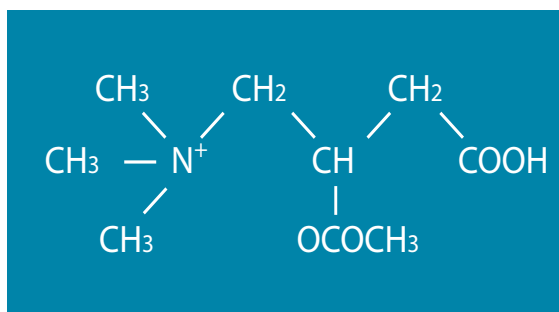


Acetyl-L-Carnitine Monograph

Introduction

Acetyl-L-carnitine (ALC) is an ester of the trimethylated amino acid, L-carnitine, and is synthesized in the human brain, liver, and kidney by the enzyme ALC-transferase. Acetyl-L-carnitine facilitates the uptake of acetyl CoA into the mitochondria during fatty acid oxidation, enhances acetylcholine production, and stimulates protein and membrane phospholipid synthesis. ALC, similar in structure to acetylcholine, also exerts a cholinomimetic effect. Studies have shown ALC may be of benefit in treating Alzheimer's dementia, depression in the elderly, HIV infection, peripheral neuropathies, ischemia and reperfusion of the brain, and cognitive impairment associated with various conditions.¹⁻³



Pharmacokinetics

L-carnitine and acetyl-L-carnitine are administered orally, intravenously (IV), or intramuscularly (IM); they are absorbed in the jejunum by simple diffusion. Transport into cellular tissue is via an active transport mechanism, with studies showing plasma concentrations of ALC and L-carnitine reaching equilibrium via carnitine acetyl-transferase activity. Both IV and oral administration result in a corresponding increase in cerebrospinal fluid (CSF) concentrations of ALC, indicating it readily crosses the blood-brain barrier. In a small study of eight healthy, fasting men, a single 500-mg dose of ALC yielded a maximal plasma concentration (C_{max}) of 1.19 µg/mL at 3.1 hours post-dose.

Half-life of ALC was 4.2 hours with an area under the curve (AUC) of 9.88 µg.h/mL.⁴ L-carnitine and its esters undergo minimal metabolism and are subsequently excreted in the urine via renal tubular reabsorption. The rate of clearance increases with the plasma concentration of these substances.^{5,6}

Mechanisms of Action

Although the exact mechanisms of action of acetyl-L-carnitine are currently unknown, research indicates they may be related to ALC's cholinergic neural transmission activity and its ability to enhance neuronal metabolism in the mitochondria. Purpura et al attribute the cholinergic effects of ALC to the blocking of post-synaptic inhibition potentials,⁷ while others suggest it is due to direct stimulation of the synapses.⁸ As to enhanced cellular energetics in the mitochondria, human studies show ALC has the ability to stabilize cell membrane fluidity via regulation of sphingomyelin levels, and also provides a substrate reservoir for cellular energy production, thereby preventing excessive neuronal cell death. Acetyl-L-carnitine has also been shown to increase hippocampal binding of glucocorticoids and nerve growth factor.⁹ ALC reduces oxidative stress and inhibits excitotoxicity in brain tissue and CSF, thereby preventing cell death and ischemia-induced neuronal damage.^{10,11} The benefits of ALC supplementation observed in HIV patients may be attributed to its role in peripheral nerve regeneration¹² and its ability to reduce blood glutamate levels, thereby reducing the neurotoxicity of nucleoside analog medications.¹³

Clinical Indications

Cognition/Mood Alzheimer's Disease

Several studies demonstrate the effectiveness of ALC in improving cognitive performance in patients suffering from Alzheimer's disease (AD). Studies were usually 3-6 months in length and oral dosages ranged from 1-3 g ALC/day. Results varied,

but in general, improvements were noted in spatial learning tasks, timed tasks of attention, discrimination-learning tasks, and tasks of personal recognition.¹⁴⁻¹⁶ At a dosage of 2 g ALC daily, one study demonstrated a decrease in deterioration of reaction time, in addition to improvement in short-term memory related tasks.¹⁴ Although studies on the long-term effects of ALC administration are few, Spagnoli et al demonstrated 1-2 g daily for one year resulted in a decrease in behavioral deterioration and an improvement in long-term memory performance.² Thal et al demonstrated a 3-gram daily dose of ALC given to patients with early onset AD (average age 58 years, n=83) resulted in slightly less decline on the Mini-Mental State Examination score, specifically the attentional component, than for those receiving placebo (n=84).¹⁷

