JFSP Vol.8, No.1, April 2022, Page: 123-130, pISSN: 2549-9068, eISSN: 2579-4558

Jurnal Farmasi Sains dan Praktis

(JFSP)

http://journal.unimma.ac.id/index.php/pharmacy

THE EVALUATION OF ANTI-EPILEPTIC DRUGS DOSAGE IN MALNOURISHED CHILDREN: CASES IN INDONESIAN COMMUNITY OF EPILEPSY

Nialiana Endah Endriastuti, Masita Wulandari Suryoputri, Dewi Latifatul Ilma

Department of Pharmacy, Faculty of Health Sciences, Jenderal Soedirman University, Purwokerto 53122, Indonesia

nialiana@unsoed.ac.id

https://doi.org/10.31603/pharmacy.v8i1.4662

Article info:

Submitted : 12-02-2021

Revised : 10-03-2021

Accepted : 16-06-2022

Publisher:

Universitas Muhammadiyah Magelang

ABSTRACT

Anti-epileptic drug (AED) has a narrow therapeutic index of drugs that a slight increase in dosage showed toxic effects. The therapeutic response is difficult to predict in malnutrition status because the patient with nutritional deficiency have more complicated problems likes hypoalbuminemia, macronutrient and micronutrients deficiency that affected the levels of AEDs. The nutritional deficiency could be a direct and indirect cause of ineffective AEDs therapy and also recurrent epilepsy. This study aims to describe the use of antiepileptic drugs in Indonesian children with poor nutritional status. The research design was observational studies with cross sectional random sampling to evaluate the AED doses of malnutrition status in children. All information was collected by spreading electronic forms and interviewing the parents by phone. The data were analyzed descriptively. Total of 8 malnourished children mostly included in the range of ages from >2 to 12 years (n=5; 62.50%) with means 3,9±2,7 years. The study showed valproic acid was bigger used in monotherapy (n=5; 62,50%) than polytherapy with carbamazepine or sodium phenytoin and phenobarbital. The means estimation of valproic acid monotherapy concentration in females' group (n=2; 33,33%) showed sub-therapeutics level were C_{ss}^{min} 26,09±0,57 mg/L and C_{ss}^{max} 64,17±1,39 mg/L, also the means in males' group (n=2; 33,33%) of valproic acid monotherapy were C_{ss}^{min} 22.07±2,71 mg/L and C_{ss}^{max} 54.27±6.66 mg/L. All of them included in good clinical outcome of free seizure > 6 months.

Keywords: Anti-epileptic drug; Concentration; Malnutrition

1. INTRODUCTION

Epilepsy in developing countries included Indonesia is one of the most common neurological disorders, especially in children under 5 years of age. Epilepsy is a neurological disorder caused by abnormal brain nerve activity that becomes repeated seizures. The malnourished children with epilepsy are a serious problem that causes management therapy of epilepsy provide no optimal responses. Malnutrition is defined as an imbalance intake of energy resulting in cumulative deficits of macronutrients and micronutrients that impact on delaying of growth, development, and global function. Malnutrition could be affected in the severity of epilepsy and Antiepileptic Drug (AED) became ineffective because of neurons, synapses, and dendritic reductions which resulted in decreasing brain size, thinning cerebral cortex, and slowing brain growth (Dipasquale et al., 2020).

The treatment of epilepsy using anti-epileptic drugs (AEDs) is long-term management that was given after the diagnosis of epilepsy was confirmed. The efficacy and unexpected drug reactions of AEDs depend on individual responses involving the type of seizure, classification of epilepsy, syndrome of epilepsy, adherence, and pharmacokinetics profile of AEDs. Monotherapy

of AEDs is the main option of epilepsy management and the regimen dosage could be increased gradually until reaches the therapeutics levels. Polytherapy which is using a combination of AEDs could be the alternative option if AEDs monotherapy was failed. However, it is difficult to ensure AEDs regimen doses have reached therapeutic levels because of individual variability response and unexpected effects of AEDs. The number of AEDs have a narrow therapeutic index of drugs that a slight increase in dosage showed toxic effects. The therapeutic response would be more difficult to predict in malnutrition status because the patient with nutritional deficiency have more complicated problems likes hypoalbuminemia, macronutrient and micronutrients deficiency that affected the levels of AEDs. The nutritional deficiency could be a direct and indirect cause of ineffective AEDs therapy and also recurrent epilepsy.

