Historical Perspective on Clinical Trials of Carnitine in Children and Adults

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Key Words

Carnitine · Carnitine deficiency · Metabolic disorders · Inborn errors of metabolism

Abstract

The metabolic roles of carnitine have been greatly clarified over the past 50 years, and it is now well established that carnitine is a key player in mitochondrial generation of energy and metabolism of acetyl coenzyme A. A therapeutic role for carnitine in treatment of nutritional deficiencies in infants and children was first demonstrated in 1958, and since that time it has been used to treat a number of inborn errors of metabolism. Carnitine was approved by the US Food and Drug Administration in 1985 for treatment of 'primary carnitine deficiency', and later in 1992 for treatment of 'secondary carnitine deficiency', a definition that included the majority of relevant metabolic disorders associated with low or abnormal plasma carnitine levels. Today, carnitine treatment of inborn errors of metabolism is a safe and integral part of many treatment protocols, and a growing interest in carnitine has resulted in greater recognition of many causes of carnitine depletion. Notwithstanding, there is still a lack of data from randomized clinical trials, even on the use of carnitine in inborn errors of metabolism, although ethical issues may be a contributing factor in this regard.

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Interest in this area of metabolism can be judged by the more than 14,500 references to carnitine in PubMed in 2015.

The First Reports of Carnitine Deficiency and Therapy with Carnitine

The first report of a potential therapeutic role for carnitine was in 1958 in treatment of nutritional deficiencies in infants and children using synthetic DL-carnitine [1]. The first known inborn error of carnitine metabolism was reported in 1975; it was a defect in a carnitine transport system across membranes, including the renal tubules and muscle [2]. The renal losses result in low levels of carnitine in blood and deficient transport into muscle result in a lipid storage myopathy. Long-term treatment with carnitine was recommended. This was followed in 1992 by the identification of a carnitine translocase deficiency [2]. The first report of carnitine treatment of an inborn error of metabolism was in 1973 in a myopathic patient in whom muscle fibers contained lipid-filled vacuoles. Homogenates of the patient's muscle oxidized fatty acids more slowly than normal, while addition of carnitine increased the oxidation rate to normal. Fifteen years later, the first recognized case of carnitine deficiency in human skeletal muscle was shown to be due to car-

nitine transporter deficiency. The primary defect is in a gene (*SLC22A5*) that codes for the carnitine transporter OCTN2.

Not unreasonably perhaps, the term 'primary carnitine deficiency' was accorded to this inborn error of metabolism, although this term led to years of confusion before the role of carnitine in other types of disorders was more fully appreciated. In fact, the low plasma carnitine was secondary to the renal tubular losses of the compound. It was not until 1982 that the first inkling of the critical role of carnitine in certain organic acidemias and other disorders was postulated [3] and the use for carnitine for treating these disorders was presented in 1983. In these cases, carnitine deficiency is also secondary, due to increased requirements arising from increased levels of acyl-carnitines that sequester increased amounts of carnitine and are excreted in the urine in that form.

True 'primary deficiency' of carnitine synthesis was reported in 2012 in autistic males (vide Winter *infra*) and is due to a deletion of exon 2 of the trimethyllysine hydroxylase epsilon gene which is the first step in carnitine synthesis [4].

Food and Drug Administration Approval of Carnitine

The United States Food and Drug Administration (FDA) first approved L-carnitine as an orphan drug in 1985 for treatment of 'primary carnitine deficiency'. This was fine for the rare cases of the transporter defect but created great confusion for the emerging, and far more numerous, disorders of fatty acid and organic acid metabolism in which blood carnitine levels are often profoundly low. This situation was partially rectified in 1992 when the FDA approved the use of carnitine for the treatment of 'secondary carnitine deficiency', a definition that at the time was still not clear but at least included the majority of the relevant metabolic disorders associated with low plasma free carnitine levels. This approval of carnitine by the FDA was based on retrospective chart analysis of 90 patients, with 18 in the untreated cohort and 72 in the treated cohort, and efficacy was based on clinical and biochemical findings [5]. The most pertinent data included increased excretion of disease-specific acylcarnitine derivatives in a dose-response relationship, decreased levels of intermediary metabolites in the blood and improved clinical status with decreased hospitalization frequency, improved growth and significantly lower mortality rates compared to historical controls. There were few adverse effects of carnitine treatment, although gastroin-

testinal disturbances and fishy odor due to intestinal bacterial production of trimethylamine were the most frequent. No laboratory or clinical safety issues were identified.

Intravenous carnitine preparations were also approved for treatment of secondary carnitine deficiency. Since only 25% of enteral carnitine is absorbed and gastrointestinal tolerance of high oral doses is poor, parenteral carnitine treatment is an appealing alternative approach particularly when large doses are required. In 7 patients treated long term with high-dose daily to weekly IV boluses of parenteral carnitine through a subcutaneous venous port, the benefits included improved health and growth, decreased frequency of metabolic decompensation, improved muscle strength and decreased reliance on medical foods with liberalization of protein intake. Not unexpectedly, port infections were the most serious complication. Today, it can be asserted that carnitine treatment of inborn errors of metabolism is a safe and integral part of many disorders.

