Exploratory Open Label, Randomized Study of Acetyl- and Propionylcarnitine in Chronic Fatigue Syndrome

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Objectives: We compared the effects of acetylcarnitine, propionylcarnitine and both compounds on the symptoms of chronic fatigue syndrome (CFS). **Methods:** In an open, randomized fashion we compared 2 g/d acetyl-L-carnitine, 2 g/d propionyl-L-carnitine, and its combination in 3 groups of 30 CFS patients during 24 weeks. Effects were rated by clinical global impression of change. Secondary endpoints were the Multidimensional Fatigue Inventory, McGill Pain Questionnaire, and the Stroop attention concentration test. Scores were assessed 8 weeks before treatment; at randomization; after 8, 16, and 24 weeks of treatment; and 2 weeks later. **Results:** Clinical global impression of change after treatment showed considerable improvement in 59% of the patients in the acetylcarnitine group and 63% in the propionylcarnitine group, but less in the acetylcarnitine plus propionylcarnitine group (37%). Acetylcarnitine significantly improved mental fatigue ($p = .015$) and propionylcarnitine improved general fatigue ($p = .004$). Attention concentration improved in all groups, whereas pain complaints did not decrease in any group. Two weeks after treatment, worsening of fatigue was experienced by 52%, 50%, and 37% in the acetylcarnitine, propionylcarnitine, and combined group, respectively. In the acetylcarnitine group, but not in the other groups, the changes in plasma carnitine levels correlated with clinical improvement. **Conclusions:** Acetylcarnitine and propionylcarnitine showed beneficial effect on fatigue and attention concentration. Less improvement was found by the combined treatment. Acetylcarnitine had main effect on mental fatigue and propionylcarnitine on general fatigue. **Key words:** acetylcarnitine, attention concentration, carnitine, chronic fatigue syndrome, propionylcarnitine.

ALC = acetyl-L-carnitine; **CFS** = chronic fatigue syndrome; **CGI** = clinical global impression of change; **CDC** = Centers for Disease Control and Prevention; **DSM-IV** = Diagnostic and Statistical Manual; **MFI-20** = multidimensional fatigue inventory; **MPQ-DLV** = McGill Pain Questionnaire–Dutch language version; **OCTN2** = organic cation transporter/carnitine transporter Na^+-stimulated; **PLC** = propionyl-L-carnitine; **RBE4** = rat brain endothelial cells; **VAS** = visual analogue scale.

INTRODUCTION

Estimations of the prevalence of chronic fatigue syndrome (CFS) range from 1‰ to 4‰ (1,2). Although the cause of CFS is not known, sets of criteria for diagnosis of the condition have been published. The most widely accepted criteria were formulated in the consensus meeting supervised by the Centers for Disease Control and Prevention (CDC) (3). Patients with CFS are defined by the presence of clinically evaluated, unexplained persistent chronic fatigue of new or definite onset (not lifelong) resulting in substantial reduction in previous levels of activities, and the occurrence of 4 or more of the following symptoms (all of which must have persisted for ≥6 months and must not have predated the fatigue): self-reported severe impairment in short-term memory or concentration, sore throat, tender lymph nodes, muscle pain, multijoint pain without swelling or redness, headache of a new type, unrefreshing sleep, and postexertional malaise lasting more than 24 hours. Exclusions include a clear underlying organic cause, substance misuse, and severe psychiatric disorder such as psychotic depression. Less severe psychiatric disorders such as major depression without Diagnostic and Statistical Manual (DSM)-IV-defined melancholic features or anxiety disorders are not exclusionary diagnoses and are frequently comorbid with CFS (4).

Kuratsune et al. (5) and Plioplys and Plioplys (6) reported a decrease in plasma acylcarnitine in CFS, but this was not confirmed by others (7–9). The first report on carnitine treatment in CFS was by Grau et al. (10), who found no effect. Plioplys and Plioplys (11) reported significant improvement of CFS symptoms after 2 months of 3 g daily orally administered L-carnitine.

In a preliminary open label study, we treated 150 CFS patients with 1 g oral L-carnitine bid. After 6 months, 104 patients (69%) reported marked improvement by clinical global impression of change (CGI) ["I feel (very) much better"]. Another 18 CFS patients were included in a randomized double-blind study. Six were treated with oral acetyl-L-carnitine 1 g/d plus L-carnitine 1 g/d (low dose), 6 received twice the dosage (high dose), and 6 received placebos. After 6 months, marked improvement was reported by 4 patients in the low dosage group, by none in the high dosage group, and by 1 in the placebo group (unpublished results).

