

# RESEARCH ARTICLE

## THE EFFECT OF ANTICONVULSANT DRUGS (PHENOBARBITAL AND VALPROIC ACID) ON THE SERUM LEVEL OF CHOLESTEROL, TRIGLYCERIDE, LIPOPROTEIN AND LIVER ENZYMES IN CONVULSIVE CHILDREN

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### Abstract

#### Objective

Studies on the effect of various antiepileptic drugs on serum lipids show contradictory results. We aimed to find the effect of Phenobarbital and Sodium Valproate monotherapy on serum lipid profile and liver function tests in epileptic children.

#### Materials & Methods

This cohort study was conducted in Amirkola Children Hospital. One hundred and ten children with epilepsy were included in this study. Children with hepatic or renal disease, those receiving medications which could alter liver function tests or serum lipid profile were excluded from the study. Patients were allocated into two groups. The first group, including 63 patients, received Phenobarbital and the second group, including 47 patients, received Sodium Valproate, both in divided doses. A venous blood sample was collected after overnight fasting to evaluate serum triglyceride, total cholesterol, LDL, HDL, and liver function tests. Data was analyzed with SPSS version 17.

#### Results

In children receiving Phenobarbital, total cholesterol, LDL, HDL, ALP, SGOT and SGPT increased significantly after treatment, but TG level showed no significant changes. In children receiving Sodium Valproate, HDL, ALP, SGOT, SGPT significantly increased after treatment but there were no statistically significant changes in total cholesterol, LDL and TG. In our study, the plasma levels of Lp(a) elevated significantly after treatment with Phenobarbital and Sodium Valproate (P Value=0.0001). This increase was more significant in patients receiving Sodium Valproate.

#### Conclusion

Our results suggested a need for monitoring serum total cholesterol, HDL, LDL, and TG levels in patients receiving Phenobarbital and Valproic Acid.

**Keywords:** Seizure, Phenobarbital, Sodium Valproate.

### Introduction

A seizure or convulsion is a paroxysmal time-limited change in motor activity and/or behavior that results from abnormal electrical activity in the brain. Seizures are common during childhood and occur in 5.2-8.1 per 1000 children, and are the most common neurologic disorder in children. However, in most cases, this disorder does not lead to a specific diagnosis and is mostly a primary disorder of CNS (Central Nervous System) which is called Idiopathic Epilepsy (1,2).

Some childhood seizures are provoked by somatic disorders originating from outside

of the brain, such as a high fever, infection, syncope, head trauma, hypoxia, toxins, or cardiac arrhythmias.

Regarding long-time treatment of epileptic patients, these treatment protocols may have some side effects. Different studies on the effect of various antiepileptic drugs on serum lipid profile have reported contradictory results (3,4,5).

The aim of this study was to find the effect of Phenobarbital and Valproic Acid monotherapy on serum lipid profile and liver function tests in epileptic children.

### Materials & Methods

This cohort study was conducted in the Department of Pediatric Neurology at Amirkola Pediatric Hospital between 2007 and 2008 in order to evaluate the effect of antiepileptic drugs of Phenobarbital and Sodium Valproate on serum lipid profile [TG (Triglyceride), Ch (cholesterol), HDL (High Density Lipoprotein), LDL (Low Density Lipoprotein), Lp(a) (Lipoprotein a)] and liver enzymes [SGOT (Serum Glutamic Oxaloacetic Transaminase), and SGPT (Serum Glutamic Pyruvic Transaminase)].

One hundred and ten patients with convulsive attacks and the diagnosis of epilepsy were included in this study but children with hepatic, renal or metabolic diseases, a positive past history of status epilepticus, those receiving medications which could alter liver function tests or serum lipids and a positive family history of atherosclerosis were excluded.

An informed written consent was signed by each subject and prior approval of the institutional ethical committee was obtained. Patients were allocated into 2 groups based on antiepileptic drug treatment. Group A, including 63 patients, received Phenobarbital (5mg/kg/d) twice a day and group B, including 47 patients, received Sodium Valproate (20mg/kg/d) twice daily.

