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RESEARCH ARTICLE

Adverse drug reaction of antiepileptic monotherapy on epileptic paediatric patients in Dr Sardjito Hospital, Yogyakarta, Indonesia

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Abstract

Introduction: Epilepsy is a neurological disease with the highest prevalence in paediatrics. Using anti-epileptic drug as monotherapy is the first-line therapy for paediatrics based on risk-benefit ratio consideration in the patients effectiveness and adverse drug reaction of anti-epileptic monotherapy drug for the cognitive function in paediatric patients. **Objectives**: The aim of the study is to assess effectivity and adverse drug reaction of anti-epileptic monotherapy drug for the cognitive function in paediatric patients. **Methods**: This was a cross sectional study. This study used patients from the Dr. Sardjito hospital's outpatient paediatric unit's Neurology division from May to July 2013 and May to June 2019 to select the subjects. Patient questionnaires and medical records provided the data that was used. Effectiveness was assessed by seizure severity with Hague Seizure Severity Scale (HASSS) questionnaire and seizure frequency, while adverse drug reactions in cognitive function were assessed by the PESQ (Pediatric Epilepsy Side Effect Questionnaire) instrument. **Results**: In total, 29 patients received monotherapy, with 26 patients (89.66%) receiving valproate, two (6.89%) receiving phenytoin, and one (3.45%) receiving phenobarbital. A total 89.66% of patients did not have severe seizures, but 6.90% had moderate seizures. The cognitive function of epileptic patients with co-morbidities receiving valproate monotherapy had moderate (27.59%) and severe (20.69%) side effects. The adverse drug reaction experienced in epileptic patients without co-morbidities using valproate was with the cognitive function, with 6.89% of patients experiencing severe effects, 13.79% moderate and 20.69% mild effects. **Conclusion**: While anti-epileptic monotherapy can control seizures in children, the commonly prescribed valproate can impair cognitive function, especially in those with co-morbidities.

Introduction

Epilepsy is one of the chronic disorders in the brain that affects all ages, including in the paediatric population. This disorder is the most common one globally, and approximately 50 million people in the world suffer from epilepsy (WHO, 2018). The clinical manifestations include seizures, change of behaviour, and loss of consciousness. Besides, epilepsy is a relapsing disease; therefore, it needs therapeutic management in the long term to control seizure recurrence. Although the antiepileptic drug can be prescribed in both single drug (monotherapy) and combined drug (polytherapy), using a single drug is more recommended in epilepsy treatment with consideration of its risk-benefit ratio in patients mainly for paediatrics. The principal therapy is to be able to control the seizure recurrence and minimize adverse drug reactions. One of the adverse drug reactions which most commonly happen in paediatric patients is cognitive function impairment in a long time of therapy (Wells, 2019). Cognition is a term referred to the mental ability that is involved in getting knowledge and understanding. This process includes thinking, knowing, recalling, evaluating, and solving a problem (Cherry, 2019). There are several factors that influence cognition function in epileptic patients, including the onset of the disorder, type of seizure, underlying aetiology, family history, the accuracy of therapy, and the presence of status epilepticus history. The cognition function disorder results in impairments in recalling ability, concentration

power, attention, visual memory, and others. This condition can cause a decreasing quality of life in paediatrics as a result of delaying the children's growth (Putra, 2015). Besides, cognitive function disorder can appear as a result of adverse drug reactions in paediatric patients. There are many studies that found the correlation between antiepileptic drugs and cognitive function disorder (Aldenkamp & Bodde, 2005; Eddy *et al*., 2011). Based on the above reasoning, a study of a single antiepileptic drug in paediatric patients is needed to assess the effectivity and adverse drug reaction in the patient's cognition function. This study can be used for monitoring a single antiepileptic drug in long-term use in paediatrics

Methods

Design of study

This was a cross-sectional study. The subjects were taken randomly from patients in the outpatient paediatric unit, neurology division, Dr Sardjito Hospital, Yogyakarta, Indonesia, from May to July 2013 and from May to June 2019. Data were taken from the completed Haque Seizure Severity Scale (HASS) questionnaire and PESQ (Pediatric Epilepsy Side Effect Questionnaire) and from observing medical records. HASS and PESQ are two outcome measures guidelines for childhood epilepsy; scales have been designed for completion by parents and have been established to be applied internationally (Carpay *et al*., 2005).

