Serum and Muscle Carnitine Levels in Epileptic Children Receiving Sodium Valproate

Murat Anil, Mehmet Helvaci, Ebru Ozbal, Onder Kalenderer, Ayse Berna Anil and Mustafa Dilek

J Child Neurol 2009 24: 80
DOI: 10.1177/0883073808321060

Original Article

Journal of Child Neurology
Volume 24 Number 1
January 2009 80-86

10.1177/0883073808321060
http://jcn.sagepub.com
hosted at
http://online.sagepub.com

Serum and Muscle Carnitine Levels in Epileptic Children Receiving Sodium Valproate

Murat Anil, MD, Mehmet Helvaci, MD, Ebru Ozbal, MD,
Onder Kalenderer, MD, Ayse Berna Anil, MD, and Mustafa Dilek, MD

The purpose of this study was to determine whether children with epilepsy undergoing valproate therapy and who are otherwise healthy have lower levels of serum and muscle carnitine. A total of 50 patients with epilepsy, 3 to 14 years of age, who were treated solely with valproate and free of abnormal neurologic findings or nutritional problems were selected. The control group consisted of 30 healthy children. The total carnitine levels in serum were 28.1 ± 10.3 and 55.6 ± 7.3 μg/mL, and the free carnitine levels in serum were 16.5 ± 10.2 and 44.6 ± 7.3 μg/mL, the total carnitine levels in muscle were 12.1 ± 1.8 and 45.3 ± 5.9 μmol/g noncollagen protein and the free carnitine levels in muscle were 5.6 ± 1.6 and 39.3 ± 6.0 μmol/g noncollagen protein in the valproic acid–treated and control groups, respectively ($P < .05$). In conclusion, valproate monotherapy depletes both muscle and serum carnitine levels in otherwise healthy epileptic children.

Keywords: valproic acid; carnitine; serum glutamic pyruvic transaminase

Valproic acid (2-n-propylpentanoic acid) is an antiepileptic drug bearing a carbohydroxy base and is thus structurally a short-chain fatty acid or an organic acid.[1] Since its introduction in 1978, it has been used as an antiepileptic drug in the management of both partial and generalized seizure disorders.[2]

Although serum carnitine levels have been reported to be within normal limits,[1] several studies have reported that blood carnitine concentrations were lower in patients taking valproic acid than in healthy controls.[3,4] The relationship between valproic acid treatment and the decreased carnitine levels in epileptic patients is controversial.[5] It has been speculated that valproic acid depletes carnitine stores through various synergistic mechanisms. First, valproic acid combines with carnitine to form valproylcarnitine, which is excreted in the urine. Second, tubular reabsorption of carnitine is reduced during valproic acid treatment. Third, valproic acid reduces endogenous synthesis of carnitine. Fourth, valproylcarnitine inhibits the membrane carnitine transporter. Fifth, valproic acid metabolites combine with mitochondrial coenzyme A (CoA-SH) so that free mitochondrial carnitine stores cannot be restored from acylcarnitine.[1,5,6] Valproic acid–induced hepatotoxicity and valproic acid–induced hyperammonaemic encephalopathy may be promoted either by a preexisting carnitine deficiency or by deficiency induced by valproic acid per se.[6]

However, the total tissue carnitine stores may not be accurately reflected by the serum concentration. Thus, valproic acid–treated patients may be carnitine depleted despite having normal carnitine serum levels. It is clear that muscle carnitine concentrations are a more accurate reflection of the true carnitine status of an individual.[6,7] In essence, low blood carnitine concentrations reflect low muscle tissue concentrations, but normal blood concentrations can be observed in conjunction with low muscle tissue concentrations.[8] Although a relationship between valproic acid treatment and decreased serum carnitine levels in epileptic patients has been studied extensively, very few data are available about the tissue carnitine levels in valproic acid–treated epileptic

Received March 6, 2008. Accepted for publication May 7, 2008.

From the Department of Pediatrics (MA, MH, EO, ABA, MD), and Department of Orthopedics (OK), Tepecik Teaching and Research Hospital, Izmir, Turkey.

The authors have no conflicts of interest to disclose with regard to this article. This study was done in the Department of Pediatrics, Tepecik Teaching and Research Hospital, Izmir-Turkey.

Address correspondence to: Murat Anil, MD, Mehmet Emin Gürkan Cad. Dostevler Sitesi, Akasya Apt. No: 10 Daire: 5, 35410 Gaziemir, Izmir, Turkey; e-mail: muratani11969@hotmail.com.

