CME

Effect of L-carnitine treatment for valproate-induced hepatotoxicity

Article abstract—The authors analyzed the association of L-carnitine treatment with hepatic survival in 92 patients with severe, symptomatic, valproate-induced hepatotoxicity. Forty-eight percent of the 42 patients treated with L-carnitine survived, but only 10% of the 50 patients treated solely with aggressive supportive care survived ($p < 0.001$). Early intervention with IV rather than enteral L-carnitine was associated with the greatest hepatic survival. Specifically, all 10 patients who were diagnosed in <5 days and treated with IV L-carnitine survived. Most patients had features of chronic illness and most children appeared to be malnourished.

NEUROLOGY 2001;56:1405–1409

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Valproate-induced hepatotoxicity, which is rare, but often fatal, is due to the direct disruption of mitochondrial processes.[1-2] It is heralded by nonspecific symptoms such as lethargy, nausea/vomiting, or worsening seizures,[1] and occurs more frequently in certain at-risk populations (e.g., mentally retarded individuals, young children, and those taking multiple drugs).[1-2] One proposed mechanism is a drug-induced carnitine deficiency.[3] This is well documented in at-risk patients[3] and, if pronounced enough, would impair mitochondrial function. Treatment can be life saving in inherited diseases that produce a similar secondary carnitine deficiency.[4] This prompted our study of L-carnitine treatment.

Methods. This retrospective inception cohort study was designed to investigate whether L-carnitine treatment was associated with better hepatic survival of patients with acute, severe, symptomatic, valproate-induced hepatotoxicity. Because the primary outcome measure was hepatic survival, deceased and liver transplant patients were combined as terminal hepatic failure. The International Registry for Adverse Reactions to Valproate identified 123 potential patients. Following review of medical records, 92 met inclusion criteria. Two had bipolar disorder and 90 had epilepsy. They included all L-carnitine–treated patients with acute, symptomatic hepatic dysfunction— regardless of outcome. The inclusion of all treated patients and the exclusion of so many deceased, untreated patients make the assessment of any positive effect of L-carnitine more conservative. Patients receiving L-carnitine to prevent hepatotoxicity were not excluded. Although none was receiving L-carnitine at the onset of hepatotoxicity, three had been so treated, but this was stopped >50 days before hepatotoxicity. The University of Texas Institutional Review Board approved this study.

Additional material related to this article can be found on the *Neurology* Web site. Go to www.neurology.org and scroll down the Table of Contents for the May 22 issue to find the title link for this article.

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Supported in part by an NIH grant K08-NS01499-02 (T.P.B.) and by a gift to the University of Texas–Houston from Sigma-Tau Pharmaceuticals, Inc., Gaithersburg, MD.

T.B., E.H., I.M., and G.K. have had current or prior financial relationships with Sigma Tau Pharmaceuticals, Inc. In the past, T.B. has consulted on matters related to valproate toxicity. Before 1995, E.H. was their Vice President for Research and Regulatory Affairs and later served as a consultant. I.M. did freelance research and foreign language translation on matters related to this project. G.K. was a consultant in the past, but not on this project.

Some data were presented in a preliminary form at the 52nd annual meeting of the American Academy of Neurology; San Diego, CA; April 29–May 6, 2000.

Received July 28, 2000. Accepted in final form January 27, 2001.

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Results. The clinical characteristics of the L-carnitine–treated and untreated patients were not significantly different except for calendar year (table 1). Untreated patients were more prevalent in the early years and L-carnitine–treated patients in recent years ($p = 0.01$). After the onset of toxicity, valproate was stopped after 7 days (median) in the L-carnitine group and after 8 days in the untreated group ($p = 0.95$). Excluding those hospitalized when toxicity developed, the median interval was 5 days until initial hospitalization and 6 days until care at a university hospital or tertiary facility in the L-carnitine–treated patients vs 7 and 8 days for the untreated patients ($p = 0.84$ and $p = 0.81$). The medical history and growth parameters often suggested poor nutrition and chronic illness. Of the children, 69% were < 25th percentile for weight and 38% were < 5th percentile (i.e., "failure to thrive"). During the preceding year, most had been hospitalized at least once. Laboratory data in the two groups were similar (additional material related to this article can be found on the *Neurology* Web site; go to www.neurology.org and scroll down the Table of Contents to find the title link for this article).

