DOI: https://doi.org/10.3329/medtoday.v35i2.69171

ORIGINAL ARTICLE OPEN ACCESS

Effects of Carbamazepine and Sodium Valproate on Serum Cholesterol in Epileptic Patients

Mohammed Khaled Mosharraf Hossain*[1], Nasima Sultana[2], Hafizur Rahman[3], Mohammad Nurul Alam[4], Md. Moshiur Rahman[5], Noor-e-Nazar Mst. Munira Begum[6]

Abstract

Introduction: *Epilepsy is a common, chronic and non-communicable disorder of the brain. Carbamazepine, increasing serum cholesterol level, causes adverse cardiovascular and cerebrovascular events. Sodium valproate causes weight gain, hyperinsulinemia and insulin resistance leading to metabolic syndrome. These all cause increased morbidity and mortality of epileptic patients in later life.* ***Objectives:*** *to find out the effects of carbamazepine and sodium valproate on serum cholesterol in epileptic patients.* ***Materials and Methods:*** *This cross-sectional study was conducted in the Department of Biochemistry, Dhaka Medical College during the period of July 2017 to June 2018. A total of sixty diagnosed epileptic patients were selected, of them, thirty patients were taking carbamazepine and thirty on sodium valproate. Data were analyzed with the help of SPSS version 22.0. Unpaired Student's t-test and Mann-Whitney U test were done to see the level of significance ($p<0.05$). For correlation, Pearson's correlation coefficient test was done.* ***Results:*** *Mean ± SD of serum total cholesterol in carbamazepine and sodium valproate patients were 218.73 ± 29.70 mg/dl and 190.14 ± 17.10 mg/dl respectively ($p<0.001$).* ***Conclusion:*** *This study reveals that hypercholesterolemia is related to carbamazepine medications.*

Keywords: *Epilepsy, Carbamazepine (CBZ), Sodium valproate (VPA), Serum total cholesterol (TC).*

Number of Tables: 03; Number of References: 11; Number of Correspondences: 04.

***1. Corresponding Author:**
Dr. Mohammed Khaled Mosharraf Hossain
M. Phil (Biochemistry)
Assistant professor
Department of Biochemistry
Chandpur Medical College, Chandpur, Bangladesh.
Email: hossainkhaled.cmc39@gmail.com
Mobile: 01818209076

2. Prof. Dr. Nasima Sultana
M. Phil (Biochemistry)
Additional Director General (ADG), DGHS, Dhaka.
Former Head of the Department of Biochemistry
Dhaka Medical College, Dhaka, Bangladesh.

3. Professor Dr. Hafizur Rahman
M. Phil (Biochemistry)
Registrar, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka.
Former Head of the Department of Biochemistry
Dhaka Medical College, Dhaka, Bangladesh.

4. Dr. Mohammad Nurul Alam
M. Phil (Biochemistry)
Assistant Professor
Department of Biochemistry
Chandpur Medical College
Chandpur, Bangladesh.

5. Dr. Noor-e-Nazar Mst. Munira Begum
M. Phil (Biochemistry)
Assistant Professor
Department of Biochemistry
Rangpur Medical College, Rangpur, Bangladesh.

6. Dr. Md. Moshiur Rahman
M. Phil (Biochemistry)
Lecturer
Department of Biochemistry
Rajshahi Medical College, Rajshahi, Bangladesh.

Introduction:

Epilepsy is a neurological disorder characterized by recurrent unprovoked seizures which is transient with abnormal, excessive and synchronous neuronal activity in the brain. It is a common and chronic neurologic disorder worldwide. It has been estimated that 80% of 50 million people with epilepsy reside in developing countries[1]. There are at least 1.5 to 2.0 million people with epilepsy in Bangladesh[2]. Epilepsy occurs in men and women with male predominance and can begin at any age, but is most frequently diagnosed in early life or in old age. Up to 5% of the world's population may have a single seizure at some time of their lives, but a diagnosis of epilepsy is reserved for those who have recurring seizures, i.e. at least two unprovoked seizures[3]. Epilepsy cases are reported higher in rural area than in urban area especially in developing countries. Epilepsy is said to be controlled when no

