Acetyl-L-Carnitine in the Management of Pain During Methadone Withdrawal Syndrome

Luigi Janiri, MD, Giovanni Martinotti, PhD,* Federico Tonioni, MD,* Carla Ghelardini, MD,† Raffaella Nicolai, PhD,‡ Nicoletta Galeotti, MD,† Luigi Mosconi, MD,‡ Menotti Calvani, MD,‡ Alessandro Bartolini, MD,† and Emerenziana Iannoni, MD‡*

Introduction: This study was designed to determine the short-term effect of acetyl-L-carnitine (ALC) on symptoms of withdrawal in opiate-dependent subjects and animals and, in particular, on pain, given the efficacy of ALC in other typologies of pain. The study consists of 2 branches: a clinical study and a preclinical one, both with a randomized placebo-controlled design.

Methods: Thirty subjects meeting clinical criteria for methadone dependence were consecutively recruited and treated with ALC 2 g/d or placebo for a 3-week detoxification period. Withdrawal symptoms and pain were evaluated through the Short Opiate Withdrawal Syndrome scale, and the Huskisson's analogue scale for pain. In the preclinical study, mice previously received a pretreatment (saline solution or morphine), and subsequently, each group was randomly divided in 4 subgroups that received a treatment of saline, methadone, ALC, or amitriptyline, respectively. Hot plate test and Writhing test were used to evaluate pain intensity.

Results: Average Short Opiate Withdrawal Syndrome total scores during the first 5 days of treatment resulted significantly higher in controls than in the ALC group ($P < 0.05$). Pain scores in the Huskisson's analogue scale were considerably lower in the group of patients taking ALC than in the control group after 1 week of ALC treatment until the end of the study. Results of the preclinical study show that the administration of methadone for 7 days in morphine-tolerant mice did not produce any modification of the pain threshold. By contrast, the 7-day coadministration of methadone and ALC in morphine-tolerant mice induced an analgesic effect evaluated 3 hours after the last injection.

Discussion: Acetyl-L-carnitine acted as an effective antihyperalgesic agent for relieving opiate-withdrawal hyperalgesia in animals and displayed clinical efficacy on other withdrawal symptoms such as muscular tension, muscular cramps, and insomnia. Considering its tolerability, the excellent side effect profile, the absence of significant interactions, and the lack of abuse potential, ALC can be considered as a useful pharmacological adjunct in the treatment of opiate withdrawal.

Key Words: acetyl-L-carnitine, pain, methadone, withdrawal

(*Clin Neuropharm* 2009;32: 35–40)

*Department of Psychiatry–Additive Behaviours Unit, Catholic University Medical School, Rome; †Department of Pharmacology, University of Florence, Florence; and ‡Sigma-Tau S.p.A., Rome, Italy.

Address correspondence and reprint requests to Giovanni Martinotti, PhD, Department of Psychiatry–Addictive Behaviours Unit, Catholic University Medical School, Rome, Italy; E-mail: giovanni.maritinotti@libero.it

Disclosure/Conflict of Interest: The authors declare that except for income received from the primary employer, no financial support or compensation has been received from any individual or corporate entity during the past 3 years for research or professional service, and there are no personal financial holdings that could be perceived as constituting a potential conflict of interest.

DOI: 10.1097/WNF.0b013e31815dd465

Opiate withdrawal, one of the longest studied and most well-described withdrawal syndromes, has been described as akin to a moderate to severe flu-like illness.[1] Pharmacological treatments of opiate-withdrawal symptoms are designed to smooth the progress of abstinence for a safe transition to a relapse prevention program, through the improvement of signs and symptoms.

Alpha-2 adrenergic agonist drugs are the main nonopiate alternative for withdrawal, although the high rates of adverse effects, including drowsiness, fatigue, lethargy, dry mouth, and mainly hypotension, make this approach generally recommended for a restricted number of patients.[2]

Among the characteristic withdrawal symptoms, pain, together with insomnia, restlessness, and anxiety, was described as the most resistant to treatment with clonidine,[3] an alpha-2 adrenergic agonist regarded as an efficacious and safe treatment both in outpatient and inpatient studies.[4] Pain, often reported as muscular aches, is considered as one of the most important factors determining relapses or dropouts,[5] therefore emphasizing the relevance of a possible strategy of treatment able to reduce pain intensity, with a good side effect profile.

