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SERUM CARNITINE, β-HYDROXYBUTYRATE AND AMMONIA LEVELS DURING VALPROIC ACID THERAPY*

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SUMMARY: Toksoy HB, Tanzer FN, Atalay A. (Departments of Pediatrics and Biochemistry, Cumhuriyet University Faculty of Medicine, Sivas, Turkey). Serum carnitine, β-hydroxybutyrate and ammonia levels during valproic acid therapy. Turk J Pediatr 1995; 37: 25-29.

This study was performed in order to determine the effects of valproic acid on serum free carnitine, β-hydroxybutyrate and blood amamonia. Serum free carnitine, β-hydroxybutyrate and blood ammonia levels were measured in 24 epileptic children and in 24 age and sex-matched controls. The mean serum free carnitine level was significantly lower in patients taking valproic acid (33.5 ± 13.1 nmol/ml) than in control subjects (50.8 ± 14.6 nmol/ml) ($p < 0.001$). The mean blood ammonia level was significantly higher in patients receiving valproic acid (93.9 ± 20.5 μg/dl) than in controls (79.6 ± 21.4 μg/dl) ($p < 0.002$). The mean serum β-hydroxybutyrate level was significantly lower in patients taking valproic acid (2.26 ± 2.24 mg/dl) than in controls (4.38 ± 2.43 mg/dl) ($p < 0.001$).

Our results support the decision that valproic acid induces hypo-carnitinemia, hypoketonemia and an increased blood ammonia level. *Key words: blood ammonia, carnitine, valproic acid.*

Valproic acid (VPA) is used for the treatment of many seizure types, including generalized tonic-clonic, absence, myoclonic seizures and recurrent febrile convulsions[1,2]. VPA therapy is known to be associated with mild abdominal disturbances, alopecia, edema, apnea, pancreatitis, thrombocytopenia, leukopenia and reversible hyperammonemia[1,3-5]. It has rare but serious side effects such as Reye-like syndrome and toxic hepatitis[5-8].

Carnitine, a naturally occurring trimethylamine, plays an essential role in mitochondrial β-oxidation of long-chain fatty acids by facilitating their transfer across the mitochondrial membrane[9]. Serum levels of carnitine have been found to be lower in patients treated with VPA than those of controls[10-16]. Thus, some investigators have suggested that carnitine deficiency has a possible role in VPA- induced hepatopathy[5,10,11]. This study was carried out in order to determine whether VPA actually induces hyperammonemia, hypocarnitinemia and hypoketonemia.

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Material and Methods

Serum free carnitine, blood ammonia and β-hydroxybutyrate levels were measured in 24 children suffering from epilepsy and 24 children who were apparently healthy. The group of patients treated with VPA monotherapy included five female and 19 male patients. The mean age of patients receiving VPA was 7.6 years (range one to 15 years). The dose of VPA in the treatment group was 20 mg/kg/day. The duration of antiepileptic treatment was between six months and seven years (mean duration 17.5 months). In all patients and controls, blood ammonia and β-hydroxybutyrate levels were determined in the same sample, and blood for serum free carnitine was taken simultaneously.

Blood ammonia was immediately analyzed by the chromatographic-spectro photometric, phenol-hypochlorite method (Bio Systems, COD 11013). Serum β-hydroxybutyrate concentrations were measured by kit (Sigma diagnostics, 310 UV). Serum free carnitine levels were determined by the enzymatic method. Free carnitine concentrations were assayed spectrophotometrically as reported by Marquis and Fritz[17].

Differences between the means were employed using at the two-tailed t test and the Mann-Whitney U test.

Results

Serum free carnitine, blood ammonia and β-hydroxybutyrate values for VPA treatment and controls are shown in Table I.

Table I: Mean Serum Free Carnitine, Blood Ammonia and Serum β-hydroxybutyrate Concentrations in Patients Treated with Valproic Acid and in Normal Subjects. (All Values Expressed as Mean ± SD)

Variable	Valproic Acid Monotherapy (n = 24)	Controls (n = 24)	p
Free carnitine (nmol/ml)	33.5 ± 13.1	50.8 ± 14.6	$p < 0.001$*
Ammonia (μg/dl)	93.9 ± 20.5	79.6 ± 21.4	$p < 0.002$*
β-hydroxybutyrate (mg/dl)	2.26 ± 2.24	4.38 ± 2.43	$p = 0.0001$**

* t test
** Mann Whitney U test.

