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EFFECT OF COMMONLY USED ANTIEPILEPTIC DRUGS ON SERUM LIPID PROFILE IN CHILDREN

Pediatrics

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ABSTRACT

OBJECTIVE: To study the effect of commonly prescribed anti epileptic drugs both enzyme inducers as Carbamazepine, Phenytoin and non enzyme inducers as Valproate on lipid profile of epileptic children(2-12 yrs) who had taken them for long term, presented in outdoor or indoor of Department of Pediatrics', Darbhanga Medical College and Hospital, Laheriasarai.

METHOD: prospective observational study done in indoor and outdoor patients 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, Valproate,) were selected for 6 months from March 2012 to august 2012 and followed up for 12 months. 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 3 groups: (1) PHT-treated subgroup (22 patients); (2) CBZ-treated group (23 patients); (3) VPA- treated group (18patients). 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: 83 patients were enrolled for the study out of which 20 patients were lost to follow up .so we ended up with 63 patients in which 31.7%(n=20)were females and 68.25%(n=43) were males.77.7%(n=49) patients were above 6 yr of age. 71.4% patients were taking older enzyme inducing AED (CBZ &PHT, n=45) while 28.5 %(n=18) of patients taking VPA .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. Valproate showed a significant decrease in Total Cholesterol, Triglycerides, LDL .Change in HDL was not significant however decrease in ratio of LDL/HDL and Total cholesterol / HDL ratio was significant.

CONCLUSION: Hepatic enzyme inducers like Carbamazepine and Phenytoin 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). Valproate has protective 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 and Phenytoin

KEYWORDS

antiepileptic drugs, serum lipid profile, hepatic enzyme inducers, atherosclerosis, cardiovascular disease

INTRODUCTION

Epilepsy is among the commonly prevalent non communicable disease, particularly related to Central nervous system[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) are 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 alter 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 AEDs[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 in contrast some studies suggested lower prevalence[12,13,14.15].

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. This study was undertaken because Phenytoin, Carbamazepine and Valproic acid is frequently used by us in our setup. So it is necessary to know about its propensity to affect lipid status thus by developing atherosclerosis.

Since the published reports has conflicting results we did this study to evaluate the effect of commonly prescribed AED on lipid profile of children (2-12 yrs) who presented in outdoor or indoor of Department of Pediatrics, Darbhanga Medical College and Hospital, Laheriasarai.

AIMS & OBJECTIVE:-

1- To assess serum lipid profile change in children taking enzyme inducing AED (Carbamazepine, CBZ and Phenytoin, PHT) for long term
2- To assess serum lipid profile change in children taking non enzyme inducing AED (Valproic acid, VPA) 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 OPD and IPD patients of Department of Pediatrics, Darbhanga Medical College and Hospital, Laheriasarai. Cases were selected for 6 months from March 2012 to august 2012. 83 cases were selected and followed up. 20 patients were lost to follow-up and 63 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 ,Valproate,)
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 3 groups: (1) PHT-treated subgroup (22 patients); (2) CBZ-treated group (23 patients); (3) VPA- treated group (18patients). 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.

STATISTICALANALYSIS

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

RESULTS

TABLE 1 : SEX RATIO

	Carbamazepine	Phenytoin	Valproic Acid	Total
Female	8	6	6	20(31.74%)
Male	15	16	12	43(68.25%)
Total	23(36.50%)	22(34.92%)	18(28.57%)	63

TABLE 2: AGE DISTRIBUTION OF PATIENTS

Age group (Yrs)	Frequency	Percent
2- 6 years	14	22.2
6-10 years	30	47.6
10- 12 years	39	30.1
Total	63	100.0

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 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	
Triglycerides Baseline	22	69.63	40.81	60	F value	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:HDLRATIO 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 RATIO 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 4. Lipid profile parameters baseline and after 6 and 12 months of Phenytoin with p values

