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Tolerability and Efficacy of *L*-Acetylcarnitine in Patients with Peripheral Neuropathies

A Short-Term, Open Multicentre Study

Domenico De Grandis

Department of Neurology, Arcispedale S. Anna, Ferrara, Italy

Summary

A total of 1097 patients, mean age 53.8 ± 15 years, with peripheral mono-, multi- or polyneuropathy of various aetiologies, were enrolled in a multicentre, open-label, noncomparative, prospective clinical trial to evaluate the short-term tolerability and efficacy of *L*-acetylcarnitine (LAC). The drug was administered intramuscularly at a dosage of 1000 mg/day for the first 10 days, then orally at a dosage of 2000 mg/day for a further 20 days. Standard laboratory tests were used to evaluate safety and tolerability. Treatment efficacy was assessed clinically in the whole population, and in a subgroup of patients with 'lower than normal' baseline nerve conduction velocities (CVs), neurophysiological investigations were also performed at the end of the treatment period. After 30 days' therapy, there were no changes in vital signs or in blood tests. Only 18 patients reported poor tolerability of the treatment, mainly because of gastrointestinal events, and only 6 withdrew from the study because of these adverse events. The general and local (i.e. injection site) tolerability of LAC was rated highly by both patients and investigators. Neurological examination revealed that a significant percentage of patients with altered indices at baseline had normal indices by the end of the treatment period. The percentage of normalised patients varied from 11.9% for muscular trophism to 29.1% for the topographic score according to the different parameters taken into account in the neurological examination. Disease was rated as improved by 83.1% of investigators and 84.2% of patients. In patients with reduced CVs, significant increments were also recorded for motor and sensory nerves. This study demonstrates that LAC is well tolerated when given either intramuscularly or orally. The beneficial effects of short-term therapy in subjects with peripheral mono-, multi- or polyneuropathy should be confirmed by long-term studies.

In the development of peripheral neuropathies of any origin, there are pathological alterations ranging from segmental demyelination to axonal degeneration. Recovery from degenerative processes requires an efficient metabolic response that might lead to a complete fibre repair. Ideally, the goals of a drug acting at this stage should be to protect the nerve fibres and/or to stimulate their regeneration.[1,2]

L-Acetylcarnitine (LAC) can improve the function of different metabolic pathways in either central or peripheral neurons. For example, LAC is essential to ensure the number of activated acetyl groups required in the cytoplasm for the synthesis of membrane phospholipid structures.[3] In the mitochondria, it acts on protein synthesis and transport and nonesterified fatty acid oxidation, thus contributing to the production of energy.[4]

In vitro studies have demonstrated that the addition of LAC fosters the maturation of cultured cerebellar neurons,[5] and activates nerve growth factor receptors in PC12 cells.[6] LAC also protects neurons against lipid peroxidation. *In vitro* studies have demonstrated a free radical scavenging effect through the enhancement of antioxidant factors.[7]

In diabetic rats, LAC administration prevents the loss of substance P in the peripheral nerves. In addition, LAC administration in rats with streptozocin-induced diabetes antagonises the reduction of nervous fibre conduction velocity (CV).[8] LAC administration has also proved effective in the treatment of peripheral neuropathies in diabetic patients.[9]

All of these effects indicate a potential activity of LAC on nerve fibres. In the wake of positive results in a limited group of patients studied in a short-term, double-blind, parallel-group, placebo-controlled trial,[10] which demonstrated the efficacy of LAC in improving some neurographic parameters in both mono- and poly- peripheral neuropathies, a multicentre open trial was conducted. The primary aim of this new clinical trial was to investigate the tolerability and, additionally, the clinical efficacy of LAC administration in a large group of patients with mono-, multi- and polyneuropathies of different origins.

