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Correlation between Level of Serum Transaminases and Duration of Antiepileptic Drugs in Epilepsy Children in Sanglah Hospital

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Abstract

BACKGROUND: Some antiepileptic drugs (AEDs), particularly sodium valproate, phenytoin, phenobarbital, and carbamazepine induce and increase production of hepatic enzymes. The adverse metabolic effects of AEDs treatments have become main concern, however data about evaluation of serum transaminases and duration of AEDs in Indonesia still limited.

AIM: The aim of the study was to investigate correlation of AEDs and serum transaminases in children with epilepsy.

METHODS: This cross-sectional research was conducted in pediatric neurology outpatient clinic in Sanglah Hospital. The target was children with epilepsy who had taken AEDs for at least 6 months. Data were collected from January 2020 to the number of samples were achieved. The exclusion criteria were concomitant liver disease, taking drugs which induce elevated serum transaminase or alcohol abuse. Data including age, gender, nutritional status, type, and duration of AEDs were obtained from medical record. Correlation was analyzed by Pearson's or Spearman's correlation, $p < 0.05$ was considered significant.

RESULTS: Total 148 epileptic children enrolled in this study. Aspartate transaminase (AST) and alanine aminotransferase (ALT) level were highest in the group receiving combination therapy (34.37 ± 24.9 U/L and 35.96 ± 23.3 U/L). There was a significant negative correlation between duration of carbamazepine and AST ($r = –0.723$, $p = 0.0001$) and ALT ($r = –0.457$, $p = 0.009$), as well as duration of valproic acid with AST and ALT ($r = –0.689$ and $–0.677$, $p = 0.0001$). Duration of phenobarbital administration was positively correlated with AST and ALT ($r = 0.546$ and 0.425, $p = 0.0001$). Combination therapy also had positive correlation with AST and ALT ($r = 0.815$ and 0.781, $p = 0.0001$, respectively).

CONCLUSION: Duration administration of carbamazepine and valproic acid had negative correlation with AST and ALT; however, phenobarbital and combination therapy were positively correlated with AST and ALT.

Introduction

Epilepsy is the most frequent chronic neurologic condition in children. Studies showed epilepsy as the most common encountered conditions in pediatric neurology especially in developing countries [1]. It can be defined by any of the following conditions: minimal two unprovoked seizures occurs >24 h apart, one unprovoked seizure and a probability of further seizure similar to general seizure recurrence risk (at least 60%) after two unprovoked seizures, occurs over the next 10 years and diagnosis of epilepsy syndrome [1], [2].

The incidence of epilepsy is still quite high. The incidence of epilepsy is estimated to be more prevalent in developing countries than industrialized countries [1]. Approximately 1 out of 150 children is diagnosed with epilepsy during the first 10 years of life, with the highest incidence rate was observed during infancy. The incidence rate of epilepsy was 144/100,000 person-years in the 1st year of life and 58/100,000 for ages 1–10 years [1]. Moreover, the prevalence of epilepsy in childhood and adolescence (children <18 years) in Upper Egypt was 9.7/1000, with the higher prevalence among children <12 years (10.8/1000) than adolescents (7.2/1000). The age-specific prevalence was the highest in early childhood (12.01/1000) and less in adolescence (7.2/1000) [1], [2]. In Indonesia, the number of epilepsy at least 700,000–1,400,000 cases with an increase of 70,000 new cases yearly and 40–50% occurs in children [3]. In 2010, Suwarba found the incidence of children with epilepsy in Denpasar was 5.3%. Most of them were male (56.9%), aged 1–5 years old (42%) and the onset age was <1 year (46%) [4].

About 70–80% of epilepsy patients may have their seizures controlled with optimal anticonvulsant [5]. All anticonvulsant medications are associated with adverse effects which may significantly impact quality of life and contribute to non-compliance and in rare circumstances, can be potentially life threatening [5], [6]. Some anticonvulsants, particularly sodium valproate, phenytoin, phenobarbital, and carbamazepine induce and increase the production of hepatic enzymes. It increases the metabolism of some co-administered drugs. Since liver is primary organ for drug metabolism and elimination for many antiepileptic drugs (AEDs)

thus, drug-induced toxicity may occurs. Hepatotoxic reactions, ranged from mild and transient elevations of hepatic enzymes to fatal hepatic failure [6], [7].

