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REVIEW PAPER

Is Oral L-Acyl-Carnitine an Effective Therapy for Hepatic Encephalopathy? Review of the Literature

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Abstract Hepatic encephalopathy (HE) is a significant cause of morbidity and mortality in patients with advanced chronic liver disease. Current therapies are associated with inconvenient side-effects, high cost, and incomplete efficacy. The quanternary ammonium compound L-acyl-carnitine has been suggested as a potent, low-cost, and safe alternative therapy for patients with cirrhosis and HE. A systematic review of the literature assessing the use of carnitine in the treatment of HE identified three high-quality human trials for review. Analysis of the selected carnitine trials compared to currently accepted therapies suggests that L-acyl-carnitine is promising as a safe and effective treatment for HE, and further trials of this drug are warranted.

Keywords Carnitine · Hepatic encephalopathy · Cirrhosis · Portal hypertension

Hepatic encephalopathy (HE) represents a broad disturbance in the central nervous system of patients with acute and chronic liver failure. HE is common in patients with advanced cirrhosis, and symptoms range from subclinical impairment of memory and concentration to frank coma. The most widely accepted pathophysiological mechanism is that endogenous and gut-derived ammonia crosses the blood-brain barrier and alters neurotransmission via glutamatergic, serotoninergic, g-aminobutyric acid (GABA)-ergic mechanisms [1]. Based on this concept of pathogenesis, current therapies of HE focus on a reduction in serum ammonia levels as a surrogate for decreased central nervous system ammonia exposure. The most common therapies, i.e., non-absorbable disaccharides and oral antibiotics, are not completely efficacious in all patients and are hampered by adverse side-effects, such as loose stools with lactulose, and high cost [2].

A model of HE based on the pathophysiology of Reye syndrome indicates that L-carnitine, an endogenous quarternary ammonium compound, may have a therapeutic benefit in HE with few side-effects [3, 4]. Most notably carnitine serves as a cofactor for the oxidation of long-chain fatty acids in mitochondria. However, carnitine is known to participate in the production of ketone bodies, optimize the function of the electron transport system, and promote maintenance the transfer of acetyl CoA from the mitochondria to the cytoplasm, a necessary step in the production of the neurotransmitter acetylcholine [5, 6].

Although the mechanism by which carnitine provides neurological protection is unclear, numerous animal and human studies suggest an effect in hyperammonemic states, including HE and valproate-induced neurotoxicity [7]. Two early HE studies in a portocaval shunt mouse model indicate a protective effect against lethal ammonia boluses [8, 9]. A later uncontrolled study in human cirrhotics corroborated a similar ammonia buffering effect [10]. More recently several small, randomized trials suggest that carnitine decreases serum ammonia levels,

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improves psychometric tests, and results in measurable electroencephalogram (EEG) changes in cirrhotic patients with a favorable safety profile [11–16].

This paper summarizes the results of high-quality randomized human trials assessing the use of carnitine to treat HE in order to clarify this agent's role in the management of clinical and subclinical HE.

Methods

A search of PubMed, Web of Science, and Scopus for randomized trials was performed using the search terms "carnitine", "L-acyl-carnitine", "HE", "carnitine and ammonia", and "carnitine and HE". The reference sections of relevant papers were manually searched for candidate papers on treatment of HE with carnitine. Studies were selected for inclusion if they scored 3 or higher on the Jaded scale—a validated scale based on randomization, placebo control, blinding, follow-up, and concealment [17].

This search strategy identified six controlled, human studies of the treatment of HE with carnitine for review. Only four studies randomized patients to carnitine or placebo therapy [11–14]. Of the trials that included a randomized cohort, one study did not include a placebo arm and was not included [11]. Three trials addressed the predetermined question of the effect of carnitine on HE in a randomized, placebo-controlled population. These three methodologically sound studies attained a Jadad score equal to or greater than 3 and were included for review.

Results

Three methodologically sound studies investigating the therapeutic effects of HE were reviewed. Two studies focused on a population with subacute to moderate encephalopathic symptoms as graded by the West Haven HE criteria (Fig. 1). Both studies demonstrated the superiority of 4 g oral carnitine over placebo in the end points of serum ammonia concentration and the number connection test (NCT). Serum ammonia concentration and NCT are both components of the widely used portosystemic encephalopathy (PSE) index originally validated by Conn et al. [18] in a study of HE therapies (Fig. 1).

