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Propionyl-L-Carnitine in Intermittent Claudication: Double-Blind, Placebo-Controlled, Dose Titration, Multicenter Study

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Objectives. **The aim of this double-blind, placebo-controlled, dose titration, multicenter trial was to assess the efficacy and safety of propionyl-L-carnitine in intermittent claudication.**

Background. **Human and animal studies indicate that propionyl-L-carnitine increases carnitine content and improves energy metabolism in the ischemic skeletal muscle.**

Methods. **After a 2-week preliminary period to assess maximal walking distance, 245 patients were randomly assigned to receive propionyl-L-carnitine (n = 118) or placebo (n = 127). The initial oral dose of 500 mg twice daily was increased at 2-month intervals to 2 g/day and then to 3 g/day in patients showing improvement in treadmill performance <30% over baseline. Efficacy analysis was conducted for the 214 patients who completed the 24 weeks of treatment by comparing the effect of placebo and propionyl-L-carnitine on day 180.**

Results. **Analysis of variance showed a significant improvement of 73 ± 9% (mean ± SE) in maximal walking distance with propionyl-L-carnitine (n = 99) compared with 46 ± 6% for placebo (n = 115, p = 0.03). For distance walked at onset of claudication, propionyl-L-carnitine showed about double the improvement of placebo; however, the difference was not statistically significant. There were no changes in electrocardiographic and routine biochemical and hematologic tests that would indicate an adverse effect of propionyl-L-carnitine. Adverse events requiring drug discontinuation (11 in the propionyl-L-carnitine group, 3 in the placebo group) were unrelated to study medication. The dose titration design of the study also provided information on the dose-response relation. Slightly less than 67% of patients were expected to improve their maximal walking distance by at least 30%, assuming 2 g/day of propionyl-L-carnitine (95% confidence interval 0.51 to 0.70). The response rate during the entire titration course was significantly in favor of propionyl-L-carnitine compared with placebo.**

Conclusions. **Although the precise mode of therapeutic action requires clarification, propionyl-L-carnitine, at a dose of 1 to 2 g/day, appears to be effective and well tolerated, with minimal adverse effects.**

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Peripheral arterial disease is one of the most common regional manifestations of arteriosclerosis obliterans and is one of the major causes of disability in the middle-aged and elderly. The main symptom, intermittent claudication, affects 5% of men >50 years of age (1,2) and may profoundly disrupt the patient's day-to-day activities. Despite the relevance of the problem, pharmacologic treatment is a challenge. The goal is to achieve greater walking capacity by improving the balance between energy supply and metabolic demand in the ischemic skeletal muscle. To date, attempts to achieve this goal have been based on drugs that increase blood flow to the affected limb. Although the efficacy of these drugs is controversial (3–9), there is general agreement that physical training lessens symptoms of claudication (10–12). This beneficial effect does not seem to be due to increased blood flow but to a metabolic adaptation leading to increased muscle efficiency (10,12). This hypothesis suggests that untrained ischemic muscles may not be functioning at maximal metabolic capacity and that the substrates available to the exercising affected limb could be used more efficiently. Therefore, an agent that improves metabolic efficiency could be an alternative way to treat the mismatch between energy supply and demand in claudicant muscles.

Carnitine is a natural substance that plays a crucial role in regulating substrate flow and energy balance in the skeletal muscle (13). Patients with primary carnitine deficiency are characterized by cardiomyopathy and progressive muscle weakness that can be partially reversed by carnitine supplementation (14,15). Also, patients with peripheral arterial disease have an alteration in carnitine homeostasis that seems to be related to severity of ischemia (16,17). In patients with intermittent claudication, L-carnitine administration increases total carnitine content in the ischemic muscle, reduces lactate production during exercise and improves walking capacity (18).

One of the most potent analogues of carnitine is propionyl-L-carnitine, a naturally occurring short-chain fatty acid ester (19), which increases carnitine levels in the ischemic muscles of patients with severe peripheral arterial disease (17). Further-

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more, propionyl-L-carnitine given intravenously increases the walking capacity of patients with claudication to greater extent than that observed with an equimolar dose of L-carnitine (20).