Hepatotoxicity is defined as damage of liver caused by drugs or chemicals. There are many chemical substances capable to damage liver with several mechanisms. These substances are called hepatotoxins, it generate free radicals, damage liver cells and causing many liver diseases [8]. There are varieties of hepatotoxic reactions, from mild and transient elevations of hepatic enzymes to fatal hepatic failure [7], [8], [9]. Elevation of serum transaminase can serve as markers of hepatocellular injury, for example, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) which is known as transaminitis. It has been found that, carbamazepine, phenytoin, phenobarbital and sodium valproate are associated with mild elevation of AST and ALT, which may occur in up to 50% of patients. Although this elevation is usually transitory or dose-related, it does not associated with hepatocellular injury, the AST and ALT can serve as biological markers of hepatocellular injury. When compared with other hepatotoxic drugs, the hepatotoxicity induced by AEDs can lead to death or acute liver failure which could imperatively requires liver transplantation [9], [10]. The hepatotoxicity induced by AEDs induced either by production of reactive metabolite/s toxic or induction of immunoallergic reactions. Carbamazepine, phenytoin and sodium valproate are associated with mild elevations of serum transaminase, which may occur in up to 50% of patients [11], [12].

ALT is intracellular enzyme found predominantly in liver, while AST is found in liver, heart, skeletal muscle, kidneys, brain, and erythrocytes. In asymptomatic patients, the most frequent causes of elevated transaminases were drug induced liver injury. Elevation can be secondary to enzyme induction, without hepatic pathology.

Lipophilic AEDs require conversion into hydrophilic/water-soluble state for renal excretion. This process comprises phase-I and -II reactions. Phase-I reactions include oxidation, reduction and hydroxylation, whereas phase-II reaction imply conjugation. Glucoronidation is a common phase-II reaction, leading to active and inactive metabolites [11], [12], [13].

Liver disease affects the metabolism of AEDs in several ways with different underlying etiologies. Drug metabolism depends on hepatic blood flow, albumin binding, the degree of drug uptake by hepatocyte, the functional integrity of hepatocytes and finally the patency of hepatobiliary system. A functional compromise at any level can potentially impair biotransformation, accumulate basic compounds or interrupt generation of active metabolites [12], [13].

Recently the adverse effects of AED treatments in metabolic process has been concerned, the objectives of the present study is to investigate the pattern and the clinical effects of these drugs on serum transaminases of young children admitted to Outpatient Department of Child Neurology, Sanglah Hospital Denpasar, Bali. This study aimed to determine the correlation between serum transaminase and duration of AEDs administration in children with epilepsy after receiving AEDs for at least 6 months.

Materials and Methods

This cross-sectional study was conducted in Sanglah hospital, Denpasar targeting children with epilepsy who had been recorded in Neurology outpatient clinic, Sanglah Hospital start from January 2020 until the number of sample required were achieved. Inclusion criterion was children aged 1–18 years old with diagnosis epilepsy and receive any of the following AED (carbamazepine, sodium valproate, phenytoin, phenobarbital, and combination) at least 6 months. The exclusion criteria were children with epilepsy and concomitant liver disease whom were taking other drugs causing elevation of serum transaminase such as antibiotics, anti-rheumatic drugs, statins, and nonsteroidal anti-inflammatory drugs.

The sample size was calculated by formula for identifying correlation between two variables. The sample size was determined by r coefficient data from previous study [12].

Nutritional status was determined by dividing actual body weight with ideal body weight according to height then was classified into well-nourished (>90%) and malnutrition (<90%). Types of medicines were divided into five groups as follows, Carbamazepine as Group 1, Valproic acid as Group 2, phenytoin as Group 3, phenobarbital as Group 4, and combination therapy (multiple drugs) as Group 5 such as valproic acid with phenobarbital or phenytoin.

Elevated serum transaminase was defined as elevation of liver enzyme (AST and ALT) level from the baseline. It was grouped into two categories, normal and abnormal. This study collected data from medical records of patients in pediatric neurology outpatient clinic in Sanglah Hospital, Denpasar. The children who met inclusion were recruited into study. The age, gender, nutritional status, type, and duration of AEDs data were obtained from medical record. Liver enzyme value was taken from electronic medical record in Sanglah Hospital.