In the earliest reviewed study, Malaguarnera et al. [12] included 120 subjects and demonstrated an average improvement in serum ammonia of 40.75 μmol/L with carnitine in West Haven grade 1 and 2 patients versus 5.75 μmol/L with placebo alone (Fig. 2). This improvement is greater than that seen in several randomized controlled studies of lactulose, lactitol, and rifaximin [19–21].

a) **The West Haven Criteria for Grading Mental State in Patients with Cirrhosis**

Grade 0	No abnormality detected
Grade 1	Trivial lack of awareness Euphoria Anxiety Shortened attention span Impairment of addition and subtraction
Grade 2	Lethargy or Apathy Disorientation of time Obvious personality change Inappropriate behavior
Grade 3	Somnolence to semistupor Responsive to stimuli Confused Gross Disorientation Bizarre behavior
Grade 4	Coma, unable to test mental state

b) **Portosystemic Encephalopathy Index**

PSE = (grade of mental state)x3 + (grade of number connection test) + (grade of flapping tremor) + (grade of blood ammonia)

Fig. 1 (**a**) The West Haven criteria (WHC) is a commonly accepted device for grading the degree on mental impairment in cirrhotic patients. (**b**) The equation for calculating the portosystemic encephalopathy index—widely used in HE therapy trials. Originally presented by Conn et al. [18]

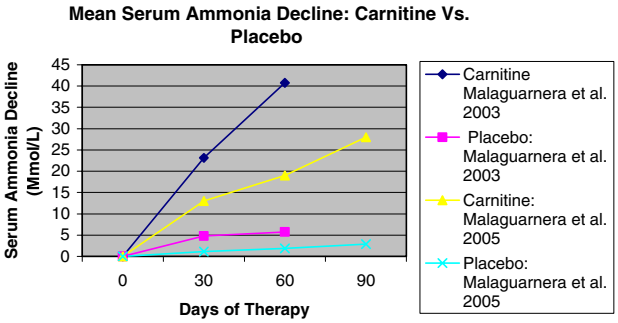

Fig. 2 Mean decline in serum ammonia with carnitine versus placebo in two randomized controlled series of WHC grade 0, 1, or 2 HE patients [12, 14]

In this same study [12], the NCT-A completion time in the carnitine arm improved a mean of 21.9 s more than that of the placebo arm, a statistically significant difference. Clinically, this favorable result would downgrade carnitine-treated patients on the NCT portion of the PSE scoring tool, rivaling the improvements seen in previous disaccharide and antibiotic trials. Adverse events were reported to be rare and mild. Five patients in the carnitine arm complained of headache, mild abdominal pain, or diarrhea. Three patients receiving placebo complained of diarrhea or mild headache. No patient withdrew from the study.

A later study of 150 patients by Malaguarnera et al. [13] confirmed similar potency with serum ammonia levels of

three West Haven treatment groups (0, 1, and 2) improving an average of 13.10 μmol/L (CI-24.3–1.8; $P < 0.05$), 19.10 μmol/L (CI-30.2–8.0; $P < 0.001$), and 28.1 μmol/L (CI-38.5–17.6; $P < 0.001$) after 30, 60, and 90 days, respectively (Fig. 2). The NCT-A completion time in seconds was shown to decrease significantly as well, with an average improved performance of 26 s at the end 90 days (Fig. 3). The gains seen would reduce overall PSE score of the carnitine treatment group versus placebo; and, as shown previously, these reductions would be equal to or better than those seen in the currently dominant therapies for HE.

Malaguarnera et al. [13] went further and showed statistically significant benefit in the additional endpoints of NCT-B times, symbol digit modalities scores, and block design test scores. The addition of these metrics in the study of HE has been recommended by some authors, and they appear adequate for the study of minimal HE (MHE) [22]. These additional studies support an overall enhancement in global neurological function with carnitine supplementation. The PSE index and safety data were not reported in this study.