Different studies documenting the analgesic efficacy of acetyl-L-carnitine (ALC) in neuropathic chronic pain have been carried out. Acetyl-L-carnitine was efficacious and well tolerated in improving neurophysiological parameters and reducing pain during a 1-year period in patients with diabetic neuropathy, by stimulating nerve regeneration and vibratory perception.[6] In HIV-positive patients affected by painful distal symmetrical neuropathy[7] and in HIV patients with established antiretroviral toxic neuropathy after a long-term treatment[8,9] ALC proved to be an efficacious and safe alternative.

Moreover, the potential efficacy of ALC in the relief of acute pain has been reported in animal models,[10] postulating an antinociceptive effect mediated by a central indirect cholinergic mechanism.[11] Conversely, in the study of Vermeulen and Scholte[12] on patients with chronic fatigue syndrome, ALC showed beneficial effects on mental fatigue and attention concentration but did not for pain complaints.

The study consists of 2 branches: a clinical study and a preclinical one. The randomized, double-blind, placebo-controlled clinical study was designed to determine the effect of short-term ALC therapy on symptoms of withdrawal in methadone-dependent subjects and, in particular, on pain, given the efficacy of ALC in other typologies of pain. The efficacy on the remaining acute withdrawal symptoms represented a secondary objective: specifically, some withdrawal symptoms such as insomnia, restlessness, and motor hyperactivity, could be a target for ALC as postulated in other studies where ALC resulted to be efficacious on similar symptoms in other psychopathological frames such as insomnia in geriatric depression[13] and restlessness and hyperactivity in attention deficit hyperactivity disorder.[14] Moreover, a preclinical study about the use of ALC in the withdrawal syndromes[15] showed the

reduction of the onset of tremors in ethanol withdrawal as well as the reduction of ethanol intake in alcohol-preferring rats during treatment with ALC, thus providing further evidence for the use of ALC in the clinical treatment of withdrawal symptoms.

Because ALC was not administered as monotherapy in dependent subjects, to clarify its actual effect, the ALC activity on pain threshold was also tested in an animal model of methadone dependence.

METHODS

Clinical Study

Subjects and Procedures

Thirty subjects meeting clinical criteria for methadone dependence (*Diagnostic and Statistical Manual of Mental Disorder, Fourth Edition* [DSM-IV]) were consecutively recruited from the Day-Hospital of Psychiatry and Drug Dependence of the University General Hospital "A. Gemelli" in Rome (male-to-female ratio 4:1, mean age 32.8 ± 6.2 years). Patients, evaluated by attending psychiatrists through the Structured Clinical Interview for DSM-IV and the European version of Addiction Severity Index, were excluded from recruitment if they had a severe physical illness and evidence of mental disorders severely interfering with their cognitive capacity or reality test (eg, a current or previous diagnosis of schizophrenia, bipolar disorder, major depression, and any substance abuse or dependence [other than methadone dependence] according to DSM-IV). Excluded from participation were subjects regularly taking anticonvulsants, antidepressants, neuroleptics, or analgesics and subjects with chronic or ongoing acute pain or with peripheral neuropathy, diabetes, and HIV.

Inclusion criteria were a daily methadone intake between 30 and 40 mg dating back at least 6 months, an age range between 18 and 45 years, and Italian speaking. All the patients recruited were effectively stabilized in treatment, defined as having been on asteady and daily dosage of methadone (30 mg) for at least 3 weeks, and were then randomized to receive ALC or placebo. Participants were selected to match on age, race, and gender. Only subjects volunteering to participate and providing full informed consent were effectively recruited.

