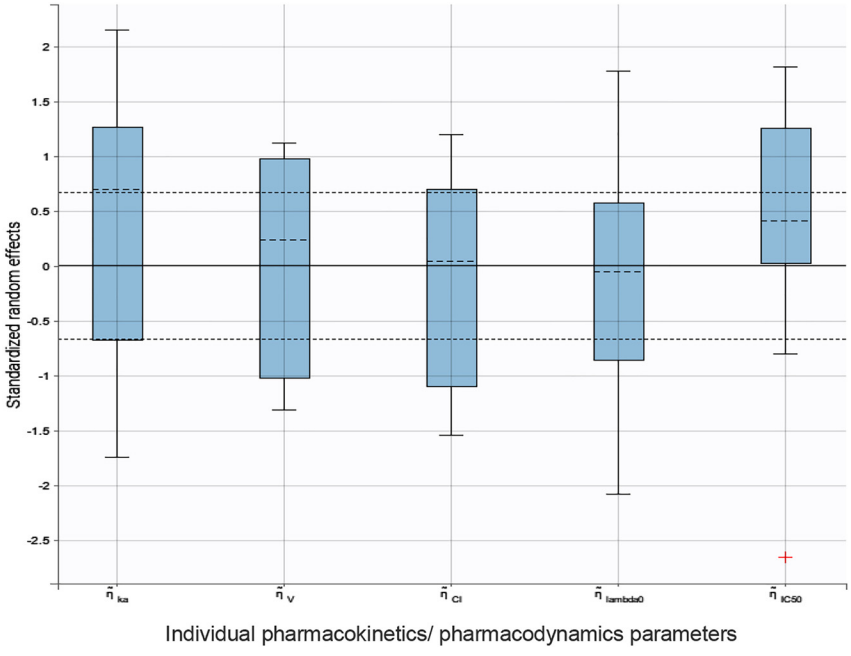


Figure 2: Random effects of pharmacokinetics and pharmacodynamics parameter of valproic acid syrup.

Table 1: Adherence to valproic acid syrup and the seizure frequency at the baseline and the end of the research period.

Drug adherence, %	No. of the subjects	Percentage, %	Baseline seizures, times/month	No. of the subjects	Percentage, %	Seizures during the research period, times/month	No. of the subjects	Percentage, %
100	38	100.00	3	23	60.53	0	36	94.74
			5	14	36.84	1	1	2.63
			10	1	2.63	10	1	2.63
Total	38	100.00		38	100.00		38	100.00

Population PK–PD parameter estimates based on predicted vs. serum VPA steady state concentration were performed using SAEM algorithm of Monolix2019RA® software (Figure 2). Correlation value between VPA's volume of distribution (Vd_pop) and clearance (Cl_pop) of 38 subjects estimates by Monolix2019R2® software was corr_V_Cl = 0.23, which means there was a weak correlation between Vd_pop and Cl_pop of 38 subjects. Correlation between valproic acid's volume of distribution and clearance of five subjects estimates by Monolix2019R2® software was corr_V_Cl = 0.97, which means there was a strong correlation between Vd_pop and Cl_pop of five subjects. This correlation coefficient was markedly improved in five subjects, comparing to its correlation in 38 subjects (Tables 2 and 3).

Table 2: Population pharmacokinetics–pharmacodynamics parameter estimates from 38 subjects adhered to valproic acid syrup monotherapy at steady state level using SAEM algorithm of Monolix2019RA® software.

Parameter	Value of fixed effects		Standard deviation of random effects
ka_pop	$2.18 \cdot e^{3}$	Omega ka_pop	2.32
V_pop	3.78	Omega V_pop	0.30
Cl_pop	$3.19 \cdot e^{-15}$	Omega Cl_pop	1.55
Lambda0	3.94	Omega lambda0	0.32
IC_{50}	$7.29 \cdot e^{-6}$	Omega IC_{50}	6.7
Correlation			
Corr_V_Cl	0.23		

ka_pop, estimated absorption rate constant based on population data (/hours); V_pop, estimated distribution volume which is hypothetical volume where drug dissolved and being distributed throughout the body based on population data (Liters); Cl_pop, estimated drug removal from the certain volume of the blood per unit time based on population data; Lambda0, intersubject variability; IC_{50}, amount of concentration which needed to controlled of seizure in 50% subjects; Corr_V_Cl, correlation coefficient between distribution volume and its clearance of the drug; Omega_ka_pop, standard deviation of random effect of absorption rate constant; Omega_V_pop, standard deviation of random effect of volume of distribution; Omega_Cl_pop, standard deviation of random effect of clearance; Omega_lambda0, standard deviation of random effect of lambda0; Omega_IC_{50}, standard deviation of IC_{50}.

The comparison of predicted valproic acid steady state concentration derived from Yukawa's clearance equation and its plasma concentration of five subjects showed that 60% prediction in three subjects were closed to its related

Table 3: Population pharmacokinetics–pharmacodynamics parameter based on valproic acid concentration in the blood of five randomly selected subjects adhered to valproic acid syrup monotherapy at steady state level using SAEM algorithm of Monolix2019RA® software.

Parameter	Value of fixed effects		Value of standard deviation of random effects (between-subject variability)
ka_pop	6.25	Omega ka_pop	1.03
V_pop	3.36	Omega V_pop	0.32
Cl_pop	$3.17 \cdot e^{-11}$	Omega Cl_pop	9.68
Lambda0	2.81	Omega lambda0	0.09
IC_{50}	$1.85 \cdot e^{-6}$	Omega IC_{50}	4.46
Correlation			
Corr_V_Cl	0.97		

ka_pop, estimated absorption rate constant based on population data (/hours); V_pop, estimated distribution volume which is hypothetical volume where drug dissolved and being distributed throughout the body based on population data (Liters); Cl_pop, estimated drug removal from the certain volume of the blood per unit time based on population data; Lambda0, intersubject variability; IC_{50}, amount of concentration which needed to controlled of seizure in 50% subjects; Corr_V_Cl, correlation coefficient between distribution volume and its clearance of the drug; Omega_ka_pop, standard deviation of random effect of absorption rate constant; Omega_V_pop, standard deviation of random effect of volume of distribution; Omega_Cl_pop, standard deviation of random effect of clearance; Omega_lambda0, standard deviation of random effect of lambda0; Omega_IC_{50}, standard deviation of IC_{50}; Fixed effect, the model which assume that the true effect size for all studies is identical, and the only reason the effect size varies between studies is sampling error (error in estimating the effect size); Random effect, the model which assume that the true effect size for all studies is not identical. Each of the study might has a different effect size. The estimate provided by small study may be imprecise, but it is information about an effect that no other study has estimated.

plasma concentrations, and there were only one subject with higher and one subject with lower predicted concentration (20%, respectively). We then calculated the mean PE as well as mean weighted prediction error (MWPE) with a cut off =25% deviation from standard deviation (SD) between the predicted VPA steady state concentration and its plasma concentration. The value of mean difference was 5.11 (CI 95% – 11.1173–21.3414; p=0.431) which means that bias effect of mean PE had a low grade of bias. The value of mean WPE was 8.20 (CI 95% – 17.4637–33.8637; p=0.425) which means that the bias effect of mean WPE had a low grade of bias.