Carnitine is essential for the mitochondrial oxidation of long-chain fatty acids (12), because it acts as a carrier of acyl groups across the inner mitochondrial membrane to the matrix for β-oxidation. Later, many more functions were detected in detoxification of acyl-CoA and acylcarnitine export from the cell, increasing free CoA/acyl-CoA in the cell affecting lipid, protein, and carbohydrate metabolism [review (13)], membrane synthesis and repair (14), and ac(et)ylation of amino acids, histones, and proteins. The latter process is involved in posttranslational modification, membrane binding, and G-protein signaling. Carnitine promoted perfusion in ischemia (15), decreased oxidative stress (16,17), and attenuated damaging effects of mitochondrial inhibitors and uncoupler in neurons (18). Mitochondria were not the only organelles participating in the actions of the carnitine system; also peroxisomes, endo- and sarcoplasmic reticulum, and nuclear membrane metabolized carnitine (19). Moreover, every human cell (including the erythrocyte) contains carnitine palmitoyltransferase activ-

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ity, and carnitine and acylcarnitines were detected in every cell compartment and body fluid (13). Many biochemical, pharmacological, and clinical studies have investigated the action of carnitine and its esters acetylcarnitine and propionylcarnitine. Acetylcarnitine is a universal mitochondrial energy source and acetyl donor. It promoted energy metabolism and neurotransmission in the aged or neurotoxin-treated or ischemic reperfused rodent brain [reviews (18,20)]. Promising results were obtained in human degenerative brain diseases [review (21)]. Propionylcarnitine is also an energy source, stimulated the Krebs cycle as a precursor of succinyl-CoA, decreased oxidative stress in various systems, and improved cardiac dysfunction in rodent models (20,23). It was found to be effective in human cardiovascular disorders [reviews (24,25)]. Acetyl- and propionylcarnitine appeared generally somewhat more effective than L-carnitine.

SUBJECTS AND METHODS

We compared the effect of acetyl-L-carnitine (ALC) and propionyl-L-carnitine (PLC) on complaints of patients with CFS. We chose to conduct an open exploratory study with a discussion with the participants about the experienced change in their clinical condition, supported by objective questionnaires. The sample size was based on the results of the 2 preliminary studies mentioned above, indicating improvement in 50% of the patients in the low dose groups and less than 20% in the high dosage group. The sample size was not based on differences between the ALC and the PLC groups because data were not available. The present trial included 90 patients with CFS according to the CDC criteria, in an open randomized study. Patients were recruited from the polyclinic at the CFS Research Centre Amsterdam. Excluded were patients with an evident underlying organic cause, substance misuse, and severe psychiatric disorder such as psychotic depression. Presence of exclusion criteria according to the CDC (3,4) was revealed by structured interview, physical examination, and extensive laboratory tests. Before entry into the study, the nature of the study was explained to the patients and written consent was obtained. An independent ethics committee approved the study. The trial was conducted in accordance with the Declaration of Helsinki (1996 revision) and under the principals of good clinical practice, as laid out in the International Conference on Harmonisation document *Good Clinical Practice Consolidated Guideline*. All analyses were conducted on an intent-to-treat basis, with the last recorded value on each outcome measure being carried forward to the end of the trial, unless stated otherwise. Randomization was performed after opening of sealed envelopes with the randomization codes and by blocks of 6 patients, stratified for gender, and assigned the patients to an ALC group, a PLC group, and an ALC+PLC group. After randomization, patients received 2 g acetyl-L-carnitine per day in the ALC group, 2 g propionyl-L-carnitine in the PLC group, and 2 g ACL plus 2 g PLC in the ALC+PLC group. The medication was taken after breakfast and dinner for 24 weeks. The dropouts were analyzed during the whole trial, and their data were included in the results.

The trial profile is presented in Figure 1. Assessed for eligibility were 114 patients, and 90 were enrolled in the study. Table 1 shows the gender distribution (78% females), the average age (37–42 years), the duration of CFS (median 3 years or more), and the plasma carnitine levels at randomization, that were (about) the same in the ALC, the PLC, and the ALC+PLC group. The plasma carnitine and carnitine esters levels showed no abnormalities and were similar to those in controls (8).