The structure of the study foresaw 3 weeks of treatment: during the first week (T-7–T0), methadone was gradually reduced to 20 mg daily (orally) from the starting dosage (30 mg), then methadone was abruptly suspended for the final 2 weeks of study. For the first week of treatment, ALC (or placebo) was given (2 g\d) orally, subdivided in 3 times daily, then intravenously at the same dosage for the remainder of the study (T1–T14). During the study period, patients were only given trazodone (100 mg\d) for the abstinence-related sympathetic responses of tachycardia and hypertension, and given diazepam (20 mg\d or equivalent) for insomnia according to established and validated protocols.[16] In case withdrawal symptoms severely interfered with the patients' clinical condition, patients were adequately treated and considered as dropouts.

For the entire study period, patients attended (daily) a self-help group based on a psychosocial program.

The following parameters were used (T7–T14) to determine the efficacy of the medication: (1) the Short Opiate Withdrawal Syndrome (SOWS)[17] scale and (2) the Huskisson's visual analogue scale (VAS) for pain,[18] both administered every day.

To evaluate the adverse event profile, physical assessment, vital signs, and laboratory analyses were performed at T0, T4, and T14.

The study was approved by the Institutional Review Boards and the national regulatory authorities in accordance with local requirements.

Statistical Analysis

Statistical analysis was performed using nonparametrical tests.

Student *t* and chi-square tests were used to compare sociodemographic and clinical data.

Chi-square was applied for the SOWS subscales and the SOWS total score at different times (T0, T4, T9, T14) to verify a possible association between the variables considered and the treatment received. The Mann-Whitney *U* test was used to analyze the differences between the group of subjects treated with ALC and the control group, in terms of average scores in the period of time between T0/T4, T5/T9, and T10/T14. The average of the differences (DELTA) between T0/T4 and T5/T9, T5/T9 and T10/T14, and T0/T4 and T10-T14 in both the ALC and the control group were analyzed through the Friedman test to verify a possible significant difference during the time course.

For the VAS scores, the Mann-Whitney *U* test was conducted to identify differences between the 2 groups of subjects at different times (T0, T4, T9, T14); for each group, DELTA variables were calculated in all the intervals considered between T0 and T14, and their differences were evidenced.

Finally, for the 2 groups separately, Friedman test was used on the VAS score at different times (T7, T0, T4, T9, T14) to verify the presence of a significant variation during the time course considered.

Preclinical Study

Animals

Male Swiss albino mice (24–26 g) from Morini (San Polo d'Enza, Italy) were used. Fifteen mice were housed per cage. The cages were placed in the experimental room 24 hours before the test for acclimatization. The animals were fed a standard laboratory diet and tap water ad libitum and kept at 23 ± 1°C with a 12-hour light/dark cycle, light at 7 AM. All experiments were carried out in accordance with the National Institutes of Health's Guide for the Care and Use of Laboratory animals. All efforts were made to minimize animal suffering and to reduce the number of animals used.

Hot Plate Test

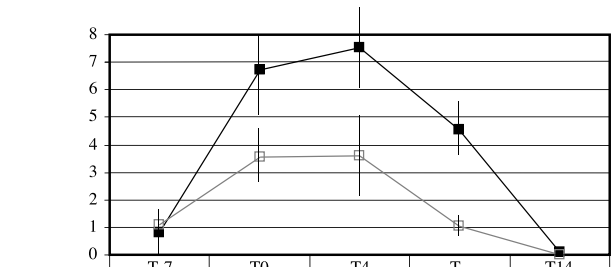
Mice were placed inside a stainless steel container that was set thermostatically at 52.5 ± 0.1°C in a precision water bath from KW Mechanical Workshop, Siena, Italy. Reaction times (seconds) were measured with a stopwatch before, 30 minutes after and 7 days after treatments. The end point used was the licking of the fore or hind paws. Those mice scoring less than 12 and more than 18 seconds in the pretest were rejected (30%). An arbitrary cutoff time of 45 seconds was adopted.

Writhing Test

Mice were injected intraperitoneal with a 0.3% solution of acetic acid (10 mL kg^{-1}). The number of stretching movements was counted for 10 minutes, starting 5 minutes after acetic acid injection.

