Intravenous L-Carnitine Increases Plasma Carnitine, Reduces Fatigue, and May Preserve Exercise Capacity in Hemodialysis Patients

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• Exercise capacity in patients with end-stage renal disease (ESRD) remains impaired despite correction of anemia. Carnitine insufficiency may contribute to impaired exercise and functional capacities in patients with ESRD. Two randomized placebo-controlled trials were conducted to test whether intravenous L-carnitine improves exercise capacity (assessed by maximal rate of oxygen consumption [VO_{2max}]) and quality of life (measured by the Kidney Disease Questionnaire [KDQ]) in patients with ESRD. In study A, patients were administered L-carnitine, 20 mg/kg (n = 28), or placebo (n = 28) intravenously at the conclusion of each thrice-weekly dialysis session for 24 weeks. In study B, a dose-ranging study, patients were administered intravenous L-carnitine, 10 mg/kg (n = 32), 20 mg/kg (n = 30), or 40 mg/kg (n = 32), or placebo (n = 33) as in study A. The prospective primary statistical analysis evaluated changes in VO_{2max} in each study and specified that changes in the KDQ were assessed only in the combined populations. L-Carnitine supplementation increased plasma carnitine concentrations, but did not affect VO_{2max} in either study. Because change in VO_{2max} showed significant heterogeneity, a secondary analysis using a mixture of linear models approach on the combined study populations was performed. L-Carnitine therapy (combined all doses) was associated with a statistically significant smaller deterioration in VO_{2max} (−0.88 ± 0.26 versus −0.05 ± 0.19 mL/kg/min, placebo versus L-carnitine, respectively; $P = 0.009$). L-Carnitine significantly improved the fatigue domain of the KDQ after 12 ($P = 0.01$) and 24 weeks ($P = 0.03$) of treatment compared with placebo using the primary analysis but did not significantly affect the total score ($P = 0.10$) or other domains of the instrument ($P > 0.11$). Carnitine was well tolerated, and no drug-related adverse effects were identified. Intravenous L-carnitine treatment increased plasma carnitine concentrations, improved patient-assessed fatigue, and may prevent the decline in peak exercise capacity in hemodialysis patients. VO_{2max} in the primary analysis and other assessed end points were unaffected by carnitine therapy.

INDEX WORDS: Acylcarnitine; fatigue; metabolism; end-stage renal disease (ESRD).

HEMODIALYSIS has dramatically improved the life expectancy of patients with end-stage renal disease (ESRD). However, despite advances in dialysis technology and adjunctive treatment, patients with ESRD continue to experience high morbidity. Impaired quality of life has been shown in these patients using a number of validated instruments,[1-3] and their ability to perform physical activity is substantially reduced. Objective exercise testing has confirmed an impaired capacity to perform physical work[4] that is only partially corrected by erythropoietin therapy.[5,6]

ESRD is associated with a number of metabolic abnormalities, including alterations in glucose and lipid homeostasis.[7,8] The metabolism of carnitine, an important endogenous cofactor in intermediary metabolism,[9] is also altered in ESRD.[10,11] Carnitine is present in biological systems as both carnitine and acylcarnitine. The distribution of the carnitine pool between carnitine and acylcarnitine provides a sensitive marker of metabolic status.[12] ESRD is characterized by a dramatic redistribution of the plasma carnitine pool toward acylcarnitine.[8,11,13] Acylcarnitine accumulation in chronic disease reflects an increased metabolic demand for carnitine despite physiologically normal total carnitine concentrations and is termed carnitine insufficiency[14] or secondary carnitine deficiency. A ratio of plasma acylcarnitine to carnitine concentration greater

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then 0.4 is indicative of carnitine insufficiency. Additionally, some patients, particularly those who have been maintained on dialysis therapy for considerable periods, may develop an absolute deficiency of carnitine because both carnitine and acylcarnitine are lost during dialysis.[15-17]

Several factors suggest that alterations in carnitine homeostasis may be of functional importance in ESRD. The status of the carnitine pool in patients undergoing hemodialysis correlated with a number of important functional abnormalities in these patients. For example, plasma or tissue carnitine or acylcarnitine concentrations correlated with cardiac ejection fraction,[18] exercise capacity,[17] performance status,[19] and erythropoietin dose requirements.[20]

Carnitine supplementation has been proposed to be of benefit in hemodialysis patients, based on the observed changes in carnitine homeostasis. Particular attention has focused on the effect of carnitine on skeletal muscle function given the important role of endogenous carnitine in muscle metabolism. Studies have shown that carnitine supplementation may improve maximal exercise performance,[21] increase muscle mass,[21,22] and decrease patient perception of fatigue.[23]

Based on these concepts, two placebo-controlled randomized studies were conducted to test the hypothesis that intravenous L-carnitine can increase plasma carnitine concentrations, increase maximal exercise capacity, and improve quality of life in patients with ESRD on maintenance hemodialysis therapy (Carnitine in Hemodialysis for Improving Exercise Function trials).

