

Effects of L-carnitine in patients with hepatic encephalopathy

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Abstract

AIM: To evaluate the influence of L-carnitine on mental conditions and ammonia effects on patients with hepatic encephalopathy (HE).

METHODS: One hundred and fifty patients (10 patients with alcoholism, 41 patients with hepatitis virus B infection, 78 patients with hepatitis C virus infection, 21 patients with cryptogenetic cirrhosis) meeting the inclusion criteria were randomized into group A receiving a 90-d treatment with L-carnitine (2 g twice a day) or into group B receiving placebo in double blind.

RESULTS: At the end of the study period, a significant decrease in NH₄ fasting serum levels was found in patients with hepatic encephalopathy ($P < 0.05$) after the treatment with levocarnitine (LC). Significant differences were also found between symbol digit modalities test and block design in patients with hepatic encephalopathy ($P < 0.05$).

CONCLUSION: Results of our study suggest an important protective effect of L-carnitine against ammonia-precipitated encephalopathy in cirrhotic patients.

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Key words: Hepatic encephalopathy; Carnitine; Cirrhosis; Ammonia; Treatment

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INTRODUCTION

Hepatic encephalopathy (HE) commonly occurs in

patients with liver cirrhosis and is characterized by impaired mental function, neuromuscular disorders and altered states of consciousness. The pathogenesis of HE is controversial although ammonia has been found to induce alterations of cerebral neurotransmitter balance especially at the astrocyte-neuron interface.

Hyperammonemia induces abnormalities such as brain edema and intracranial hypertension in cirrhotic patients. In cirrhotic patients, the relation between blood levels of ammonia and brain events is also influenced by the changes in the permeability-surface area of the blood-brain barrier^[1].

In hepatic encephalopathy, the Alzheimer type II astrocytes are the main neuropathological alteration, characterized by swollen cellular nuclei, with their chromatin displaced to the periphery.

The accumulation of glutamine, a product of ammonia detoxification generated within astrocytes expressing activity of glutamine synthetase, is a major factor for the swelling of astrocytes^[2].

Previous studies have reported a significant protective effect of L-carnitine in mice, rats, and human beings. In fact L-carnitine treatment is associated with a significant reduction of blood and brain ammonia concentration^[3-6]. Carnitine is a natural substance involved in regulating substrate flux and energy balance across cell membranes.

The pharmacological activity of L-carnitine presents various aspects. The carnitine acts by shuttling acetyl-CoA into mitochondria, enhances the metabolic flux in the tricarboxylic acid cycle by sparing free CoA and activating the transport of adenine nucleotides across the inner mitochondrial membrane and prevents adenylate translocase inhibition of the activity of pyruvate dehydrogenase by decreasing the acetyl-CoA/CoA ratio, thus enhancing the oxidative utilization of glucose.

Increased extra-intestinal ammonia production and reduced ammonia detoxification capacity in patients with cirrhosis^[7-9] and HE, have not been studied^[10].

L-carnitine, inducing ureagenesis, may decrease blood and brain ammonia levels^[4,5]. In order to assess the clinical efficacy of L-carnitine in the treatment of HE, a randomized, double-blind, placebo-controlled study with oral administration in cirrhotic patients with hyperammonemia was carried out.

MATERIALS AND METHODS

Patients

One hundred and fifty patients (10 with alcoholism, 41 with hepatitis B virus infection, 78 with hepatitis C virus infection, 21 with cryptogenetic cirrhosis) meeting

the following inclusion criteria were enrolled in the study: chronic hepatitis with spontaneous manifest HE (mental state grade 1 or 2 according to the West Haven criteria) minimal HE (MHE) (mental status grade 0) and a number connection test performance time >30 s^[11-13]; hyperammonemia (venous ammonia concentration >50 mmol/L); cooperative, hospitalized, adult patients with liver cirrhosis diagnosed by clinical, histological, and ultrasonographic findings.

