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Serum lipids, vitamin B12 and folic acid levels in children receiving long-term valproate therapy

G. GEDA[1], H. ÇAKSEN[2] and D. IÇAĞASIOĞLU[3]

[1]Professor of Pediatrics, Ankara University Faculty of Medicine
[2]Associate Professor of Pediatrics, Yüzüncü Yıl University Faculty of Medicine
[3]Professor of Pediatrics, Cumhuriyet University Faculty of Medicine
From the Department of Pediatrics, Ankara University Faculty of Medicine, Ankara, Turkey

Abstract

In this study, serum triglyceride, total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), very low-density lipoprotein cholesterol (VLDL-C), vitamin B12 and folic acid levels were studied in children with epilepsy who had been receiving long-term valproate (VPA) therapy. Our purpose was to determine that whether or not there was any affect of VPA therapy on serum lipids, vitamin B12 and folic acid levels. The study includes 26 patients (13 males, 13 females) with epilepsy who had been receiving long-term VPA therapy and in 28 healthy children (14 males, 14 females). The age ranged from 14 months-12 years (8.22 ± 3.64 years) and 9 months-18 years (8.97 ± 4.85 years) in the study and control group, respectively. Because serum lipid ranges may be changed according to the age groups in childhood, the children were divided into three groups as follows ; younger than < 5 years, between 5-10 years, and older than > 10 years. The duration of VPA use was between 10 months and 7 years (1.83 ± 1.80 years). Serum VPA level changed between 42-108 µg/ml (75.09 ± 21.42 µg/ml). When comparing the results we did not find any significant difference in all parameters including lipid profiles, vitamin B12 and folic acid levels between the groups (P > 0.05). Additionally, we did not find any correlation between lipid profile and age at start of therapy, duration of therapy, serum VPA level (P > 0.05). In conclusion, our findings showed that VPA therapy did not change serum lipids, vitamin B12 and folic acid concentrations ; therefore, we suggest that VPA may be safely used with regard to lipid composition, vitamin B12 and folic acid levels in childhood epilepsy.

Key words : Valproate ; lipid ; B12 ; folic acid ; child.

Introduction

Valproate (VPA) is a commonly administrated antiepileptic drug, which is being used in increasingly higher doses as a single agent in seizures that are difficult to control. (Dastur and Dave 1987 ; Demircioglu *et al.,* 2000 ; May and Sunder 1993 ; Sözüer *et al.,* 1997). VPA is not a microsomal enzyme inducer, and lipid profile during VPA treatment is controversial. Decreased, normal, and increased levels of lipid have been reported in epileptic patients (Aynacı *et al.,* 2001 ; Berlit *et al.,* 1982 ; Calandre *et al.,* 1991 ; Eiris *et al.,* 1995 ; Franzoni *et al.,* 1992 ; Heldenberg *et al.,* 1983 ; Reddy 1985 ; Yılmaz *et al.,* 2001). Isojarvi *et al.,* 1998 and 2001 reported that obese VPA-treated women with polycystic ovaries or hyperandrogenism, or both, had hyperinsulinemia and associated unfavorable changes in serum lipid levels consistent with insulin resistance ; therefore, they concluded that use of VPA was associated with risk factors for cardiovascular disease in obese women. They have noted that these VPA-related risks can be reduced by substituting lamotrigine for VPA. Stephen *et al.,* 2001 have noted that VPA therapy may be associated with subclinical elevation in fasting insulin levels, and testosterone and triglyceride levels were higher in VPA-treated women compared with the levels in those taking lamotrigine. However, Rattya *et al.,* 1999 reported that VPA did not affect fasting serum insulin, insulin-like growth factor binding protein-1, or insulin-like growth factor-binding protein-3 concentrations in pubertal girls. Similarly, vitamin B12 and folate status in patients under treatment with VPA are also controversial (Fröscher *et al.,* 1995 ; Kishi *et al.,* 1997 ; Krause *et al.,* 1988 ; May and Sunder 1993). In this study, serum lipid profile, vitamin B12 and folic acid levels were studied in children with epilepsy who had been receiving long-term VPA therapy. Our purpose was to determine that whether or not there was any affect of VPA therapy on these parameters.

Material and methods

The study included 26 children with epilepsy who had been receiving VPA and 28 healthy age-matched children. The patients who received combined antiepileptic therapy were not included in the study. The fasting venous blood samples were

Table 1

Distribution of the children according to age groups and sex

Age groups/ Sex	Study group (n : 26) n (%)	Control group (n : 28) n (%)
Younger than < 5 years *		
Girl **	5 (19.5)	3 (11)
Boy	3 (11.5)	5 (18)
Between 5-10 years		
Girl	2 (7.5)	3 (11)
Boy	7 (27)	6 (21)
Older than > 10 years		
Girl	6 (23)	8 (28)
Boy	3 (11.5)	3 (11)
Total	26 (100)	28 (100)