METHODS

Study Design

Two placebo-controlled, double-blinded, randomized studies of carnitine supplementation were performed. Study A was a comparison of placebo and 20 mg/kg of intravenous L-carnitine for 24 weeks. Study B was a placebo-controlled dose-ranging study using 10-, 20-, and 40-mg/kg doses of L-carnitine for the same duration. Both studies used identical placebo-controlled study designs, differing only in the number of patients recruited and the carnitine doses administered. Four centers participated in study A and 12 centers participated in study B (Appendix).

Patients were recruited from the maintenance hemodialysis populations at each center. Patient enrollment requirements included a diagnosis of ESRD, hemodialysis treatment three times weekly for a period of at least 6 months, age older than 18 years, and medical suitability to undergo graded ergometer exercise testing. Patients with claudication were excluded from participation. During a screening period, plasma carnitine and acylcarnitine concentrations were measured. The ratio of acylcarnitine to carnitine concentrations was calculated, and a value greater than 0.40 (an accepted criteria for carnitine insufficiency) was required for randomization. During the screening period, it was also confirmed that patients were effectively dialyzed and unlikely to require changes in dialysis prescription. This assessment was based on stability in urea clearance, assessed by Kt/V at a value greater than 1.2 with less than 20% variation during the previous 3 months, during which time postdialysis weight had to be stable within 3 kg.

At screening, patients underwent a familiarization bicycle exercise test. Patients were excluded from further evaluation if screening identified a medical condition that precluded safe performance of maximal exercise testing, inability to cooperate with exercise testing, or the use of immunosuppressives, growth hormones, androgens, or anabolic steroids within the 3 months before study entry. Erythropoietin and iron therapies were permitted, and dosages were varied over the course of the study as needed to maintain the hemoglobin concentration in a stable range. The relevant institutional review boards reviewed all protocols and procedures, and informed consent was obtained from all patients.

Baseline blood samples were obtained to define baseline predialysis chemistry, lipid profile, and liver function test results for safety purposes. After baseline evaluations, patients were randomized to drug or placebo. In study A, patients were administered either placebo or 20 mg/kg of L-carnitine intravenously at the conclusion of each dialysis session. In study B, patients were randomized to placebo or 10, 20, or 40 mg/kg of L-carnitine intravenously at the conclusion of each dialysis session. Blood samples were obtained every 4 weeks for safety purposes, and maximal exercise testing was repeated at 12 and 24 weeks of therapy. A 2-week window was used to define an acceptable range for the time of study assessments. Study therapy was continued until the last assessments were completed in each patient. Quality of life was assessed using the Kidney Disease Questionnaire (KDQ), and maximal rate of oxygen consumption (VO_{2max}) was determined by maximal exercise testing at baseline and 12 and 24 weeks of therapy in each study. All treatment-emergent adverse events occurring during the course of the study were recorded.

Specific Testing Methods

Incremental symptom-limited maximal exercise testing was performed using cycle ergometry as previously described.[24] During each test, a mouthpiece and nose clip were fitted to the patient to allow measurement of exhaled gas volumes and partial pressures. Blood pressure and electrocardiograms (ECGs) were evaluated every 2 minutes throughout the test. Rates of oxygen consumption and carbon dioxide production were obtained on a breath-by-breath basis or by means of a mixing chamber, depending on the specific instrumentation available at individual study sites. Exercise protocols were typically initiated using resistance-free cycling and increments in workload programmed at a rate sufficient to allow patients to reach maximal oxygen

consumption in a period of approximately 10 minutes. Patients with exercise capacity limited by such comorbid conditions as ischemic heart disease or chronic lung disease were excluded from the study before randomization. All exercise tests were performed on a nondialysis day between 16 and 26 hours after completion of dialysis and at the same time of day as the baseline test for each patient. Gas exchange data were summarized as 20-second averages, and VO_{2max} was identified as the highest 20-second average at end exercise.

The KDQ is a validated questionnaire for measuring quality of life in patients with ESRD.[25] It was administered in English or Spanish by trained interviewers on nondialysis days. The instrument is divided into five domains: physical symptoms, fatigue, depression, relationships with others, and frustration. The physical symptom dimension is patient specific, with patients identifying problems that most affect their life during the first administration of the questionnaire. All questions are scored on a seven-point Likert scale (7 = no problem, 1 = severe problem). Independent scores are generated for each of the five domains, as well as a total score.

A standardized chemistry panel was assessed during screening, at baseline, and after 12 and 24 weeks of treatment. Complete blood counts were obtained at baseline and every 4 weeks. Single-pool urea kinetics (Kt/V) were calculated using the following equation[26]:

$$Kt/V = k(\ln[BUN_{initial} - BUN_{final}]/BUN_{initial}) \times 100$$

where BUN is blood urea nitrogen.

