Epilepsia, 39(11):1216–1225, 1998
Lippincott Williams & Wilkins, Philadelphia

Special Article

L-Carnitine Supplementation in Childhood Epilepsy: Current Perspectives

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Summary: In November 1996, a panel of pediatric neurologists met to update the consensus statement issued in 1989 by a panel of neurologists and metabolic experts on L-carnitine supplementation in childhood epilepsy. The panelists agreed that intravenous L-carnitine supplementation is clearly indicated for valproate (VPA)-induced hepatotoxicity, overdose, and other acute metabolic crises associated with carnitine deficiency. Oral supplementation is clearly indicated for the primary plasmalemmal carnitine transporter defect. The panelists concurred that oral L-carnitine supplementation is strongly suggested for the following groups as well: patients with certain secondary carnitine-deficiency syndromes, symptomatic VPA-associated hyperammonemia, multiple risk factors for VPA hepatotoxicity, or renal-associated syndromes; infants and young children taking VPA; patients with epilepsy using the ketogenic diet who have hypocarnitinemia; patients receiving dialysis; and premature infants who are receiving total parenteral nutrition. The panel recommended an oral L-carnitine dosage of 100 mg/kg/day, up to a maximum of 2 g/day. Intravenous supplementation for medical emergency situations usually exceeds this recommended dosage. **Key Words:** L-Carnitine—Epilepsy—Pediatric—Ketogenic diet—Metabolism.

In August of 1989, the Pediatric Neurology Advisory Committee (on Carnitine and Seizures) to Sigma-Tau Pharmaceuticals issued a consensus statement on the subject of L-carnitine supplementation for patients taking valproate (VPA) for epilepsy. The Committee recommended the prophylactic administration of L-carnitine to all children younger than 2 years who were taking VPA and the selective administration of L-carnitine to all children who had evidence of carnitine deficiency. Carnitine deficiency was defined as a plasma free concentration of ≤ 20 μM at an age older than 1 week after term or a plasma esterified-to-free ratio of ≥ 0.4 at an age older than 1 week after term. Many neurologists still subscribe to these two treatment recommendations, although certain issues remain controversial.

Accepted June 1, 1998.

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This article summarizes a roundtable on the role of L-carnitine supplementation in children with epilepsy. The meeting was held on Amelia Island, Florida, November 23, 1996.

1996 CONSENSUS CONFERENCE

On November 23, 1996, a panel of nine pediatric neurologists convened to review the present state of knowledge about L-carnitine supplementation in infants and children with epilepsy and to develop guidelines for the appropriate use of L-carnitine replacement therapy for these patients. The panelists addressed the role of L-carnitine supplementation in children who are taking any antiepileptic drug (AED) not only VPA. Because of the resurgence of interest in the ketogenic diet for seizure control, the appropriateness of L-carnitine therapy for children with epilepsy who are receiving the ketogenic diet also was considered. In addition, the panelists discussed the relation between seizures, metabolic disease, and the potential for carnitine deficiency. This article reviews the basic functions of carnitine and its role in

cellular energy metabolism and provides an overview of the interaction between epilepsy and metabolic disease. Recommendations for L-carnitine supplementation in pediatric patients with epilepsy, based on available evidence and clinical experience, are provided.

For the purposes of this article, the panel has chosen to use the general term "blood carnitine" throughout, with the acknowledgment that specific measurements may be made in blood, plasma, or serum, and vary from one report to another.

CARNITINE FUNCTIONS AND METABOLISM

The amino acid derivative carnitine is present in most human tissues. Its major sources are the diet and de novo synthesis. Blood carnitine increases during the first month of life and remains in the body in adequate amounts for life. Dietary carnitine is thought to be actively transported across the intestine in a sodium-dependent manner. It is excreted intact by the kidneys either as free carnitine or as acylcarnitine. The concentration of blood carnitine is regulated mainly by the kinetics of carnitine reabsorption by the kidney, the proximal renal tubule reabsorbing >90% of filtered carnitine at normal physiologic concentrations. The first known physiologic function of carnitine was the transport of long-chain fatty acids across the mitochondria for beta-oxidation. Recently other functions have been suggested, as listed in Table 1. L-carnitine is now prescribed as a therapeutic supplement in a growing number of diseases (1,2).