Discussion

Pediatric patient is a special care group which needs special attention due to the great variability in their physical conditions. Children grow up fast physically as well as hormonally from the newborn up to adolescent, despite of suboptimal physiology of most of their organs. This conditions leads to variability in pharmacokinetics and therapeutic response profile to numerous drug administered to the pediatric patient – in comparation to the adults. Thus knowledge of PK–PD properties of medication used to treat pediatric patients is utmost important [1, 2]. Previous study at Sanglah General Hospital showed a relatively high incidence of epilepsy in children and the needs of drug information services assisted by pharmacist in order to reach concordance between parents and the healthcare professionals. Parental concordance to their children therapy will further lead to drug adherence and compliance, thus it will improved clinical outcome – which in the case of valproic acid represents by its seizure control [10].

Underlying brain disorders and structural abnormalities, type of seizure, etiology, genetics, physicochemical properties of drug therapy, and drug compliance are factors that may affect seizure outcome. These factors could not fully explain wide variability of seizure outcome demonstrated in pediatric epilepsy patients. Wide variability of response to anticonvulsant therapy is not uncommon – especially in relation to older generation of antiepileptic drugs, such as valproic acid [10, 11]. Parents role is important in administering anticonvulsant therapy to their children who suffered from epilepsy. Thus this research controlled this potential bias with maintaining parental adherence to drug dosage regimen giving to their epilepsy children over a period of 1 month, so that there was 94.74% seizure free subjects at the end of research period. In general there always be difficult to control seizure in about 40% of the epilepsy patients, despite of their compliance to take the antiepileptic drugs [1]. This emphasized the importance of pharmacists role in improving parents' knowledge and behavior to adhere in administration of VPA syrup to their children. Inter professional collaboration between healthcare professionals as a solid healthcare team in maintaining chronic drug therapy adherence and to improve clinical outcome, especially in younger children, is utmost important [12, 13].

The result of this research was population PK–PD parameters which derived from multi ethnicity of the subjects voluntary participating in this research. The subjects referred to Sanglah General Hospital which serves as tertiary care for patients in Central Indonesia. However, the results cannot be considered as national representation of Indonesian pediatric epilepsy due to limited number of research subjects. Further research should be conducted as multicenter study across Indonesia in order to represent national population. As far as our knowledge, this is the first VPA PK–PD research in pediatric epilepsy patient conducted in Indonesia. So, the results of this study are important data to guidance clinical judgement of dosing adjustment in selected pediatric epilepsy at Sanglah General Hospital in the near future; which guidance had never existed before.

Population PK–PD parameter was successfully determined using free access of Monolix2019R2® software (Tables 2 and 3). Clearance of the drug and volume of distribution at steady state are considered to be the primary pharmacokinetic measurements obtained from *in vivo* experiments. Steady state level is a state where concentration of the drug is maintained with the lowest fluctuation between the minimum and its maximum level. In that situation the effect of the VPA is stabilized, and optimal as the steady state concentration maintained in the minimum effective concentration (MEC) range of 50–100 mg/L. Ninety nine percent of drug concentration after multiple dose therapy will normally reach the steady state level in around seven times the drug's half-life ($t_{1/2}$, 6–8 h in pediatric patients receiving VPA monotherapy); which was 42–56 h [13]. By ensuring drug adherence for at least one month, we convince that valproic acid steady state level had been achieved. In this research, pharmacokinetics parameters predicted under steady state level; which means that the concentration of valproic acid in the blood was constant at all the time. This phenomenon is due to the equal rate of drugs absorbed from its absorption site into the blood circulation and the rate of drugs distributed from the blood vessels into the tissue. This reflected the pharmacodynamics effect of valproic acid, which is its efficacy in controlling the seizures. In this research there was no sign or symptom of valproic toxicity during the research

period. This is clinically important, due to there is no need to adjust the dosage, once the steady state level is achieved in the MEC range.

Relatively small volume of distribution of VPA determined in this research means that there was a greater concentration of VPA in the plasma bound to albumin than the unbound VPA in the tissue. As a small free fatty acid, VPA is largely hydrophobic, imparting efficient entry to the central nervous system (CNS) with good oral bioavailability. Approximately 90% VPA binds to albumin in the blood vessels, with the unbound fraction increasing linearly from approximately 10% at concentration of 50 mg/L up to approximately 30% at 200 mg/L [14]. Instead, small concentrations of unbound VPA in the CNS tissue which bound to its receptor was adequately inhibit the seizure. This finding was in concert to the relatively small of 50% inhibition concentration (IC_{50}) resulted in this research, which was the smallest valproic acid concentrations needed to inhibit 50% of the seizure incident. The strong correlation (r=0.97) between VPA's volume of distribution with its clearance of five subjects randomly selected for determination of serum VPA concentration in this research reflected that the smaller concentration of VPA in CNS tissue at any particular time would distributed back into the systemic circulation which then underwent elimination from the blood VPA mostly cleared from the body through hepatic metabolism [15].