Eight patients stopped because of side effects—3 in the ALC group, 2 in the PLC group, and 3 in the ALC+PLC group. They experienced an overstimulated feeling and sleeplessness. Another 8 patients stopped, because they did not experience any effect from the treatment—4 in the ALC group, 1 in

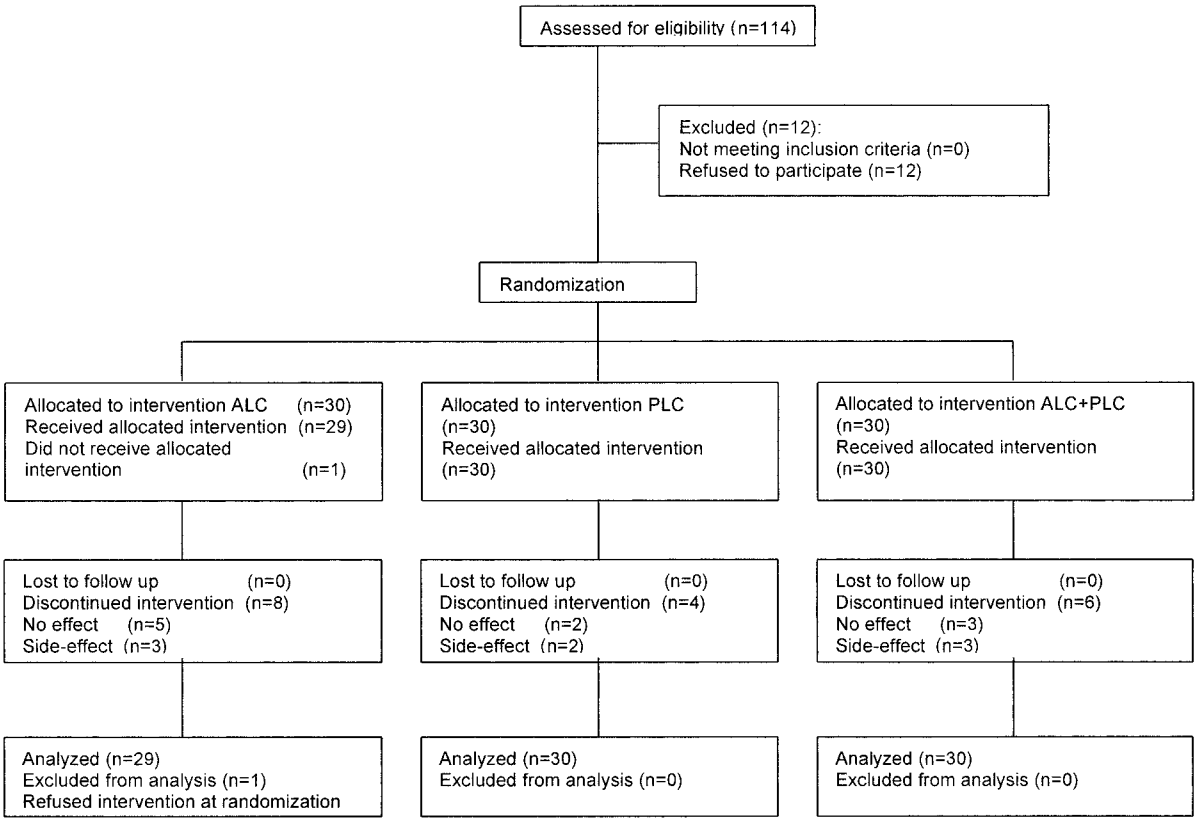

Figure 1. Trial profile

TABLE 1. Gender, Year of Birth, Duration of CFS, and Plasma Carnitine Levels at Randomization

Group	ALC	PLC	ALC + PLC
Total/females	30/23	30/23	30/23
Age (y)	37 ± 11	38 ± 11	42 ± 12
Duration CFS, median (y)	5.5	3.0	6.0
Duration CFS, range (y)	1.0–23.0	0.5–25.0	1.0–21.0
Plasma LC (μM)	34 ± 10	35 ± 9	36 ± 8
Plasma ALC (μM)	4.9 ± 1.4	5.3 ± 1.7	5.3 ± 1.3
Plasma PLC (μM)	0.32 ± 0.14	0.31 ± 0.14	0.32 ± 0.14

Age and carnitine levels were expressed as means ± SD.
CFS = chronic fatigue syndrome; ALC = acetyl-L-carnitine; PLC = propionyl-L-carnitine; LC = L-carnitine.

the PLC group, and 3 in the ALC+PLC group. Two patients stopped for reasons unrelated to the treatment.