The collected data were analyzed by using computer program descriptive analysis to describe the sample's characteristics. Continuous data were presented in mean and deviation standard if distributed normally, or median and range if was not

distributed normally. Categorical data were presented in percentage. Analysis bivariate was conducted to evaluate correlation between the duration of antiepileptic treatment and age with serum transaminases level. As well as the association between gender and nutritional status with serum transaminases level. $p < 0.05$ was considered statistically significant. This study had been approved by Research Ethics Committee at Medical Faculty Udayana University/Sanglah Hospital, Denpasar number 983/UN14.2.2.VII.14/LT/2021.

Results

There were 148 patients included in this study, 32 patients in both Group 1 dan 2, 31 patients in Group 3, 26 patients in Group 4, and 27 patients in Group 5. Table 1 showed characteristic of patients in which the median age was dominant in Group 3 and 4 compared to the rest. Overall the number of female and male patients was equal between each group. Nineteen male patients and 13 female in the first group, 15 male versus 17 female in the second group, 17 male versus 14 female in the third group, 16 male versus 10 female in the fourth group, and 11 male versus 16 female in the fifth group. Moreover most of them were well-nourished. AST level was the highest in group of combination therapy 34.37 ± 24.9 U/L, followed by fourth group with 31.54 ± 25.6 U/L, second group with 31.9 ± 24.0 U/L, first group with 24.84 ± 19.7 U/L, and third group with 21.51 ± 9.5 U/L. ALT level was also found to be highest in the fifth group with 39.59 ± 27.3 U/L. While, the AST level for group 1, 2, 3, and 4 was 29.37 ± 17.38 U/L, 35.43 ± 24.4 U/L, 25.58 ± 8.5 U/L, and 35.96 ± 23.3 U/L, respectively.

The values of serum transaminases in epileptic patients among five study groups are shown in Table 2. There was elevation in AST level in each group, in which the fifth group has the highest number of patients with elevated AST level 25.9% compared to other. ALT level was found increased in all groups but most dominant in the fifth group 29.6% compared to others.

The correlation between duration of drug administration and serum transaminases showed in Table 3 and Figures 1-3. In group 1, there was statistically significant negative correlation between duration in administration of carbamazepine and AST (r coefficient = –0.723, p = 0.0001) as shown in Figure 1. Significant correlation was also found between duration in administration of carbamazepine and ALT even though the correlation was weak (r coefficient = –0.457, p = 0.009).

Table 2: Categories level of serum transaminases among study groups

Groups	Serum Transaminases			
	AST, n (%)		ALT, n (%)	
	Normal	Abnormal	Normal	Abnormal
Group 1 (n = 32)	29 (90.6)	3 (9.3)	26 (81,6)	6 (18.7)
Group 2 (n = 32)	27 (84.3)	5 (15.6)	27 (84.3)	5 (15.6)
Group 3 (n = 31)	28 (90.3)	2 (6.5)	26 (83.8)	2 (6.5)
Group 4 (n = 26)	20 (76.9)	6 (23.1)	19 (73.0)	7 (26.9)
Group 5 (n = 27)	20 (74.1)	7 (25.9)	19 (70.3)	8 (29.6)

AST: Aspartate aminotransferase, ALT: Alanine aminotransferase.

Table 3: Correlation between the duration of drug administration and serum transaminases level

Duration of drug administration in months	Serum transaminase			
	AST		ALT	
	r	p	r	p
Group 1 (n = 32)	–0.723	0.0001	–0.457	0.009
Group 2 (n = 32)	–0.689	0.0001	–0.677	0.0001
Group 3 (n = 31)	–0.184	0.322	–0.313	0.087
Group 4 (n = 26)	0.546	0.004	0.425	0.030
Group 5 (n = 27)	0.815	0.0001	0.781	0.0001

r = Pearson's correlation coefficient, P < 0.05 is considered significant, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase.