Patients and Methods

Patients

A total of 1097 patients with clinically and instrumentally diagnosed peripheral mono-, multi- or polyneuropathies of various origins were enrolled at 113 centres. Patients included were those over 18 years of age with peripheral neuropathies of entrapment, traumatic, toxic/alcoholic, diabetic, metabolic, idiopathic, vascular or infective origins. Patients who had neoplasia compressing the peripheral nerve roots, surgically restricted medullary canal disease, severe diseases affecting the heart, lungs, kidneys or liver, or who were enrolled in other clinical trials up to 3 months previously, were excluded from the study.

The trial was performed in accordance with the Italian laws governing clinical studies and the principles of the Helsinki Convention; all patients provided informed consent prior to enrolment.

Methods

Eligible patients were treated for 30 days with LAC 1000 mg/day intramuscularly for 10 days and then 2000 mg/day orally for 20 days. In order to be included in the study, patients underwent clinical and neurophysiological examinations on day 0. Most subjects presented with neurophysiological abnormalities, including spontaneous activity, poor recruitment pattern, small motor or sensory responses and 'lower than normal' nerve CVs. Neurophysiological examinations were repeated on day 30. Analysis was limited to those patients presenting pathological conduction values at the beginning of the trial: less than 56 m/sec for the motor median nerve, 52 m/sec for motor ulnar nerves, 42 m/sec for the peroneal nerve, sensory median nerve and ulnar conduction, and 38 m/sec for the sural nerve.

Standard laboratory tests were used to evaluate safety and tolerability. Any adverse event and any reason for drug discontinuation was recorded on the clinical report form. At the end of the treatment period, investigators and patients judged global and local tolerability on a 4-point scale, ranging

from 0 (low tolerability) to 3 (high tolerability), and efficacy on a 7-point scale, ranging from –3 (major worsening) to +3 (major improvement).

Clinical investigations included a neurological examination, standard laboratory testing and evaluation of pain. The neurological assessment scored motility (as a topographic score from 0 = absence of contraction to 5 = complete excursion of movement against gravity and resistance), muscular tone and trophism (for the left and right sides of the upper and lower limbs), reflexes (classified as normal, absent, feeble or accentuated) [bicipital, tricipital, stylo-radialis, rotulean and achillean nerves], and distal and proximal sensibility to tactile, thermodolorific and vibratory stimuli (classified as normal, anaesthesia, hypesthesia or dysesthesia).

The motor nerve CVs of the median, ulnar and common peroneal nerves were detected in the elbow-wrist and in the knee-ankle segments using standard methods. CVs for the sensory nerves were determined at the level of the median, ulnar and sural nerves, in most cases antidromically, with cutaneous electrodes. For both motor and sensory nerves, the length of the segment and the nerves investigated were chosen by expert physicians on the basis of their clinical judgement.

Distal latency and amplitude of responses were also recorded. Since the method of registration and the type of electrodes differed among the participating centres, their values lacked homogeneity and analysis was limited to nerve CVs. Separate comparisons were performed for sensory and motor nerves and for patients with mono- and polyneuropathies. Sufficient data to perform a subgroup analysis were available only for patients with diabetic neuropathies. On the basis of both clinical and neurophysiological data, all patients were divided into three groups: (a) mononeuropathies with the involvement of only one nerve or root; (b) multineuropathies involving more than one nerve or root; and (c) polyneuropathies in the presence of distal and symmetrical deficits.

Evaluation of the effect of LAC on pain intensity was performed using the Scott-Huskisson visual analogue scale on days 0 and 30. This is a 10cm scale which measures pain from 0 (absent) to 10 (unbearable).[11]

Statistical Analysis

All comparisons were performed using the Wilcoxon paired test. Statistical analyses were 2-tailed, and p values of ≤0.05 (whenever specified) were considered to indicate statistical significance.

With regard to CVs, whenever two measurements for the left and right sides were available, the worst of the two was considered for the analysis.

Results

The final analysis was performed on data from 1097 patients (mean age 53.8 ± 15 years; males 53.1 ± 15.6 years; females 54.4 ± 14.1 years). 645 patients were affected by mononeuropathies and 452 patients were affected by multi- and polyneuropathies. Baseline clinical characteristics are shown in table I.