Clinical Assessment

At screening patients' complaints, cognitive performance and pain were assessed. This was repeated after a no-treatment period of 8 weeks, and then the patients were randomly distributed in 3 groups and treated for 24 weeks. During treatment, patients were reassessed at 8, 16, and 24 weeks. Patients reported after 2 weeks of no-treatment whether the withdrawal of medication had influenced their condition compared with 2 weeks earlier. The primary endpoint of the study was the CGI (26). CFS is a condition without objective criteria. Accordingly, in this study of CFS, the CGI was rated according to the subjective experience of the patient, who had to answer the question: Do you experience a change in your condition compared with the time of randomization? The CGI was rated on a 5-point scale, ranging from −3 very much worse, to +3 very much better. Secondary endpoints were the fatigue axes of the Multidimensional Fatigue Inventory (MFI-20) (27), the Stroop test for attention concentration (28), and the McGill Pain Questionnaire-Dutch Language Version (MPQ-DLV) for pain (29). The MFI-20 consists of 20 questions, the general, physical, and mental fatigue axes were used in the study. The score on each axis is 5 to 20 points, indicating no fatigue to extreme fatigue. The Stroop test estimates attention concentration. The result of the reading time of the third card minus that of the second card of the Stroop test is shown because in the preliminary studies (mentioned above) this gave the best results to differentiate patients from controls. The score given is the time needed to read aloud the names of 100 words of colors printed in another color minus the time needed to read aloud the colors of 100 stripes. The Stroop test can be used more than 1 time without affecting the interference score by a practice or learning effect (30). The McGill Pain Questionnaire-Dutch Language Version (MPQ-DLV) was used for the assessment of pain. The result of the visual analogue scale (VAS) pain score is expressed as a distance of 0 to 100 mm, indicating no pain to extreme pain. A trained psychologist administered all questionnaires and tests.

Biochemical Procedures

Blood was sampled by venipuncture in heparin tubes at randomization and after the 24-week treatment period, for the assay of free carnitine and carnitine esters in plasma, using tandem mass spectrometry as described by Vreken et al. (31).

Statistical Analysis

Data are expressed as mean and SD, unless indicated otherwise. Statistical analysis was done with SPSS 11.0. Correlations were calculated by Pearson's correlation test for continuous data with a normal distribution. Data with a not-normal distribution were tested with Spearman rank correlation test. Changes of scores during therapy were tested by Friedman's test for multiple related variables. Significant levels were assumed at $p < .05$. Bonferroni correction was applied for multiple observations.

Role of the Funding Source

The funding source had no role in the decision to publish the data and in the writing of the paper.

RESULTS

Table 2 summarizes the CGIs after 8 weeks of no treatment and after 8, 16, and 24 weeks of treatment. Improvement was reported after 24 weeks of treatment by 59% of the ALC group, 63% of the PLC group, and 37% of the ALC+PLC group, whereas 10% in the ALC group, 3% in the PLC group, and 16% in the ALC+PLC group felt worse.

After 24 weeks of therapy, the medication was stopped and all patients returned 2 weeks later for follow-up. Worsening of CFS in the 2 weeks was reported by 52% in the ALC group, 50% in the PLC group, and by 37% in the ALC+PLC group. No patients improved (Table 2). In the ALC group, 4 of the 17 patients who improved at 24 weeks experienced no change at follow-up, 2 weeks later. In the PLC group, improvement continued in 7 patients and in the ALC+PLC group in 3 patients (not shown). In the ALC group, 2 patients had not improved at 24 weeks, but worsened at follow-up. This oc-

TABLE 2a. Experienced Benefit From the Medication Number of Patients (%)