Protein catabolic rates (PCRs) were calculated using the following equation[27]:

$$\text{PCR (grams of protein per kilogram per day)} = [(0.0076 \times Kt/V) \times (BUN_{initial} + BUN_{final} \times 0.93)] + 0.17$$

Carnitine and acylcarnitine concentrations were determined using a radioenzymatic method.[28]

Statistical Methods

All primary efficacy analyses were based on the intention-to-treat population, defined as all patients who were randomized and received at least one postbaseline assessment of VO_{2max}. Week 12 values were carried forward for missing 24-week data. For patients terminating at less than 12 weeks of study, every effort was made to perform an early-termination exercise test. The primary end point in each study was the change in VO_{2max} (adjusted for baseline dry body weight) from baseline to 24 weeks. The natural log of this measure was used in the analysis in an effort to generate a normal distribution and allow for heterogeneity in the values. Comparisons of placebo versus each carnitine dose were made using analysis of covariance in which baseline VO_{2max} was used as a covariant. Each study was powered to yield a $\beta = 0.8$ with an $\alpha = 0.05$ to detect a 10% effect of drug.

After completion of the primary statistical analysis of the VO_{2max} data, significant heterogeneity in patient responses was identified. A secondary residual analysis–based statistical analysis of VO_{2max} data (corrected for dry body weight at the time of initial and final assessments) was performed using a mixture of linear models (MLM) approach[29] to allow for such response heterogeneity. An MLM is more general than a general linear model and is used to explain population heterogeneity when the population consists of unrecognized subpopulations with different mean responses and/or variances.[30] Cumulative distribution functions were used to characterize the mixed responses. An MLM accommodates the mixed responses conforming to the flow of data reflected in the cumulative distribution functions. Consequently, no imposed data transformation is needed other than the global entropy applied to the likelihood function. The entropy for a specific MLM takes into account the mixing of the response data and inherently and indirectly measures the change from baseline by decomposing the response data into components for responder and nonresponder patients. The association between the four treatment/component groups and their baseline characteristics was tested with Kendall's test of concordance.

The prospective statistical analysis plan specified that studies A and B be combined for the KDQ analysis to achieve adequate power given the limitations in the KDQ test characteristics. All patients administered placebo in either study were compared with all patients administered carnitine, regardless of dose. The change in total KDQ score, as well as the change in each domain of the KDQ from baseline to week 24, was analyzed using the Cochran-Mantel-Haenszel (CMH) test, which was applied on the ranked KDQ changes (the modified ridits were used as the ranking system[31]).

The relationship between changes in VO_{2max} and KDQ scores was examined after characterizing individual responses as decrease (decrease $>$ 0.1 mL/kg/min in VO_{2max} or 0.1 in the KDQ score), increase (increase $>$ 0.1 mL/kg/min in VO_{2max} or 0.1 in the KDQ score), or no change (failure to meet decrease or increase criteria). The presence of a significant relationship was assessed controlling for treatment by using the generalized CMH test.

Changes in laboratory values and occurrence of adverse events were reported using descriptive statistics only.

RESULTS

Study Population

Study A randomized 60 patients, 30 patients on each study arm. Four patients (2 patients from each group) were excluded from the intention-to-treat population because they withdrew before postbaseline exercise tests (2 patients received renal transplants, 1 patient relocated, and 1 patient withdrew after developing elevated serum transaminase levels). Within the intention-to-treat population (n = 56), 7 patients (1 patient, placebo; 6 patients, L-carnitine) withdrew before completing the 24-week protocol. Three patients received renal transplants, 1 patient withdrew consent, 1 patient became pregnant, 1 patient was unable to perform the exercise test, and 1 patient withdrew from the study after a serious adverse event unrelated to study drug.

Table 1. Patient Demographics in the Intention-to-Treat Population

	Study A		Study B			
	Placebo (n = 28)	20 mg/kg LC (n = 28)	Placebo (n = 33)	10 mg/kg LC (n = 32)	20 mg/kg LC (n = 30)	40 mg/kg LC (n = 32)
Age (y)	45 (23-64)	42 (19-76)	43 (24-67)	48 (27-76)	48 (26-76)	46 (25-79)
Dialytic age (y)	3.8 (0.8-23.6)	4.1 (0.6-23.1)	4.9 (0.6-20.4)	4.8 (0.7-16.0)	7.2 (0.7-23.6)	4.6 (0.8-17.5)
Female (%)	43	43	39	34	20	34
Race (%)						
Black	25	29	42	47	50	44
White	29	32	36	31	30	44
Hispanic	36	36	18	12	6	9
Oriental	11	4	3	6	10	3
Other	0	0	0	3	3	0
Congestive heart failure (%)	11	4	6	12	17	13
Diabetes (%)	21	11	12	25	23	22
PCR (g/kg/d)	1.14 (0.68-2.16)	1.13 (0.17-2.09)	1.15 (0.73-1.77)	1.17 (0.09-2.98)	1.02 (0.09-1.64)	1.09 (0.75-1.76)
Albumin (mg/dL)	4.0 (3.3-4.4)	4.0 (2.9-4.4)	4.0 (3.6-4.4)	4.0 (3.8-4.4)	4.0 (3.1-4.9)	3.9 (3.3-4.4)

NOTE. Values expressed as mean (range), excluding missing data.
Abbreviation: LC, L-carnitine.