Anil M, Helvaci M, Ozbal E, Kalenderer O, Anil AB, Dilek M. Serum and muscle carnitine levels in epileptic children receiving sodium valproate. *J Child Neurol.* 2009;24:80-86.

children. The present study was therefore undertaken to evaluate the actual carnitine status of epileptic children taking valproic acid by determining both serum and muscle carnitine levels.

Material and Methods

Participants

This study was performed at the Pediatric Clinics of the Izmir Tepecik Teaching and Research Hospital from January 2002 to June 2006. The patients who were to undergo carnitine measurement (valproic acid–treated group) were selected accordingly during the study period if they met the following criteria: (1) the diagnosis of epilepsy was made based on both electroencephalographic findings and clinical manifestations; (2) cranial magnetic resonance imaging was interpreted as normal; (3) valproic acid therapy was the sole treatment for epilepsy; (4) valproic acid therapy had continued for more than 1 month before carnitine measurement; (5) participants had normal intelligence and neurologic examination findings; (6) both weight and height of participants were within $\pm$ 2 SD units of the mean for age; and (7) diet was regular and given orally.

A total of 50 patients (25 males, 25 females) met the criteria during the study period. Their ages ranged from 3 to 14 years, with a mean of 8.0 $\pm$ 3.1 years. Compliance of the patients with medication was evaluated by measurement of serum valproic acid concentration at least once before carnitine measurement. Because previous valproic acid concentrations of the participants were within appropriate limits for epilepsy treatment, all participants entered in this study were judged to have good compliance with medication.

An age-matched control group (n = 30) was chosen from outpatients who visited the Pediatric Clinics of Izmir Tepecik Teaching and Research Hospital with a minor illness such as upper respiratory tract infection or from inpatients who received a surgical process with an acute surgical condition such as acute appendicitis, accidental fractures of extremities, or other similar conditions during the same period and who met criteria 5 to 7 described above. Complete blood count and routine blood biochemistry analyses (glucose, kidney, and liver function tests) were normal in the control group.

Demographic data, body mass index, and blood valproic acid concentrations of participants are presented in Table 1. Neither the valproic acid–treated group nor the control group included any patient with organic acidemia or other metabolic disorders. No patient in either group had been treated with antibiotics containing pivalic acid, which is known to reduce blood carnitine level.[1]

Table 1. Demographic Characteristics, BMI and Blood VPA Concentrations of Participants

	VPA-treated Group (n = 50)	Control Group (n = 30)	*P*
Mean age (y)	8.0 $\pm$ 3.1	7.3 $\pm$ 3.7	.41
Male:female	25:25	15:15	1.00
Mean BMI	17.2 $\pm$ 2.5	16.8 $\pm$ 1.4	.40
Mean blood VPA level (μg /mL)	62.8 $\pm$ 12.6	ND	

ND, not determined; BMI, body mass index; VPA, valproic acid.

Ethics Approval and Consent

This study was approved by the local ethical committee and written informed consent was obtained from the parents of the children for the study and control groups.

Methods

The serum level of valproic acid was determined with a TDX analyzer (Abbott Laboratories, Diagnostic Division Co., USA). Serum glutamic pyruvic transaminase was measured using an automatic analyzer (Olympus AU 5400, Olympus Optical Co., Lt., Japan). Blood samples were obtained in the morning after fasting for 8 hours.

In study and control groups, muscle biopsies were only performed on children who underwent acute surgery and those whose written informed consent was obtained. Of the participants, 15 valproic acid–treated patients and 10 control children were eligible for muscle biopsy performance. The biopsies were performed on the vastus lateralis or the biceps brachii. The sample was then immediately frozen in liquid nitrogen and stored.

The frozen tissue was homogenized 1:30 (by weight) in a solution containing 50 mmol/L Tris (pH 7.5), 100 mmol/L KCl, 5 mmol/L $MgCl_2$, and 1 mmol/L EDTA with a 2-mL glass/glass homogenizer (0.025-mm clearance; Kontes Glass Co.) as described previously.[9]

Total carnitine and free carnitine levels were radiochemically assayed directly in either serum or skeletal muscle homogenates with a modified method of Barth et al.[10] The samples were incubated 30 minutes at 30°C with 35 μmol/L ^{14}C-labeled acetyl-CoA in the presence of carnitine-acetyl-transferase (2 kU/L) and 3.5 mmol/L *N*-ethylmaleimide. Thereafter, the ^{14}C-labeled acetylcarnitine was separated from the ^{14}C-labeled acetyl-CoA by ion-exchange chromatography with AG 1-X8 resin (100-200 mesh, chloride form). The eluate was measured in a 10-mL scintillation mixture with an LS-6500 counter (Beckman Instruments Inc.). For analysis of total carnitine, the sample was boiled with an equal volume of 0.2 mmol/L KOH at 56°C for 1 hour before analysis.