Treatment (wks)		0	8	16	24	Follow-up
ALC	Improved	0 (0)	13 (45)	14 (48)	17 (59)	0 (0)
	No change	30 (100)	12 (41)	14 (48)	9 (31)	14 (48)
	Worse	0 (0)	4 (14)	1 (4)	3 (10)	15 (52)
PLC	Improved	0 (0)	15 (50)	19 (63)	16 (63)	0 (0)
	No change	30 (100)	13 (43)	9 (30)	10 (34)	15 (50)
	Worse	0 (0)	2 (7)	2 (7)	1 (3)	15 (50)
ALC + PLC	Improved	0 (0)	10 (33)	11 (37)	11 (37)	0 (0)
	No change	30 (100)	16 (53)	16 (53)	14 (47)	18 (60)
	Worse	0 (0)	4 (14)	3 (10)	5 (16)	12 (40)

TABLE 2b. Friedman Test of CGI at 0 (Randomization), 8, 16, and 24 Weeks of Treatment

Group	ALC	PLC	ALC + PLC
CGI χ^2	20.24 $p = 0.000$	30.25 $p = 0.000$	6.60 $p = 0.084$

The first part of the table summarizes the clinical global impression of change (CGI) during treatment and 2 weeks later. Improved: CGI ≥ 2; no change: $-1 \leq$ CGI $\leq +2$; worse: CGI ≤ -2. The CGI at randomization (0 weeks treatment) was relative to 8 weeks before. The CGI at 8, 16, and 24 weeks were relative to the situation at 0 weeks (randomization). The CGI at follow-up (24 weeks of treatment, followed by 2 weeks without treatment) was relative to the condition at 24 weeks.
ALC = acetyl-L-carnitine; PLC = propionyl-L-carnitine.

curred in 3 patients in the PLC group and 2 patients in the ALC+PLC group (not shown).

Table 3 summarizes the general fatigue, physical fatigue, and mental fatigue scores. Significant improvement of general fatigue score was found in the PLC ($p = .004$) and in the ALC+PLC group ($p = .000$), and that of mental fatigue in the ALC group ($p = .015$). The physical fatigue score was not significantly improved in the PLC group ($p = .069$).

Table 4 show the scores of the attention concentration test and the pain test. The score of the Stroop test is presented as median and quartiles because the distribution of the data in the PLC group at randomization showed a not-normal distribution. The attention concentration score improved significantly in all groups (Table 4b). The pain score was unexpectedly low in the ALC group (Table 4a). None of the treatments had significant effect on the pain scores (Table 4b).

The CGI was correlated with the improvement in the general fatigue, physical and mental fatigue score in all the groups ($r \geq 0.362$, $p < .05$), and with the attention concentration score in the ALC ($r = 0.476$, $p = .010$) and the ALC+PLC ($r = 0.489$, $p = .006$), but not in the PLC group. The CGI was not correlated with the pain score in any of the groups.

The levels of plasma L-carnitine increased significantly in all groups of patients, but somewhat less in the responders. Surprisingly, carnitine levels in the group receiving ALC plus PLC became not considerably higher than in the other 2 groups. The levels of the carnitine esters increased in all groups, but remained low compared with L-carnitine (Table 5). The increase of carnitine levels in women was not different from that in the male participants.

The change of the plasma L-carnitine concentration in the ALC group was inversely related to clinical improvement, and the least increase of carnitine was related to most improvement. This was not found in the PLC and ALC+PLC group. Change of plasma carnitine was related to improvement of general and mental fatigue in the ALC group, but not in the PLC and ALC+PLC group. Change of plasma carnitine was not related to change in attention-concentration or pain score. Plasma ALC and PLC were not related to clinical outcome (correlations not shown).

DISCUSSION

The first aim of the study was to compare the different influences of acetylcarnitine and propionylcarnitine on symptoms of CFS. The second goal was to obtain an indication of the percentage of responders. Therefore, the study was designed as an observation period of 8 weeks, followed by a randomized trial and an observation period of 2 weeks.

