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Original Research Article

A Study of Effects of Antiepileptic Drugs on Lipid Profile in Subjects with Seizure Disorder

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ABSTRACT

Background
In India, 12 million people suffer from epilepsy and bears 1/6 of the world's weight.[1] Epilepsy has an incidence of approximately 0.3-0.5% in various groups worldwide with a prevalence estimated at 5–30 persons per 1000.[2] It has been observed that antiepileptic drugs (AED) raise serum levels of lipoproteins, total cholesterol and low-density lipoprotein (LDL) which accelerate atherosclerosis and risk of vascular illness.[3] As there is chronic use of AED for epilepsy, chronic neuropathic pain, migraine, there is need for study to determine AED effect on Lipid profile.

Methods
This cross sectional study included 62 patients with Seizure disorder. Patients were categorized into two groups based on treatment they were receiving for epilepsy for a minimum of 6 months into Phenytoin and Levetiracetam groups. Lipid profile status was compared in between the 2 groups.

Results
The mean age of patients receiving phenytoin was 59.81 ± 14.94 and mean age of patients receiving Levetiracetam was 41.97 ± 15.63 years. The mean total cholesterol was 165.90 ± 23.70 and 113.06 ± 17.22 in phenytoin and levetiracetam group respectively. The mean LDL-C in patients who received phenytoin was 95.54 ± 13.66 and in patients who received levetiracetam was 72.37 ± 11.45. The mean triglycerides in patients who received phenytoin was 148.07 ± 33.11 and in patients who received levetiracetam was 101.38 ± 9.22

Conclusion
We observed patients on phenytoin displayed elevated serum lipid profile levels (TC, LDL-C and TG). Thus their levels can be an important marker for estimating the risk of cardiovascular disease in epilepsy patient.

Keywords: Seizure disorder, Lipid profile, phenytoin, Levetiracetam.

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INTRODUCTION

Seizure is a transient occurrence of signs or symptoms due to abnormal excessive or synchronous neuronal activity in brain.[2,4] It can present as anything from violent convulsions to unusual experiences that are difficult to witness by others.[2] Epilepsy is the two or more unprovoked seizure due to chronic , underlying process.[2] Epilepsy One of the most prevalent brain disorders that affects not only the individual but also families and society.[5] In India, 12 million people suffer from epilepsy, Just India bears 1/6 of the world's weight.[1] Epilepsy has an incidence of approximately 0.3-0.5% in various groups worldwide with a prevalence estimated at 5–30 persons per 1000.[2] It has been observed that raise in serum levels of lipoproteins, total cholesterol and low-density lipoprotein (LDL) which accelerate atherosclerosis and risk of vascular illness.[3]

OBJECTIVES

To study the lipid profile status in subjects with seizure disorder who are on commonly used AED (phenytoin and levetiracetam).

MATERIALS & METHODOLOGY

The present Cross sectional study was conducted on 62 patients attending the department of medicine, neurology OPD and patients admitted in department of General medicine, Krishna Rajendra Hospital, Mysuru from August 2022 to August 2023.

Sample Size Estimation

Based on previous study conducted by Manimekalai K et al. Evaluation of effect of antiepileptic drugs on serum lipid profile among young adults with epilepsy in a tertiary care hospital in Pondicherry.

Sample size is calculated using the formula.

$n= 2\ S^2(Z1+Z2)^2/ (M1-M2)^2$

M1	Mean LDL-C in Control group	82.75*
M2	Mean LDL-C in Phenytoin group	88.75*
S1	Standard deviation of LDL-C in Control group	7.85*
S2	Standard deviation of LDL-C in Phenytoin group	7.49*
S	Pooled SD	7.67
AH	Two-sided Alternative Hypothesis	2
1-α	level of confidence	0.95
1-β	level of power of test	0.80
Z1	Z value associated with alpha	1.96
Z2	Z value associated with beta	0.84
n	Minimum sample size	31

Substituting the values in the above formula, sample size obtained is 31.
Since there are 2 groups, total sample size is 31*2= 62.

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Inclusion Criteria

Patients with seizure disorder who are on AEDs (Phenytoin and Levetiracetam).
Patient willing to give informed consent.