Parameters	Count	Mean	Standard deviation	Median	Repeat Measures ANNOVA test applied	
Total cholesterol Baseline	18	176.11	26.78	170	F value	P value
At the end 6 months	18	166.33	16.86	165	13.542	<0.001
At the end of 12 months	18	151.11	15.46	150	Difference is significant	
Triglycerides Baseline	18	146.56	52.21	160	Chi-Square	P value
At the end 6 months	18	137.89	47.44	150	10.88	0.003
At the end of 12 months	18	129.72	37.72	137.5	Difference is significant	
HDL-Cholesterol Baseline	18	52.04	10.25	55	F value	P value
At the end 6 months	18	52.56	8.55	54	1.245	0.314
At the end of 12 months	18	53.6	7.97	53.5	Difference is not significant	
LDL-Cholesterol Baseline	18	94.76	35.68	87.2	F Value	P value
At the end 6 months	18	86.2	18.81	85	7.948	0.004
At the end of 12 months	18	71.57	19.6	71.2	Difference is significant	
LDL:HDL Ratio Baseline 0 months	18	2.03	1.25	1.58	F value	P value
At the end 6 months	18	1.74	0.73	1.61	5.8	0.013
At the end of 12 months	18	1.42	0.67	1.27	Difference is significant	
Cholesterol:HDL Ratio Baseline	18	3.62	1.42	3.21	F value	P value
At the end 6 months	18	3.29	0.93	3.24	7.349	0.005
At the end of 12 months	18	2.92	0.83	2.8	Difference is 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 one AED over the other with respect to their effect on lipid profiles. 83 patients were enrolled for the study out of which 20 patients were lost to follow up .so we ended up with 63 patients in which 31.7%(n=20)were females and 68.25%(n=43) were males.77.7%(n=49) patients were above 6 yr of age. In this study 71.4% patients were taking older enzyme inducing AED which is widely used in our hospital (CBZ &PHT, n=45) while 28.5 %(n=18) of patients taking VPA. Recent drugs like levetiracetam and lamotrigine are not prescribed commonly. 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 Carbamazepine (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 [19], Brown[20], Nermann Bolukkal [21] in which there was increase in all the lipid profile parameter. However, K. Manimekalai [22] etal and Yis U etal [23] 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[24]. Con trary to it, Calandre et al[25], and Dewan P et al [26] 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[30, 31, 32]. Carbamazepine also stimulates cholesterol synthesis in liver[33]. The drug Valproate showed a significant decrease in Total Cholesterol (p<0.001), Triglycerides (p<0.003), LDL (P<0.004) .The change in HDL was not significant however decrease in ratio of LDL/HDL (p<0.013) and Total cholesterol / HDL ratio (p<0.013) was also significant. These results are in correlation with the study by EP Calandre et al [27] and Nikolas T et al [28].however study by K. Manimekalai [22] etal and E Yilmaz et al[29] showed no significant change in Total cholesterol, HDL-C, LDL-C and TG levels.

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 except Valproate .Valproate significantly decrease the total cholesterol by a mean value of 25. 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 44.97 followed by Phenytoin with mean increase by 16.7 and a decrease of mean by 16.84 was seen with Valproate.
3) Increase in HDL was greatest with Phenytoin ,mean of 17.60 followed by Carbamazepine mean 13.9 and least affected with Valproate mean 1.56
4) Maximum rise in LDL was seen by Phenytoin with a mean increase of 40.35 followed by Carbamazepine where mean increase of 27.74 and a mean decrease of 23.19 was seen with Valproate.
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 whereas decrease was seen with Valproate.

CONCLUSIONS

It could be 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. Valproate causes significant decrease in total cholesterol, LDL, triglycerides and the ratios of total cholesterol to HDL and LDL/HDL. However, it does not significantly decrease HDL.

2. Hepatic enzyme inducers like Carbamazepine and Phenytoin 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. Valproate has protective 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 and Phenytoin
5. Atherogenic diet should be avoided, at least during AED therapy with enzyme inducers

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.

