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COMPARISON BETWEEN CARBAMAZEPINE AND VALPROATE ON LIPID PROFILE AND LIPOPROTEIN (a)

Pediatrics

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ABSTRACT

Introduction: A seizure is a sudden, uncontrolled electrical disturbance in the brain. It can cause changes in behaviour, movements or feelings, and in level of consciousness The high incidence of epilepsy in children coupled with the need of long term antiepileptic treatment could lead to development of metabolic complications at an early age and hence the risk of atherosclerosis. The changes in serum lipid and lipoprotein (a) levels do play an important role in atherosclerosis and cardiovascular complications in later life. **Aim:** In view of the above facts the present study aims to evaluate the change in the level of lipids and lipoprotein (a) during the course of treatment of epilepsy with different antiepileptic drugs. **Materials and Methods:** A prospective follow up study was conducted on 19 children (10 on carbamazepine and 9 on valproate) in Department of Paediatrics at Maharishi Markandeshwar Institute of Medical Sciences and Research, Mullana, Ambala, Haryana. The duration of study was one and a half year. A detailed history was taken with complete clinical examination. Biochemical parameters like lipid profile, Lipoprotein(a), liver enzymes along with relevant investigations were done before starting anti- epileptic monotherapy and were followed up after 6 month of treatment.**Results:** Out of 19 children with seizure 10 on carbamazepine showed significant increase ($p < 0.05$) in the levels of lipoprotein (a), TG (triglyceride), TC (total cholesterol), LDL (low density lipids), VLDL (very low density lipids) after six months of treatment and 9 children on Valproate didn't show significant increase in lipid profile and lipoprotein (a) whereas has significant change in levels of SGPT ($p <0.05$) after six month of monotherapy. **Conclusion:** Several antiepileptic drug like carbamazepine with CYP450 enzyme inducers activity may cause significant rise in levels of lipids and lipoprotein (a), hence causing a potent risk factor for atherorsclerosis and cardiovascular complications in long term antiepileptic therapy; thus lipid profile and lipoprotein (a) should be monitored during the course of treatment.

KEYWORDS

carbamazepine, valproate,Lipoprotein(a), Lipid profile, Seizure, Epilepsy

INTRODUCTION

The oldest description of epilepsy is noted in Babylonian textbook of medicine which dates back to 2000 B.C. It back then was described as "the sacred disease" and thus was being treated in a spiritual manner. It was Hippocrates in 5th century who believed that epilepsy is a disease of brain. The word epilepsy was coined from Greek word 'Epilepsia' that means 'to stop' or 'to hold'. Sir Charles Locock in 1857 introduced Bromide as the first effective antiepileptic drug and was then used in North America and Europe, thereafter came Phenobarbitone which was discovered in 1912 by German chemist Emil Fischer and was used for seizure, it is the oldest antiepileptic drug which is still in use. In 1953 Carbamazepine was discovered by Swiss chemist Walter Schindler.

Valproic acid was discovered by Pierre Emymard 1962 during a study of anti- seizure compound.

The modern understanding is now enhanced by organisations like International League against Epilepsy (ILAE) which was founded in 1909. According to ILAE older classification, epilepsy was divided in 3 groups of partial, generalized, unclassified respectively which was modified by ILAE in 2017 and divides epilepsy into four basic groups: focal, generalized, generalized and focal and unknown.

Lipoprotein(a) is a very potent atherogenic factor and also an independent risk factor for vascular disease[1]. Lp(a) was identified as LDL variant with additional structural protein named apo(a) which is covalently bounded [2].

Also there is conclusion of high LDL and low HDL with high levels of Lipoprotein (a) [3] . Increase in concentration of lipoprotein (a) and lipids like total cholesterol, triglyceride, LDL with decrease in HDL are likely to be risk factor for coronary artery disease, thus choice of appropriate anti-epileptic drug is very important [4].