A meta-analysis of 21 ALC-versus-placebo trials (n=591 patients in the ALC groups, n=613 in the placebo groups) for treatment of mild cognitive impairment or mild AD revealed a significant advantage for those receiving ALC (1.5-2.0 g daily in most trials) compared to those in the placebo groups. Subjects receiving ALC had significantly better scores than subjects receiving placebo for both composite measure of effect size on clinical and psychometric assessment scales and clinicians' assessment of improvement. Significant score improvements were noted in subjects receiving ALC versus placebo as early as three months after supplementation began.¹⁸

Depression

In cases of major depression the circadian rhythm of cortisol secretion appears to be altered, with depressed patients having an increase in total cortisol secretion,¹⁹ probably as a result of increased activation of the hypothalamic-pituitary-adrenocortical (HPA) axis. Animal studies indicate ALC administration may have an inhibitory effect on HPA activity, resulting in a reduction of cortisol levels and thereby an improvement in depressive symptoms. No data is available on ALC's effectiveness in modulating HPA activity in humans.²⁰

In a two-month study of 24 depressed elderly patients, ALC treatment was highly effective, particularly in patients with serious depressive symptoms.²¹ In another study of 28 elderly patients, Garzya et al demonstrated that 500 mg ALC three times daily was effective in counteracting symptoms of depression. Patients in both studies were evaluated using the Hamilton Rating

Scale for Depression, with decreased scores representing a relief of depressive symptomology.²²

Dysthymia, a chronic depressive disorder characterized by considerable social dysfunction and disability, is less severe than major depression. If untreated, the outcome is poor and symptoms may persist for a decade or more.²³ Dysthymia is often treated with amisulpride, an anti-psychotic medication shown to be effective in minimizing symptoms, but with potentially significant side effects for some patients. A randomized, double-blind, multicenter trial compared 500 mg ALC twice daily with 50 mg amisulpride daily for three months in 204 men and women, mean age 50 years (n=105 receiving ALC, n=99 receiving amisulpride). Subjects were assessed at baseline and two, four, eight, and 12 weeks using five different depression or dysthymia rating scales. In terms of symptom improvement, ALC supplementation yielded similar scores to those observed with amisulpride; but ALC had a better tolerability profile, with only 9.5 percent of patients experiencing adverse events, compared to 29.3 percent in the amisulpride group.²⁴ These results indicate ALC has an advantage over amisulpride for the treatment of dysthymia due to its similar clinical efficacy and superior safety profile.

Attention Deficit/Hyperactivity Disorder (ADHD) and Fragile X Syndrome

Fragile X Syndrome (FXS), the most common form of inherited mental retardation, is caused by an X chromosome mutation. Boys with FXS appear normal at birth but become symptomatic as they grow, with approximately 90 percent exhibiting mild-to-severe mental retardation. In comparison, only 30 percent of girls with FXS develop symptoms.²⁵ Among boys with FXS, 73 percent meet criteria for ADHD.²⁶ FXS boys with ADHD typically have issues with hyperactivity, attention span, mood, and socialization skills that are often exacerbated by treatment with the stimulant medications typically used for ADHD.²⁷ As a result, alternative, non-stimulant treatments for FXS boys with ADHD have been investigated. Torrioli et al conducted two double-blind trials of ALC on hyperactivity and attention in FXS boys. In the earlier trial, 20 FXS boys, ages 6-13 years, were given 50 mg/kg ALC or placebo twice daily for one year. Seventeen boys completed the study (8 receiving ALC and 9 receiving placebo) and neuropsychological testing was performed at baseline and one, six, and twelve months. At the

end of one year a significant reduction in hyperactive behavioral scores (-0.325 ± 0.098) was reported in the ALC-treated group compared to the placebo group, for whom the same scores increased (0.244 ± 0.164). No side effects were reported.²⁸

In the second, larger study, 51 FXS males with ADHD, ages 6-13 years, (27 in the placebo group and 24 in the ALC group) received 500 mg ALC or placebo twice daily for one year. Although hyperactivity decreased in the ALC-treated boys, the difference between the treatment and placebo groups did not reach statistical significance, possibly due to missed observation points over the summer months for approximately one-third of the boys. However, the scores for both the Vineland Adaptive Behavior Scales Survey and the Socialization Domain improved significantly at the end of one year for boys in the ALC group compared to the placebo group, whose scores actually declined. ALC treatment was well-tolerated, confirming the safety of 1,000 mg ALC daily for one year in children. The authors conclude ALC treatment is safe and effective at improving both adaptive behavior and socialization skills in this population.²⁹