Protein was determined as noncollagen protein by the bicinchoninic acid protein assay (Pierce)[11] in the

Table 2. Serum and Muscle Carnitine Levels in the VPA-treated and Control Groups

	VPA-treated Group (n = 50)		Control Group (n = 30)		*P*
	Mean ± SD	Range	Mean ± SD	Range	
Serum					
T-CAR (μmol/L)	28.1 ± 10.3	16.0-55.0	55.6 ± 7.3	41.0-81.0	<.05
F-CAR (μmol/L)	16.5 ± 10.2	5.0-44.0	44.6 ± 7.3	30.0-70.0	<.05
Muscle	(n = 15)		(n = 10)		
T-CAR (μmol/g NCP)	12.1 ± 1.8	8.4-16.5	45.3 ± 5.9	37.4-55.0	<.05
F-CAR (μmol/g NCP)	5.6 ± 1.6	3.4-8.5	39.3 ± 6.0	31.4-49.0	<.05

VPA, valproic acid; T-CAR, total carnitine; F-CAR, free carnitine; NCP, noncollagen protein.

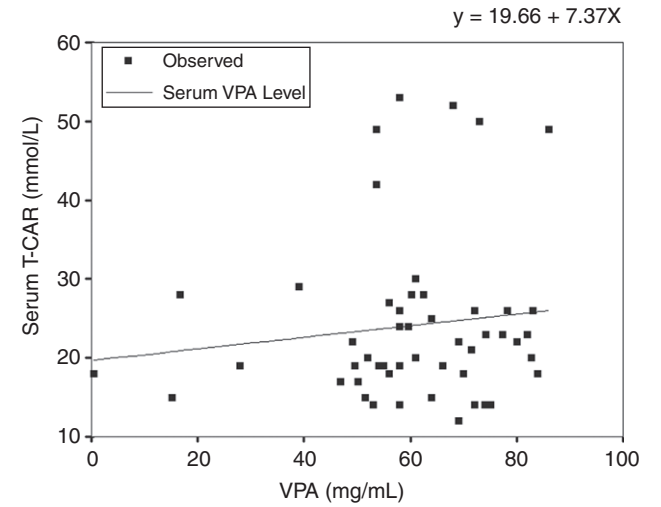

Figure 1. The regression analysis shows no significant correlation between the serum total carnitine concentration and serum level of valproic acid. T-CAR, total carnitine; VPA, valproic acid.

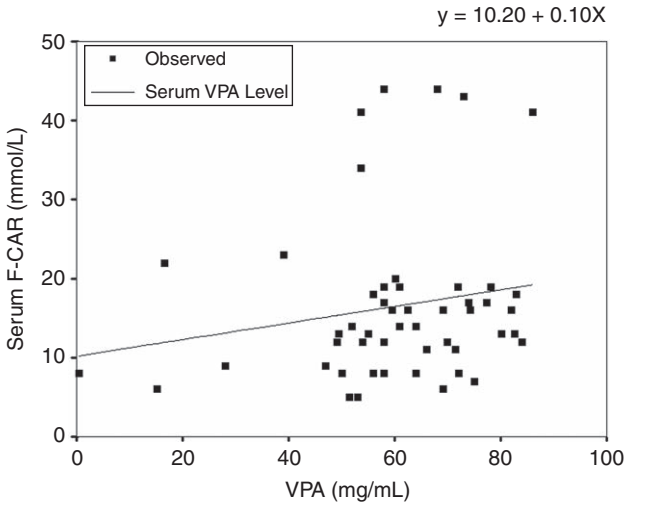

Figure 2. The regression analysis shows no significant correlation between the serum free carnitine concentration and serum level of valproic acid. F-CAR, free carnitine; VPA, valproic acid.

supernatant after a 24-hour digestion in 50 mmol/L NaOH and sedimentation at 13 000*g*. Bovine serum albumin was used as the calibrator.

All chemicals were of analytical grade. L-Carnitine-L-tartrate was obtained from Lonza, ^{14}C-labeled acetyl-CoA from NEN Life Science, nonlabeled acetyl-CoA as trilithium salt from Merck (Merck Eurolab GmbH), and all other chemicals were obtained from Sigma.

