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A Review of Valproic Acid–Induced Carnitine Deficiency and Replacement

NAVNEET S AHLUWALIA AND PETER G BERNAD

Objective: To review valproic acid–induced carnitine deficiency and subsequent carnitine replacement.

Data Sources: Articles indexed in MEDLINE from 1966 to May 2000, as well as other published works and standard references.

Data Extraction: Studies investigating clinical epidemiologic and pathologic evidence of the role of valproic acid–induced carnitine deficiency and double-blind clinical trials evaluating the effectiveness of carnitine replacement with anticonvulsant therapy are presented.

Data Synthesis: Clinical epidemiologic and pathologic studies provide evidence of valproic acid–induced carnitine deficiency. There is no clear consensus for providing carnitine supplementation to all patients taking valproic acid — it is only indicated for children with valproic acid–induced hepatotoxicity and those with valproic acid overdose.

Conclusions: There is evidence that implicates valproic acid in inducing carnitine deficiency. Patients should be evaluated clinically for signs and symptoms of carnitine deficiency before beginning supplementation. Currently, carnitine supplementation should be reserved for children with valproic acid–induced hepatotoxicity and valproic acid overdose until the results of further clinical studies are available.

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Valproic acid is widely used in the treatment of bipolar disorder and epilepsy in the pediatric population, and is an effective treatment for absence and myoclonic seizures of generalized epilepsy in patients of all ages. Its anticonvulsant effects appear to be related to its effects on increasing concentrations (by preventing degradation) of the inhibitory neurotransmitter gamma-aminobutyric acid in the brain, thereby increasing the seizure threshold. Valproic acid is a branched medium-chain fatty acid that forms acyl derivatives with both coenzyme A (CoA) and carnitine and undergoes limited mitochondrial beta-oxidation.[1] Metabolism of the drug occurs in the liver, and the major metabolic routes are glucuronidation, mitochondrial oxidation, and microsomal oxidation, with the latter two requiring carnitine. Valproic acid is protein-bound and is distributed widely throughout extracellular water; the distribution seems to be more extensive in younger rather than older subjects.[2]

Overall, valproic acid is well tolerated. Adverse effects of valproic acid therapy include sedation, weight gain, nausea, diarrhea, tremor, and transient effects on coagulation and hepatic transaminase enzymes. Fatal hepatotoxicity has been reported in both children and adults, but the rate seems to be higher in children under two years of age. Valproic acid–induced hepatotoxicity may be described by four subtypes, including a transient elevation of hepatic transaminase enzymes, reversible hyperammonemia, toxic hepatitis, and a Reye-like syndrome. The mechanisms of these reactions are unknown, but it is hypothesized that valproic acid induces carnitine deficiency by impairing beta-oxidation of fatty acids in the liver and is hepatotoxic by the increase of valproic acid metabolites, primarily 4-en valproate.[1] Valproic acid is also believed to be teratogenic, causing neural tube defects.[3]

Carnitine

Carnitine plays an essential role in human nutrition and metabolism; it transports long-chain fatty acids into the mitochondria for beta-oxidation and, ultimately, en-

NAVNEET S AHLUWALIA BA, Medical Student, School of Medicine, The George Washington University, Washington, DC; and **PETER G BERNAD MD MPH FACP**, Associate Professor, Department of Neurology, School of Medicine, The George Washington University, Metropolitan Medical Center, 2112 F St., N.W., Ste. 303, Washington, DC 20037-2754, FAX 202/638-7869, E-mail pgbernad@aol.com. *Reprints:* Peter G Bernad MD MPH FACP.

ergy production for cells and tissues of the body. L-Carnitine, along with carnitine-palmitoyl translocase (CPT)[1] and CPT 2, provides the mechanism whereby the long-chain fatty acyl-CoAs undergo beta-oxidation. Until the discovery in the 1970s of human disorders in which muscle or systemic concentrations of carnitine were markedly depressed, and in which clinical improvement followed treatment with carnitine, there was little medical interest in this substance.[4]

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Muscles preferentially use fatty acids for energy, and carnitine stores are localized to skeletal and cardiac muscles. The majority of carnitine (75%) is derived from the diet in red meat or milk; the remaining 25% is endogenously synthesized from the amino acids lysine and methionine in the liver and kidney. The primary role of carnitine is to transport long-chain (12–20 carbon) fatty acids into the mitochondria where they are catabolized to acetyl-CoA and enter the Krebs cycle for production of adenosine triphosphate.

Tissue concentrations of carnitine are much higher (20–50 times) than those in plasma; the plasma concentration only reflects a small portion of total body carnitine stores.[5] The total carnitine concentration in adult human tissues is higher in the heart and skeletal muscle than in liver, kidney, and brain. Generally, these values parallel the rate of fatty-acid oxidation in the different tissues. Because carnitine concentrations in tissues correlate poorly with serum concentrations, it is difficult to correlate the patient's symptoms with laboratory evidence of carnitine deficiency or insufficiency.