The prevalence of Indonesian malnourished children is still above 39% (Medisa & Diesty Anita Nugraheni, 2017). The Indonesian Central Statistics in 2018 showed the highest prevalence of malnutrition in toddlers ages <23 months at Gorontalo Province was 15.20%. Research at the hospital in Surabaya showed the number of 103 (45.63%) new cases of epilepsy in children aged 1-5 years mostly 89.32% of the therapy given was Valproic acid (Andrianti et al., 2016). Role of protein-energy, micronutrient deficiency, immunodeficiency, diet, drug therapy, drug-resistant epilepsy, and socio-cultural burden in developing countries were possible reasons of malnutrition and epilepsy were interrelated (Crepin et al., 2009). The study of 40 patients at an Indian hospital showed an increase in the concentration of the free drug sodium valproate in malnourished children compared to children with good nutritional status (Gampala et al., 2017). The pharmacological therapy using antiepileptic drugs has not been fully effective in overcoming seizures, where most antiepileptic drugs belong to a class of drugs with a narrow therapeutic index so that the therapeutic response is difficult to predict, especially in pediatric patients with poor nutritional status which could affect the effectiveness of therapy. So, this study aims to describe the use of antiepileptic drugs in Indonesian children with malnutrition.

2. METHODS

2.1. Designs

The research design was observational studies with cross sectional random sampling to evaluate the AED doses of malnutrition status in children. The ethical of the research was approved by The Research Ethis Committee of Faculty of Health Sciences Jenderal Soedirman University No: 100/EC/KEPK/V/2020.

2.2. Participants

The respondent is the outpatient children with epilepsy that joined The Indonesian Community of Epilepsy (ICE). The researcher found the access to ICE from social media and they received our permission for research by giving phone numbers to the researchers. All information of the respondents was collected from the parents or someone who had responsibility to the patients. The inclusion criteria of the respondent included outpatient children with epilepsy in ages between 0 and 17 years old, received oral AEDs as therapy for 6 months, accepted to fill the inform consent and assent, also filled the case report forms (sex, birth date, weight, hight, diagnosis, history of illness, medications, and frequency of seizure). The respondent who rejected to follow the inclusion criteria was excluded. The classification of malnutrition is determined from the calculation of weight/ height according to the regulation from the Health Minister of Republic Indonesia number 2 (2020) about Children Anthropometric Standards based on the guidelines from The World Health Organisation (WHO). Anthropometrics standards are used as a method to assess the proportion of the human body. The categories of children nutritional status based on body mass index (BMI) to length or height (weight/length or weight/height) including severe malnutrition (<-3SD), moderate malnutrition (-3 SD to -2SD), good nutrition status (-2SD

to +1SD), possible high risks overweight (+1SD to +2SD), overweight (+2SD to +3SD), and obese (>+3SD).

2.3. Collecting data procedure

The data was collected by spreading electronic form and interviewing by phone. The documents of inform consents and assents was delivered by email and media social massager. The respondents full filled the documents completely then send it back to the researchers. The interview by phone was on schedule and appointments with the parents. All conversations by phone were recorded and noted by following steps: 1). Greeting by say hallo to the parents and their children, 2). Asking permission to make interview by phone, 3) Introduction to follow the research completely, 3) Asking research questions, 4) Listening to the parent answers carefully, 5) Asking permission to take pictures of all AEDs medications from label of medications or the doctor prescription, 6) Confirmation the answers to make sure that the information is all clear, 7) saying thank you for the participations.

2.4. Data analysis

The data was analyzed descriptively. The prediction of AEDs concentrations calculated by the average steady state concentrations (C_{ss}^{ave}), the minimum steady state concentrations (C_{ss}^{min}), and the maximum steady state concentrations (C_{ss}^{max}). The pharmacokinetic estimation of AEDs levels can be calculated based on the literature using the Concentration Steady State (C_{ss}) formula with parameters: bio-availability of oral delivery (F = 1); salt factor (S), volume distribution (Vd), constanta (K), clearance (Cl), dosage (D), interval(t), maximum metabolism rate of sodium phenytoin (Vm), and concentration of sodium phenytoin in a half rate of Vm (Km). The pharmacokinetic parameters of valproic acid used based on the literature are S=1 and F=1. The pharmacokinetic parameters of valproic acid can be used with Vd values of 0.2L/kg and Cl 15 ml/kg/hour for patients in group ages <12 years. When valproic acid is combined with enzyme-inducing AEDs, the Cl value of valproic acid is 25ml/kg/hour. Besides, the valproic acid Vd value of 0.15L/kg and the Cl value of 10ml/kg/hour were used for aged >12 years. Phenobarbital pharmacokinetic parameters were used: S=0.9; F=1; Cl=0.008L/kg/hour; Volume distribution (Vd neonates 0.9 L / kg; Vd pediatric 0.7 / L / kg) were used on this research. Carbamazepine pharmacokinetic parameters were used: S=1; F= 1; Cl=0,10L/kg/hour; Vd=1,4L/kg. Sodium phenytoin pharmacokinetic parameter were used: S=0,92; F=1; Vm 12mg/kg/hour; Km=6mg/L (Methaneethorn, 2018; Winter, 2013).