CARNITINE DEFICIENCY

A subnormal concentration of total carnitine may result from decreased biosynthesis, inadequate dietary intake, inadequate absorption, defective tissue transport, excessive renal excretion, or inborn errors of metabolism. An overview of fatty acid oxidation and the role of carnitine in this metabolic pathway is shown in Fig. 1. Carnitine deficiency may be classified as primary or secondary. Primary disorders are marked by a profound reduction of carnitine in affected tissues. The underlying mechanism is defective transport of carnitine from blood into affected cell. The carnitine-transporter defect is transmitted as an autosomal recessive trait and presumably involves skeletal muscle, heart, kidney, and gut (3). This condition is thought to be rare, but its true incidence and prevalence remain unknown.

Much more common are secondary disorders of carnitine deficiency, which produce a less striking decrease in blood or tissue concentrations of carnitine or an increased ratio (>0.4) of esterified to free carnitine or both. In the majority of patients, the cause is either an underlying genetically determined inborn metabolic error, an acquired disease (e.g., chronic renal disease, Fanconi syndrome), or an iatrogenic factor such as drug administration (1).

When attempting to determine whether a patient with an epileptic encephalopathy or intractable seizures has an underlying metabolic disorder and carnitine deficiency, the clinician should consider the factors listed in Table 2.

Alternatively, we can screen for metabolic disorders associated with the patient's particular epilepsy syndrome. For example, the following metabolic disorders are associated with West syndrome: phenylketonuria (PKU); nonketotic hyperglycinemia; and hyperornithinemia, hyperammonemia, and homocitrullinuria (known as the HHH syndrome). Unfortunately, specific epilepsy syndromes are often difficult to identify in infants and young children with inborn errors of metabolism (4).

TABLE 1. *Metabolic functions of carnitine*

- Transfer of long-chain fatty acids across the inner mitochondrial membrane
- Facilitation of branched-chain α-ketoacid oxidation
- Shuttling of acyl-CoA products of peroxisomal β-oxidation to mitochondrial matrix in the liver
- Modulation of the acyl-CoA/CoA ratio in mammalian cells
- Esterification of potentially toxic acyl-CoA metabolites that impair the citric acid cycle, urea cycle, and pathways for gluconeogenesis and fatty acid oxidation during acute clinical crises

Adapted with permission from De Vivo DC, Tein I. Primary and secondary disorders of carnitine metabolism. *Int Pediatr* 1990;5(2): 135.

VALPROIC ACID–ASSOCIATED CARNITINE DEFICIENCY

A number of clinical studies have shown a significant decrease in total or free blood carnitine concentrations or both in patients taking multiple AEDs, including VPA (5–11) or VPA alone (6; see Table 1). Low blood carnitine concentrations commonly accompany long-term VPA therapy for epilepsy (6,12–18). Blood carnitine concentrations were lower in patients taking VPA in combination with other AEDs than in patients taking VPA alone (6,8–11). In several studies, carnitine concentrations in patients taking VPA alone did not differ significantly from those of controls (9,19). In a 1991 study by Bohan et al. (20), carnitine concentrations in VPA-treated younger children (1–10 years) were significantly lower than those in older children (10–18 years). Decreased blood carnitine levels appear to be more common in young patients with coexisting severe disabilities such as cerebral palsy (7,17,21) than in relatively healthy, older patients with epilepsy (9).

In one study of 21 children taking VPA, the mean blood carnitine concentration did not correlate with the dose of VPA or blood level of VPA (22). Even in the

