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

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Running head
Developing pharmacokinetics-pharmacodynamics model of Valproic Acid in pediatric epilepsy subjects

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 valproic acid's pharmacokinetics profile in Indonesian pediatric subjects, partly due to limited pediatric blood volume taken for conducting therapeutic drug monitoring. This study aimed to determined 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 subject of this research were 38 pediatric epilepsy patients who adhered to valproic acid syrup monotherapy for at least 3 weeks. Five subject randomly selected for blood sample collection. Thus, valproic acid 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 valproic acid population PK-PD parameters at steady state level.
Results: Population pharmacokinetics-pharmacodynamics of valproic acid syrup at steady state level were ka_pop = 6.25/hour, Vd pop = 3.36 L, Cl pop = $3.17.e^{-11}$ mL/min., IC50 pop = $1.85.e^{-6}$, correlation of Vd_and Cl = 0.966. Kendall Tau Correlation of predicted valproic acid steady state concentration and frequency of seizure was -0.66. Mean prediction error between predicted steady state concentration of 5 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 valproic acid syrup at steady state condition in pediatric epilepsy.

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

Introduction

According to International League of Anti 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, 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 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, valproic acid has a narrow therapeutic index and high protein binding, which means discrepancies between minimum concentration of valproic acid to be effectively act as AED with its minimum toxic concentration level is relatively near. Thus pediatric patients have increased risk of sub or supra optimal valproic acid therapy [2, 3].

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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 supra therapeutic concentration of AED. Sub-therapeutic concentration means that there was no or minimal effect of the drug, while supra-therapeutic 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 valproic acid concentration is not uncommon in pediatric epilepsy. Adapting individual doses is complicated, due to the presence of factors including: a) the considerable inter-individual 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 [9]. There is lack of pharmacokinetics data population for AEDs in Indonesian pediatric epilepsy as a 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 [5-8]. Yukawa et.al conducted PK-PD study of valproic acid (VPA) administered to pediatric patients and developed an equation for calculating the clearance of VPA from population data [6]. In this research, we used Yukawa's equation for calculating valproic acid clearance, due to similarities in research design which is conducted for assessing valproic acid syrup in its steady state condition among pediatric epilepsy patients. Aim of this research was to analyze the estimated concentration of valproic acid 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 pharmacokinetics – pharmacodynamics (PK-PD) analysis in the future research. As far as our knowledge, this is the first PK-PD study of valproic acid 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 – December 2019, and fulfilled all of the following inclusion criteria : (1) aged 6-18 years, (2) had been receiving valproic acid (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, (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 was comply 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 valproic acid monotherapy adherence. We supplemented

written education material (booklet) for each subjects. Subjects had been asked to bring their valproic acid syrup bottle in every visit, and its volume measurement conducted by comparing the volume left in the subject's bottle to a standardized scaled vaproic acid syrup bottle. All of the subjects included in this research had 100% valproic acid syrup adherence during this stage of research, so that drug adherence was not be the confounding factor.

Estimated steady state concentrations of VPA was calculated based on pharmacokinetics population data using Yukawa's equation for valproic acid clearance as follow: [6]

$$Cl\ (ml.kg^{-1}.h\text{-}1) = 18.9 \times \text{body weight (kg)}^{-0.276} \times \text{VPA daily dose}(mg.kg^{-1}.day^{-1})^{0.142} \times \text{gender (which is 1 for male, and 0.887 for female)} \quad \text{..... Eq.1}$$

Predicted valproic acid steady state concentration of each subjects then was calculated from this estimated clearance, thus the results were so called "predicted valproic acid 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 valproic acid'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 valproic acid steady state concentrations based on population data. The comparative results between predicted valproic acid steady state concentrations based on population data with the valproic acid plasma concentration of the five subject 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 (IC50), 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 kilograms), the total dose of valproic acid syrup administered was 19.55 ± 6.19 (8 – 37 mg/kg body weight/ day). There were a great inter subject 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 5 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 valproic acid 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 5 subjects and their frequency of seizures that had a strong association (r = -0.62).

Population pharmacokinetics – pharmacodynamics parameter estimates based on predicted versus serum valproic acid steady state concentration were performed using SAEM algorithm of Monolix2019RA® software. Correlation value between valproic acid'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 5 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 5 subjects. This correlation coefficient was markedly improved in 5 subjects, comparing to its correlation in 38 subjects (Table 2, 3).