Clinical outcome was measured by duration of free seizure for 6 months based on interview process with the parents. Good clinical outcome was defined as a patient of free seizure ≥ 6 months, and Poor clinical outcome was defined as a patient of free seizure <6 months.

3. RESULTS AND DISCUSSION

3.1. Characteristic of patients

Total subjects involved 106 patients from the community of epilepsy in Indonesia. Total of 8 patients were collected as inclusion criteria. The respondents who were rejected to interview were excluded. Besides, the respondents were also excluded due to incomplete data filling, good nutritional status, AEDs used less than 6 months, unstable and uncertain dosage regimen for 6 months. The determination of the seizure type was obtained based on the patient's parent memory regarding the doctor's diagnosis or based on the interpretation results of electroencephalography (EEG) examination. The results from 8 patients showed the number of four patients (50%) were unknown type of seizure. This could be due to the patient's parent's knowledge or lost information by the doctor. The results of this study showed that the number of four patients (50%) have generalized seizure types and no one included in focal category. This is similar to research (Suwarba, 2011) which states that the most types of epilepsy were found in general types of epilepsy.

Characteristics of patients showed in **Table 1** mostly included in the range of ages from >2 to 12 years (n=5; 62.50%) with means 3,9±2,7 years. The gender of patients seems to similar amount between male (n=4; 50%) and female (n=4; 50%). The result showed valproic acid was bigger used in monotherapy (n=5; 62.50%) than polytherapy. The polytherapy of valproic acid included in combinations with carbamazepine (CBZ) or sodium phenytoin and phenobarbital. Valproic acid monotherapy is effective initial therapy for generalized and focal epilepsy types (Wijayatri et al., 2013). There was only one patient (12.50%) that were used in phenobarbital monotherapy and none was found in phenobarbital polytherapy. The prevalence of clinical outcomes showed the number of five patients in good outcomes (62.50%) and three patients in poor outcomes (37.50%). The clinical outcomes were described as a good outcome for seizure-free ≥6 months and poor outcome for seizure free <6 months. Regarding of nutritional status, patients in severe malnutrition categories (n=6; 75%) was majority than moderate malnutrition status (n=2; 25%).

Table 1. Characteristics of patients

Characteristics	Patients (N=8)	
	N	%
Ages		
1 month – 24 months	3	37,50
> 2 years – 12 years	5	62,50
Gender		
Male	4	50,00
Female	4	50,00
Type of Epilepsy		
General	4	50,00
Focal	0	0
Unknown	4	50,00
Nutritional status		
Severe malnutrition	6	75,00
Moderate malnutrition	2	25,00
Type of Antiepileptic Drugs		
Monotherapy (n=6)		
VA	5	62,50
PB	1	12,50
Polytherapy (n=2)		
Valproic acid + Carbamazepine	1	12,50
Valproic acid + Sodium Phenytoin + Phenobarbital	1	12,50
Clinical Outcome		
Seizures free		
≥ 6 months	5	62,50
< 6 months	3	37,50

3.2. The Evaluation of AED Dosage in Children

Table 2 shows the results of the calculation of the estimated levels of anti-epileptic drugs in the monotherapy group that consist of 5 patients with valproad acid monotherapy and 1 patient receiving phenobarbital monotherapy. One female patient was found to have a seizure-free duration of <6 months with a Css max value of > 100mg/L. Meanwhile, pediatric patients with seizure-free duration 6 months were obtained as many as 2 male patients (33.33%) and 2 female patients (33.33%) with Css ave and Css min values <50mg/L. In the phenobarbital monotherapy group, there was only 1 male patient with an outcome of seizure-free duration 6 months who's entire Css ave, Cssmin, Css max values were in the therapeutic range of 15-40 mg/L. Clinically, drug levels that are in the therapeutic range are correlated with the therapeutic effect of the drug. With the suitability of drug levels, it is hoped that the drug therapy given will be more optimal. Drugs at levels below the minimum effective concentration (MEC) will not cause a therapeutic effect, while drugs at levels above the maximum toxic concentration (MTC) are at risk of toxicity. In this study, there was 1 patient who showed valproic acid monotherapy levels with Cssmax

>100mg/L but no toxicity (131.65mg/L) was seen because serious toxicity could potentially occur at valproic acid levels more than 450mg/L (Abbasi, 2020). The patients with Cs save and Css min below MEC <50mg/L showed good outcomes with seizure-free duration 6 months.