* With respect to age X^2 0.12 ; P > 0.05
** With respect to sex X^2 0.0 ; P > 0.05

taken and laboratory tests including serum triglyceride (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), very low-density lipoprotein cholesterol (VLDL-C), vitamin B12 and folic acid levels were studied at same day. In addition, serum VPA levels were determined in the study group. Serum TG, TC, and HDL-C concentrations were measured by colourometric photometric method using a commercial kit (Olympus Diagnostica GmbH). Serum LDL-C, VLDL-C levels were calculated by using the following formulas :

$$\text{VLDL-C} = \frac{\text{TG}}{5} \quad \text{LDL-C} = \text{TC} — \text{HDL-C} — (\text{VLDL-C})$$

Serum vitamin B12 and folic acid levels were measured by radioimmunoassay using Diagnostic Products Corporation dualcount solid phase no boil assay for vitamin B12/folic acid kits. Serum VPA level was studied by fluorescence polarization immunoassay using Abbott Laboratories Diagnostics kits. Statistical analyses were performed by using Chi-square, Mann-Whitney U, Student t and Pearson test.

Results

Our study included 26 patients (13 males, 13 females) with epilepsy receiving VPA and 28 healthy age-matched controls (14 males, 14 females). The age ranged from 14 months-12 years (8.22 ± 3.64 years) and 9 months-18 years (8.97 ± 4.85 years) in the study and control group, respectively. Because serum lipid profile ranges may be changed according to the age groups in childhood, the children were divided into three groups as follows ; younger than < 5 years, between 5-10 years, and older than > 10 years.

Distribution of the children according to age groups and sex is seen in Table 1. There was not a difference for sex and age between the study and control group ($P > 0.05$). The duration of VPA use was between 10 months and 7 years (1.83 ± 1.80 years). Serum VPA level changed between 42-108 µg/ml (75.09 ± 21.42 µg/ml). Distribution of serum lipid profile according to age groups in the study and control group is appeared in Table 2. When comparing the results we did not find any significant difference in respect to lipid profiles between the study and control group. Aside from these, we did not find any correlation between age at start of therapy and serum triglyceride, TC levels in the study group ($P > 0.05$). Additionally, there was not a significant correlation between serum triglyceride and duration of therapy, serum VPA level ; and serum TC and duration of therapy, serum VPA level in the study group ($P > 0.05$).

Mean serum vitamin B12 level was 715.2 ± 422.7 pmol/L and 411.2 ± 210.0 pmol/L in the study and control group, respectively ($P > 0.05$) Mean serum folic acid concentration was 13.0 ± 4.9 nmol/L and 10.5 ± 4.4 nmol/L in the study and control group, respectively ($P > 0.05$). We did not find any significant difference for both serum vitamin B12 and folic acid levels between the study and control group ($P > 0.05$).

Discussion

Several studies were performed on lipid profile during VPA treatment ; however the results were controversial. VPA therapy has been reported to be associated with a decreased serum LDL-C or TC (Calandre *et al.,* 1991 ; Eiris *et al.,* 1995 ; Franzoni *et al.,* 1992 ; Heldenberg *et al.,* 1983) and increased HDL-C levels (Heldenberg *et al.,* 1983). No significant change in serum lipid fractions has been observed by others (Berlit *et al.,* 1982 ; Reddy 1985). Eiris *et al.,* 1995 recorded in the group receiving VPA, mean TC level, mean LDL-C level, mean TC/HDL-C ratio, and mean LDL-C/HDL-C ratio were significantly lower than the control group. In the treated group mean levels of VLDL-C or TG was not different significantly from the corresponding control-group's mean levels (Eiris *et al.,* 1995). In another study of the same authors TC and LDL-C serum levels were high in children receiving CBZ or PB and low in those treated with VPA. In the group receiving VPA, HDL2-C, HDL2-C/HDL3-C ratio and apo-B were significantly lower than the control group. In neither group did TGs, VLDL-C levels and TC/HDL-C or LDL-C/HDL-C ratios differ significantly from the corresponding control group (Eiris *et al.,* 2000). Verrotti *et al.,* 1997 noted that children treated with VPA had low TG and LDL-C levels with high levels of HDL-C.

Yalçın *et al.,* 1997 noted that patients receiving VPA showed increased apo-B levels. Additionally, there was no significant difference in TC, TG,

Table 2

Distribution of serum lipid profile according to age groups in the study and control group

