

ARCHIVES OF DISEASE IN CHILDHOOD

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Annotation

L-Carnitine

L-Carnitine (β -hydroxy- γ -trimethylaminobutyric acid) is a small water soluble molecule important in mammalian metabolism; it is essential for the normal oxidation of fats by the mitochondria and is involved in the transesterification and excretion of acyl-CoA esters, the oxidation of branched chain α -ketoacids, and removal of potentially toxic acylcarnitine esters from within mitochondria. L-Carnitine is found in both plasma and tissue as free carnitine or bound to fatty acids as acylcarnitine derivatives. Quantitative reductions in total and/or acylcarnitine concentrations and changes in the concentration of different acylcarnitine species are known to occur in a number of inherited and acquired disorders. The measurement of free and acylcarnitine is now a standard method for the investigation of children with certain inherited metabolic disorders of intermediary metabolism. More recently the identification of abnormal acylcarnitines by tandem mass spectrometry is being used for the purposes of newborn screening. Treatment with exogenous L-carnitine has been advocated for a number of inherited and acquired disorders. It is the purpose of this article to review conditions affecting infants and children that involve L-carnitine metabolism and to discuss the efficacy of L-carnitine in their treatment.

Primary disorders

L-Carnitine can be synthesised in the liver from methionine and protein bound lysine but the majority of the requirement for L-carnitine is supplied by the diet, particularly from red meat and dairy products.^{1,2} To date no inherited disorders of carnitine synthesis have been described, although there is evidence that in newborn babies, particularly those born prematurely, synthetic pathways are immature. Plasma and tissue concentrations of L-carnitine are low in newborn infants compared with older children,^{3,4} possibly related to a lower renal threshold combined with reduced synthesis.⁵⁻⁷ Both human milk and whey based formula feeds contain L-carnitine but soya preparations and parenteral nutrition solutions usually do not.⁸⁻¹⁴ Consequently sick preterm infants requiring long term treatment with intravenous feeding or those being

given soya preparations may be at risk of L-carnitine deficiency. Reduced concentrations of ketone bodies have been reported in preterm infants suggesting that lipolysis and/or ketogenesis may be limited, although this may be due to causes other than carnitine deficiency.^{8,9,15,16} In theory any reduction in the ability of infants to oxidise fats could have a deleterious effect upon energy dependent processes with an increased risk of hypothermia, hypoglycaemia, respiratory distress, infection, and delayed growth.

Primary genetic disorders of L-carnitine metabolism are due to inherited enzyme deficiencies involved either in the transfer of L-carnitine across cellular membranes or of long chain fats into mitochondria. All of these are rare and show autosomal recessive inheritance. They include a defect of L-carnitine uptake across plasma membranes (carnitine transport defect), and three disorders affecting the transfer of long chain fatty acids from the cytoplasm into mitochondria namely carnitine palmitoyltransferase (CPT) I deficiency, CPT II deficiency, and carnitine/acylcarnitine translocase. The clinical presentation of these disorders is varied and includes non-ketotic hypoglycaemia, encephalopathy, myopathy with myoglobinuria, or cardiomyopathy.¹⁷⁻²⁸

Secondary disorders

A number of genetic conditions affecting intermediary metabolism result in a reduction in total plasma concentrations and/or an increase in the acyl:free L-carnitine ratio. In the organic acidaemias such as propionic acidaemia and methylmalonic acidaemia there is an accumulation within the mitochondria of short chain acyl-CoA derivatives.^{29,30} L-Carnitine facilitates their removal into the cytoplasm and also their excretion by the kidneys as acylcarnitine derivatives. The loss of acylcarnitine by the kidneys is, at least in part, responsible for the reduction in total L-carnitine that is commonly seen in the organic acidaemias.^{31,32} Inherited fatty acid oxidation disorders due to enzyme deficiencies involved in mitochondrial β -oxidation, also cause a similar disturbance in L-carnitine concentration.^{33,34} Medium chain acyl-CoA dehydrogenase (MCAD) deficiency is the most common of these with an incidence in the white