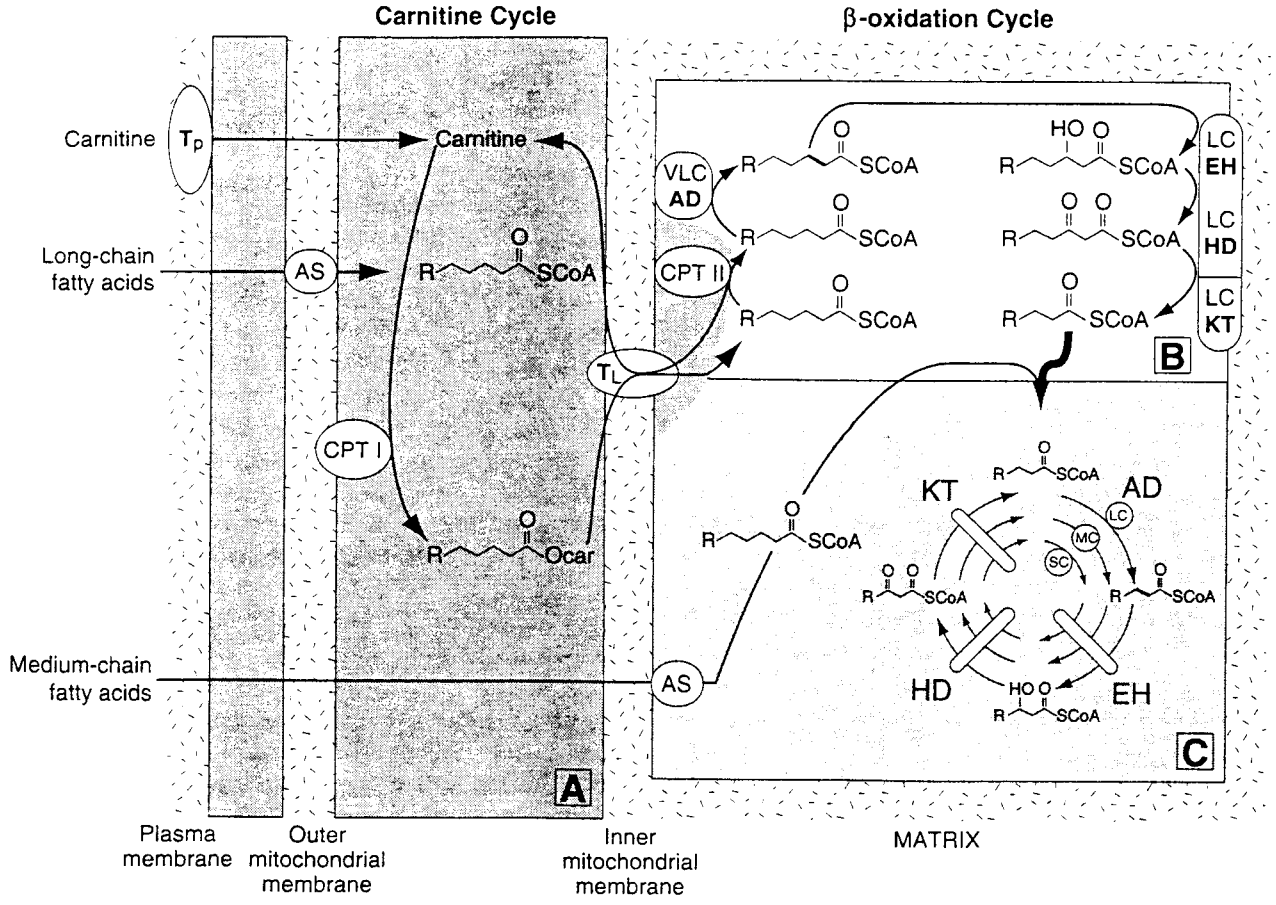

FIG. 1. Fatty acid oxidation: carnitine cycle **(A)**; inner mitochondrial membrane system **(B)**; and mitochondrial matrix system **(C)**. The carnitine cycle includes the plasma membrane transporter, carnitine palmitoyltransferase (CPT) I, carnitine-acylcarnitine translocase (T_L) system, and CPT II. The inner mitochondrial membrane system includes very-long-chain (VLC) acyl-coenzyme A dehydrogenase (AD CoA) and the trifunctional protein with three catalytically active sites. Long-chain acylcarnitines enter the mitochondrial matrix by the action of the CPT II to yield long-chain acyl-CoAs. These thioesters undergo one or more cycles of chain shortening catalyzed by the membrane-bound system. Chain-shortened acyl-CoAs are degraded further by the matrix β-oxidation system. T_p, carnitine transporter; EH, 2-enoyl-CoA hydratase; HD, 3-hydroxyacyl-CoA dehydrogenase; QT, 3-ketoacyl-CoA thiolase; MC, medium chain; SC, short chain; AS, acyl-CoA synthase (Adapted from *Handbook of Clinical Neurology*. vol. 22 (66) De Vivo DC, Hirano M, DiMauro S. Neurodystrophies and Neurolipidoses, p. 399; 1997 with kind permission of Elsevier Science-NL, Sara Burgerhartstraat 25, 1055 KV Amsterdam, The Netherlands.)

presence of normal blood carnitine concentrations, isolated muscle carnitine deficiency was documented in three children receiving long-term VPA therapy for intractable seizures (23). Given that 90% of body carnitine stores are contained within skeletal muscle (which contains ~70 times the serum concentration; 1), this finding suggests that blood carnitine concentrations are not always informative and that muscle carnitine concentrations may provide a more accurate reflection of the carnitine status of the patient. In essence, low blood carnitine concentrations reflect low muscle tissue concentrations, but normal blood concentrations may be present with low muscle tissue concentrations (24).

