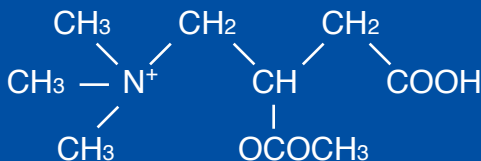


Acetyl-L-Carnitine**Acetyl-L-Carnitine****Introduction**

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 for fatty acid oxidation, enhances acetylcholine production, and stimulates protein and membrane phospholipid synthesis. Similar in structure to acetylcholine, ALC exerts a cholinomimetic effect. Studies have shown ALC may be of benefit in treating Alzheimer's dementia, depression in the elderly, HIV infection, diabetic neuropathies, ischemia and reperfusion of the brain, and cognitive impairment of alcoholism.

Pharmacokinetics

L-carnitine and acetyl-L-carnitine 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 intravenous and oral administration result in a corresponding increase in cerebral spinal fluid concentrations of ALC, indicating it readily crosses the blood-brain barrier. L-carnitine and its esters undergo little metabolism and are subsequently excreted in the urine via renal tubular reabsorption. The rate of clearance increases with the plasma concentration of these substances.^{1,2}

Mechanisms of Action

The exact mechanisms of action of acetyl-L-carnitine are unknown, but current research indicates they may be related to both ALC's cholinergic neural transmission activity and its ability to enhance neuronal metabolism in the mitochondria. Researchers have attributed the cholinergic effects of ALC to blocking of post-synaptic inhibition potentials,³ while others have suggested it is due to direct stimulation of nerve cells.⁴ Human studies have shown ALC has the ability to stabilize cell membrane fluidity via regulation of sphingomyelin levels. ALC can increase ATP levels in humans,⁵ thereby preventing excessive neuronal cell death. Acetyl-L-carnitine has also been shown to increase hippocampal binding of glucocorticoids and nerve growth factor.⁶

Clinical Indications

Alzheimer's Dementia

Several studies have demonstrated the effectiveness of ALC in improving cognitive performance in patients with Alzheimer's dementia. These studies were three to six months in length and oral dosages ranged from 1-3 g ALC per day. Results varied, but generally, improvements were noted in spatial learning tasks, timed tasks of attention, discrimination-learning tasks, and tasks of personal recognition.⁷⁻⁹ 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.⁷ Studies on the long-term effects of ALC administration are few, but Spagnoli et al demonstrated 1-2 g daily for one year resulted in decreased behavioral deterioration and an improvement in long-term memory performance.¹⁰

Depression

In cases of major depression it has been demonstrated that the circadian rhythm of cortisol secretion appears to be altered, with depressed patients having an increase in total cortisol secretion.¹¹ This is probably a result of an increased activation of the hypothalamo-pituitary-adrenocortical (HPA) system. 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.¹² In a two-month study of 24 depressed elderly patients it was demonstrated that ALC treatment was highly effective, particularly in patients with more serious depressive symptoms.¹³ In another study of 28 elderly patients, Garzya et al demonstrated 500 mg ALC three times per day was effective in reducing symptoms of depression. Patients in both studies were evaluated using the Hamilton Rating Scale for Depression.¹⁴

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, researchers investigated the effects of ALC (3 grams daily for five months) on CD4 and CD8 cell counts, apoptosis, and insulin-like growth factor-1 (IGF-1). Results indicated ALC administration 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 decreased apoptosis.¹⁵

Diabetic Neuropathy and Cataracts

Approximately one-third of diabetic patients are affected by peripheral neuropathy.¹⁶ Animal studies have demonstrated a link between imbalances in carnitine metabolism and several metabolic and functional abnormalities associated with diabetic polyneuropathy,¹⁷ although currently no human studies of oral ALC and its effects on diabetic neuropathy are available. Human studies using an injectable form of the supplement resulted in decreased neuropathy-associated pain and improved nerve function.^{18,19} Patients with diabetes mellitus frequently develop cataracts as a result of the formation of advanced glycation end-products. Studies have shown a dramatic depletion of lenticular L-carnitine and acetyl-L-carnitine in experimentally-induced diabetic rats. An *in vitro* study of the effect of ALC and L-carnitine on calf lens tissue incubated with both of these substances for 15 days found L-carnitine had no effect on glycation, whereas acetyl-L-carnitine decreased crystallin glycation by 42 percent.²⁰

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,²¹ prevents free radical-mediated protein oxidation, normalizes levels of brain energy metabolites,²² and decreases lactic acid content during early post-ischemic reperfusion.²³ 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 intravenous administration of 1,500 mg ALC.²⁴

Cardiovascular Applications

Like L-carnitine, acetyl-L-carnitine enhances fatty acid transport for ATP production in the mitochondria of both skeletal and heart muscle, thereby affording protection from free-radical damage.²⁵ Animal studies have also shown ALC administration reverses the age-associated decline in cardiolipin content of heart tissue mitochondria.²⁶

Ethanol Ingestion

Animal studies have investigated the effects of both carnitine and ALC on hepatic detoxification of ethanol. Cha and Sachan demonstrated that administration of carnitine and ALC retarded ethanol oxidation, but that it required 100 times the concentration of carnitine to equal the maximal inhibition produced by acetyl-L-carnitine. They concluded acetyl-L-carnitine is the mediator of carnitine inhibition of ethanol oxidation and the inhibition is of a competitive nature with NAD⁺.^{27,28} In a 90-day study of 55 chronic alcoholics, ALC administration improved cognitive performance, suggesting acetyl-L-carnitine may be a useful therapeutic agent for treating cognitive disturbances in these individuals.²⁹

Peyronie's Disease

An open trial compared ALC (1 g twice daily) with tamoxifen (20 mg twice daily) in the treatment of Peyronie's disease, a condition of unknown cause in which fibrosis of the cavernous sheaths of the penis leads to contracture, abnormal curvature, and painful erections. After three months, ALC was significantly more effective than tamoxifen in reducing penile curvature and pain, and inhibiting progression of the disease.³⁰

Side Effects and Toxicity

ALC is considered safe at therapeutic dosages and without incidence of significant side effects, even with long-term (one year) administration. The most common adverse reactions noted have been agitation, nausea, and vomiting.^{7,10}

Dosage

Acetyl-L-carnitine is usually given orally in dosages ranging from 1-3 grams daily. When administered intravenously the dosage is usually 1,500-2,000 mg.

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