Reprint from
International Journal of

clinical pharmacology therapy and toxicology

Official Publication of the International Society of Chemotherapy

Volume 23 No 10 1985

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Gustav Fischer Verlag · Kart Feistle
München-Pfeisenhofen

International Journal of Clinical Pharmacology, Therapy and Toxicology, Vol. 23, No. 10 – 1985 (pp. 569–572)

Effects of L-carnitine on exercise tolerance in chronic stable angina: a multicenter, double-blind, randomized, placebo controlled crossover study

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Abstract. L-carnitine was studied in forty-four men with stable chronic angina in a multicenter, double-blind, randomized, placebo controlled crossover trial. A cycloergometer exercise test was performed after a 10-day wash-out with placebo and at the end of each 4-week treatment period with either L-carnitine (1 g twice daily) or placebo. The mean (± SD) exercise work load showed an increase after L-carnitine compared to placebo (102.73 ± 22.23 and 97.05 ± 22.77 watts respectively, $p = 0.001$), as did the watts to onset of angina (95.7 ± 24.07 and 87.44 ± 24.67, $p = 0.000$). On the contrary, the ST segment depression was reduced by L-carnitine compared to placebo both at the maximum work load (1.40 ± 0.90 and 1.69 ± 0.82 mm, $p = 0.05$) and at the maximum work load common to L-carnitine and placebo (1.24 ± 0.90 and 1.66 ± 0.79 mm, $p = 0.005$). 22.7% of the patients became free of angina with L-carnitine and 9.1% with placebo. Resting and exercise blood pressure, heart-rate and double product were unaffected by L-carnitine. 1 patient decided to discontinue the trial because of gastric pyrosis while taking the active drug. The results of this study show that treatment with L-carnitine increases exercise tolerance and reduces ECG indices of ischemia in stable effort-induced angina.

Key words: L-carnitine – chronic stable angina – exercise test

Introduction

During cardiac hypoxia the rate of oxidation of fatty acids is decreased with a consequent increase of long chain fatty acyl levels. This accumulation induces impairment in adenine nucleotide translocase activity which is responsible for the transfer of adenine nucleotide into and out of the mitochondria [Shug et al. 1975].

Administration of L-carnitine, the physiological carrier of acyl groups across the mitochondrial membrane, can reduce the concentration of acyl CoA by producing acyl carnitine. The compound thus relieves the inhibition of adenine translocase.

Moreover, the reduction of tissue carnitine levels observed during myocardial ischemia [Schwartz et al. 1973, Shug et al. 1978, Whitmer et al. 1978, Suzuki et al. 1980] could increase ischemic damage by accelerating the accumulation of fatty acyl CoA esters.

Some studies have demonstrated that acute administration of L-carnitine produces an improvement in myocardial metabolism during pacing inducing myocardial ischemia in patients with coronary artery disease [Thomsen et al. 1979, Ferrari et al. 1984]. Furthermore, increased exercise tolerance as well as an antiischemic and antianginal effect have been demonstrated by Cherchi and his collaborators in stable effort-induced angina after D, L-carnitine i. v. [Cherchi et al. 1978] and after L-carnitine i. v. [Cherchi et al. 1982] and orally [Lai et al. 1982].

† We regret having to inform that Dr. Angelino died in April.

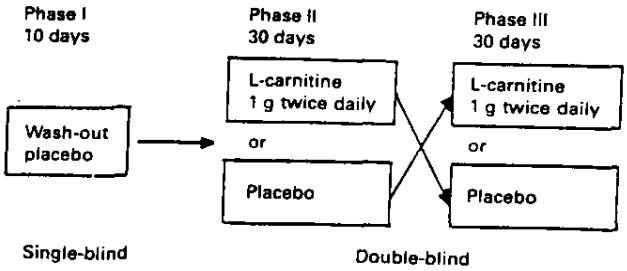

Fig. 1 Study design.