Hepatic survival was much more prevalent after L-carnitine treatment ($p = 0.001$); this was apparent in all subgroups (table 2) and with an adjustment for the variables defining those subgroups. Although patients were evenly split between IV and enteral treatment, survival was more prevalent after IV treatment (14/21 vs 6/21). Because the German patients probably include most cases in that region for 1977–1991, the positive conclusions

Table 1 *Demographic and clinical characteristics of patients with hepatotoxicity: comparison of L-carnitine–treated and untreated patients*

	L-Carnitine treated		Untreated		
Characteristics	Available n	Percent	Available n	Percent	*p* Value*
All patients	42	46	50	54	0.98
Country					
United States	26	62	30	60	
Germany	13	31	16	32	
Other	3	7	4	8	
Sex	42		50		0.78
M		57		60	
F		43		40	
Cognitive abilities	42		50		0.97
Normal		52		52	
Mentally retarded		48		48	
Valproate therapy†	42		50		0.66
Polytherapy		76		80	
Monotherapy		24		20	
Year of hepatotoxic event	42		50		0.01
1977–1987		26		44	
1988–1992		33		40	
1993–1997		40		16	
Age, y	42		50		0.49
<2		21		22	
2–5		45		36	
5–10		17		16	
>10		17		26	
Weight percentile	25		30		0.50
>25		24		37	
≤25 >5		36		27	
≤5		40		37	
Hospitalizations in last year	37		44		0.70
None		27		14	
One		38		57	
Two or more		35		30	
Initial symptoms	42		50		
Nausea/vomiting		36		52	0.12
Anorexia		19		22	0.73
Lethargy		33		38	0.64
Increased seizures		26		24	0.81
Infection		52		42	0.32

Data were obtained from clinic and hospital notes, and autopsy reports. The weight percentiles were limited to patients under 18 and based on the weight before hepatotoxicity and possible edema.

* The *p* values are for comparison of the L-carnitine–treated and untreated group for demographic and clinical characteristics. This comparison was performed using a χ^2 test.

† Polytherapy refers to the concomitant, chronic use of any other medication. For the patients with epilepsy, this was often phenobarbital, carbamazepine, and/or phenytoin and less frequently clorazepate or clonazepam. The two bipolar patients were also receiving lithium. The median dose of valproate (mg/kg/d) was 39 (range 14 to 92) for the L-carnitine–treated patients and 43 (range 12 to 108) for the untreated patients. The median duration of valproate therapy was 81 days (range 12 to 2,596) for the treated patients and 72 (range 1 to 846) for the untreated patients. Three patients, all in the L-carnitine–treated group, had received prophylactic L-carnitine to prevent toxicity. This was stopped 60 to 100 days before the hepatotoxic event. They had received valproate therapy for 169, 923, and 943 days, which was longer than for all but one other treated patient. Excluding these three, the median duration of valproate therapy was 74 days. This suggests that the prophylactic use of L-carnitine only delayed the onset of the hepatoxic event.

Table 2 *Hepatic survival in the L-carnitine–treated and untreated groups*

Variable	L-Carnitine treated	Untreated
All Patients	20/42 (47)	5/50 (10)
Country		
United States	13/26 (50)	3/30 (10)
Germany*	5/13 (38)	2/16 (13)
Other	2/3 (67)	0/4 (0)
Sex		
M	14/25 (54)	5/30 (17)
F	7/17 (39)	0/20 (0)
Cognitive abilities		
Normal	9/22 (41)	1/26 (4)
Mentally retarded	11/20 (55)	4/24 (17)
Valproate therapy		
Polytherapy	17/32 (54)	3/40 (8)
Monotherapy	3/10 (30)	2/10 (20)
Year of event		
1977–1987	2/11 (18)	1/22 (5)
1988–1992	7/14 (50)	4/20 (20)
1993–1997	11/17 (65)	0/8 (0)
Age, y		
<2	4/9 (44)	2/11 (18)
2–5	9/19 (47)	3/18 (17)
5–10	5/7 (71)	0/8 (0)
>10	2/7 (29)	0/13 (0)
Hospitalizations in last year		
None	8/10 (80)	1/6 (17)
One	6/14 (43)	3/25 (12)
Two or more	5/13 (38)	1/13 (8)

Values are expressed as n/N (%).
The direct comparison of the two groups for all patients was made by χ^2 test, $p < 0.001$. The adjusted p value for the association of treatment with survival controlling separately for each demographic and clinical characteristics was determined by the Mantel–Haenszel test. With such adjustments for each factor, the different between L-carnitine–treated and untreated patients was significant for all variables, $p = 0.001$.

