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Levocarnitine Administration in Elderly Subjects with Rapid Muscle Fatigue

Effect on Body Composition, Lipid Profile and Fatigue

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Abstract

Aim: Levocarnitine is an important contributor to cellular energy metabolism. This study aims to evaluate the effects of levocarnitine supplementation on body composition, lipid profile and fatigue in elderly subjects with rapid muscle fatigue.

Method: This was a placebo-controlled, randomised, double-blind, two-phase study. Eighty-four elderly subjects with onset of fatigue following slight physical activity were recruited to the study. Prior to randomisation all patients entered a 2-week normalisation phase where they were given an *'ad libitum'* diet, according to the National Cholesterol Education Program (Step 2). Subjects were asked to record their daily food intake every 2 days. Before the 30-day treatment phase, subjects were randomly assigned to two groups (matched for male/female ratio, age and body mass index). One group received levocarnitine 2g twice daily (n = 42) and the other placebo (n = 42). Efficacy measures included changes in total fat mass, total muscle mass, serum triglyceride, total cholesterol, high-density lipoprotein-cholesterol (HDL-C), low-density lipoprotein-cholesterol (LDL-C), apolipoprotein (apo)A1, and apoB levels. The Wessely and Powell scale was used to evaluate physical and mental fatigue. Subjects were assessed at the beginning and end of the study period.

Results: At the end of the study, compared with placebo, the levocarnitine-treated patients showed significant improvements in the following parameters: total fat mass (−3.1 vs −0.5 kg), total muscle mass (+2.1 vs +0.2 kg), total cholesterol (−1.2 vs +0.1 mmol/L), LDL-C (−1.1 vs −0.2 mmol/L), HDL-C (+0.2 vs +0.01 mmol/L), triglycerides (−0.3 vs 0.0 mmol/L), apoA1 (−0.2 vs 0.0 g/L), and apoB (−0.3 vs −0.1 g/L). Wessely and Powell scores decreased significantly by 40% (physical fatigue) and 45% (mental fatigue) in subjects taking levocarnitine, compared with 11% and 8%, respectively, in the placebo group ($p < 0.001$ vs placebo for both parameters). No adverse events were reported in any treatment group.

Conclusion: Administration of levocarnitine to healthy elderly subjects resulted in a reduction of total fat mass, an increase of total muscle mass, and appeared to exert a favourable effect on fatigue and serum lipids.

In the elderly, age-related loss of muscle mass is often characterised by a reduction in muscle strength and rapid muscle fatigue.[1-3] This may compromise physical performance and quality of life, significantly increasing the risk of falls and fractures.[4,5] Previous studies have shown that muscle fatigue is often associated with changes in body composition, such as a progressive increase in the ratio between total fat and muscle mass.[6] This results in an overall imbalance between energy intake and expenditure.[7]

Levocarnitine is found ubiquitously in mammalian tissues and is an important contributor to cellular energy metabolism.[8] Carnitine is essential for the transport of long-chain fatty acids across the inner mitochondrial membrane to the mitochondrial matrix, the site of β-oxidation.[9] Carnitine deficiency in humans is therefore associated with myopathy and impaired fatty acid oxidation.[10,11]

In line with this theory, previous studies have shown that administration of supplemented levocarnitine to chronic haemodialysis patients with reduced muscle mass can evoke a 3-fold increase in muscular carnitine concentration.[12]

As a follow-up to these previously reported data, the aim of our study was to evaluate the efficacy of levocarnitine in reducing fat, increasing muscle mass, improving the serum lipid profile and decreasing fatigue in elderly subjects with rapid muscle fatigue.

