Carnipure™ *Focus*

Infants

Lonza

Introduction

All parents want their children to reach their full potential, both mentally and physically. The right nutrition plays an important role in this process. That is why breast milk is always considered to be the best form of nutrition for a baby. Infant formulas are intended to serve as a substitute for breast milk in infants who cannot be fed at the breast, or should not receive breast milk due to allergies, or for whom breast milk is not available. The inclusion of functional ingredients to pediatric milk formulas nowadays is the matter of many research studies that aim at a formula composition very close to the "gold standard". Technological advances have made it possible to guarantee the highest quality of ingredients, and both animal and human studies provide a solid scientific basis regarding efficacy, bioavailability and recommended dosages.

What is Carnipure™?

Carnipure™ is a special grade of L-Carnitine, manufactured by the Swiss life sciences company Lonza. Thanks to a unique production process based on fermentation, Lonza is the only L-Carnitine manufacturer capable of producing L-Carnitine in the same way as nature. Products carrying the Carnipure™ quality seal on the packaging show the consumer that they contain pure Lonza L-Carnitine.

Carnipure™ offers purest L-Carnitine and is a trademark of Lonza Ltd, Switzerland.

What is L-Carnitine?

Over the past years increased attention has been paid to the significance of L-Carnitine in the infant's diet. It is well-known that L-Carnitine from Carnipure™ plays an essential role in the transfer of long-chain fatty acids across the inner mitochondrial membrane and ultimate energy generation, in the detoxification of acyl-moieties, and in maintaining normal levels of free coenzyme A[1].

Although L-Carnitine can be synthesized in liver and kidneys, adults obtain the majority of L-Carnitine from the diet[2]. Foods of animal origin are good sources of L-Carnitine, especially red meat, whereas foods of plant origin are relatively poor in this nutrient[3]. Since newborns have both a reduced capacity to synthesize L-Carnitine and limited dietary sources of this important nutrient, it is worthwhile looking at their supply of L-Carnitine in more detail.

L-Carnitine synthesis in the infant

L-Carnitine synthesis in the newborn is less efficient than in the adult and appears to be insufficient to meet the requirements of infants. Therefore, L-Carnitine is regarded as a conditionally essential nutrient for infants[4–6]. L-Carnitine is synthesised in the liver and kidneys from the essential amino acids lysine and methionine. The activity of gamma-butyrobetaine hydroxylase, the final enzyme in the L-Carnitine biosynthetic pathway, has been suggested to be age-dependent[7–9]: hepatic activity of gamma-butyrobetaine hydroxylase in infants was reported to be only 12% of that found in adults. By 2.5 years the activity rises to 30% and by 15 years is within the standard deviation of the adult mean[10].

In tissues and body fluids, L-Carnitine is present in free and esterified forms. The sum of free L-Carnitine (FC) and acyl-L-Carnitine (AC) equals total L-Carnitine (TC). The fraction of esterified L-Carnitine varies depending on the tissue and on the metabolic state.

Reduction of FC and accumulation of AC is a common feature of inborn errors of metabolism affecting fatty acid oxidation and other mitochondrial disorders. Knowledge of L-Carnitine metabolism in neonates is essential if these diseases are to be recognized and treated[11].

Adequate blood and tissue concentrations of L-Carnitine may be important in enhancing utilization of fat and energy, and in promoting growth in neonates[12]. The elevated L-Carnitine level of breast milk seems to be a factor which enhances the metabolic adaptation of the newborn to the utilization of fatty acids[13].

Dietary soures of L-Carnitine for the infant

The American Academy of Pediatrics is committed to the use of maternal breast milk as the ideal source of nutrition for infant feeding[14]. Mother's milk represents the only natural source of L-Carnitine for the newborn infants unless meat is introduced into the infant's diet[15]. In the first postpartum weeks, L-Carnitine concentration in mother's milk is highest (80-100 nmol/mL) and thereafter settles at around 60 nmol/mL[16, 17]. Since L-Carnitine content is higher in breast milk than in maternal plasma after birth, active secretion by the mammary gland has been suggested[18].

A study relating breast milk L-Carnitine concentrations to dietary habits of the mothers reported that the L-Carnitine content of milk of lacto-ovo-vegetarian mothers was lower than that of omnivorous mothers at any time throughout the study[19]. L-Carnitine deficiency as a consequence of a vegetarian diet in infancy has been described by various scientists[20–24].