In the first observation period the scores for fatigue, concentration, and pain of the patients proved to be stable. The medication was well accepted by the patients, with a dropout number of 8 because of side effects. The nature of the side effects—overstimulation and sleeplessness—is different from

TABLE 3a. Clinical Measures of Fatigue Before and During Treatment

Treatment		ALC	PLC	ALC + PLC
General fatigue (MFI-20)	Screening	18.6 ± 1.9	18.4 ± 1.8	19.1 ± 1.4
	0 wks	17.6 ± 2.1	18.0 ± 2.4	19.0 ± 1.5
	8 wks	16.7 ± 3.5	17.0 ± 2.9	18.0 ± 2.8
	16 wks	16.5 ± 4.1	15.7 ± 4.0	16.9 ± 3.2
	24 wks	15.9 ± 4.2	16.5 ± 3.1	17.3 ± 3.3
Physical fatigue (MFI-20)	Screening	18.1 ± 2.6	17.8 ± 2.3	18.5 ± 1.6
	0 wks	16.9 ± 2.6	17.4 ± 3.0	17.9 ± 2.2
	8 wks	16.5 ± 3.6	16.5 ± 3.0	17.3 ± 2.9
	16 wks	15.8 ± 4.4	15.8 ± 4.0	16.1 ± 3.5
	24 wks	15.7 ± 4.4	16.4 ± 3.2	16.5 ± 3.4
Mental fatigue (MFI-20)	Screening	17.0 ± 3.3	16.3 ± 2.5	15.7 ± 3.9
	0 wks	16.4 ± 2.8	15.1 ± 3.4	15.3 ± 3.7
	8 wks	15.1 ± 3.2	15.1 ± 3.2	14.3 ± 4.1
	16 wks	15.0 ± 2.9	13.8 ± 4.1	14.2 ± 4.0
	24 wks	15.1 ± 3.6	13.9 ± 3.5	14.6 ± 4.0

Mean ± SD. MFI-20 = multidimensional fatigue inventory; ALC = acetyl-L-carnitine; PLC = propionyl-L-carnitine.

TABLE 3b. Friedman Test of Fatigue Scores at 0, 8, 16, and 24 Weeks Treatment

Group	ALC	PLC	ALC + PLC
General fatigue χ^2	4.41 $p = 0.218$	13.02 $p = 0.004$	18.70 $p = 0.000$
Physical fatigue χ^2	3.62 $p = 0.313$	7.13 $p = 0.069$	6.24 $p = 0.102$
Mental fatigue χ^2	10.13 $p = 0.015$	2.78 $p = 0.428$	6.51 $p = 0.083$

TABLE 4a. Clinical Measures of Attention Concentration and Pain

Group		ALC	PLC	ALC + PLC
Attention concentration	Screening	50 (38–70)	46 (30–66)	50 (33–63)
	Randomization	46 (37–67)	33 (24–49)	40 (28–54)
	8 wks	38 (29–51)	36 (25–41)	39 (28–47)
	16 wks	38 (26–52)	33 (22–40)	39 (27–47)
	24 wks	38 (27–51)	32 (24–40)	37 (27–42)
Pain score	Screening	23 (14–35)	43 (25–62)	48 (25–74)
	Randomization	27 (13–57)	45 (24–63)	37 (14–68)
	8 wks	19 (3–44)	47 (13–69)	26 (7–72)
	16 wks	17 (0–44)	25 (0–68)	33 (7–55)
	24 wks	20 (6–56)	25 (13–54)	38 (9–69)

Median (25–75 percentile). ALC = acetyl-L-carnitine; PLC = propionyl-L-carnitine.

TABLE 4b. Friedman Test of Attention Concentration and Pain Scores at 0, 8, 16, and 24 Weeks Treatment

Group	ALC	PLC	ALC + PLC
Attention concentration χ^2	17.46 $p = 0.000$	10.84 $p = 0.011$	12.97 $p = 0.004$
Pain score χ^2	0.86 $p = 0.840$	3.09 $p = 0.380$	0.74 $p = 0.877$

TABLE 5. Plasma Carnitine Levels in Patients Benefiting From the Treatment (Responders) and Nonresponders