Study B randomized 133 patients. Six patients (all administered carnitine) did not have postbaseline exercise assessments and were thus excluded from the intention-to-treat population (2 patients received renal transplants, 1 patient withdrew from the study, 1 patient experienced worsening of arthralgia, 1 patient died, and 1 patient withdrew because of ECG changes). Within the intention-to-treat population (n = 127), 9 patients (2 patients, placebo; 3 patients, 10 mg/kg of L-carnitine; 2 patients, 20 mg/kg of L-carnitine; 2 patients, 40 mg/kg of L-carnitine) failed to complete the full 24-week study. One patient had exercise-related problems, 1 patient was unable to exercise because of carpal tunnel syndrome, 4 patients received renal transplants, 1 patient withdrew because of back spasms, 1 patient refused the study drug because of abdominal pain, and 1 patient withdrew because of ECG changes.

In studies A and B, the placebo and carnitine treatment groups were similar with respect to patient age, sex, dialytic age, and prevalence of both diabetes and congestive heart failure at baseline (Table 1). The nutritional status of the study population was very good, assessed by PCRs and serum albumin concentrations (Table 1).

VO_{2max}: Primary Analysis

Exercise capacity was evaluated at baseline and after 12 and 24 weeks of treatment in each patient in both studies. Baseline peak exercise capacity in each group averaged approximately 19 mL/kg/min (Table 2). Validity of the exercise test data is supported by high respiratory ex-

Table 2. Effect of L-Carnitine Supplementation on $VO_{2\ max}$

	Study A		Study B			
$VO_{2\ max}$ (mL/kg/min)	Placebo (n = 28)	20 mg/kg LC (n = 28)	Placebo (n = 33)	10 mg/kg LC (n = 32)	20 mg/kg LC (n = 30)	40 mg/kg LC (n = 32)
Baseline	18.5 ± 5.0	20.0 ± 6.6	18.7 ± 6.3	18.1 ± 7.1	20.1 ± 8.5	17.6 ± 4.6
Week 24	19.2 ± 5.1	20.7 ± 7.3	18.1 ± 6.5	17.9 ± 7.2	19.6 ± 9.8	17.2 ± 5.2
Change (week 24-baseline)	0.6 ± 2.3	0.7 ± 3.2	−0.6 ± 2.7	−0.2 ± 2.3	−0.5 ± 3.5	−0.4 ± 2.9

NOTE. Values expressed as mean ± SD. Values given for the intention-to-treat population, including last observation carried forward.
Abbreviation: LC, L-carnitine.

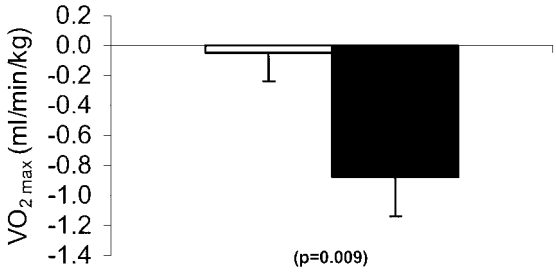

Fig 1. Effect of L-carnitine on VO_{2max} in hemodialysis patients. Data from studies A and B were combined to yield a placebo group (■; n = 61) and patients treated with L-carnitine at any dose (□; n = 122). Populations were analyzed using an MLM approach, incorporating treatment and site as covariants. Mean (minus SE) changes in baseline and final dry body weight–adjusted VO_{2max} over the 24-week study period in patients administered placebo or L-carnitine incorporating the site adjustment to the data set are shown.

change ratio (RER) values at end exercise (1.2 ± 0.15), with no differences between groups. Intravenous carnitine supplementation of 10, 20, or 40 mg/kg at the conclusion of each thrice-weekly dialysis session had no effect on VO_{2max} after 24 weeks in either study (Table 2). Carnitine was also without effect at 12 weeks (data not shown).

VO_{2max}: Secondary Analysis

MLM analysis of VO_{2max} data compared patients (including studies A and B) administered placebo versus those administered L-carnitine (any dose). As shown in Fig 1, MLM analysis (incorporating site and treatment as covariants) showed a statistically significant difference in the change in VO_{2max} adjusted for baseline and final dry body weight in patients treated with placebo (–0.88 ± 0.26 mL/kg/min; n = 61) compared with those administered L-carnitine (–0.05 ± 0.19 mL/kg/min; n = 122; $P = 0.009$; Fig 1). Inclusion of the presence of diabetes, hematocrit, sex, or dialytic age as potential covariants failed to improve the MLM fit to the data set.

Patients responding to intravenous L-carnitine, identified by the MLM procedure (n = 34), had a longer dialysis age, slightly greater body weight and albumin level, and slightly lower hematocrit ($P = 0.05$, Kendall test).