The present study describes the results of a multicenter, double-blind, placebo-controlled study undertaken to investigate the therapeutic efficacy, safety and tolerability of oral treatment with propionyl-L-carnitine in a large number of patients with intermittent claudication. The trial was conducted according to a dose titration design and thus also provides dose-response information.

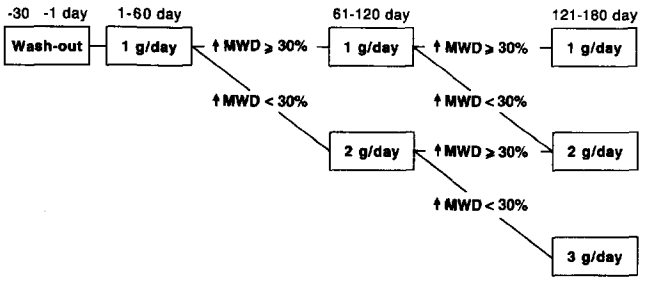

Figure 1. Study protocol (see Methods for details). ↑MWD = increase in maximal walking distance.

Methods

Patients. Patients affected by intermittent claudication for at least 1 year were selected. The diagnosis of peripheral arterial disease was established on the basis of history, Doppler examination and decrease in ankle/arm systolic blood pressure ratio (ankle/brachial index) after exercise. After the screening visit, only patients at least 40 years old with a rest ankle/brachial index <0.80 and a maximal walking capacity between 30 and 400 m (as tested by treadmill speed 4 km/h, inclination 7°) were included in the study. To ensure that patients admitted to the study had a stable walking capacity, three treadmill tests were conducted at weekly intervals during a 2-week preliminary period, and only patients whose maximal walking distance between the three tests varied <20% were included. The only drugs allowed during the study were oral antidiabetic agents and diuretic drugs. Patients with any other condition that limited exercise capacity were excluded. Other major exclusion criteria were sympathectomy or angioplasty during the previous 6 months, severe venous insufficiency and peripheral neuropathy.

Study design. A double-blind, placebo-controlled, dose titration design was adopted by 13 centers for the study. All patients gave written informed consent before participation. The primary efficacy variables were distance walked before onset of claudication ("initial claudication distance") and maximal walking distance, as measured by treadmill, as previously described. A secondary aim of the study was to evaluate the effect of treatment on quality of life by a self-administered questionnaire. However, these data will be reported separately. Measurements of ankle/brachial index were obtained at rest and at 2, 5 and 10 min after exercise. The same basic protocol was followed at all 13 centers (Fig. 1). After a screening visit, all current treatments for peripheral arterial disease were discontinued, and patients entered a 2-week washout phase during which they were familiarized with the treadmill. A 2-week preliminary period followed, during which stability of the maximal walking distance was assessed. At the end of this period, patients who met the inclusion criteria were randomly allocated to orally administered placebo or propionyl-L-carnitine. The initial dose of 500 mg twice daily was increased at 2-month intervals to 2 g/day and then to 3 g/day in patients with an improvement in treadmill performance <30% over baseline; patients showing an improvement ≥30% continued with the same dose as in the previous 2 months.

The double-blind medication lasted 6 months. During this period, initial claudication distance, maximal walking distance and ankle/brachial index at rest and after exercise were measured monthly. Treadmill tests were carried out in a quiet room before the morning dose. Electrocardiographic (ECG) and routine biochemical and hematologic tests were performed at the end of the preliminary phase and every 2 months during the double-blind phase. Drug compliance was assessed by tablet count without the patient's knowledge every 2 months. Patients taking <70% of the prescribed dose were considered noncompliant and were excluded from the efficacy analysis. Although all participants were advised of the beneficial effects of a therapeutic walking program and nicotine abstinence, no persistent or aggressive effort was made to change their lifestyle.