Peripheral Neuropathy Diabetic Neuropathy

Approximately one-third of diabetic patients are affected by peripheral neuropathy.³⁰ Animal studies demonstrate a link between imbalances in carnitine metabolism and several metabolic and functional abnormalities associated with diabetic polyneuropathy.³¹ Few human studies have investigated the use of oral ALC for diabetic neuropathy, although some have been conducted using an injectable form. These studies indicate ALC administration via injection results in decreased neuropathy-associated pain and better nerve function.^{32,33}

A double-blind, placebo-controlled, clinical trial of 333 patients with diabetic neuropathy found IM injections of 1,000 mg ALC daily for 10 days, followed by 2,000 mg oral ALC daily, resulted in significant decreases in pain scores at 12 months using the visual analog scale (VAS).³⁴ An analysis of two one-year, multi-center, randomized, placebo-controlled trials involving 1,257 type 1 and 2 diabetic patients with neuropathy revealed doses of 500 or 1,000 mg ALC three times daily significantly improved VAS pain scores and vibratory perception. A significant reduction in pain scores was present at 26 weeks after starting treatment, and the

effects were more pronounced in type 2 diabetics whose blood sugars were not well controlled. In addition, patients receiving 500 mg ALC three times daily had significant increases in sural nerve fiber number and nerve regeneration when compared to placebo. Increases in nerve regeneration for the 1000-mg dose group were not statistically significant when compared to placebo.³⁵

Antiretroviral Neuropathy

Patients with human immunodeficiency virus (HIV) being treated with nucleoside analogue therapy drugs stavudine, zalcitabine, or didanosine commonly experience peripheral neuropathy and myopathy as adverse effects of the medication and often must discontinue therapy as a result. Recent studies suggest acetyl-L-carnitine and recombinant human nerve growth factor may be beneficial in managing antiretroviral toxic neuropathy (ATN).^{36,37} In an open label trial of 20 HIV patients with ATN, Osio et al demonstrated 2,000 mg oral ALC daily for one month decreased mean pain intensity scores significantly from 7.35 ± 1.98 at baseline to 5.80 ± 2.63 at week four. Treatment was well tolerated in all patients.³⁸ In a separate open trial, researchers investigated the efficacy of oral ALC (1,500 mg twice daily) over a 33-month period in 21 HIV patients with established ATN (ages 29-60). Five HIV-negative, non-neuropathic controls provided normal skin parameters for comparison. Skin biopsies were taken at baseline and at six- and 12-month intervals for a total of four biopsies per patient. Patients were assessed for nerve regeneration, innervations, and neuropathic pain grade. After six months of treatment with ALC, significant increases in sensory fiber numbers in the dermis and epidermis were reported. Epidermal, dermal, and sweat gland innervations reached 92-, 80-, and 69 percent that of controls after six months treatment and persisted after 24 months of treatment. Neuropathic pain grade also improved in 76 percent of patients.¹²

Only one double-blind, placebo-controlled trial has explored the effects of ALC for treatment of ATN. Ninety patients received either 500 mg IM ALC twice daily (n=43) or placebo (n=47) for 14 days, followed by six weeks of 1,000 mg twice daily oral ALC or placebo. Pain was assessed weekly via VAS, total symptom score (TSS), Clinical Global Impression of Change (CGIC), and McGill Pain Questionnaire (MPQ). Statistically significant improvements in VAS scores were noted for

evaluable patients receiving ALC compared to controls. In addition, patients in the ALC group had a higher rate of improvement in TSS scores than those in the control group, although the improvements did not reach statistical significance. No statistically significant differences were reported between groups for the CGIC or MPQ assessments.³⁹

Chemotherapy-induced Neuropathy

Up to 50 percent of cancer patients given taxane, Vinca alkaloid, or platinum-based chemotherapeutic agents develop chemotherapy-induced peripheral neuropathy (CIPN), particularly when high doses are necessary. Preliminary research in rats shows ALC is effective at preventing CIPN when given prophylactically.⁴⁰ This research prompted two open-label studies of patients with paclitaxel or cisplatin-induced CIPN. In the first study, 25 CIPN patients received 1,000 mg oral ALC three times daily for eight weeks. In 23 of 25 patients, total neuropathy scores improved by at least one grade and symptomatic improvement persisted in 92 percent of evaluable patients 13 months after ALC treatment.⁴¹ In the second study, 26 patients with paclitaxel or cisplatin-induced CIPN received 1,000 mg IV ALC daily for 10-20 days (median=14 days) and were evaluated for improvement in neuropathic pain grade. Symptomatic relief was reported within 14 days and neuropathic pain improved by at least one grade in 19 of 26 patients (73%). The IV treatment was well tolerated with no serious side effects.⁴²