Table 2. Estimation of AED steady concentration in monotherapy group (n=6)

Gender	n (%)	Outcome	Estimation Value (mean ± SD)		
			C_{ss}^{ave} (mg/L)	C_{ss}^{min} (mg/L)	C_{ss}^{max} (mg/L)
Valproic acid monotherapy Group (n=5)					
Male	0	< 6 months	-	-	-
Female	1 (16,66)		86,81	53,52	131,65
Male	2 (33,33)	≥ 6 months	35,79 ± 4,39	22,07 ± 2,71	54,27 ± 6,66
Female	2 (33,33)		42,32 ± 0,91	26,09 ± 0,57	64,17 ± 1,39
Phenobarbital monotherapy group (n=1)					
Male	0	< 6 months	-	-	-
Female	0		-	-	-
Male	1 (16,66)	≥ 6 months	31,25	29,19	33,48
Female	0		-	-	-

C_{ss}^{ave}, averages of steady state concentrations; C_{ss}^{min}, trough plasma concentration; C_{ss}^{max}, peak plasma concentration

Table 3 shows the results of calculating the estimated levels of antiepileptic drugs in the group of malnourished children receiving combination therapy. There was 1 female patient who received combination therapy of valproic acid and carbamazepine with seizure-free duration < 6 months. This patient showed Cssmin and Css ave values of valproic acid <50mg/L. In addition, Css ave, Cssmin, and Css max in the combined carbamazepine were outside the 4-12mg/L range. The use of valproic acid and carbamazepine polytherapy showed the incidence of drug interactions that affected each antiepileptic drug level so that the drug concentration did not match the therapeutic range. Antiepileptic drug polytherapy was also found in 1 patient using a combination of valproic acid, phenytoin, and penobarbital, 1 male patient with seizure-free duration < 6 months and Css max valproic acid exceeding 100 mg/L. In addition, there were no patients with seizure-free duration 6 months on any combination therapy.

Table 3. Estimation of AED steady concentration in polytherapy group

Gender	n	Outcome		Estimation Value		
				C_{ss}^{ave} (mg/L)	C_{ss}^{min} (mg/L)	C_{ss}^{max} (mg/L)
Combination Group (Valproic acid + Carbamazepine)						
Male	0	< 6 months		-	-	-
Female	1		Valproic acid	46,30	19,93	89,39
			Carbamazepine	19,44	14,47	25,38
Combination Group (Valproic acid + Sodium Phenytoin + Phenobarbital)						
Male	1	< 6 months	Valproic acid	92,59	57,09	140,43
			Sodium phenytoin	4,45	-	-
			Phenobarbital	31,25	29,23	33,52
Female	0			-	-	-

C_{ss}^{ave}, averages of steady state concentrations; C_{ss}^{min}, trough plasma concentration; C_{ss}^{max}, peak plasma concentration

Duration of seizure free became our clinical outcome in this research. Patients with seizure free >6 months were defined as good outcome while seizure free <6 months were defined as poor outcome (Lingga et al., 2013). The research found VA and FB concentration variability could be fluctuated in clinical outcomes. Malnutrition patient with VA monotherapy showed poor outcome with C_{ss}^{max} >100mg/L although C_{ss}^{ave} was appropriate in range of therapeutic. That means AEDs efficacy become ineffective because of toxicity levels. The contrast is patients with good outcome

were found in subtherapeutic levels of VA monotherapy that could be influenced by variability of drug receptor sensitivity, pharmacogenomics, polymorphism, adverse drug reactions, or pharmacokinetics-pharmacodynamics. Previous research found that some patients need VA trough concentrations greater than 50-100mg/L to reduce 50% seizure frequency (Ghodke-Puranik et al., 2013; Methaneethorn, 2018). The free serum drug concentrations and clinical response in malnourished children was uncorrelated same as previous report study (Gampala et al., 2017). Severity of illness, comorbidities, history of illness, adverse drug reaction, adherence, and nutritional status were considered factors of clinical outcomes.