Our research shared similarity with Yukawa study in the subjects' profile, including sex and age of the subjects, as well as average body weight, dosage and predicted concentration of valproic acid at steady state condition. In this research we only managed to draw blood samples from five subjects, due to the limited time in every subject's visit to Outpatient Department. The comparison of predicted VPA steady state concentration derived from Yukawa's clearance equation and its plasma concentration of five subjects showed that there was one subject who had higher and one subject who had lower predicted concentration. Higher concentration potentially lead to higher risk of adverse events or toxicity, while lower one could lead to seizure attacks [16]. In fact, the five subjects had experienced no seizure attack at all during our research period, which means that the individual valproic acid concentration was in the optimum level for these pediatric subjects. Despite of these differences, the bias effect of mean PE and WPE were at low grade of bias [17]. Mean prediction error between predicted steady state concentration levels of five subjects and their related blood levels was ≤25% and considered as within clinically acceptable limit. According to Bondareva et al. (2011) the cut off ≤25% deviation is considered to be "clinically good"; while mean difference cut off ≤35% is considered as clinically acceptable [18]. Thus, the results of this research are robust enough to guide dosing adjustment of valproic acid syrup monotherapy in pediatric patients. The lack of PK–PD model of antiepileptic drugs in pediatric appears to hinder identification of suitable dosing regimens for pediatric patients with epilepsy [19]. Volume of distribution for Indonesian epilepsy pediatrics succesfully determined in this research. The volume of distribution at steady state is considered to be one of the primary pharmacokinetic measurements obtained from *in vivo* experiments [20]. Based on these results of the research, valproic acid syrup therapy administered to pediatric epilepsy patients safely managed to reach steady state level, thus effective in controlling the seizure without any adverse events; so that no dosage adjustment needed. In other word, the valproic acid syrup was a safe and effective therapy for pediatric epilepsy patients; thus the whole treatment was "on the right track".

Conducting an ideal therapeutic drug monitoring (TDM) is cost consuming, so this impractical to be developed in everyday practice. VPA concentration in this research measured in the blood as a total VPA, instead of unbound VPA; thus we could not determine the possibility of its level which out of MEC range. Sub therapeutic concentration would lead to less VPA's efficacy in controlling the seizure frequency. In contrast, the valproic acis concentration higher than MEC range would leads to toxic effect that could be life threatening. Difficult to control seizure in one subject who still experienced seizures 10 times per month at the baseline as well as at the end of this research period would probably due to VPA's sub therapeutic concentration.

Pharmacokinetics and pharmacodynamics parameters based on population data had successfully determined, but we have not developed a PK–PD modelling yet due to our research limitations. There were several limitations of the study. The design of this research was observational study with a limited number of subjects who were involved in the research, due to unwillingness of the potentially eligible pediatric epilepsy patients to performed blood sampling. We tried to overcome this limitation by randomly assigned blood sampling between the 38 subjects who managed to adhere to VPA therapy for one month. The other obstacle in this research was the limited blood volume of the pediatric subjects, so that we could not performed several blood sampling on the estimated peak and through concentration at steady state level. The last limitation was that the analysis procedures could only measure total VPA concentration, instead of unbound VPA; thus conducting a therapeutic drug monitoring is cost consuming to be performed in daily practice. Unbound VPA is reflecting the amount of VPA which can interact with the receptor in order to actively control the seizures. This limitation leads to less accuracy in

measuring VPA plasma concentration for pharmacokinetics parameters determination. These obstacles should be overcome in the future research.

Conclusions

Developing PK–PD model of VPA syrup at steady state condition based on population data in pediatric epilepsy subjects had been undertaken, and some of the parameters were sets. It needs further study to develop best matched PK–PD model of VPA syrup at steady state condition in Indonesian pediatric epilepsy outpatient due to limitation of the study.

Acknowledgments: We acknowledge the Director of Sanglah General Hospital and the Head of the Pediatric Outpatient Department of Sanglah General Hospital, and Lixoft University, Antony, France – for providing free access of the Monolix2019RA® software for our research.
Research funding: University of Surabaya on scheme of internal lecturer's research grant (2020).
Author contributions: All authors have accepted responsibility for the entire content of this manuscript and approved its submission.
Competing interests: Authors state no conflict of interest.
Informed consent: Informed consent was obtained from all individuals included in this study.
Ethical approval: Research involving human subjects complied with all relevant national regulations, institutional policies and is in accordance with the tenets of the Helsinki Declaration (as revised in 2013), and has been approved by the authors' institutional review board or equivalent committee.

References

1. Patsalos PN, Berry DJ, Burgeois BFD, Cloyd JC, Glauser TA, Johannessen SI, et al. Antiepileptic drugs—best practice guidelines for therapeutic drug monitoring: a position paper by the subcommission on therapeutic drug monitoring, ILAE Commission on Therapeutic Strategies. Epilepsia 2008;49:1239–76.
2. Scheffer IE, Berkovic S, Capovilla G, Connolly MB, French J, Guilhoto J, et al. ILAE classification of the epilepsies: position paper of the ILAE Commission for Classification and Terminology. Epilepsia 2017;58:512–21.
3. Nevitt SJ, Sudell M, Weston J, Smith CT, Marson AG. Antiepileptic drug monotherapy for epilepsy: a network meta-analysis of individual participant data. Cochrane Database Syst Rev 2017;6:CD011412.
4. Aldaz A, Ferriols R, Aumente D, Calvo MV, Farre MR, García B. Pharmacokinetic monitoring of antiepileptic drugs. Farm Hosp 2011;35:326–39.
5. Suwarba IGNM. Incidents and clinical characteristics of epilepsy in children. Sari Pediatri 2011;13:123.
6. Yukawa E, Hideto T, Ohdo S, Higuchi S, Aoyama T. Population-based investigation of valproic acid relative clearance using nonlinear mixed effects modeling: influence of drug–drug interaction and patient characteristics. J Clin Pharmacol 2013;37:1160–67.
7. Yukawa E. A feasibility study of the multiple-peak approach for pharmacokinetic screening: population-based investigation of valproic acid relative clearance using routine clinical pharmacokinetic data. J Pharm Pharmacol 1995;47:1048–52.
8. Methaneethorn J. A systematic review of population pharmacokinetics of valproic acid. Br J Clin Pharmacol 2018;84:816–34.
9. Nakashima H, Oniki K, Nishimura M, Ogusu N, Shimomasuda M, Ono T, et al. Determination of the optimal concentration of valproic acid in patients with epilepsy: a population pharmacokinetic-pharmacodynamic analysis. PloS One 2015;10:e0141266.
10. Febriansiswanti NMD. The parental adherence level in administrating oral antiepileptic drug to their epilepsy children [Master thesis]. University of Surabaya; 2018.
11. Modi AC, Wu YP, Rausch JR, Peugh JL, Glauser TA. Antiepileptic drug nonadherence predicts pediatric epilepsy seizure outcomes. Neurology 2014;83:2085–90.
12. Suwarba IGNM. Comprehensive management of neonatology, emergency, cardiology, and neurology aspect in daily practices. Denpasar: University of Udayana Press; 2014.
13. Parfati N, Purnamayanti A. Phenytoin and valproate profile in epilepsy therapy. Surabaya: Universitas Surabaya; 2018.
14. Williams, JH, Jayaraman, B, Swoboda, KJ, Barrett, JS. Population pharmacokinetics of valproic acid in pediatric patients with epilepsy: considerations for dosing spinal muscular atrophy patients. J Clin Pharmacol 2012;52:1676–88.
15. Shargel L, Yu ABC, editors. Applied biopharmaceutics and pharmacokinetics, 7thed. New York: Mc Graw Hill Education; 2016.
16. Ray S, Skellet S, Valproate toxicity in a child. Clin Toxicol 2013;51:194.
17. Jiang D, Wang L, Wang Y, Li L, Lu W, Bai X. Population pharmacokinetics of valproate in Chinese children with epilepsy. Acta Pharmacol Sin 2007;28:1677–84.
18. Bondareva IB, Jeliffe RW, Andreeva OV, Bondareva KI. Predictability of individualized dosage regimens of carbamazepine and valproate mono- and combination therapy. J Clin Pharm Therapeut 2011;36:625–36.
19. van Dijkman SC. Personalised pharmacotherapy in pediatric epilepsy: the path to rational drug and dose selection [Dissertation]. Leiden University; 2017. Available from: http://hdl.handle.net/1887/59470.
20. Yates JWT, Arundel PA. On the volume of distribution at steady state and its relationship with two-compartmental models. J Pharm Sci 2008;97:111–22..