Exclusion criteria included: major complications of portal hypertension, such as gastrointestinal blood loss, hepatorenal syndrome or bacterial peritonitis; acute superimposed liver injury; patients with other neurological disease and metabolic disorders, diabetes mellitus, unbalanced heart failure and/or respiratory failure or end-stage renal disease; severe HE (mental state grade 3-4); administration of anti-HE medications such as neomycin, lactulose, lactitol, branched-chain aminoacids; any additional precipitating factors such as high protein intake (additional high-protein meals), constipation or intake of psychostimulants, sedatives, antidepressants, benzodiazepines, or benzodiazepines-antagonists (flumazenil); patients with fever, sepsis or shock were also excluded to avoid variations caused by body temperature.

Study design

Patients meeting the inclusion criteria were randomized either into group receiving a 90-d treatment with L-carnitine (2 g twice daily) or into group receiving placebo in double-blind. Concomitant medications throughout the study included diuretics and beta-blockers.

Patients were visited weekly throughout the treatment period for the assessment of adherence to the study protocol, blood pressure and cognitive functions, as well as recording of adverse events. Throughout the trial, levocarnitine was supplied as 2 g vials for oral use.

All administered drugs were identical in appearance, and neither investigators nor patients were informed of the selected agents at the end of the study. Administration instructions were provided with each patient pack. All patients were instructed to take the trial medication as prescribed. Patients were considered compliant, if the number of returned vials was between 80% and 120% of the planned treatment regimen. For the duration of the trial, concomitant drugs were administered at the lowest possible therapeutic dosage, and unchanged as far as possible.

Study series

A total of 150 cirrhotic hepatopathic patients met the criteria for inclusion in this study performed between January 2000 and December 2001. They were randomly assigned to receive placebo (75 patients) or L-carnitine (75 patients). The two groups had similar demographic characteristics, etiology, course of disease and Child-Pugh grade. All study series were subdivided into groups of MHE or HE 1 or HE 2 according to the initial HE grade (West-Haven criteria). Group A consisted of patients with MHE (21 patients receiving LC, 19 patients receiving

placebo). Group B consisted of patients with initial HE 1 (30 patients receiving LC, 30 patients receiving placebo). Group C consisted of patients with initial HE 2 (25 patients receiving LC, 25 patients receiving placebo). The effectiveness of therapy was compared and evaluated separately in the different subgroups.

The groups were homogeneous with regard to anamnestic and diagnostic criteria. Differences in composition of the two groups with respect to precipitant factors might be minimized, because the patient population was well defined by inclusion and exclusion criteria.

Diagnosis of minimal hepatic encephalopathy

Psychometric tests and automated EEG analysis were performed for all the patients.

Minimal hepatic encephalopathy was defined as the presence of at least one of the abnormal psychometric tests.

Trail making test: The trail making test was used to evaluate abstract reasoning, tactile performance, tactile-visual and spatial memory, rhythm perception and memory, speech-sound perception, primary motor speed, intelligence, psychomotor speed, sequencing abilities, language function, sensory function, grip strength, and personality functioning.

Time was recorded in seconds. This test included part A and B.

In part A, patients were asked to serially connect digits that were scattered on a page as quickly as possible. In part B, patients were asked to sequentially alternate numbers and letters (i.e. 1-A-2-B-3-C) as quickly as possible. A decrease in the time indicated an improvement in neuropsychological function.

Wechsler adult intelligence scale-revised: Block design test and symbol digit modalities test. The Wechsler adult intelligence scale-revised (WAIS-R) could provide information on global intellectual functioning.

Cognitive functions assessed in the block design test (BDT) were construction, praxis, spatial reasoning motor function, and processing speed. The symbol digit modalities test (SDMT) was used to assess attention, concentration executive function, motor function, and processing speed.

An increase in the number of points in the BDT and SDMT indicated an improvement in neurological function.

Diagnosis of hepatic encephalopathy

Hepatic encephalopathy grade was diagnosed on the basis of the evaluation of consciousness, intellectual functions, behavior and neuromuscular functions according to West Haven criteria introduced by Conn and Liebertahl^[11].