Methods

Subjects

A total of 84 elderly subjects aged from 70–92 years (38 female, 46 male; mean age 81.5 ± 6.7 and 80.7 ± 6.9 years, respectively) with onset of fatigue following slight physical activity, were recruited to the study. The study participants were recruited from rest homes (n = 53) or among subjects who presented to our clinic for periodic health evaluation (n = 31). The degree of fatigue experienced after slight daily physical activitity (such as walking, going upstairs, cooking etc.) was measured by using the method described by Wessely and Powell.[13] Briefly, this consists of two scales measuring physical fatigue (eight items scored from 0 = no fatigue to 2 = highest possible fatigue; total score range 0–16) and mental fatigue (five items; total score range 0–10). Subjects with a score of ≥8 for physical and ≥5 for mental fatigue were eligible for the study.

Subjects were excluded if they had experienced any of the following: a significant medical or surgical event within the previous 3 months, significant cardiac failure (New York Heart Association Class III or IV), acute or chronic renal failure, severe respiratory disorders, severe digestive disorders, diabetes mellitus or other endocrine diseases. Patients taking corticosteroids, HMG-CoA reductase inhibitors, or diuretics were also excluded from the trial.

This study was designed and conducted in compliance with the ethical principles of Good Clinical Practice and the Declaration of Helsinki.[14] The study protocol was approved by local ethics committees, and all patients gave written informed consent before any study procedures were initiated.

Study Design

This was a randomised, double-blind, placebo-controlled study conducted between January 2002 and May 2002. The study was designed as a two-phase trial.

Normalisation phase

During this initial 2-week phase, subjects were instructed by a dietician to follow an '*ad libitum*' diet, as classified by the National Cholesterol Education Program (Step 2).[15] Subjects were required to document all caloric intake using a diary, completed every 2 days. This pre-randomisation period

was designed to nullify the effects of dietary changes on metabolic parameters.

Randomisation Phase

Subjects were randomised by a computer-generated randomisation schedule to receive 30-days supply of either levocarnitine 2g twice daily or placebo (n = 42 for both groups). Subjects underwent weekly visits throughout the treatment period for 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 2g vials for oral use (Carnitene®[1], Sigma-Tau, Italy). All administered drugs were identical in appearance, and neither investigators nor patients were informed of the selected agent at the end of the study phase.

Administration instructions were provided with each patient pack. All patients were instructed to take trial medication as prescribed. Subjects were considered compliant if the number of returned tablets 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 as far as possible, were unchanged.

Efficacy Assessment

The primary efficacy measures were changes in: total fat mass, total muscle mass, serum triglycerides, total cholesterol, high-density lipoprotein-cholesterol (HDL-C), low-density lipoprotein-cholesterol (LDL-C), apolipoprotein (apo)A1, and apoB levels. These parameters were measured at the beginning and the end of the study period. Blood samples were collected in the morning, following an overnight fast.

Anthropometric data were measured at baseline and at the end of the study period. Body mass index (BMI) was calculated from bodyweight and body height using the equation BMI = bodyweight (kg)/body height (m^2). In order to measure fatty mass and muscle mass, bioelectrical impedance analysis (BIA) was used. Prior to measurement, subjects were instructed to refrain from physical activity for 12 hours, liquids for 4 hours, and asked to urinate 30 minutes prior to examination. For the 5 minutes leading up to the measurement period, subjects were told to adopt a supine position with their legs apart. After the skin was cleaned with 70% alcohol, four adhesive electrodes (3M Red Dot T™, 3M Health Care, Borken, Germany) were placed on the surface of the right hand and right foot, according to the manufacturer's guidelines. We used a BioZ2 generator (Spengler, Paris, France). The inter-observer and inter-day variability was 0.002kg for fat-free mass (95% CI -0.2–0.2), with a variation coefficient of 1.3% for subjects with a BMI ≤27 kg/m^2. Since only a few subjects were enrolled whose BMI was >27 kg/m^2, and these were equally distributed between the two groups, we considered that a higher BIA variability in these subjects would not have a relevant impact on the final results.

Physical and mental fatigue were assessed before and after treatment by means of the Wessely and Powell scale. Standard laboratory parameters for the assessment of hepatic and renal function were monitored at the beginning and at the end of treatment.