Supplementary Material: The online version of this article offers supplementary material (https://doi.org/10.1515/jbcpp-2020-0488).


DE GRUYTER
JOURNAL OF BASIC AND CLINICAL PHYSIOLOGY AND PHARMACOLOGY

also developed by scimago: SCIMAGO INSTITUTIONS RANKINGS

SJR Scimago Journal & Country Rank

Enter Journal Title, ISSN or Publisher Name

Home Journal Rankings Country Rankings Viz Tools Help About Us

Journal of Basic and Clinical Physiology and Pharmacology

COUNTRY

Germany

Universities and research institutions in Germany

SUBJECT AREA AND CATEGORY

Biochemistry, Genetics and Molecular Biology
Physiology

Medicine
Medicine (miscellaneous)

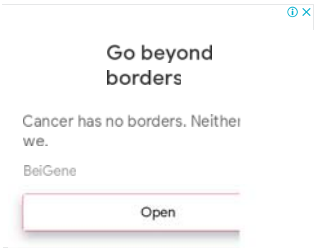
Pharmacology, Toxicology and Pharmaceutics
Drug Discovery
Pharmacology

PUBLISHER

Walter de Gruyter GmbH

H-INDEX

33



PUBLICATION TYPE

Journals

ISSN

07926855, 21910286

COVERAGE

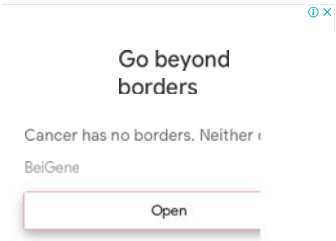
1985-1988, 1990-2020

INFORMATION

Homepage

How to publish in this journal

m.horowitz@mail.huji.ac.il



SCOPE

The Journal of Basic and Clinical Physiology and Pharmacology (JBCPP) is a peer-reviewed bi-monthly published journal in experimental medicine. JBCPP publishes novel research in the physiological and pharmacological sciences, including brain research; cardiovascular-pulmonary interactions; exercise; thermal control; haematology; immune response; inflammation; metabolism; oxidative stress; and phytotherapy. As the borders between physiology, pharmacology and biochemistry become increasingly blurred, we also welcome papers using cutting-edge techniques in cellular and/or molecular biology to link descriptive or behavioral studies with cellular and molecular mechanisms underlying the integrative processes. Topics: Behavior and Neuroprotection, Reproduction, Genotoxicity and Cytotoxicity, Vascular Conditions, Cardiovascular Function, Cardiovascular-Pulmonary Interactions, Oxidative Stress, Metabolism, Immune Response, Hematological Profile, Inflammation, Infection, Phytotherapy.