Administration Schedule

Animals received a pretreatment (saline or morphine) and a treatment (saline, methadone, ALC, or amitriptyline). Mice were randomly assigned to saline or morphine pretreatment group. Pretreatment with morphine was conducted as follows: 10 mg kg^{-1} s.c. on day 1, 20 mg kg^{-1} s.c. on day 2, 40 mg kg^{-1}



	T-7	T0	T4	T	T14
Controls	0.8	6.73	7.53	4.54	0.07
ALC	1.1	3.56	3.58	1.02	0

FIGURE 1. Pain average scores in the Huskisson's analogue scale in ALC and control groups at different times.

s.c. on day 3, 50 mg kg^{-1} s.c. on day 4, 60 mg kg^{-1} s.c. on day 5, 70 mg kg^{-1} s.c. on day 6, and 80 mg kg^{-1} s.c. on day 7. After pretreatment, each pretreated group was divided into 4 subgroups that received a treatment of saline, methadone, ALC, or amitriptyline, respectively. Methadone was injected at the dose of 10 mg kg^{-1} s.c. once daily for 7 days; ALC was administered at the dose of 100 mg kg^{-1} i.p. twice daily for 7 days, whereas amitriptyline was injected at the dose of 15 mg kg^{-1} s.c. twice daily for 7 days. After pretreatment, each drug was coadministered with saline, and 2 groups were coadministered with methadone and ALC, and methadone and amitriptyline, respectively.

Statistical Analysis

Results from hot plate and writhing tests are given as the mean ± SEM; analysis of variance, followed by Fisher protected least significant difference procedure for post hoc comparison, was used to verify the significance between 2 means. *P* values of less than 0.05 were considered significant. Data were analyzed with the StatView for the Macintosh computer program.

RESULTS

Clinical Study

Among the 30 subjects recruited, 10 subjects did not complete the treatment: 8 of them dropped out in the first week of treatment (T7/T0), during the methadone reduction and stabilization period, and 2 in the second week during the withdrawal period, both of them receiving placebo. The 2 groups of treated subjects (10 patients each) were not significantly different in term of sex (ALC group male-to-female ratio 2.6:1; controls 2.8/1), age (ALC group 31 ± 3; controls 30 ± 2.4), employment condition, marital status, and level of education.

Pain scores in the Huskisson's analogue scale were considerably lower in the group of patients taking ALC than in the control group both at T0 ($P < 0.05$), which means after 1 week of ALC treatment but before the methadone suspension, T4 ($P = 0.01$) and T9 ($P = 0.01$) (Fig. 1). Moreover, the reduction of pain values normally observed after the first days of acute withdrawal resulted to be significantly higher in the ALC group than in placebo, considering the period T4/T14 ($P = 0.01$) and particularly between T9/T14 ($P < 0.01$).

Average SOWS total scores during the first 5 days of treatment were significantly higher in controls than in the ALC group ($P < 0.05$).

Figure 2 shows the time course of the SOWS subscale for pain; the average decreasing of intensity of this symptom between the first period of treatment (T0/T4) and the second (T5/T9) was significantly higher in the ALC group with respect to controls ($P < 0.05$).

The average decreasing of the SOWS subscale for muscular tension was significantly higher in the ALC group with respect to controls ($P = 0.05$), considering the first period of treatment (T0/T4) toward the second (T5/T9).

With regard to muscular spasm intensity during the first 5 days of treatment, they resulted to be significantly higher in controls ($P < 0.05$) than in the ALC group, whereas the average decreasing of muscular spasm intensity between both the periods of T0/T4 and the following of T5/T9 was higher in the ALC group than controls ($P = 0.05$).

The symptoms of insomnia and feeling of coldness significantly reduced in the ALC group ($P < 0.005$; $P < 0.05$) during the entire study period, whereas they did not for the control group; all the other withdrawal symptoms rated through SOWS significantly reduced both in ALC and in control groups.

Stomach cramps and yawning were the only withdrawal symptoms significantly more represented in the ALC group with respect to controls ($P < 0.05$), at T0 and T14, respectively; otherwise, these SOWS subscores did not significantly differ between the 2 groups.

There were no adverse events during the study. No patients showed craving for the drug; at discontinuation, we observed no drug withdrawal syndrome or side effects due to drug suspension.

