ELSEVIER

Brain & Development 25 (2003) 113–115

BRAIN & DEVELOPMENT
Official Journal of the Japanese Society of Child Neurology

www.elsevier.com/locate/braindev

Original article

Effects of valproate and carbamazepine on serum levels of homocysteine, vitamin B12, and folic acid

Hamza Karabiber[a,*], Ergün Sonmezgoz[b], Elif Ozerol[c], Cengiz Yakinci[b], Baris Otlu[d], Saim Yologlu[e]

[a]*Kahramanmaras Sutcuimam Universitesi, Tip Fakultesi, Pediatri Anabilim Dalý 46050, Kahramanmaras, Turkey*
[b]*Department of Pediatrics, Inonu University Medical School, Malatya, Turkey*
[c]*Department of Biochemistry, Inonu University Medical School, Malatya, Turkey*
[d]*Department of Microbiology, Inonu University Medical School, Malatya, Turkey*
[e]*Department of Biostatistics, Inonu University Medical School, Malatya, Turkey*

Received 17 May 2002; received in revised form 20 August 2002; accepted 6 September 2002

Abstract

Homocysteine (HMC) is a sulfur containing amino acid, which plays a role in methionine metabolism. Folic acid (FA) and vitamin B12 (B12) are essential for remethylization of HMC to methionine. HMC level increases in the deficiency of these vitamins. Hyperhomocysteinemia causes vascular endothelial damage, which causes atherosclerosis. The aim of this study is to investigate the effect of valproate (VA) and carbamazepine (CBZ) on the serum levels of HMC, B12, and FA.

Thirty-six children receiving CBZ and 30 children receiving VA for epilepsy for the last 1-year period and 29 healthy children as control were the population of this study. After 6 h of fasting serum HMC, B12, and FA levels were measured and results were compared statistically.

Mean values of HMC, FA, and B12 levels in control group were 9.2 ± 2.7 μmol/l, 9.0 ± 2.0 ng/ml, and 342 ± 162 pg/ml, in VA group 14.0 ± 6.8 μmol/l, 7.3 ± 2.9 ng/ml, and 368 ± 159 pg/ml, in CBZ group 16.0 ± 13.1 μmol/l, 7.5 ± 3.3 ng/ml, and 285 ± 158 pg/ml, respectively. Serum HMC levels were higher in VA and CBZ groups than control group ($P < 0.01$ and $P < 0.05$, respectively). Serum FA levels were lower in VA and CBZ groups compared to control group ($P < 0.05$). Serum levels of B12 were not different between VA and control groups ($P > 0.05$). In CBZ group serum B12 levels were lower than control group ($P < 0.05$).

FA may be added to the treatment protocol (if the patients take only CBZ, then B12 should also be added) for patients taking these antiepileptic drugs to decrease the degenerative effect of VA and CBZ on vascular endothelium.

Keywords: Homocysteine; Sodium valproate; Carbamazepine; Folic acid; Vitamin B12

1. Introduction

The relationship between hyperhomocysteinemia and vaso-occlusive diseases is known for a long time. Antiepileptic drugs (AEDs) lead to hyperhomocysteinemia by affecting the levels of folic acid (FA) and vitamin B12 (B12) which have a role in the metabolism of homocysteine (HMC). Hyperhomocysteinemia in turn causes vascular endothelial dysfunction and results in atherosclerosis [1–4].

The aim of this study is to investigate the effect of valproate (VA) and carbamazepine (CBZ) on serum levels of HMC, B12, and FA in epileptic children.

2. Patients and method

Children aged between 2 and 16 and having no illnesses other than epilepsy were included in the study. Thirty-six patients were taking VA (14 boys, 22 girls), 30 were taking CBZ (18 boys, 12 girls) as an AED for at least 1-year, and 29 healthy children (17 boys, 12 girls) as a control group formed the groups of our study. The patients were taking only one AED and none of them had severe seizures.

