Carnitine Levels in Valproic Acid–Treated Psychiatric Patients: A Cross-Sectional Study

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Background: Carnitine facilitates the transport of long-chain fatty acids across the mitochondria for beta oxidation, and the removal of potentially toxic acylcoenzyme-A metabolites from the inner aspect of mitochondrion as acylcarnitines. Previous studies suggest a significant decrease in carnitine concentrations and changes in the ratio of acylcarnitine to free carnitine in seizure-disordered patients treated with valproic acid (VPA), which may lead to clinical manifestations of carnitine deficiency. This study sought to explore whether the same decrease in plasma free carnitine and increase in acylcarnitines are seen when VPA is used in the treatment of patients with psychiatric disease.

Method: Thirty psychiatric patients treated with VPA for at least 6 months were selected for the study and granted informed consent for participation. Exclusion criteria included liver disorder or pancreatitis, metabolic defects known to affect plasma carnitine levels, or noncompliance with VPA regimen. Plasma free carnitine, total carnitine, acylcarnitine, VPA, and amylase levels were determined, and liver function tests (LFTs) were performed. Pearson correlations were conducted between VPA levels, levels and ratios of carnitines, as well as LFTs and amylase levels.

Results: Plasma free and total carnitine levels were lower than the reported normal range for the laboratory performing the assay, and the ratio of acylcarnitine to free carnitine was increased. There was a significant positive correlation of VPA levels and acylcarnitine–free carnitine ratio, a trend toward significance between VPA levels and acylcarnitine levels, and a marginal negative correlation between VPA levels and free carnitine levels. VPA levels correlated also with several LFTs and acylcarnitine levels. Octanoyl carnitine and acylcarnitine levels, as well as acylcarnitine–free carnitine and octanoyl–free carnitine ratios, correlated significantly with amylase levels.

Conclusion: Although the study was limited by a cross-sectional design without direct control comparison, the findings suggest that patients with various psychiatric conditions treated with polypharmacy that includes VPA may have lower plasma carnitine levels than would be expected in healthy controls.

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The amino acid derivative carnitine is present in most human tissues. Its major sources are the diet and de novo synthesis. The 2 major physiologic functions of carnitine are the transport of long-chain fatty acids across the mitochondria for beta oxidation and the esterification of potentially toxic acylcoenzyme-A metabolites with subsequent export from the inner aspect of the mitochondrion.[1]

Although decreased biosynthesis, inadequate intake, inadequate absorption, defective transport, or excessive renal excretion may lead to decreases in plasma and tissue carnitine levels, for most patients, the underlying cause of decrease in carnitine levels is renal insufficiency with dependence on dialysis, an inborn error of metabolism affecting mitochondrial metabolism, or iatrogenic factors such as chronic administration of certain drugs. The clinical manifestations of severe carnitine deficiency may include hypotension, muscle weakness, failure to thrive, encephalopathy, hypoketotic hypoglycemia, and/or cardiomyopathy.

A number of clinical studies have shown a significant decrease in total or free blood carnitine concentrations in seizure-disordered patients treated with valproic acid (VPA).[2–9] The VPA metabolite valproyl-CoA, when transformed into valproyl-carnitine, may cause excessive renal excretion of carnitine as the valproyl moiety, interfere with tissue free-carnitine transport, or interfere with its renal reabsorption.[10]

Carnitine deficiency in the context of VPA therapy has been a major concern in the field of child neurology because of the higher incidence of VPA-related hepatotoxicity in young children treated for seizure disorder with this

agent as well as the possible relationship between other observed complications of VPA therapy and carnitine deficiency.[11] VPA therapy has been associated with serious side effects such as Reye-like syndrome, pancreatitis, and idiosyncratic life-threatening hepatotoxicity (the latter 2 merited U.S. Food and Drug Administration black box warnings for VPA).[12–14] The association of hepatotoxicity and VPA has been insufficiently studied. Most importantly, as a treatment intervention for VPA-associated hepatotoxicity, carnitine supplementation leads to greater survival (59% of 17 patients) when compared with no supplementation (8% of 48 patients).[15] Early and aggressive intravenous carnitine administration during acute hepatotoxicity leads to significantly better outcomes than oral delayed administration or no treatment.[15,16] Carnitine supplementation in children and young adults with VPA monotherapy–induced hyperammonemia has been associated with significant decreases in ammonia levels.[17]

A position statement[11] concluded that VPA-associated hepatotoxicity is related to tissue carnitine deficiency, normal blood carnitine levels do not exclude tissue deficiency, and intravenous L-carnitine treatment is efficacious in the treatment of VPA-induced hepatotoxicity, particularly if initiated early. This expert panel recommended prophylactic use of carnitine supplementation in pediatric neurology patients who were thought to be at particularly high risk for carnitine deficiency and its clinical consequences. Groups deemed at particularly high risk for VPA-induced carnitine deficiency include patients who are very young, malnourished, chronically ill, receiving antiepileptic polypharmacy, and having clinical comorbidities with other nonepileptic central nervous system pathology.