* For German patients in the time period 1977–1991, the survival was 33% for L-carnitine–treated and 13% for untreated patients. For L-carnitine–treated patients, the dissimilar survival of American and German patients may be related to differing use of intravenous L-carnitine (60% of American, but only 40% of German patients) during the crucial first 5 days of the hepatotoxic episode.

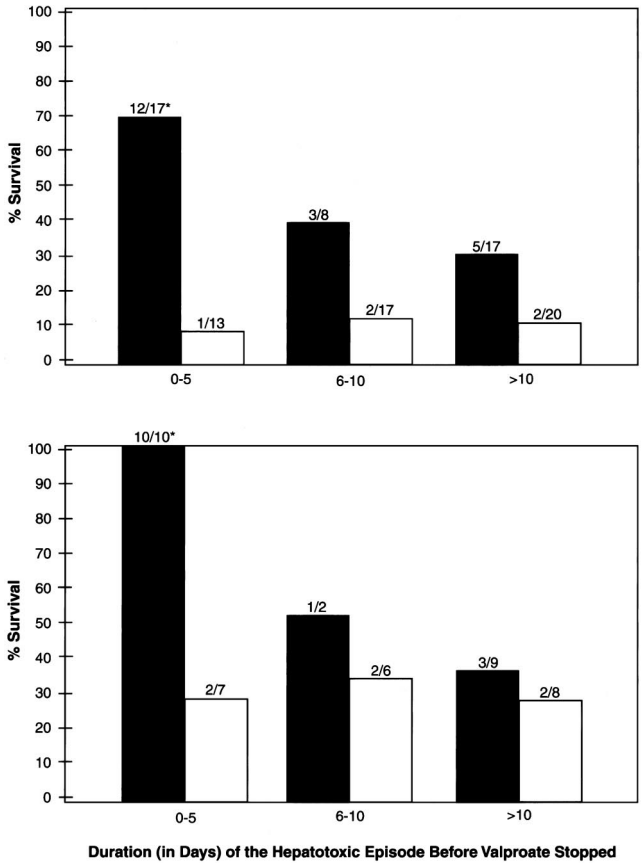

Figure. Upper panel: *The effect on survival of the duration of hepatotoxicity before stopping valproate treatment: comparison of L-carnitine–treated patients and untreated patients. Closed bar = L-carnitine treated; open bar = untreated. Because much of the study's strength is due to the different outcomes of patients diagnosed early (<5 days), the characteristics of the L-carnitine–treated and untreated patients in this subgroup are summarized below. The two groups are remarkably similar except for the year of the event. L-Carnitine group: median age 3.4 years; male:female ratio 5:12; valproate monotherapy:polytherapy ratio 4:13; cognitively normal patients:mentally retarded patients 8:9. Untreated group: median age 5.1 years; male: female ratio 6:10; valproate monotherapy:polytherapy ratio 3:13; cognitively normal patients:mentally retarded patients 7:9. Years of events: 1977–1987: 2 L-carnitine, 7 untreated; 1988–1992: 5 L-carnitine, 5 untreated; 1993–1997: 10 L-carnitine, 4 untreated.* Lower panel: *The effect on survival of the duration of hepatotoxicity before stopping valproate treatment: comparison of patients treated with IV L-carnitine and patients treated with enteral L-carnitine. Closed bar = IV L-carnitine treated; open bar = enteral L-carnitine treated. * Indicates* $p < 0.001$ *for the association of IV treatment with survival for patients with valproate treatment stopped within the first 5 days of the hepatotoxic event (Fisher's exact test).*

about L-carnitine in this subgroup would seem to represent that population reasonably. Although the non-German patients were acquired in a less systematic manner, the comparable results in all patients and the American subgroup suggest that the overall conclusions represent the outcomes for the two regimens. The differences were most apparent when valproate was stopped early (<5 days) and L-carnitine was administered IV (figure). All treated survivors had a total or near total neurologic recovery and survived for more than a year. Regardless of the route of administration, most patients received 50 to 100 mg/kg/d of L-carnitine for variable periods.