A Venous blood sample (5ml) was collected after overnight fasting. Serum levels of Alanin Amino Transferase (ALT) and Aspartate Amino Transferase (AST) were evaluated through IFCC method, Alkaline Phosphatase (ALP) through DGKC method (Deutsche Gesellschaft für Klinische Chemie), and serum cholesterol and HDL levels through GOD-PAP.

Low-density lipoprotein cholesterol (LDL) was calculated using Friedewald formula. The serum level

of Lipoprotein A was estimated through ELISA method before and during treatment (at the 3<sup>rd</sup> and 6<sup>th</sup> month)

Data was analyzed using SPSS version 17 and paired T-test was applied to compare lipid levels in different groups.

### Results

Sixty three patients were included in group A but 13 cases were excluded during the follow-up period, 3 patients for drug resistance and recurrent convulsion, one patient for post treatment rashes, one for discontinuing drug and 8 for not attending in the next sampling. Therefore, we had 50 patients in group A with a mean age of 6.22±2.01 years; 48% were male and 52% were female.

Group B included 47 patients but 11 were excluded during the follow-up, one for Sodium Valproate induced rashes, 2 for drug resistance, 2 for discontinuing drug and 6 for not attending in the next sampling. Finally, we had 36 patients in this group with a mean age of 8.14±3.46 years; 44.4% were male and 15.6% were female.

Mean changes of cholesterol, HDL, LDL, TG, liver enzymes, ALP and Lp(a) in patients treated with Phenobarbital and Sodium Valproate are recorded in the following graphs and tables.

Based on Graphs 1-6 and tables No 1 and 2, in group A, there was a significant difference in all parameters except for TG but in group B, a significant difference was only seen in Lp(a) (P value=0.0001), HDL (P value=0.049), SGOT (P value=0.0001), SGPT (P value=0.0001) and ALP (P value=0.049). However, there were no statistically significant changes in total cholesterol (P value=0.62), LDL (P value=0.148) and TG (P value=0.136).

### Discussion

In our study, the plasma level of Lp(a) showed a significant elevation after treatment with Phenobarbital (P value=0.0001) and Sodium Valproate (P value=0.0001). Moreover, this increase was more significant in patients receiving Sodium Valproate (Table 1-2)

Our results suggested a need for monitoring serum total cholesterol, HDL, LDL, and TG levels and perhaps prescribing a low cholesterol diet in patients receiving antiepileptic drugs.

**Table 1:** Group A, treatment with Phenobarbital

	First Sample Mean $\pm$ SD	3 <sup>rd</sup> Month Treatment Mean $\pm$ SD	6 <sup>th</sup> Month Treatment Mean $\pm$ SD	Normal Range	P value. Primary 3 <sup>rd</sup> Month Treatment	P value. Primary 6 <sup>th</sup> Month Treatment
Ch	152.90 $\pm$ 30.798	161.88 $\pm$ 31.702	175.62 $\pm$ 35.340	<200	0.083	0.0001
TG	140.14 $\pm$ 50.28	129.96 $\pm$ 42.23	130.41 $\pm$ 48.17	<200	0.057	0.172
LDL	68.81 $\pm$ 23.048	77.31 $\pm$ 24.538	79.06 $\pm$ 22.905	29-80	0.002	0.020
HDL	48.74 $\pm$ 17.656	63.52 $\pm$ 25.515	67.33 $\pm$ 26.097	29-80	0.0001	0.0001
SGPT	24.94 $\pm$ 10.918	29.36 $\pm$ 11.414	35.74 $\pm$ 10.997	<41	0.007	0.0001
SGOT	33.20 $\pm$ 12.401	38.36 $\pm$ 12.106	41.44 $\pm$ 10.358	<37	0.001	0.001
ALP	483.80 $\pm$ 132.012	607.52 $\pm$ 189.867	729.70 $\pm$ 544.901	Female: 64-306 Male: 80-306	0.0001	0.009
LPa	22.70 $\pm$ 10.016	27.22 $\pm$ 11.496	31.74 $\pm$ 10.984	<30 mg/dl	0.0001	0.0001