VA is a weak acid with pKa 4,7 and ionized at high pH (Fazeli-Bakhtiyari et al., 2015). VA is almost completely absorbed depend on dosage form (Methaneethorn, 2018). In children with poor nutritional status, there are potential impacts on oral drug absorption likes reducing saliva pH, reducing saliva secretion, reducing saliva enzyme levels, increasing gastric pH, and reducing acid secretion in the stomach. Previous studies explained the unknown impact on gastric emptying that giving consequences for the risk of an increased drug variability in plasma profiles. Malnutrition condition is reducing ability to solubilize poorly soluble drugs that could reduce overall bioavailability (Freerks et al., 2019). Nonionized form of VA was lower than ionized form on malnourished children that giving possible reasons of subtherapeutic range concentrations on VA monotherapy group. VA absorption was lower because non-ionized form was limited even though it soluble easily on the lipophilic membrane barrier, especially blood-brain barrier.

Valproic acid is an inhibitor of the CYP3A4 enzyme which causes a decrease in carbamazepine metabolism thereby increasing the concentration of carbamazepine in the blood. In addition, valproic acid can displace carbamazepine from the protein binding site so that the free fraction of carbamazepine is increased. The levels of Css^{ave}, Css^{min}, Css^{max} carbamazepine also exceeded the MTC limit of 12mg/L which was the result of concurrent use of valproic acid (Winter, 2013). Phenytoin as an inducer of the CYP3A4 enzyme causes a decrease in blood levels of the drug. The effect of using phenytoin, valproic acid, and phenobarbital in combination in patients raises the potential for drug interactions. Phenytoin concentrations may fall below the therapeutic range due to competition for plasma protein binding between valproic acid and phenytoin. Meanwhile, valproic acid is also able to decrease the clearance of phenobarbital which causes the concentration of phenobarbital to increase (Winter, 2013).

The limitations in this study were collecting information only based on interviews on limited subjects even all information obtained just from parents or family perceptions based on doctor's prescriptions. The patient medical reports were unavailable in blood and urine sample tests on this research and real conditions related to drug concentrations were undetected expecially for albumin level to identify the potential for protein binding that affects drug levels in the blood. Adverse drug reactions related to VA concentration in a malnourished child is difficult to assess because of lacking information on liver and renal function.

Malnutrition and epilepsy in children with cerebral palsy becomes significant comorbidities that influence the clinical outcomes (Aydin et al., 2019). Malnutrition is related to nutritional deficiency which causing hypoalbuminemia. VA highly protein-bound (87-95%) leads to a disproportioned increase in free fraction and increased risk for dose-dependent, adverse effects, and toxicity (Ghodke-Puranik et al., 2013). Variability of VA concentrations could be affected by pharmacokinetics and pharmacodynamics factors included polymorphism, gender, ages, protein binding, dosage form, malnutrition, and drug interactions (Marvanova, 2016; Methaneethorn, 2018). The patients with poor nutritional status need to be monitored individually on AEDs use, especially patients who show symptoms of severe drug side effects (Gampala et al., 2017). Even patients who treated with VA and PB were reported the risk of bone disease and micronutrients deficiency (Soltani et al., 2016). Therefore, malnutrition can give an indirect impact on drug toxicity or suboptimal therapeutic effects (Freerks et al., 2019).

4. CONCLUSION

The means estimation of valproic acid monotherapy concentration in females group were C_{ss}^{min} 26.09±0.57 mg/L and C_{ss}^{max} 64.17±1.39 mg/L, also the means in males group of valproic acid monotherapy were C_{ss}^{min} 22.07±2.71 mg/L and C_{ss}^{max} 54.27±6.66 mg/L. Future research must analyse the correlation of malnutrition and AEDs concentrations based on laboratory tests. The real patient conditions can be monitored accurately regarding the adverse drug reactions and clinical outcomes.

5. ACKNOWLEDGMENT

Thank you to Nurhaya Nurdin, S.Kep.Ns.MN.MPH. as founder of Komunitas Epilepsi Indonesia (Indonesian epilepsi Community) that allow in respondent recruitment. We thank to Mia Nurul F, Taqiyahni, and Diah Ayu rohmaningtias for helping in data acquisition. Thank you to Lembaga Penelitian dan Pengabdian Kepada Masyarakat (the Institute of Research and Community Service) Jenderal Soedirman University for funding this research (Grant No: Kept. 122/Un23.18/PT.01.05/2020).