population of between one in 9000 to one in 15 000.³⁵⁻³⁷ Patients with this disorder usually first become ill after 9 months of age with profound hypoketotic hypoglycaemia often with a Reye-like illness, although presentation in newborn infants and asymptomatic adults is described.³⁸⁻⁴² Although in organic acidaemias and fatty acid oxidation disorders plasma carnitine concentrations are often reduced, with an abnormal acyl:free ratio, a normal L-carnitine profile using standard assays does not exclude these defects. More sensitive methods using tandem mass spectrometry, which quantifies different acylcarnitines, demonstrate persistent abnormalities even when patients are well.⁴³ Genetic disorders, such as cystinosis or Lowe's syndrome, which cause a renal tubular Fanconi's syndrome, result in increased urinary loss of L-carnitine and subsequent reduction in total plasma concentrations.⁴⁴⁻⁴⁵ L-Carnitine deficiency has also been reported in other inborn errors of metabolism including mitochondrial myopathies, and disorders of the urea cycle.⁴⁶⁻⁴⁷ In addition a number of non-genetic conditions have been implemented as a cause of reduced plasma L-carnitine including AIDS, chronic haemodialysis, chronic fatigue syndrome, and treatment with sodium valproate or antibiotics that contain pivalic acid (pivampicillin and pivmecillinam).⁴⁸⁻⁵⁷

Therapeutic role of L-carnitine

Carnitine treatment has been advocated in a large number of inherited and acquired disorders, both to restore low concentrations in conditions associated with deficiency states, but also as a means of removal of toxic metabolites even when plasma and tissue carnitine concentrations are normal. Both oral and intravenous preparations are available. However despite the widespread use of L-carnitine the rarity of most of the individual disorders for which it is used has meant that reports of its efficacy has been largely anecdotal and there have been few controlled studies. Fortunately adverse effects from L-carnitine treatment are infrequent and not severe. Large oral doses may cause diarrhoea and an unpleasant fishy smell but these are usually stopped by a reduction in dose.

PRIMARY DISORDERS OF L-CARNITINE METABOLISM

The necessity for L-carnitine supplements in preterm infants has not been proved. In some studies of newborn infants fat oxidation or ketogenesis has been shown to be enhanced by additional L-carnitine,⁹⁻¹⁶⁻⁵⁸⁻⁶¹ but a beneficial effect has not been demonstrated in others.⁶²⁻⁶⁴ A large double blind placebo controlled trial failed to show any beneficial effect on growth or morbidity in premature infants from birth to 3 months,⁶⁵ and this suggests that the effects of L-carnitine supplementation on fat oxidation may not be of any significant clinical benefit. Premature infants who are particularly at risk from L-carnitine deficiency, such as those on long term parenteral nutrition,⁹⁻¹⁶⁻⁵⁸⁻⁵⁹⁻⁶⁶ should probably be given supplements but there is little evidence to support this in other infants.¹¹⁻⁶⁵

Treatment of carnitine transport defect with oral L-carnitine (100 mg/kg/day) is dramatic; it results in resolution of cardiomyopathy and prevents further episodes of hypoketotic hypoglycaemia.²⁴⁻²⁶⁻²⁸⁻⁶⁷⁻⁶⁸ Although the plasma concentration of L-carnitine can be brought within the normal range, muscle levels remain less than 5% of control values despite treatment, but this appears to be sufficient for normal fat oxidation within muscle. As there is continued loss of L-carnitine in the urine, treatment needs to be continued indefinitely.

L-Carnitine has also been used in the treatment of carnitine-acylcarnitine translocase deficiency and CPT II deficiency. In the former the outcome for the small number of patients described has been poor with the majority dying

within infancy.²⁰ Treatment with L-carnitine and medium chain triglycerides in these children does not appear to have significantly altered the course of their disease. However one child with carnitine-acylcarnitine translocase deficiency, who presented with neonatal hypoglycaemia and subsequently developed severe hypotonia, cardiomyopathy, and hepatomegaly, had shown considerable improvement by 10 months after treatment with a low fat diet, propranolol, and L-carnitine.⁶⁹