Table I. Clinical characteristics of the patients investigated in relation to their age

Neuropathy	18-40 years	41-64 years	≥ 65 years	Total
Mononeuropathy				
Carpal tunnel syndrome	28	70	11	109
Other entrapment neuropathy	76	185	78	339
Traumatic	72	74	27	173
Other	10	6	8	24
Total	186	**335**	**124**	**645**
Multi- and polyneuropathy				
Toxic/alcoholic	15	43	19	77
Diabetic	10	79	102	191
Metabolic	2	6	2	10
Idiopathic	27	51	28	106
Vascular	2	2	7	11
Infective	8	20	10	38
Other	6	5	8	19
Total	70	**206**	**176**	**452**

Table II. Laboratory parameters (mean ± SD) at baseline and after 30 days of treatment with *L*-acetylcarnitine. None of the changes were statistically significant

Parameter (units)	Baseline	30 days
RBC ($\times 10^6$/mm^3)	4.62 ± 0.57	4.66 ± 0.58
WBC ($\times 10^3$/mm^3)	7.12 ± 2.35	6.86 ± 2.04
HCT (%)	41.82 ± 4.47	42.01 ± 4.08
Glucose (mg/dl)	106.62 ± 40.88	106.20 ± 35.87
Uric acid (mg/dl)	4.93 ± 1.47	4.90 ± 1.40
BUN (mg/dl)	35.16 ± 12.94	34.80 ± 12.81
Creatinine (mg/dl)	0.96 ± 0.23	0.95 ± 0.24
Total cholesterol (mg/dl)	204.71 ± 40.54	204.22 ± 39.59
Triglycerides (mg/dl)	140.61 ± 66.69	142.38 ± 63.29
Total protein (g/dl)	6.97 ± 0.62	6.99 ± 0.58
Total bilirubin (mg/dl)	0.80 ± 0.37	0.80 ± 0.33
AST (U/L)	24.33 ± 19.22	23.26 ± 11.76
ALT (U/L)	24.80 ± 17.97	24.30 ± 18.64
Na^+ (mEq/ml)	140.76 ± 4.13	140.95 ± 4.00
K^+ (mEq/ml)	4.25 ± 0.49	4.27 ± 0.46
Ca^{++} (mEq/ml)	8.38 ± 1.91	8.35 ± 1.90
Phosphate (mEq/ml)	4.25 ± 0.49	4.27 ± 0.46

Abbreviations: ALT = alanine aminotransferase (SGPT); AST = aspartate aminotransferase (SGOT); BUN = blood urea nitrogen; HCT = haematocrit; RBC = red blood cells; WBC = white blood cells.

Drug Tolerability, Withdrawals and Adverse Events

No statistically significant changes occurred in either vital signs or blood tests after 30 days' LAC therapy (table II). It is noteworthy that no alterations were found in standard tests such as blood glucose, BUN, creatinine, total cholesterol, total protein, triglycerides, AST (SGOT) and ALT (SGPT) levels, demonstrating that LAC administration does not negatively influence organs or metabolic pathways.

The general and local tolerability of LAC was rated highly by both patients and investigators alike (fig. 1); local tolerability refers to adverse events experienced at/near to the site of injection. General and local tolerability were judged 'excellent' in 75.1 and 74.4% of patients, respectively, by clinicians and in 73.4 and 71.9%, respectively, by patients themselves. General and local tolerability were rated 'good' in 22 and 22.1% of patients, respectively, by investigators and in 23.4 and 23.5%, respectively, by patients.

Adverse events occurred in 18 patients (1.64%); these included gastrointestinal events (12 patients), allergic reactions (2 patients), headache (1 patient), and mild persistent pain at the injection site (3 patients). Of these, only 6 patients (0.55%) withdrew from the study and discontinued drug administration, mainly because of gastrointestinal events (4 patients), headache and allergic reactions. Although it was not possible to establish a relationship between these adverse events and treatment, gastrointestinal adverse effects are known to be associated with LAC administration (Sigma Tau, data on file).