Received: 28 April 2023 *Accepted revised version:* 19 July 2023

seizure for more than six months and uncontrolled when one or more seizures over a period of six months during treatment of epilepsy[4]. The effects of antiepileptic drug carbamazepine may be due to induction of cytochrome P450 (CYP) enzymes in the liver. The CYP450 enzyme system is involved in the synthesis and biotransformation of cholesterol. In particular, CYP51A1 plays a key role in cholesterol synthesis. Also carbamazepine stimulates hepatic synthesis of cholesterol and increase the formation and pool size of bile acids, which in turn raise the level of intestinal absorption of cholesterol by facilitating micelle formation. An elevated serum cholesterol level may increase the risk of adverse cardiovascular and cerebrovascular events[3]. Sodium valproate (VPA) interferes with insulin metabolism in the liver, resulting in hyperinsulinemia in the peripheral circulation leading to increased glucose uptake by the cells[5]. As the structure of VPA is similar to a fatty acid derivative, it directly stimulates pancreatic insulin secretion[6]. Due to structural similarity, sodium valproate competes with other long chain fatty acids for carnitine in the beta-oxidation system, suppressing fatty acids oxidation. Also valproate replaces fatty acids from their binding sites with albumin. These all are leading to increased fatty acids (dyslipidemia) in the blood which are taken up by the peripheral tissues by the anabolic actions of insulin leading to increased body weight[7]. Sodium valproate stimulates appetite and causes hyperleptinemia leading to weight gain. All these metabolic changes are in favour of development of insulin resistance and in the long run, metabolic syndrome[8]. Thus, assessing change in serum cholesterol level following antiepileptic drugs may be useful to choose the safest drug and prevention of cardiovascular complications in later life. So, the study was planned to find out and compare the effects of carbamazepine and sodium valproate on serum cholesterol in epileptic patients to select drugs and diets.

Materials and Methods:

This cross-sectional study was carried out in the Department of Biochemistry, Dhaka Medical College, Dhaka, during the period of July 2017 to June 2018. For this study, sixty (60) diagnosed epileptic patients were selected from the Outpatient Department of Neurology, Dhaka Medical College Hospital, Dhaka. Patients were divided into group A (30) taking carbamazepine and group B (30) taking sodium valproate. Diagnosed epileptic male and female patients of age between 18 to 65 years taking antiepileptic drugs for at least 6 months or more were included as the study subjects. Patients taking more than one antiepileptic drugs, antidyslipidaemic or antipsychotic drugs, pregnant women on antiepileptic drugs and patients with malignancy, diabetes mellitus, chronic kidney disease, liver disease, stroke and ischemic heart disease were excluded. Informed written consents were taken from all the patients and ethical approval for the study was taken from the Ethical Review Committee of Dhaka Medical College. Initial evaluation of the patients by history and clinical examination were performed and recorded in the preformed data collection sheet. Baseline parameters such as age, BMI (Body mass index) and blood pressure were measured and recorded. Then with all aseptic precautions blood samples were collected in the labeled test tubes and serum was separated by centrifugation. Serum total cholesterol level was measured by enzymatic methods in the Department of Biochemistry, Dhaka Medical College, Dhaka. All the data were recorded in a pre-designed data collection sheet. Continuous variables were expressed as Mean ± SD and compared between groups of patients by unpaired Student's t-test. Categorical variables were compared using a Chi-square test and were presented as absolute frequencies with percentages. Correlation was done by Pearson's correlation coefficient test. All p values were two-tailed with significance defined as $p < 0.05$ at the level of 95% confidence interval (CI). All analyses were done using the SPSS 22.0 (Statistical Package for Social Science) package for windows.

Result:

Mean (± SD) age of patients taking carbamazepine (Group A) was 27.90 ± 7.31 years and that of sodium valproate (Group B) was 28.73 ± 7.02 years showing no statistically significant difference ($p > 0.05$). Also Mean (±SD) BMI, duration of antiepileptic drugs, systolic and diastolic blood pressure showed no statistically significant differences ($p > 0.05$) between the groups as shown in table I. Mean (± SD) total cholesterol of patients taking carbamazepine was 218.73 ± 29.70 mg/dl and that of sodium valproate was 190.14 ± 17.10 mg/dl showing statistically significant difference ($p < 0.001$) between the groups. Duration of carbamazepine showed significant positive correlation ($r = +0.441$ and $p = 0.024$) with serum total cholesterol. Duration of sodium valproate showed non-significant ($p = 0.103$) positive correlation with serum total cholesterol.

