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Acetyl L-carnitine (ALC) treatment in elderly patients with fatigue

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Abstract

Fatigue is one of the conditions most frequently complained by the elderly. There are few effective treatment options for patients with chronic fatigue syndrome. To determine the efficacy, tolerability and impact on the fatigue, as well as on cognitive and functional status of elderly subjects with acetyl L-carnitine (ALC), 96 aged subjects (>70 years, range 71–88) were investigated (50 females and 46 males; mean age 76.2 ± 7.6 and 78.4 ± 6.4 years, respectively). They met four or more of the Holmes major criteria or at least six of Fukuda minor criteria. Fatigue was measured with the Wessely and Powell [Wessely, S., Powell, R., 1989. Fatigue syndromes: a comparison of chronic postviral fatigue with neuromuscular and affective disorders. J. Neurol. Neurosurg. Psychiatry 52, 940–948] scores, with the fatigue severity scale. At the end of the treatment, we observed a decrease of physical fatigue: 6.2 ($p < 0.001$), of mental fatigue: 2.8 ($p < 0.001$), of severity fatigue: 21.0 ($p < 0.001$) and improvements in functional status: 16.1 ($p < 0.001$) and cognitive functions: 2.7 ($p < 0.001$). By the end of the treatment, significant differences between the two groups were found for the following parameters: muscle pain −27% versus −3% ($p < 0.05$); prolonged fatigue after exercise: 51% versus −4% ($p < 0.0001$); sleep

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disorders: 28% versus 4% ($p < 0.05$); physical fatigue: 7 versus −0.5 ($p < 0.0001$); mental fatigue: −3.3 versus 0.6 ($p < 0.0001$); fatigue severity scale: −22.5 versus 1.2 ($p < 0.0001$); functional status 17.1 versus 0.6 ($p < 0.0001$); mini mental state examination (MMSE) improvements: 3.4 versus 0.5 ($p < 0.0001$). Our data show that administering ALC may reduce both physical and mental fatigue in elderly and improves both the cognitive status and physical functions.

Keywords: L-Carnitine; Chronic fatigue syndrome in the elderly; ALC; Cognitive status; Physical status; Physical fatigue; Mental fatigue; Severity of fatigue

1. Introduction

The reduction of birth rates and the increase of life expectancy are influencing the demographic picture of the industrialized countries causing a major presence of older subjects (Havlik et al., 1994). Unfortunately, there is no corresponding amelioration of the quality of life (QoL) (Malaguarnera et al., 1995). One of the conditions most frequently complained by elderly is the fatigue (Lou et al., 2001). Fatigue is a subjective sensation with decreased energy, decreased concentration and decreased motivation (Servaes et al., 2002). Fatigue is invisible and without an objective unit of measure, yet it disturbs the life of most of the elderly patients, causing substantial distress (Cimprich, 1995), because of its influence on daily activities (Buchwald et al., 1995; Jason et al., 1995). Some patients present with persistent and disabling fatigue, but show no abnormalities on physical examination or screening laboratory tests.

Patients with chronic fatigue syndrome show reduced exercise tolerance, and post-exercise fatigue induced by minimal physical activity, suggesting decreased muscle function, is considered as one of the causes of this syndrome (Jones et al., 2005). Abnormal mitochondria have been observed in muscle of some elderly patients with fatigue, suggesting some underlying abnormalities in muscle mitochondrial energy production (Behan et al., 1991).

ALC is a member of the family of carnitines, a group of natural compounds that have an important role in intermediary metabolism. ALC is an amino acid that can be purchased as an individual supplement. It is present in the lists of nutritional agents promoted as producing cognitive benefits for middle-aged and elderly people (Salvioli and Neri, 1994; Calvani and Arrigoni-Martelli, 1999).

ALC facilitates the uptake of acetyl-coenzyme-A into the mitochondria during fatty acid oxidation, enhances acetylcholine production and stimulates protein and membrane phospholipid synthesis (Costell and Grisolia, 1993).