Statistical analysis. Efficacy analysis was conducted by analysis of variance for patients who completed the study by comparing the effect of placebo and propionyl-L-carnitine on day 180. The choice of an efficacy rather than an intention to treat approach was justified by the causal nature of the study (21) and the fact that not all patients received the optimal dose throughout the study because of the titration procedure. For the latter reason, data recorded at intermediate visits (days 30, 60, 90, 120 and 150) were not analyzed; 95% confidence intervals were also computed for mean treatment difference on day 180. One of the participating centers studied 98 patients recruited from six outpatient medical centers. Therefore, we also performed an efficacy analysis of the results obtained at that center.

The dose-response relation was estimated using the method of Chuang (22) and the approach of Shih et al. (23). In brief, these methods estimate the probability of obtaining a response at a dose lower or equal to a prefixed one (cumulative density function). With the former approach, which is based on life-table analysis, we evaluated the difference in cumulative density function between placebo and propionyl-L-carnitine through use of the log-rank and Wilcoxon tests. Using the second approach, we computed confidence intervals for probability estimates of responding to a dose lower or equal to the predefined one and for the conditional probability estimates of responding to a higher dose than the predefined one, given no response up to this dose.

Data are expressed as mean value ± SE. Baseline values of initial claudication distance, maximal walking distance and

Table 1. Demographic and Clinical Characteristics of 245 Randomized Patients

	PLC Group (n = 118)	Placebo Group (n = 127)
Age (yr)	61.8 ± 0.7	58.9 ± 0.7
Male	110 (93)	114 (90)
Female	8 (7)	13 (10)
Diabetic	17 (14)	26 (20)
Smoker	114 (97)	120 (94)
Hyperlipidemia	39 (33)	36 (28)
Systolic blood pressure (mm Hg)	149.3 ± 1.5	145.8 ± 1.4
Diastolic blood pressure (mm Hg)	82.6 ± 0.7	83.4 ± 0.6
Ankle/brachial index at rest	0.63 ± 0.01	0.64 ± 0.01
Initial claudication distance (m)	123.5 ± 5.9	128.2 ± 6.6
Maximal walking distance (m)	211.6 ± 10.1	213.4 ± 9.5

Data presented are mean value ± SE or number (%) of patients. PLC = propionyl-L-carnitine.

ankle/brachial index are the mean values of the three measurements taken during the preliminary phase.

Results

Efficacy analysis. A total of 245 patients were included in the double-blind treatment phase: 118 were assigned to propionyl-L-carnitine and 127 to placebo. Clinical and demographic characteristics of these patients are reported in Table 1. No statistical differences were observed between the two groups. Thirty-one patients (19 in the propionyl-L-carnitine group, 12 in the placebo group) dropped out of the study for various reasons (Table 2); thus, the efficacy evaluation was performed for the remaining 214 patients who completed the 24 weeks of treatment. The effect of propionyl-L-carnitine on maximal walking distance was significantly greater than that with placebo ($p = 0.03$). After 24 weeks of treatment, maximal walking distance increased from 207.8 ± 10 to 298.1 ± 18 m (+45.6 ± 6%) in the placebo group (n = 115) and from 214.6 ± 11 to 354.1 ± 22 m (+72.7 ± 9%) in the propionyl-L-carnitine group (n = 99). For initial claudication distance, although the percent increase with propionyl-L-carnitine was about two times greater than with placebo, analysis of variance did not show a difference between treatments at day 180. In the placebo group, initial claudication distance increased from 125.1 ± 6 m at baseline to 191.6 ± 14 m (+58.5 ± 8%) at the end of the study, whereas it increased from 125.6 ± 6 to 222.6 ± 18 m (+91.1 ± 16%), respectively, in the propionyl-L-carnitine group. Mean values of maximal walking distance and initial claudication distance at each control visit and the percent changes from baseline throughout the study are reported in Table 3 and Figure 2, respectively. Exercise-induced changes in ankle/brachial index observed at baseline were not modified by treatments. Similarly, there were no clinically important findings on repeat ECG, biochemical and hematologic tests in either group. In particular, plasma lipid levels remained unchanged. Before treatment, plasma cholesterol was 220.3 ± 51.8 mg/dl in the control group and 214.1 ± 40.2 mg/dl in the propionyl-L-carnitine group. At the end of treatment, the corresponding values were 218.1 ± 38.6 and 218.1 ± 38.3 mg/dl. Baseline plasma triglyceride levels were 158.1 ± 57.3 mg/dl in the placebo group and 150.4 ± 61.5 mg/d in the propionyl-L-carnitine group. After treatment, they were 148.5 ± 44.6 and 150.4 ± 65.7 mg/dl, respectively. No patient stopped smoking during the trial. There were seven adverse effects not requiring treatment discontinuation in the placebo group and five in propionyl-L-carnitine group; nausea and gastric pain were the most frequent effects.