Exclusion Criteria

1. Patients on hypolipidemic drugs
2. patients with Diabetes Mellitus
3. Patients with stroke, IHD.
4. Patients on isoniazid ,warfarin.
5. Patients on more than one antiepileptic drug.
6. Patients with chronic liver and kidney disease.

Statistical analysis

Data obtained from the study will be entered in excel sheets and it will be double checked. Data analysed using SPSS software version 29.0.2.0 By IBM Corp, New York, United States Of America and will be presented as descriptive statistics in the form of frequency tables, figures and graphs. Association between variables will be done using chi-square test and unpaired t test for qualitative and quantitative variables. Results will be expressed as mean ± SD. A p value of <0.05 is considered statistically significant

RESULTS

Treatment	N	Minimum	Maximum	Mean	S.D	Mean diff	p value
Phenytoin	31	22.0	86.0	59.81	14.94	17.83	0.001*
Levetiracetam	31	22.0	77.0	41.97	15.63		

Table 1. Comparison of the mean age between the groups using unpaired T test

The mean age of patients receiving phenytoin was 59.81 ± 14.94 and mean age of patients receiving Levetiracetam was 41.97 ± 15.63 years. Using unpaired T test, comparison of the mean age between the groups was statistically significant. (p=0.001)

Age Groups		Treatment		Total
		Phenytoin	Levetiracetam	
22 to 30 yrs	Count	1	9	10
	%	3.2%	29.0%	16.1%
31 to 40 yrs	Count	3	8	11
	%	9.7%	25.8%	17.7%
41 to 50 yrs	Count	5	6	11
	%	16.1%	19.4%	17.7%
51 to 60 yrs	Count	6	3	9
	%	19.4%	9.7%	14.5%
61 to 70 yrs	Count	10	3	13
	%	32.3%	9.7%	21.0%
> 70 yrs	Count	6	2	8
	%	19.4%	6.5%	12.9%

Total	Count	31	31	62
	%	100.0%	100.0%	100.0%
***Chi-squared test**				

Table 2. Distribution of the subjects based on age groups

10 patients (16.1%) belonged to the age group of 22 to 30 years, of which, 1 patient (3.2%) received phenytoin and 9 patients (29%) received levetiracetam. 11 patients (17.7%) belonged to the age group of 31 to 40 years, of which, 3 patients (9.7%) received phenytoin and 8 patients (25.8%) received levetiracetam. 11 patients (17.7%) belonged to the age group of 41 to 50 years, of which, 5 patients (16.1%) received phenytoin and 6 patients (19.4%) received levetiracetam. 9 patients (14.5%) belonged to the age group of 51 to 60 years, of which, 6 patients (19.4%) received phenytoin and 3 patients (9.7%) received levetiracetam. 13 patients (21%) belonged to the age group of 61 to 70 years, of which, 10 patients (32.3%) received phenytoin and 3 patients (9.7%) received levetiracetam. 8 patients (12.9%) belonged to the age group of >70 years, of which, 6 patients (19.4%) received phenytoin and 2 patients (6.5%) received levetiracetam. The association between age groups and treatment received was statistically significant. (p=0.008).

Gender		**Treatment**		**Total**
		Phenytoin	**Levetiracetam**	
Females	Count	10	9	19
	%	32.3%	29.0%	30.6%
Males	Count	21	22	43
	%	67.7%	71.0%	69.4%
Total	Count	31	31	62
	%	100.0%	100.0%	100.0%
*Chi-squared test				

Table 3. Distribution of the subjects based on gender

19 patients (30.6%) were females of which, 10 patients (32.3%) received phenytoin and 9 patients (29%) received levetiracetam. 43 patients (69.4%) were males of which, 21 patients (67.7%) received phenytoin and 22 patients (71%) received levetiracetam. The distribution of the subjects based on gender was statistically not significant. (p=0.78)

Groups	**N**	**Minimum**	**Maximum**	**Mean**	**S.D**	**Mean diff**	**p value**
Phenytoin	31	6.0	360.0	57.26	66.34	29.64	0.032*
Levetiracetam	31	6.0	180.0	27.61	35.13		
**Unpaired T test*							