Children having mental-motor retardation, abnormalities in hepatic and renal function tests in the laboratory and taking multivitamins in the last 2 months were excluded from the study. No children had convulsions by 4 months prior to this study. All children were well nourished and their percentile values were over 25%.

Four ml of venous blood sample was drawn from each

* Corresponding author. Tel.: +90-344-215-2465; fax: +90-344-221-2371.
E-mail address: hkarabiber@hotmail.com (H. Karabiber).

0387-7604/02/$ - see front matter © 2002 Elsevier Science B.V. All rights reserved.
doi:10.1016/S0387-7604(02)00163-8

Table 1
Mean homocysteine, B12, and folic acid levels in VA and CBZ groups

	Homocystein (μmol/l) (mean ± SD)	Folic acid (ng/ml) (mean ± SD)	Vitamin B12 (pg/ml) (mean ± SD)
VA group (n:30)	14.0 ± 6.8	7.3 ± 2.9	368 ± 159
CBZ group (n:36)	16.0 ± 13.1	7.5 ± 3.3	285 ± 158
Control group (n:29)	9.2 ± 2.7	9.0 ± 2.0	343 ± 162

patient taking CBZ or VA and healthy children after an overnight fast. Blood samples were immediately centrifuged at 2000 rpm for separation of serum. Hemolysed and hyperlipemic serum samples were excluded from the study. All serum samples were stored in deep freeze at −20°C until analyses.

Serum B12 and FA were measured using Immulyte 2000 autoanalyser by immune-assay method. Serum HMC was analyzed with micro enzyme-linked immunosorbent assay (ELISA) method by utilizing Axis homocysteine enzyme immune-assay kit.

The data obtained were evaluated with independent samples one-way analysis of variance by SPSS for Windows version 7.5 statistical program. Least significant difference was used for post-hoc tests. A P-value of less than 0.05 was considered as significant.

3. Results

Mean HMC, FA, and B12 levels were determined as 9.2 ± 2.7 μmol/l (5–15 μmol/l), 9.0 ± 2.0 ng/ml (3–17 ng/ml), 343 ± 162 pg/ml (180–900 pg/ml) in control group; 14.0 ± 6.8 μmol/l, 7.3 ± 2.9 ng/ml, 368 ± 159 pg/ml in VA group, and 16.0 ± 13.1 μmol/l, 7.5 ± 3.3 ng/ml, 285.2 ± 158 pg/ml in CBZ group, respectively (Table 1). HMC levels were significantly higher both in VA and CBZ groups than the control group ($P < 0.05$) (Fig. 1). Hyperhomocysteinemia (HMC > 15 μmol/l) was found in 23.3% of patients taking CBZ (seven patients) and 30.5% taking VA (11 patients).

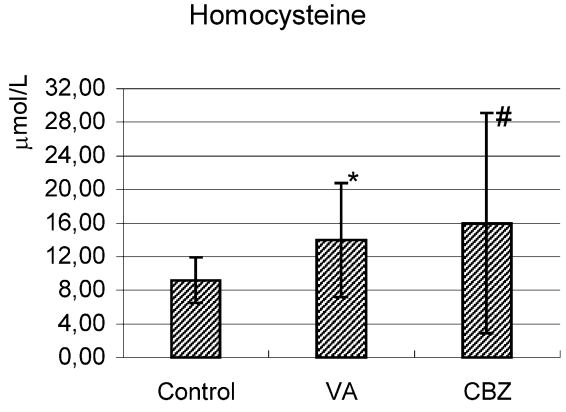

Fig. 1. Comparison of serum HMC levels among VA, CBZ, and control groups (*$P < 0.01$, #$P < 0.05$).

FA levels were significantly lower both in VA and CBZ groups than the control group ($P < 0.05$) (Fig. 2). There was no statistically significant difference in B12 levels between VA and control groups ($P > 0.05$) (Fig. 3).

In CBZ group serum B12 levels were lower than VA and control groups ($P < 0.05$). There was no difference between VA and CBZ groups for HMC and FA levels ($P > 0.05$).