ALC is a compound of great interest in various neurological disorders: it may be of benefit in treating Alzheimer's dementia, HIV-infection, diabetic neuropathies and aging (Rai et al., 1990; Patrick, 2000; De Grandis and Minardi, 2002; Calabrese and Gambassi, 2003).

The aim of this study was to evaluate the effect of exogenous ALC on the physical functions and cognitive status in elderly patients with fatigue.

2. Study design and methods

A single center, randomized, double blind, comparative clinical trial was performed. The procedures followed were approved by the institutional ethics committee and were designed and conducted in compliance with the ethical principles of Good Clinical Practice and the Declaration of Helsinki (World Medical Association Declaration of Helsinki, 1997).

Randomization started in February 2000 and was stopped in September 2001 after reaching the present inclusion of 96 subjects: 48 subjects in each group. At enrollment, anthropometric measurements have been performed and baseline laboratory findings were obtained. Among these, serum aspartate- and alanine-amino transferase (AST and ALT, respectively), gamma glutamyl transpeptidase, cholinesterase, bilirubin, total protein, triglyceride (TG) and total cholesterol (TCH) levels were recorded. The subjects were invited to fill in a questionnaire.

2.1. Subjects

The study pool comprised 96 subjects aged >70 years (range 71–88 years) (50 females, 46 males, of mean age 76.2 ± 7.6 and 78.4 ± 6.4 years, respectively). They were recruited from nursing homes ($n = 41$) or among the subjects who presented to our clinic for periodic health evaluation ($n = 55$). We recruited them on the basis of the criteria of Holmes et al. (1988) and Fukuda et al. (1994). They had met four or more of Holmes et al. major criteria (1988), or at least six of Fukuda et al. (1994) minor criteria (Table 1).

Patients showed the symptoms in two consecutive clinical visits carried out in a blind manner by two different researchers. We ruled out the patients with infections, anemia,

Table 1
Fatigue characteristics of the patients at enrolment

	ALC group % of patients	PLACEBO group % of patients
Major criteria (Holmes et al., 1988)		
New onset	100	100
No previous history	100	100
Does not resolve with best rest	100	100
Activity reduction >50%	81	77
Activity ≥6 months	100	100
Exclude all other illnesses	77	79
Exclude all psychiatric disorders	100	100
Minor criteria (Fukuda et al., 1994)		
Sore throat	81	80
Painful lymph nodes	16	12
Muscle discomfort (pain)	96	95
Prolonged fatigue after exercise	100	100
Neuropsychiatric complaints (impaired memory or concentration)	77	73
Migratory arthralgias	86	77
Generalized headaches	64	61
Sleep disorders	88	91

electrolyte imbalances, metabolic or endocrine disturbances, and malignancies. Subjects were excluded if they had experienced any of the following diseases or states: a significant medical or surgical intervention within the previous 3 months, significant cardiac failure (NYHA Class III or IV) (Hurst et al., 1999), acute or chronic renal failure, severe respiratory disorders, severe digestive disorders, diabetes mellitus, or hormonal disturbances. Subjects taking cortisone, statins, or diuretics were also excluded from the trial. The baseline characteristics were evenly distributed in the two cohorts (Table 1).

2.2. Methods

During an initial 2-week phase, subjects were administered with an ''ad libitum'' diet, as classified by the National Cholesterol Education Program (Step Two) (1994). In order to realize this, a dietician gave them specific instructions. Subjects were required to document all calorific intake using three alimentary diaries, completed every 2 days. This pre-randomization period was designed to nullify the eventual effects of dietary changes on metabolic parameters. After this period, subjects were randomized by a computer-generated randomization schedule into two groups: 48 subjects were given ALC and the remainder 48 was given placebo throughout a 180-day period. Body weight, age, sex, and height of each subject were measured before and after the study. The study series underwent clinical visit each week throughout the administration period. ALC was supplied as tablets per os, 2 g twice-a-day. 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.

Dosing instructions were provided with each patient pack. All trial medication was instructed to be taken as prescribed.