HIV Infection

The main immunological abnormality of HIV-infected patients is decreased CD4 cell counts via lymphocyte apoptosis. In a small study of 11 asymptomatic HIV-infected patients, Di Marzio et al investigated the effects of 3 g ALC daily for five months on CD4 and CD8 cell counts, apoptosis, and insulin-like growth factor1 (IGF-1). ALC substantially decreased lymphocyte apoptosis, possibly due to a reduction in ceramide generation and/or an increase in serum levels of IGF-1, a factor important to apoptosis survival.⁴³

Diabetic Cataracts

Patients with diabetes frequently develop cataracts as a result of the formation of advanced glycation end-products (AGEs). Studies have shown a dramatic depletion of lenticular L-carnitine and acetyl-L-carnitine in experimentally-induced diabetic rats, and numerous studies have since

demonstrated ALC's effectiveness in preventing experimentally-induced cataractogenesis in rats.⁴⁴⁻⁴⁶ In another study, calf lens tissue was incubated with L-carnitine and ALC for 15 days. While L-carnitine had no effect on *in vitro* glycation, acetyl-L-carnitine decreased crystallin glycation by 42 percent.⁴⁷ To date, no human studies using ALC for cataract prevention have been published.

Cerebral Ischemia and Reperfusion

The neuro-regenerative effects of ALC have been studied extensively in experimental animal models of post-ischemic cerebral injury. These studies demonstrate ALC administration improves neurological outcome,⁴⁸ prevents free radical-mediated protein oxidation, normalizes levels of brain energy metabolites,⁴⁹ and decreases lactic acid content during early post-ischemic reperfusion.⁵⁰ Although human studies are not as numerous, Rosadini et al investigated the effects of ALC on regional cerebral blood flow in 10 male patients with brain ischemia and observed beneficial effects in 8 of 10 patients one hour after IV administration of 1,500 mg ALC.⁵¹

Men's Health Infertility

Research demonstrates the efficacy of a combination of L-carnitine (LC) and ALC for increasing sperm motility in infertile men with asthenozoospermia. A double-blind, randomized, placebo-controlled trial involving 56 infertile men (ages 20-40) demonstrated oral administration of 2 g LC and 1g ALC daily (n=30) for six months was effective at increasing sperm motility (both total and forward), compared to subjects receiving placebo (n=26), especially in subgroups with lower baseline levels. Among the 56 infertile subjects, four female partners became pregnant and unblinding revealed that the patients who had initiated a pregnancy were in the treatment group.⁵²

A second trial of 60 infertile men with idiopathic asthenozoospermia (ages 24-38 years) investigated the effects of daily doses of 3 g LC (n=15), 3 g ALC (n=15), 2 g LC/1 g ALC (n=15), or placebo (n=15) for six months. Statistically significant improvements were observed in total and forward sperm motility in subjects treated with ALC (alone or in combination with LC). A greater improvement was observed in subjects receiving the combination therapy, with the most improvement noted in subjects with the lowest baseline levels of sperm

motility. In subjects receiving ALC alone, a statistically significant increase in sperm concentration (6.95 ± 22.06 at baseline to 42.88 ± 50.80) was also found. Subjects in the LC-only group also had a statistically significant reduction in atypical sperm cells at six months compared to baseline; all treatment groups demonstrated a statistically significant improvement in oxyradical scavenging capacity of seminal fluid. Over the course of the study 12 pregnancies were reported in the female partners of study subjects and unblinding revealed nine to be initiated by men in the treatment groups – five from the LC/ALC group and two each from the LC- and ALC-only groups.⁵³

Peyronie's Disease

Peyronie's disease is a condition involving inflammation and curvature of the penis and is classified as acute, early chronic, or chronic. It is characterized by a plaque, or hard lump, that forms on the erection tissue of the penis. The plaque often begins as inflammation that may develop into fibrous tissue.⁵⁴ Many standard medications and treatments are associated with a high rate of side effects. Oral ALC therapy has been investigated as a therapeutic tool, based on its ability to influence mitochondrial energetics and male infertility. In a randomized trial, 48 men (mean age, 53) with acute (n=15) or early chronic (n=33) Peyronie's disease were divided into two groups. One group received 20 mg tamoxifen twice daily for three months while the second received 1 g ALC twice daily for three months. Subjects were assessed at baseline and after therapy for pain, penile curvature, plaque size, and disease progression. ALC therapy significantly reduced pain and penile curvature and inhibited disease progression, while tamoxifen did not. Although both treatments reduced plaque size significantly, the incidence of side effects with tamoxifen therapy was higher than for ALC.⁵⁵