SECONDARY DISORDERS

In disorders of fatty acid β -oxidation and organic acid metabolism the use of L-carnitine treatment is based on its ability to remove toxic acyl-CoA intermediates from within the mitochondria. The efficacy of giving L-carnitine in fat oxidation disorders has been questioned,⁷⁰⁻⁷¹ and there are concerns that it might increase the uptake of long chain fatty acids into the mitochondria, place an additional load on the β -oxidation pathway, and lead to an increase rather than a decrease in acyl-CoA intermediates. However an increase in fatty acid oxidation after intravenous L-carnitine was not shown in one patient with MCAD deficiency,⁷² and there are advocates for its use in this condition and in other disorders of fatty acid oxidation, particularly if plasma L-carnitine concentrations are very low.⁷³⁻⁷⁵ In our experience patients with MCAD deficiency remain well without specific treatment provided fasting stress can be avoided. In view of the possible detrimental effects we do not, at present, use L-carnitine in fatty acid β -oxidation disorders but there is little clinical data to either support or refute its use in these conditions.

In organic acidaemias the theoretical basis for treatment with L-carnitine is less controversial and an increase in the urine excretion of fatty acyl-CoA esters has been demonstrated.³¹⁻⁷⁶⁻⁷⁸ Clinical benefit has been claimed after treatment in a number of organic acidaemias including propionic acidaemia,⁷⁸⁻⁷⁹ methylmalonic acidaemia,⁸⁰ isovaleric acidaemia,⁸¹⁻⁸⁴ and glutaryl-CoA dehydrogenase deficiency.⁸⁵ There are, however, no large scale studies to confirm significant clinical benefit. Despite the lack of strong evidence to support the efficacy of treatment most units give oral L-carnitine as a regular medication for children with organic acidaemias and intravenous L-carnitine during periods of metabolic decompensation. Although not widely used, L-carnitine has also been advocated in disorders of the urea cycle where it may protect the brain from some of the toxic effects of hyperammonaemia.⁴⁶⁻⁸⁶⁻⁸⁷

There are a number of reports of L-carnitine deficiency in patients on treatment with sodium valproate,⁸⁸⁻⁸⁹ some of which detail disturbances in mitochondrial β -oxidation.⁹⁰⁻⁹² The clinical significance of such abnormalities is not clear. One child taking sodium valproate who developed a cardiomyopathy, improved after L-carnitine treatment but may have had a primary deficiency of L-carnitine metabolism. L-Carnitine given with sodium valproate did not prevent the development of fatal liver disease in another child,⁹³ and a double blind crossover study of children on either sodium valproate or carbamazepine failed to show any benefit in terms of patients wellbeing compared with placebo.⁹⁴

Significant loss of L-carnitine occurs during haemodialysis and L-carnitine deficiency has been suggested as a cause, or at least a contributory factor, in the hyperlipidaemia and muscle weakness associated with chronic haemodialysis. Although total L-carnitine concentrations in plasma may be normal, low free carnitine and raised acylcarnitine have been reported.⁹⁵ Infusions of L-carnitine after dialysis failed to have any significant effect upon blood lipid profiles in a multicentre, double blinded, placebo controlled trial.⁹⁵ However the same study found a

reduction in muscle cramps and hypotension during dialysis, an improvement in exercise capacity, reduction in serum urea nitrogen, creatinine, and phosphorous, and sense of wellbeing in the L-carnitine treated patients. A beneficial effect upon muscle function was also found in another placebo controlled trial⁹⁶ but not in two others.⁹⁷⁻⁹⁸

Conclusions

The measurement of plasma and occasionally tissue L-carnitine should be considered in children with hypoketotic hypoglycaemia, cardiomyopathy, or skeletal myopathy where very low concentrations are indicative of carnitine transport defect. Low concentrations of L-carnitine may also be associated with a number of other disorders. Apart from carnitine transport defect the case for treatment with L-carnitine is not clearly established, although there are good theoretical reasons for using L-carnitine in patients with organic acidaemias. Placebo controlled trials are necessary to confirm whether there is a real clinical benefit in these and in other disorders but, as many are individually rare, such studies will be difficult to undertake unless they involve a number of centres. Some clinicians are already convinced of the efficacy of treatment with L-carnitine and may find such studies unethical but others remain more sceptical.⁹⁹ Without properly conducted trials treatment with L-carnitine will not be based on robust evidence.

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