**Table 2:** Group B, treatment with Sodium Valproate

	First Sample Mean $\pm$ SD	3 <sup>rd</sup> Month Treatment Mean $\pm$ SD	6 <sup>th</sup> Month Treatment Mean $\pm$ SD	Normal Range	P value. Primary 3 <sup>rd</sup> Month Treatment	P value. Primary 6 <sup>th</sup> Month Treatment
Ch	148.72 $\pm$ 20.084	149.78 $\pm$ 19.803	152 $\pm$ 23.031	<200	0.778	0.620
TG	106.03 $\pm$ 43.312	111.86 $\pm$ 46.810	116.38 $\pm$ 51.691	<200	0.314	0.136
LDL	76.11 $\pm$ 25.255	74.58 $\pm$ 24.492	67.68 $\pm$ 20.407	29-80	0.783	0.148
HDL	50.86 $\pm$ 21.842	60.36 $\pm$ 14.337	61.58 $\pm$ 13.873	29-80	0.021	0.049
SGPT	21.47 $\pm$ 9.470	24.86 $\pm$ 9.628	33.31 $\pm$ 8.014	<41	0.010	0.0001
SGOT	32.72 $\pm$ 11.899	36.89 $\pm$ 11.858	41.61 $\pm$ 10.490	<37	0.015	0.0001
ALP	555.22 $\pm$ 165.420	622.25 $\pm$ 180.360	628.25 $\pm$ 198.735	Female: 64-306 Male: 80-306	0.025	0.065
LP a	28.79 $\pm$ 12.735	33.85 $\pm$ 14.722	36.36 $\pm$ 16.698	<30 mg/dl	0.002	0.0001

Sonmez et al found that antiepileptic drugs (Phenobarbital and Sodium Valproate) significantly increased the level of Lp(a), which is a major risk factor for atherosclerosis and also has variable effects on other lipid parameters. This increase was more obvious in patients receiving Phenobarbital (1).

Verrotti et al showed that patients treated with Phenobarbital and Sodium Valproate revealed significant changes in lipid and lipoproteins (2).

Aynaci et al reported that in patients treated with Phenobarbital, all the parameters of lipid profile significantly increased except for triglycerides and that triglyceride reduction was not statistically significant ( $P$  value  $< 0.25$ ) (6).

Plasma levels of Lp(a) depend on the rate of Lp(a) production in liver. Antiepileptic drugs change Lp(a) levels by inducing the microsomal enzymes system of the liver which is the reason why the level of plasma Lp(a) is elevated in patients receiving Phenobarbital.

On the other hand, the biotransformation pathway of Sodium Valproate occurs with changes in glucuronic acid structure and the beta-oxidation pathway; therefore, we do not expect any changes in lipid and Lp(a) levels. However, Sonmez et al showed that there was a remarkable rise in Lp(a) level in patients receiving Sodium Valproate (1-7).

Our results showed that patients receiving Phenobarbital and Sodium Valproate experienced a significant increase in HDL which was more obvious in the Phenobarbital group.

In group A, the serum levels of cholesterol and LDL had a significant increase but in group B, there was no significant increase in serum cholesterol and LDL levels. Also, serum triglyceride level did not change in the two

groups.

Franzoni et al reported a significant increase in total cholesterol plasma level with Phenobarbital but patients receiving Sodium Valproate were very similar to those in the control group. The results may be explainable by the different biotransformation pathway of these drugs (8).

In our study, there was a significant increase in ALT, AST and ALP with Phenobarbital and Sodium Valproate which was more significant in patients receiving Phenobarbital.

Mendis et al studied 123 unselected patients who were on anticonvulsants. The results were compared with 123 control patients. They found that plasma activities of AST and ALP were similar in the two groups but ALT was elevated in patients on anticonvulsants (9).

Wall et al reported that ALP was elevated in 29.7% and Alanin Transferase in 25.2% of the cases receiving anticonvulsant medication (10).

Closed monitoring of serum lipid levels and a long-term follow-up of children receiving antiepileptic drugs to observe the incidence of ischemic heart disease is needed to obtain a clinically significant result (10).

One of the main limitations of our study was the lack of long-term follow-up of children on antiepileptic drugs.

We also recommend long-term serial monitoring of the changes of lipid fractions from the beginning until the end (or even after the end) of the treatment period.