Join the conversation about this journal

Go beyond borders
Cancer has no borders. Neither do we.
BeiGene
Open

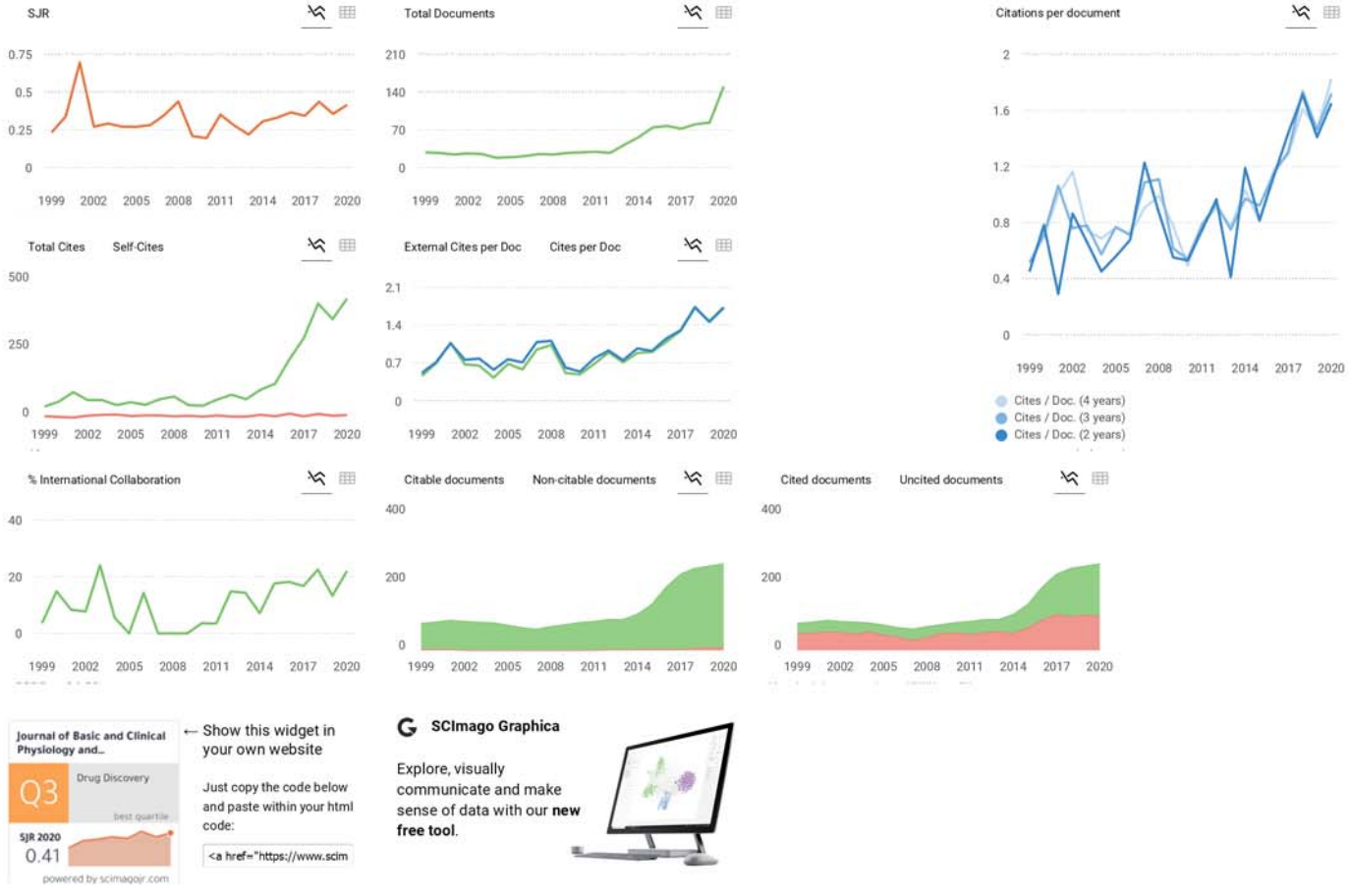
Quartiles

FIND SIMILAR JOURNALS

options

1	2	3	4	5
Archives of Physiology and Biochemistry	**International Journal of Pharmacology**	**Pathophysiology**	**Tropical Journal of Pharmaceutical Research**	**Iranian Journal of Basic Medical Sciences**
GBR	PAK	CHE	NGA	IRN
65% similarity	62% similarity	60% similarity	60% similarity	59% similarity

Go beyond borders
Cancer has no borders. Neither do we.
BeiGene



← Show this widget in your own website

Just copy the code below and paste within your html code:

<a href="https://www.scim

SCImago Graphica

Explore, visually communicate and make sense of data with our **new free tool**.

Get it

Metrics based on Scopus® data as of April 2021

O **Oman** 12 months ago

How much money to publis in this journal

reply

SCImago Team

Melanie Ortiz 12 months ago

Dear Oman,
thank you for contacting us.
Unfortunately, we cannot help you with your request, we suggest you visit the journal's homepage or contact the journal's editorial staff , so they could inform you more deeply.
Best Regards, SCImago Team

D **Daniel Orieke** 1 year ago

Please how do you get original article submitted.

reply

SCImago Team

Melanie Ortiz 1 year ago

Dear Daniel, thank you very much for your comment, we suggest you look for author's instructions/submission guidelines in the journal's website. Best Regards, SCImago Team

D **dr jhanvi vaghela** 2 years ago

Is Journal of Basic and Clinical Physiology and Pharmacology is online only journal ??

reply

SCImago Team

Melanie Ortiz 2 years ago

Dear Jhanvi,
thank you for contacting us.
Sorry to tell you that SCImago Journal & Country Rank is not a journal. SJR is a portal with scientometric indicators of journals indexed in Elsevier/Scopus.
Unfortunately, we cannot help you with your request, we suggest you to visit the journal's homepage or contact the journal's editorial staff , so they could inform you more deeply.
Best Regards, SCImago Team

N **Nilufar** 2 years ago

Dear Sir/Madam,

I couldn't find how to publish the article at this journal. Could you possibly send the requirements of publishing at this journal, please?

Kindest regards,
Nilufar

reply

SCImago Team

Melanie Ortiz 2 years ago

Dear Nilufar,

You can see the updated information just above. Best Regards, SCImago Team

Leave a comment

Name

Email
(will not be published)

I'm not a robot
reCAPTCHA
Privacy - Terms

Submit

The users of Scimago Journal & Country Rank have the possibility to dialogue through comments linked to a specific journal. The purpose is to have a forum in which general doubts about the processes of publication in the journal, experiences and other issues derived from the publication of papers are resolved. For topics on particular articles, maintain the dialogue through the usual channels with your editor.

Developed by: SCImago

Powered by: Scopus

Follow us on @ScimagoJR

Scimago Lab, Copyright 2007-2020. Data Source: Scopus®

EST MODUS IN REBUS

Source details

Journal of Basic and Clinical Physiology and Pharmacology

Formerly known as: Reviews in Clinical and Basic Pharmacology

Scopus coverage years: from 1985 to 1988, from 1990 to Present

Publisher: Walter de Gruyter

ISSN: 0792-6855 E-ISSN: 2191-0286

Subject area: Pharmacology, Toxicology and Pharmaceutics: Pharmacology

Pharmacology, Toxicology and Pharmaceutics: Drug Discovery

Biochemistry, Genetics and Molecular Biology: Physiology

Source type: Journal

CiteScore 2020
2.7

SJR 2020
0.414

SNIP 2020
0.682

View all documents > Set document alert Save to source list Source Homepage

CiteScore CiteScore rank & trend Scopus content coverage

¡ Improved CiteScore methodology

CiteScore 2020 counts the citations received in 2017-2020 to articles, reviews, conference papers, book chapters and data papers published in 2017-2020, and divides this by the number of publications published in 2017-2020. Learn more >

CiteScore 2020

$$2.7 = \frac{859 \text{ Citations } 2017 - 2020}{323 \text{ Documents } 2017 - 2020}$$

Calculated on 05 May, 2021

CiteScoreTracker 2021

$$2.1 = \frac{831 \text{ Citations to date}}{390 \text{ Documents to date}}$$

Last updated on 04 September, 2021 • Updated monthly

CiteScore rank 2020

Category	Rank	Percentile
Pharmacology, Toxicology and Pharmaceutics — Pharmacology	#185/297	37th
Pharmacology, Toxicology and Pharmaceutics — Drug Discovery	#96/145	34th

View CiteScore methodology > CiteScore FAQ > Add CiteScore to your site

About Scopus

What is Scopus
Content coverage
Scopus blog
Scopus API
Privacy matters

Language

日本語に切り替える
切换到简体中文
切換到繁體中文
Русский язык

Customer Service

Help
Contact us

ELSEVIER

Terms and conditions ↗ Privacy policy ↗

Copyright © Elsevier B.V ↗. All rights reserved. Scopus® is a registered trademark of Elsevier B.V.
We use cookies to help provide and enhance our service and tailor content. By continuing, you agree to the use of cookies.

