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Original Article

A Hospital Based Comparative Study on Effect of Lipid Profile in Patients Treated with Older and Newer Anti Epileptic Drugs

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Abstract

Objective: *To study the effect of commonly prescribed anti epileptic drugs as Carbamazepine, Phenytoin and newer antiepileptic drug as Lamotrigine, Levetiracetam on lipid profile of epileptic children (2-12 yrs) who had taken them for long term presented in outdoor or indoor Department of Pediatrics, Darbhanga Medical College and Hospital, Laheriasarai.*

Method: *Prospective observational study done in indoor and outdoor of Department of Pediatrics, Darbhanga Medical College and Hospital, Laheriasarai. All children aged 2 years to 12 years, of either sex having partial or generalized seizures and recently started on anti-epileptic drugs, (Carbamazepine, Phenytoin, Lamotrigine, Levetiracetam) were selected for 6 months from March 2012 to august 2012. Patients who had taken prior anticonvulsant or taking more than one AED, family history of dyslipidemia, metabolic disease or disease which has propensity to alter lipid profile like diabetes mellitus, nephrotic syndrome, hypothyroidism, storage diseases, renal failure and cholestatis were excluded from the study. Patients were classified into 4 groups: (1) PHT-treated subgroup (22 patients); (2) CBZ-treated group (23 patients); (3) Lamotrigine - treated group (6patients) (4). Levetiracetam treated group (10 patients) in all cases patients were adequately treated. Serum lipid profile included total cholesterol (TC), triglycerides (TG), LDL-Cholesterol (low density lipoprotein cholesterol) and HDL-Cholesterol (high density lipoprotein cholesterol). These were done before and after treatment with AED over 6 and 12 months The study was approved by ethical committee of DMCH. All investigations were done in department of pathology, DMCH.*

Results: *Cases were selected for 6 months from March 2012 to august 2012 and followed up for 12 months, total 18 months .79 cases were selected and followed up. 18 patients were lost to follow-up and 61 cases were followed up till 12 months. So we ended up with 61 patients in which 31.1% (n=19) were females and 68.8 %(n=42) were males.77.0 %(n=47) patients were above 6 yr of age. 73.7% patients were taking older enzyme inducing AED (CBZ & PHT, n=45) while 26.2% (n=16) of patients taking Levetiracetam & Lamotrigine. Carbamazepine (CBZ) significantly increases the total cholesterol, HDL cholesterol, Triglycerides, LDL cholesterol. Increase in the Total Cholesterol: HDL and LDL: HDL ratio is not significant. There was significant increase in mean Total Cholesterol, Triglycerides, HDL, LDL in patients treated with Phenytoin (PHT). There was no significant increase in ratio of LDL/HDL and Total cholesterol / HDL. Lamotrigine produces no significant increase in the Total Cholesterol, HDL, LDL, Triglycerides or any other alterations in the ratio of Total Cholesterol: HDL and LDL: HDL Levetiracetam showed a significant increase in Total cholesterol , Triglycerides , HDL, But there was no statistical significance of its effect on LDL*

cholesterol or the ratios of Total Cholesterol: HDL and LDL: HDL ratio.
Conclusion: *Hepatic enzyme inducers like Carbamazepine, Phenytoin and new AED Levetiracetam may have adverse effect on serum lipid profile. These alterations in serum lipids may have clinical relevance in development of atherosclerosis thus causing cardiovascular disease (CVD). Lamotrigine has no significant effect on lipid profile thus may be preferred over enzyme inducing AED when effect on serum lipid profile is considered. Monitoring of serum lipid should be done in children with epilepsy taking Carbamazepine Phenytoin and levetiracetam.*
Keywords: *older antiepileptic drugs, Newer antiepileptic drugs, serum lipid profile, hepatic enzyme inducers, cardiovascular disease.*

Introduction

Epilepsy is among the commonly prevalent non communicable disease, particularly related to Central nervous system (CNS) [1]. For common clinical and epidemiological purposes epilepsy is considered to be present when 2 or more unprovoked seizures occurs in a time frame of longer than 24 hour. It affects nearly 70 million people worldwide[1]. Its prevalence in low and middle income countries (as India) is about twice that of high income countries[2]. India has approximately 10 million people affected with epilepsy[3]. Anticonvulsant drugs are used for controlling seizure disorder including epileptic seizure. Epilepsy requires long term anticonvulsant treatment.