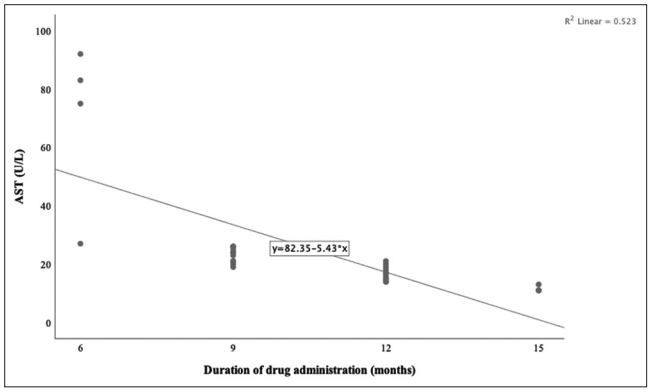

Figure 1: Correlation between the duration of carbamazepine administration in months and aspartate transaminase in Group 1

In the second group, significant correlation was found between duration in administration of sodium valproate and serum transaminases as shown in Table 3 and Figures 2-3. Negative correlations was found with correlation coefficient (r) = –0.689 and –0.677,

Table 1: Characteristic of samples

Characteristic	Group 1 (n = 32)	Group 2 (n = 32)	Group 3 (n = 31)	Group 4 (n = 26)	Group 5 (n = 27)
Age, median (range), years	3.5 (1–17)	2.5 (1–16)	4 (1–17)	3.5 (1–17)	4 (1–16)
Gender					
Male, n (%)	19 (59.4)	15 (46.9)	17 (54.8)	16 (61.5)	11 (40.7)
Female, n (%)	13 (40.6)	17 (53.1)	14 (45.2)	10 (38.5)	16 (59.3)
AST, mean ± SD (U/L)	24.84 ± 19.7	31.9 ± 24.0	21.38 ± 9.5	31.54 ± 25.6	34.37 ± 24.9
ALT, mean ± SD (U/L)	29.37 ± 17.38	35.43 ± 24.4	25.58 ± 8.5	35.96 ± 23.3	39.59 ± 27.3
Duration					
6–9 months, n (%)	11 (34.4)	16 (50.0)	12 (25.8)	4 (15.3)	8 (29.6)
9–12 months, n (%)	15 (46.8)	9 (28.1)	12 (25.8)	12 (46.1)	12 (44.4)
12–15 months, n (%)	6 (18.7)	7 (21,8)	7 (19.4)	10 (38.4)	6 (22.2)
Nutritional Status					
Well-nourished, n (%)	27 (84.3)	29 (90.6)	29 (93.5)	23 (88.4)	25 (92.5)
Malnutrition, n (%)	5 (15.7)	3 (9.4)	2 (6.5)	3 (11.6)	2 (7.5)

AST: Aspartate aminotransferase, ALT: Alanine aminotransferase.

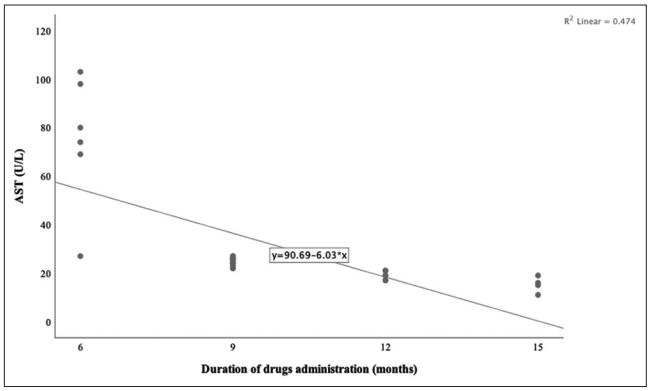

Figure 2: Correlation between the duration of sodium valproate administration

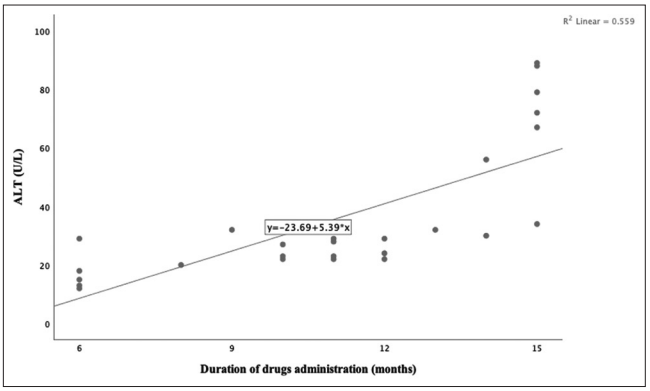

Figure 5: Correlation between the duration of phenobarbital administration in months and alanine aminotransferase in Group 4

respectively. Significant positive correlation was found in the fourth group between duration in administration of phenobarbital and combination as shown in Table 3 and Figures 4 and 5. A weak positive correlation was found in phenobarbital with correlation coefficient (r) = 0.546 and 0.425, respectively.