The purpose of this study was to evaluate the effects of L-carnitine on exercise tolerance in patients with chronic stable angina.

Materials and methods

Seven centers took part in the trial.

Selection of patients

Male patients with typical chronic exertional stable angina were recruited. The subjects were admitted to the trial following an abnormal cycloergometer exercise test that induced chest pain and ≥0.01 mV of ST segment depression. Patients having suffered myocardial infarction within the 4 months preceding entry into the study were excluded as were those with clinically relevant hepatic or renal disease, diabetes, hypertension or conduction disturbances. Each patient gave his informed consent for participation in the study.

Trial design

All cardioactive drugs were withdrawn and therapy with placebo began during a 10-day, single-blind wash-out period (Phase I).

After this period patients were randomly allocated either to 1 g of L-carnitine or placebo administered twice daily for 4 weeks in double-blind fashion (Phase II).

At the end of this phase patients crossed over to the alternate therapy for another 4 weeks (Phase III) (Figure 1).

Medical examinations were scheduled at the end of each phase. Drugs were supplied as identical bottles containing either L-carnitine 1 g or placebo. No other antianginal treatments were allowed during the study, except for the trial medication and short-lasting glyceril trinitrate tablets, administered to abort anginal attacks, but not prophylactically.

Table 1 Clinical data.

Age (years)	53.4
Height (cm)	167
Weight (kg)	70.3
History of myocardial infarction %	50.0
History of angina (years)	2.7

Exercise tests

Cycloergometer exercise tests were performed with a pedal frequency of 50 cycles/min, starting at 10 watts for 1 minute and then increasing by 10 watts each minute. The exercise tests were stopped when moderately severe angina, dyspnea or exhaustion developed.

Twelve standard lead ECGs were recorded at 25 mm/s after 10 minutes in the supine position and after 3 minutes in the sitting position on the bicycle. The ECG was monitored during exercise. Blood pressure and heart-rate were recorded every 2 minutes during exercise.

Measurements

Time to onset of angina, exercise work to 1 mm of ST-segment depression, maximum work and maximum work load common to L-carnitine and placebo were recorded. BP measurements were made at rest and during exercise using a standard sphygmomanometer. All the ECG readings were taken by a physician under blind conditions.

Statistical analysis

Statistical analysis was performed using analysis of variance for an unbalanced crossover design and sign test. Analysis of variance for an unbalanced crossover design was used to compare mean values. Frequencies were compared by 2-sided t-test.

Results

Fifty-two patients were admitted. 44 of them completed the trial. Clinical features are reported in Table 1.

Drop-out

Eight patients were withdrawn; 2 patients developed unstable angina, 1 during wash-out and the other during the placebo period; 1 patient dropped out of the trial during the placebo period because of increasing angina attacks; 2 patients developed congestive heart failure during the wash-out period and 2 others failed to attend medical examinations. Only 1 patient decided to discontinue the trial because of side-effects (gastric pyrosis during L-carnitine treatment).

Table 2 Exercise test measurements.

	L-carnitine	Placebo	
Maximum exercise work load (watts)	102.73 ± 22.23	97.05 ± 22.27	p = 0.001
Watts to onset of angina	95.7 ± 24.07	87.44 ± 24.67	p = 0.000
ST depression at onset of angina	1.15 ± 1.1	1.33 ± 0.7	p = 0.64
Time to 1 mm of ST depression (min)	8.6 ± 2.6	8.38 ± 2.6	p = 0.73
ST depression at maximum work (mm)	1.40 ± 0.90	1.69 ± 0.82	p = 0.05
ST depression at maximum common work (mm)	1.24 ± 0.90	1.66 ± 0.79	p = 0.005
Double product at maximum common work/10^3	22.95 ± 4.56	23.51 ± 4.39	p = 0.65

Wash-out

All 44 patients developed angina during exercise testing at a mean ± SD work load of 85.11 ± 23.36 watts. The greatest mean value of ST segment depression was 1.87 ± 0.86 mm and the mean 1 mm ST depression work load was 74.5 ± 28.8 watts.