4. Discussion

HMC is a sulfur containing amino acid, which plays a role in methionine metabolism. FA and B12 are essential for remethylization of HMC to methionine. The deficiencies of these vitamins cause an increase in HMC level and decrease in methionine level [1]. Accumulation of homocysteine, which produces atheromatous changes on vascular endothelium, increases the risk of thromboembolism and atherosclerosis [2,5].

It is well known that FA deficiency occurs in some epileptic patients taking AEDs such as VA and CBZ. Although the mechanisms by which anticonvulsants induce FA deficiency are unclear, the proposed mechanisms can be summarized as interference with the intestinal absorption of FAs, induction of enzymes in the liver and finally deplete FA, and interference with the metabolism of FA co-enzymes [6].

The present study demonstrates that epileptic patients taking AEDs have increased plasma levels of homocysteine. Our data are in agreement with the previous reports on homocysteine concentrations in patients with epilepsy. HMC levels of patients taking AEDs were determined to increase 11.4% by Tamura et al. [1] and 25% by Yoo et al.

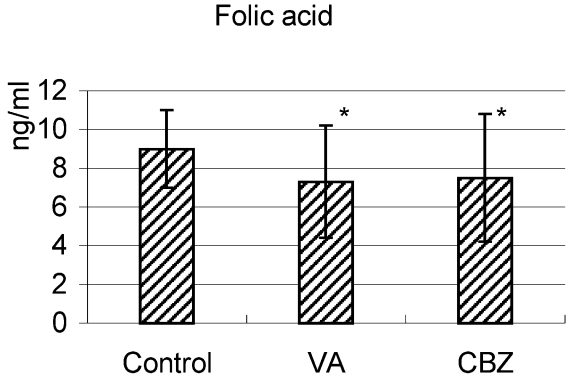

Fig. 2. Comparison of serum FA levels among VA, CBZ, and control groups (*$P < 0.05$).

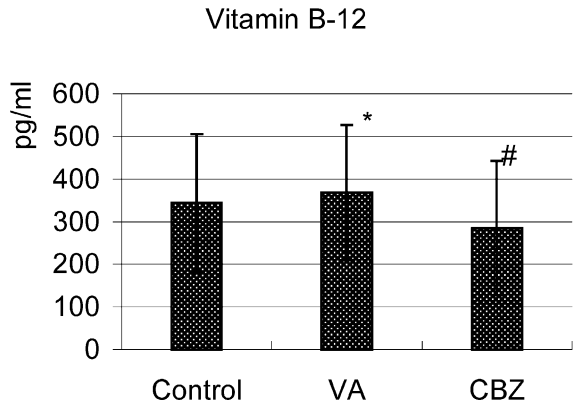

Fig. 3. Comparison of serum B12 levels among VA, CBZ, and control groups (*$P > 0.05$, #$P < 0.05$).

[7]. In our study, the rate with an increase of 23.3% was similar to the study of Yoo et al. and higher than the study of Tamura et al.

The elevated levels of HMC may occur due to a deficiency in vitamins that are necessary for the metabolism of HMC [8]. The levels of serum B12 and FA were also determined in order to better understand the cause of increment in HMC level. We found significantly lower concentrations of serum FA in both groups of patients taking VA or CBZ than controls. FA deficiency might be due to hepatic enzyme induction by some AEDs, resulting in accelerated FA degradation. However the mechanism(s) of such an alteration caused by these AEDs is unknown for now [1].

The literature on B12 status in patients under treatment with AEDs is controversial. Decreased [9], normal [5,8], and increased [1,10,11] B12 levels have been reported in patients with epilepsy. We found that serum B12 levels were significantly lower in patients who received CBZ. But there was no difference between VA and control groups. Our observation is in agreement with the data reported previously. Tamura et al. [1] reported that mean serum B12 concentrations in patients who received VA were significantly higher than those in patients who received either phenytoin, lamotrigine or CBZ.