Quality of Life

Twenty-four weeks of intravenous carnitine therapy significantly improved patient sense of fatigue (Table 3). The fatigue domain of the KDQ also significantly improved after 12 weeks of carnitine therapy (change from baseline, 0.05 ± 0.82 in controls and 0.40 ± 0.81 in patients administered carnitine; $P = 0.01$). Trends for benefit of carnitine were also seen in the KDQ total score and the domains of depression and relationship with others of the instrument (Table 3). Subgroup analysis failed to identify differences between the 10-, 20-, and 40-mg/kg carnitine dose KDQ responses. Inclusion of the presence of diabetes, hematocrit, albumin level, sex, and dialytic age as covariants in the analysis of covariance for the KDQ data failed to identify a significant impact on the placebo-versus-carnitine comparison or the overall model fit of the data. Using a categorical analysis (decrease, no change, or improvement), the response to L-carnitine in dry body weight–adjusted VO_{2max}

Table 3. Effect of L-Carnitine Supplementation on Quality of Life Assessed by KDQ for All Patients

	Placebo				L-Carnitine				
	No. of Patients	Baseline	24 Weeks	Change	No. of Patients	Baseline	24 Weeks	Change	*P**
Total score	59	5.00 ± 1.06	5.29 ± 1.08	0.29 ± 0.74	121	4.83 ± 1.12	5.27 ± 1.03	0.44 ± 0.76	0.10
Physical symptoms	57	4.20 ± 1.11	4.88 ± 1.36	0.68 ± 1.22	118	4.23 ± 1.17	5.04 ± 1.11	0.81 ± 1.15	0.76
Fatigue	59	4.90 ± 1.34	5.14 ± 1.22	0.24 ± 0.89	121	4.65 ± 1.26	5.09 ± 1.28	0.44 ± 0.95	0.03
Depression	59	5.38 ± 1.37	5.53 ± 1.39	0.16 ± 1.14	121	5.07 ± 1.48	5.36 ± 1.29	0.29 ± 0.99	0.11
Relationship with others	59	5.38 ± 1.06	5.59 ± 1.09	0.20 ± 0.86	121	5.23 ± 1.06	5.55 ± 1.00	0.32 ± 0.83	0.13
Frustration	59	5.00 ± 1.34	5.28 ± 1.44	0.28 ± 1.25	121	4.91 ± 1.54	5.23 ± 1.29	0.33 ± 1.08	0.59

NOTE. Values expressed as mean ± SD.
*Change in placebo versus change in L-carnitine patients.

Table 4. Hematocrit, Hemoglobin, and Kt/V During Course of Study in Intention-to-Treat Population

	Study A		Study B			
	Placebo (n = 28)	20 mg/kg LC (n = 28)	Placebo (n = 33)	10 mg/kg LC (n = 32)	20 mg/kg LC (n = 30)	40 mg/kg LC (n = 32)
Hematocrit (%)						
Baseline	32.9 ± 3.3	34.1 ± 3.2	34.2 ± 3.2	33.9 ± 3.6	33.7 ± 3.5	33.6 ± 3.3
24 Weeks	33.9 ± 2.9	32.8 ± 4.0	35.1 ± 4.2	33.3 ± 3.4	33.9 ± 3.4	33.5 ± 2.7
Hemoglobin (mg/dL)						
Baseline	11.0 ± 1.0	11.3 ± 1.2	11.4 ± 1.0	11.3 ± 1.2	11.2 ± 1.1	11.1 ± 0.9
24 Weeks	11.3 ± 0.9	11.0 ± 1.3	11.6 ± 1.3	11.1 ± 1.0	11.3 ± 1.3	11.1 ± 0.9
Kt/V						
Baseline	1.80 ± 0.46	1.70 ± 0.47	1.66 ± 0.26	1.74 ± 0.68	1.69 ± 0.27	1.76 ± 0.36
24 Weeks	1.78 ± 0.53	1.73 ± 0.26	1.62 ± 0.23	1.75 ± 0.81	1.72 ± 0.52	1.65 ± 0.30
Dry body weight (kg)						
Baseline	66.9 (37.8-98.1)	65.6 (40.0-94.5)	69.8 (44.7-101.5)	69.4 (48.4-102.1)	69.1 (50.0-102.1)	70.4 (39.3-94.5)
24 Weeks	65.2 (40.7-95.2)	67.2 (37.5-96.5)	70.4 (45.4-103.2)	69.2 (50.1-101.1)	69.0 (49.9-104.7)	70.2 (37.1-96.2)

NOTE. Values expressed as mean ± SD and mean (range).
Abbreviation: LC, L-carnitine.

correlated with the response in KDQ total score (CMH test, $P = 0.04$). A similar trend was observed in the relationship of VO_{2max} to KDQ fatigue (CMH test, $P = 0.11$).

Other Parameters

In both studies, hematocrit and hemoglobin concentrations were stable over the 24-week study period in all groups (Table 4). Similarly, all groups were well dialyzed on entry, assessed by urea kinetics, which were constant over the course of the trials (Table 4). Similarly, dry body weight was constant over the 24 weeks of treatment within each treatment arm (Table 4). Carnitine therapy had no effect on predialysis BUN, plasma creatinine, or plasma phosphate concentrations (data not shown).