Statistical Analysis

Student's *t* test and simple linear regression were used for statistical evaluation using SPSS 11.0 statistical software program (SPSS, Chicago, Illinois). Statistical significance was defined as a P value < .05.

Results

Valproic acid concentrations were comparable to the value recommended for epilepsy treatment and indicated both compliance with medication and appropriate dosage of valproic acid therapy.

Table 2 shows serum and muscle total and free carnitine levels in the valproic acid–treated and control groups. There were significant differences in the carnitine levels between the valproic acid–treated and control groups ($P < .05$).

There was no significant correlation between serum carnitine concentrations and serum levels of valproic acid in valproic acid–treated group ($r^2 = 0.12$, $P > .05$ for total carnitine; $r^2 = 0.18$, $P > .05$ for free carnitine; Figures 1 and 2) but there was a significant inverse correlation between muscle carnitine concentrations and serum levels of valproic acid in valproic acid–treated patients ($r^2 = -0.42$, $P < .05$ for total carnitine; $r^2 = -0.41$, $P < .05$ for free carnitine; Figures 3 and 4), indicating tissue carnitine concentration better reflects carnitine status in a patient receiving valproic acid.

Similarly, a significant inverse correlation was determined between the duration of valproic acid treatment

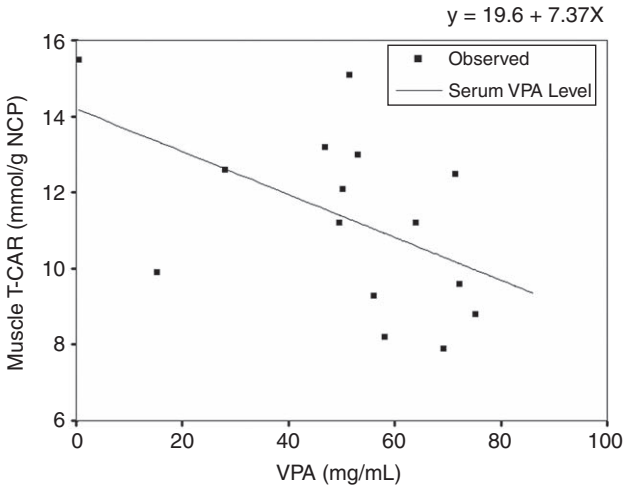

Figure 3. The regression analysis shows a significant inverse correlation between muscle total carnitine concentration and serum level of valproic acid. T-CAR, total carnitine; VPA, valproic acid.

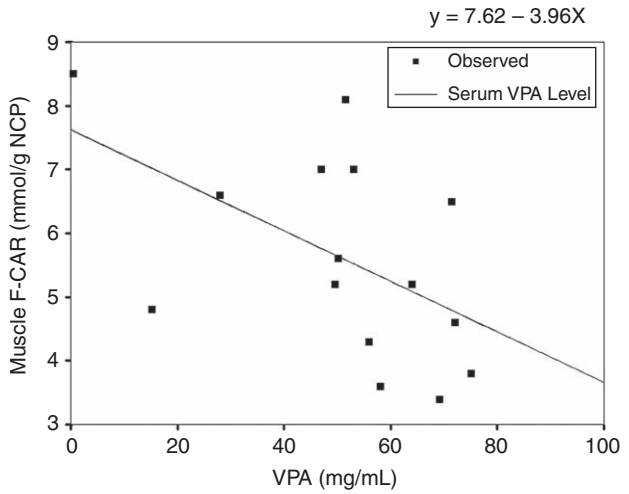

Figure 4. The regression analysis shows a significant inverse correlation between muscle free carnitine concentration and serum level of valproic acid. F-CAR, free carnitine; VPA, valproic acid.

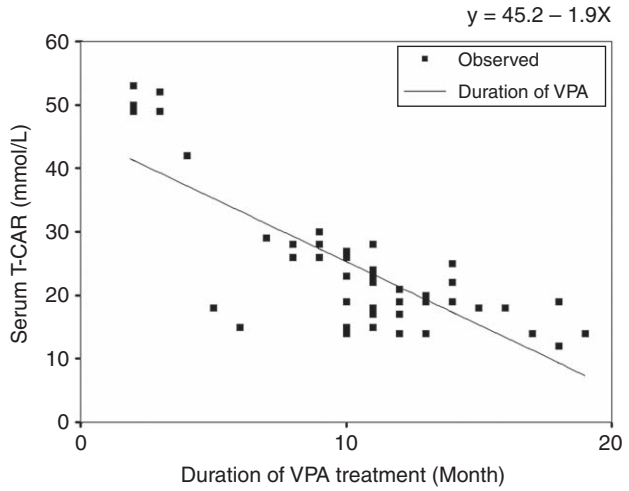

Figure 5. The regression analysis shows a significant inverse correlation between serum total carnitine concentration and the duration of valproic acid treatment. T-CAR, total carnitine; VPA, valproic acid.