Millington et al. (25) proposed that valproyl-coenzyme A (valproyl-CoA) is converted into valproylcarnitine by the action of one or more of the carnitine acyltransferases, predominantly carnitine octanoyltransferase, at the inner surface of the inner mitochondrial membrane. Valproylcarnitine may then be transported out of the mitochondrion, releasing free valproyl-CoA in the mitochondrion. The valproylcarnitine may diffuse across the plasmalemma and then interfere with tissue free carnitine transport or with renal tubular reabsorption

TABLE 2. *Clues favoring an underlying metabolic abnormality in patients with epileptic encephalopathies or seizures*

- Family history of unusual neurologic problems or deaths in infancy or childhood
- Episodic metabolic derangement or progressive epileptic disorder
- Intractable early-onset seizures
- Failure to thrive
- Ataxia
- Strokes at an early age
- Seizures with minor motor manifestations
- Extrapyramidal syndrome
- Peripheral neuropathy

of free carnitine. Depressed renal tubular reabsorption of free carnitine was documented by Matsuda and Ohtani (15) in children receiving VPA therapy. Stanley et al. (26) examined the renal free carnitine threshold (blood level at which urinary free carnitine decreases to <5% of the filtered load) and found that it was below the normal range of plasma free carnitine (35–50 μM) in medium-chain acyl-CoA dehydrogenase deficiency (17 μM) and in long-chain acyl-CoA dehydrogenase deficiency (40 μM).

The mechanisms by which VPA can interfere with carnitine uptake over time include (a) the sequential formation of valproyl-CoA (27) and valproylcarnitine (25,28), leading to direct competitive inhibition of carnitine uptake at the transporter site; (b) the formation of VPA metabolites (29) with secondary inhibition of β-oxidation and excessive acyl-CoA; and (c) a decrease in intracellular adenosine triphosphate (ATP) due to inhibition of β-oxidation, pyruvate metabolism, oxidative phosphorylation, and gluconeogenesis (30–34), leading to decreased efficiency of the energy-dependent carnitine transporter.

Carnitine deficiency in the context of VPA therapy for epilepsy is of major clinical concern because of the high incidence of VPA toxicity—in particular, hepatoxicity—in infants and young children. VPA therapy may be associated with such serious side effects as a Reye-like syndrome, pancreatitis, and idiosyncratic and life-threatening hepatotoxicity (35–37). The clinical pattern of hepatoxicity associated with carnitine deficiency and VPA treatment is variable, ranging from mild to severe. Coulter (16) proposed the carnitine hypothesis of human VPA hepatotoxicity in 1984. He identified four patterns of VPA-induced hepatotoxicity: common transient increase in liver enzymes, reversible hyperammonemia, Reye-like illness, and progressive hepatic failure. In practice, physicians may see patients who develop increased liver enzyme levels shortly after taking VPA, with and without manifestations of clinical symptoms. These enzyme levels often return to normal with a reduction in VPA dosage (38) or with L-carnitine supplementation (39). The principal risk factors for hepatotoxicity are age younger than 24 months, the presence of concomitant neurologic or metabolic disorders or both, AED polypharmacy, and the addition of VPA therapy within 3 months of liver dysfunction (16,37,38,40).

Epidemiology of VPA-associated hepatotoxicity

The association between VPA and hepatotoxicity was extensively studied by Dreifuss et al. (37,41,42). In a recent retrospective review of all suspected cases of fatal hepatotoxicity associated with VPA therapy between 1987 and 1993, Bryant and Dreifuss (37) reported 29 fatal cases out of more than one million new prescriptions. Risk factors for mortality included age younger than 2 years, polytherapy, developmental delay, and concomitant metabolic disease. The greatest risk was in patients aged younger than 2 years with a complex neurologic disorder who were receiving polytherapy, with an incidence of fatal outcome of one in 600.