An explanatory logistic regression model indicated that better survival was significantly associated with IV relative

to enteral L-carnitine ($p = 0.002$) and to supportive care ($p < 0.001$) (additional material related to this article can be found on the *Neurology* Web site; go to www.neurology.org). There was a suggestive association ($p = 0.110$) for better survival with enteral treatment relative to supportive care. Those relationships had homogeneous odds ratios across the three intervals for delay before valproate stopped and across the three sets of years for the event, although most of their strength tended to be from patients diagnosed early (i.e., <5 days). A more wide-ranging exploratory logistic regression model substantiated the positive conclusions about IV L-carnitine (additional material related to this article can be found on the *Neurology* Web site; go to www.neurology.org). It also revealed noteworthy associations of better survival with the absence of recent hospitalizations, concomitant infection at presentation, and male sex. The last of these was surprising and may be spurious; nonetheless, only five untreated patients survived, all male. Furthermore, the majority (54%) of treated males survived but only a minority (39%) of treated females survived.

Over the course of the study, the survival of L-carnitine–treated patients, but not untreated patients, increased dramatically (table 2). This was probably related to a combination of speedier diagnosis and more frequent use of IV L-carnitine. The meager survival of untreated patients suggests that the L-carnitine group's better survival over time was not entirely secondary to advancements in medical care. This was apparently due to intentional differences in management related to the treating physician's knowledge of L-carnitine rather than a better advanced tertiary facility. In fact, during the last 5 years of the study, four of the six untreated American patients were in hospitals where L-carnitine treatment had been, or would later be, used. Furthermore, these six, none of whom survived, were in hospitals ranked, in one or more specialties, in the top forty in the United States.[5]

Discussion. The typical treatment for drug-induced hepatotoxicities is withdrawal of the toxic agent and supportive care, but the mortality rate is usually greater than 80%.[6] In this study, hepatic survival without L-carnitine treatment was even worse and did not improve over time. In contrast, L-carnitine treatment was associated with better survival in all patient subgroups. Two critical factors were early recognition of the hepatotoxicity and prompt treatment with L-carnitine, particularly the IV formulation. Because the low (15%) bioavailability of enteral L-carnitine was probably further compromised by gastrointestinal dysfunction, the better survival with IV treatment may be related to higher blood levels. Although survival was enhanced even with delayed diagnosis and treatment, subgroup analysis specifically revealed increased survival with early treatment. In recent years, recognition of hepatotoxicity has occurred earlier in both the United States and Germany.[1,7] However, our study shows that without L-carnitine treatment, the liver failure is usually fatal. This is not inconsistent with recent German publications[7-8] that included six survivors, four treated with L-carnitine. The two untreated survivors had anorexia, which may be self-protective by limiting valproate intake.

These results must be viewed within the limitations of a retrospective cohort study. The registry raises issues of ascertainment bias, but the similar outcome in the population-based German cohort supports the conclusions of the overall study. Another potential confounder is that during the later years of the study, there was both increased survival after L-carnitine treatment and increased use of L-carnitine. The absence of any untreated survivors during the last 5 years of the study supports the conclusion that the increased survival of L-carnitine–treated patients during the same period was related to L-carnitine treatment and not just improved care. The increased survival since 1988 and the increased use of IV L-carnitine in the last 5 years may have been related to their increased availability in the United States after approval in 1985 and 1992, respectively. A key issue is why were not all patients treated with L-carnitine, even when readily available? This appears to be related to the preferences of individual physicians and certainly was not related to the quality of the tertiary care institution.

Carnitine facilitates fatty acyl group transport into mitochondrial and helps maintain the ratio of acyl to free coenzyme A (CoA).[4] In certain inherited metabolic diseases in which acyl CoA accumulate and disrupt mitochondrial function, carnitine facilitates transport of these acyl groups out of the mitochondria and eventually into the urine, thereby causing a secondary carnitine deficiency.[4] When catabolism is stimulated by stress (e.g., infections), such patients often develop severe, potentially fatal metabolic crises.[4] L-carnitine treatment is able to reverse these autointoxication-induced problems.[4] Unlike the branched chain amino acids, valproate is metabolized incompletely and valproyl CoA accumulates.[9] Although due to an inferior substrate rather than an abnormal enzyme, the process is similar to branched-chain disorders; a metabolic crisis occurs when there is inadequate carnitine.