To date, no studies have been conducted to determine the role of VPA in carnitine depletion in psychiatric patients regardless of age. Similarly, we have no data assessing the association between indices of liver or pancreatic toxicity and carnitine status in psychiatric patients treated with VPA.

The present study is a cross-sectional determination of carnitine levels and their correlation to liver and pancreatic function in a small sample of VPA-treated psychiatric patients.

METHOD

Participants

Thirty subjects who had been receiving treatment with VPA for at least 6 months for the treatment of psychiatric conditions including mood, anxiety, personality, or impulse control disorders were included in the study. Diagnoses of psychiatric disorders were made using standard diagnostic tools (e.g., DSM-IV). Subjects of either sex and any racial and ethnic group who were 18 to 80 years of age were invited to participate. They were recruited from varied Tucson, Arizona–area psychiatric clinics. The study was approved by the University of Arizona Institutional Review Board and the Community Partnership of Southern Arizona Human Subjects Committee. All participant subjects provided written informed consent.

Subjects were excluded if they had preexisting documented liver disorder or pancreatitis; had a fatty acid or other metabolic defect known to affect carnitine status; were undergoing dialysis; were using "statin" drugs, retinoid derivatives, or cephalosporins within 2 weeks of blood sampling; had acute or severe physical illness requiring medical attention within 2 weeks of blood draw (e.g., severe congestive heart failure, severe respiratory conditions, prolonged fevers, prolonged diarrhea); or had failure to comply with at least 75% of VPA oral doses based on self-report or treatment provider's report.

Procedures

Subjects were invited to participate by their treatment providers; those interested gave written informed consent. Clinical charts were audited to confirm study eligibility. Other parameters noted included a brief medical, psychiatric, and substance abuse history primarily for screening purposes. In addition, concomitant medications at the time of sampling were recorded. Subjects were urged to fast after midnight prior to morning blood sampling and underwent venipuncture approximately 10 to 12 hours after the most recent oral dose of VPA. Approximately 15 cc of blood were obtained for measurement of VPA, aspartate aminotransferase, alanine aminotransferase, direct and total bilirubin, blood ammonia, albumin, γ-glutamyltransferase, lactate dehydrogenase, amylase, free carnitine, and acylcarnitine levels, as well as prothrombin time. VPA and amylase levels were determined and liver function tests (LFTs) were performed at the Arizona Health Sciences Center Clinical Laboratory (Tucson, Ariz.), and free carnitines and acylcarnitines were measured at Pediatrix Laboratories Division of BioAnalytical Chemistry and Mass Spectrometry (Bridgeville, Pa.).

Statistical Analysis

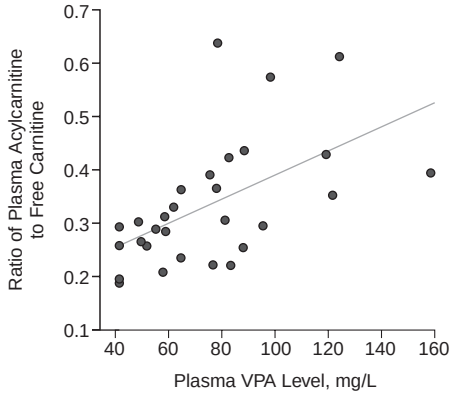
Descriptive statistics, as well as cross-sectional Pearson correlation of carnitine levels, VPA levels, concomitant medications, and liver function and pancreatic parameters were analyzed utilizing SPSS version 11.5 (SPSS Inc., Chicago, Ill.). Pearson correlations are reported as both 1- and 2-tailed analysis. Statistical significance was set at $p \leq .05$.

RESULTS

Subjects

Of 30 participants, data were excluded for 1 of them since we learned retrospectively that the patient had hepatitis C. Of the remaining sample, 17 women (58.6%) and

Figure 1. Correlation Between Valproic Acid (VPA) Levels and Acylcarnitine–Free Carnitine Ratio in Subjects Taking VPA for at Least 6 Months (N = 29)[a]



[a]Pearson R = 0.553, p = .002 (2-tailed analysis).

Table 1. Correlations of Liver Function Test Outcomes With VPA Levels and Duration of VPA Treatment in Subjects Taking VPA for at Least 6 Months (N = 29)

Test	Pearson R	1-Tailed p Value	2-Tailed p Value
Correlations of VPA Levels and Liver Function Test Outcomes			
Ammonia	0.272	.077	.154
LDH	0.302	.059	.118
AST	0.331	.040	.08
GGT	0.327	.045	.09
Correlations of Duration of VPA Treatment and Liver Function Test Outcomes			
Total bilirubin	0.308	.056	.111
Direct bilirubin	0.276	.078	.155
Albumin	0.346	.036	.071

Abbreviations: AST = aspartate aminotransferase, GGT = γ-glutamyltransferase, LDH = lactate dehydrogenase, VPA = valproic acid.