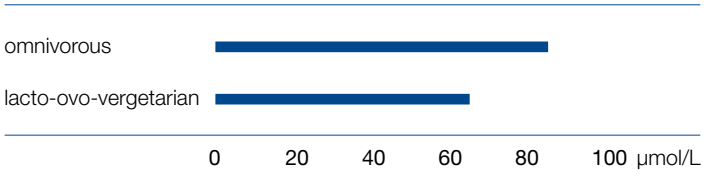

Figure 1: Average total L-Carnitine concentrations in milk of omnivorous or lacto-ovo-vegetarian mothers during lactation[19].

Data on the composition of human milk of healthy, well-nourished women can provide some guidance for the composition of infant formulas[25–27]. Most cow milk formulas have a similar or even higher L-Carnitine concentration than human milk. Nevertheless, L-Carnitine blood concentrations in breast-fed newborns have been reported to be higher than those in formula-fed infants[28]. This has led to the speculation that the bioavailability of L-Carnitine is better in mother's milk[18].

Unsupplemented soy-based infant formulas were reported to contain less than 2 nmol L-Carnitine/mL[4]. Several studies have been performed that examined the effects of unsupplemented, soy-based versus L-Carnitine supplemented formulas on growth and metabolic parameters of term infants[29]. Plasma L-Carnitine concentrations in unsupplemented infants were found to be markedly lower than in L-Carnitine supplemented infants and in infants fed human milk or cow's milk based formulas. It is a positive development now that infant formula contains L-Carnitine at a level similar to that of human milk[30].

Energy sources in infancy

Birth represents a sudden increase in energy requirements which represents a major metabolic challenge for the neonate. In addition to ongoing needs for growth and differentiation, there are new requirements to generate metabolic energy for breathing, movement and maintenance of body temperature[31]. After the sudden interruption of glucose supply through the placenta to the fetus, the newborn is increasingly dependent on endogenous fat sources[18]. The newborn infant rapidly develops the capacity to oxidise fatty acids and ketone bodies as fuels alternative to glucose. Fatty acids derived both from the diet and endogenous fat stores become the preferred fuel of heart and other tissues with high energy demands during the breast-feeding period.

Lipid metabolism

Gradual increase of L-Carnitine in plasma, tissue and urine after birth is a normal response of breast-fed infants and those receiving L-Carnitine containing formulas[32]. Marked reduction of L-Carnitine levels was noted in infants given diets not containing L-Carnitine[33]. There's also a postnatal increase of L-Carnitine concentration in newborn white adipose tissue which coincides with the onset of L-Carnitine containing oral feedings[18, 34].

Data from studies in healthy full-term infants given soy-based formulas with and without added L-Carnitine suggested differences in lipid metabolism. The supplemented group had higher serum L-Carnitine, lower plasma concentrations of triglycerides, VLDL lipoproteins and free fatty acids and a lower excretion of medium-chain dicarboxylic acids as compared with the non-supplemented group, suggesting that the exogenously supplied L-Carnitine plays an active role in increasing utilization of lipids[32, 35]. The increased levels of fatty acids in tissues and plasma might be explained by under-utilization of fat as an energy substrate because of inhibition of mitochondrial beta-oxidation of long-chain fatty acids. For the same reason there might be increased metabolism of fat by the Carnitine-independent microsomal omega-oxidation, which produces medium-chain dicarboxylic acids[20].

Consumption of medium-chain triglycerides is associated with an increased rate of excretion of acyl-L-Carnitine and medium-chain dicarboxylic acids[5]. Thus L-Carnitine may promote efficient utilisation of these acids acting as a sink for short-chain acyl moieties generated by beta-oxidation, thus relieving intramitochondrial coenzyme A for participation in fatty acid activation pathways[36].

Numerous studies have shown that hypothermia in the newborn baby is a serious hazard and that maintenance of adequate body temperature is critical for survival[37]. Brown adipose tissue plays an important role in heat production for infant mammals[31]. The rate at which fatty acids are oxidized by mitochondria from brown adipose tissue for heat production is almost entirely dependent on the presence of L-Carnitine and ATP. The L-Carnitine content increases rapidly after birth and can be further increased by exposure to the cold. Thus L-Carnitine plays an important role in non-shivering thermogenesis[38].

Addition of L-Carnitine was found to stimulate ketogenesis. Because ketone body production and utilization constitutes an important

part of the neonate's energy metabolism, impaired ketogenesis as a result of L-Carnitine deficiency could have severe metabolic consequences for the neonate[37, 39].