Neurophysiological assessment

The EEG was recorded using standardized techniques. Five electrodes were attached to the skin at the positions T3, T4, O1, O2, and Cz according to the international "10-20 system". Electrode impedance was kept lower than 5 K Ω . After applying the usual handpass filters (0.53-35 Hz), 2 runs of 100 s each were recorded and

compared for reproducibility. Artefact-free recordings were selected and fed into a computer after digital conversion (sample frequency 102.4 Hz). Ten epochs of 10 s each were analyzed by applying fast Fourier transformation, and the mean power spectrum was calculated.

Patients were graded into different studies of hepatic encephalopathy according to their mean dominant frequency (MDF) and the relative powers of delta and theta activity^[14].

Liver function assessment

The Child-Pugh^[15] score was determined to assess the severity of cirrhosis, including three biochemical variables (serum albumin, bilirubin, and prothrombin time) and two clinical characteristics (presence or absence of ascites and clinical hepatic encephalopathy).

A patient had a Child-Pugh score A cirrhosis if the score was ≤ 6 points, a Child-Pugh B cirrhosis if the score was 7-9 points and a Child-Pugh C cirrhosis if the score was > 9 points. Patients without signs of ascites were scored as two points for ascites^[15].

Venous ammonia concentration

The ammonia was determined according to the enzymatic determination of ammonia with glutamate dehydrogenase in a rapid and interference-free photometric determination (340 nm) of NH_4^+ in native blood plasma as previously described^[16].

Due to reasons of safety, blood was immediately sent to the laboratory for determination of NH_4^+ .

Safety parameters

Safety parameters included blood tests (hemoglobin, hematocrit, white blood cell count, and thrombocytes) and liver function tests (alanine amino transferase, aspartate amino transferase, gamma glutamyl-transpeptidase, cholinesterase activity, serum bilirubin concentrations, prothrombin time and partial thromboplastin time) on d 0, 30, 60 and 90.

Statistical analysis

Descriptive statistics was proposed from the study sample and results were expressed as mean \pm SD.

Statistical analyses were performed by two-way analysis of variance (ANOVA), as well as by controlling for multiple correction of Bonferroni.

All *P* values were two-sided, using $\alpha = 0.05$ as the reference standard for determining the significance of the principal outcomes.

Statistical Analysis System (Cari, NC, USA) software version 6.11 was used for all analyses.

The primary population for statistical analysis was to intent to treat population of all randomized patients (I.T.T.).

RESULTS

Baseline values

The two groups had similar general characteristics. Serum NH_4^+ fasting concentrations were not significantly

different before the treatment.

Comparison with baseline

In MHE, ammonia serum levels were significantly decreased to 13.10 $\mu\text{mol/L}$ (CI-24.3 to -1.8; $P < 0.05$), to 19.10 $\mu\text{mol/L}$ (CI-30.2 to -8.0; $P < 0.001$), to 28.1 $\mu\text{mol/L}$ (CI-38.5 to 17.6; $P < 0.001$) after 30, 60, and 90 d of treatment, respectively.

The trial making test-A and trial making test-B were significantly decreased to 13.80 s (CI-19.87 to -7.73; $P < 0.05$), to 25.00 s (CI-29.09 to -20.91; $P < 0.05$), to 18.00 s (CI-23.50 to -12.50; $P < 0.05$) and to 26.00 s (CI-29.61 to -22.39; $P < 0.05$), to 21.50 s (CI-26.62 to -16.38; $P < 0.05$), and to 28.9 (CI-32 to -25; $P < 0.05$) respectively, after 30, 60 and 90 d of treatment.

The symbol digit modalities test was significantly increased from 4.00 points (CI 3.51 to 4.49; $P < 0.05$), after 30 d of treatment, to 8.00 points (CI 7.56 to 8.44; $P < 0.05$), and 8.00 points (CI 7.53 to 8.47; $P < 0.05$) after 60 and 90 d of treatment, respectively.

The block design in MHE were significantly increased from 4.10 points (CI 3.59 to 4.61; $P < 0.05$), to 7.90 points (CI 7.35 to 8.45; $P < 0.05$), and to 12.90 points (CI 12.53 to 13.27; $P < 0.05$) respectively after 30, 60, and 90 d of treatment.