12 men (41.4%) with an age range of 19 to 72 years (mean ± SD = 41.2 ± 14.1) had received VPA for 6 to 112 months (31.9 ± 34.2). Primary psychiatric diagnoses were bipolar affective disorder, 69.1%; schizoaffective disorder, 6.9%; schizophrenia, 17.2%; unipolar major depression, 3.4%; and posttraumatic stress disorder, 3.4%.

Biochemical Findings

The mean ± SD plasma free carnitine level was 27.02 ± 8.69 μmol/L in male patients (normal value = 44.11 ± 10.1 μmol/L) and 24.47 ± 6.30 μmol/L in female patients (normal value = 38.22 ± 7.87 μmol/L). The mean plasma total carnitine level was 34.84 ± 10.21 μmol/L in male patients (normal value = 53.05 ± 11.50 μmol/L) and 32.97 ± 6.95 μmol/L in female patients (normal value = 46.65 ± 9.29 μmol/L).[18] The ratio of acylcarnitine to free carnitine was increased (0.34 ± 0.12 μmol/L) compared with normal (0.25) (references 18 and 19 and data on file, Sigma-Tau Pharmaceuticals Inc., Gaithersburg, Md.).

VPA levels were a mean ± SD of 75.4 ± 28.3 mg/L, and duration of treatment was 30.83 ± 33.8 months. There was a trend toward a negative correlation between VPA levels and free carnitine levels (Pearson R = –0.301, 1-tailed p = .056, 2-tailed p = .113), and there were significantly positive correlations between VPA levels and acylcarnitine levels (Pearson R = 0.328, 1-tailed p = .041, 2-tailed p = .083), octanoyl carnitine levels (Pearson R = 0.419, 1-tailed p = .012, 2-tailed p = .024), and VPA levels and acylcarnitine–free carnitine ratio (Pearson R = 0.553, 1-tailed p = .001, 2-tailed p = .002) (Figure 1). VPA levels and duration of treatment correlated with several liver function indicators (Table 1).

Amylase levels correlated significantly with acylcarnitine levels (Pearson R = 0.376, 1-tailed p = .022, 2-tailed p = .044), acylcarnitine–free carnitine ratio (Pearson R = 0.497, 1-tailed p = .003, 2-tailed p = .006), and octanoyl–free carnitine ratio (Pearson R = 0.323, 1-tailed p = .044, 2-tailed p = .088). There was a nonsignificant trend associating plasma amylase and octanoyl carnitine levels (Pearson R = 0.301, 1-tailed p = .056, 2-tailed p = .12).

Duration of VPA treatment correlated significantly with free carnitine (Pearson R = 0.417, 1-tailed p = .014, 2-tailed p = .027) and total carnitine ratio (Pearson R = 0.440, 1-tailed p = .010, 2-tailed p = .0019). There was a nonsignificant trend associating duration of treatment and acylcarnitine levels (Pearson R = 0.267, 1-tailed p = .085, 2-tailed p = .170). The number of concomitant medications as well as the type of antipsychotic agents utilized did not correlate with changes in ammonia or carnitine levels or ratios.

DISCUSSION

Although limited by a cross-sectional design without direct comparison with either healthy or non–VPA-treated psychiatric patients, this study suggests that patients with various psychiatric conditions treated with polypharmacy that includes VPA may have lower plasma carnitine levels than would be expected in healthy controls. It is possible that factors such as nutritional differences, differences in lifestyle, and iatrogenic factors may explain some of the difference in carnitine status.

Further studies are needed to firmly establish whether the depletion of carnitine is caused by VPA in these subjects, and whether the observed correlations of VPA with ammonia and other LFT indicators is mediated by tissue carnitine deficits. The correlations between amylase levels and carnitine levels also require further exploration, but they support the suggestion of a role of carnitine depletion in the mechanism of pancreatic toxicity. The significance of the correlation between duration of VPA therapy and carnitine levels is difficult to interpret given the fact that all patients were required to be taking VPA for at least 6 months (a period in which carnitine depletion

is most likely to occur). Additionally, a selection bias may have allowed those who had a lesser degree of carnitine depletion to tolerate VPA for a longer period of time. The kinetics of carnitine depletion with VPA therapy could only be determined by a longitudinal study in which serial carnitine and VPA levels are prospectively recorded. Such studies have been conducted in children with neurologic conditions, and a progressive decrease of carnitine level over time has been reported.[20,21] However, given that VPA is known to lead to a decrease in tissue carnitine and an increase in ammonia levels and other LFT indicators, and that carnitine supplementation in patients treated with VPA for seizure disorder may have a beneficial effect in reverting hyperammonemia and its clinical manifestations (i.e., vomiting, lethargy, changes in mental status, encephalopathy) as well as hepatotoxicity, clinical trials on the effects of carnitine supplementation in psychiatric subjects treated with VPA in polypharmacy may prove useful in the future.

Drug name: valproate (Depakote, Depakene, and others).

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