Effect on exercise test

The responses to exercise test are reported in Table 2.

Maximum exercise work load

Forty-eight % of the patients increased their maximum exercise work load during L-carnitine therapy, while 11% improved during placebo. Maximum exercise work load increased significantly during L-carnitine compared to placebo (102.73 ± 22.23 and 97.05 ± 22.77 watts respectively, p = 0.001).

Total work increased by 11% after L-carnitine compared with placebo.

Watts to onset of angina

Watts to onset of angina after L-carnitine and after placebo were 95.7 ± 24.07 and 87.44 ± 24.67 respectively (p = 0.000).

61.4% of the patients showed angina both after L-carnitine and placebo, 9.1% only after L-carnitine, 22.7% only after placebo, while the remaining 6.8% became free of angina with both treatments (p = 0.18). Total work to the onset of angina increased by 18% after L-carnitine compared with placebo.

Time to 1 mm of ST segment depression

No difference was found between L-carnitine and placebo as regards the time to 1 mm of ST segment depression (8.6 ± 2.6 and 8.38 ± 2.6 minutes respectively, p = 0.73).

ST depression at maximum and maximum common work load

The ischemic depression of the ST segment was significantly lower after L-carnitine compared to placebo (1.40 ± 0.90 and 1.69 ± 0.82 mm, for the maximum work load, p = 0.05; 1.24 ± 0.9 and 1.66 ± 0.79 for the maximum common work load, p = 0.005 respectively).

Blood pressure, heart-rate, double product

No difference was found in systemic blood pressure, heart-rate and double product.

The observed values at the maximum common work load after L-carnitine were 179.44/95.93 ± 21.27/12.28 mmHg, 127.67 ± 18.13 beats/min and 22.95 ± 4.56, while after the placebo period they were 185.00/98.52 ± 18.75/10.39 mmHg, 126.93 ± 18.65 beats/min and 23.51 ± 4.39 for blood pressure, heart-rate and double product, respectively.

Discussion

The results of this study demonstrate that L-carnitine, administered 1 g twice daily to patients with chronic stable effort-induced angina, increased the total exercise work load and maximum watts to onset of angina and reduced the ST segment depression both at the maximum work load and at the maximum work load common to the active drug and placebo.

These data agree with those of Thomsen et al. [1979] and Ferrari et al. [1984] who found an improvement of myocardial metabolism during atrial pacing in subjects with coronary artery disease treated with L-carnitine and confirm those of Cherchi [Cherchi et al. 1978, Cherchi et al. 1982, Lai et al. 1982], demonstrating the antianginal effect of the drug administered both intravenously and orally to patients with angina on effort.

As the main objective of this study was to evaluate the influence of L-carnitine on exercise tolerance, no data are available on glyceril trinitrate tablet consumption and angina frequency.

The mechanism of improvement of angina by L-carnitine is not clear.

As ischemic myocardial fibres have been found to be depleted of L-carnitine [Suzuki et al. 1982, Spagnoli et al. 1982], treatment may restore energy utilization by fatty oxidation. Any improvement comes probably from better use of kinetic energy by the myocardium.

The main beneficial changes resulting from this study are related to the onset of angina and ST segment depression.

Patients tolerated an increased work load before the onset of angina with L-carnitine.

Furthermore, the maximum work load was increased during L-carnitine compared to placebo and the related ST segment depression was reduced.

The results suggest that treatment with L-carnitine in patients with angina pectoris has a beneficial effect on exercise induced angina and objectively modifies the ECG indices of myocardial ischemia. The changes evidenced by our study are smaller than those demonstrated for other antianginal drugs. They have been obtained by a metabolic intervention which could produce further useful improvements when used in combination with other antianginal drugs.

The interaction between these different therapeutic approaches is an interesting aim for further studies.

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