Clinical Evaluation

After 30 days' LAC therapy, the neurological examination revealed that a significant percentage of patients who had baseline pathological indices had normal indices (table III). The percentage of normalised patients varied according to the different indices taken into consideration, ranging from 11.9% for muscular trophism to 29.1% for the topographic score.

The positive outcome at clinical examination was also confirmed by the investigators' and

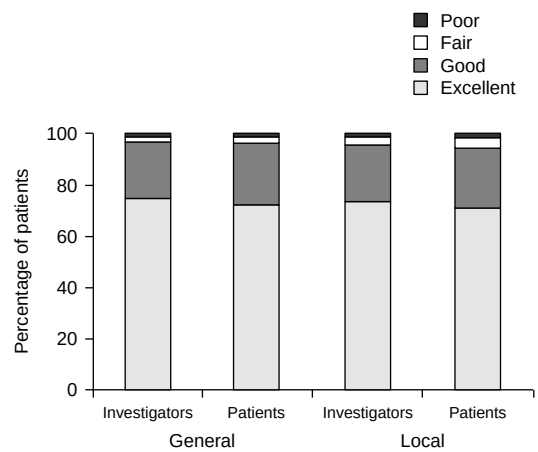

Fig. 1. General and local (injection site) tolerability: investigators' and patients' judgement.

Table III. Neurological examination: comparison between baseline and end-of-study data

Neurological examination	No. of pts with pathological indices at baseline	No. (%) of pts with normalised indices after 30 days' LAC therapy
Topographic score	798	232 (29.1)
Sensibility	766	221 (28.9)
Motility	675	130 (19.3)
Reflexes	603	100 (16.6)
Muscular trophism	506	60 (11.9)
Muscular tone	379	96 (25.3)

Abbreviation: LAC = *L*-acetylcarnitine.

Table IV. Clinical efficacy: investigators' and patients' judgement

	Investigators (%)	Patients (%)
Excellent improvement	30.7	31.9
Moderate improvement	28.2	29.2
Slight improvement	24.2	23.1
Total improvement	83.1	84.2
Unchanged	15.2	13.9
Slight worsening	1.5	1.4
Moderate worsening	0.1	0.3
Major worsening	0.2	0.2

Table V. Mean (± SD) changes from baseline conduction velocities (CVs) after 30 days' LAC therapy. Data refer only to patients with lower than normal baseline CVs

Neuropathy	No. of patients	Change from baseline (m/sec)
Mononeuropathy		
Motor nerves	90	+1.52 (2.27)*
Sensory nerves	61	+1.88 (2.35)*
Polyneuropathy		
Motor nerves	152	+1.43 (2.21)*
Sensory nerves	86	+1.61 (2.07)*

Abbreviation: LAC = *L*-acetylcarnitine. * p = 0.01 *vs* baseline.

patients' judgement on drug efficacy. Disease was rated as improved by 83.1% of investigators and 84.2% of patients (table IV).

Electromyographical Testing

Data from a subgroup of 389 patients with 'lower than normal' baseline CVs were evaluated. Compared with baseline, significant ($p < 0.01$) changes in CVs were recorded for both motor and sensory nerves as well as mono- and polyneuropathies. Mean changes from baseline are provided in table V.

In diabetic patients, mean CV changes after 30 days' treatment with LAC were +1.28 (± 2.23) m/sec (n = 79) for motor nerves and +1.18 (± 1.78) m/sec (n = 41) for sensory nerves. Data for other subgroups were not sufficient to perform a subgroup analysis.

Pain Reduction

Patients were analysed as a whole, or divided according to the intensity of pain recorded at baseline into: mild (VAS score <25), moderate (VAS score between 26 and 70) or unbearable (VAS score >70) pain. After 30 days of treatment with LAC, substantial pain reduction and, in some cases, even pain resolution, was recorded by patients as assessed by changes in the VAS score (fig. 2). Nearly 60% of the assessed patients rated pain intensity as mild (VAS score <25) at the end of the treatment period.