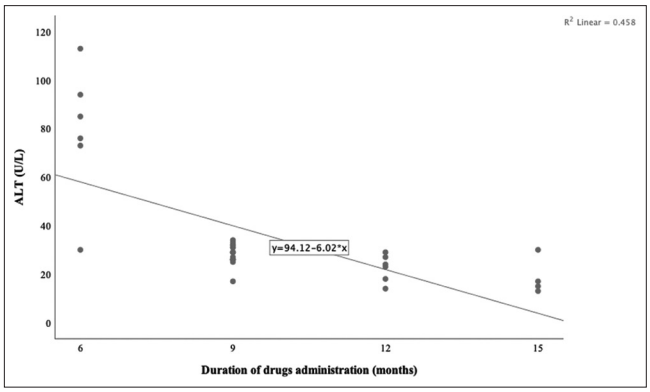

Figure 3: Correlation between the duration of sodium valproate administration in months and alanine aminotransferase in Group 2

Table 3 showed correlation between duration in administration of multiple AEDs and elevated serum transaminases level in Group 5. A strong positive correlation was found with correlation coefficient (r) = 0.815 and 0.781, respectively, as shown in Figures 6 and 7. There was no significant correlation between duration in administration and elevated serum transaminases level in the third group that used phenytoin. The correlations were all negative with correlation coefficient (r) = –0.184 and –0.313, respectively.

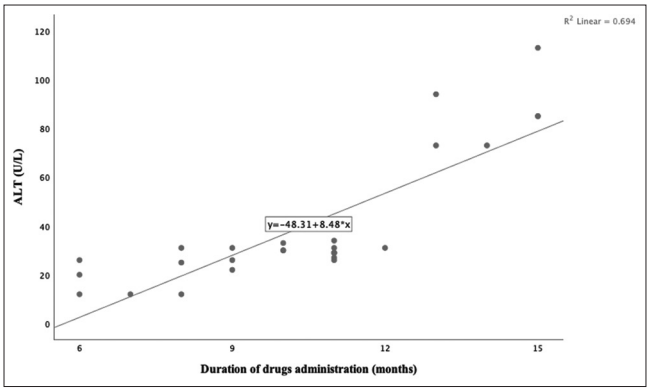

Figure 6: Correlation between the duration of multiple antiepileptic drug administration in months and alanine aminotransferase in Group 5

Table 4 presented the correlation between age and serum transaminases, in which none was significantly correlated. Gender as well as nutrition status, was found have no significant relation to elevated serum transaminases level in all group categories as presented in Tables 5 and 6, respectively.

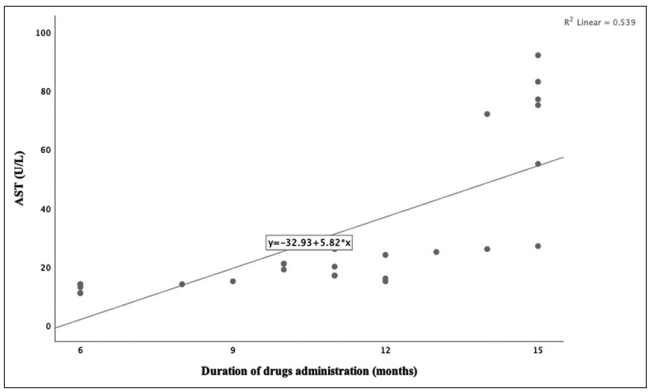

Figure 4: Correlation between the duration of phenobarbital administration in months and aspartate transaminase in Group 4

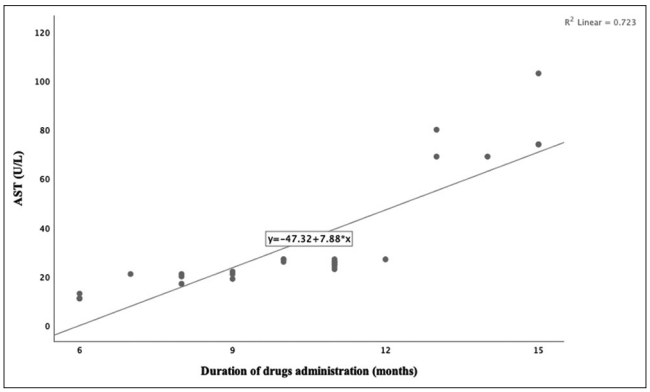

Figure 7: Correlation between the duration of multiple antiepileptic drug administration in months and aspartate transaminase in group

Discussion

The study was conducted in 148 epileptic patients; 32 patients were using carbamazepine, 32 patients were using sodium valproate, 31 patients were using phenytoin, 26 patients were on phenobarbital, and 27 patients were using multiple AEDs.