The HASS questionnaire was used to assess the effectiveness of the drug by measuring the severity of the seizure and counting the number or frequency of seizures. The HASS is a questionnaire developed by Carpay and Arts to measure the severity of seizure in the last one month according to the parents' parents, which HASS score is 13 (no severe seizure) – 54 (severe seizure) (Carpay & Arts, 1996). The HASS is a valid and reliable measure of parent-perceived seizure severity that can be useful as an outcome measure in childhood epilepsy.

The PESQ was used to assess adverse drug reactions by evaluating cognitive function. The PESQ questionnaire used in this study was PESQ version 1.2 (Morita, Glauser, and Modi-Cincinnati Children's Hospital Medical Centre). The instrument is a questionnaire based on the self-report/parent report method used in measuring the severity of adverse drug reactions in epilepsy patients. It contains 19 questions grouped into six questions for measuring cognition change, four questions for assessing motoric change, three questions for measuring behaviour change, four questions for measuring neurologic change, and two questions for evaluating body weight change. The researchers instructed the patients' families to fill all of the questionnaires in PESQ, although the authors only used questions related to the cognition function of the patient. HASS and PESQ are two outcome measures guidelines for childhood epilepsy; scales have been designed for completion by parents and have been established to be applied internationally (Carpay *et al*., 2005).

Inclusion criteria

The patient inclusion criteria were patients who had been diagnosed as epilepsy outpatients between the ages of four to eighteen years old with completely and clearly written medical records, patients who were treated regularly starting from May to July 2013 and from May to June 2019 with regular prescriptions of a single antiepileptic drug at least three months before, and patients whose families had agreed and signed the informed consent forms.

Data analysis

The data were analysed descriptively based on the patient's characteristics, patterns of medication, the number or frequency of seizure, and severity of seizure, as well as the appearance of adverse drug reaction in cognitive function impairment. HASS scale is divided into three groups, including scale scores of 13–26 (mild seizure), 27–40 (moderate seizure), and 41–54 (severe seizure). PESQ scale is divided into three groups: 1-20 (mild side effects), 21-60 (moderate side effects), and 61-100 (severe side effects).

Results

The characteristics of patients

Table I showed the characteristics of patients in this study. The number of patients collected during the study was 29 patients in accordance with the inclusion criteria within the study period. The study explored that there were more female patients (59.17%) than male patients (40.83%). The majority of patients in this study were in the children group (4-11 years old).

According to Table I, the study divided the length of therapy into two groups, including ≤ 1 year (34.48%) and >1 year (65.52%). The study showed that there were two types of seizure: 1) General seizure including tonic-clonic (62.07%) and myoclonic seizures (6.90%); and 2) Focal with/without secondary generalisation (31.03%). There were 51.72% of patients without comorbidities, and the most common comorbidity was intellectual disability (ID).

The study divided the length of therapy into two groups, including ≤ 1 year (22.72%) and > 1 year (77.27%). The study showed that there were two types of seizure: general seizure including tonic-clonic and myoclonic seizures (77.27%) and focal with/without secondary generalisation (22.73%). There were 59.09% of patients without comorbidities, and the most common comorbidity was ID (Intellectual Disability).

Table I: The characteristics of patients based on gender, age, onset of seizure, length of therapy, type of seizure, and comorbidities

Variable	Number of patients	Percentage (%)
Gender		
Female	16	55.17
Male	13	44.83
Age (years old)		
0-3	4	13.79
4-11	13	44.83
12-18	12	41.38
Onset of seizure		
28 days–23 months	6	20.69
2–11 years	22	75.86
≥ 12 years	1	3.45
Length of therapy		
≤ 1 year	10.5	34.48
> 1 year	19.17	65.52
Type of seizure		
General tonic-clonic	18	62.07
Myoclonic	2	6.90
Focal with/without secondary generalisations	9	31.03
Comorbidities		
Without comorbidities	15	51.72
With comorbidities	14	48.28
Type of comorbidities		
ALL	2	6.89
ID	3	10.37
NFB	1	3.45
ASD	2	6.89
HCP	2	6.89
NS	2	6.89
HT Stage II	1	3.45
ANS	1	3.45
Total	**29**	**100**