Table 4. Comparison of the mean duration of treatment (in months) between the groups

The mean duration of treatment in patients receiving phenytoin was 57.26 ± 66.34 months and mean duration of treatment in patients receiving levetiracetam was 27.61 ± 35.13. Using Unpaired T test, the comparison of mean duration of treatment between the groups was statistically significant. (p=0.03)

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Lipid Profile	Groups	N	Minimum	Maximum	Mean	S.D	Mean diff	p value
Total Cholesterol	Phenytoin	31	112.0	220.0	165.90	23.70	52.83	0.001*
	Levetiracetam	31	82.0	149.0	113.06	17.22		
HDL-C	Phenytoin	31	24.0	68.7	48.78	9.35	3.41	0.110
	Levetiracetam	31	28.7	58.9	45.36	7.07		
LDL-C	Phenytoin	31	63.80	133.20	95.54	13.66	23.17	0.001*
	Levetiracetam	31	45.80	99.90	72.37	11.45		
Triglycerides	Phenytoin	31	92.6	253.0	148.074	33.11	46.69	0.001*
	Levetiracetam	31	82.5	126.0	101.384	9.22		

Unpaired T test

Table 5. Comparison of the mean lipid profile between the groups

The mean total cholesterol in patients who received phenytoin was 165.90 ± 23.70 and in patients who received levetiracetam was 113.06 ± 17.22 (p=0.001). The mean HDL-C in patients who received phenytoin was 48.78 ± 9.35 and in patients who received levetiracetam was 45.36 ± 7.0 (p=0.11). The mean LDL-C in patients who received phenytoin was 95.54 ± 13.66 and in patients who received levetiracetam was 72.37 ± 11.45. (p=0.001). The mean triglycerides in patients who received phenytoin was 148.07 ± 33.11 and in patients who received levetiracetam was 101.38 ± 9.22. (p=0.001). Using Unpaired T test, the comparison of mean lipid profile between the groups was statistically significant. (p=0.001)

DISCUSSION

This study conducted to study lipid profile changes in subjects who are antiepileptic drugs. In the present study, the mean age of patients receiving phenytoin was 59.81 ± 14.94 and mean age of patients receiving Levetiracetam was 41.97 ± 15.63 years (p=0.001). Majority of the patients (32.3%) receiving phenytoin belonged to the age group of 61 to 70 years and majority of the patients (29%) receiving levetiracetam belonged to the age group of 22 to 30 years. (p=0.008). A higher male preponderance was observed in the present study in phenytoin group (67.7%) and in levetiracetam group (71%). Similarly, Mintzer et al noted that the inducer group averaged 8 years older and had a much higher percentage of male subjects (54% male vs 36% female).[3] In a study by Seetlani NK et al lipid values found to be more deranged in patients aged 41-50 years.[6] On the contrary, another study by Tejashwini V B conducted among young healthy medical students showed a higher female proponderance with a median age of 22 years.[7] A higher male preponderance was found in a study by Chen Z et al (51%) which were in concurrence with the findings of the present study.[8]

In this study mean total cholesterol in patients who received phenytoin was 165.90 ± 23.70 and in patients who received levetiracetam was 113.06 ± 17.22 thereby showing increased TC levels in the phenytoin group compared to levetiracetam. (p=0.001) These results were in concurrence with another study by Manimekalai K et al which showed that TC in patients receiving phenytoin was 186.5 ± 7.87 and mean TC in patients receiving levetiracetam was 170.90 ± 8.41.[5] Another study by Sudha et al compared the TC levels at baseline and at 6 months and they observed that TC levels in patients on phenytoin were 180.86±23.85 and at 6 months were 189.43±21.07.