Table 4: Correlation between age and serum transaminases level

Age in years	Serum Transaminase			
	AST		ALT	
	r	p	r	p
Group 1 (n = 32)	0.141	0.441	0.062	0.736
Group 2 (n = 32)	–0.274	0.129	–0.256	0.158
Group 3 (n = 31)	–0.103	0.580	–0.080	0.669
Group 4 (n = 26)	–0.361	0.129	–0.130	0.596
Group 5 (n = 27)	–0.317	0.107	–0.277	0.162

r = Spearman's correlation coefficient, p < 0.05 is considered significant, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase.

There was statistically significant negative correlation between duration of carbamazepine administration and serum transaminases level. In accordance with our results, O'Hare *et al.* demonstrated statistically significant correlation between duration in administration of carbamazepine and ALT elevation [11]. The study also attributed this effect on serum transaminase, induce microsomal hepatic enzymes. Controversially, Bjornsson *et al.* [12] reported there was no correlation between duration of carbamazepine and elevated serum transaminases.

Table 5: Comparison level of serum transaminases between gender

Gender	Serum Transaminase	
	AST	ALT
	p	p
Group 1 (n = 32)	0.957	0.870
Group 2 (n = 32)	0.814	0.939
Group 3 (n = 31)	0.566	0.833
Group 4 (n = 26)	0.839	0.329
Group 5 (n = 27)	0.221	0.323

Using independent t-test, P < 0.05 is considered significant, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase.

Patients using sodium valproate have significant correlation between level of sodium valproate and serum transaminases. Contrary to this findings, Huang *et al.* [14] suggested that severe hepatotoxicity reaction may be unrelated to dosage or duration of valproic acid. Similarly, Star *et al.* [15] suggested that there was no correlation between elevation in ALT and AST and dosage of valproic acid. In addition, during initiation of AEDs, the liver enzymes were elevated due to enzyme inducing property. This occurs during the first 6 months administration of AED, especially this study was conducted on epileptic patients taking AED at least 6 months. As time goes by, the liver tests can normal despite continued therapy probably due to adaptation of the liver. Consequently, this thought explains the statistically significant negative correlation between duration of AED and AST [14], [15]. Young age (<2 years) stated concurrent use of other anticonvulsants appears as important risk factor for acute liver failure due to valproate [15], [16]. In this study, 68% sample were children above 2 years with appropriate dosage and minimal duration of treatment, 6 months. This can explain why the results of this study are significantly negative. Valproate has been rarely associated with anticonvulsant hypersensitivity syndrome and generally known as safe alternative. Many studies suggested that VPA-induced hepatotoxicity is more frequent in children compared with adults and the risk of hepatotoxicity is estimated up to 1 in 600 for children <2 years of age and decreases thereafter. Only 1–3% of dosage is excreted unchanged in urine. The usual half-life elimination of valproic acid in adults and children is 9–16 h [16]. Young children have prolonged elimination (17–40 h). Valproic acid is recommended to be initiated at dosages 15–20 mg/kg/day in children and titrated at weekly intervals by 5–10 mg/kg/day until seizures are controlled or adverse effects become intolerable [17], [18]. The maximum recommended dosage is 60 mg/kg/day; however, some children with refractory seizures may require higher dosages to achieve the desired degree of seizure control. Hepatotoxic effects typically occur during six months of therapy [16].

Table 6: Comparison level of serum transaminases between nutritional status

Nutrition Status	Serum Transaminase	
	AST	ALT
	p	p
Group 1 (n = 32)	0.415	0.625
Group 2 (n = 32)	0.670	0.501
Group 3 (n = 31)	0.894	0.364
Group 4 (n = 26)	0.230	0.158
Group 5 (n = 27)	0.450	0.333

Using independent t-test, P < 0.05 is considered significant, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase.