Parameters	Study group (n : 26)	Control group (n : 28)	Z	*P*
Younger than ≦ 5 years				
Triglyceride (mg/dl)	94.7 ± 54.0	97.7 ± 22.3	-0.3	> 0.05
TC (mg/dl)	160.2 ± 42.5	172.1 ± 41.2	-0.5	> 0.05
HDL-C (mg/dl)	59.8 ± 20.3	62.7 ± 16.4	-0.4	> 0.05
LDL-C (mg/dl)	81.4 ± 28.6	89.6 ± 32.3	-0.2	> 0.05
VLDL-C (mg/dl)	25.4 ± 16.2	19.6 ± 4.5	-0.4	> 0.05
Between 5-10 years				
Triglyceride (mg/dl)	73.0 ± 22.5	80.4 ± 34.4	-0.8	> 0.05
TC (mg/dl)	153.3 ± 16.6	159.0 ± 22.5	-0.3	> 0.05
HDL-C (mg/dl)	56.3 ± 12.0	66.2 ± 11.5	-1.5	> 0.05
LDL-C (mg/dl)	82.3 ± 13.6	76.4 ± 19.1	-0.4	> 0.05
VLDL-C (mg/dl)	14.6 ± 4.7	16.2 ± 6.9	0.3	> 0.05
Older than > 10 years				
Triglyceride (mg/dl)	83.5 ± 31.1	90.0 ± 45.9	-0.03	> 0.05
TC (mg/dl)	149.1 ± 19.6	146.9 ± 29.4	-0.4	> 0.05
HDL-C (mg/dl)	58.0 ± 16.4	54.9 ± 22.4	-0.6	> 0.05
LDL-C (mg/dl)	74.5 ± 18.5	73.8 ± 15.6	-0.2	> 0.05
VLDL-C (mg/dl)	16.5 ± 6.1	17.9 ± 9.0	-0.03	> 0.05

LDL-C or VLDL-C between the study and control group (Yalçın *et al.,* 1997). Sözüer *et al.,* 1997 reported that none of the mean levels of serum lipids evaluated in patients receiving VPA was significantly different from the corresponding control group's mean levels. Demircioglu *et al.,* 2000 noted that VPA did not alter the levels of serum lipids. In the study of Verrotti *et al.,* 1998 patients treated with the drugs (CBZ, VPA and phenobarbital) revealed significant changes in lipids and lipoproteins, but when the authors reevaluated the three groups of children 1 year after the end of treatment, a complete return to normal of all parameters was observed. Because serum lipid ranges may be changed according to the age groups in childhood, the children were divided into three groups in our study. We did not find any significant difference between the study and control group for serum TG, TC, HDL-C, LDL-C and VLDL-C levels. Additionally, we did not find any correlation between lipid profile and age at start of therapy, duration of therapy, serum VPA level ($P > 0.05$).

In the literature on the vitamin B12 status in patients under treatment with VPA is controversial. Decreased, normal, and increased vitamin B12 concentrations have been reported in patients with epilepsy (Fröscher *et al.,* 1995 ; Kishi *et al.,* 1997 ; Krause *et al.,* 1988 ; May and Sunder 1993). Hauser *et al.,* 1996 and Tamura *et al.,* 2000 noted that VPA administration increased serum vitamin B12 concentrations. Increased circulating vitamin B12 levels, however, served as a sensitive biochemical index of hepatic damage due to anticonvulsants, i.e., reduction of the liver for vitamin B12 (Dastur and Dave 1987). Prolonged drug treatment was possibly the cause of the slightly impaired ability of the liver to store vitamin B12 as compared with the controls (Frank 1964). Notably, VPA, an antiepileptic drug with less enzyme-inducing activity, is associated with only a small risk of folate deficiency (Fröscher *et al.,* 1995 ; Kishi *et al.,* 1997 ; Ono *et al.,* 1997). Kishi *et al.,* 1997 noted that patients treated with the non-enzyme-inducer VPA exhibited serum folate levels that did not differ significantly from values in controls. To these findings they stated that the induction of microsomal liver enzymes may be critical to the depletion of folate by antiepileptic drugs (Kishi *et al.,* 1997).

It was noted that concentrations of B vitamins as well as of folate were distinctly lower in patients under monotherapy with enzyme-inducing drugs than in those under VPA (Krause *et al.,* 1988). Verrotti *et al.,* 2000 noted that after 1 year of therapy, patients treated with VPA showed a significant decrease of serum folate but serum vitamin B12 and erythrocyte folate, levels remained in the normal ranges. In the study of Nimmo *et al.,* 1987 serum folate level was found to be decreased, but vitamin B12 levels were normal in all subjects with epilepsy using anticonvulsant therapy. Ganick *et al.,* 1990 reported elevated vitamin B12 levels, but normal serum folic acid levels in four patients who were treated with VPA. May and Sunder 1993 reviewed 60 patients receiving long-term VPA monotherapy and found that serum B12 levels were increased in 51 of the patients. Serum folate levels were always normal. An increase in irreversible B12 binding capacity has been suggested as an explanation, but no published information supports this theory (May and Sunder 1993 ; Sudden and May 1988).

In our study, although serum vitamin B12 and folic acid levels were found higher in the study

group than those of the controls, there was not a significant difference between the groups ($P > 0.05$).

In conclusion, our findings showed that VPA therapy did not change serum lipids, vitamin B12 and folic acid concentrations ; therefore, we suggest that VPA may be safely used with regard to lipid composition, vitamin B12 and folic acid levels in childhood epilepsy.

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H. ÇAKSEN, M.D.
K. Karabekir C. Gölbaşı 3. S.
Erkam sitesi. B Blok. No. 3/7 VAN/ Turkey.
E-mail : huseyincaksen@hotmail.com.