Recent data from the International Registry for Patients with Adverse Reactions to Valproate provide further insights regarding the frequency and severity of VPA-associated hepatotoxicity (43). Data for the registry were acquired from a review of primary source documents (clinical summaries, progress notes, laboratory data, or pathology and autopsy reports or a combination of these) from 75 patients with VPA-induced hepatic dysfunction. Among the registry's findings are the following: Clinical features of many of the patients were mental retardation (51%), polytherapy (75%), chronic illness, frequent hospitalizations, malnutrition, and low body mass. The hospitalizations were due to infections, to the illness that was the indication for VPA, or both. More than 50% of the children were below the 25th percentile in weight, and 27% were below the 5th percentile. Thus many of the children exhibited failure to thrive. Survival was significantly greater for the patients taking VPA who received L-carnitine than for those who did not. Although 59% of the patients who received intravenous (i.v.) carnitine (n = 17) survived, only 8% of the patients who did not receive carnitine (n = 48) survived. Survival varied with the route of administration of carnitine. Intravenous treatment was superior to enteral administration, and early aggressive administration was more likely to effect a positive outcome. These findings are similar to the response pattern of patients with acetaminophen-associated hepatotoxicity when treated with *n*-acetylcysteine, who respond favorably to early, aggressive treatment (44,45).

On the basis of epidemiologic surveys and registry data, the following conclusions can be drawn about VPA-associated hepatotoxicity: (a) Hepatotoxicity is related directly or indirectly to tissue carnitine deficiency; (b) This deficiency is presumably due to drug-induced aggravation of acquired nutritional problems; (c) Normal blood carnitine levels do not exclude tissue carnitine deficiency; and (d) Intravenous L-carnitine treatment is efficacious in the treatment of VPA-induced hepatotoxicity, particularly if initiated early.

EFFECTS OF OTHER AEDs ON CARNITINE METABOLISM

The database of medical literature suggesting a relation between VPA and carnitine is considerable; information regarding the effects of the other AEDs on carnitine metabolism is more limited. In a study of 471 patients of various ages who were given AEDs for seizures, Hug et al. (10) found the following percentages of

patients in each of eight treatment groups to be deficient in total carnitine: 23% of those taking VPA (n = 53), 36% of those taking phenobarbital (PB; n = 43), 12% of those taking phenytoin (PHT; n = 11), 8% of those taking carbamazepine (CBZ; n = 141), 37% of those taking PB and PHT (n = 19), 18% of those taking PB and CBZ (n = 17), and 44% of those taking VPA and CBZ (n = 18). One limitation of the study was that the subjects' blood carnitine levels were not measured before AED therapy began.

In a study of carnitine concentrations in 183 adult outpatients compared with 49 controls, Rodriguez-Segade et al. (8) found the following percentages of patients in each treatment group to be deficient in free carnitine (defined as >2 standard deviations below the mean): 77% of those taking VPA (n = 34), 27% of those taking PHT plus PB (n = 41), 23% of those taking CBZ (n = 57), and 16% of those taking PHT (n = 25).

Zelnik et al. (46) measured blood carnitine levels in 37 children before and after AED therapy. Total carnitine levels in the VPA group declined from 45.3 μM before treatment to 34.9 μM after treatment, in the CBZ group from 45.7 to 43.4 μM, and in the PB from 44.9 to 42.1 μM. Only the VPA-treated patients showed a significant decrease ($p < 0.001$) in their carnitine levels with therapy.

With a mouse model, Carmiña et al. (47) found that PB, PHT, and CBZ did not reduce blood free carnitine but that, like VPA, these agents did reduce blood acylcarnitines. The authors suggested that these drugs alter renal reabsorption of acylcarnitines and that VPA alters renal reabsorption of both acylcarnitine and free carnitine. These suggestions need to be examined in light of the studies cited later. Of all the AEDs that have come to market in recent years, vigabatrin (VGB) appears, from its structure (i.e., the presence of a fatty acid group), to be the most likely to interact with carnitine. Because VGB is prescribed mostly for patients with epilepsy who have other problems, such as inborn errors of metabolism, these other problems rather than the drug itself could cause excess excretion of carnitine. Interactions between AEDs and carnitine could also be caused by a liver-toxicity reaction in the presence of a dietary deficiency. Patients with chronic epilepsy, in particular, are often malnourished with respect to protein.