A Growing Interest in Carnitine

Since the first reports, the number of PubMed citations related to carnitine has increased dramatically from 142 in 1965 to 7,439 in 2002. As of November 2015, there were more than 14,500 with 2,873 related to carnitine deficiency and 1,667 on its use in treatment. This increase has been mirrored by the total number of known inborn errors of metabolism, which has increased from 70 in the 1st edition of metabolic and molecular bases of inherited metabolic diseases *Metabolic and Molecular Bases of Inherited Metabolic Diseases* to around 900 in the 8th edition published in 2015. The increased interest in carnitine has also resulted in greater recognition of causes of carnitine depletion (fig. 1).

Symptoms of Carnitine Depletion

In 1987, when the clinical manifestations of carnitine deficiency were ill-understood, Winter et al. [5] described the clinical spectrum associated with secondary plasma carnitine deficiency in 51 pediatric patients with plasma-free carnitine <20 $\mu\text{mol/l}$ (table 1). The most common were hypotonia/gross motor delay, recurrent infections and failure to thrive. Following treatment with carnitine, subjective improvement in muscle tone was seen in 24 of 38 patients, 22 of 33 patients showed acceleration of

Causes of carnitine depletion	
Increased loss of acyl carnitine	<ul style="list-style-type: none"> • Inborn errors of metabolism • Pharmacologic (valproate, pivalate) • Diabetes
Increased loss of free carnitine	<ul style="list-style-type: none"> • Transporter deficiency (primary carnitine deficiency) • Renal tubular loss (Fanconi syndrome) • Haemodialysis, peritoneal dialysis
Decreased supply	<ul style="list-style-type: none"> • Defects of synthesis • Unsupplemented infant formulas • Malnutrition

Fig. 1. Causes of carnitine depletion.

Table 1. Frequency of symptoms associated with carnitine depletion

Symptom	Frequency, %
Hypotonia/gross motor delay	85
Recurrent infections with metabolic decompensation	85
Failure to thrive	75
Mental retardation	40
Cardiomyopathy	30
Encephalopathy	5

growth and infection frequency appeared to decrease in 18 of 33 patients. After therapy, the echocardiograms of all patients with cardiomyopathy also normalized. Thus, investigation of the symptoms listed in table 1 should include quantitation of plasma carnitine.

The Need for Additional Data

In recent years, the role of carnitine is being studied in a burgeoning number of clinical conditions, many of which seem, at first sight, to be far removed from its basic biochemical functions. Examples include premenstrual cramps, heart failure, chronic fatigue, Alzheimer's disease, chronic pancreatitis, multiple sclerosis, narcolepsy and even smoking cessation. In 2015, ClinicalTrials.gov listed a total of 95 trials in which carnitine was cited, 50 were open or pending and about 50 of them included children.

The lack of randomized, controlled clinical data on the use of carnitine in inborn errors of metabolism was emphasized in a recent Cochrane review from 2012 [6]. In that

publication, it was stated that there are no published or ongoing relevant randomized controlled clinical trials in this area. Importantly, the review noted that in the absence of any high level evidence, that clinicians should base their decisions regarding the use of carnitine on clinical experience and that the lack of randomized data does not mean that carnitine is ineffective. The authors did note, however, the ethical issues that arise when considering placebo-controlled trials in potentially lethal diseases, for example, carnitine transporter disorder or glutaric aciduria type I.

Ongoing Debate and the Analogy to Mitochondrial Repair Cocktails

The ongoing debate about the use of carnitine involves those who would like to see more evidence for the efficacy of carnitine treatment based on randomized clinical trials and those who believe strongly that it is beneficial and who do not see the need for additional data. Personal and anecdotal reports are sufficient for this latter group. This situation is analogous to the current state of treatment for proven or suspected mitochondrial diseases which includes various combinations of coenzyme Q, various vitamin B supplements, carnitine, succinic and citric acid and vitamins C and K. In fact, a recent review identified at least 83 medicines used in various inborn errors of metabolism [7]. Among these, the dosages of 17 medications (21%) had grade 1 level of evidence, 61 (74%) had grade 4, 2 medications were in levels 2 and 3 and 3 had grade 5. Moreover, there are no actual controlled clinical trials to support the benefit of any of these substances; indeed, none has been rigorously tested for treatment of mitochondrial disease. Some analogy can also be drawn between carnitine and vitamin D. Both are nutrients and can be completely supplied from in vivo synthesis in the absence of a genetic disease. Insufficiency of either is often asymptomatic, while both are touted as having widespread beneficial effects.

Concluding Remarks

There is a major need for rigorously controlled clinical trials with carnitine, although in many inborn errors of metabolism, ethical issues may preclude such efforts. Moreover, since current opinion and experience are so entrenched, a proper randomized trial may be nearly impossible to perform in some settings. There is also an objective need for greater awareness and education on the

role of carnitine in intermediary metabolism and associated primary and secondary deficiencies. One approach might be to perform a large survey of current practices and outcomes. However, it should be remembered that rigorously controlled studies are needed if the use of carnitine is ever to lose its controversial status.

Disclosure Statement

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