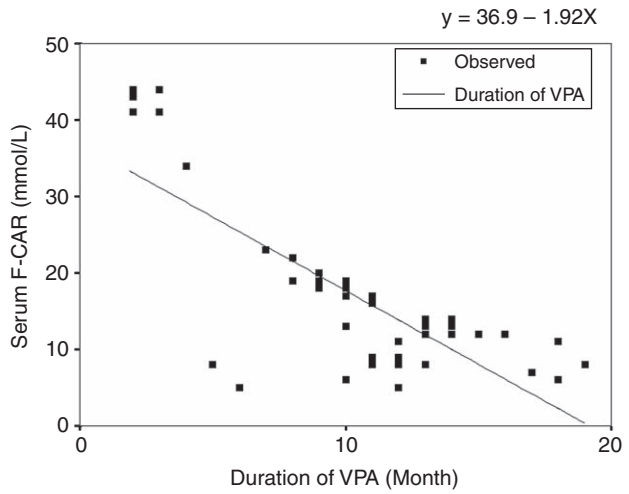

Figure 6. The regression analysis shows a significant inverse correlation between serum free carnitine concentration and the duration of valproic acid treatment. F-CAR, free carnitine; VPA, valproic acid.

and either serum or muscle carnitine concentrations in patients treated with valproic acid (serum total carnitine: $r^2 = -0.78$, $P < .05$; serum free carnitine: $r^2 = -0.77$, $P < .05$; muscle total carnitine: $r^2 = -0.42$, $P < .05$; muscle free carnitine: $r^2 = -0.51$, $P < .05$; Figures 5-8).

The mean level of serum glutamic pyruvic transaminase in patients was 18.0 ± 11.2 U/L (range, 3.0-62.0 U/L). No correlation was observed between the concentrations of serum and muscle tissue carnitine and the level of serum glutamic pyruvic transaminase (serum total carnitine: $r^2 = -0.07$, $P > .05$; serum free carnitine: $r^2 = 0.09$, $P > .05$; muscle total carnitine: $r^2 = 0.29$, $P > .05$; muscle free carnitine: $r^2 = 0.30$, $P > .05$).

Discussion

Today, valproic acid is a broad-spectrum antiepileptic drug and is effective in the treatment of many different types of partial and generalized epileptic seizures in both adults and children.[12] It has been reported that valproic acid therapy might be associated with a secondary decrease in serum carnitine in vivo, with an increased

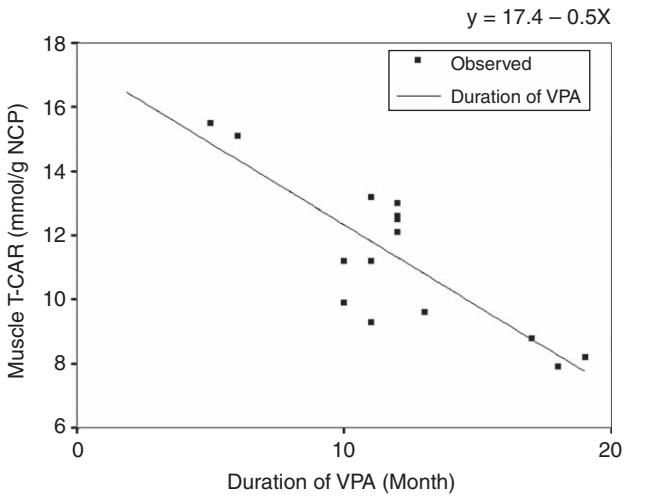

Figure 7. The regression analysis shows a significant inverse correlation between muscle total carnitine concentration and the duration of valproic acid treatment. T-CAR, total carnitine; VPA, valproic acid.

