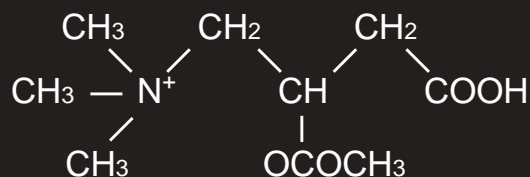


# Monograph



## 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 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 that 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.<sup>1-3</sup>

### Pharmacokinetics

L-carnitine and acetyl-L-carnitine are administered orally or intravenously and are then 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 an equilibrium via carnitine acetyl-transferase activity. Both IV and oral administration result in a corresponding increase in CSF 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.<sup>4</sup>

### 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. Purpura et al have attributed the cholinergic effects of ALC to the blocking of post-synaptic inhibition potentials,<sup>6</sup> while others have suggested it is due to direct stimulation of the synapses.<sup>7</sup> As to enhanced cellular energetics in the mitochondria, human studies have shown 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 of nerve growth factor.<sup>8</sup>

### Clinical Indications

#### Alzheimer's Dementia

Several studies have demonstrated the effectiveness of ALC in improving cognitive performance in patients suffering from Alzheimer's dementia. These studies were usually 3-6 months in length and oral dosages ranged from 1-3 g ALC/day. Results varied, but generally speaking, improvements were noted in spacial learning tasks, timed tasks of attention, discrimination-learning tasks, and tasks of personal recognition.<sup>9-11</sup> 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.<sup>9</sup> Studies

on the long-term effects of ALC administration are few, but Spagnoli et al demonstrated that 1-2 g daily for one year resulted in a decrease in behavioral deterioration, and an improvement in long-term memory performance.<sup>2</sup>

### **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.<sup>12</sup> This is probably a result of an increased activation of the hypothalamo-pituitary-adrenocortical (HPA) system. Animal studies have indicated 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.<sup>13</sup> 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.<sup>14</sup> In another study of 28 elderly patients, Garzya et al demonstrated that 500 mg ALC three times per day 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.<sup>15</sup>

### **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 ALC on CD4 and CD8 cell counts, apoptosis, and insulin-like growth factor-1 (IGF-1). The dosage was 3 grams daily for a period of five months. 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 apoptosis survival.<sup>16</sup> In addition, HIV-infected patients on nucleoside analogue therapy commonly experience peripheral neuropathy as an adverse effect of the medications. Patients taking stavudine, zalcitabine, or didanosine may have to discontinue therapy as a result. Recent studies have suggested acetyl-L-carnitine as well as recombinant human nerve growth factor may be beneficial in managing this condition.<sup>17</sup>

### **Diabetic Neuropathy/Cataracts**

Approximately one-third of diabetic patients are affected by peripheral neuropathy.<sup>18</sup> Animal studies have demonstrated a link between imbalances in carnitine metabolism and several metabolic and functional abnormalities associated with diabetic polyneuropathy.<sup>19</sup> Currently no human studies of oral ALC and its effects on diabetic neuropathy are available. The human studies that have been done used an injectable form of the supplement. These studies indicated ALC administration via injection resulted in decreased neuropathy-associated pain and better nerve function.<sup>20-21</sup> Patients with diabetes mellitus also frequently develop cataracts as a result of the formation of advanced glycation end-products (AGE). Studies have shown a dramatic depletion of lenticular L-carnitine and acetyl-L-carnitine in experimentally-induced diabetic rats. In another study, calf lens tissue was incubated with both L-carnitine and ALC for 15 days. The results showed that while L-carnitine had no effect on *in vitro* glycation, acetyl-L-carnitine decreased crystallin glycation by 42 percent.<sup>22</sup>

### **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 demonstrated ALC administration improved

neurological outcome,<sup>23</sup> prevented free radical-mediated protein oxidation, normalized levels of brain energy metabolites,<sup>24</sup> and decreased lactic acid content during early post-ischemic reperfusion.<sup>25</sup> Human studies are not as numerous, but 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 1500 mg ALC.<sup>26</sup>

### 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.<sup>27</sup> Animal studies have also shown that ALC administration reverses the age-associated decline in cardiolipin content of heart tissue mitochondria.<sup>28</sup>

### 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 that acetyl-L-carnitine is the mediator of carnitine inhibition of ethanol oxidation and the inhibition is of a competitive nature with NAD<sup>+</sup>.<sup>29-30</sup> In a 90-day study of 55 chronic alcoholics, ALC administration improved cognitive performance in chronic alcoholics, suggesting acetyl-L-carnitine may be a useful therapeutic agent for treating cognitive disturbances of chronic alcoholics.<sup>31</sup>

### Dosage/Toxicity

Acetyl-L-carnitine is usually given orally in tablet or capsule form with dosage ranging from 1-3 grams daily, in divided doses. If administered intravenously, the dosage is usually 1500-2000 mg. ALC is considered safe at these 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.<sup>2,9</sup>

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