2.2.1. Efficacy assessment

Throughout the randomization phase of the study, thrice-weekly diary was given in order to collect dietary data thrice a week. The primary efficacy measures were changes in physical, mental fatigue severity. These measures have been performed at the start and the end of the study period. Blood withdrawal has been performed in the morning, after an overnight fast.

Fatigue has been evaluated by Wessely and Powell (1989) scores. The first measures the physical fatigue by eight items, while the second evaluates the mental fatigue by five items (maximum score 26), allowing to break down the symptom into slight (0), moderate (1) or severe (2). We also employed the fatigue severity scale (FSS) (Krupp et al., 1989), composed of nine items. Total score ranged 9–63 and is directly related to the severity observed. Physical functions were assessed using the physical functioning (PF) scale, which encompasses the domains of functional limitations and disability (Lee et al., 2002). Items on functional limitations covered upper and lower body movements of walking 400 m; walking up 10 steps without resting; stooping, crouching or kneeling; reaching up over one's head and lifting or carrying a bag of rice (8 kg).

The resulting functional limitation and disability scores were then converted to a 0–100 scale, higher scores indicating better physical function.

Cognitive status was assessed with the MMSE (Folstein et al., 1975). The MMSE score ranges between 0 and 30. Test administration detects the following parameters: space and time cognition (0–10), recent memory (0–3), attention and computing ability (0–5), recall (0–3) and language (0–9). This test may be applied in different linguistic areas without changes of its significance. The MMSE is used as a bedside screen for cognitive dysfunction (Folstein et al., 1975).

2.3. The compliance

On the basis of the number of tablets gave back by the patients, we estimated the real compliance of our study series. Patients who had taken less than 80% or more than 120% of the prescribed treatment have been considered as dropped out. These patients have been mentioned in ''intention to treat'' analysis and safety analysis.

2.4. Concomitant therapy

We also reported all concomitant drugs taken by the enrolled subjects. Wherever it was possible, we did not change the doses of these drugs.

2.5. 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 with either the Chi-square test or Fisher's exact test where appropriate. Physical fatigue, mental fatigue and fatigue severity data were analyzed with the repeated measurement analysis of variance (ANOVA). Statistical Analysis System (SAS, Cari, North Carolina) software Version 6.11 was used for all analyses. All *p*-values were two-sided, using $p = 0.05$ as the reference standard for determining the significance of the principal outcomes. All subjects completed the study.

3. Results

3.1. Baseline data

The two groups were homogeneous for main characteristics (Table 2). Daily activity reduction >50%, painful sore throat, painful lymph nodes, muscle pain, prolonged fatigue after exercise, neuropsychiatric complaints, spreading arthralgias, headaches, sleep disorders, physical fatigue, mental fatigue and fatigue severity scale values did not show significant differences at randomization neither at baseline conditions.

3.2. Comparison with baseline

Patients treated with ALC showed significant decreases in the following parameters: daily activity reduction >50%: −25% ($p = 0.03$); muscle discomfort: −27% ($p = 0.005$);

Table 2
The baseline characteristics of the patients (mean ± S.D.)

	ALC group	PLACEBO group	p
Age	76.2 ± 7.6	78.4 ± 6.4	NS
Sex (Male/Female)	23/25	24/24	NS
Height (cm)	161.2 ± 7.9	160.4 ± 7.7	NS
Weight (kg)	68.1 ± 8.7	67.9 ± 8.4	NS
Systolic blood pressure (mmHg)	156.4 ± 20.4	157.2 ± 20.6	NS
Diastolic blood pressure (mmHg)	87.4 ± 10.2	87.7 ± 10.1	NS
Heart rate (bpm)	83.7 ± 9.8	82.6 ± 11.1	NS

prolonged fatigue after exercise: −51% ($p < 0.0001$); sleep disorders: −28% ($p = 0.007$); physical fatigue: −7 points ($p < 0.0001$); mental fatigue: −3.3 points ($p < 0.0001$); fatigue severity scale: −22.50 points ($p < 0.0001$) and a significant increase of functional status: 7.10 points ($p = 0.05$); MMSE: 3.40 points ($p < 0.0001$). There was no significant difference in the patients treated with placebo, as compared to their baseline data.