Table 2. Patients Excluded From Efficacy Analysis

Reason for Exclusion	PLC Group	Placebo Group
Angina pectoris	2	0
Arrhythmias	0	1
Transitory ischemic attack	0	1
Cholecystectomy	0	1
Neoplasia	1	0
Gastric pain	0	1
Herniated disk	1	0
Acute ischemia of lower limbs	2	0
Worsening of claudication	3	0
Anxiety, sweating	0	1
Poor compliance	10	7

Data presented are number of patients. PLC = propionyl-L-carnitine.

Treatment effects were also analyzed by Student *t* test in 98 patients studied at one center (group A). Although this subset of patients was only 50% of the patients who completed the study, the group differences significantly favored propionyl-L-carnitine, which, on day 180, showed higher values for initial claudication distance ($p = 0.03$) and maximal walking distance ($p = 0.03$) than those with placebo. Conversely, in the 116 patients studied at the other 12 centers (group B), analysis of variance did not show differences between treatments. However, in group B, treatment differences on day 180 favored propionyl-L-carnitine for initial claudication distance and maximal walking distance more so than in group A (Fig. 3). The intention to treat approach confirmed these results. In group A, the effect with propionyl-L-carnitine was significantly greater than that with placebo for both initial claudication distance ($p = 0.029$) and maximal walking distance ($p = 0.049$); in group B, no difference was observed between placebo and active treatment.

Analysis of titration course. The difference between the density function estimates obtained by the two methods was negligible (Table 4). The probability of obtaining an increase in maximal walking distance ≥30% was 36% to 37% in patients receiving 1 g/day of propionyl-L-carnitine and only 28% in those receiving placebo. The probability of responding to 2-g/day increased by 22% to 24% in the propionyl-L-carnitine group and by 17% to 18% in the placebo group. Finally, the probability that a patient will respond to 3 g/day after having failed to respond to 2-g/day increased by only 8% in both propionyl-L-carnitine and placebo groups. The overall response rate during the entire titration course was significantly

Table 3. Initial Claudication Distance and Maximal Walking Distance From Baseline to Week 24 of the Study

	Initial Claudication Distance (m)		Maximal Walking Distance (m)	
	PLC Group (mean ± SE)	Placebo Group (mean ± SE)	PLC Group (mean ± SE)	Placebo Group (mean ± SE)
Baseline	125.6 ± 6	125.1 ± 6	214.6 ± 11	207.8 ± 10
Wk 4	147.3 ± 12	146.3 ± 8	250.8 ± 17	243.3 ± 14
Wk 8	165.2 ± 12	157.1 ± 10	285.2 ± 18	255.5 ± 15
Wk 12	175.9 ± 12	177.3 ± 12	296.3 ± 18	279.1 ± 17
Wk 16	185.5 ± 13	185.9 ± 14	321.2 ± 20	290.0 ± 18
Wk 20	203.5 ± 16	188.6 ± 14	325.8 ± 19	293.3 ± 17
Wk 24	222.6 ± 18	191.6 ± 14	354.1 ± 22	298.1 ± 18

On day 180 the effect of propionyl-L-carnitine (PLC) on maximal walking distance was significantly greater than that of placebo ($p = 0.03$).

in favor of propionyl-L-carnitine ($p = 0.04$, log-rank test; $p = 0.05$, Wilcoxon test).