### Acknowledgement

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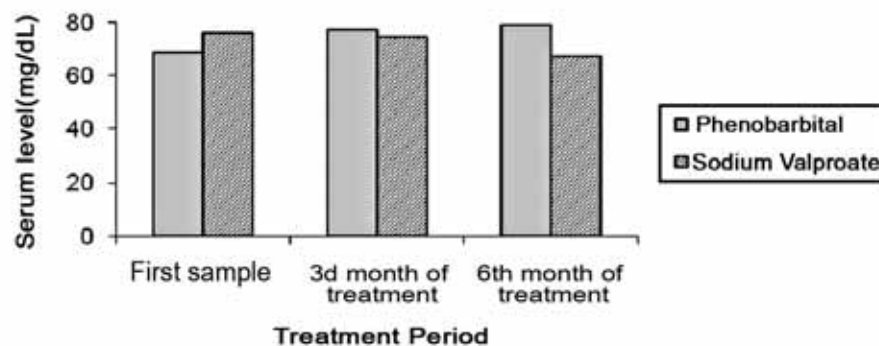


Fig 1. Mean serum level of LDL before and after treatment

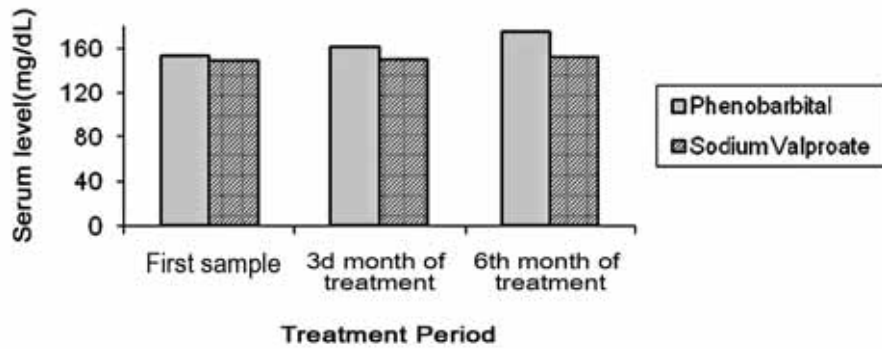


Fig 2. Mean serum level of Cholestrol before and after treatment

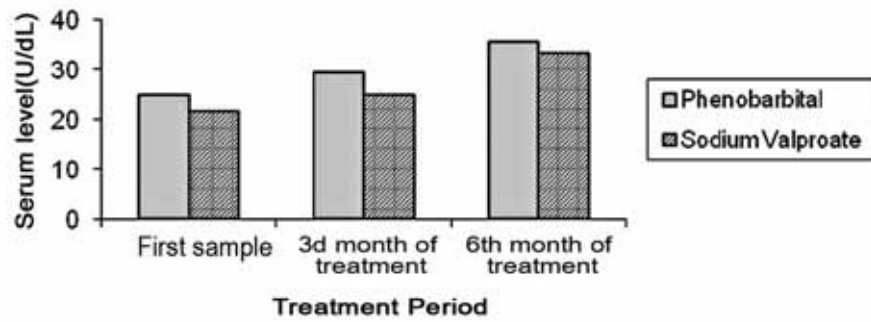


Fig 3. Mean serum level of SGPT before and after treatment

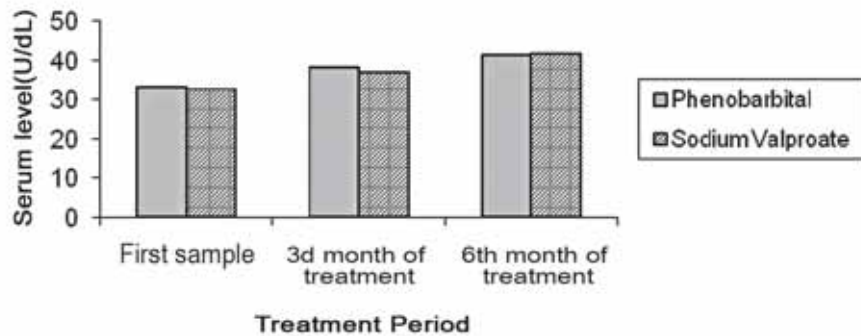


Fig 4. Mean serum level of SGOT before and after treatment

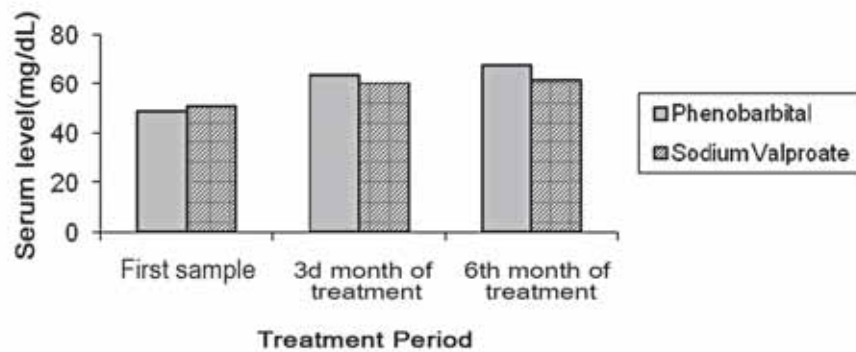


Fig 5. Mean serum level of HDL before and after treatment

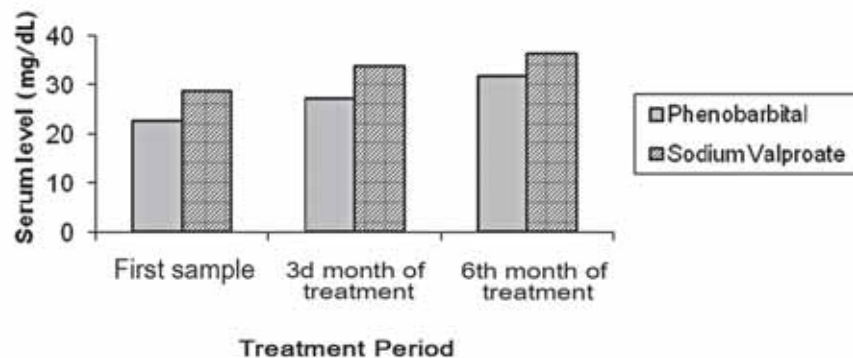


Fig 6. Mean serum level of Lp(a) before and after treatment

## References

1. Sonmez FM, Demir E, Orem A, Yildirmis S, Orhan F, Aslan A, Toobas M. Effect of antiepileptic drugs on plasma lipids, lipoprotein (a), and liver enzymes. *J Child Neurol* 2006; 21:70-74.
2. Verrotti A, Basciani F, Dominizo S, Sabatino G, Morgese G, Chiarelli F. Serum lipids and lipoproteins in patients with antiepileptic drugs. *Pediatr Neurol* 1998;19:364-367.
3. Demircioglu S, Soylu A, Dirik E. Carbamazepin and Valproic acid's effect on serum lipid and liver function in children. *Pediatr Neurol* 2000;23:142-146.