Anticonvulsants alters liver function and increase the activity of hepatic microsomal enzyme system which causes altered metabolism of various substances such as drugs and lipids[4,5] Many authors reported significant changes in serum lipids after giving prolonged anti epileptic drugs(AED)[6-10]. There is clear evidence linking abnormalities in lipid and lipoprotein levels to premature Atherosclerotic vascular changes [11]. Many study suggested increased prevalence and death rates among epileptic patients taking prolonged AED from atherosclerosis related CVD[12,13,14]. In contrast some studies suggested lower prevalence[15].

Hypercholesterolemia, i.e., increased total cholesterol (TC), increased low-density lipoprotein Cholesterol (LDL-c and elevated triglyceride (TG) levels are known atherogenic risk factor whereas high-density lipoprotein cholesterol (HDL-c) has protective effect[16]. Cholesterol fractions ratio has better predictions of atherosclerosis. Lesser value of TC/HDL-c and LDL-c/HDL-c are powerful protectors of atherosclerosis, while higher ratios increase the risk[17, 18]. In the light of so many researches it can be said that adverse drug effects of AEDs represent an area of legitimate concern. Since most of these effects develop insidiously over many years, they are generally overlooked.

Older enzyme inducing AED like Carbamazepine and Phenytoin are frequently used by us in our setup. Newer non enzyme inducing AED as Lamotrigine and Levetiracetam are used less frequently. Many researches show that newer AED have lesser side effects and improved tolerance[19,20] compared to older ones. Their effect on lipid profile, thus propensity to develop atherosclerosis is also less.

So this study was undertaken to compare the effect of newer AED against commonly prescribed AED (CBZ, PHT) on serum lipid profile in children.

Aims and Objectives

We did this study to evaluate the effect of commonly prescribed enzyme inducing AED (CBZ,PHT) and newer AED (Lamotrigine, Levetiracetam) on lipid profile of children (2-12 yrs) who presented in outdoor or indoor of Department of Paediatrics, Darbhanga Medical College and Hospital, Laheriasarai.

Objective

1- To asses serum lipid profile change in children taking commonly used AED (Carbamazepine, CBZ and Phenytoin, PHT) for long term

2- To asses serum lipid profile change in children taking newer AED (Lamotrigine and levetiracetam) for long term
3- To compare the effects of both type of AED on lipid profile of children.

Material and Methods

This was a prospective observational study done in outdoor and indoor patients of Department of Pediatrics, Darbhanga Medical College and Hospital, Laheriasarai. Cases were selected for 6 months from March 2012 to August 2012 and followed up for 12 months, total 18 months .79 cases were selected and followed up .18 patients were lost to follow-up and 61 cases were followed up till 12 months.

Inclusion Criterion

1. All children aged 2 years to 12 years, of either sex having partial or generalized seizures and recently started on anti-epileptic drugs, (Carbamazepine, Phenytoin, Lamotrigine, and Levetiracetam).
2. Those cases that attended outdoors and later admitted were considered as single cases.

Exclusion Criterion

1. Patients who had taken prior anticonvulsant or taking more than one AED
2. Patients who had a family history of dyslipidemia or metabolic disease.
3. Children having diseases like diabetes mellitus, nephrotic syndrome, hypothyroidism, storage diseases, renal failure and cholestatic disease like, congenital biliary atresia. These have propensity to alter lipid profile.
4. Children taking drugs such as corticosteroids, thiazide diuretics, B-blockers.
5. Patients with gross developmental delay or congenital abnormalities.
6. Cases which did not co operate and did not come for follow up

The study was carried out with the approval of the ethics committee of DMCH Laheriasarai Darbhanga. Informed parental consent was obtained. According to AED used, patients were classified into 4 groups: (1) CBZ-treated subgroup (23 patients); (2) PHT-treated group (22 patients); (3) Lamotrigine treated group (6 patients) ;(4) Levetiracetam treated group (10 patients).In all cases patients were adequately treated.

Serum lipid profile included total cholesterol (TC), triglycerides (TG), LDL-Cholesterol (low density lipoprotein cholesterol) and HDL-Cholesterol **(**high density lipoprotein cholesterol). These were done before and after treatment with AED over 6 and 12 months.

All investigations were done in department of pathology, DMCH.