RELX

JOURNAL OF BASIC AND CLINICAL PHYSIOLOGY AND PHARMACOLOGY

EDITOR-IN-CHIEF
Ugo Oliviero, Naples, Italy

DEPUTY EDITOR
Alberto M. Marra, Naples, Italy/Heidelberg, Germany

EDITORIAL BOARD
Giorgio Bosso, Naples, Italy
Ewelyine Biskup, Basel, Switzerland/ Shanghai, China
Pablo Demelo-Rodriguez, Madrid, Spain
Antonio Valvano, Legnano, Italy
Theodor Voisou, Bucarest, Romenia
Andrei Voisou, Bucarest, Romenia
Lorenzo Falsetti, Ancona, Italy
Valeria Raparelli, Ferrara, Italy
Ieva Ruza, Riga, Latvia
Mariarosaria De Luca, Naples, Italy
Andrea Salzano, Leicester, UK
Antonio Cittadini, Naples, Italy
Salvatore Torrisi, Catania, Italy
Leonardo Bencivenga, Naples, Italy
Gilda Varricchi, Naples, Italy
Domenico Sambataro, Catania, Italy
Raffaella Spina, Baltimora,USA
Francesca Vinchi, New York, USA,
Roberta D'Assante, Naples, Italy

DE GRUYTER

ABSTRACTED/INDEXED IN Baidu Scholar · Case · Chemical Abstracts Service (CAS): CAplus · Chemical Abstracts Service (CAS) - SciFinder · CINAHL · CNKI Scholar (China National Knowledge Infrastructure) · CNPIEC: cnpLINKer · Dimensions · EBSCO (relevant databases) · EBSCO Discovery Service · Embase · FSTA: Food Science & Technology Abstracts · Genamics JournalSeek · Google Scholar · Japan Science and Technology Agency (JST) · J-Gate · JournalGuide · JournalTOCs · KESLI-NDSL (Korean National Discovery for Science Leaders) · Medline · Meta · Microsoft Academic · MyScienceWork · Naver Academic · Naviga (Softweco) · Primo Central (ExLibris) · ProQuest (relevant databases) · Publons · PubMed · PubsHub · QOAM (Quality Open Access Market) · ReadCube · Reaxys · SCImago (SJR) · SCOPUS · Semantic Scholar · Sherpa/RoMEO · Summon (ProQuest) · TDNet · Text Mining · Ulrich's Periodicals Directory/ulrichsweb · WanFang Data · Web of Science: Biological Abstracts; BIOSIS Previews · WorldCat (OCLC)

e-ISSN 2191-0286

All information regarding notes for contributors, subscriptions, Open access, back volumes and orders is available online at www.degruyter.com/jbcpp.

RESPONSIBLE EDITOR Prof. Ugo Oliviero, Department of Translational Medical Sciences, Federico II University, Via pansini 5, Napels, Campania, 80131 Italy, e-mail: ugo.oliviero@unina.it

PUBLISHER Walter de Gruyter GmbH, Berlin/Boston, Genthiner Straße 13, 10785 Berlin, Germany

JOURNAL MANAGER Katharina Appelt, De Gruyter, Genthiner Str. 13, 10785 Berlin, Germany, Tel.: +49 (0)30 260 05-325, e-mail: jbcpp.editorial@degruyter.com

RESPONSIBLE FOR ADVERTISEMENTS Kevin Göthling, De Gruyter, Genthiner Straße 13, 10785 Berlin, Germany, Tel.: +49 (0)30 260 05-170, e-mail: anzeigen@degruyter.com

© 2021 Walter de Gruyter GmbH, Berlin/Boston, Germany

TYPESETTING TNQ Technologies, Chennai, India

Published since December 1, 1986

Journal of Basic and Clinical Physiology and Pharmacology

ISSN: 2191-0286
Editor-in-chief: Ugo Oliviero
Managing Editor: Alberto Marra

Editorial

Editor-in-Chief:
Ugo Oliviero (Federico II University, Naples, Italy)

Deputy Editor:
Alberto M. Marra (Federico II University, Naples, Italy and University of Heidelberg, Germany)

Associate/Section Editors:

Emergency Medicine: Giorgio Bosso (S. Maria delle Grazie Hospital, Pozzuoli, Naples)

Oncology: Evelyne Bischof (prev.Ewelina Biskup; University Hospital Basel, Switzerland, Shanghai University of Medicine & Health Sciences, Shanghai, China)

Hematology and Coagulation disorders: Pablo Demelo-Rodriguez (G. Marangon Hospital and Universidad Complutense de Madrid, Spain)

Vascular Medicine: Antonio Valvano (Legnano Hospital, Legnano, Italy)

Gastroenterology: Theodor Voiosu (University of Bucharest, Bucarest, Romenia)

Liver Disease: Andrei Voiosu (University of Bucharest, Bucarest, Romenia)

Neurology and Cerebrovascular: Lorenzo Falsetti (Azienda Ospedaliero-Universitaria "Ospedali Riuniti" di Ancona, Italy)

Gender Medicine: Valeria Raparelli (University of Ferrara, Ferrara, Italy)

Endocrinology: Ieva Ruza, (University of Riga, Riga, Latvia)

Diabetology and Metabolism: Mariarosaria De Luca (Federico II University, Naples)

Cardiovascular Diseases: Andrea Salzano (Glenfield General Hospital, University of Leicester, Leicester, UK)

Heart Failure: Antonio Cittadini (Federico II University of Naples, Naples, Italy)

Respiratory Medicine: Salvatore Torrisi (University of Catania, Catania, Italy)

Geriatrics: Leonardo Bencivenga (Federico II University, Naples, Italy)

Immunology: Gilda Varricchi (Federico II University, Naples, Italy)

Rheumatology: Domenico Sambataro (Artroreuma, Catania, Italy)

Basic Science: Raffaella Spina (University of Maryland, School of Medicine, Baltimora,USA), Francesca Vinchi (New York Blood center, New York, USA), Roberta D'Assante (Federico II, Naples), Jia Liu (University of Virgina Health System, Charlottesville, USA)