It was in 1968 when carbamazepine was first approved for partial and generalized tonic- clonic seizures. It acts by inhibiting inactivated voltage dependent sodium channel and thus limiting high frequency neuronal firing. Valproic acid is active against voltage dependent sodium and calcium channel, it also acts on enzyme involved in GABA metabolism and downregulates phospholipase A2 [5]

MATERIALAND METHOD

A prospective follow up study was conducted on 19 children (10 on carbamazepine and 9 on valproate) in Department of Paediatrics at Maharishi Markandeshwar Institute of Medical Sciences and Research, Mullana, Ambala, Haryana. The duration of study was one and a half year. A detailed history was taken with complete clinical examination. Biochemical parameters like lipid profile, Lipoprotein (a), liver enzymes along with relevant investigations were done before starting anti-epileptic monotherapy and were followed up after 6 month of treatment. Other blood tests such as complete blood count, renal function test, liver function test, C reactive protein, blood culture were done in required cases. A written informed consent was taken from all newly diagnosed cases of seizure.

Lumber puncture was done for testing glucose, protein, TLC, DLC and culture. Cranial ultrasonography, cranial CT and MRI was done in required cases.

RESULTS

Out of 19 patients 1 children was between 1 to 5 yr of age, 9 were between 6 to 10 year of age, 10 children were above 10-18 yr. Males presented more wtih 17 out of 19. GTCS was the most common type of seizure with 13 out of 17 with 68% followed by focal 4 (21%) and generelized tonic 2 (10%) respectively.

10 patients who were started on Carbamazepine had significant change in Lipoprotein a, triglycerides, chloesterol, LDL, VLDL when followed up after 6 months of monotherapy, where as no significant change was observed on follow up in levels of HDL, SGOT, SGPT levels. The mean level of pre-treatment TC, LDL,VLDLand TG were 127.2±13.3 mg/dl, 73±9.1mg/dl, 46.2±10.2mg/dl, 97±27mg/dl respectively. The followup serum levels of TC, LDL,VLDLand TG after six month of treatment were 135.4±15.4 mg/dl, 79.1±12.8mg/dl, 52.5±10.6 mg/dl, 103.2±27.2mg/dl respectively and the difference among the two was statistically significant (i.e. p value <0.05) whereas the level of HDL, SGPT and SGOT were not significantly altered after six month of treatment (p value > 0.05) (graph 1).

No staistically significant change in 9 patients who were on Valproate monoterapy for 6 months. Only change seen was in levels of SGPT post therapy with p value of 0.038. The mean level of pre-treatment TC, TG, HDL, VLDL,

LDL were134±37 mg/dl, 96.67±17.51 mg/dl, 59.78±8.87 mg/dl, 42.22±14.85 mg/dl, 76.44±10.09 mg/dl respectively. The followup serum levels of TC, TG, HDL, VLDL, LDLafter six month of treatment were 136±24.45 mg/dl, 96.67±17.58 mg/dl, 62.67±11.49 mg/dl, 43±14.32 mg/dl, 78±8.25 mg/dl respectively.

In our study the mean level of pre-treatment SGPTwas 57.56±23 U/L.

The followup serum levels of SGPT after six month of treatment was 69.78±10.79 U/L which was significant with p value 0.038 whereas, TC, TG, LDL, VLDL, HDL, SGOT levels were not significantly raised after six months of treatment (p >0.05) (graph 2)

DISCUSSION

Comparision of both pre and post carbamazepine therapy on lipid parameters with other study

CBZ drug	Present Study (Mean ± SD)mg/dl	p value	Kantoush et al (Mean ± SD) mg/dl	p value
Pre TC	127.2±13.3	0.005	174.85±15.85	< 0.05
Post TC	135.4±15.4		200.93±35.8	
Pre LDL	73±9.1	0.017	93.41±12.9	< 0.05
Post LDL	79.1±12.8		117.93±15.78	
Pre VLDL	46.2±10.2	0.024	15.85±2.11	< 0.05
Post VLDL	52.5±10.6		17.90±2.43	
Pre TG	97±27	0.041	79.24±10.5	< 0.05
Post TG	103.2±27.2		89.50±12.15	
Pre HDL	57.7±7.8	0.171	39.54±3.76	< 0.05
Post HDL	60.4±9.56		49.56±3.63	