Preclinical Study

Mice were pretreated with morphine once daily for 7 days. On day 8, morphine pretreatment was stopped, and animals were treated with methadone once daily for 7 days, from days 8 to 14. The licking latency values in the hot plate test were recorded on day 8 before starting the methadone treatment and 30 minutes after methadone administration, evidencing the absence of any modification of the pain threshold induced by methadone. By contrast, in the control group, which received a pretreatment with saline, methadone was able to induce antinociception 30 minutes after administration (Fig. 3).

The licking latency values were also recorded on day 14 after a 7-day treatment with methadone and, in particular, 3 hours after the last injection. No modification of the pain threshold was observed in the morphine + methadone-treated mice. In the saline + methadone-treated mice (control group), the antinociceptive effect of methadone disappeared (Fig. 3).

In the same experimental conditions, the effect of treatment with ALC was observed. In control animals, ALC did not produce any effect 30 minutes after administration. Conversely, administered twice daily for 7 days, ALC produced an increase of the pain threshold. Similar results were obtained when ALC was coadministered with methadone (Fig. 3).

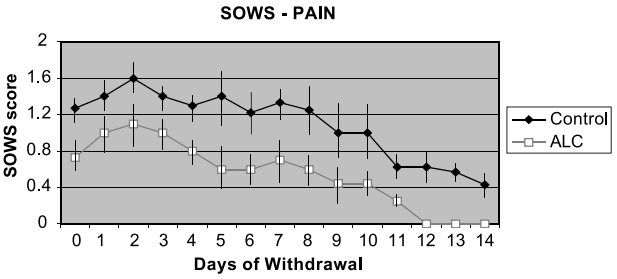


FIGURE 2. SOWS subscale for pain in ALC and control groups at different times from methadone suspension.

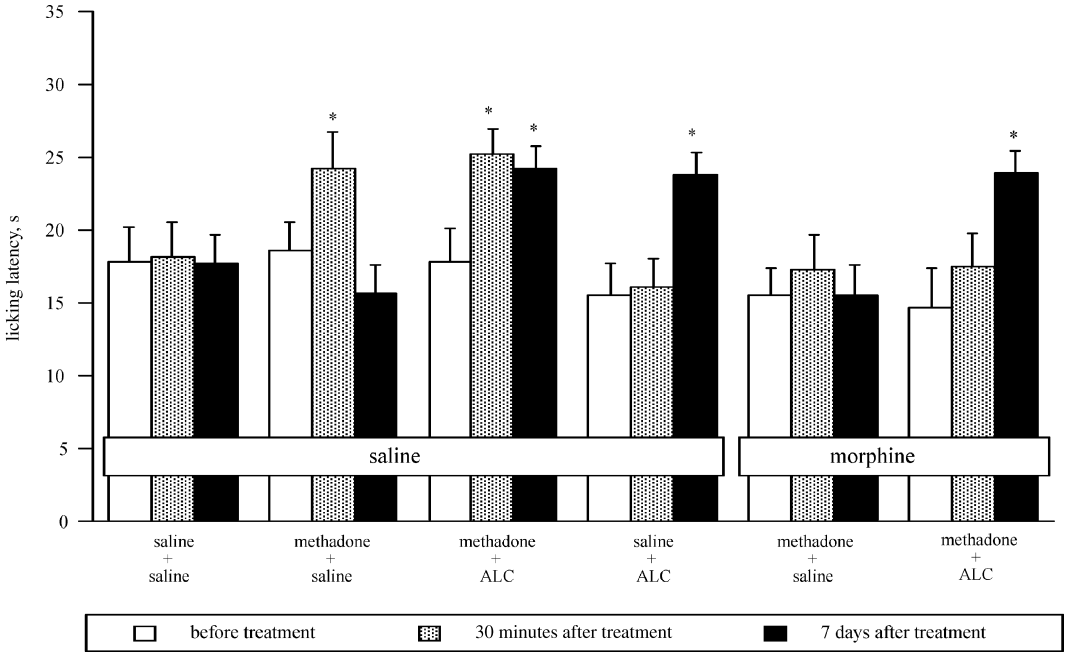


FIGURE 3. Effect of ALC on methadone-dependent mice in the hot plate test. Animals were pretreated with saline or morphine for 7 days (from days 1 to 7). Then animals received a treatment for further 7 days (from days 8 to 14) with saline, methadone, or ALC, as reported below each column. Vertical lines represent SEM; $*P < 0.05$, in comparison with the licking latency value recorded before treatment.