Statistical Analysis

Results were analyzed using repeat measure ANOVA test, Pearson Chi-Square

Result

Table 1: Sex Ratio

	Carbamazepine	Phenytoin	levetiracetam	lamotrigine	total
female	8	6	3	2	19(31.1%)
male	15	16	7	4	42(68.8%)
	23	22	10	6	61

Table 2 : Age incidence

Age group	Frequency
2-6yrs	14 (22.9%)
6-10 yrs	29 (47.5%)
10-12yrs	18 (29.5%)

Table 3 Lipid profile parameters baseline and after 6 and 12 months of Carbamazepine with p values

Parameters	**Count**	**Mean**	**Standard deviation**	**Median**	**Repeat measures ANNOVA test applied**	
Total Cholesterol Baseline	23	146.48	26.84	144	Chi Square	P value
At the end of 6months	23	168.95	34.73	168.28	24	< 0.001
At the end of 12 months	23	197.12	42.32	190.5	Difference is significant	
Triglycerides Baseline	23	83.33	50.17	63	Chi square	P value
At the end of 6 months	23	108.84	52.59	82.95	24.337	<0.001
At the end of 12months	23	128.3	59.01	103.4	Difference is significant	
LDL-Cholesterol Baseline	23	81.37	19.39	80.5	Chi Square	P value
At the end of 6 months	23	90.93	25.16	82.94	19.5	<0.001
At the end of 12 months	23	109.11	31.05	106.55	Difference is significant	
HDL-Cholesterol Baseline	23	48.45	9.64	47.2	Chi Square	P value
At the end of 6months	23	56.25	10.12	57	22.167	<0.001
At the end of 12months	23	62.35	8.89	61.5	Difference is significant	
LDL:HDL Baseline	23	1.74	0.53	1.78	F value	P value
At the end of 6 months	23	1.65	0.52	1.52	0.634	0.54
At the end of 12 months	23	1.77	0.53	1.79	Difference is not significant	
Cholesterol :HDL Baseline	23	3.1	0.65	3.16	F value	P value
At the end of 6 months	23	3.05	0.67	2.97	0.907	0.418
At the end of 12 months	23	3.19	0.71	3.08	Difference is not significant	

Table 4 Lipid profile parameters baseline and after 6 and 12 months of Phenytoin with p values

Parameters	Count	Mean	Standard deviation	Median	Repeat Measures ANOVA test applied	
Total Cholesterol Baseline	22	164.82	43.86	159	F value	P value
At the end 6 months	22	179.88	35.23	174	23.157	<0.001
At the end of 12 months	22	226.11	61.25	227	Difference is significant	
TriglyceridesBaseline	22	69.63	40.81	60	Chi Square	P value
At the end 6 months	22	72.14	26.82	63.55	18.5	<0.001
At the end of 12 months	22	86.33	45.9	72	Difference is significant	
HDL-Cholesterol Baseline	22	50.9	10.75	51.8	F value	P value
At the end 6 months	22	61.24	8.81	61	75.145	<0.001
At the end of 12 months	22	68.5	7.39	71	Difference is significant	
LDL-Cholesterol Baseline	22	99.99	35.32	96.7	Chi Square	P value
At the end 6 months	22	104.21	32.41	98.09	9.5	0.009
At the end of 12 months	22	140.34	55.69	134.6	Difference is significant	
LDL:HDL ratio Baseline	22	2.04	0.81	1.83	Chi Square	P value
At the end 6 months	22	1.74	0.63	1.66	3.167	0.205
At the end of 12 months	22	2.04	0.75	2.04	Difference is not significant	
Cholesterol:HDL Baseline	22	3.33	0.98	3.1	Chi Square	P value
At the end 6 months	22	2.99	0.73	2.86	4.667	0.097
At the end of 12 months	22	3.3	0.82	3.32	Difference is not significant	

Table 5 Lipid profile parameters baseline and after 6 and 12 months of Lamotrigine with P values

