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L-Carnitine and its Role in Medicine: A Current Consideration of its Pharmacokinetics, its Role in Fatty Acid Metabolism and its Use in Ischaemic Cardiac Disease and Primary and Secondary L-Carnitine Deficiencies

by

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The physiological role of L-carnitine (1-9)

L-Carnitine (L-β-hydroxy-4-N-trimethylaminobutyric acid) is an essential nutrient in animals and humans, which is synthesised endogenously, mainly in liver and kidney, or obtained from diet, with principal sources red meat in adults and human milk in infants.

L-Carnitine is a cofactor of several enzymes, including carnitine-acylcarnitine translocase embedded in the inner mitochondria membrane, and two acylcarnitine (palmimitoyl) transferases I and II, located respectively in the outer and inner mitochondrial membrane; these biomolecules are required in mammalian tissues to transfer long-chain acyl CoAs across the inner membrane for β-oxidation in the matrix. Furthermore, intramitochondrial L-carnitine and the matrix enzyme L-carnitine acetyltransferase can react with short- and medium-chain acyl CoAs to produce acylcarnitines, which can be shuttled out of mitochondria. Through this mechanism, L-carnitine is able to modulate the intracellular concentrations of free CoA and acetyl CoA via reversible formation of acetylcarnitine. Therefore, besides shuttling long-chain fatty acids into mitochondria, L-carnitine facilitates the oxidation of pyruvate and branched-chain ketoacids and, by preventing their accumulation, it contributes to the protection of cells from the potentially membrane-destabilising acyl CoAs. In the absence of L-carnitine, the accumulation of free fatty acids in the cytoplasm produces a toxic effect on the cell, and an energy deficit arises from the unavailability of fatty acids within the mitochondria.

Pharmacokinetics of L-carnitine (10-14)

L-Carnitine is present in tissues and biological fluids in free and esterified forms. In humans, acylcarnitine esters account for about 25% of total L-carnitine in serum and for about 15% of total

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L-carnitine in liver and skeletal muscle. Total L-carnitine concentration in human tissues is higher in the heart and skeletal muscle (3.5-6.0 and 2.0-4.6 μmol/g, respectively) than in the liver and the brain (1.0-1.9 and 0.5-1.0 μmol/g, respectively): these values reflect the higher rates of fatty acid oxidative metabolism in the former tissues.

Clinical Pharmacokinetics of L-carnitine (15-20)

The pharmacokinetics of exogenously administered L-carnitine have not been completely described. In the case of L-carnitine preparations from *Sigma Tau Pharmaceuticals,* peak plasma concentrations of free L-carnitine of 25 and 91 μmol/l have been attained 3 and 3,5 hours following single oral 30 and 100 mg/kg doses, respectively. L-Carnitine is actively transported into tissues via a saturable system, although passive diffusion also occurs. The apparent volume of distribution is about 37 l. The compound is likely metabolised in humans by partial conversion to acyl-carnitine esters and therefore is eliminated through the kidneys. The portion of a dose of L-carnitine excreted in the urine within 24 hours depends on the route of administration; thus, after an intravenous dose 86% has been recovered, in contrast to 7% of a dose recovered within 24 hours after an oral dose. Faecal elimination accounts for less than 2% of a dose. In healthy volunteers, the biological half-life of L-carnitine varies from 3 to 12 hours, depending the dosage schedule.

Use of L-carnitine in patients with ischaemic cardiac disease (21-51)

Over the past decade many clinical trials have suggested that L-carnitine may be administered to patients with ischaemic cardiac disease. The rationale for the use of L-carnitine in such patients initially originated from the findings that myocardial L-carnitine concentrations are lower in patients with fatal myocardial infarction, due to an increased lactate production and decreased energy output of cardiac muscle, than in those dying from non-cardiac causes. L-Carnitine has been shown to improve pyruvate metabolism, to reduce lactate production and acidosis and to act as a scavenger of toxic catabolic products of free fatty acids, which accumulate in the heart during ischaemia. Also, there is evidence for skeletal muscle L-carnitine deficiency in some patients with atherosclerotic vascular disease; therefore, L-carnitine supplementation may have potential to improve skeletal muscle metabolic and mechanical function. This double effect in cardiac and skeletal muscle makes L-carnitine attractive for patients with ischaemic heart disease; L-carnitine seems to play an important metabolic role, not only by enhancing carbohydrate utilisation, but also by reducing FFA toxicity and acting as a metabolic modulator in the hart. The available clinical trials include more than 2,000 patients where L-carnitine was administered either intravenously or orally for up to 1 year and show some consistent findings: decrease in signals of ischaemia, such as ST segment depression during stress testing, improved clinical status, such as reduced frequency of anginal attacks, greater exercise tolerance and reduction in consumption of cardiac drugs (p.ex. nitroglycerin). Since L-carnitine does not have haemodynamic effects, its anti-ischaemic action may be additive to the anti-ischaemic action resulting from drugs with haemodynamic effects, such as nitrates, β-blockers and calcium antagonists.