Verotti et al. [8] compared plasma HMC concentrations in children receiving VA and CBZ. Their measurements were performed before the beginning of therapy and after 1 year of therapy. They found that patients treated with VA and CBZ showed a significant increase of the plasma concentrations of HMC when compared to baseline data and control values. Moreover, they observed a significant decrease of serum FA and B12 levels remained in the normal range similar to our study.

Stampfer et al. [12] reported that plasma concentration of HMC > 15 μM is associated with about a three-fold increased risk of myocardial infarction. Ono et al. [6] reported that plasma HMC concentrations had been increased and serum FA levels had been decreased in patients receiving AEDs. They observed that plasma HMC concentrations decreased following FA administration in patients who had FA deficiency and hyperhomocysteinemia. For these reasons administration of FA has been recommended by Ono et al. [6] to prevent vascular disease in epileptic patients with hyperhomocysteinemia due to FA deficiency.

In conclusion, our data demonstrate that fasting plasma HMC concentrations significantly increased in children taking VA or CBZ. Administration of these drugs also induces a decrease in serum levels of FA. We advise to measure HMC levels in all patients treated with these AEDs. Addition of FA to the antiepileptic therapy to prevent vascular diseases may be useful in patients receiving VA or CBZ.

Similarly serum B12 levels might be measured due to the possibility of a significant decrease in B12 levels in CBZ receiving patients and if necessary B12 may be added to the treatment.

References

[1] Tamura T, Aiso K, Johnston KE, Black L, Faught E. Homocysteine, folate, vitamin B-12 and vitamin B-6 in patients receiving antiepileptic drug monotherapy. Epilepsy Res 2000;40:7–15.
[2] Chambers JC, Seddon MD, Shah S, Kooner JS. Homocysteine – a novel risk factor for vascular disease. J R Soc Med 2001;94:10–13.
[3] Dasheiff RM. Sudden unexpected death in epilepsy: a series from an epilepsy surgery program and speculation on the relationship to sudden cardiac death. J Clin Neurophysiol 1991;8:216–222.
[4] Annegers JF, Hauser WA, Shirts SB. Heart disease mortality and morbidity in patients with epilepsy. Epilepsia 1984;25:699–704.
[5] Schwaninger M, Ringleb P, Winter R, Kohl B, Frehn W, Rieser P, et al. Elevated plasma concentrations of homocysteine in antiepileptic drug treatment. Epilepsia 1999;40:345–350.
[6] Ono H, Sakamoto A, Eguchi T, Fujita N, Nomura S, Ueda H, et al. Plasma total homocysteine concentrations in epileptic patients taking anticonvulsants. Metabolism 1997;46:959–962.
[7] Yoo JH, Hong SB. A common mutation in the methylenetetrahydrofolate reductase gene is a determinant of hyperhomocysteinemia in epileptic patients receiving anticonvulsants. Metabolism 1999;48:1047–1051.
[8] Verrotti A, Pascarella R, Trotta D, Giuva T, Morgese G, Chiarelli F. Hyperhomocysteinemia in children treated with sodium valproate and carbamazepine. Epilepsy Res 2000;41:253–257.
[9] Krause KH, Bonjour JP, Berlit P, Kynast G, Schmidt-Gayk H, Schellenberg B. Effect of long-term treatment with antiepileptic drugs on the vitamin status. Drug Nutr Interact 1988;5:317–343.
[10] Dastur DK, Dave UP. Effect of prolonged anticonvulsant medication in epileptic patients: serum lipids, vitamins B_6, B_{12}, and folic acid, proteins, and fine structure of liver. Epilepsia 1987;28:147–159.
[11] May RB, Sunder TR. Hematologic manifestations of long-term valproate therapy. Epilepsia 1993;34:1098–1101.
[12] Stampfer MJ, Malinow MR, Willet WC, Newcomer LM, Upson B, Ullmann D, et al. A prospective study of plasma homocysteine and risk of myocardial infarction in US physicians. J Am Med Assoc 1992;268:877–881.