Note: ALL: Acute Lymphoblastic Leukemia; ID: Intellectual Disability, NFB: Neurofibromatosis; ASD: Autism Syndrome Disorder; HCP: Hydrocephalus; NS: Nephrotic Syndrome; HT: Hypertension; AGNS: Acute Glomerulonephritis post Streptococcus

The pattern of anti-epileptic monotherapy drug

The pattern of antiepileptic monotherapy can be seen in Table II. There were three types of single antiepileptic drugs involving valproate, phenytoin, and phenobarbital. The most commonly prescribed in the study was valproate (89.66%).

Table II: The pattern of anti-epileptic monotherapy

Type of drug	Number of patients	Percentage (%)
Valproate	26	89.67
Phenytoin	2	6.90
Phenobarbital	1	3.44
Total	**29**	**100**

The seizure frequency and severity of seizure

The number or frequency of seizure and severity of seizure can be seen in Table III. The study showed that among 29 patients, the ones with a free seizure condition were 24 patients (82.76%) and the rest of the patients with several numbers of seizures in the last three months. According to Table III, the study found that 89.66% of the patients did not suffer from severe seizure, but 6.90% of the patients had a moderate seizure. 91.67% of the patients did not suffer from severe seizure, but 38.33% of the patients had a moderate seizure.

Table III: The number and severity of seizures

Variable	Number of patients	Percentage (%)
Number of seizure		
0	24	82.76
1-5	4	13.79
6-10	1	3.45
Score scales (Severity of seizure)		
13-26 (not severe)	26	89.66
27-40 (moderate)	3	6.90
Total	**29**	**100**

Adverse drug reaction in cognitive function

The pattern of adverse drug reaction in cognitive function from 29 patients can be seen in Table IV. The study shows that valproate, the most commonly prescribed drug, has moderate (27.59%) and severe (20.69%) adverse effects. The varying results of adverse drug reaction in the cognitive function in epilepsy without comorbidities were valproate, with 27.59% of patients experiencing severe effects, 41.40% of patients experiencing moderate effects, and 20.69% of patients experiencing mild effects. Antiepileptic monotherapy in patients with comorbidities has lower adverse drug reactions in cognitive function than in patients without comorbidities. This result is shown in Table IV; there was still severe and moderate side effects in patients with comorbidities. On the other hand, in the case of those without comorbidities, the majority of patients had mild and moderate side effects in cognitive function.

Table IV: Patterns of anti-epileptic monotherapy, comorbidities, and severity of adverse effect on cognitive function

Variable	Comorbidities	Severity of adverse effect in cognitive function	Number of patients (%)
Type of drug			
Valproate	HCP, ID	Moderate	5(17.24)
	ASD, ID	Severe	5 (17.24)
	ID	Moderate	3(10.34)
	NFB	Severe	1(3.45)
	With comorbidities	Moderate	8 (27.59)
		Severe	6 (20.69)
	Total comorbidities		**14 (48.28)**
	Without comorbidities	Mild	6(20.69)
		Moderate	4 (13.79)
		Severe	2 (6.89)
	Total without comorbidities		**12 (41.37)**
	Comorbidities + without Comorbidities	Mild	6(20.69)
		Moderate	12(41.40)
		Severe	8 (27.59)
Total valproate			**26 (89.66)**
Phenobarbital	**Without Comorbidities**	Mild	1(3.45)
		Moderate	1 (3.45)
Phenytoin	**Without Comorbidities**	mild	1 (3.45)
Total phenobarbital + phenytoin			**3(10.35)**
Total prescription			**29(100.00)**

Note: HCP: Hydrocephalus; ASD: Autism Syndrome Disorder; ID: Intellectual Disability; NFB: Neurofibromatosis