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, **VPA** Valproic acid

REFERENCES

1. WHO Epilepsy in the WHO region :Bridging the Gap:The Global Campaign Against Epilepsy.:"Out Of the Shadows".Geneva:WHO;2004
2. Ngugi AK, Bottomley C, Kleinschimdt I, Sander J W ,Newton C R. Estimation of the burden of active and life time epilepsy: a meta-analytiacal approach.Epilepsia 2010;51:883-890 Pubmed
3. Mac TL, Tran DS, Quet F, Odermatt P. Epidemiology, aetiology, and clinical management of epilepsy in Asia: a systematic review. Lancet Neurol. 2007; 6:533–43.
4. Luoma, P.V., Pelkonen, R.O., Myllyla, V., Sotaneimi, E.A. (1989) Relationship between serum lipid levels and indices of drug metabolism in epileptic on anticonvulsant. Clinical.Pharmaocol.Therp.25, 235-237.
5. Smith, D.B., Delgade, E.S., Cueta, A.V., Cramer, J.A., Maltson, R.H. (1983) Historical prospective on the choice of antiepileptic drug for the treatment of seizures in adults. Neurology. 33, 2-4.
6. Chang BS, Lowenstein DH. Epilepsy. N Engl J Med 2003;349:1257-66.
7. Fisher RS, Boas WVE, Blume W, Elger C, Genton P, Lee P, et al. Epileptic seizures and epilepsy: Definitions proposed by the Interna-tional League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE). Epilepsia 2005;46:470-2.
8. Sridharan R, Murthy BN. Prevalence and pattern of epilepsy in India. Epilepsia 1999; 40:631-6.
9. Finkelstein JD. Methionine metabolism in mammals. J Nutr Biochem 1990;I:228-37.
10. Billings RE. Interactions between folate metabolism, phenytoin metabolism, and liver microsomal cytochrome P450. Drug Nutr Interact 1984;3:21-32.
11. Tümer L, Serdaroglu A, Hasanoglu A, Biberoglu G, Aksoy E: Plasma homocysteine and lipoprotein (a) levels as risk factors for atherosclerotic vascular disease in epileptic children taking anticonvulsants. Acta Paediatr, 2002, 91, 923–926.
12. Annegers JF, Hauser WA, Shirts SB: Heart disease mortality and morbidity in patients with epilepsy. Epilepsia, 1984, 25, 699–704.
13. Elliott JO, Jacobson MP, Haneef Z: Cardiovascular risk factors and homocysteine in epilepsy. Epilepsy Res, 2007, 76, 113–123.
14. Gaitatzis A, Carroll K, Majeed A, WSander J: The epidemiology of the comorbidity of epilepsy in the general population. Epilepsia, 2004, 45, 1613–1622.
15. Muuronen A, Kaste M, Nikkilä EA, Tolppanen EM: Mortality from ischaemic heart disease among patients using anticonvulsive drugs: a case-control study. Br Med J, 1985, 23, 1481–1483.
16. Glass CK, Witztum JL: Atherosclerosis: the road ahead. Cell, 2001, 104, 503–516.
17. Demircioðlu S, Soylu A, Dirik E: Carbamazepine and valproic acid: effects on the serum lipids and liver functions in children. Pediatr Neurol, 2000, 23, 142–146.
18. Hamed S, Hamed E, Hamdy R, Nabeshima T: Vascular risk factors and oxidative stress as independent predictors of asymptomatic atherosclerosis in adult patients with epilepsy. Epilepsy Res, 2007, 74, 183–192.
19. Luoma PV, Myllyla¨ VV, Sotaniemi EA, Lehtinen IA, and Hokkanen EJ.Plasma high-density lipoprotein cholesterol in epileptics treated with various anticonvulsants. EurNeurol19:67–72, 1980.
20. Brown DW, Ketter TA, Crumlish J, Post RMCarbamazepine-induced increases in total Serum cholesterol: clinical and theoretical implications.. J ClinPsychopharmacol12: 431–437,1992
21. Nermin Bolukbasi, FerdaAkar, SinanBir the effects of Antiepileptic Drugs on Lipid Profiles and Liver Enzymes (Archives of Neuropsychiatry 2011; 48: 11-6).
22. K. Manimekalai, B. Visakan etal Journal of Clinical and Diagnostic Research. 2014 Aug, Vol-8(8): HC05-HC09
23. Yis U, Dog an M. Effects of oxcarbazepine treatment on serum lipids and carotid intima media thickness in children. Brain Dev. 2012;34(3):185-88.
24. E. Nikkila, M. Kaste, C.Ehnholm, J.ViikariIfrom the Third Department of Medicine, University of Helsinki, Finland Increase of serum high-density lipoprotein in phenytoin users.ActaMedicaScandinavicaVolume 204, Issue 1-6,517–520, January/December 1978.
25. 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.
26. 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.
27. Calandre EP, Rodriguez-Lopez C, Blazquez A, and CanoD. Serum lipids, lipoproteins and apolipoproteins A and B in Epileptic patients treated with valproic acid, carbamazepine or phenorbital. ActaNeurolScand83: 250–253, 1991
28. NikolaosT, StylianosG, Chryssoula N,Irini P , Christos M ,Dimitrios Tet al. The Effect of long-term antiepileptic treatment on serum cholesterol (TC, HDL, and LDL) and triglyceride levels in adult epileptic patients on monotherapy. Med Sci Monit.2004; MT50-MT52.
29. Yilmaz E, Dosan Y, Gurgoze MK, Gunggor S. Serum lipid changes during anticonvulsive treatment Serum lipids in epileptic children. Acta neurol belg. 2001;101:217-20.
30. Castro-Gago M, Novo-Rodríguez MI, Blanco-Barca MO, Urisarri-Ruíz de Cortázar A, Rodríguez-García J, Rodríguez-Segade S, Eirís-Puñal J: Evolution of serum lipids and lipoprotein (a) levels in epileptic children treated with carbamazepine, valproic acid, and phenobarbital. J Child Neurol, 2006, 21, 48–53.
31. Demircioðlu S, Soylu A, Dirik E: Carbamazepine and valproic acid: effects on the serum lipids and liver functions in children. Pediatr Neurol, 2000, 23, 142–146.
32. Franzoni E, Govoni M, D'Addato S, Gualandi S, Sangiorgi Z, Descovich GC, Salvioli GP: Total cholesterol, high-density lipoprotein cholesterol, and triglycerides in children receiving antiepileptic drugs. Epilepsia, 1992, 33, 932–935.
33. Gibbons GF. The role of cytochrome P450 in the regulation of cholesterol biosynthesis. Lipids. 2002;37:1163-70.