In HE1, ammonia serum levels were significantly decreased to 12.0 $\mu\text{mol/L}$ (CI-22.57 to -3.65; $P < 0.05$), to 23.90 $\mu\text{mol/L}$ (CI-33.23 to -14.57; $P < 0.05$) and to 41.00 (CI -50.23 to 31.77; $P < 0.05$) respectively after 30, 60, 90 d of treatment.

The TMT A and B were significantly decreased to 11.60 s (CI-18.08 to -5.12; $P < 0.05$) and to 9.20 s (CI-12.62 to -5.78; $P < 0.05$), to 21.60 s (-27.73 to -15.47; $P < 0.05$) and to 19.10 s (CI-22.70 to -15.50; $P < 0.05$), to 28.80 s (CI-34.87 to -22.73; $P < 0.05$) and to 23.80 s (CI-27.06 to 20.54; $P < 0.05$) respectively after 30, 60, 90 d of treatment.

The SDMT were significantly increased from 5.10 (CI 4.45 to 5.75; $P < 0.05$) to 8.00 (CI 7.30 to 8.70; $P < 0.05$) and to 14.00 (CI 13.39 to 14.10; $P < 0.05$) respectively after 30, 60, 90 d of treatment.

The BDT were significantly increased from 3.00 points (CI 2.40 to 3.60; $P < 0.05$) from 6.10 points (CI 5.47 to 6.73; $P < 0.05$) and from 12.10 points (CI 11.62 to 12.58; $P < 0.05$) respectively after 30, 60 and 90 d of treatment.

In HE2, ammonia serum levels were significantly decreased to 15.10 $\mu\text{mol/L}$ (CI-23.44 to -6.76; $P < 0.05$) and to 36.00 $\mu\text{mol/L}$ (CI-44.84 to -27.16; $P < 0.05$) respectively after 60 and 90 d of treatment.

The TMT A and B were significantly decreased to 10.50 s (CI-16.97 to -4.03; $P < 0.05$) and to 9.50 s (CI-13.31 to -5.60; $P < 0.05$), to 26.20 s (CI 32.97 to -22.39; $P < 0.05$) and 21.79 s (CI-25.70 to 17.88; $P < 0.05$), to 30.20 s (CI-36.48 to 23.92; $P < 0.05$) and 35.00 s (CI 39.13 to 30.87; $P < 0.05$) respectively after 30, 60, and 90 d of treatment.

The SDMT were significantly increased to 3.10 points (CI 2.56 to 3.64; $P < 0.05$), to 7.00 points (CI 4.15 to 9.85; $P < 0.05$) and to 12.90 points (CI 12.27 to 13.53; $P < 0.05$) respectively after 30, 60, and 90 d of treatment.

The BDT were significantly increased from 4.10 points (CI 3.5 to 4.7; $P < 0.05$) to 8.10 points (CI 7.60 to 8.60; $P < 0.05$) and to 13.00 points (CI 12.40 to 13.60; $P < 0.05$) respectively after 30, 60, and 90 d of treatment.

No significant differences were observed in the patients treated with placebo compared to baseline (Table 1).

Table 1 Baseline data of patients

Parameter	Carnitine group, $n = 75$	Placebo group, $n = 75$
Male/female	50/25	45/30
Age (yr)	51.7 \pm 9.6	53.2 \pm 9.2
Cirrhosis etiology		
Alcohol	7	5
Post-hepatitis B	20	22
Post-hepatitis C	38	38
Cryptogenetic	10	10
Child-Pugh class		
A	30	31
B	34	34
C	11	10
Prothrombin time (%)	62.8 \pm 6.9	63.1 \pm 6.8
Serum albumin level (g/dL)	2.9 \pm 0.7	2.8 \pm 0.9
Serum bilirubin level (mg/dL)	3.1 \pm 1.2	3.2 \pm 1.4
Serum alanine aminotransferase level (IU/L)	119 \pm 74	116 \pm 77
Blood urea nitrogen (mg/dL)	40 \pm 9	39 \pm 11
Serum creatinine level (mg/dL)	0.88 \pm 0.21	0.82 \pm 0.30
Natriemia (mEq/L)	136 \pm 3.4	138 \pm 4.7
Kaliemia (mEq/L)	4.1 \pm 1.2	4.2 \pm 0.9