The mean serum free carnitine concentration in the VPA monotherapy group was 33.5 ± 13.1 nmol/ml (range 16.0-54.2 nmol/ml). It was 50.8 ± 14.6 nmol/ml in the age- and sex-matched control group (range 19.5-70.5 nmol/ml) (Fig. 1). The difference was statistically significant ($p < 0.001$).

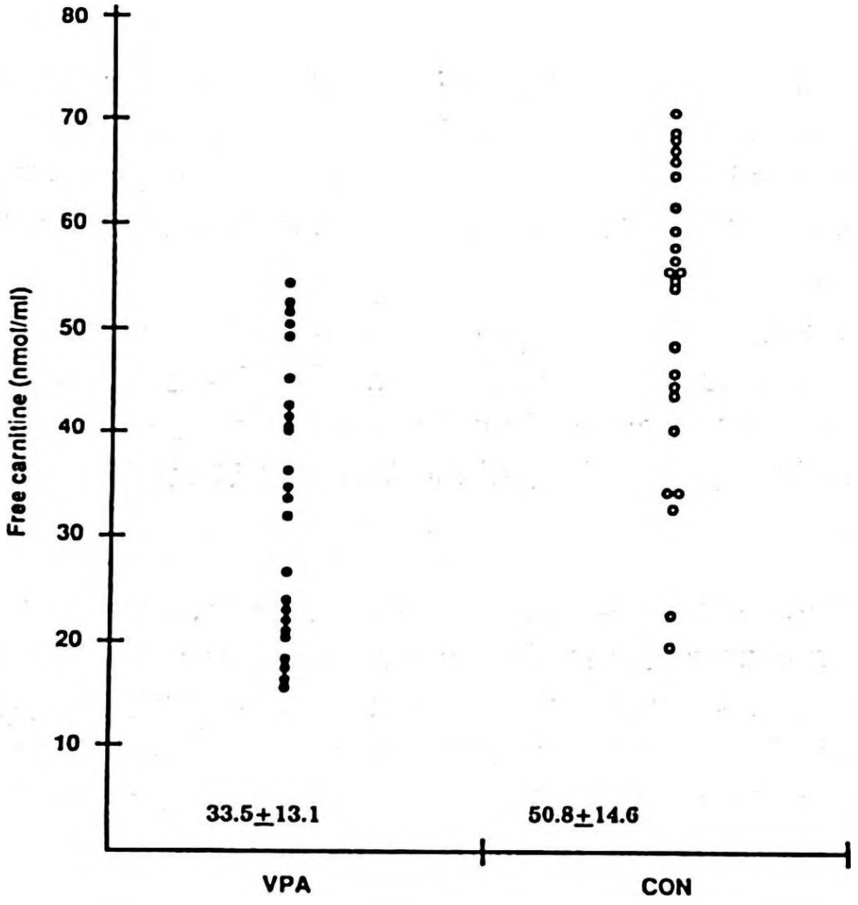

Fig. 1: Serum free carnitine in two study groups (VPA: valproic acid; CON: control).

