SHORT COMMUNICATION

Effect of Phenytoin and Valproic Acid Therapy on Serum Lipid Levels and Liver Function Tests

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ABSTRACT

We conducted a case control study to evaluate the effect of phenytoin and valproic acid on serum lipids and liver function tests in epileptic children. Seventy-nine children receiving atleast 6 months of antiepileptic monotherapy were categorized into two groups, depending on whether they were receiving phenytoin or valproic acid. Age matched healthy controls were also included. The mean total cholesterol (TC) in children on phenytoin therapy was significantly higher than the control group (P=0.03). Serum triglycerides, low density lipoprotein cholesterol, very low density lipoprotein cholesterol, and high density lipoprotein cholesterol, were not significantly different in the three groups. The proportion of children with TC >200mg/dL was significantly higher in the phenytoin group. We recommend monitoring of serum lipids of epileptic children receiving phenytoin.

Keywords: *Children, Cholesterol, Epilepsy, Phenytoin, Valproic acid.*

INTRODUCTION

Adult studies on the effects of various antiepileptic drugs on serum lipids (and by extrapolation, on the risk of atherosclerosis), have reported contradictory results(1-4). We aimed to find the effect of phenytoin and valproic acid monotherapy on serum lipid profile and liver function tests in epileptic children.

METHODS

This case-control study was conducted in the pediatric out-patient department of a tertiary care hospital. Children who had received monotherapy with phenytoin or valproic acid for atleast six months were included. Children with hepatic or renal disease, those receiving medications which may alter liver functions or serum lipids, and those with a family history of obesity, atherosclerosis or metabolic disease were excluded. Age and sex-matched healthy controls were enrolled from the out-patient department. An informed consent from each subject and a prior approval from the institutional ethical committee were obtained.

Weight and height were obtained and BMI calculated as per standard procedure. A venous blood sample (5 mL) was collected after overnight fasting. All epileptic children were in the interictal period or seizure free for at least 48 hours at the time of sampling.

Serum triglycerides (TG) and total cholesterol (TC) were estimated colorimetrically, while high density lipoprotein cholesterol (HDL-C) was determined using Autozyme HDL-C precipitating reagent. Very low density cholesterol (VLDL-C) and low density lipoprotein cholesterol (LDL-C) were calculated using Friedewald formula (LDL-C=TC-(HDL-C × 0.2 TG)). Serum bilirubin was estimated by Van der Bergh method while serum glutamic pyruvic transaminase (SGPT) and alkaline phosphatase were estimated by a spectrophotometer.

Based on a previous study, a sample size of 22 in each group was calculated to detect a difference of 25 mg/dL in mean TC with a power of 80% and alpha error of 0.05(1). Data were analyzed using SPSS version 10. ANOVA test was applied to compare

lipid levels and liver function tests in the three groups. Correlation between lipid profile and liver function tests were obtained with the dose and duration of AED treatment.

RESULTS

Seventy-nine children, mean age 7.5±3.44 (SD) years, were included in this study (27 in valproic acid group, 25 in phenytoin group and 27 in control group). All epileptic children had been treated for atleast six months with either phenytoin alone, in a dose ranging from 3 to 8 mg/kg/d (mean dose 5.4±1.2 mg/kg/d), or valproic acid alone, in a dose ranging from 10 to 31.4 mg/kg/d (mean dose 20.2±6.6 mg/kg/d).

The characteristics of study population are shown in ***Table* I**. Among 52 epileptic children, 6 had developmental delay (3 in phenytoin group and 3 in valproic acid group). Computed tomographic scan of head, done in 38 epileptic children, revealed the presence of inflammatory granuloma (9/38), encephalomalacia (2/38), subependymal tumours (2/38), hydrocephalus (5/38) and, edema (6/38). Electroencephalography done at onset of treatment showed epileptiform pattern in 11 out of 23 children.