Editorial Office:
E-mail: jbcpp.editorial@degruyter.com

(Deutsch)

Published by De Gruyter

Volume 32 Issue 4 - INTERNATIONAL CONFERENCE OF PHARMACY AND HEALTH SCIENCES: The 3rd JOINT CONFERENCE UNAIR - USM; Guest Editors: Suciati & Andang Miatmoko

July 2021

Issue of Journal of Basic and Clinical Physiology and Pharmacology

Original Articles

Requires Authentication June 25, 2021

Inhibition of Ras and STAT3 activity of 4-(*tert*-butyl)-*N*-carbamoylbenzamide as antiproliferative agent in HER2-expressing breast cancer cells

Aguslina Kirtishanti, Siswandono Siswodihardjo, I Ketut Sudiana, Desak G. A. Suprabawati, Aristika Dinaryanti

Page range: 363–371

More ▾ Cite this

Requires Authentication June 25, 2021

Predicting the molecular mechanism of glucosamine in accelerating bone defect repair by stimulating osteogenic proteins

Maria Apriliani Gani, Ahmad Dzulfikri Nurhan, Aniek Setiya Budiatin, Siswandono Siswodihardjo, Junaidi Khotib

Page range: 373–377

More ▾ Cite this

Requires Authentication June 25, 2021

Larvicidal toxicity and parasporal inclusion of native *Bacillus thuringiensis* BK5.2 against *Aedes aegypti*

Salamun, Fatimah, Ahmad Fauzi, Seling N. Praduwana, Ni'matuzahroh

Page range: 379–384

More ▾ Cite this

Requires Authentication June 25, 2021

Synthesis, ADMET predictions, molecular docking studies, and *in-vitro* anticancer activity of some benzoxazines against A549 human lung cancer cells

Melanny Ika Sulistyowaty, Retno Widyowati, Galih Satrio Putra, Tutuk Budiati, Katsuyoshi Matsunami

Page range: 385–392

More ▾ Cite this

Requires Authentication June 25, 2021

Thymoquinone and its derivatives against breast cancer with HER2 positive: *in silico* studies of ADMET, docking and QSPR

Adinda Adelia Wulandari, Achmad Aziz Choiri, Fitria, Tri Widiandani

Page range: 393–401

More ▾ Cite this

Requires Authentication June 25, 2021

Assessment of patient understanding of their conventional cardiac medicines and herbal prepared/derived products: preliminary survey and interviews with selected community-dwelling elderly patients in the Philippines

Jay P. Jazul, Trisha Michaela G. Arciga, Mary Angelie C. Ante, Danavin Gwyneth B. Berlin, Loise Francoise L. Ravana, Samantha A. Reyes, Jashanjit Singh

Page range: 403–413

More ▾ Cite this

Requires Authentication June 25, 2021

The development and validation of the health belief model questionnaire for measuring factors affecting adherence in the elderly with hypertension

Rodhiyatul Fithri, Umi Athiyah, Elida Zairina

Page range: 415–419

More ▾ Cite this

Requires Authentication June 25, 2021

Analysis of the side effect of QTc interval prolongation in the bedaquiline regimen in drug resistant tuberculosis patients

Denny Ardhianto, Suharjono, Soedarsono, Umi Fatmawati

Page range: 421–427

More ▾ Cite this

Requires Authentication June 25, 2021

Shallot skin profilling, computational evaluation of physicochemical properties, ADMET, and molecular docking of its components against P2Y12 receptor

Juni Ekowati, Kholidah Febriani, Itsna N. A. Yaqin, Adinda A. Wulandari, Indra H. Mulya, Kholis A. Nofianti, Achmad Syahrani

Page range: 429–437

More ▾ Cite this

Developing pharmacokinetics–pharmacodynamics model of valproic acid syrup based on prediction of population pharmacokinetics parameter and seizure frequency in Indonesian pediatric epilepsy outpatients

I Komang Prawira Nata Nugraha, Anita Purnamayanti, I Gusti Ngurah Made Suwarba and Nani Parfati

From the journal Journal of Basic and Clinical Physiology and Pharmacology
https://doi.org/10.1515/jbcpp-2020-0488

Cite this

You currently have no access to view or download this content. Please log in with your institutional or personal account if you should have access to this content through either of these. Showing a limited preview of this publication:

Abstract

Objectives

Valproic acid (VPA) is a broad-spectrum antiepileptic drug with known efficacy profile in pediatric patients, despite of its narrow therapeutic index. There is lack of VPA's pharmacokinetics profile in Indonesian pediatric subjects, partly due to limited pediatric blood volume taken for conducting therapeutic drug monitoring. This study aimed to determine the correlation between VPA pharmacokinetics parameters based on population data and seizure frequency in pediatric epilepsy outpatients.

Methods

This observational study was conducted at Sanglah General Hospital during June–December 2019. The subjects of this research were 38 pediatric epilepsy patients who adhered to VPA syrup monotherapy for at least 3 weeks. Five subjects randomly selected for blood sample collection. Thus, VPA concentration level in the blood being analysed as a comparison to its concentration predicted from Yukawa's steady state equation. Monolix2019R2® software was used to identify VPA population pharmacokinetics–pharmacodynamics (PK–PD) parameters at steady state level.

Results

Population PK–PD of VPA syrup at steady state level were ka_pop = 6.25/h, Vd_pop = 3.36 L, Cl_pop = $3.17e^{-11}$ mL/min, IC_{50}_pop = $1.85e^{-6}$, correlation of Vd_pop and Cl_pop = 0.966. Kendall Tau Correlation of predicted VPA steady state concentration and frequency of seizure was −0.66. Mean prediction error between predicted steady state concentration of five subjects and their related blood levels was ≤25% and considered as within clinically acceptable limit.

Conclusions

It needs further study to develop best matched PK–PD model of VPA syrup at steady state condition in pediatric epilepsy.

Keywords: pediatric; population pharmacokinetics; prediction of concentration; seizure frequency; valproic acid

Corresponding author: Anita Purnamayanti, Department of Clinical Pharmacy, Faculty of Pharmacy, University of Surabaya, Surabaya, Indonesia, Phone: +62 813364444888, E-mail: anita_p_rahman@yahoo.com

Funding source: Universitas Surabaya

Award Identifier / Grant number: 047/ST-Lit/LPPM-01/FF/V/2020

Acknowledgments

We acknowledge the Director of Sanglah General Hospital and the Head of the Pediatric Outpatient Department of Sanglah General Hospital, and Lixoft University, Antony, France – for providing free access of the Monolix2019RA® software for our research.