In our study children who received carbamazepine the mean level of pre- treatment TC, LDL,VLDLand TG were 127.2±13.3 mg/dl, 73±9.1mg/dl, 46.2±10.2mg/dl, 97±27mg/dl respectively. The followup serum levels of TC, LDL,VLDLand TG after six month of treatment were 135.4±15.4 mg/dl, 79.1±12.8mg/dl, 52.5±10.6 mg/dl, 103.2±27.2mg/dl respectively and the difference among the two was statistically significant (i.e. p value <0.05)

whereas the level of HDL, SGPT and SGOT were not significantly altered after six month of treatment (p value > 0.05). the result were similar to the study done by Kantoush et al (1998) [6].

In study done by Manimekalai et al (2014) between control and cases with 20 subject in each group receiving carbamazepine for six month showed significant rise in the TC, HDL and TG post treatment (p value < 0.05)[7]. The study done by Rakesh et al [8] depicts higher levels of cholesterol with mean 160.6±19.17 mg/dl (p value 0.008) in children on carbamazepine whereas other parameters of lipid profile were not altered significantly.

Comparision of both pre and post Carbamazepine therapy on Lipoprotein(a) with other study

CBZ drug	Pre AED lipoprotein (a) (Mean±SD)	Post AED lipoprotein(a) (Mean±SD)	p value	Sample
Present study	108.7± 8.7 mg/dl	121.47±13.53 mg/dl	0.001	10
Fatma et al	134.9±11 mg/dl	144.0±21.5 mg/dl	<0.05	22

In the present study, children on carbamazepine had statistically significant ((p value = 0.001) increase levels of Lipoprotein (a) .The results were similar to study conducted by Fatmamujgam et al (2006) [9] where they found signficant increase (p value <0.05) in serum levels of Lipoprotein (a) in cases receiving carbamazepine.

In our study children who recieved valproate the mean level of pre-treatment TC, TG, HDL, VLDL, LDL were134±37 mg/dl, 96.67±17.51 mg/dl, 59.78±8.87 mg/dl, 42.22±14.85 mg/dl, 76.44±10.09 mg/dl respectively. The followup serum levels of TC, TG, HDL, VLDL, LDLafter six month of treatment were 136±24.45 mg/dl, 96.67±17.58 mg/dl, 62.67±11.49 mg/dl, 43±14.32 mg/dl, 78±8.25 mg/dl respectively.

In our study the mean level of pre-treatment SGPTwas 57.56±23 U/L. The followup serum levels of SGPT after six month of treatment was 69.78±10.79 U/L which was significant with p value 0.038 whereas, TC, TG, LDL, VLDL, HDL, SGOT levels were not significantly raised after six months of treatment (p >0.05)

The results were supported by study done by Muzamil m mugloo et al (2017) [10]which was a case versus control study with 25 patients on Valproate and concluded insignificant change in lipid profile.

Manimekalai et al(2014) [7] in their study on 20 patients on Valproate for six months when compared to control group concluded no statistical change in lipid profile with (p> 0.05) when on valproate In follow up study by Kantoush et al (1998) [6] on 10 patients on valproate monotherapy for six months, they found significant decrease in levels of TC, TG, LDL and statistical significant rise in HDL levels after 6 month of monotherapy of valproate with (p<0.05)

Comparision of both pre and post Valproate therapy on Lipoprotein (a) with other study

Valproate drug	Pre AED lipoprotein (a) (mean±SD)	Post AED lipoprotein(a) (mean±SD)	p value
Present study	118.74±7.93 mg/dl	126.73±12.4 mg/dl	0.09
Fatma et al	128.6±36.8 mg/dl	135±46.0 mg/dl	< 0.05

In present study there was an increase in levels of Lipoprotein (a) post valproate therapy but was not statistical significant (p = 0.09) whereas Study by Fatmamujgan et al (2006) [9] concluded that there is statistical significant rise in levels of Lipoprotein a when followed at 3,6,12 month of valproate therapy (p<0.05)

CONCLUSION

From the present study we can conclude that CYP enzyme inducer anti epileptic drugs like phenytoin and carbazepine has association with increased levels of Lipid profile and Lipoprotein (a) where as valproate and phenobarbitone showed insignificant change. Therefore, the serum lipid profile and lipoprotein(a) level should be regularly monitored in patients undergoing antiepileptic therapy as the need of long term antiepileptic treatment could lead to development of metabolic complications at an early age and hence the risk of atherosclerosis. It may be reasonable to advice children recieving CBZ, PHT, to follow a balanced diet with low animal fat.