THE KETOGENIC DIET

In recent years, physicians have shown renewed interest in using the ketogenic diet for seizure control, especially in patients whose seizures are refractory to AED therapy or who experience unacceptable side effects from AEDs (46,48–50). The current popularity of the ketogenic diet prompted the panelists to consider the effects of L-carnitine supplementation in patients who are following the diet.

Ketogenic diet rationale and possible mechanisms

The rationale for the ketogenic diet is as follows: the brain derives most of its energy from the aerobic oxidation of glucose. Under certain conditions, such as fasting or consumption of a high-fat diet, the brain can use ketone bodies for energy. The ketogenic diet, which is high in fat and low in carbohydrates and protein (usually in a 3:1 or 4:1 ratio by weight), produces a state of ketosis that mimics the fasting state. Consumption of the ketogenic diet causes the main source of fuel used by the brain to shift from carbohydrates to fats. This metabolic shift somehow causes the seizure threshold to rise, although this protective effect is rapidly reversed when the diet is discontinued (51). For many centuries, even in biblical times, fasting was observed to have a beneficial effect on seizures. Systematic attempts to exploit the beneficial effects of ketosis to treat epilepsy date back to the 1920s, before most of the AEDs now in use became available.

The mechanism(s) by which the ketogenic diet exerts its anticonvulsant effect are not fully understood, although many theories have been proposed (49,51–55). Ketosis is associated with improved brain cellular energetics and elevated tissue ATP concentrations (53).

Efficacy of the Diet

Age limits should be set when discussing efficacy of the ketogenic diet in infants and young children. The ketogenic diet seems most effective in young children and has even been cited as effective in infants (1,56,57). In addition, their dietary intake can be monitored relatively easily. Older children, teenagers, and adults may not respond as well to the diet; large studies have not been performed with these populations (48). The efficacy of the diet varies not only with the patient's age but also with the types of seizures experienced by the patient. Various studies and clinical experience have shown that about a third of patients who try the diet have an excellent response (≥50% fewer seizures, fewer AEDs needed, increased alertness). Another third have a partial response (a decline in seizures of <50%). The remaining third will not experience a significant reduction in the number of seizures (48,52). Recent results suggest an even more favorable outcome (58).

Carnitine and the ketogenic diet

The ketogenic diet may deplete carnitine stores by several potential mechanisms. The diet may decrease carnitine intake, increase the demand on carnitine utilization, or increase urine excretion of carnitine acyl conjugates. L-Carnitine supplementation would be expected to facilitate ketogenesis and thus contribute to the anticonvulsant action of the diet. The recommendation that patients on the ketogenic diet be given L-carnitine is warranted if it can be shown that (a) carnitine concentrations decline as a result of the diet; (b) low levels of

carnitine contribute to signs of carnitine deficiency, reduce effectiveness of the diet, attenuate the systemic ketosis, and accentuate the hypoglycemia; and (c) carnitine supplementation restores carnitine levels and improves clinical response. Some research supports the observation that the ketogenic diet may induce carnitine deficiency, which in turn may interfere with the seizure-reducing effect of the diet (59).

Demeritte et al. (60) and E. Demeritte and M. Nigro (unpublished observation) studied 61 children on the ketogenic diet. Of these, 23 had prediet carnitine concentrations checked. Seven of the 23 had normal (<0.4) prediet carnitine ratios (mean acyl/free ratio, 0.19), but their carnitine levels on the ketogenic diet were not checked. Sixteen of the 23 patients had abnormal ratios (mean acyl/free ratio, 1.22); it is unknown how many were taking VPA simultaneously. All 16 of these children were given the ketogenic diet and given L-carnitine. The carnitine levels were retested in four children after they started the diet and carnitine therapy. Because all four still had abnormal carnitine levels, their carnitine dosage was increased to 300 mg/kg/day, until the ratio normalized. The carnitine levels of some, but not all, of the children improved with carnitine supplementation.