Research funding: University of Surabaya on scheme of internal lecturer's research grant (2020).

Author contributions: All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

Competing interests: Authors state no conflict of interest.

Informed consent: Informed consent was obtained from all individuals included in this study.

Ethical approval: Research involving human subjects complied with all relevant national regulations, institutional policies and is in accordance with the tenets of the Helsinki Declaration (as revised in 2013), and has been approved by the authors' institutional review board or equivalent committee.

References

1. Patsalos, PN, Berry, DJ, Burgeois, BFD, Cloyd, JC, Glauser, TA, Johannessen, SI, et al.. Antiepileptic drugs—best practice guidelines for therapeutic drug monitoring: a position paper by the subcommission on therapeutic drug monitoring, ILAE Commission on Therapeutic Strategies. *Epilepsia* 2008;49:1239–76. https://doi.org/10.1111/j.1528-1167.2008.01561.x. Search in Google Scholar

2. Scheffer, IE, Berkovic, S, Capovilla, G, Connolly, MB, French, J, Guilhoto, J, et al.. ILAE classification of the epilepsies: position paper of the ILAE Commission for Classification and Terminology. *Epilepsia* 2017;58:512–21. https://doi.org/10.1111/epi.13709. Search in Google Scholar

3. Nevitt, SJ, Sudell, M, Weston, J, Smith, CT, Marson, AG. Antiepileptic drug monotherapy for epilepsy: a network meta-analysis of individual participant data. *Cochrane Database Syst Rev* 2017;6:CD011412. Search in Google Scholar

4. Aldaz, A, Ferriols, R, Aumente, D, Calvo, MV, Farre, MR, García, B. Pharmacokinetic monitoring of antiepileptic drugs. *Farm Hosp* 2011;35:326–39. https://doi.org/10.1016/j.farmae.2011.09.001. Search in Google Scholar

5. Suwarba, IGNM. Incidents and clinical characteristics of epilepsy in children. *Sari Pediatri* 2011;13:123. Search in Google Scholar

6. Yukawa, E, Hideto, T, Ohdo, S, Higuchi, S, Aoyama, T. Population-based investigation of valproic acid relative clearance using nonlinear mixed effects modeling: influence of drug–drug interaction and patient characteristics. *J Clin Pharmacol* 2013;37:1160–67. https://doi.org/10.1002/j.1552-4604.1997.tb04301.x. Search in Google Scholar

7. Yukawa, E. A feasibility study of the multiple-peak approach for pharmacokinetic screening: population-based investigation of valproic acid relative clearance using routine clinical pharmacokinetic data. *J Pharm Pharmacol* 1995;47:1048–52. https://doi.org/10.1111/j.2042-7158.1995.tb03295.x. Search in Google Scholar

8. Methaneethorn, J. A systematic review of population pharmacokinetics of valproic acid. *Br J Clin Pharmacol* 2018;84:816–34. https://doi.org/10.1111/bcp.13510. Search in Google Scholar

9. Nakashima, H, Oniki, K, Nishimura, M, Ogusu, N, Shimomasuda, M, Ono, T, et al.. Determination of the optimal concentration of valproic acid in patients with epilepsy: a population pharmacokinetic-pharmacodynamic analysis. *PloS One* 2015;10: e0141266. https://doi.org/10.1371/journal.pone.0141266. Search in Google Scholar

10. Febriansiswanti, NMD. *The parental adherence level in administrating oral antiepileptic drug to their epilepsy children* [Master thesis]. University of Surabaya; 2018. Search in Google Scholar

11. Modi, AC, Wu, YP, Rausch, JR, Peugh, JL, Glauser, TA. Antiepileptic drug nonadherence predicts pediatric epilepsy seizure outcomes. *Neurology* 2014;83:2085–90. https://doi.org/10.1212/wnl.0000000000001023. Search in Google Scholar

12. Suwarba, IGNM. *Comprehensive management of neonatology, emergency, cardiology, and neurology aspect in daily practices*. Denpasar: University of Udayana Press; 2014. Search in Google Scholar

13. Parfati, N, Purnamayanti, A. *Phenytoin and valproate profile in epilepsy therapy*. Surabaya: Universitas Surabaya; 2018. Search in Google Scholar

14. Williams, JH, Jayaraman, B, Swoboda, KJ, Barrett, JS. Population pharmacokinetics of valproic acid in pediatric patients with epilepsy: considerations for dosing spinal muscular atrophy patients. *J Clin Pharmacol* 2012;52:1676–88. https://doi.org/10.1177/0091270011428138. Search in Google Scholar

15. Shargel, L, Yu, ABC, editors. *Applied biopharmaceutics and pharmacokinetics*, 7thed. New York: Mc Graw Hill Education; 2016. Search in Google Scholar

16. Ray, S, Skellet, S, Valproate toxicity in a child. *Clin Toxicol* 2013;51:194. https://doi.org/10.3109/15563650.2013.776070. Search in Google Scholar

17. Jiang, D, Wang, L, Wang, Y, Li, L, Lu, W, Bai, X. Population pharmacokinetics of valproate in Chinese children with epilepsy. *Acta Pharmacol Sin* 2007;28:1677–84. https://doi.org/10.1111/j.1745-7254.2007.00704.x. Search in Google Scholar

18. Bondareva, IB, Jeliffe, RW, Andreeva, OV, Bondareva, KI. Predictability of individualized dosage regimens of carbamazepine and valproate mono- and combination therapy. *J Clin Pharm Therapeut* 2011;36:625–36. https://doi.org/10.1111/j.1365-2710.2010.01215.x. Search in Google Scholar

19. van Dijkman, SC. *Personalised pharmacotherapy in pediatric epilepsy: the path to rational drug and dose selection* [Dissertation]. Leiden University; 2017. Available from: http://hdl.handle.net/1887/59470. Search in Google Scholar

20. Yates, JWT, Arundel, PA. On the volume of distribution at steady state and its relationship with two-compartmental models. *J Pharm Sci* 2008;97:111–22. https://doi.org/10.1002/jps.21089. Search in Google Scholar

Supplementary Material

The online version of this article offers supplementary material (https://doi.org/10.1515/jbcpp-2020-0488).

Received: 2020-11-29
Accepted: 2021-04-01
Published Online: 2021-06-25

© 2021 Walter de Gruyter GmbH, Berlin/Boston