Carnitine Concentrations

As expected, carnitine therapy dramatically increased the plasma carnitine and acylcarnitine concentrations (Tables 5 and 6). Acylcarnitine concentrations, reflecting carnitine access to metabolically active pools, increased in proportion to the carnitine concentration. Thus, the acylcarnitine-carnitine ratio was not dramatically influenced by carnitine administration. The increase in plasma carnitine concentration was dose dependent and had reached an approximate steady state at 12 weeks, showing a small increase in carnitine concentration over the second 12 weeks of therapy. The 24-week carnitine and acylcarnitine concentrations were proportional to L-carnitine dose in the 10- to 40-mg/kg range.

Adverse Events

Overall, carnitine was well tolerated by the hemodialysis population studied. The most commonly reported adverse events were flu syndrome, injection-site reaction, pain, pharyngitis, headache, and hypertension and showed no dif-

Table 5. Plasma Carnitine Pool for Intention-to-Treat Population in Study A

	Placebo (n = 28)			20 mg/kg LC (n = 28)		
	Total Carnitine	Free Carnitine	A/F Ratio	Total Carnitine	Free Carnitine	A/F Ratio
Baseline	42.5 ± 14.8	23.7 ± 8.9	0.84 ± 0.83	48.8 ± 11.1	27.1 ± 6.4	0.82 ± 0.22
12 Weeks	45.8 ± 15.4	27.0 ± 10.5	0.73 ± 0.20	322 ± 127	190 ± 70	0.69 ± 0.27
24 Weeks	43.5 ± 16.3	27.6 ± 11.2	0.63 ± 0.29	384 ± 116	243 ± 76	0.64 ± 0.28

NOTE. Values expressed as mean ± SD.
Abbreviations: LC, L-carnitine; A/F, plasma acylcarnitine/free carnitine.

ference in frequency between L-carnitine and placebo.

Several serious adverse events occurred during the course of the study, with no differences between active and placebo groups (Table 7). No serious adverse event was believed by the investigators to be certainly or probably drug related and they were consistent with the population's underlying disease and maintenance hemodialysis treatment.

DISCUSSION

Patients undergoing chronic maintenance hemodialysis therapy have a dramatically impaired exercise tolerance that contributes to their decreased quality of life.[1,2,4] Carnitine therapy has been suggested to improve muscle function,[21,22] exercise capacity,[21] and quality of life[23] in small clinical trials. In the two large placebo-controlled trials currently reported, intravenous carnitine treatment at any of the administered doses failed to improve exercise capacity, assessed by the change in VO_{2max} using the primary statistical analysis. In contrast, carnitine therapy significantly improved the sense of fatigue assessed by the KDQ. However, a secondary statistical method showed a small positive effect of L-carnitine therapy on VO_{2max}.

The mechanism of exercise limitation in ESRD is multifactorial.[4] Erythropoietin therapy improves exercise tolerance by improving blood oxygen-carrying capacity, but residual impairment persists.[5,6] Evidence indicates that peripheral factors are a major determinant of exercise limitation in these patients[32,33] and that VO_{2max} deteriorates routinely over time.[4]

Carnitine homeostasis is altered in ESRD, reflecting the chronic metabolic derangements associated with this condition.[8,11] ESRD is characterized by an increase in acylcarnitine accumulation, reflecting incomplete oxidation of endogenous substrates and their accumulation in the coenzyme A and carnitine pools.[11] This situation is analogous to that in inherited metabolic diseases in which supraphysiological amounts of carnitine are required to maintain effective acyl group removal.[14] Collectively, these have been termed conditions of carnitine insufficiency[14] or secondary carnitine deficiency. The carnitine insufficiency of ESRD can be correlated with a

Table 6. Plasma Carnitine Pool for the Intention-to-Treat Population in Study B

	Placebo (n = 33)			10 mg/kg LC (n = 32)			20 mg/kg LC (n = 30)			40 mg/kg LC (n = 32)		
	Total Carnitine	Free Carnitine	A/F Ratio	Total Carnitine	Free Carnitine	A/F Ratio	Total Carnitine	Free Carnitine	A/F Ratio	Total Carnitine	Free Carnitine	A/F Ratio
Baseline	43.2 ± 13.5	24.4 ± 8.7	0.81 ± 0.47	41.6 ± 15.4	22.3 ± 9.1	0.92 ± 0.30	43.0 ± 13.5	25.3 ± 8.7	0.77 ± 0.47	42.0 ± 12.8	24.1 ± 8.7	0.80 ± 0.37
12 Weeks	48.4 ± 26.1	28.9 ± 21.0	0.78 ± 0.26	184 ± 104	115 ± 70.6	0.64 ± 0.28	320 ± 87.5	209 ± 57.4	0.54 ± 0.26	633 ± 178	371 ± 111	0.79 ± 0.44
24 Weeks	47.0 ± 22.3	27.6 ± 11.4	0.80 ± 0.34	220.0 ± 73.4	148 ± 50.3	0.54 ± 0.36	400 ± 92.0	240 ± 61.6	0.68 ± 0.34	788 ± 233	455 ± 162	0.85 ± 0.64

NOTE. Values expressed as mean ± SD.
Abbreviations: LC, L-carnitine; A/F, plasma acylcarnitine/free carnitine.