The coadministration of ALC and methadone in morphine-tolerant mice did not produce any modification of the licking latency values before and 30 minutes after administration of methadone. By contrast, after the 7-day treatment, an antinociceptive effect was evidenced in the ALC-treated group (Fig. 3).

By following the same administration schedule, the effect produced by the coadministration of methadone and

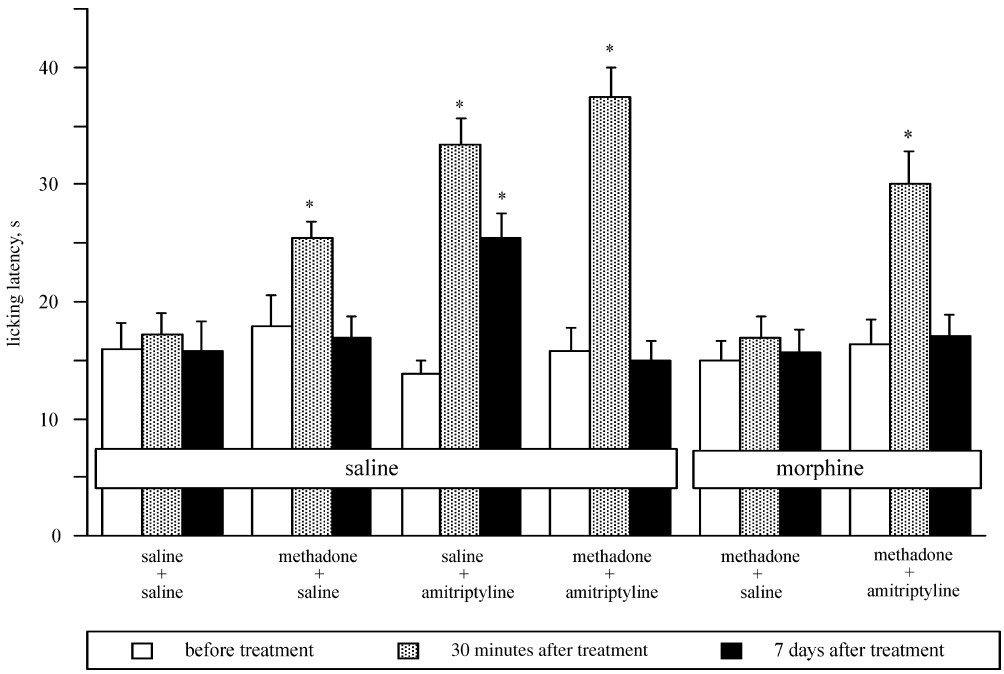


FIGURE 4. Effect of amitriptyline on methadone-dependent mice in the hot plate test. Animals were pretreated with saline or morphine for 7 days (from days 1 to 7). Then animals received a treatment for further 7 days (from days 8 to 14) with saline, methadone, or amitriptyline, as reported below each column. Vertical lines represent SEM; $*P < 0.05$, in comparison with the licking latency value recorded before treatment.

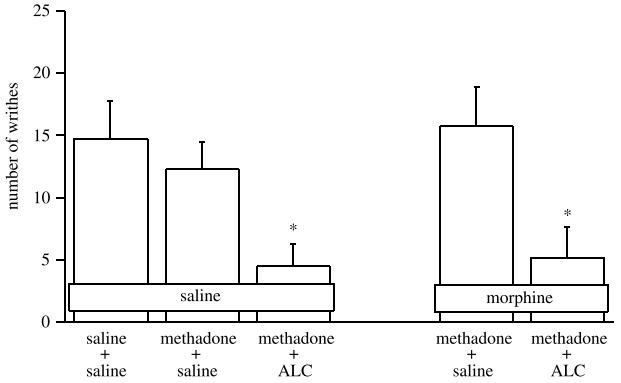


FIGURE 5. Effect of ALC on methadone-dependent mice in the writhing test. Animals were pretreated with saline or morphine for 7 days (from days 1 to 7). Then animals received a treatment for further 7 days (from days 8 to 14) with saline, methadone, or ALC, as reported below each column. Vertical lines represent SEM; $*P < 0.05$, in comparison with the corresponding control group.