TABLE I CLINICAL AND BIOCHEMICAL CHARACTERISTICS OF EPILEPTIC CHILDREN RECEIVING VALPROIC ACID AND PHENYTOIN

Parameter	Valproic acid group (*n*=27)	Phenytoin group (*n*=25)	Control group (*n*=27)	*P* value (ANOVA)
Clinical Characteristics				
Age (years ± SD)	7.2 ± 3.4	7.73± 3.6	7.4 ± 3.4	0.56
Males : Females	17 : 10	14 : 11	13 : 14	0.55
Weight (kg) (mean ± SD)	21.7 ± 8.3	21.7 ± 7.7	19.9 ± 7.0	0.63
Height (cm) (mean ± SD)	114.0 ± 19.7	116.4 ± 21.3	114.1 ± 21.8	0.91
BMI (kg/m^2) (mean ± SD)	16.1 ± 2.3	15.2 ± 1.5	14.85 ± 1.9	0.89
Type of epilepsy [*n*(%)]				
Generalized	20 (74%)	22 (88%)		
Localized	6 (22.2%)	3 (12%)		
Myoclonic	1(3.7%)	0		
Biochemical Characteristics				
TC (mg/dL)	133.1 ± 31.7	146.7 ± 18.5*	126.3 ± 30.1*	0.03
HDL-C (mg/dL)	33.4 ± 8.0	38.0 ± 7.2	35.9 ± 24.1	0.56
VLDL-C (mg/dL)	20.0 ± 8.8	20.8 ± 9.5	24.8 ± 10.6	0.16
LDL-C (mg/dL)	80.9 ± 31.1	86.5 ± 19.1	69.4 ±28.6	0.07
TG (mg/dL)	101.7 ± 66.4	105.5 ± 46.7	115.4 ± 54.7	0.66
TC/HDL-C	4.2 ± 1.1	4.0 ± 0.8	4.0 ± 1.1	0.79
HDL-C/LDL-C	0.5 ± 0.3	0.5 ± 0.4	0.8 ± 1.2	0.25
Serum bilirubin (mg/dL)	0.6 ± 0.2	0.5 ± 0.2	0.6 ± 0.2	0.12
Albumin (g/dL)	4.1 ± 1.2	4.1 ± 1.5	4.0 ± 1.3	0.81
SGPT (U/L)	35.4 ± 37.1	25.2 ± 22.1	21.9 ± 9.5	0.14
ALP (U/L)	463.8 ± 239.5	567.4 ± 395.6 *	363.1 ± 141.2 *	0.03

**P <0.05; Abbreviations: TC = Total cholesterol, HDL-C = High density lipoprotein cholestrol, LDL-C = Low density lipoprotein cholestrol, VLDL-C = Very low density lipoprotein cholestrol, TG = Triglycerides, SGPT = Serum glutamic pyruvic transaminase, ALP = Alkaline phosphatase*

WHAT THIS STUDY ADDS?

- The serum lipids of Indian epileptic children receiving antiepileptic monotherapy, especially phenytoin, were found to be deranged.

Serum levels of lipids and biochemical liver functions are also shown in ***Table* I**. Mean cholesterol in children receiving phenytoin was 15.9% higher as compared to children receiving valproic acid who had 5.5% higher mean TC, than controls. Children receiving phenytoin had higher mean HDL-C and LDL-C, than the control and valproic acid group. TC, TC/HDL-C and HDL-C/TC were comparable for all the three groups. Statistically significant correlation was obtained between the dose of phenytoin and serum TG levels (r=0.54, $P<0.001$) as well as serum VLDL-C level (r=0.55, $P<0.001$). There was no correlation between the duration of treatment with phenytoin and serum lipid fractions. Proportion of children with abnormal serum TC (≥ 200 mg/dL) and HDL (≥35 mg/dL), were significantly higher in the phenytoin group as compared with controls *i.e.*, 10/25 versus 2/27 ($P=0.005$, OR= 8.3, 95% CI= 1.6-43.3), and, 18/25 versus 10/25 ($P=0.012$, OR= 4.4, 95% CI= 1.3-14.1), respectively. Serum alkaline phosphatase levels in children in the phenytoin group were significantly higher than control group ($P=0.03$).

DISCUSSION

This study shows higher lipid levels in children on chronic phenytoin treatment as compared to children receiving valproic acid or controls. Our results are similar to the findings reported earlier(3,5,6). However, O'Neill, *et al.*(4) found an increase in serum HDL-C in patients receiving phenytoin and suggested a protective effect of phenytoin use in epileptic patients from ischemic heart disease. Serum lipid fractions in valproic acid group were comparable to those seen in control group and phenytoin group, as reported previously(1,5,7). Some of these changes have been reported to be transient, reversible, and influenced by a low-fat diet(8,9). It is noteworthy that there are case reports of atherosclerosis following carbamazepine therapy(10).

Close monitoring of serum lipid levels, and a long-term follow up of children receiving AEDs especially phenytoin, to observe the incidence of ischemic heart disease is needed to obtain a clinically significant result. One of the main limitations of our study was a lack of long term follow up of children on AED. We also recommend serial monitoring of changes of lipid fractions from the beginning of therapy to completion of therapy and beyond.

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