The comparison of predicted valproic acid steady state concentration derived from Yukawa's clearance equation and its plasma concentration of 5 subjects showed that 60% prediction in three subjects were closed to its related plasma concentrations, and there were only one subject with higher and one subject with lower predicted concentration (20%, respectively). We then calculated the mean prediction error (PE) as well as mean weighted prediction error (MWPE) with a cutt off = 25% deviation from standard deviation (SD) between the predicted valproic acid 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 prediction error (PE) had a low grade of bias. The value of mean weighted prediction error (WPE) was 8.20 (CI 95% – 17.4637 – 33.8637; p=0.425) which means that the bias effect of mean weighted prediction error (WPE) had a low grade of bias.

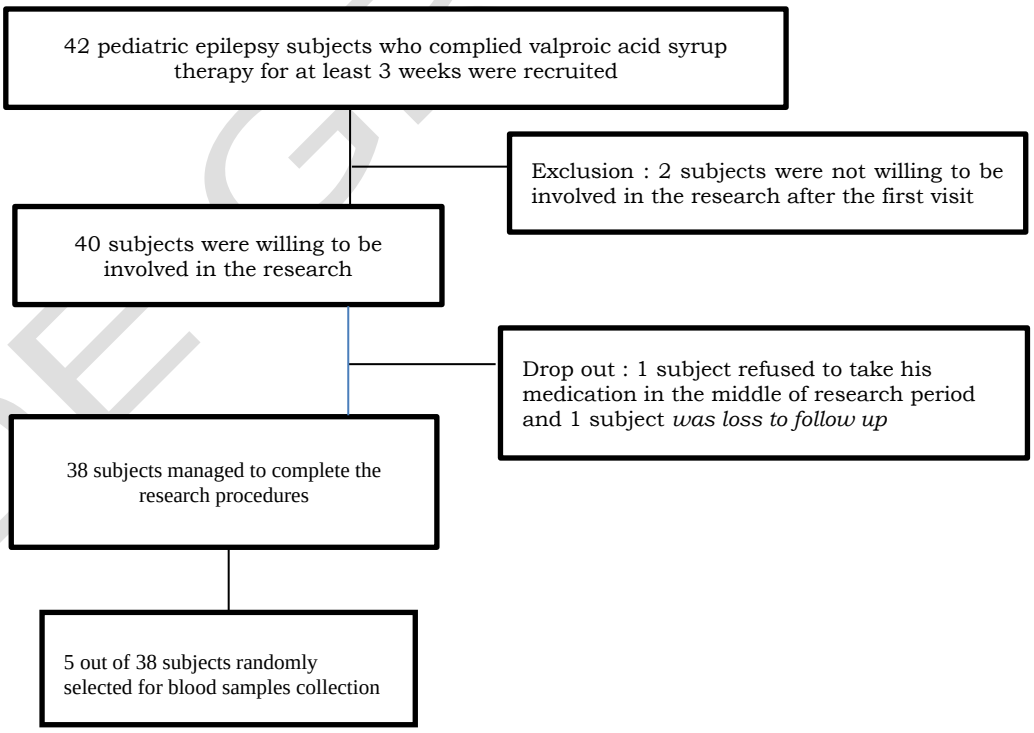

Figure 1. Patient selection process

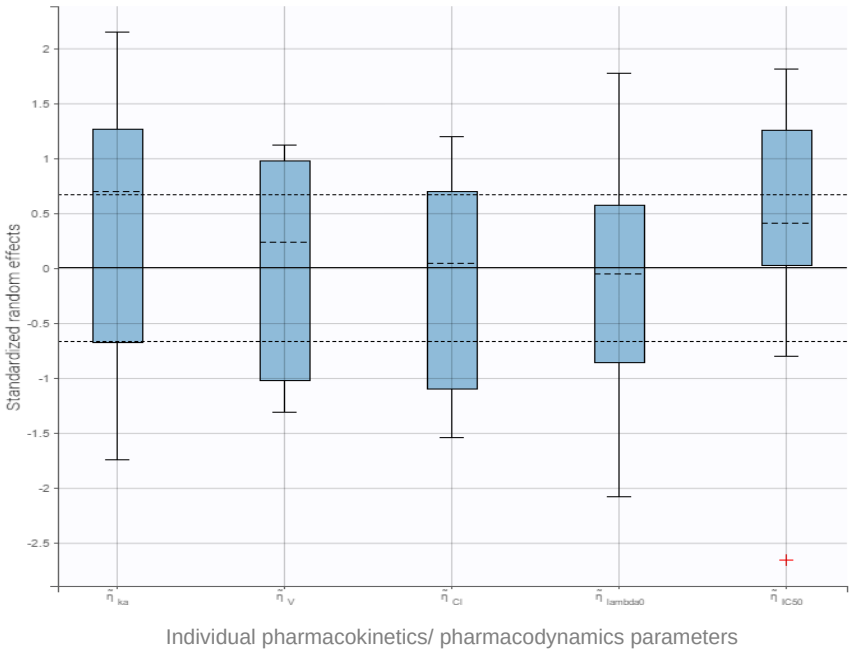

Figure 2. Random effects of pharmacokinetics and pharmacodynamics parameter of valproic acid syrup