amitriptyline was also evaluated in the hot plate test. In the control group, amitriptyline produced antinociception, which persisted after 7 days of repeated administration (Fig. 4). Similarly, in the morphine-pretreated animals, amitriptyline produced an increase of the pain threshold 30 minutes after administration. By contrast, when coadministered with methadone for 7 days, the antinociceptive effect completely disappeared when detected 30 minutes after the last injection (Fig. 4).

The effect produced by ALC in methadone-dependent animals was also evaluated against a chemical, painful stimulus by means of the writhing test. As reported in Figure 5, the administration of methadone for 7 days in morphine-tolerant mice did not produce any modification of the pain threshold. By contrast, the 7-day coadministration of methadone and ALC in morphine-tolerant mice induced an analgesic effect evaluated 3 hours after the last injection. Similar results were obtained in the control group in which methadone and ALC were coadministered for 7 days in mice that received saline as pretreatment (Fig. 5).

CONCLUSIONS

The present results demonstrate that the withdrawal symptom of pain can be blunted significantly using ALC, which can be considered as a valid and effective option in the management of pain during opiate-withdrawal syndromes.

The significant reduction of muscular tension and muscular cramps in the ALC group may be interpreted by a direct effect of ALC on muscular functioning, postulating ALC as an active molecular group that represents an intermediate substrate usable directly in the working tissue.[19] However, muscular ache is the most common type of pain presentation during opiate-withdrawal syndrome; therefore, the reduced perception of pain determined by ALC at this level could lead the patient to underestimate symptoms coming from the muscular system.

In regard to insomnia, a secondary effect of ALC might be hypothesized: the reduced pain intensity could account for increased sleep duration and for a reduction of time required to fall asleep. However, insomnia evaluated by a nonspecific instrument such as SOWS, cannot be adequately assessed and differentiated.

A limitation of the present study was that ALC was not administered as monotherapy; consequently, it is difficult to understand the actual effect of ALC, although the low dosage of trazodone used should not interfere with the typical development of pain during withdrawal states, as described in different studies showing the inefficacy of trazodone at dosage lower than 150 to 200 mg/d in different pain syndromes.[20,21]

Results obtained from preclinical studies further confirm the antihyperalgesic activity of ALC. In methadone-dependent mice, a 7-day cotreatment of methadone with ALC increased the pain threshold against an acute thermal stimulus as well as against a chemical stimulus. In these studies, mice received ALC as monotherapy, suggesting that the effect on the pain threshold observed is only related to ALC. It should be taken into account that conversely to ALC, repeated administration of other analgesic drugs, such as amitriptyline, on methadone-dependent mice induced a complete loss of anticociceptive activity.

The lack of relevant side effects and the absence of abuse liability make ALC a good alternative in the treatment of a central symptom of opiate withdrawal such as pain together with other antiwithdrawal drugs in a composite therapeutic program.

In summary, in this work, ALC acted as an effective antihyperalgesic agent for relieving opiate-withdrawal hyperalgesia in animals and displayed clinical efficacy on other withdrawal symptoms such as muscular tension, muscular cramps, and insomnia. Considering its tolerability, the excellent side effect profile, the absence of significant interactions, and the lack of abuse potential, ALC can be considered as a useful pharmacological adjunct in the treatment of opiate withdrawal and deserves further research through other controlled studies with larger samples of subjects.

ACKNOWLEDGMENTS

The authors wish to thank Drs P. Urbano and R. Lacerenza for clinical assistance in the recruitment of patients and R. Mason for language revision.