Statistical Analysis

For all non-parametric data, discrete and continuous variables were compared using either the Student's T-test or Wilcoxon-Mann-Whitney test. Categorical variables were compared using either the Chi-square test or Fisher's exact test. Statistical Analysis System (Cari, North Carolina) software version 6.11 was used for all analyses. Energy requirements for maintaining bodyweight were evaluated using data from Lipid Research Clinical Tables,[16] and were adjusted and personalised according to the physical activity of each subject. Physical activity was evaluated 3–5 days/week for ≥30 minutes based on the performance of routine activities such as washing windows/floors, gardening, self-wheeling on a wheelchair, pushing a stroller, raking dead leaves, walking for ≥2 miles, shovelling snow, going upstairs/downstairs etc.[17] All p-values were

1 Use of tradenames is for product identification only and does not imply endorsement.

two-sided, using $\alpha = 0.05$ as the reference standard for determining the significance of the principal outcomes. The primary population for statistical analysis was the intent-to-treat (ITT) population of all randomised subjects. All subjects completed the study.

Results

Baseline characteristics were evenly distributed across the two cohorts (table I). The mean age of the ITT population was 81.1 years. Table II shows the mean energy intake for each of the two study groups throughout the study period.

Comparisons with Baseline

For subjects treated with levocarnitine, there were significant differences in the following parameters after 30-days' treatment compared with baseline (table III): serum levels of total cholesterol −1.2 mmol/L ($p < 0.02$), LDL-C −1.1 mmol/L ($p < 0.03$), HDL-C +0.2 mmol/L ($p < 0.01$), triglyceride −0.3 mmol/L ($p < 0.03$), apoA1 −0.2 g/L ($p < 0.05$), apoB −0.3 g/l ($p < 0.05$) and total fat mass −3.1 kg ($p < 0.02$).

The score for the physical fatigue component of the Wessely and Powell scale decreased by 5.3 points after treatment ($p < 0.001$), while the mental fatigue score decreased by 3.5 points ($p < 0.001$) (table IV).

For the subjects treated with placebo, compared with baseline there was only a significant difference in LDL-C (−0.2 mmol/L; $p < 0.05$) after 30-days' treatment (table III).

Table I. Baseline characteristics (±SD) of the levocarnitine and placebo cohorts

	Levocarnitine (n = 42)	Placebo (n = 42)
Age (years)	81.5 ± 6.7	80.7 ± 6.9
Gender (% M)	52.4	57.1
Height (cm)	161.1 ± 6.0	159.0 ± 6.1
Weight (kg)	66.9 ± 9.4	65.4 ± 11.3
BMI (kg/m^2)	25.7 ± 3.8	25.8 ± 4.2
SAP (mm Hg)	156.1 ± 24.2	155.2 ± 25.8
DAP (mm Hg)	88.2 ± 9.6	87 ± 10.4
Heart rate (bpm)	82 ± 11	84 ± 10

BMI = body mass index; **bpm** = beats per minute; **DAP** = diastolic arterial pressure; **M** = male; **SAP** = systolic arterial pressure.

Table II. Composition of mean energy intake of the two study cohorts throughout the trial period, expressed as mean percentage (±SD) of total energy intake

	Levocarnitine (n = 42)	Placebo (n = 42)
Total energy intake (Kcal/day)	2070 ± 684	2120 ± 700
Total fats	29.3 ± 3.2	28.7 ± 2.4
Saturated fats	6.7 ± 0.8	6.4 ± 0.7
Monounsaturated fats	12.7 ± 2.1	12.2 ± 2.6
Polyunsaturated fats	9.9 ± 1.7	10.1 ± 0.8
Total serum proteins	16.2 ± 2.6	15.6 ± 3.1
Available carbohydrates	54.5 ± 9.4	55.7 ± 7.3
Glucose	11.2 ± 0.9	10.5 ± 1.4