Parameters	Count	Mean	Standard deviation	Median	Repeat Measures ANOVA test applied	
Total Cholesterol Baseline	6	163.33	11.55	170	F value	P value
At the end of 6 months	6	166	10.39	172	4.409	0.097
A t the end 12 months	6	167	13.08	173	Difference is not significant	
Triglycerides Baseline	6	98.67	44.06	120	F value	P value
At the end of 6 months	6	102.67	45.62	128	5.725	0.067
At the end of12 months	6	104.33	45.54	126	Difference is not significant	
HDL-Cholesterol Baseline	6	49	9.54	50	F value	P value
At the end of 6 months	6	52.33	7.64	54	3.608	0.127
At the end 12 months	6	52.83	6.83	56	Difference is not significant	
LDL-Cholesterol Baseline	6	94.6	24.48	107	F value	P value
At the end of 6 months	6	93.13	21.09	102.4	0.423	0.682
At the end of 12 months	6	93.3	22.35	105.8	Difference is not significant	
LDL:HDL ratio Baseline	6	2.03	0.81	2.21	F value	P value
At the end of 6 months	6	1.83	0.6	2	2.64	0.186
At the end of 12 months	6	1.81	0.59	1.9	Difference is not significant	
Cholesterol:HDL ratio Baseline	6	3.45	0.89	3.4	F value	P value
At the end of 6 months	6	3.23	0.65	3.19	2.343	0.212
At the end of 12 months	6	3.21	0.64	3.09	Difference is not significant	

Table 6 Lipid profile parameters baseline and after 6 and 12 months of Levetiracetam with p values

Parameters	Count	Mean	StdDev	Median	Repeat Measures ANOVA test applied	
Total Cholesterol Baseline	10	165.45	22.75	166.35	F value	P value
At the end of 6 months	10	182.78	12.87	181.35	10.448	0.004
At the end of 12 months	10	202.5	19.16	204	Difference is significant	
Triglycerides Baseline	10	128.9	37.23	134.2	F value	P value
At the end of 6 months	10	133.97	37.76	140.7	24.948	<0.001
At the end of 12 months	10	136.17	39.89	142.35	Difference is significant	
HDL-Cholesterol Baseline	10	52.17	6.15	52	Chi-Square	P value
At the end 6 of months	10	59.3	4.32	59	12	< 0.001
At the end of 12 months	10	66.38	6.38	67.5	Difference is significant	
LDL-Cholesterol Baseline	10	87.5	24.38	87	F value	P value
At the end of 6 months	10	96.69	11.76	94.9	3.909	0.056
At the end of 12 months	10	108.88	16.35	104.48	Difference is not significant	
LDL:HDL ratio Baseline	10	1.7	0.54	1.57	F value	P value
At the end of 6 months	10	1.64	0.23	1.54	0.0951	0.91
At the end of 12 months	10	1.65	0.27	1.56	Difference is not significant	
Cholesterol:HDL ratio Baseline	10	3.2	0.54	3.03	F value	P value
At the end of 6 months	10	3.09	0.26	3.05	0.522	0.608
At the end of 12 months	10	3.06	0.32	2.95	Difference is not significant	

Discussion

This study was done to find out whether any correlation exists between use of different AED (antiepileptic drugs) and lipid profile. It also compares older enzyme inducing AED (CBZ, PHT) over newer AED (Lamotrigine, Levetiracetam) with respect to their effect on lipid profiles.

79 patients were enrolled for the study out of which 18 patients were lost to follow up .So we ended up with 61 patients in which 31.1% (n=19) were females and 68.8% (n=42) were males .77.0 % (n=47) patients were above 6 yr of age. In this study 73.7% (n=45) patients were taking older enzyme inducing AED which is widely used in our hospital (CBZ &PHT, n=45) while 26.2 %(n=16) of patients were taking newer non enzyme inducing drugs (levetiracetam and lamotrigine).

In our study we compared various parameters of lipid profiles of different drugs before initiation of treatment and at the end of 6 and 12 months.

The statistical analysis showed that Carbamaz-epine (CBZ) significantly increases the total cholesterol ($p<0.001$), HDL cholesterol ($p<0.001$), Triglycerides ($p<0.001$), and LDL cholesterol ($p<0.001$). However increase in the Total Cholesterol: HDL and LDL: HDL ratio is not significant. These results are similar to the study done by Luoma et al [21], Brown[22], Nermann Bolukkal[23] in which there was increase in all the lipid profile parameter. However, K. Manimekalai [24] etal and Yis U etal [25] did not observe any statistically significant difference among mean LDL-Cho levels.

Our study showed significant increase in mean Total Cholesterol ($p<0.001$), Triglycerides ($p<0.001$), HDL ($p<0.001$) and LDL ($P<0.009$) in patients treated with Phenytoin(PHT). These results are similar to studies done by Nikila et al[26]. Contrary to it, Calandre et al[27]., and Dewan P et al [28] observed higher HDL-C and TC levels but no effect on LDL-C levels . However there was no significant increase in ratio of LDL/HDL and Total cholesterol / HDL.