Discussion

The characteristics of patients based on gender and age

This result was similar to the result of a study by Allain, which stated that the prevalence of female patients with epilepsy was 59.17% (Allain *et al*., 2006). Sabaz and authors (2001) also found that the number of female patients was higher than male patients in an Australian hospital. Based on age, this was similar to the study by Pinzon (2006), which found that the incidence of epilepsy was dominated by the children group. The onset of seizure was also divided according to European Medicine Agency in ICH Guideline E11

(2001) so that there were three groups including 28 days–23 months (infants), 2–11 years old (children), and 12–18 years old (teenagers) (EMA, 2001). The highest prevalence in the onset of seizure was the children group (75.86%), and the lowest prevalence was the teenager group (3.45%). The unknown onset of the seizure, the longer scale between the onset of a seizure and the second seizure, the lower parent knowledge about the disorder, and social factors, as well as economic states, might contribute to epilepsy incidence in paediatrics in Indonesia.

The characteristics of patients based on the length of therapy, type of seizure and comorbidities

Another characteristic of the patient was the length of therapy, which is a bad prognoses predictor in epileptic patients. The result was similar to NICE (The National Institute for Health and Care Excellence) guideline 2014 stating that antiepileptic drug was prescribed when the patient suffered a second seizure so that the highest in the length of therapy was the more than one year group (NICE, 2012). Based on comorbidities, there were two groups in the study (with comorbidities and without comorbidities). Among all comorbidities, there were disorders related to epilepsy, the risk factors of epilepsy, and the complications of epilepsy.

The pattern of anti-epileptic monotherapy drug

This study was similar to a study by Malerba and authors (2010), which found that valproate was the most common prescription in epileptic paediatric patients.

The seizure frequency and severity of seizure

Seizure frequency is one of the factors that are mostly related to a patient's quality of life. Besides, the length of disorder, polytherapy, adverse drug reaction, epilepsy stigma, and incompliance affects a patient's quality of life significantly (Virag *et al*., 2012). Comorbidities can influence the severity of the seizure, and certain comorbidities can be related to adverse drug reactions in cognition function. Evaluating the effectiveness of therapy in epilepsy does not only need to decrease the frequency of seizures but also decrease the severity of seizures (Carpay & Arts, 1996).

Adverse drug reaction in cognitive function

All commonly used antiepileptic drugs have some effects on cognitive function, and the effect may be substantial when crucial functions are involved, such as learning in children. (Veenendaal *et al*., 2017). The old antiepileptic drugs, which include valproate, phenytoin, phenobarbital, and carbamazepine, may have more influence on cognitive functions, but this aspect has not been systematically studied. Meanwhile, the new agent, including oxcarbazepine, vigabatrin, lamotrigine, zonisamide, gabapentin, tiagabine, topiramate, and levetiracetam, may have less influence on cognitive function (Brunbech & Sabers, 2012). According to the study, valproate exerts little detrimental impact on cognitive function (Eddy *et al*., 2011); meanwhile, phenobarbital, which has a high risk for serious cognitive effects, affects attention and memory function. The drug may affect mental speed, mainly in higher dosage and polytherapy (Veenendaal *et al*., 2017). This agent is considered to have worse cognitive effects than valproate or carbamazepine (Eddy *et al*., 2011).

A number of cognitive and psychomotor effects have been linked to carbamazepine. Certain individuals may be more vulnerable to the adverse drug reaction in cognitive function associated with a particular antiepileptic drug. These include refractory cases, patients with different kinds of epilepsy, and younger or older patients (Veenendaal *et al*., 2017). According to Bayu and authors (2019), comorbidity with neuro-developmental disorder significantly affects cognitive impairment in children with epilepsy. There were many factors contributing to effects in cognitive function in epileptic paediatric patients, including antiepileptic agent, the disorder itself, complications or seizure severity, and comorbidities. Further studies are needed with a larger number of samples utilising a better design to determine the association of adverse drug reaction with cognitive impairment in epileptic patients. It is needed to explore the patients' characteristics clearly to compel further investigation in more focused and rigorous experimental designs.

Conclusion

Antiepileptic monotherapy is effective for controlling seizures in paediatrics, but using valproate, which is commonly prescribed, can affect cognitive function mainly in patients with comorbidities.

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