Comparison Between Treatment Groups

At the end of the study period, compared with placebo, the levocarnitine-treated patients showed significant improvements in the following parameters (table III): total fat mass (−3.1 vs −0.5 kg; $p < 0.01$), total muscle mass (+2.1 vs +0.2 kg; $p < 0.01$), serum levels of total cholesterol (−1.2 vs +0.1 mmol/L; $p < 0.01$), LDL-C (−1.1 vs −0.2 mmol/L; $p < 0.01$), HDL-C (+0.2 vs +0.01 mmol/L; $p < 0.02$), triglyceride (−0.3 vs 0.0 mmol/L; $p < 0.02$), apoA1 (−0.2 vs 0.0 g/L; $p < 0.05$), and apoB (−0.3 vs −0.1 g/L; $p < 0.05$). Significant differences were also found in mental fatigue (−3.5 vs −0.6; $p < 0.001$) and physical fatigue (−5.3 vs −1.4; $p < 0.001$).

Tolerability

All 84 patients completed the trial. This indicated that the repeated administration of levocarnitine was well tolerated with good compliance. No adverse events or laboratory abnormalities were reported during the trial in either of the two groups.

Discussion

Muscular metabolism is based on a complex network that involves energy-producing enzymes and substrates. The transition of chemical energy to mechanical energy involves many biochemical steps before the primary energy source is converted to myofibrillar contractions.[7,18] The first step in the

utilisation of energy-producing substrates takes place within the mitochondria. The main mitochondrial substrates are fatty acids, and levocarnitine has been shown to hold a fundamental role in their metabolism. Fatty acid, glucose, and amino acid metabolism result in the production of acetyl-CoA, a vital intermediate in the respiratory chain. This series of reactions produces water, carbon dioxide, and the energy required for the synthesis of adenosine triphosphate.[7,18] This biochemical step needs adequate oxygenation. Adenosine triphosphate is synthesised by mitochondria in skeletal muscle tissue and is used in cytoplasm for myofibrillar contraction.

Levocarnitine administration in elderly subjects reduces fatty mass and significantly enhances muscle mass.[7,18] It is known that decreased muscle mass and function can lead to a reduction in physical activity, and may cause adverse metabolic effects such as decreased bone density, obesity, impaired glucose tolerance, and an abnormal lipid profile.[7]

In our study, we found that 1 months' treatment with exogenous levocarnitine in elderly subjects was associated with an increase in total muscle mass (as well as a reduction of total fat mass), an improvement in the serum lipid profile and, importantly, a significant reduction in muscle fatigue compared with placebo. Baseline characteristics were similar in the two groups (although no formal statistical analyses were performed to confirm that groups were homogeneous for all the relevant parameters).

Subjects with severe heart failure, diabetes or renal failure (or other conditions that may have confounded the results) were excluded from enrolment, as our aim was to assess how 'healthy' elderly subjects responded to supplemental levocarnitine. Of course, we cannot exclude that some of the institutionalised subjects (who were not regularly attending our clinic for periodic health checks) might have had mild undiagnosed chronic heart failure, peripheral vascular disease or other conditions know to benefit from levocarnitine supplementation. However, we think it is unlikely that inadvertent inclusion of just a few such cases might have had a relevant impact on the results.

Table III. Comparisons with baseline of efficacy measurements (±SD) for levocarnitine and placebo at the end of the study

	Levocarnitine (n = 42)		Placebo (n = 42)	
	before	after	before	after
Fatty mass (kg)	23.8 ± 6.8	20.7 ± 5.4	23.7 ± 7.3	23.2 ± 7.1
Muscle mass (kg)	43.1 ± 6.2	45.2 ± 5.8	41.9 ± 5.1	42.1 ± 5.0
Total cholesterol (mmol/L)	6.2 ± 0.3	5.0 ± 0.2	6.0 ± 0.4	6.1 ± 0.2
LDL-C (mmol/L)	3.9 ± 0.2	2.8 ± 0.3	3.8 ± 0.3	3.6 ± 0.2
HDL-C (mmol/L)	0.90 ± 0.1	1.10 ± 0.1	0.88 ± 0.2	0.89 ± 0.1
Triglycerides (mmol/L)	3.1 ± 0.3	2.8 ± 0.2	3.0 ± 0.2	3.0 ± 0.4
ApoA1 (g/L)	1.5 ± 0.2	1.3 ± 0.2	1.5 ± 0.1	1.5 ± 0.2
ApoB (g/L)	1.6 ± 0.2	1.3 ± 0.1	1.6 ± 0.1	1.5 ± 0.8

ApoA1 = apolipoprotein A1; **ApoB** = apolipoprotein B; **HDL-C** = high-density lipoprotein-cholesterol; **LDL-C** = low-density lipoprotein-cholesterol.