Carnitine deficiencies may be primary or secondary in nature. Primary deficiencies can be the result of reduced dietary intake, and secondary deficiencies may result from inborn errors of metabolism or treatment with multiple antiepileptic drugs. Carnitine deficiency has been defined as either total carnitine concentration below 25 µmol/L in infancy or an acylcarnitine/unbound carnitine ratio greater than 0.4.[6] These disorders lead to clinical disorders of muscle function.

Primary carnitine deficiencies can be categorized as systemic and myopathic. Systemic carnitine deficiency does not produce any myopathic signs; its chief clinical manifestations are similar to those of Reye's syndrome, with weakness and liver failure. Myopathic carnitine deficiency manifests as marked clinical weakness after prolonged fasting, resulting in exhaustion of muscle glycogen stores and variable accumulation of lipids within muscle tissue. Patients at high risk for developing carnitine deficiency include children less than two years of age, all patients being treated chronically with high-dose valproic acid (>45 mg/kg), young children with small muscle mass, patients of any age with severe seizure disorder plus mental retardation and/or organic brain disorders, and all patients on long-term low-protein diets.[7] Common characteristics of carnitine deficiency include hypoglycemia, hyperammonemia, hyperlactic acidemia, hypothrombinemia, increased concentrations of hepatic enzymes, and excess storage of fat in the liver and muscle.[8] Nonspecific signs include failure to thrive, anorexia, nausea, vomiting, listlessness, hypotonia, weakness, anemia, cardiomyopathy, and hepatic insufficiency.

Current knowledge of primary carnitine deficiency suggests that there is defective carnitine transport in tissues. The serum carnitine concentration is also depressed, which may be due to defective intestinal and renal carnitine transport. There are two clinical phenotypes of primary carnitine deficiency: progressive cardiomyopathy and episodes of hypoketotic hypoglycemia. Both disorders are associated with muscle weakness and lipid excess in skeletal muscle.[9]

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Biochemically, it is logical that supplementation results in improvement, but clinically, there is no clear support.

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Secondary carnitine deficiencies are both genetic and acquired. These disorders include primary defects of beta-oxidation with organic aciduria, defects of mitochondrial respiratory chain, chronic treatment with valproic acid, and renal Fanconi's syndrome. The mechanism for this depletion is unclear; one postulated cause is a metabolic block that results in excessive accumulation of acyl-CoAs in the mitochondria. These acyl-CoAs react with carnitine to form acylcarnitine and exit the cell; they are then excreted in the urine. Initial carnitine buffering by plasma carnitine is depleted, leading to a negative carnitine balance.[9]

Carnitine Replacement

Since the 1970s, when clinical disorders of carnitine were identified and improvement followed treatment

with supplementation, carnitine has gained enormous popularity. Numerous studies have examined carnitine's effect on fatty acid and organic acid metabolism in the past 15 years, but there have been few well-controlled, double-blind clinical trials evaluating carnitine supplementation in patients on anticonvulsant therapy. In addition, multiple case reports have demonstrated conflicting evidence that valproic acid–induced carnitine deficiency and hepatotoxicity respond to carnitine supplementation. The metabolic actions of carnitine that support its supplementation include correcting an absolute or relative carnitine deficiency, enhancing fatty acid oxidation, accepting and shuttling unmetabolized acyl groups from mitochondria, and increasing concentrations of unbound CoA.[10] Biochemically, it is logical that supplementation results in improvement, but clinically, there is no clear support.

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The Pediatric Neurology Advisory Committee recommends supplementation only for valproic acid–induced hepatotoxicity and overdose.

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Freeman et al.[11] performed a double-blind, crossover study to determine whether carnitine supplementation produced symptomatic improvement in patients taking anticonvulsant therapy. They found that carnitine administration did not result in substantial benefit compared with placebo. Their results indicate that it does not appear warranted to prophylactically administer carnitine to children to alleviate symptoms of carnitine deficiency. There is a need to better identify children in need of carnitine supplementation, appropriate clinical and laboratory tests to perform, and best time to administer carnitine therapeutically to children receiving valproic acid or other anticonvulsant therapy.

Young children have a decreased ability to synthesize carnitine and may have more difficulty compensating for valproic acid–induced carnitine deficiency. Children with multiple neurologic abnormalities may be undernourished and may have preexisting metabolic syndromes associated with carnitine depletion. Lacking conclusive data, the Pediatric Neurology Advisory Committee recommends supplementation only for valproic acid–induced hepatotoxicity and overdose. All patients receiving valproic acid should be monitored by clinical signs and symptoms of hepatotoxicity, especially during the first six months of therapy. Patients should also be screened for primary and secondary carnitine deficiency syndromes, and risks versus benefits of valproic acid administration should always be considered.

Summary

The exact mechanism for valproic acid causing carnitine deficiency remains unclear; however, it is postulated that valproic acid impairs beta-oxidation of fatty acids in the mitochondria of liver cells. Studies demonstrating response to carnitine supplementation for patients with valproic acid–induced carnitine deficiency are conflicting. Further research is needed to clarify the mechanism by which valproic acid induces carnitine deficiency and the therapeutic role of carnitine supplementation. ≏

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