Carbamazepine and phenytoin are enzyme inducing drugs. They are principally metabolized by hepatic cytochrome P450 drugs. This enzyme complex also catalyses transformation of cholesterol into biliary acids. Thus, during long-term treatment, they compete with cholesterol in the utilization of the P450 enzyme system, thus causing reduced transformation rate of cholesterol into bile acids and hence increased TC[29,30,31]. Carbamazepine also stimulates cholesterol synthesis in liver[32].

The above results suggest that the use of drug Lamotrigine produce no significant increase in the Total Cholesterol, HDL, LDL, Triglycerides or any other alterations in the ratio of Total Cholesterol: HDL and LDL: HDL .These results were in agreement with the studies done by S. Svalheim et al[(33)], Chuang et al [(34)]. Thus it appears that the non microsomal inducing property of Lamotrigine is responsible for no effect on the lipid profile.

Analysis of the data of effect of Levetiracetam on lipid profile showed a significant increase in Total cholesterol ($p<0.004$), Triglycerides ($p<0.001$), HDL ($p<0.001$). But there was no statistical significance of its effect on LDL cholesterol or the ratios of Total Cholesterol: HDL and LDL: HDL ratio. This is in contrast to the study done by S.Svalheim et al[33] which suggested lipid profiles were not affected by Levetiracetam.

After comparing the final results of different drugs at the end of 12 months from baseline results were analyzed as follows. All analysis was done from baseline to end of 12 months.

1) All drugs increase total cholesterol significantly except Lamotrigine. Phenytoin had maximum increase in the mean by 61.29 and it was followed by Carbamazepine with a mean increase of 50.64.
2) In triglyceride maximum increase was seen in Carbamazepine where mean increased by 30 followed by Levetiracetam with mean increase by 7.Lamotrigine has insignificant effect on triglyceride levels.
3) Increase in HDL was greatest with Phenytoin, mean of 17.50 followed by Carbamazepine mean 12.4 and least affected with Lamotrigine.
4) Maximum rise in LDL was seen by Phenytoin with a mean increase of 40.35 followed by Carbamazepine where mean increase of 27.75.Lamotrigine shows a significant increase with mean of 21.38 while Lamotrigine had insignificant effect.
5) The increase in the ratio of LDL/HDL at the end of twelve months for all groups was not significant and increase was maximum with Carbamazepine.
6) All drugs have insignificant effect on total cholesterol: HDL ratio

Conclusion

It is concluded that:

1. Anticonvulsant drugs modify serum lipids in a significant way in epileptic children.
   A. Phenytoin deranges all the parameters. It increases total cholesterol, LDL, HDL and triglycerides. Ratios of total cholesterol to HDL and LDL/HDL are not significantly affected.
   B. Carbamazepine increases total cholesterol, LDL, HDL and triglycerides. Ratios of total cholesterol to HDL and LDL/HDL are not affected.
   C. Lamotrigine causes no significant increase in the total cholesterol, LDL, HDL, triglycerides, ratios of total cholesterol to HDL and LDL/HDL. Hence is a very safe drug as far as affecting lipid profile is concerned.
   D. Levetiracetam increases total cholesterol, LDL, HDL and triglycerides. Ratios of total cholesterol to HDL and LDL/HDL are not affected.
2. Hepatic enzyme inducers like Carbamezipine , Phenytoin and new AED Levetiracetam may have adverse effect on serum lipid profile. These alterations in serum lipids may have clinical relevance in development of atherosclerosis thus causing cardiovascular disease (CVD) .
3. Lamotrigine has no significant effect on lipid profile thus may be preferred over enzyme inducing AED when effect on serum lipid profile is considered.
4. Monitoring of serum lipid should be done in children with epilepsy taking Carbamazepine Phenytoin and levetiracetam. Atherogenic diet should be avoided, at least during AED therapy with these drugs.
5. More study needs to be done to asses lipid profile changes with long term AED therapy.

Limitations of the Study

1) Sample size in this study is small.
2) Longer follow up should be done to know whether these changes are of any consequence, whether the changes in lipid profile worsen or improve or remain the same.

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Abbreviation

AED Antiepileptic drugs, **CVD** Cardiovascular disease, **TC** Total cholesterol, **TG** Triglyceride, **LDL-C** Low density lipoprotein cholesterol, **HDL-C** High density lipoprotein cholesterol, **CBZ** Carbamazepine, **PHT** Phenytoin,