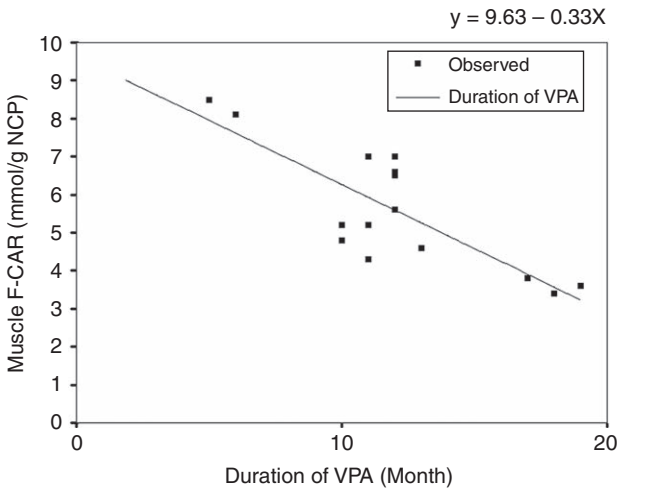

Figure 8. The regression analysis shows a significant inverse correlation between muscle free carnitine concentration and the duration of valproic acid treatment. F-CAR, free carnitine; VPA, valproic acid.

acylcarnitine/carnitine ratio.[7,13] Also, in a control cultured skin fibroblast model, valproic acid related serum and tissue carnitine depletion had been demonstrated and this effect was directly proportional to the duration and concentration of valproic acid exposure. Because conflicting data exist regarding the disposition of carnitine during valproic acid treatment, valproic acid–induced carnitine deficiency is a controversial issue. Most of the reported side effects including Reye syndrome or Reye-like syndrome hepatic failure during valproic acid therapy have been attributed to carnitine deficiency.[7,9,14]

In humans, approximately 75% of carnitine sources come from diet and 25% from endogenous synthesis. But in strict vegetarians, endogenous carnitine synthesis provides more than 90% of total available carnitine.[7] Most body carnitine is stored in skeletal muscles, but it is also stored in other tissues with high energy demands (myocardium, liver, suprarenal glands).[6] Risk factors that have been associated with carnitine deficiency include young age, treatment with multiple antiepileptic drugs, the presence of multiple neurologic disabilities, nonambulatory status, and being underweight.[5,10] In one study, a positive correlation was found between blood carnitine levels and arm circumference as a reflection of the patient's nutritional status.[15] So, in assessing carnitine levels, the nutritional condition and the muscle mass of participants therefore must be taken into account.[1] It is well known that anthropometric measurements such as body mass index, body mass index percentile, triceps skin-fold thickness, mid–upper-arm circumference and mid–upper-arm muscle circumference provide portable, universal applicable, inexpensive, and noninvasive techniques for assessing the size, proportion, and composition of the human body. These parameters reflect both health and nutritional status.[15,16] The population of patients with epilepsy we studied was normal nourished and within the normal body mass index for the corresponding age groups. Furthermore, the participants examined in the present study were solely epileptic with no other neurologic findings.

Hypocarnitinemia in valproic acid-treated patients has not been confirmed in all studies. In a cross-sectional surveillance study conducted in 43 pediatric patients taking valproic acid, only two were found to have carnitine levels below the normal limit. Moreover, no statistical associations between carnitine levels and age, body mass index, additional antiepileptic drugs used, presence of mental retardation, cerebral palsy, feeding problems, nonambulatory status, or dosage of valproic acid were demonstrated.[5] Similar observations were reported by Hirose et al,[1] who found there was no significant difference in serum carnitine levels between valproic acid-treated patients and otherwise healthy and control group. This is in contrast with the results of Castro-Gago et al[3] who found a significant decline in carnitine levels after commencing on valproic acid treatment. In that study, children with metabolic disorders or with serious encephalopathy or malnutrition were excluded. In addition, Opala et al[4] reported that valproic acid polytherapy and monotherapy yielded significantly lower free carnitine levels. Our study showed significantly lower serum and muscle carnitine (in both total and free) levels in the valproic acid-treated group as compared to normal controls. An important issue complicating the interpretation of serum carnitine level is the distribution of carnitine in the body. It is well known that approximately 90% of total body carnitine is deposited in the muscle tissue, in which the concentration of carnitine