Protein metabolism

When 140 premature infants received strictly calculated amounts of expressed breast milk with or without L-Carnitine supplementation, the maximal postnatal birth weight loss was found to be lower in the L-Carnitine group, and the time after which birth weight was regained shorter. The authors concluded that L-Carnitine exerted a metabolic effect by improving protein utilization[40]. These facts are supported by other researchers who added extra L-Carnitine to pooled pasteurized breast milk for premature infants. A marked decrease in plasma urea level as well as a significant fall in the urea and total N excretion was observed, suggesting a reduced amino acid and protein catabolism during L-Carnitine supplementation[15]. Besides they could demonstrate that the L-Carnitine supplement was taken up by the tissues and entered the intermediary metabolism, increasing acylcarnitines in plasma and urine.

L-Carnitine deficiency in infants

Data suggest that newborn infants are born with limited reserves of L-Carnitine[6, 41, 42]. The premature baby has particularly L-Carnitine needs in view of its metabolic immaturity and its frequent need for parenteral feeding[9, 17, 18, 43]. Various L-Carnitine products are utilised as drugs around the world in order to address these needs.

Whereas profound clinical signs of deficiency are rather rare in healthy, normal-weight infants, mild deficiency may be more common than commonly thought, and clinical signs of deficiency may go undetected. The subclinical consequences of marginal L-Carnitine deficiency are unknown.

It has been suggested that in L-Carnitine deficiency, defined as a condition where there is insufficient L-Carnitine to buffer the acyl-CoA-compounds, metabolism of several metabolites may be affected. Whether impairment of fat utilization or of other metabolic processes in which L-Carnitine may be involved has any long-term effect for infants who develop L-Carnitine deficiency remains a subject for further research.

Recommended L-Carnitine dosage levels in infant food

Consideration that varying degrees of L-Carnitine insufficiency may arise in infants receiving an L-Carnitine-free diet prompted the evaluation of the rationale for adding L-Carnitine to soy protein-based formulas. In the course of the current revision of the Codex Alimentarius Standard on Infant Formula established in 1981[44] , an ESPGHAN coordinated international expert group has provided a proposal on nutrient levels in infant formulas, based on analysis of all available scientific evidence[45]. The ESPGHAN Committee on

Nutrition has supported the recommendations of previous expert reviews[46–48] for a minimum L-Carnitine content of 1.2 mg/100 kcal, which is similar to the L-Carnitine content of human milk. A maximum level has not been specified in this recent position paper[45]. For many years now, legislation in many countries requires the addition of L-Carnitine to infant formula based on soy protein isolate and hydrolysed protein to give a certain level of L-Carnitine. In Europe, both Carnipure™ crystalline and Carnipure™ tartrate are listed in the Infant Formula Directive (2006/141/EC) and approved for use in infant and follow-on formulae[49].

And so to conclude

Mother's milk contains L-Carnitine, which is required for the transport of long-chain fatty acids and other organic acids across mitochondrial membranes. Young infants fed diets with low L-Carnitine contents develop reduced plasma and tissue L-Carnitine levels, and they further may develop disturbances of fatty acid oxidation, metabolism of acyl-CoA compounds, ketogenesis and nitrogen balance. As recently recommended by the ESPGHAN Committee on Nutrition, infant formula should contain L-Carnitine at least at a similar concentration as human milk.

Reasons to include Carnipure™ in infant formula

Fat is the major source of energy during infancy.
L-Carnitine is required for optimal oxidation of fatty acids.
Infants have a small storage capacity for L-Carnitine and a relatively undeveloped capacity to synthesise L-Carnitine in their body.
The infant's plasma and tissue L-Carnitine levels are low.
Dietary L-Carnitine intake from unsupplemented soy-based infant formulas is negligible.
Infants fed an unsupplemented soy-based formula appear to have altered lipid metabolism compared to breast-fed infants and to infants fed a soy-based formula supplemented with L-Carnitine.

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Note: This document is an overview of published scientific information on L-Carnitine and published scientific information on clinical and nutritional trials with L-Carnitine and its derivatives. No claims are made herein for any particular consumer product, nor can these statements be used on such consumer products.

The recommended use for L-Carnitine is as a nutrient or dietary supplement. The statements in this document have not been evaluated by any Food and Drug Administration. Lonza's Carnipure™ is not intended to diagnose, treat, cure or prevent any disease.

No statement is intended or should be construed as a recommendation to infringe any existing patent. The information contained herein is believed to be correct and corresponds to the latest state of scientific and technical knowledge.

This Carnipure™ Focus has been reviewed by Senior Assistant Professor Heinz Löster from the University of Leipzig, Germany.

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