Discussion

Efficacy and safety. The present study was designed to investigate the efficacy, safety and tolerability of propionyl-L-carnitine in patients with intermittent claudication. Patients who received propionyl-L-carnitine walked a longer distance than those who received placebo. For maximal walking distance, propionyl-L-carnitine produced a progressive improvement over placebo starting from the second month of treatment. At week 12, placebo improvement appeared to peak, whereas the improvement with propionyl-L-carnitine continued. At the end of the treatment, group difference significantly favored propionyl-L-carnitine. The significantly greater efficacy of propionyl-L-carnitine over placebo for maximal walking distance was confirmed by the finding that the dose of the drug was titrated up to the maximal level of 3 g/day in 64 patients in the placebo group and only 38 patients in the propionyl-L-carnitine group. For initial claudication distance measurement, propionyl-L-carnitine showed about double the improvement of placebo at the end of treatment, although the difference was not statistically significant.

Initial claudication distance has been considered a more reproducible and thus a more reliable indicator of walking performance than maximal walking distance (24,25). However, according to another study (26), reproducibility of the two measurements is similar using both single- and multistage treadmill tests (26). In a disease such as intermittent claudication, the primary goal of treatment should be to improve functional capacity. Many patients with claudication are still able to continue walking for long distances after pain onset in the affected leg and thus experience few limitations in daily

Figure 2. Percent changes in initial claudication distance (**top**) and maximal walking distance (**bottom**) throughout the study. **Dashed line** = changes in placebo group; **solid line** = changes in propionyl-L-carnitine group. For maximal walking distance, group difference significantly favored propionyl-L-carnitine ($p = 0.03$).

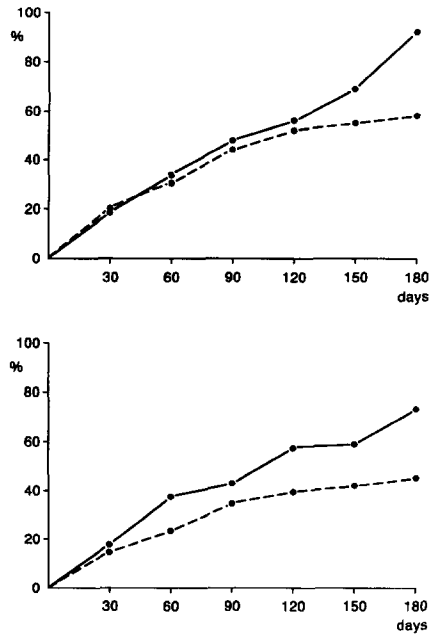

Figure 3. The 95% confidence intervals for mean treatment differences on day 180. Group A = 98 patients studied at one center; group B = 116 patients studied at the remaining 12 centers. ICD = initial claudication distance; MWD = maximal walking distance; PLC = propionyl-L-carnitine.

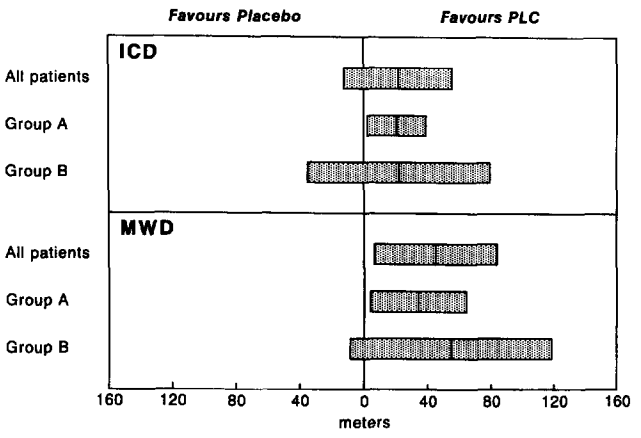

Table 4. Cumulative Density Functions Estimated Using the Chuang Method and the Approach Proposed by Shih et al.

Dose Level	Chuang Method (ref. 22)		Shih et al. Method (ref. 23)	
	Placebo Group (%)	PLC Group (%)	Placebo Group (%)	PLC Group (%)
1 g/day	28	36	28	37
2 g/day	45	58	46	61
3 g/day	54	66	55	69

Overall response rate during the entire titration course significantly favored propionyl-L-carnitine (PLC) ($p = 0.04$, log-rank test; $p = 0.05$, Wilcoxon test). Data presented are percent of patients. ref. = reference.

life; however, the more severely affected patients are forced to stop after short distances and are thus restricted in their social and occupational activities. Therefore, the significant propionyl-L-carnitine–induced improvement in maximal walking distance observed in the present study is a relevant clinical outcome.