TABLES AND GRAPHS

Carbamazepine	Sample size	Mean ± Stdev	Median	Min-Max	Inter quartile Range	P value
triglycerides pre AED	10	97 ± 27.01	91	68-166	86 - 102	0.041
triglycerides post AED	10	103.2 ± 27.2	96	72-172	89 - 110	
cholesterol pre AED	10	127.2 ± 13.34	122	110-150	118 - 140	0.005
cholesterol post AED	10	135.4 ± 15.46	131	116-166	124 - 144	
LDL pre AED	10	73 ± 9.15	72	62-88	66 - 78	0.017
LDL post AED	10	79.1 ± 12.81	82	57-94	70 - 88	
HDL pre AED	10	57.7 ± 7.86	57.5	46-68	52 - 64	0.171
HDL post AED	10	60.4 ± 9.56	57	50-78	54 - 68	
VLDL pre AED	10	46.2 ± 10.22	48	32-60	36 - 54	0.024
VLDL post AED	10	52.5 ± 10.66	57	36-68	46 - 60	
RBS pre AED	10	94 ± 16.73	92	74-122	78 - 108	0.735
RBS post AED	10	92.5 ± 12.29	90	72-112	85 - 98	
Lipoprotein a pre AED	10	108.75 ± 8.7	106.5	102.4-132.4	104.500 - 107.800	0.001
Lipoprotein a post AE D	10	121.47 ± 13.53	123	100.5-149.5	115.200 - 125.600	
SGOT pre AED	10	56.6 ± 15.38	57	30-78	46 - 68	0.798
SGOT post AED	10	54.8 ± 11.94	53	40-80	46 - 56	
SGPT pre AED	10	68 ± 17.05	69	32-98	62 - 78	0.959
SGPT post AED	10	70 ± 9.38	68	50-86	68 - 76	

Graph 1

Valproate	Sample size	Mean ± Stdev	Median	Min-Max	Inter quartile Range	P value
triglycerides pre AED	9	96.67 ± 17.51	96	72-131	87.250 - 103.500	0.439
triglycerides post AED	9	96 ± 16.58	98	70-120	83 - 107	

cholesterol pre AED	9	134 ± 16.37	136	112-164	121.500 - 143	0.905
cholesterol post AED	9	136 ± 24.45	142	106-166	113.500 - 156	
LDL pre AED	9	76.44 ± 10.09	78	62-90	67 - 85	0.48
LDL post AED	9	78 ± 8.25	78	66-90	71.500 - 82.500	
HDL pre AED	9	59.78 ± 8.87	64	48-71	51.500 - 66.500	0.355
HDL post AED	9	62.67 ± 11.49	62	46-88	57 - 65	
VLDL pre AED	9	42.22 ± 14.85	40	22-76	35 - 46.500	0.695
VLDL post AED	9	43 ± 14.32	44	26-74	31.500 - 47.750	
RBS pre AED	9	86.44 ± 6.31	86	76-98	84.500 - 89	0.481
RBS post AED	9	89.78 ± 15.67	88	68-122	80 - 97	
Lipoprotein a pre AED	9	118.74 ± 7.93	120.5	103.6-131.6	115.025 - 122.425	0.09
Lipoprotein a post AED	9	126.73 ± 12.4	120.4	109.4-144.7	118.525 - 136.925	
SGOT pre AED	9	46.78 ± 12.42	47	21-64	42.500 - 55.250	0.26
SGOT post AED	9	51.78 ± 8.91	52	40-68	43.500 - 55.500	
SGPT pre AED	9	57.56 ± 23	58	17-86	40.500 - 76.500	0.038
SGPT post AED	9	69.78 ± 10.79	68	52-88	65 - 77.500	

Graph 2

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