Group	ALC		PLC		ALC + PLC	
CGI	≤1	≥2	≤1	≥2	≤1	≥2
Participants	12	17	11	19	20	10
LC before (μM)	33 ± 7	36 ± 11	29 ± 5	37 ± 9[a]	34 ± 5	39 ± 12
LC after (μM)	46 ± 5[b]	42 ± 11[b]	43 ± 6	47 ± 12[b]	41 ± 9[b]	44 ± 12[b]
ALC before (μM)	5.0 ± 1.6	5.0 ± 1.1	4.6 ± 1.1	5.7 ± 1.8[a]	5.0 ± 1.2	5.7 ± 1.5
ALC after (μM)	5.5 ± 1.3	6.5 ± 1.7[b]	5.7 ± 2.2	6.5 ± 2.4	6.0 ± 1.4[b]	7.1 ± 2.4
PLC before (μM)	0.31 ± 0.11	0.34 ± 0.17	0.23 ± 0.05	0.34 ± 0.16[a]	0.29 ± 0.06	0.37 ± 0.22
PLC after (μM)	0.38 ± 0.08[b]	0.36 ± 0.17[b]	0.44 ± 0.10	0.93 ± 1.07[b]	0.52 ± 0.50	0.58 ± 0.41

Data on L-carnitine (LC), acetyl-L-carnitine ALC, and propionyl-L-carnitine (PLC) at randomization and after 24 weeks therapy in nonresponders [clinical global impression (CGI) ≤ 1] and responders (CGI ≥ 2). "After" and "before" refer to the treatment.

[a] Significant difference between nonresponders vs. responders ($p < 0.05$).

[b] Significant difference between before treatment vs. after treatment ($p < 0.05$).

those reported in most other studies, describing trimethylamine formation or diarrhea in a few patients.

In advance, we had expected that ALC would have most effect on attention concentration, PLC on physical fatigue, and ALC+PLC on both. The CGI improved in the ALC and the PLC group, but not significantly in the ALC+PLC group, likely because of the higher total carnitine ester dose and indicating an inversed U-form dose–response curve. An indication for the same effect was found in the preliminary double-blind pilot study. The effect of ALC on mental fatigue and attention concentration was significant. The PLC group showed most improvement in general and physical fatigue and slightly less in attention concentration. The ALC+PLC group improved very well on general fatigue and also, but not significantly, on physical and mental fatigue. The pain score was not influenced in a significant way by any medication.

The CGI as an overall impression correlated significantly with the change of the 3 separate fatigue scores, thus validating the concept (not shown).

In the present study, all patients had normal plasma free carnitine levels, and a normal spectrum of the acylcarnitine species, excluding primary and secondary carnitine deficiency (Table 1).

In the second observation period, 50% of patients deteriorated in the ALC and PLC groups. For most the relapse was hardly acceptable, because they had adapted their activity to

the improvement. The improved patients in the ALC+PLC group (37%) all deteriorated in the second observation period.

The different effects of acetylcarnitine and propionylcarnitine could be explained by a different transport of the esters from plasma to the tissues and the brain. If so, the observation that the concentration of carnitine in the plasma in the ALC group increased more in patients with less therapeutic effect, indicates lower transport. It is conceivable that ALC and PLC are not transported as such, because the plasma ALC and PLC levels were relatively low and showed no correlation with improvement. The precise mode of action of the carnitine esters in alleviating the CFS symptoms is not clear. In this study, acetylcarnitine apparently had a more "central" action and propionylcarnitine a more "peripheral" action, which is in line with other human studies. It is generally thought that acetylcarnitine can easily pass the blood–brain barrier, and that propionylcarnitine preferentially enters the heart. The fate of double-labeled acetylcarnitine has been studied by Kuratsune et al. (32). They showed that only the acetyl moiety is rapidly taken up by the brain, leaving the carnitine moiety in the circulation. This was in line with older studies [reviewed in (13)] establishing that carnitine import in the brain is a slow process with low affinity. Recently, however, with immortalized RBE4 cells, an in vitro model of the blood–brain barrier, it was shown that these cells expressed the high-affinity carnitine transporter OCTN2, and transported carnitine, acetylcarnitine, and propionylcarnitine (33). When this is the case, a preferential uptake of acetylcarnitine by brain and a preferential uptake of propionylcarnitine by heart are less likely, because OCTN2 is also present in muscle and several other cells. Perhaps another messenger contributes to, or is involved in, the action of the carnitine esters, such as purines (34) or cortisol.

CONCLUSIONS

This study indicates that both ALC and PLC are successful in the treatment of symptoms of CFS in a major subset of CFS patients. The fact that the pattern of improvement by acetylcarnitine, propionylcarnitine, and their combination was not identical suggests that differences in transport and/or metabolism are involved in their action.

Conclusive evidence for the effects of carnitine esters on CFS will have to await a double blind, placebo-controlled, randomized trial.

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