in muscle is as much as 10 times higher than that in the blood. This results in a lag time between the decline in plasma carnitine and carnitine depletion in the body. Therefore, whereas low serum carnitine concentrations reflect low muscle concentrations, normal serum carnitine concentrations do not necessarily represent normal body carnitine status.[3,5,17] This was underlined in a study of 3 children receiving chronic valproic acid therapy for intractable seizures who were shown to have normal serum carnitine concentrations, but clinically significant muscle carnitine deficiency.[17] Although the number of patients was limited, this study showed that muscle carnitine concentrations more accurately reflect the true carnitine status of an individual. However, most of the previous studies of carnitine status during valproic acid therapy did not show the tissue carnitine levels of participants studied. In our study, serum carnitine levels decreased below the normal level (normal $\geq$ 20 μmol/L)[8] in 7 patients in the valproic acid-treated group. Their mean duration of valproic acid treatment was longer than for the others (12.9 months vs 4.4 months; data not shown). Nevertheless, we were not able to perform muscle biopsy on these 7 patients (not approved by parents); so, this is a limitation for our study. However, since we compared the blood and muscle carnitine levels in valproic acid-treated and control groups, this study shows that determining the tissue carnitine levels is more likely to reflect the actual carnitine stores in patients on valproic acid treatment.

It has been reported that valproic acid depletes carnitine stores, especially during long-term or high-dose therapy, through various synergistic mechanisms.[6] In the present study, although we have found lower serum and muscle carnitine levels in the valproic acid-treated group, no significant correlation was seen between the concentrations of free carnitine and serum levels of valproic acid in valproic acid-treated patients. This finding agrees with those of Laub et al[18] and Beghi et al[19] who found that the effect of valproic acid on carnitine was not dose-dependent. In contrast, Hug et al[20] and Dreifuss et al[21] claimed that there was an inverse correlation between the serum concentration of the drug and serum carnitine concentration. Furthermore, the present study also highlights the relationship between valproic acid treatment and muscle carnitine level. From this point of view, our study might be superior to the others because we have examined the valproic acid effect on muscle and serum carnitine while other reports in the literature only studied serum samples. Based on our study results, we concluded that the serum level of valproic acid affects the muscle carnitine level.

It has been reported that long-term administration of valproic acid that was conjugated to carnitine may produce carnitine deficiency by excretion of valproylcarnitine.[6,12] Some of the previous studies showed that the duration of valproic acid affects the serum carnitine level.[15,18,19] Our findings are in agreement with these studies indicating the longer duration of valproic acid treatment associated with lower serum carnitine levels. Furthermore, we showed that the degree of muscle carnitine deficiency was affected by the duration of valproic acid treatment. In contrast to these findings, Ohtani et al[22] found no significant correlation between serum carnitine level and valproic acid duration in patients treated with valproic acid.

Carnitine deficiency can impair the transport of long-chain fatty acids into the mitochondrial matrix, with a subsequent decrease in β-oxidation, acetyl-CoA, and adenosine triphosphate (ATP) production. The impairment in β-oxidation causes valproic acid-induced hepatotoxicity. Carnitine depletion can also result in impairment in several enzymatic processes, including the urea cycle.[6] However, we found no significant differences between serum and muscle carnitine concentrations and serum glutamic pyruvic transaminase level in valproic acid-treated patients. Similar to our results, Chung et al[14] also stated that the correlation between serum carnitine level and activities of serum transaminases was not significant. Ohtani et al[22] reported that in severely handicapped patients carnitine deficiency was related with hyperammonaemia and also D,L-carnitine supplementation corrected the carnitine and ammonia levels. Nevertheless, they did not find a significant correlation between serum carnitine and serum glutamic pyruvic transaminase levels. On the contrary, Hirose et al[1] found no significant correlation between serum carnitine and blood ammonia levels in valproic acid-treated otherwise healthy epileptic children. These observations led us to believe that the activity of serum glutamic pyruvic transaminase in valproic acid-treated patients cannot be used as an indicator of valproic acid–induced hypocarnitenemia and/or hepatic dysfunction.

In conclusion, the results of the present investigation support that valproic acid monotherapy reduces serum and muscle carnitine levels in otherwise healthy epileptic children and the duration of valproic acid treatment likely affects muscle and serum carnitine levels. Furthermore, the depletion of muscle carnitine is related to serum levels of valproic acid. On the other hand, serum glutamic pyruvic transaminase levels do not reflect the carnitine deficiency or hepatic dysfunction. However, the present study also has several limitations. One such limitation is the fact that we could not perform muscle biopsy on all of the children. Also, it should be noted that the sample size is small. Another limitation of the study is that we were not able to determine blood ammonia levels in the children (may be a better indicator than serum glutamic pyruvic transaminase for valproic acid-induced carnitine depletion). Despite its limitations, this study demonstrates the tissue carnitine depletion induced by valproic acid treatment. Large sample and well-designed studies of the effects of valproic acid on tissue carnitine levels in otherwise healthy epileptic children may help to elucidate the controversial issues.