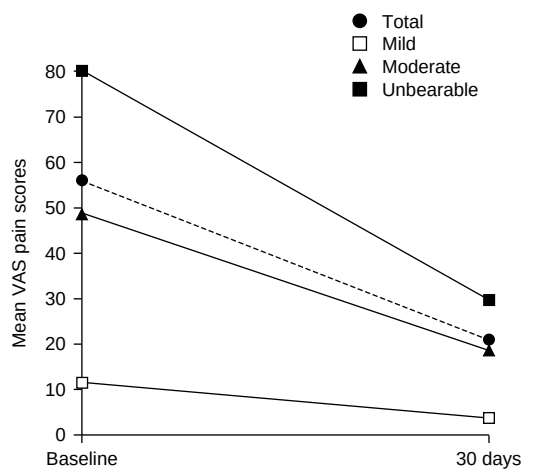

Fig. 2. Reduction in pain intensity: mean visual analogue scale (VAS) scores (see text for details), at baseline and after 30 days' LAC therapy. Data are shown for the total mean of the sample, and for patients with baseline mild (VAS score <25), moderate (VAS score between 26 and 70), or unbearable (VAS score >70) pain.

Discussion

Although the aetiology of peripheral mono- and polyneuropathies may vary, the end-stage of the degenerative process is shared by various subtypes of neuropathies. An ideal agent should interfere with these processes, protecting against degeneration and/or promoting fibre regeneration.

Despite the well known limitations of open clinical studies and the fact that evaluation of clinical efficacy was a secondary goal of this trial, our data confirm and extend the results of De Grandis et al.[10] Clinical examinations of patients revealed improvement in both motor and sensory components, which was more evident for the latter. Indeed, sensory function was the most frequently impaired (>80%), implying that sensory impairment in peripheral neuropathies is the first to be subjectively reported and, thus, is the first to respond to treatment. This clinical judgement was mirrored by improvement of the conduction properties of peripheral nerves. Again, this was more evident for the sensory component. These results are in keeping with those reported by De Grandis et al.,[10] who also found an immediate response in the sensory components of both mono- and polyneuropathies after short-term LAC treatment, but failed to detect a significant difference in the improvement of motor nerve CVs in polyneuropathies. Supporting their results, our larger patient sample allowed us to evaluate and detect a significant difference between baseline and end-of-study values for sensory and motor nerves in mono- and polyneuropathies. As a consequence, muscular trophism, which is strictly dependent on motor nerve function, recovered in 12% of subjects, despite the short-term treatment period.

The data from diabetic patients confirm the positive findings of other studies. Quatraro et al.[9] evaluated, in a single-blind crossover study, the effect of LAC administration in 20 diabetic subjects with peripheral neuropathies. Significant amelioration of symptoms was observed during LAC treatment as compared with placebo.

Although there was no placebo control group in the present study, it is noteworthy that pain reduction was of the same magnitude as that recorded in previous trials.[9,10] We observed beneficial effects of LAC on pain intensity, both considering the patient sample as a whole and by analysing different patient subgroups according to the pain level.

As regards tolerability, it should be emphasised that only 18 of the 1097 patients (1.6%) exhibited adverse events, and only 6 (0.5%) withdrew from the study and discontinued therapy with LAC. Laboratory data provided no evidence of alterations, confirming the high safety profile of this agent.

Clinical Implications

Our results show that LAC is a well tolerated agent when given both intramuscularly and orally. The adverse events associated with its use are mild and rare, and mainly restricted to gastrointestinal events. Clinical and neurophysiological evaluations showed that short-term treatment may be beneficial in patients with mono-, multi- or polyneuropathies of different aetiologies. Since these diseases require a long period of treatment, these encouraging results provide a strong rationale for evaluating the efficacy of LAC during long-term treatment in various, well-defined populations.

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Correspondence and reprints: Dr *Domenico De Grandis,* Department of Neurology, Arcispedale S. Anna, Corso Giovecca 203, 44100 Ferrara, Italy.