In patients with moderately impaired left ventricular function, the intravenously administration of L-carnitine (40 mg/kg) exerts a positive inotropic effect, since there is evidence that L-carnitine supplementation decreases the left ventricular diastolic pressure and the pre-ejection period/left ventricular ejection time ratio. These results were confirmed in patients treated with L-carnitine 2 g intravenously daily for 10 days.

The results of some interesting clinical trials suggest that L-carnitine exerts a benefit action in patients with acute myocardial infarction or arrhythmias.

Effects of L-carnitine in primary deficiency (51-63)

L-Carnitine concentrations are below normal in the skeletal muscle (but not in plasma, liver or

heart) of patients with myopathic L-carnitine deficiencies (MCD) and in the plasma, liver, muscle and heart of those with the systemic form (SCD). These primary L-carnitine deficiencies are possibly due to impaired transport or biosynthesis of L-carnitine. In patients with the less debilitating MCD, there has been objective and subjective evidence of improved muscle strength within 1 week after oral L-carnitine administration of 2-6 g L-carnitine daily. Several cases of SCD have been treated with oral L-carnitine (up to 4 g per day): under treatment the metabolic attacks disappeared, muscle strength improved, and L-carnitine content increased in the tissues of some of the patients reported.

L-Carnitine in secondary deficiencies (64-100)

In organic acidurias and in defects of β-oxidation (secondary L-carnitine deficiencies), L-carnitine supplementation was shown to have positive metabolic effects, probably because exogenously administered L-carnitine was able to buffer the excess of acyl CoAs, which accumulates in mitochondria as a consequence of specific metabolic blocks.

A L-carnitine deficiency exists in the skeletal muscle and myocardium of patients undergoing chronic intermittent haemodialysis, showing that dialysis produces plasma L-carnitine losses that are not compensated for by its endogenous synthesis. In these patients total plasma L-carnitine concentrations are usually normal or elevated, free L-carnitine concentrations are significantly decreased, and L-carnitine esters or acylcarnitine concentrations are markedly elevated. The oral and parenteral administration of L-carnitine to dialysis patients increases plasma concentrations of both free L-carnitine and acylcarnitine and can decrease the elevated plasma concentrations of triglycerides and total cholesterol. A few blind and non-blind clinical trials in small numbers of patients with symptoms of the post-dialysis syndrome suggest that intravenous L-carnitine administration appears to be associated with a decrease in dialytic symptoms, an improvement in exercise capacity, sense of well-being and certain serum chemistries and possibly an increase in muscle mass. The recommended dosage schedule is 20 mg/kg L-carnitine administered intravenously at the end of each dialysis treatment.

In newborn infants receiving total parenteral nutrition, the addition of L-carnitine increases plasma concentrations of total and free L-carnitine, which are lower than in infants fed by enteral methods; L-carnitine supplementation seems to result in better metabolism of intravenously administered fat emulsion, especially in premature infants.

In patients who had received anthracycline in cumulative doses of less than 500 mg/m^2, the orally or intravenously administered L-carnitine may decrease the severity of cardiotoxicity associated with doxorubicin administration.

Side effects of L-carnitine

L-Carnitine, with LD50 values approximately equivalent to amino acids, is very well tolerated. At doses of up to 15 g/day few side effects have occurred, including infrequent dose-related diarrhoea, gastralgia and nausea. A symptom similar to *myasthenia gravis* has been reported in patients undergoing haemodialysis who were treated only with racemic carnitine.

Dosage

The recommended dose of L-carnitine in adults with primary or secondary L-carnitine deficiencies or ischaemic cardiomyopathies is 1 g given orally or parenterally 1 to 3 times per day. In patients with myocardial infarction and acute myocardial insufficiency, the suggested starting dose is 3 to 6 g/day given parentarally. In children with primary deficiencies, the usual dose is 50 to 100 mg/kg/day administered orally in 2 to 3 divided doses to a maximum of 3 g/day

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