In the present trial, propionyl-L-carnitine proved to be a safe and well tolerated drug. There were no changes in the safety parameters that would indicate an adverse effect of propionyl-L-carnitine. There were 11 adverse events resulting in drug discontinuation in the propionyl-L-carnitine group and 3 in the placebo group. However, the medical problems requiring drug discontinuation in the propionyl-L-carnitine group were unrelated to study medication.

Study limitations. The lack of angiographic definition of the extent of peripheral arterial disease in the patient cohort represents a methodologic limitation of our study. In addition, two findings warrant comment.

1. *Pronounced placebo effect.* The extent and variability in the placebo response has always been a major difficulty in evaluating drugs in intermittent claudication. Placebo-induced improvements in walking performance >50% over baseline have been observed in several trials (5,7,27–29). This remarkable placebo effect is generally attributed to a tendency toward improved exercise tolerance on repeated examinations (*training effect*). Moreover, the end point of repeated treadmill testing is pain; thus, it is conceivable that an outcome such as walking performance is strongly influenced by the subject's enhanced motivation in response to the intense surveillance.

2. *Outcome discrepancy between groups A and B.* After the primary statistical analysis was performed for the overall cohort, we classified our patients into two groups because 98 were studied at one center (group A) and the remaining 116 at 12 centers (group B). This classification implies a different statistical stability between the two groups due to the inter-center variability observed in group B. Indeed, group B showed wider confidence intervals than group A for both initial claudication distance and maximal walking distance. This greater variability was probably responsible for the lack of statistical significance in group B. However, in group B, treatment differences on day 180 favored propionyl-L-carnitine for initial claudication distance and maximal walking distance more than in group A.

Dose-response relation. To investigate the dose-response relation, we adopted a titration design that could assess the most important aspects of a long-term treatment (30). The titration procedure provides information on the usefulness of the starting dose, the overall effectiveness of the whole titration course and the worth or necessity of the highest dose (23). We found that the overall response rate was significantly in favor of propionyl-L-carnitine compared with placebo. Slightly less than 67% of patients can be expected to improve their maximal walking distance by at least 30% if they receive 2 g/day of propionyl-L-carnitine (95% confidence interval, 0.51 to 0.70). In patients not responding to this dose, the probability that they will respond to 3 g/day increases only by 8%.

Metabolic effects of propionyl-L-carnitine. The data derived from this study do not provide an explanation for the beneficial effect of propionyl-L-carnitine in patients with claudication. However, previous studies suggest that the efficacy of this drug may be related to a metabolic mechanism that promotes a higher yield of energy in the ischemic muscle. Propionyl-L-carnitine is easily transported into mitochondria, where it is converted into free carnitine and propionyl coenzyme A. Within mitochondria, free carnitine, acting as an acetyl group buffer, reduces the acetyl coenzyme A/coenzyme A ratio and thus stimulates pyruvate dehydrogenase activity, with a consequent improvement in oxidative utilization of glucose (31–33). Indeed, in patients with peripheral arterial disease, carnitine administration reduces lactate production by the ischemic working muscle (18). Propionyl coenzyme A does not affect beta-oxidation, but it may be converted into succinyl coenzyme A and then into succinate (34), an intermediate of the Krebs' cycle. Through this anaplerotic mechanism, confirmed by a recent experimental study (35), propionyl-L-carnitine may provide the ischemic muscle with additional substrates for energy production. Indeed, in a rat model of peripheral arteriopathy (36), propionyl-L-carnitine restored normal levels of adenosine triphosphate and phosphocreatine in ischemic muscle and resulted in an increase in walking capacity.

Conclusions. Although the precise mode of therapeutic action requires clarification, propionyl-L-carnitine at a dose of 1 to 2 g/day appears to be effective in improving walking capacity in patients with intermittent claudication and is well tolerated, with minimal adverse effects.

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