Acknowledgment

We thank Nejat Aksu, MD, Tepecik Teaching and Research Hospital, Department of Pediatrics, for his help and advice in preparing this manuscript.

References

1. Hirose S, Mitsudome A, Yasumoto S, et al. Valproate therapy does not deplete carnitine levels in otherwise healthy children. *Pediatrics*. 1998;101:5-9.
2. Sztajnkrycer MD. Valproic acid toxicity: overview and management. *Clin Toxicol*. 2002;40:789-801.
3. Castro-Gago M, Eiris-Punal J, Novo-Rodriguez MI, et al. Serum carnitine levels in the epileptic children before and during treatment with valproic acid, carbamazepine, and phenobarbital. *J Child Neurol*. 1998;13:546-549.
4. Opala G, Winter S, Vance S, et al. The effect of valproic acid on plasma carnitine levels. *Am J Dis Child*. 1991;145:999-1001.
5. Fung ELW, Tang NLS, Ho CS, et al. Carnitine level in Chinese epileptic patients taking sodium valproate. *Pediatr Neurol*. 2003;28:24-27.
6. Lheureux PER, Penaloza A, Zahir S, Gris M. Science review: carnitine in the treatment of valproic acid-induced toxicity—what is the evidence. *Critical Care*. 2005;9:431-440.
7. Tein I. Carnitine transport: pathophysiology and metabolism of known molecular defects. *J Inherit Metab Dis*. 2003;26:147-169.
8. De Vivo DC, Bohan TP, Coulter DL, et al. L-Carnitine supplementation in childhood epilepsy: current perspectives. *Epilepsia*. 1998;39:1216-1225.
9. Trumbeckaite S, Opalka JR, Neuhof C, et al. Different sensitivity of rabbit heart and skeletal muscle to endotoxin-induced impairments of mitochondrial function. *Eur J Biochem*. 2001;268:1-9.
10. Barth PG, Scholte HR, Berden JA, et al. An X-linked mitochondrial disease affecting cardiac muscle, skeletal muscle and neutrophil leukocytes. *J Neurol Sci*. 1983;62: 327-355.
11. Wiechelmann K, Braun R, Fitzpatrick J. Investigation of the bicinchoninic acid protein assay: identification of the groups responsible for color formation. *Annal Biochem*. 1988;175: 231-237.
12. Verrotti A, Trotta D, Morgese G, Chiarelli F. Valproate-induced hyperammonemic encephalopathy. *Metabolic Brain Dis*. 2002;17:367-373.
13. Riva R, Albani F, Gobbi G, et al. Carnitine disposition before and during valproate therapy in patients with epilepsy. *Epilepsia*. 1993;34:184-187.
14. Chung S, Choi J, Hyun T, et al. Alterations in the carnitine metabolism in epileptic children treated with valproic acid. *JKMS*. 1997;12:553-558.
15. Morita J, Yuge K, Yoshino M. Hypocarnitinemia in the handicapped individuals who receive a polypharmacy of antiepileptic drugs. *Neuropediatrics*. 1986;17:203-205.
16. World Health Organization Expert Committee. Physical status: the use and interpretation of anthropometry. *World Health Organ Tech Rep Ser*. 1995;854:1-452.
17. Shapira Y, Gutman A. Muscle carnitine deficiency in patients using valproic acid. *J Pediatr*. 1991;118:646-649.
18. Laub LC, Paetzke-Brunner I, Jaeger G. Serum carnitine during valproic acid therapy. *Epilepsia*. 1986;27:559-552.
19. Beghi E, Bizzi A, Codegoni AM, et al. Valproate, carnitine metabolism and biochemical indicators of liver function. *Epilepsia*. 1990;31:346-352.
20. Hug G, McGraw CA, Bates SR, Landrigan EA. Reduction of serum carnitine concentrations during anticonvulsant therapy with phenobarbital, valproic acid, phenytoin, and carbamazepine in children. *J Pediatr*. 1991;119:799-802.
21. Dreifuss FE, Santilli N, Langer DH, et al. Valproic acid hepatic failure. *Neurology*. 1987;37:379-395.
22. Ohtani Y, Endo F, Matsuda I. Carnitine deficiency and hyperammonemia associated with valproic acid therapy. *J Pediatr*. 1982;101:782-785.