REFERENCES

1. Farrell M. Opiate withdrawal. *Addiction* 1994;89:1471–1475.
2. American Psychiatric Association. Practice guideline for the treatment of patients with substance use disorders: alcohol, cocaine, opioids. *Am J Psychiatry* 1995;152:381–387.
3. Charney DS, Heninger GR, Kleber HD. The combined use of clonidine and naltrexone as a rapid, safe, and effective treatment of abrupt withdrawal from methadone. *Am J Psychiatry* 1986;143:831–837.
4. Kleber HD, Riordan CE, Rounsaville B, et al. Clonidine in outpatient detoxification from methadone maintenance. *Arch Gen Psychiatry* 1985;42:391–394.
5. Liebmann PM, Lehofer M, Moser M, et al. Nervousness and pain sensitivity: II. Changed relation in ex-addicts as a predictor for early relapse. *Psychiatry Res* 1998;79:55–58.
6. De Grandis D, Minardi C. Acetyl-L-carnitine (levacecarnine) in the treatment of diabetic neuropathy. A long-term, randomised, double-blind, placebo-controlled study. *Drugs RD* 2002;3:223–231.
7. Scarpini E, Sacilotto G, Baron P, et al. Effect of acetyl-L-carnitine in the treatment of painful peripheral neuropathies in HIV+ patients. *J Peripher Nerv Syst* 1997;2:250–252.
8. Hart AM, Wilson AD, Montovani C, et al. Acetyl-L-carnitine: a pathogenesis based treatment for HIV-associated antiretroviral toxic neuropathy. *AIDS* 2004;18:1549–1560.
9. Youle M, Osio M. A double-blind, parallel-group, placebo-controlled,

multicentre study of acetyl L-carnitine in the symptomatic treatment of antiretroviral toxic neuropathy in patients with HIV-1 infection. *HIV Med* 2007;8:241–250.

10. Ghirardi O, Vertechy M, Vesci L, et al. Chemotherapy-induced allodinia: neuroprotective effect of acetyl-L-carnitine. *In Vivo* 2005;19:631–637.
11. Ghelardini C, Galeotti N, Calvani M, et al. Acetyl-L-carnitine induces muscarinic antinocieption in mice and rats. *Neuropharmacology* 2002;43:1180–1187.
12. Vermeulen RC, Scholte HR. Exploratory open label, randomized study of acetyl- and propionylcarnitine in chronic fatigue syndrome. *Psychosom Med* 2004;66:276–282.
13. Pettegrew JW, Levine J, Gershon S, et al. 31P-MRS study of acetyl-L-carnitine treatment in geriatric depression: preliminary results. *Bipolar Disord* 2002;4:61–66.
14. Van Oudheusden LJ, Scholte HR. Efficacy of carnitine in the treatment of children with attention-deficit hyperactivity disorder. *Prostaglandins Leukot Essent Fatty Acids* 2002;67:33–38.
15. Mangano NG, Clementi G, Costantino G, et al. Effect of acetyl-L-carnitine on ethanol consumption and alcohol abstinence syndrome in rats. *Drugs Exp Clin Res* 2000;26:7–12.
16. Pozzi G, Conte G, De Risio S. Combined use of trazodone-naltrexone versus clonidine-naltrexone in rapid withdrawal from methadone treatment. A comparative inpatient study. *Drug Alcohol Depend* 2000;59:287–294.
17. Gossop M. The development of a Short Opiate Withdrawal Scale (SOWS). *Addict Behav* 1990;15:487–490.
18. Scott J, Huskisson EC. Graphic representation of pain. *Pain* 1976;2:175–184.
19. De Palo E, Gatti R, Varnier M, et al. Plasma acetyl-carnitine concentrations during and after a muscular exercise test in patients with liver disease. *Eur J Clin Chem Clin Biochem* 1992;30:179–186.
20. Davidoff G, Guarracini M, Roth E, et al. Trazodone hydrochloride in the treatment of dysesthetic pain in traumatic myelopathy: a randomized, double-blind, placebo-controlled study. *Pain* 1987;29:151–161.
21. Goodkin K, Gullion CM, Agras WS. A randomized, double-blind, placebo-controlled trial of trazodone hydrochloride in chronic low back pain syndrome. *J Clin Psychopharmacol* 1990;10:269–278.