We propose two related hypotheses to explain the potential benefit of L-carnitine; 1) patients taking valproate have an ongoing detoxification process that utilizes carnitine to maintain mitochondrial metabolism; and 2) when there is stress-induced catabolism (e.g., seizures, infection, etc.), rare patients develop terminal hepatic failure due to an insufficient carnitine reserve for detoxification. Before the onset of hepatotoxicity, most patients had clinical characteristics (e.g., small size, young age, polytherapy, mental retardation, and frequent hospitalizations) that are known to be associated with a serum carnitine deficiency.[3] Furthermore, some valproate-treated patients may have normal serum carnitine in spite of tissue deficiency.[10] Although several factors had modest associations with survival, only IV L-carnitine treatment, particularly early IV treatment (see the figure), had a truly robust association with survival. The prompt and often dramatic reversal of hepatotoxicity suggests reversal of a carnitine deficiency.

Acknowledgment

The authors thank the late Dr. Fritz Dreifuss for his encouragement, Maya Misra and Alicia Powers for assistance with data management, and Russell Green for data management and editorial assistance.

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Cricopharyngeal achalasia is a common cause of dysphagia in patients with mtDNA deletions

Article abstract—To assess dysphagia, the authors examined 12 patients with Kearns–Sayre syndrome (KSS) or chronic progressive external ophthalmoplegia (CPEO) due to mitochondrial DNA (mtDNA) deletion by videofluoroscopy and manometry. Cricopharyngeal achalasia was documented in nine of 12 patients (75%), whereas deglutitive coordination problems were found in one patient. Cricopharyngeal myotomy may be an effective treatment in selected cases with severe cricopharyngeal obstruction.

NEUROLOGY 2001;56:1409–1412

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Dysphagia is a well-known and potentially fatal complication in a wide variety of neurologic disorders.[1] Although documented in a few cases, dysphagia and deglutitive oropharyngoesophageal functions have not been studied systematically in patients with mitochondrial encephalomyopathies.[2,3] The aim of this study was to assess the frequency and nature of dysphagia in 12 patients with Kearns–Sayre syndrome (KSS) or chronic progressive external ophthalmoplegia (CPEO) due to genetically proven, single large-scale mitochondrial DNA (mtDNA) deletion.

Methods. The study was performed in a series of 12 consecutive patients with KSS or CPEO seen at the Department of Neurology at the University of Bonn between July 1999 and October 1999. Inclusion criteria for KSS were as follows: 1) progressive external ophthalmoplegia, 2) age at onset less than 20 years, 3) pigmentary retinopathy, and 4) cardiac conduction block. Inclusion criteria for CPEO were as follows: 1) progressive external ophthalmoplegia, and 2) exercise intolerance. All KSS and CPEO patients showed ragged-red fibers (modified Gomori trichrome stain) and cytochrome c oxidase (COX)-negative fibers in skeletal muscle biopsy. Molecular genetic analysis for the detection of mtDNA deletions was performed in all patients as previously described.[4] Swallowing problems were assessed by a personal structured interview and by videofluoroscopy. In addition, computed pharyngoesophageal manometry (CPM) was performed in eight patients. For videofluoroscopy (frame rate: 50 Hz), liquid barium was given self-administered by cups in unmeasured volumes. Swallowing examinations were repeated in different upright and supine positions. A severe form of cricopharyngeal obstruction was indicated by a local esophageal diameter reduction of at least 50% at the level of the upper esophageal sphincter (UES) during swallowing. For CPM, a sequential computer manometry system (PC Polygraph®, Synectics Medical Comp., Frankfurt, Germany) with a 4-intraluminal pressure transducer assembly (Konigsberg Instruments Inc., Pasadena, CA) and recording sites 5 cm apart was used. The assembly was placed transnasally into the oro- and hypopharynx, the UES, and the proximal part of the esophagus (figure 1A). We evaluated UES pressure and pharyngeal and esophageal peristalsis during resting and dry swallows with each swallow repeated at least five times (see figure 1B).

Results. *Clinical and genetic findings.* Mean age at examination was 46 ± 10 years. There were five men and seven women. The clinical diagnosis was KSS in two and CPEO in the remaining patients. Age at onset was 12 and

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Received September 6, 2000. Accepted in final form February 3, 2001.

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