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# Serum lipid changes during anticonvulsive treatment Serum lipids in epileptic children

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*Abstract*

*Serum lipid profile changes were investigated in 53 children receiving phenobarbital (n = 14), carbamazepine (n = 21), and valproic acid (n = 18) for their newly diagnosed seizure disorder. The patients were followed prospectively. Serum total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and triglyceride concentrations increased after 3 months of treatment with carbamazepine and remained high after one year. Serum total cholesterol levels increased after 3 months of treatment with phenobarbital and remained high after one year. Serum lipid concentrations did not change during valproic acid therapy. Serum lipid profiles should be carefully monitored in children receiving enzyme inducing antiepileptic drugs.*

*Key words* : Epilepsy ; anticonvulsants ; hyperlipidemia ; atherosclerosis.

## Introduction

Atherosclerotic cardiovascular disease, which results in ischemic heart disease and stroke, is the leading cause of death in adults. Although the clinical manifestations of atherosclerosis typically do not present until adulthood, the pathologic changes begin in childhood. There is clear evidence linking abnormalities in lipid and lipoprotein levels to premature atherosclerosis (Hackman, Bricker,1998). The Pathobiological Determinants of Atherosclerosis in Youth (PDAY) study and the autopsy data from the Bogalusa Heart Study show a positive correlation between total cholesterol (TC) and low density lipoproteins cholesterol (LDL-C) levels and the extent of atherosclerosis in young men (Berenson *et al*., 1992 ; PDAY Research Group, 1990). The risk of coronary heart disease is negatively correlated with high serum levels of high density lipoproteins cholesterol (HDL-C) and with a high ratio of serum HDL-C to serum LDL-C (Berenson *et al*., 1988 ; Newman *et al*., 1986).

Some authors have reported that some antiepileptic drugs, particularly phenytoin, phenobarbital, and carbamazepine, are able to increase HDL-C concentrations ; this effect has been attributed to the hepatic enzyme- inducing activity of these drugs ( Berlit *et al*., 1982 ; Louma *et al*., 1980). Other studies have suggested that treatment with carbamazepine leads to long term increases in all cholesterol fractions or short term treatment with hepatic enzyme-inducing antiepileptic drug leads to increases in the levels of TC but not of HDL-C (Franzoni *et al*., 1992 ; Heldenberg *et al*., 1983).

The present study investigated serum lipid status in children with epilepsy who had been receiving carbamazepine, phenobarbital, or valproic acid therapy, in monotherapy.

## Materials and methods

We studied 53 children with epilepsy (31 boys and 22 girls) aged between 2 years and 14 years (7.5 ± 2.3 years). None of them had received any antiepileptic drug, before this study. Symptoms or signs of illness other than epilepsy, regular medication, unavailable for follow-up, serum levels of the antiepileptic drug outside of the therapeutic range were used as exclusion criteria. The study was carried out with the approval of the ethics committee of the medical faculty of the University of Fırat. Informed parental consent was obtained.

Serum TC, HDL-C, LDL-C, and tryglycerides (TG) concentrations were measured before antiepileptic drug medication, and after 3 and 12 months of medication. Venous blood samples were taken between 8:30 and 9:30 AM after an overnight fast. TC, HDL-C, and TG concentrations were determined by enzyme calorimetric assay (Olympus AU-600 autoanalyser, Olympus Corp, Japan) using a test kit (Randox, UK). LDL-C was calculated with the Friedewald formula (Friedewald *et al*., 1972). Plasma anticonvulsants concentrations were measured by fluorescence polarization immunoassay (TDX analyser ; Abbott, USA).

Friedman two-way ANOVA was used for repeated measures to analyze the changes in serum lipids concentrations. Values are expressed as mean ±

Table I

Concentrations of serum lipids in patients with epilepsy, before and during carbamazepine treatment (n = 21)

| | Before carbamazepine treatment | After 3 months | After 12 months |
|---|---|---|---|
| Triglycerides (mg/dl) | 115.3 ± 7.9 | 128.5 ± 10.8* | 128.7 ± 11.3** |
| Total cholesterol (mg/dl) | 142.5 ± 20.9 | 155.7 ± 18.5* | 155.9 ± 21.6** |
| HDL- cholesterol (mg/dl) | 41.5 ± 4.9 | 46.3 ± 4.5* | 45.9 ± 4.1** |
| LDL-cholesterol (mg/dl) | 84.9 ± 11.7 | 89.7 ± 9.8* | 89.1 ± 10.3** |

* $p < 0.05$ versus treatment.
** not significant between 3 and 12 months for treatment.