6. CONFLICT OF INTEREST

The author declared that there was no conflict of interest.

7. REFERENCES

Abbasi, A. A. (2020). *Valproate Toxicity Medication*. https://emedicine.medscape.com/article/819315-medication

Andrianti, P. T., Gunawan, P. I., & Hoesin, F. (2016). Profil Epilepsi Anak dan Keberhasilan Pengobatannya di RSUD Dr. Soetomo Tahun 2013. *Sari Pediatri*, *18*(1), 34. https://doi.org/10.14238/sp18.1.2016.34-39

Aydin, K., Kartal, A., & Keles, E. A. (2019). High rates of malnutrition and epilepsy: two common comorbidities in children with cerebral palsy. *Turkish Journal Of Medical Sciences*, *49*(1), 33–37. https://doi.org/10.3906/sag-1803-79

Crepin, S., Godet, B., Chassain, B., Preux, P. M., & Desport, J. C. (2009). Malnutrition and epilepsy: A two-way relationship. *Clinical Nutrition*, *28*(3), 219–225. https://doi.org/10.1016/j.clnu.2009.03.010

Dipasquale, V., Cucinotta, U., & Romano, C. (2020). Acute Malnutrition in Children: Pathophysiology, Clinical Effects and Treatment. *Nutrients*, *12*(8), 2413. https://doi.org/10.3390/nu12082413

Fazeli-Bakhtiyari, R., Panahi-Azar, V., Sorouraddin, M. H., & Jouyban, A. (2015). Determination of valproic acid in human plasma using dispersive liquid-liquid microextraction followed by gas chromatography-flame ionization detection. *Iranian Journal of Basic Medical Sciences*, *18*(10), 979–988. https://doi.org/10.22038/ijbms.2015.5461

Freerks, L., Papadatou Soulou, E., Batchelor, H., & Klein, S. (2019). A review of GI conditions critical to oral drug absorption in malnourished children. *European Journal of Pharmaceutics and Biopharmaceutics*, *137*(September 2018), 9–22. https://doi.org/10.1016/j.ejpb.2019.02.001

Gampala, V. R., Peraboina, S. R., Ajmeera, S., Kalam, S., Adla, N., & Puchchakayala, G. (2017). Evaluation Of Sodium Valproate Levels In Malnourished Childhood Epilepsy and Its Consequences. *Romanian Journal of Neurology*, *XVI*(2), 53–61.

Ghodke-Puranik, Y., Thorn, C. F., Lamba, J. K., Leeder, J. S., Song, W., Birnbaum, A. K., Altman, R. B., & Klein, T. E. (2013). *Valproic acid pathway: pharmacokinetics and pharmacodynamics*. https://doi.org/10.1097/FPC.0b013e32835ea0b2

Lingga, H. N. (2013). *Evaluasi Dosis Asam Valproat Yang Digunakan Pada Pasien Epilepsi Anak Di Rsud Sleman Yogyakarta*. *Disertasi*, Universitas Gadjah Mada.

Marvanova, M. (2016). Pharmacokinetic characteristics of antiepileptic drugs (AEDs). *Mental Health Clinician*, *6*(1), 8–20. https://doi.org/10.9740/mhc.2015.01.008

Medisa, D., & Diesty Anita Nugraheni. (2017). *Jurnal Kedokteran dan Kesehatan Indonesia Ward Mental Disorders*. *2*(3), 146–153.

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

Soltani, D., Ghaffar pour, M., Tafakhori, A., Sarraf, P., & Bitarafan, S. (2016). Nutritional Aspects of Treatment in Epileptic Patients. *Iran J Child Neurol. Summer*, *10*(3), 1–12.

Suwarba, I. G. N. M. (2011). Insidens dan Karakteristik Klinis Epilepsi pada Anak. *Sari Pediatri*, *13*(2), 123. https://doi.org/10.14238/sp13.2.2011.123-8

Wijayatri, R., Ikawati, Z., & Ghofir, A. (2013). Perbandingan Monoterapi dan Politerapi pada Epilepsi Jenis Idiophatic Generalised Tonic Clonic. *Jurnal Manajemen Dan Pelayanan Farmasi*, *3*(2).

Winter, M. (2013). *Basic Clinical Pharmacokinetics* (J. Manurung, J. I. Panggabean, & S. Rachmawati (eds.); 5th ed.). Penerbit Buku Kedokteran EGC.