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Also, TC levels in patients on levetiracetam were 183.03±42.16 and at 6 months were 183.20±41.81.[9]

The mean HDL-C in patients who received phenytoin was 48.78 ± 9.35 and in patients who received levetiracetam was 45.36 ± 7.07 (p=0.11) thereby showing increased HDL-C levels in the phenytoin group compared to levetiracetam, however, the comparison was not statistically significant. (p=0.11) Study results conducted by Calandre et al., and Dewan P et al., observed higher HDL-C and TC levels in the phenytoin group.[10,11] This is in contrary with another study by Manimekalai K et al which showed that HDL-C in patients receiving phenytoin was 71.1 ± 3.14 and mean HDL-C in patients receiving levetiracetam was 65.90 ± 3.16. which showed significant increase in HDL-C levels.[5]

In the present study, the mean LDL-C in patients who received phenytoin was 95.54 ± 13.66 and in patients who received levetiracetam was 72.37 ± 11.45. (p=0.001) thereby showing increased LDL-C levels in the phenytoin group compared to levetiracetam. These results were in concurrence with another study by Manimekalai K et al which showed that LDL-C in patients receiving phenytoin was 82.75 ± 7.85 and mean LDL-C in patients receiving levetiracetam was 81.85 ± 7.66.[5] Another study by Sudha et al compared the HDL-C levels at baseline and at 6 months and they observed that LDL-C levels in patients on phenytoin were 114.66±20.26 and at 6 months were 119.631±9.09. Also, LDL-C levels in patients on levetiracetam were 112.7±33.08 and at 6 months were 113.5±32.29.[9]

In the present study, the mean triglycerides in patients who received phenytoin was 148.07 ± 33.11 and in patients who received levetiracetam was 101.38 ± 9.22. (p=0.001) thereby showing increased triglycerides levels in the phenytoin group compared to levetiracetam. These results were in concurrence with another study by Manimekalai K et al which showed that triglycerides level in patients receiving phenytoin was 133.7 ±4.50 and mean TG in patients receiving levetiracetam was 125.80 ± 4.78.[5] Another study by Sudha et al compared the TG levels at baseline and at 6 months and they observed that TG levels in patients on phenytoin were 178.26±60.53 and at 6 months were 186.2±58.18.[9]Also, TG levels in patients on levetiracetam were 176.8±78.66 and at 6 months were 179.1±78.42.[9]

The results in our study findings are similar to those other investigations done by P Kumar et al., Pelkonen et al., Nikkila et al., and Luoma et al., also reported same findings i.e. an increase in TG, LDL-C and HDL-C levels in epileptic patients on long-term treatment with Phenytoin.[12,13,14,15]

Interestingly, Mintzer et al., observed that when epileptic patients on inducing agents like phenytoin switch to the non-inducing AEDs lamotrigine and levetiracetam demonstrated a decline in total cholesterol.[3]

It is possible that phenytoin will cause the CYP enzyme to get activated. The housekeeping gene

CYP51, which is a member of the cytochrome P450 super family is involved in the biological process of cholesterol synthesis in humans. The enzyme system known as CYP450 is involved in the processes of cholesterol production as well as cholesterol metabolism. Particularly important for the synthesis of cholesterol is the enzyme CYP51A1. There have been no detectable effects on lipid metabolism suggests that levetiracetam does not seem to be an inducer of the CYP51 enzyme.[16,17]

Long term phenytoin administration causes it to compete with cholestrol for utilisation by liver microsomal enzymes leading to lesser conversion of cholestrol to bile salts causing hypercholesterolemia.[18]

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Overall, the comparison of mean lipid profile between the groups was statistically significant in the present study with patients on phenytoin displaying elevated serum lipid profile levels(TC, LDL-C and TG). (p=0.001) Thus, TC levels, LDL-C levels and TG levels can be an important marker for estimating the risk of cardiovascular disease in epilepsy patients.

CONCLUSION

We observed patients on phenytoin displayed elevated serum lipid profile levels (TC, LDL-C and TG). Thus, TC levels, LDL-C levels and TG levels can be an important marker for estimating the risk of cardiovascular disease in epilepsy patients.

According to this study, phenytoin and other CYP enzyme inducer anti-epileptic drugs are linked to higher amounts of TC, LDL-C, and TG while levetiracetam did not show any major changes. Therefore, people who are taking inducer anti-epileptic drugs should have their blood cholesterol level checked on a regular basis.