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

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. e^{3}	Omega ka_pop	2.32
V_pop	3.78	Omega V_pop	0.30
Cl_pop	3.19. e^{-15}	Omega Cl_pop	1.55
Lambda0	3.94	Omega lambda0	0.32
IC50	7.29. e^{-6}	Omega IC50	6.7
Correlation			
Corr_V_Cl	0.23		

Note :

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
IC50 = 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_IC50 = standard deviation of IC50

Table 3. Population pharmacokinetics – pharmacodynamics parameter based on valproic acid concentration in the blood of 5 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. e^{-11}	Omega Cl_pop	9.68
Lambda0	2.81	Omega lambda0	0.09
IC50	1.85. e^{-6}	Omega IC50	4.46
Correlation			
Corr_V_Cl	0.97		

Note :

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
IC50 = 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_IC50 = standard deviation of IC50
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

Discussion

Pediatric patient is a special care group which needs special attention due to the great variability in their physical conditions. Children grown 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 respons 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 valproic acid 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 were population pharmacokinetics-pharmacodynamics parameters which derived from multi ethnicity of the subjects voluntary participating in this research. The subjects refered 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 valproic acid 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 (Table 2, 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 valproic acid 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 7 times the drug's

half-life (t ½, 6 – 8 hours in pediatric patients receiving valproic acid monotherapy); which was 42-56 hours [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 valproic acid determined in this research means that there there was a greater concentration of valproic acid in the plasma bound to albumin than the unbound valproic acid in the tissue. As a small free fatty acid, valproic acid is largely hydrophobic, imparting efficient entry to the central nervous system with good oral bioavailability Approximatly 90% Valproic acid 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 [16]. Instead, small concentrations of unbound valproic acid in the central nervous system (CNS) tissue which bound to its receptor was adequately inhibit the seizure. This finding was in concert to the relatively small of 50% inhibition concentrtaion (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 valproic acid's volume of distribution with its clearance of 5 subjects randomly selected for determination of serum valproic acid concentration in this research reflected that the smaller concentration of valproic acid in CNS tissue at any particular time would distributed back into the systemic circulation which then underwent elimination from the blood Valproic acid mostly cleared from the body through hepatic metabolism [14].

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 valproic acid steady state concentration derived from Yukawa's clearance equation and its plasma concentration of 5 subjects showed that there was 1 subject who had higher and 1 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 [17]. In fact, the 5 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 prediction error (PE) and mean weighted prediction error (WPE) were at low grade of bias [18]. Mean prediction error between predicted steady state concentration levels of 5 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 [19]. 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 appear to hinder identification of suitable dosing regimens for pediatric patients with epilepsy [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. Valproic acid concentration in this research measured in the blood as a total valproic acid, instead of unbound valproic acid; thus we could not determine the possibility of its level which out of minimum effective concentration (MEC) range. Sub therapeutic concentration would lead to less valproic acid’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 1 subject who still experienced seizures ten times per month at the baseline as well as at the end of this research period would probably due to valproic acid’s sub therapeutic concentration.

Pharmacokinetics and pharmacodynamics parameters based on population data had succescfully 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 asigned blood sampling between the 38 subjects who managed to adhere to valproic acid 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 anlaysis procedures could only measure total valproic acid concentration, instead of unbound valproic acid; thus conducting a therapeutic drug monitoring is cost consuming to be performed in daily practice. Unbound valproic acid is refelcting the amount of valproic acid which can interact with the receptor in order to actively control the seizures. This limitation lead to a less acurate in measuring valproic acid plasma concentration for pharmacokinetics parameters determination. These obstacles should be overcome in the future research.

Conclusions

Developing pharmacokinetics – pharmacodynamics (PK-PD) model of valproic acid 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 valproic acid syrup at steady state condition in Indonesian pediatric epilepsy outpatient due to limitation of the study.

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