Gopaul and Sonmez suggested that the divergence in results may be due to variations in risk factors of valproic acid induced hepatotoxicity, for example, younger age, mental retardation, history of metabolic disorders or inborn error of metabolism, polypharmacy, and stressful condition such as infection and underlying liver disease [19], [20].

Patients using phenytoin have significant lower serum transaminases than those using carbamazepine or sodium valproate. Our results also revealed that there was no statistically significant correlation between duration of phenytoin and elevation of serum transaminases. Similar to this finding, Craig [21] found no statistically significant correlation between serum level of phenytoin and the risk for hepatotoxicity. Meythaler [22] reported statistically significant positive correlation between dosage of phenytoin with serum alkaline phosphatase. Other study found that the elevations of ALT and AST were transient nature, and the absence of specific histopathology during chronic treatment with phenytoin does not result in hepatotoxicity but rather in enzyme induction and dose-dependent degree of enzyme induction in epileptic patients receiving therapeutic doses of phenytoin [23]. The present study indicated that patients using carbamazepine and sodium valproate have significant higher level of serum transaminases than those using phenytoin.

There was statistical significant positive correlation between duration of phenobarbital

administration and elevation of serum transaminases level. Foster *et al.* [24] in retrospective analysis of post-mortem liver samples, found about 50% of patients receiving long-term phenobarbital showed hepatocellular damage. Phenobarbital has been found to produce acute hepatonecrosis, while chronic elevation of serum transaminases associated with phenobarbital are attributed to enzyme induction alone. Concomitant use of AEDs that induce microsomal P450 enzymes, such as phenobarbital and phenytoin, may enhance the production of toxic metabolite and hence increase the risk of hepatotoxicity with combined therapy [24]. The mechanism of phenobarbital hepatotoxicity is thought to be hypersensitivity or immunological response to metabolically generated drug-protein complex [23]. Liver involvement is common, but usually mild and anicteric and overshadowed by other features of hypersensitivity (rash and fever). In some cases, hepatic involvement is more prominent with marked elevations in serum enzyme, jaundice and even signs of hepatic failure [5]. The typical pattern of serum enzyme elevations is mixed, but can be hepatocellular or cholestatic. Phenobarbital is potent cytochrome P450 enzyme inducer when concentration >40 mg/L, leading to interactions with other drugs by increasing their clearance [23], [24].

A strong positive correlation between duration of multiple AEDs and elevation of serum transaminases level was found significant. Rao [25] in his study found that serum transaminases were elevated in patients receiving either single or multiple AEDs in period of 2 years. This toxicity is directly related to the number of drugs being consumed and leads to chronic toxicity. However, it was noted that the levels of these enzymes were higher in those receiving polytherapy than those receiving single drug. The elevation of serum transaminases after chronic antiepileptic medication would reflect hepatocellular damage [25], [26].

No significant correlation found between age and incident of elevated serum transaminases. It has been reported that females were 1, 5 fold greater risk of developing an adverse drug reaction compared to males [27]. Gender as well as nutrition status, have no significant relation to the incident of elevated serum transaminase in this study [28]. Certain risk factors such as polytherapy, younger age and malnutrition could determine the chance of developing hepatotoxicity [29]. Hussein *et al.* [26] found no correlation between age and gender as well as nutrition status and incident of elevated serum transaminases [12].

The advantage of this research was large sample size which representative for population. The weakness of this research was secondary data that may not answer the researcher's specific research questions or contain specific information that researcher would like to have. In the combination group, there was no specific explanation about the kind of AEDs. Further study is required to determine the type of combination AEDs with serum transaminases. We did not categorize the dosage pattern of AEDs in each patient and perform complete liver enzyme examination. Further study in dosage with complete liver enzyme examination is needed to correlate the rise of liver enzymes noted in those patients.

Conclusion

The combination of AEDs was found to be more hepatotoxic rather than monotherapy alone. Phenobarbital, sodium valproate, and carbamazepine are more hepatotoxic than phenytoin. Positive correlation was found between duration of multiple AEDs administration and phenobarbital toward elevated serum transaminases. There was negative correlation between duration in administration of carbamazepine as well as sodium valproate to serum transaminases. Routine screening of hepatic enzymes level during chronic administration of AEDs is recommended. It is important to obtain baseline liver function tests before starting antiepileptic therapy and perform serial follow-up of liver function study might be helpful to prevent hepatotoxicity. Precautions should be taken while using AEDs in epileptic patients with pre-existing hepatic disorders.

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