Table I: Shows that there were no significant differences in terms of baseline characteristics (age, gender, BMI and BP) between the groups.

Table I: Baseline characteristics of study subjects in groups (N= 60)

	Groups		p-value
	Group A (n= 30)	Group B (n= 30)	
Age (years) (Mean ± SD)	27.90 ± 7.31	28.73 ± 7.02	0.654[a]
Gender			
Male	20 (66.7)	18 (60.0)	0.592[b]
Female	10 (33.3)	12 (40.0)	
BMI (kg/m^2) (Mean ± SD)	24.22 ± 1.77	24.80 ± 1.41	0.167[a]

Table I: Baseline characteristics of study subjects in groups (N= 60)

	Groups		p-value
	Group A (n= 30)	Group B (n= 30)	
Duration of AEDs (months) (Mean ± SD)	25.40 ± 23.14	32.63 ± 23.66	0.180[c]
Systolic BP (mm of Hg) (Mean ± SD)	117.33 ± 7.40	117.67 ± 7.74	0.865[a]
Diastolic BP (mm of Hg) (Mean ± SD)	75.17 ± 5.49	75.67 ± 4.87	0.710[a]

aUnpaired Student's t- test was done to measure the level of significance

bChi- square test was done to measure the level of significance

cMann-Whitney U test was done to measure the level of significance

Values within the parenthesis indicate percentage (%)

Level of significance, $p < 0.05$

Group A= Carbamazepine (CBZ)

Group B= Sodium valproate (VPA)

Table II: Shows total cholesterol was significantly higher in patients taking carbamazepine compared to patients taking sodium valproate.

Table II: Laboratory findings of patients in groups (N= 60)

	Groups		p-value
	Group A (n= 30)	Group B (n= 30)	
Total cholesterol (mg/dl) (Mean ± SD)	218.73 ± 29.70	190.14 ± 17.10	<0.001[s]

Unpaired Student's t-test was done to measure the level of significance.

Level of significance, $p < 0.05$

s= significant

Group A= Carbamazepine (CBZ)

Group B= Sodium valproate (VPA)

Table III: Shows significant positive correlation of duration of carbamazepine with serum total cholesterol and nonsignificant positive correlation of duration of sodium valproate with serum total cholesterol.

Table III: Correlation of duration of antiepileptic drugs with serum total cholesterol in two groups (N= 60)

	Group A (n= 30)		Group B (n= 30)	
	r value	p value	r value	p value
Total cholesterol	+0.441	0.024s	+0.304	0.103

Pearson's correlation coefficient (r) test was done to measure the level of significance.

Level of significance, $p < 0.05$

s= significant

Group A= Carbamazepine (CBZ)

Group B= Sodium valproate (VPA)

Discussion:

In this study, there were no statistically significant differences ($p > 0.05$) in terms of baseline characteristics (age, gender, body mass index and blood pressure) as shown in table I. Mean (±SD) age in carbamazepine (Group A) and sodium valproate (Group B) groups were 27.90 ± 7.31 years and 28.73 ± 7.02 years respectively. Mean ± (SD) BMI in group A was 24.22 ± 1.77 kg/m² and in group B, 24.80 ± 1.41 kg/m². Mean ± (SD) duration of antiepileptic drug in group A, 25.40 ± 23.14 months and in group B, it was 32.63 ± 23.66 months. Mean ± (SD) systolic blood pressure in group A, 117.33 ± 7.40 mmHg and in group B, 117.67 ± 7.74 mmHg. Mean ± (SD) diastolic blood pressure in group A was 75.17 ± 5.49 mmHg and in group B, 75.67 ± 4.87 mmHg. According to the findings from this study, mean ± SD of serum total cholesterol was 218.73 ± 29.70 mg/dl in group A and 192.48 ± 17.69 mg/dl in group B. Mean ± SD of total cholesterol level was significantly higher ($p < 0.001$) in group A patients in comparison to group B patients. The same statistically significant result was obtained in the study done by Mahmood and M ded, 2012[9], where mean ± SD of total cholesterol level in carbamazepine group A was 194.34 ± 44.72 mg/dl ($p < 0.05$). A study done by Nikolas et al., 2004[10], found mean ± SD of serum total cholesterol level in carbamazepine group, 225.8 ± 49.3 mg/dl ($p < 0.001$) and total cholesterol level in sodium valproate group was 183.1 ± 39.8 mg/dl ($p < 0.05$). Pearson's correlation coefficient test was done to observe the relationship of duration of antiepileptic drugs with serum total cholesterol in the patients of both groups. Duration of carbamazepine showed a significant positive correlation with serum total cholesterol (for CBZ, r= +0.441 and p= 0.024) and duration of sodium valproate showed a non-significant positive correlation with serum total cholesterol (for VPA, r= +0.304 and p= 0.103). A significant positive correlation ($p < 0.05$) between duration of carbamazepine and serum total cholesterol was established in a study done by Kumar et al., 2003[11].