Cardiovascular Applications

Like L-carnitine, ALC enhances fatty acid transport for ATP production in the mitochondria of both skeletal and heart muscle, thereby affording protection from free-radical damage.⁵⁶ Animal studies have also shown ALC administration reverses the age-associated decline in cardiolipin content of heart tissue mitochondria.⁵⁷ Human trials have shown ALC to be effective in ameliorating hypertension, vascular function, and insulin resistance in metabolic syndrome and coronary artery disease. In 36 non-diabetic patients with

insulin resistance and hypertension at increased risk for cardiovascular disease, 1 g ALC twice daily for 24 weeks increased glucose disposal rate (GDR) from 4.89 ± 1.47 mg/kg/minute to 6.72 ± 3.12 mg/kg/minute and improved glucose tolerance in patients with $GDR \leq 7.9$ mg/kg/minute. Among patients with $GDR \leq 7.9$, reductions in systolic blood pressure from 144.0 ± 13.6 to 135.1 ± 8.4 mm Hg were reported; for those with $GDR \geq 7.9$, systolic blood pressure decreased from 130.8 ± 12.4 to 123.8 ± 10.8 mm Hg.⁵⁸

In a double-blind, placebo-controlled, crossover trial of 36 subjects with stable coronary artery disease (ages, 55 or older), 500 mg oral ALC and 200 mg oral alpha-lipoic acid twice daily were evaluated for their effect on vascular function and blood pressure. The trial consisted of two eight-week treatment periods separated by a four-week washout period, after which subjects were crossed over to the other group. Brachial artery diameter and flow velocity, blood pressure, and lipid and blood sugar changes were assessed. The combination treatment increased brachial artery diameter by 2.3 percent and decreased systolic blood pressure by an average of 9 mm Hg, compared to placebo; no significant differences were observed on lipid and blood sugar values.⁵⁹

Alcoholism and Cirrhosis *Ethanol Ingestion*

Animal studies have investigated the effects of LC and ALC on hepatic detoxification of ethanol. Cha and Sachan demonstrated that administration of LC and ALC retards ethanol oxidation, although it requires 100 times the concentration of carnitine to equal the maximal inhibition produced by acetyl-L-carnitine. They concluded ALC is the mediator of carnitine inhibition of ethanol oxidation, which is competitive with NAD⁺.^{60,61} In a 90-day study of 55 chronic alcoholics, ALC administration improved cognitive performance, suggesting ALC may be a useful therapeutic agent for treating cognitive disturbances of chronic alcoholics.⁶²

Hepatic Encephalopathy and Coma

Hepatic encephalopathy (HE) is a common, serious complication in cirrhotic patients, characterized by personality changes, memory reduction, and impaired concentration and reaction times. In a randomized, double-blind, placebo-controlled study of 115 men and women (mean age, 48) with cirrhotic HE, 2 g ALC twice daily (n=60) or placebo (n=55) were administered for 90 days. Subjects

were assessed for changes in blood ammonia levels and improvements in neuropsychological, neurophysiological, and metabolic parameters. ALC significantly reduced ammonia and bilirubin levels and improved short-term memory and neuropsychological function.⁶³

Hepatic coma is the most severe form of HE. In a clinical trial of 24 patients with hepatic coma, 13 subjects received 4 g IV ALC daily (n=13) or placebo (n=11) for three days. ALC reduced serum ammonia and blood urea nitrogen levels and improved neurological parameters. In the ALC group, seven of 13 patients experienced a one-grade improvement in HE classification (from grade 4 to grade 3); no side effects were observed.⁶⁴

Other Clinical Indications

Other clinical trials demonstrate ALC's effectiveness at alleviating pain associated with methadone withdrawal syndrome⁶⁵ and sciatica from herniated discs.⁶⁶ ALC has also been found to be effective for treating multiple sclerosis-related fatigue with fewer side effects than conventional medications such as amantadine.⁶⁷

Side Effects and Toxicity

ALC is considered safe and without incidence of significant side effects, even with long-term (one year) administration. The most common adverse reactions were agitation, nausea, and vomiting.^{2,9}

Dosage

Oral doses of ALC typically range from 1-3 g daily, in divided doses. IV doses are typically 1,500-2,000 mg.

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