3.3. Comparison between ALC-treated and placebo-treated patients

At the end of the treatment, significant differences between the two groups were found for the following parameters: muscle pain −27% versus −3% ($p = 0.02$); prolonged fatigue after exercise: 51% versus −4% ($p < 0.001$); sleep disorders: 28% versus 4% ($p = 0.05$); physical fatigue: 7 versus −0.5 ($p < 0.001$); mental fatigue: −3.3 versus 0.6 ($p < 0.001$); fatigue severity scale: −22.5 versus 1.2 ($p < 0.001$); functional status 17.1 versus 0.6 ($p < 0.001$); MMSE 3.4 versus 0.5 ($p < 0.001$) (Table 3).

3.4. Tolerability

The administration of ALC was well tolerated with good compliance. No adverse events or laboratory abnormalities were reported during the trial in either of the two groups.

Table 3
Mean values (±S.D.) of fatigue scores, physical functions and cognitive activity in the two groups

	ALC group (48 patients)		PLACEBO group (48 patients)	
	Before treatment	After treatment	Before treatment	After treatment
Physical fatigue*	13.4 ± 2.3	6.4 ± 2.2	13.1 ± 2.4	12.6 ± 2.4
Mental fatigue■	7.7 ± 2.4	4.4 ± 1.6	7.8 ± 1.9	7.2 ± 1.9
Fatigue severity scale¥	50.4 ± 7.6	27.9 ± 9.7	50.1 ± 7.8	48.9 ± 6.9
Functional§ limitation PF score	69.8 ± 18.9	86.9 ± 17.4	70.2 ± 18.6	70.8 ± 19.1
Disability PF score●	89.1 ± 18.2	89.8 ± 19.4	90.1 ± 19.5	90.4 ± 18.9
MMSE▲	23.4 ± 2.9	26.8 ± 3.1	23.6 ± 2.8	24.1 ± 2.9

Comparison before and after ALC treatment—(*) $p = 0.000$ (C.I. 6.09–7.91); (■) $p = 0.000$ (C.I. 2.47–4.13); (¥) $p = 0.000$ (C.I. 18.97–26.03); (§) $p = 0.000$ (C.I. −24.46 to −9.74); (●) $p = 0.856$ (C.I. −8.32 to 6.92); (▲) $p = 0.000$ (C.I. −4.62 to –2.18). Comparison ALC and placebo patients—(*) $p = 0.000$ (C.I. −7.13 to −5.27); (■) $p = 0.000$ (C.I. 3.51 to −2.09); (¥) $p = 0.000$ (C.I. −24.41 to −17.59); (§) $p = 0.000$ (C.I. 8.70–23.50); (●) $p = 0.878$ (C.I. −8.36 to 7.16); (▲) $p = 0.000$ (C.I. 1.48 to 3.92).

4. Discussion

We observed reductions in severity in both physical and mental fatigue and improvements in functional and cognitive status after ALC administration, while poor improvements have been recorded in the placebo recipients. Exertional fatigue, muscle fatigability, and exercise intolerance, with or without muscle weakness are symptoms of neurological diseases attributable to alterations in mitochondrial DNA (Chaudhuri and Behan, 2004). The relationship between fatigue and physical activity has been investigated only rarely in the elderly. There seems to be a negative relationship between physical activity and fatigue. In addition, sports or walking programs during treatment for elderly caused some positive results.

The prevalence of chronic fatigue was found highest in people aged >60 (Steele et al., 1998). This syndrome is a noteworthy cause of sorrow among elderly subjects, due to sleep disturbances, impaired memory or concentration, post-exercise fatigue, muscle pain, severe headaches, painful throat, general weakness and neuropsychiatric symptoms (Sharpe et al., 1997), such as difficult concentrating or learning new information, poor memory, irritability or emotional lability, dysphoria, clumsiness, loss of interest in people or the things (Rhodes et al., 1988). The root of the frustration of fatigue is the complex nexus between fatigue, expectations, anxiety and depression. Fatigue can trigger a cascade of practical, social, financial and emotional problems that interfere with patients' functioning and resting, and which, in turn, exacerbate the fatigue, dampen patients' outlook, and worsen anxiety and depression, all of which can exacerbate fatigue.