Table II

Concentrations of serum lipids in patients with epilepsy, before and during valproic acid treatment (n = 18)

| | Before valproic acid treatment | After 3 months | After 12 months |
|---|---|---|---|
| Triglycerides (mg/dl) | 112.6 ± 7.6 | 113.1 ± 5.9 | 112.9 ± 6.3 |
| Total cholesterol (mg/dl) | 141.7 ± 25.8 | 142.3 ± 26.1 | 142.4 ± 29.6 |
| HDL-cholesterol (mg/dl) | 41.3 ± 6.8 | 41.8 ± 7.3 | 41.6 ± 7.5 |
| LDL-cholesterol (mg/dl) | 83.9 ± 11.3 | 84.1 ± 15.6 | 84.1 ± 17.4 |

Table III

Concentrations of serum lipids in patients with epilepsy, before and during phenobarbital treatment (n = 14)

| | Before phenobarbital treatment | After 3 months | After 12 months |
|---|---|---|---|
| Triglycerides (mg/dl) | 115.6 ± 6.3 | 124.6 ± 5.9* | 123.4 ± 6.7** |
| Total cholesterol (mg/dl) | 140.8 ± 21.2 | 141.5 ± 25.7 | 141.4 ± 20.8 |
| HDL-cholesterol (mg/dl) | 40.8 ± 5.7 | 41.2 ± 6.5 | 41.5 ± 5.9 |
| LDL-cholesterol (mg/dl) | 85.6 ± 10.3 | 85.9 ± 12.3 | 85.5 ± 12.7 |

* $p < 0.05$ versus treatment.
** not significant between 3 and 12 months for treatment.

standard deviation (SD) and a two-tailed p value $< 0.05$ was considered significant.

## Results

Serum TC, HDL-C, LDL-C and TG concentrations increased after 3 months treatment with carbamazepine (n = 21). The increases in serum lipid levels remained high after 1 year treatment. Serum lipid levels were not significantly different between after 3 months treatment and after 1 year treatment (Table I).

Levels of serum lipid showed no significant alterations by treatment with valproic acid (n = 18) (Table II). Serum TG levels increased after 3 months treatment with phenobarbital (n = 14) and remained high after 1 year. No difference was found for TC, for HDL-C,and for LDL-C values. Mean serum TG levels after 1 year treatment were not significantly different from mean serum TG levels after 3 months treatment (Table III).

## Discussion

Changes in serum lipids caused by antiepileptic treatment have often been discussed controversially. The risk of atherosclerosis has been the main point of discussion (Zeitlhofer *et al*., 1993). High serum TC, LDL-C, and TG levels are considered risk factors for development of atherosclerosis and coronary heart disease whereas HDL-C is acknowledged protective against these diseases (Austin, 1991 ; Barth, Arntzenius, 1991 ; Frohlich, Pritchard, 1989). The Expert Panel on Blood Cholesterol Levels in Children and Adolescent of the National Cholesterol Education Program (NCEP, 1992) suggests that prevention of premature atherosclerosis should start in childhood.

In this prospective study, we have shown that 3 months of carbamazepine medication is associated with an increase serum TC, TG, HDL-C, and LDL-C concentrations. The increases in serum lipid levels are similar after 1 year of carbamazepine medication. Similar investigations in adults and children with epilepsy, previously reported by others, demonstrated similar and different results (Brown *et al*., 1992 ; Calandre *et al*., 1991 ; Sözüer *et al*., 1997 ; Sudhop *et al*., 1999 ; Verroti *et al*., 1997 ; Yalcin *et al*., 1997). In a prospective study of an adult population, Isojarvi *et al*. (1993) found permanent increases in serum TC, LDL-C and HDL-C levels after 2 months and

1 year of carbamazepine therapy and remained high levels after 1 year. They showed that the increases serum TC, HDL-C concentrations remained after 5 years of carbamazepine medication. Eirıs *et al*. (1995) demonstrated high TC, LDL-C and HDL-C levels in children after 5.8 years of carbamazepine therapy.

We found that levels of serum lipids were not significantly different after valproic acid treatment. Some authors reported no significant changes with valproic acid treatment (Aynacı *et al*., 2001 ; Demircioğlu *et al*., 2000 ; Eiris *et al*., 2000 ; Reddy, 1985 ; Sözüer *et al*., 1997), while the others found increased HDL-C levels (Beghi *et al*., 1990 ; Serra *et al*., 1983). Calandre *et al*. (1991) found that in relation to controls, subjects treated with valproic acid showed significantly lower values of TC and LDL-C. A lowering effect of valporic acid on LDL-C in rats has been demonstrated by Horie and Suga (1985) ; these authors found that valproate acted by enhancing hepatic peroxisomal beta-oxidation. Zeitlhofer *et al*. (1993) reported that valproate-treated subjects showed decreased HDL-C levels.

As a result of this study, we showed that serum TG concentrations increased after 3 months treatment with phenobarbital and remained high after 1 year. An increase in TC and HDL-C concentrations has been reported in epileptic children treated with phenobarbital (Aynacı *et al*., 2001 ; Calandre *et al*., 1991 ; Eirıs *et al*., 1995 ; Eiris *et al*., 2000 ; Reddy, 1985 ; Verrotti *et al*., 1998).

In conclusion, the use of carbamazepine and phenobarbital is associated with a change in lipid metabolism. More prospective studies are needed to clarify the effects of the different antiepileptics on serum lipid profiles. Despite the need for more prospective studies, our results indicate that serum lipid profiles should be carefully monitored in children receiving antiepileptic drugs.

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