Table 7. Serious Adverse Events in the Combined Studies for All Patients

Body System (COSTART term)	Treatment			
	Placebo (n = 63)	10 mg LC (n = 34)	20 mg LC (n = 62)	40 mg LC (n = 34)
Body				
Injection site reaction	6	1	1	2
Infection	4	1	1	0
Chest pain	0	1	1	1
Abdominal pain	0	1	0	1
Fever	0	0	0	1
Accidental injury	0	0	1	0
Neck pain	0	0	1	0
Cardiovascular				
Tachycardia	0	0	1	2
Atrial fibrillation	0	0	0	1
Hypertension	0	0	1	0
Hypotension	0	0	1	0
Aortic stenosis	0	0	1	0
Digestive				
Colitis	0	1	0	0
Vomiting	0	0	1	1
Endocrine				
Parathyroid disease	0	0	1	0
Metabolic and nutritional				
Hyperkalemia	0	1	0	1
Hypervolemia	0	0	0	1
Respiratory				
Lung edema	0	1	0	0
Pneumonia	0	0	1	0
Skin				
Carcinoma	0	0	1	0
Special senses				
Amblyopia	0	0	1	0
Urogenital				
Kidney failure	3	2	4	2

NOTE. Number of patients reporting serious adverse events. Events that occurred only in placebo groups are not listed.

number of functional impairments in this population.[17-20]

Despite optimal dialysis therapy on entry, the hemodialysis patients studied had substantial exercise impairment. Entry VO_{2max} assessments were only approximately 50% to 60% of age- and sex-based predictions for healthy subjects and were consistent with literature reports of erythropoietin-treated patients.[6] Impairment was also reflected in baseline KDQ assessments (Table 3), which were similar to the values obtained after erythropoietin therapy in earlier trials.[34]

Previous studies have shown that L-carnitine supplementation can increase muscle carnitine content[35-37] and suggested that supplementation can increase muscle mass,[22] decrease intradialytic muscle cramping,[21,38] and improve exercise capacity[21] in patients on maintenance hemodialysis therapy. The current studies failed to show an effect of carnitine therapy on increasing VO_{2max} using the primary statistical analysis (Table 2). In contrast to earlier reports, all patients in the current studies were on erythropoietin therapy, with hemoglobin concentrations averaging 11 mg/dL (Table 4). Additionally, the patients were well dialyzed, evidenced by urea kinetics and PCRs (Table 1 and 4), and had good nutritional status, assessed by serum albumin concentration. Recent improvements in hemodialysis therapy may have decreased the impact of carnitine therapy on exercise performance. The effects of carnitine therapy on other aspects of muscle function may have preferentially decreased fatigue and improved exercise tolerance without proportional changes in VO_{2max}.

Analysis of VO_{2max} using the MLM approach showed statistically significant superiority of L-carnitine over placebo. The MLM method uses a cumulative response distribution function to describe the full population in each treatment arm. The MLM defined a net benefit of L-carnitine on VO_{2max} of approximately 0.83 mL/kg/min, or approximately 5% of the baseline value. The MLM approach shows that VO_{2max} decreased in the placebo group during the 6 months of observation in a range consistent with the deterioration reported in the literature,[4] and that this decrease was not observed in the L-carnitine group. Also, VO_{2max} is inversely correlated with dialytic age and positively correlated with muscle carnitine content in hemodialysis patients.[17] Increased muscle carnitine content with carnitine therapy[35-37] may be relevant to the decreased deterioration in exercise capacity identified with the MLM analysis. Thus, L-carnitine therapy may be viewed as preventing the decline in exercise capacity seen in hemodialysis patients. The 5% improvement is approximately half the

L-carnitine effect observed by Ahmad et al[21] in patients not administered erythropoietin. The clinical significance of a change in VO_{2max} of this magnitude is unclear, but responses in VO_{2max} and KDQ correlated (discussed next), thus suggesting a consistent therapeutic benefit. This finding also suggests that the changes in KDQ and exercise physiological characteristics were related to a common effect of L-carnitine and were not nonspecific findings. More clinically dramatic effects of L-carnitine supplementation on exercise capacity in specific subsets of the hemodialysis population cannot be excluded and were not evaluated.

Consistent with previous reports,[3,23] carnitine therapy improved patient sense of fatigue and tended to improve other domains in the KDQ, as well as its total score. The fatigue domain of the KDQ is the most relevant to the study hypothesis that carnitine therapy will improve physical function in hemodialysis patients. Fatigue and other individual assessments of physical well-being reflect multiple complex phenomena in patients with chronic disease[39-41] and may not be fully reflected in the VO_{2max} data. However, as noted, treatment responses in KDQ and VO_{2max} correlated in the current study. Sloan et al,[3] using the Medical Outcomes Study Short-Form 36-item instrument, showed that oral L-carnitine therapy significantly improved patient-assessed physical functioning and general health after 12 but not after 24 weeks and had no effect on other domains, including emotional role, social function, and mental health. This spectrum of response is similar to that observed in the current study using the KDQ, but importantly, the beneficial effects of carnitine on fatigue observed in the treated patients after 12 weeks of treatment were sustained through the 24-week trial. The statistically significant improvement in KDQ fatigue and the non–statistically significant changes in KDQ total and KDQ physical symptoms were approximately 50% of the magnitude of changes reported in response to erythropoietin administration only.[34] Nonetheless, this effect of L-carnitine may still be important because treatment to improve the sense of well-being in patients on hemodialysis therapy is a primary clinical objective; this population continues to have limited return to normal activities despite optimal clinical management, including erythropoietin.[42]