In the third study reviewed, Malaguarnera et al. [13] focused on a smaller, critically ill cohort of patients with hepatic coma as described by the West Haven criteria. Interestingly, this randomized cohort experienced a statistically significant worsening in Glasgow coma score (GCS) with carnitine therapy (5.9 ± 3.2, $P < 0.0001$; 95% CI = 2.72–6.68) (Fig. 4). The placebo arm experienced no significant decline in GCS. Conversely, carnitine was associated with improved serum ammonia levels ($P < 0.01$; 95% CI = 7.04–55.36), blood urea nitrogen (BUN) ($P < 0.01$; 95% CI = 1.85–16.75), and EEG coma scores. Mortality data were not available.

Discussion

Very few randomized controlled studies have been performed to evaluate the effect of L-acyl-carnitine on HE in

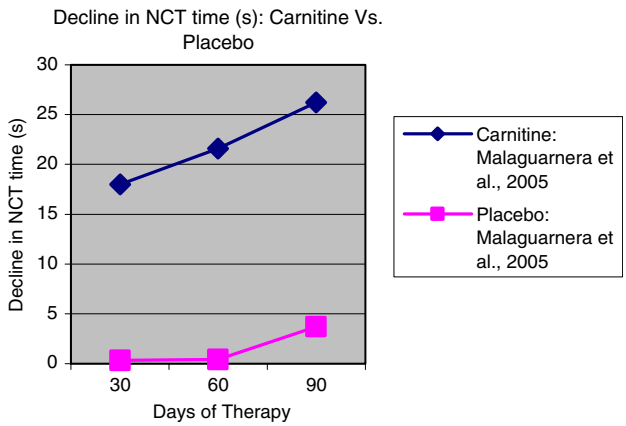

Fig. 3 Mean improvement in NCT-A times (s) with carnitine therapy versus placebo in WHC grade 0, 1, or 2 HE patients [14]

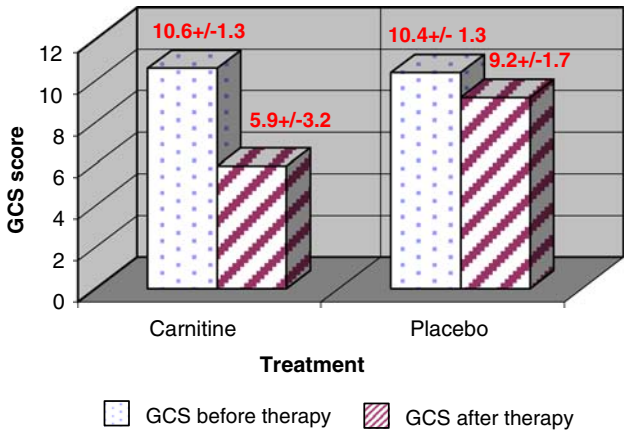

Fig. 4 Mean change in the Glasgow coma scale of critically ill cirrhotic patients treated with L-carnitine versus placebo [13]

cirrhotic patients. However, the three small but well-designed trials by Malaguarnera et al. [12–14] indicate that oral doses of carnitine can significantly reduce serum ammonia levels and improve patient performance on a variety of psychometric tests in a population of patients with grade 0, 1, or 2 West Haven criteria encephalopathy. Although the PSE index was not recorded, the favorable effect of carnitine in improving ammonia and NCT is comparable to that of the current standard therapies of HE. Furthermore, the safety profile of carnitine appears to be excellent and the cost relatively low.

The role of carnitine in critically ill patients with hepatic coma is less clear. Serum ammonia levels did improve, but the clinically important outcome of Glasgow coma score appears to have worsened compared to placebo. Given this result, the significance of EEG improved coma scoring (which was favorable in this cohort) seems in doubt in this small critically ill, cirrhotic population.

The results of L-acyl-carnitine for HE reviewed in this paper are promising. The available studies were randomized placebo-controlled trials with intention-to-treat analysis including a clinically applicable cohort of patients. However, the fact that these trials were conducted in a single center by one investigator is a limitation of this literature and reason for cautious interpretation of the role of carnitine for HE. Larger, multicenter, randomized controlled trials of carnitine versus currently used agents with clinically important end points such as PSE index, expanded psychometric testing, and performance of activities of daily living are needed to clarify carnitine's role in the management of HE. Future studies might focus on use of higher doses of carnitine, combination of carnitine with standard therapies of HE such as nonabsorbable disaccharides or antibiotics, treatment for a longer duration, and inclusion of all pertinent safety, morbidity, and mortality data.

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