In order to assess potential treatment effects on fatigue, we chose to use the assessment scale described by Wessely and Powell for use in patients with chronic fatigue syndrome, rather than more conventional measures of muscle strength or exercise performance. In our experience this instrument, which evaluates both the physical and mental fatigue experienced while performing routine daily activities, is quite appropriate in elderly subjects as its endpoints reflect more closely than other measures real-life situations that are perceived as meaningful by elderly subjects. Of course, our results cannot be directly compared with data on exercise performance or muscle strength derived by application of other techniques.

In our study, compared with baseline, substantial improvements were observed in both physical and mental fatigue after levocarnitine administration, while hardly any change was registered in placebo recipients. This is in line with the findings of Plioplys et al., who reported benefits related to levocarnitine treatment in patients with chronic fatigue syndrome.[19] Our previous study in centenarians (mean age 102 years)[20] showed that these subjects have higher mean serum carnitine levels (8.99 mg/L) than elderly (mean age 66 years) control individuals (7.71 mg/L), and this is associated with improved physical and mental activity. Centenarians did not receive supplemental levocarnitine.

Table IV. Mean values (±SD) of fatigue scores (according to Wessely and Powell[13]) in our study

	Levocarnitine (n = 42)		Placebo (n = 42)	
	before	after	before	after
Physical fatigue (0–16)	13.1 ± 2.4	7.8 ± 2.6*	12.8 ± 2.5	11.4 ± 2.3
Mental fatigue (0–10)	7.8 ± 1.9	4.3 ± 1.7*	7.7 ± 1.9	7.1 ± 1.8

* $p < 0.001$ vs placebo.

The benefits of levocarnitine supplementation in improving muscle function and physical performance in patients with end-stage renal disease or peripheral vascular disease are well known. In patients undergoing chronic haemodialysis, levocarnitine therapy resulted in increased intramuscular carnitine levels, which were found to be associated with increased muscle strength and an amelioration of physical activity.[12] However, not many studies have been performed on the metabolic effects of levocarnitine in healthy subjects, and, as reviewed by Brass and Hiatt, the results are controversial.[21]

In moderately obese women undergoing mild aerobic training, levocarnitine supplementation for 8 weeks was found to induce no significant changes in total body mass or total fat mass.[22] Similarly, the beneficial effects of carnitines in modifying the serum lipid profile have been mostly observed in patients with hyperlipidaemia secondary to long-term dialysis, not in healthy subjects.[23,24] Notably, there appears to be scarce information on the metabolic effects of carnitine in elderly patients. To our knowledge, our study is the first to report beneficial effects of exogenous levocarnitine on both body composition (i.e. an increase of total muscle mass and a reduction of total fat mass) and the serum lipid profile of elderly healthy subjects.

Questions remain as to physiological mechanisms underlying our findings. We did not measure whether supplemental levocarnitine increased serum or intramuscular levels of carnitine, nor did we assess whether changes in biochemical parameters were related to the changes in body composition. Further research is needed to explore in detail the metabolism of carnitines in the elderly.

Conclusion

Our study indicates that oral administration of levocarnitine evokes a reduction of fat mass, enhances lean muscular mass, and facilitates an increased capacity for physical activity by reducing physical and mental fatigue. Furthermore, levocarnitine treatment has been shown to affect hepatic lipoprotein metabolism, and significantly improve the lipid profile. The agent is also well tolerated and produces no adverse events.[25-28]

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