4. Eiris JM, Lojo S, Del Rio MC, et al. Effect of long-term treatment with antiepileptic drugs on serum lipid levels in children with epilepsy. *Neurology* 1995;45:1155-1157.
5. Franzoni E, Govoni M, D'Addato S, Gualandi S, Sangiorgi Z, Descovich GC, et al. Total cholesterol, high-density lipoprotein cholesterol, and triglycerides in children receiving antiepileptic drugs. *Epilepsia* 1992 Sep-Oct;33(5):932-5.
6. Aynaci FM, Orhan FOrem A, Yildirmis, S, Gedik, Y. Effect of antiepileptic drugs on plasma lipoprotein (a) and other lipid levels in childhood. *J Child Neurol* 2001; 16:367-369.
7. Hobbs HH, White AL. Lipoprotein (a) intrigues and insights. *Curr Opin Lipidol* 1999;10:225-236.
8. Dewan P, Aggarwal A, Faridi M. Effect of Phenytoin and Valproic acid therapy on serum lipid level and liver function tests. *Ind Ped J* 2008;28(1):91-93.
9. Mendis GP, Gibberd FD, Hunt HA. Plasma activities of hepatic enzymes in patients on anticonvulsant therapy. *Seizure* 1993;2(4):319-23.
10. Wall M, Baird-Lambert J, Buchanan N, Farrell G. Liver function tests in persons receiving anticonvulsant medications. *Seizure* 1992 Sep;1(3):187-90.