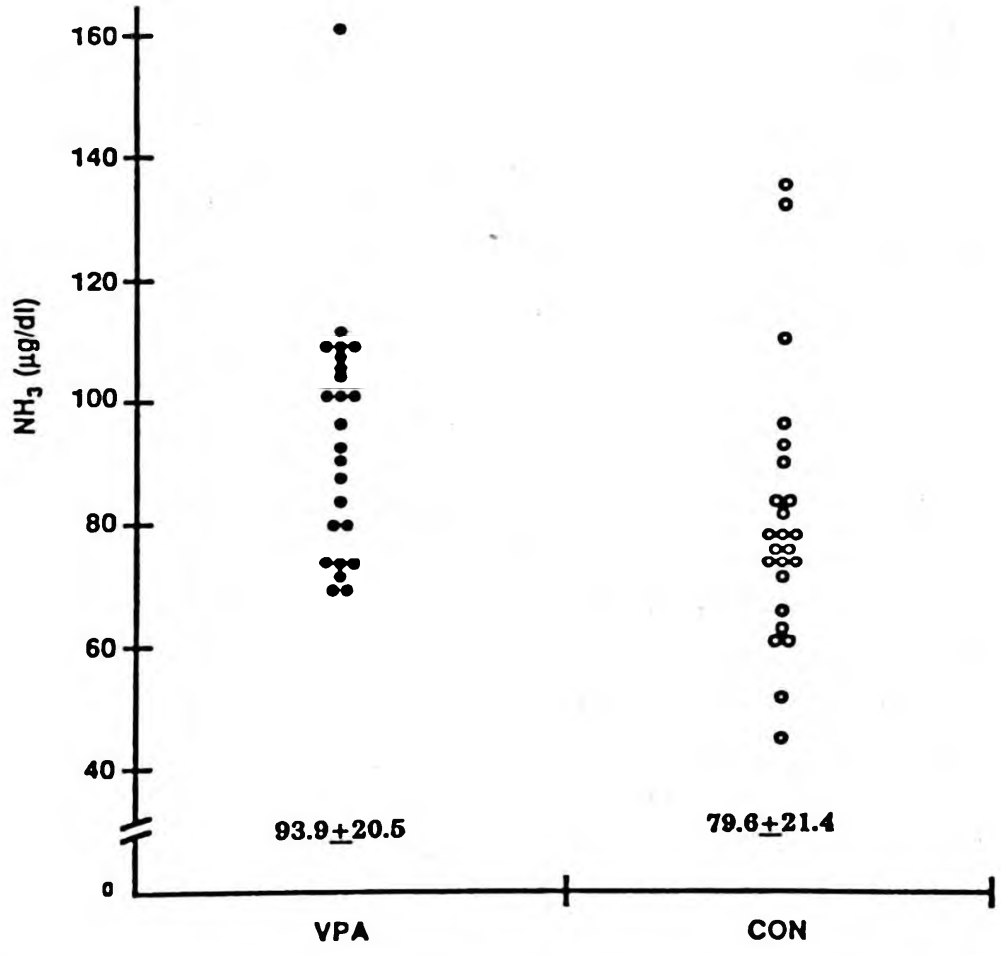

Fig. 2: Blood ammonia values in two study groups (VPA: valproic acid; CON: control).

The mean blood ammonia level in the VPA monotherapy group (93.9 ± 20.5 µg/dl) was significantly higher than that in the control group (79.6 ± 21.4 µg/dl) ($p < 0.02$) (Fig. 2). The levels of blood ammonia ranged from 68.7 µg/dl to 161.4 µg/dl in the VPA monotherapy groups and from 44.9 µg/dl to 136.2 µg/dl in the control group.

The mean β-hydroxybutyrate level of patients receiving VPA monotherapy was 2.26 ± 2.24 mg/dl (range 0-9.26 mg/dl); it was 4.38 ± 2.43 mg/dl (range 0.74-10.50 mg/dl) in the control group. The difference between the two groups was statistically significant ($p = 0.0001$, Mann Whitney U test).

Discussion

It has been reported that VPA treatment causes hypocarnitinemia in epileptic patients[5,10-16]. In our data, serum free carnitine levels in the VPA monotherapy group were significantly lower than those in controls. This finding is consistent with the findings of Opala et al.[15] and Hug et al.[16] Our report supports previous findings that administration of VPA results in a lowering of carnitine levels[10-16].

The mechanisms by which VPA administration produces hypocarnitinemia remain obscure. Several investigators have reported that the lowest serum free carnitine levels were found in the group treated with VPA polytherapy[11,13,15]. They suggested that drug interactions can lead to enhanced VPA metabolism and further impairment of carnitine values[11,13,15]. Laub et al.[11] found that patients taking VPA had significantly higher serum acylcarnitine levels and a significantly higher acylcarnitine/free carnitine ratio than patients taking other antiepileptic drugs without VPA. They suggested that there was a loss of carnitine via carnitine esters through a renal leak. In addition to this, Laub et al.[11] suggested that the impairment of β-oxidation might therefore be another factor leading to low cranitine values during VPA treatment. However, some authors suggested that carnitine deficiency could distrub β-oxidation[5,14].

In our study, serum levels of β-hydroxybutyrate in VPA-treated children were significantly lower than those of controls. This finding was in contrast to Beghi et al.[13], but was in accord with the findings of Melegh et al.[14] These findings show that hypoketonemia may be due to impairment of β-oxidation of fatty acids.

Hyperammonemia-associated VPA has also been reported in the literature[10,18-21]. We found significantly higher blood ammonia levels in VPA-treated patients than in controls. The mechanisms of VPA-induced hyperammonemia are not fully understood. Suggestions from investigators include a reduction of N-acetylglutamate in the liver, a carbamylphosphate synthetase deficiency, and inhibition of mitochondrial ammonia metabolism[10,19,20]. An increase in blood ammonia concentration observed in this study might well be a reflection of mitochondrial dysfunction induced by VPA.

In conclusion, we suggest that further controlled trials are required in order to clarify the benefits of carnitine supplementation in chronic VPA patients, on hypoketonemia, hypocarnitinemia and hyperammonemia induced by VPA.

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