Intravenous carnitine administration increased both plasma carnitine and acylcarnitine concentrations in a dose-dependent manner (Tables 5 and 6). L-carnitine appeared to show linear kinetics (plasma concentration proportional to dose) and a long time to reach true steady state, consistent with previous observations and the drug's very large physiological volume of distribution.[43,44] Consistent with ESRD as a state of carnitine insufficiency, the acylcarnitine-carnitine ratio was elevated on entry and remained elevated despite carnitine therapy. However, carnitine therapy clearly corrected the hypocarnitinemia found in dialysis patients, and the supraphysiological carnitine concentrations achieved may be effective at removing metabolic intermediates from the active intramitochondrial coenzyme A pool. In models of carnitine insufficiency[45,46] and in several inherited organic acidurias,[14,47] enhanced carnitine availability and its induced shunting of acyl groups to acylcarnitine improves cellular metabolism.

Intravenous carnitine was well tolerated, and all measured laboratory parameters remained constant. Previous studies suggested that carnitine therapy may be associated with decreases in plasma creatinine and phosphate concentrations, as well as BUN concentrations.[21] These changes were not replicated in the current studies, which included a large number of subjects. Improvements in dialysis therapy may be responsible for these apparently discrepant results.

Carnitine therapy has been suggested for a variety of clinical abnormalities in hemodialysis patients, including refractory anemia,[48,49] cardiomyopathy,[18] hyperlipidemia,[36] and intradialytic symptoms.[21,38] Hematocrit and hemoglobin concentrations were unaffected by intravenous carnitine therapy in the current studies, but erythropoietin dosing was titrated during the study and not held constant. Similarly, although triglyceride concentrations did not change with therapy, their baseline values were not elevated. The use of carnitine therapy in selected patients with dialysis-associated metabolic syndromes should continue to be considered as therapeutic trials.

In conclusion, intravenous carnitine therapy increased plasma carnitine concentrations, signifi-

cantly decreased patient sense of fatigue, and may stabilize maximal exercise capacity. Carnitine was well tolerated and was effective in increasing acyl group removal from tissues. Intravenous carnitine therapy should be considered in hemodialysis patients with severe functional impairment secondary to fatigue.

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APPENDIX

Study Centers

Study A:

Harbor-UCLA Medical Center, Torrance, CA; nephrologist, Sharon Adler, MD; exercise physiologist, Kathy Sietsema, MD

Vanderbilt University Medical Center, Nashville, TN; nephrologist, Simin Goral, MD; exercise physiologist, Jay Grovers, PhD

UCI Medical Center, Orange, CA; nephrologist, Madeleine Pahl, MD; exercise physiologist, Kathy Sietsema, MD

University Hospital, Stony Brook, NY; nephrologist, Nand Wadhwa, MD; exercise physiologist, Adam Hurewitz, MD

Study B:

Renal Center, Valhalla, NY; nephrologist, Stephen Adler, MD; exercise physiologist, Stewart Lehrman

Scribner Kidney Center, Seattle, WA; nephrologist, Suhail Ahmad, MD; exercise physiologist, H. Thomas Robertson, MD

Oregon Health Sciences University, Portland, OR; nephrologist Cynthia L. Gaboury, MD; exercise physiologist, Melvin Morganroth, MD

Cleveland Clinic Foundation, Cleveland, OH; nephrologist, Robert Heyka, MD; exercise physiologist: Mani Kavuru, MD

George Washington University, Washington, DC; nephrologist, Susie Lew, MD; exercise physiologist, Patrick Gorman, MD

University of Colorado Health Sciences Center, Denver, CO; nephrologist, David Spiegel, MD; exercise physiologist, William Hiatt, MD

University of Vermont, Burlington, VT; nephrologist, Wolfgang Weise, MD; exercise physiologist, Philip Ades, MD

Western Nephrology Clinic, Thornton, CO; nephrologist, Melissa Yanover, MD; exercise physiologist, William Hiatt, MD

Washington University, St Louis, MO; nephrologist, David Windus, MD; exercise physiologist, Robert Spina, PhD

Vanderbilt University Medical Center, Nashville, TN; nephrologist, Simin Goral, MD; exercise physiologist, Jay Groves, PhD

UCI Medical Center, Orange, CA; nephrologist, Madeleine Pahl, MD; exercise physiologist, Kathy Sietsema, MD

Harbor-UCLA Medical Center, Torrance, CA; nephrologist, Sharon Adler, MD; exercise physiologist, Kathy Sietsema, MD

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