Round Table Discussion

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still not sufficient to make any firm conclusions in this regard. Preliminary data on carnitine levels in children and adolescents with primary hypertension, low birth weight and nephrotic syndrome was also presented. Lastly, the panelists stressed that there remains an objective need to harmonize the terminology used to describe carnitine deficiencies (e.g., primary, secondary and systemic deficiency).

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Key Words
Carnitine · Hypertension · Low birth weight · Autism · Nephrotic syndrome

Abstract
The 1st International Carnitine Working Group concluded with a round table discussion addressing several areas of relevance. These included the design of future studies that could increase the amount of evidence-based data about the role of carnitine in the treatment of fatty acid oxidation defects, for which substantial controversy still exists. There was general consensus that future trials on the effect of carnitine in disorders of fatty acid oxidation should be randomized, double-blinded, multicentered and minimally include the following diagnoses: medium-chain acyl coenzyme A (CoA) dehydrogenase deficiency, very long-chain acyl-CoA dehydrogenase deficiency, long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency and mitochondrial trifunctional protein deficiency. Another area that generated interest was trials of carnitine in cardiomyopathy and, especially, the use of biomarkers to identify patients at greater risk of cardiotoxicity following treatment with anthracyclines. The possibility that carnitine treatment may lead to improvements in autistic behaviors was also discussed, although the evidence is still not sufficient to make any firm conclusions in this regard. Preliminary data on carnitine levels in children and adolescents with primary hypertension, low birth weight and nephrotic syndrome was also presented. Lastly, the panelists stressed that there remains an objective need to harmonize the terminology used to describe carnitine deficiencies (e.g., primary, secondary and systemic deficiency).

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Carnitine Supplementation in Fatty Acid Oxidation Defects

The discussion during the round table addressed several areas. It began with considering potential studies that could increase the amount of evidence-based data regarding the role of carnitine in the treatment of fatty acid oxidation defects – an area in which, after 30 years, there is still considerable controversy. In a Canadian survey of 18 metabolic specialists, it was concluded that there is little agreement on carnitine usage or other treatment modalities in these disorders \cite{1}. However, the authors agreed that high priority should be given to rigorous studies of treatment modalities, including L-carnitine supplementation, in these disorders \cite{1}. General consensus of our
The full role of carnitine in cardiac function is still unclear. While it clearly plays a central role, there is no standardized therapeutic protocol and little understanding of its role in the management of cardiomyopathy. There are a growing number of inborn errors of metabolism that are known to be associated with cardiomyopathy, many of which relate to the generation and maintenance of energy in the heart. In some centers, carnitine is included in the general therapeutic armamentarium, while in others it is never considered.

The panelists discussed a trial in which biomarkers of cardiac remodeling could be used to study the evolution of cardiomyopathy in children/adolescents undergoing treatment with anthracyclines, which has a high risk of causing cardiomyopathy. Such a trial would have to be multicenter and should include exercise testing. It was noted that heart failure in these patients is a major issue. Insulin resistance may be present in a damaged heart. In these patients, carnitine supplementation may help to stimulate carnitine O-acetyltransferase and help provide a more beneficial bioenergetic profile. It was further noted that some SNPs were already available that could be used to identify patients at greater risk of cardiotoxicity following treatment with anthracyclines, which could be integrated within a future trial.

**Carnitine in Autism**

Anecdotal reports of improvement in autistic behaviors associated with carnitine treatment have been reported. The transport of carnitine across the blood-brain barrier is necessary for carnitine therapy to improve brain function, but this process is not well understood. In 2012, a possible mechanism of carnitine’s role in autism was discussed – a mutation in trimethyllysine hydroxylase epsilon (TMLHE), an enzyme involved in the initial step in carnitine synthesis in both muscle and brain. Deletions in exon 2 of this X-linked gene are found in 1/360 males in the population, but more frequently (1/120) in males with autism where there are 2 or more autistic males in the sibling. The penetrance of the mutation to cause autism is estimated at 2–4%. Potential clinical studies of carnitine treatment of autism related to TMLHE deficiency were discussed [2]. One study could be limited to those with deletion of TMLHE exon 2 and could include newborn male siblings born to families with a previous male diagnosed with autism and TMLHE deficiency. Tests would include plasma/urine TML, HTML, gamma butyrobetaine and carnitine (total, free and esterified) with TMLHE exon 2 deletion results blinded until study completion. One participant suggested that all male infants be administered oral carnitine at a dose of 100 mg/kg/day regardless of result of testing to simplify the trial, although others preferred a double blind crossover trial. Long-term follow-up of the infants will provide data regarding the role of presymptomatic L-carnitine administration in THMLE-associated autism. Another idea was forwarded to administer carnitine or not to 2 large groups of children and observe at rates of autism after a long-term interval, perhaps 5 years. Others, however, suggested that more evidence was needed before embarking on such a trial.