Comparison between treatments

At the end of the study period, fasting serum levels of NH₄, TMT-A, TMT-B were significantly decreased in patients with hepatic encephalopathy compared to controls ($P < 0.05$) after treatment with LC and placebo respectively. MHE-28.10 *vs* -2.00, $P < 0.05$; HE1-41.00 *vs* -1.50, $P < 0.05$; HE2-36.00 *vs* 3.90, $P < 0.05$; TMT-A MHE -21.50 *vs* -7.30, $P < 0.05$; HE1 -28.8 *vs* -7.30, $P < 0.05$; HE2 -30.20 *vs* -2.90, $P < 0.05$; TMT-B MHE-28.9 *vs* 1.0, $P < 0.05$; HE1-23.8 *vs* -4.00, $P < 0.05$; HE2-12.29 *vs* 0.90, $P < 0.05$.

Significant differences were also found between symbol digit modalities test and block design.

The SDMT was increased to 4.00 *vs* 0.20, 2.90 *vs* 0.80, 3.90 *vs* 0.20, respectively in MHE, HE1, and HE2 ($P < 0.05$). The block design was increased to 3.80 *vs* 0.40, 3.10 *vs* 0.40, 4.00 *vs* 1.00, respectively in MHE, HE1, and HE2 ($P < 0.05$) (Table 2).

DISCUSSION

The pathogenetic mechanisms underlying the development of hepatic encephalopathy are complex.

Symptoms of hepatic encephalopathy are generally reversible, suggesting a metabolic cause. Among the possible neurotoxins implicated in hepatic encephalopathy, ammonia is considered as a leading candidate^[17,18].

The majority of blood ammonia results from muscle protein catabolism at the intestinal level. The remnant is produced by the action of colic bacteria on the nitrogen present in digested foods. Ammonia is vehicled to the liver throughout the portal flux and normally eliminated as urea. The liver damage or the presence of porto-systemic shunts increases its serum levels^[19-21]. The excess ammonia is eliminated from the blood by transforming glutamate into glutamine in skeletal muscle and central nervous system. Neurotoxicity of ammonia is probably due to a direct action on neurons, because the reduction of glutamate and the increase of glutamine may induce swelling of the astrocytes^[22,23].

O'Connor *et al*^[19] observed that mice treated with L-carnitine experience a continuous rise in blood urea N until a plateau is reached 1 h after injection, whereas mice not treated with L-carnitine experience a rise in blood urea N, but one died within 15 min after ammonium acetate administration.

Intravenous L-carnitine significantly can lower plasma ammonia N levels in ewes after an oral urea challenge even though the concentration of ruminal free, non-ionized ammonia N is similar to those in ewes treated only with the urea solution, suggesting that L-carnitine administration may prevent hyperammonemia in ruminants^[24].

Carnitine has been shown to be efficacious in valproic acid hyperammonemia^[25]. Preventive supplementations with L-carnitine might afford some benefits. Ohtani *et al*^[26] have showed that oral administration of carnitine for 4 wk corrects hyperammonemia in patients treated with valproic acid. Studies in valproate-treated rats indicate that L-carnitine supplementation can correct hyperammonemia, hypocarnitinemia and protect rat liver against mitochondrial swelling^[27].

Results of our study showed a protective effect of L-carnitine against ammonia-precipitated encephalopathy in cirrhotic patients^[6].

In patients with MHE, HE 1, or 2, we observed a significant reduction of ammonia serum levels after 30 d of treatment. After 60 and 90 d of treatment, we observed a persistent trend of decreased ammonia serum levels.