REFERENCES

1. Gururaj G, Satishchandra P, Amudhan S. Epilepsy in India I: Epidemiology and public health. Annals of Indian Academy of Neurology. 2015;18(3):263.
2. Lowenstein DH, Rao VR. Seizures and Epilepsy. In; Loscalzo J (Eds). Harrison's Principles of Internal Medicine. 21st Edition. New York: McGraw Hill Publication; 2022. p 3305-3323
3. Mintzer S, Skidmore CT, Abidin CJ, Morales MC, Chervoneva, Capuzzi DM. Effects of Antiepileptic Drugs on Lipids, Homocysteine, and C-Reactive Protein. Ann Neurol. 2009;65:448–56.
4. McNamara JO. Goodman Gilman: The pharmacological basis of therapeutics. 12th edition. New Delhi: McGraw Hill Medical; 2011. Pharmacotherapy of Epilepsies. In, Brunton LL (ed) p. 583.
5. Manimekalai K, Visakan B, Salwe KJ, Murugesan S. Evaluation of Effect of Antiepileptic Drugs on Serum Lipid Profile among Young Adults with Epilepsy in a Tertiary Care Hospital in Pondicherry. J Clin Diagn Res. 2014 Aug;8(8):HC05-9.
6. Seetlani NK, Kumari G, Yasmin F, Hasan CA, Hussaini M, Awan S, et al. Frequency and pattern of deranged lipid profile in patients with ischemic stroke: a retrospective study. Acta Bio Medica : Atenei Parmensis . 2022;93(3):e2022178.
7. Tejashwini V B, Ganashree C P. Correlation between serum lipid profile and body mass index in young healthy medical students. Indian J Clin Anat Physiol 2021;8(2):106-109
8. Chen Z, Brodie MJ, Liew D, Kwan P. Treatment Outcomes in Patients With Newly Diagnosed Epilepsy Treated With Established and New Antiepileptic Drugs: A 30-Year Longitudinal Cohort Study. JAMA Neurol. 2018 Mar 1;75(3):279-286. doi: 10.1001/jamaneurol.2017.3949. Erratum in: JAMA Neurol. 2018 Mar 1;75(3):384
9. Sudha P, Suresh T, Gowthami V and Dhivya K: Assessment of potential effect of antiepilpetic drugs on lipid profile and C-reactive protein as predictors of vascular disease in epilepsy patients. Int J Pharm Sci Res 2017; 8(12): 5215-20.
10. Calandre EP, Porta BS, Dolores Calzada GDL. The Effect of Chronic phenytoin Treatment on Serum Lipid Profile in Adult Epileptic Patients. Epilepsia. 1992;33(1):154–57.

ISSN: 0975-3583, 0976-2833 VOL 15, ISSUE 11, 2024

11. Dewan P, Aggarwal A, Faridi A. Effect of phenytoin and valproic acid therapy on serum lipid levels and liver function tests. Indian Pediatrics. 2008;45:855–58.
12. Kumar P, Tyagi M, Tyagi Kumar Y, Kumar A, Rai Kumar Y. Effect of anticonvulsant drug on lipid profile in epileptic patients. J of Neurology. 2004;3(1):202–10.
13. Palkonen R, Foegelholm R, Nikkila EA. Increase in serum cholesterol during Phenytoin treatment. Br. Med J. 1975;4:85–87.
14. Nikkila EA, Kaste M, Ehnbolm C, Viikari J. Increase in serum high-density lipoprotein in Phenytoin users. Br Med J. 1978;2:99–103.
15. Luoma PV, Myllyla VV, Sotaniemi EA, Hokkanan TEJ. Plasma HDL cholesterol in epileptics with elevated tryglycerides and cholesterol. Acta Neural Scand. 1979;60:56–63.
16. Isojarvi JI, Pakarinen AJ, Myllyla VV. Serum lipid levels during carbamazepine medication. A prospective study. Archives of Neurology. 1993;50:590–93.
17. Gibbons GF. The role of cytochrome P450 in the regulation of cholesterol biosynthesis. Lipids. 2002;37:1163–70.
18. Sangeetha, A & Bobby, Zachariah & Wadwekar, Vaibhav & Nisha, Yadav. Atherogenic Risk Factors among Young Indian Adults with Epilepsy on Treatment with Phenytoin: Need for Novel Therapeutic Strategies. Neurology India. 69. 957-61. . 2021. 10.4103/0028-3886.325371.