ALC is a betaine required for the transport of long chain fatty acids into the mitochondria for fuel. It also facilitates the removal from the mitochondria of excess short and medium chain fatty acids that accumulate during metabolism (Rebouche, 1992). The ALC treatment in our study reduced significantly both physical and mental fatigue and improved physical activity and cognitive status. Various mechanism can explain the therapeutic effect of ALC, such as the beneficial effects of ALC on mitochondrial alterations and on the progressive impairment of neurotransmission, the correction on deficits of cellular energy supply. Carnitine and its derivative, ALC affect other cellular functions, including maintenance of key proteins and lipids of the mitochondria at sufficient levels, proper membrane orientation and maximum energy production (Iossa et al., 2002). The improvement of energetic metabolism in myocardial tissue and in muscular-skeletal tissue is probably the factor that reduces the presence and the severity of physical fatigue in treated subjects (Tomassini et al., 2004).

Previous studies showed that when ALC was administered to elderly with lean body mass reduction, one observed an increase of muscular mass up to threefold, with resulting amelioration of muscular power and activity (Neri et al., 2003; Pistone et al., 2003). Plioplys and Plioplys (1997) investigating the oral administration of carnitine as a potential treatment for chronic fatigue syndrome observed clinical improvements in 12 of 18 patients. Campos et al. (1993) observed improvements in muscle weakness, failure to thrive cardiomyopathy in the patients classified as insufficient with L-carnitine. Cavallini et al. (2004) observed that L-carnitine in combination with propionyl-L-carnitine decreased fatigue and improved the erectile functions in aging males.

Table 4
Change of occurrence (%) of fatigue criteria after treatment in the two groups

	ALC group (48)		PLACEBO group (48)	
	Before	After	Before	After
Activity reduction >50%[*]	81	56	77	75
Painful throat	81	77	80	77
Painful lymph nodes	17	16	13	12
Muscle pain[**]	94	67	93	90
Prolonged fatigue after exercise[***]	100	48	100	96
Neuropsychiatric complaints[****]	76	52	75	71
Spreading arthralgias	85	80	82	83
Headaches	65	60	63	61
Sleep disorders[*****]	90	62	88	84

Comparison before and after ALC treatment—([*]) $p = 0.02$ (C.I. 51% to 44.9%); ([**]) $p = 0.005$ (C.I. 9.8–44.2%); ([***]) $p = 0.000$ (C.I. 32.1–69.9%); ([****]) $p = 0.04$ (C.I. 0.03–0.21); ([*****]) $p = 0.007$ (C.I. 9.5–46.5%). Comparison ALC and placebo patients—([**]) $p = 0.026$ (C.I. −41% to −49%); ([***]) $p = 0.000$ (C.I. −66.7% to −27.3%); ([*****]) $p = 0.05$ (C.I. −41.5% to 2.5%).

In our experience, which evaluates both the physical and mental fatigue, experienced while performing routine daily activities, is quite appropriate in subjects with C.F.S., as its end point reflect more closely than other measures real life situations that are perceived as meaningful by the subjects in this age bracket (Malaguarnera et al., 2005). In mild cognitive impairment and in mild Alzheimer's disease, the efficacy of ALC was investigated with a meta-analysis and showed a significant advantage for ALC, as compared to placebo in various psychometric tests applied (Montgomery et al., 2003). We also observed a decrease of sleep disorders, a muscle discomfort, and of the prolonged fatigue after exercise (Table 4). Thus the present study demonstrates that the ALC treatment produce beneficial effects on severity of fatigue, this underestimated syndrome that influences noteworthy the elderly life and is very expensive worldwide.

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