**Metabolic Abnormalities in Children and Adolescents with Primary Hypertension**

There was much interest in metabolic abnormalities in children and adolescents with hypertension. In this regard, Prof. Wasilewska presented her preliminary data in 3 adolescent patient populations:
- Children with hypertension
- Children with low birth weight
- Children with nephrotic syndrome

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**References**

1. Lopaschuk/Wasilewska

2. Winter/Buist/Longo/Armenian/Lopaschuk/Wasilewska

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Children with Hypertension

Children and adolescents with hypertension (n = 112), with a median age of 10–18 years, were divided into a hypertensive group and a white coat hypertension group. It was observed that there were increased urine levels of L-carnitine in subjects with hypertension compared to the white coat hypertension group, and that the most likely reason for this excessive urinary loss was disturbed renal tubular reabsorption.

Children with Low Birth Weight

This small study included 59 low birth weight (LBW) children (mean 2,165 g) and 22 children with normal birth weight as a reference group (mean 3,500 g). In LBW children, increased urinary loss of carnitine was observed. In these subjects, it could be hypothesised that this was due to increased urinary loss of carnitine caused by hyperfiltration and impaired proximal tubular reabsorption.

Children with Nephrotic Syndrome

She also presented data in which she measured urinary carnitine levels in 23 children with idiopathic nephrotic syndrome and a reference group of 31 healthy children. Significantly lower levels of excretion of urinary free, total and acyl carnitine were observed when corrected for urinary creatinine in children with nephrotic syndrome. Moreover, there was a positive correlation between all carnitines and serum triglycerides. One possible explanation is lower intake of carnitine and lower intestinal absorption, although this needs to be confirmed. Lastly, it is also possible that increased excretion of creatinine alters the excretion rate of urinary carnitine species.

All participants agreed that further studies examining concurrent plasma and urine concentration of L-carnitine and correlation with proximal tubular markers are needed in subjects with hypertension and other conditions such as LBW and nephrotic syndrome.

Terminology in Current Use

The panelists stressed that there remains an objective need to 'clean up' the terminology used to describe carnitine deficiencies (e.g., primary, secondary and systemic deficiency).

Disclosure Statements

S.W. is a member of an advisory group on carnitine for Sigma-Tau, SPA and received a travel grant and honorarium for participation in the December 2015 conference which resulted in this publication. In the past, she was the principle investigator for the IV and Oral NDA applications for Sigma-Tau Pharmaceuticals, Inc. and received honorariums and research grants from Sigma-Tau Pharmaceuticals, Inc. and Sigma-Tau, SPA.

N.R.M.B. was a member of the International Working Group on the use of L-carnitine in clinical situations. He has received an honorarium for assisting in the panel; he has received no other financial support from the sponsors of the conference. He has no conflicts of interest with the sponsors of the conference.

N.L. received travel sponsorship and honorarium from Sigma-Tau to attend the carnitine symposium.

G.L. is a member of the Cardiovascular Translational Research Institute of the University of Alberta. He has received research grants from the Canadian Institutes of Health Research and the Heart and Stroke Foundation of Canada. He is Professor in the Faculty of Medicine and Dentistry at the University of Alberta.

S.H.A. and A.W. has no conflicts of interest relevant to this article to disclose. A.W. also received travel sponsorship and honorarium from Sigma-Tau to attend the carnitine symposium.

References