Conclusion:

The present study demonstrates that hypercholesterolaemia is related to carbamazepine medication. So, it is advocated that regular screening of serum cholesterol in epileptic patients might help reducing complications of dyslipidaemia.

Conflict of Interest: None.

Acknowledgement:

We are grateful to all the teachers and staffs of the Department of Biochemistry, Dhaka Medical College and all doctors, nurses and staffs of the Department of Neurology, Dhaka Medical College Hospital, Dhaka. We are also

grateful to all the patients who willingly participated in our research work with their kind consent and cooperations.

References

1. Hussain ME. Burden of Epilepsy in Bangladesh: Current Approach. Journal of Current and Advanced Medical Research. 2017; 4(1): 1-2.
https://doi.org/10.3329/jcamr.v4i1.36249
https://doi.org/10.3329/jcamr.v3i1.29353
2. Habib M, Khan SU, Hoque MA, Mondal MBA, Hasan ATMH, Chowdhury RN, et al. Antiepileptic drug utilization in Bangladesh: Experience from Dhaka Medical College Hospital. BioMed Central 2013; 6(473): 1-12.
https://doi.org/10.1186/1756-0500-6-473
PMid:24245810 PMCid:PMC4225505
3. Manimekalai K, Visakan B, Salwe KJS and Murugesan S. Evaluation of Effect of Antiepileptic Drugs on Serum Lipid Profile among Young Adults with Epilepsy in a Tertiary Care Hospital in Pondicherry. Journal of Clinical and diagnostic Research. 2014; 8(8): HC05-HC09.
https://doi.org/10.7860/JCDR/2014/8744.4682
PMid:25302212 PMCid:PMC4190734
4. Mian MF, Jobayer M, Afroz Z, Chowdhury AH, Chowdhury RN, Habib M, et al. Demographic profiles of epileptic patients and their awareness towards epilepsy with the influence on compliance. Bangladesh Medical Journal. 2016; 45(1): 20-23.
https://doi.org/10.3329/bmj.v45i1.28961
5. Pylvanen V, Pakarinen A and Knip M. Characterization of insulin secretion in valproate-treated patients with epilepsy. Epilepsia 2006; (Available at https://scinapse.io/papers/1991821311, accessed on 18 July, 2018).
6. Luef G, Lechleitner M and Bauer G. Valproic acid modulates islet cell insulin secretion: A possible mechanism of weight gain in epilepsy patients. Epilepsy Research. 2003; 2(37): 1-3.
https://doi.org/10.1016/S0920-1211(03)00091-3
PMid:12948616
7. Pylvanen V. Insulin-related metabolic and endocrine effects of Valproate in patients with epilepsy. Oulu University Press 2005; (Available at jultika.oulu.fi/files/isbn9514278240; accessed on 12 May, 2018).
8. Mania M, Kasradz S and Okujava N. Valproic Acid related metabolic syndrome in patients with epilepsy. Georgian Medical News. 2011; (194): 43-47.
9. Mahmood IH and M ded ZK. Effects of Carbamazepine on blood pressure, serum glucose concentration, lipid profile and prevalence of metabolic syndrome in epileptic patients.Tikrt Journal of Pharmaceutical Sciences. 2012; 8(2): 1-8.
10. Nikolaos T, Stylianos G, Irhristos M and Antonis T. The effect of long term antiepileptic treatment on serum cholesterol (TC, HD, LDL) and triglyceride levels in adult epileptic patients on monotherapy. Medical Science Monitor. 2004; 10(4): 50-52.
11. Kumar P, Tyagi MY, Tyagi Y, Kumar A and Rai Y. Effects of Anticonvulsant Drugs On Lipid Profile in Epileptic Patients.The Internet Journal of Neurology. 2003; 3(1): 1-7.
https://doi.org/10.5580/137b