A significant therapeutic effect of carnitine was also observed in the NCT-A, which is an accepted and reliable psychometric test for the assessment of mental function in cirrhotic patients with HE^[12,28]. L-carnitine crosses the hemato-encephalic barrier slowly (brain uptake index 5.5%) but its amount in brain is relatively large^[29]. The protective effect of L-carnitine is accompanied with a significant attenuation of the increased cerebrospinal fluid and brain alanine as well as cerebrospinal fluid lactate content, caused by ammonium acetate administration^[30], suggesting that mitochondrial respiration is at least partially restored in L-carnitine-treated animals. The possible beneficial effect of carnitine may be related to an improved pyruvate oxidation, Krebs cycle and flux through

Table 2 Comparison between evaluated parameters of the two groups (mean±SD)

Duration of treatment (days)		Carnitine group (A)				Placebo group (B)			
		0	30	60	90	0	30	60	90
NH ₄ fasting	MHE	68.2±38.2	55.1±31.4	49.1±30.1	40.1±25.1	69.1±39.2	68.2±38.2	68.2±33.6	67.1±34.1
	HE1	82.1±29.1	69.2±28.2	58.2±28.7	41.4±28.1	80.1±30.1	78.7±36.2	77.2±33.4	76.2±31.8
	HE2	89.2±34.2	80.1±28.1	74.1±12.9	53.2±18.2	88.2±34.1	87.1±35.2	86.1±38.1	85.4±39.2
Trail making test-A	MHE	48.9±18.7	35.1±18.9	30.9±15.2	27.4±12.4	51.4±19.2	50.2±18.9	52.1±20.1	50.4±20.2
	HE1	62.4±21.2	50.8±18.9	40.8±16.5	33.6±16.1	60.9±19.9	59.9±19.8	58.4±20.1	53.6±19.8
	HE2	69.3±21.8	58.8±18.1	43.1±20.1	39.1±16.8	64.3±22.4	65.6±20.4	64.9±21.9	61.4±22.9
Trail making test-B	MHE	66.1±12.1	41.1±13.2	40.1±10.2	37.2±12.1	65.2±13.1	61.1±14.1	60.1±13.2	59±14.1
	HE1	74.2±10.1	65±11.1	55.1±12.1	50.4±10.1	75.8±11.9	74.2±12.1	70.11±12.8	71.4±13.2
	HE2	96.9±12.4	87.4±11.2	75.11±11.8	61.9±13.2	91.4±12.1	90.6±10.8	91.5±10.6	93.4±11.8
Symbol digit modalities test	MHE	36±1.2	40±1.8	44±1.5	44±1.7	35±1.9	36±2.1	36.2±11.8	36.4±22.2
	HE1	30±1.9	35.1±2.1	38±2.4	44±1.9	31.2±1.8	32.4±1.9	33.2±1.8	34.1±1.9
	HE2	25.1±1.4	28.2±1.9	32.1±12.4	38±2.4	26.1±2.1	27.2±2.4	28.1±1.9	27.9±1.8
Block design test	MHE	31.1±1.2	35.2±1.9	39±2.1	44±1.1	30.1±2.8	32±2.6	32.4±2.9	32.7±1.8
	HE1	27±1.8	30±1.9	33.1±2.1	39.1±1.1	26±2.9	28±1.9	28.4±2.1	27.1±2.2
	HE2	22±1.9	26.1±1.8	30.1±1.1	35±1.8	22.6±2.1	23.2±1.4	24.2±1.9	24.8±2.1

glutamate dehydrogenase. The latter could then explain the lowering of blood ammonia levels that follows L-carnitine administration.

The best-known function on L-carnitine is the facilitation of β -oxidation by transforming activated long-chain fatty acids into mitochondria. High concentration of fatty acids has numerous deleterious effects upon mitochondrial metabolism.

Acyl-CoA derivatives competitively inhibit the activation of the gluconeogenic enzyme pyruvate carboxylase with acetyl-CoA^[51]. Thus when mitochondrial β -oxidation is inhibited, not only is acetyl-CoA, but also the activating effect of acetyl-CoA is further inhibited by non-esterified acyl-CoA esters, an effect that further decreases gluconeogenesis.

High levels of acyl-CoA derivatives also may inhibit ureagenesis (resulting in hyperammonemia and the tricarboxylic acid cycle)^[52].

Treatment with levocarnitine decreases the serum levels of ammonia and improves the mental functions in cirrhotic patients, and has been proven effective with small adverse events.

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