In the same study, 14 children had carnitine concentrations checked only after they began the diet and carnitine therapy; two had normal levels, and 12 had abnormal levels (mean acyl/free ratio, 1.15). The carnitine dosage for these children was also increased to ≤300 mg/kg/day if necessary, until an effect was seen. Again, in some but not all cases, the children's carnitine levels improved. The finding that the ratio of bound to free carnitine decreased significantly in some patients was compatible with increased β-oxidation of fatty acids. The investigators suggested that carnitine supplementation was warranted to correct carnitine deficiency. Organic acid screening was performed on 26 patients, and 28% showed a profile consistent with a β-oxidation defect. They concluded, "Organic acid screening should be done prior to and after initiation of the diet, and carnitine supplements should be given routinely" (60).

As a general rule, the panelists added that all children being considered for ketogenic diet therapy should be screened for an underlying metabolic defect that would contradict use of the diet. The introductory fast also serves as an effective provocation. It is useful to obtain a urine organic acid screen and an acylcarnitine profile at the end of this fast. Many children with chronic epilepsy, exposed for years to multiple AEDs, develop carnitine deficiency. A recent study of children about to begin the ketogenic diet supports this observation (61). Twelve children with chronic epilepsy in whom multiple standard AEDs had failed had their carnitine levels checked before starting the ketogenic diet. Total carnitine levels were deficient in nine patients, and acylcarnitine levels were increased in six. There was a strong correlation of symptomatic hypoglycemia on ketogenic diet initiation in seven of the nine patients with low total blood carnitine levels and in five of the six patients with increased blood acylcarnitine levels. Therefore, prior carnitine deficiency, presumably a result of long-term AED therapy, may be associated with adverse sequelae (hypoglycemia), particularly during fasting before initiation of the ketogenic diet. These findings further support the need to evaluate the patient's carnitine profile before starting the ketogenic diet.

The panelists expressed one important concern about the use of VPA in children with epilepsy: that some physicians might prescribe VPA with the ketogenic diet. Because VPA is an inhibitor of fatty acid oxidation, its administration to patients who are consuming a ketogenic diet creates the potential risk of mitochondrial dysfunction (48). Available evidence suggests that carnitine deficiency may accompany long-term use of VPA or the ketogenic diet. It is likely that this effect would be additive if VPA and the ketogenic diet were used together. VPA, as a partial inhibitor of fatty acid oxidation, may attenuate the desired ketosis associated with a high-fat diet. Therefore, the panelists perceived a potential danger associated with the simultaneous use of VPA and the ketogenic diet.

Clinical experience suggests also that some children on the ketogenic diet have decreased carnitine concentrations. The magnitude of that decrease may be a function of the duration of the diet alone. It is not clear whether children on the diet who become carnitine deficient are symptomatic, and no data have been reported on the effect of L-carnitine supplementation in patients on the ketogenic diet.

CARNITINE DEFICIENCY IN EPILEPSY: RISK FACTORS AND TREATMENT

Clinical experience has shown that the aggregate number of risk factors for carnitine deficiency is inversely related to the carnitine concentration. The panelists reviewed research findings on various risk factors for carnitine deficiency, including mental retardation and associated neurologic disorders, malnutrition, polypharmacy, and hyperammonemia.

Hunt and Pellock (62) reported on a survey of 640 residents at the Southside Virginia Training Center, a residential facility for people with mental retardation, mostly older teenagers and adults. Almost half of the residents had abnormal carnitine levels (defined as low total, low free, or a high acyl/free ratio). Some of these patients had epilepsy and were taking AEDs. Most of the residents were taking AEDs other than VPA. The survey suggests a correlation between carnitine deficiency and multiple neurologic handicaps sufficiently severe to war-

rant institutionalization. Vance et al. (63) alluded to similar findings and apparent benefits after carnitine supplementation.

It has been suggested that the smallest and most malnourished children seem to be at greatest risk for carnitine deficiency. One study found a positive correlation between blood carnitine levels and arm circumference as a reflection of the patient's nutritional status (5). Both total and free blood carnitine levels were significantly lower in patients with smaller arm circumferences, reflecting a loss in muscle mass.

The literature has demonstrated consistently that carnitine levels are lower in patients taking VPA and lowest in those taking valproate plus other drugs (9,11). VPA-associated hyperammonemia has been reported by several investigators (14,64,65). Ohtani et al. (14) were the first to report a correlation between VPA therapy or hyperammonemia and low carnitine levels. Hyperammonemia is associated with lethargy, but ammonia may not be the causative toxin. Rather it may be a marker for some other metabolic alteration, such as free fatty acids. Not all instances of coma in patients who are taking VPA are due to hyperammonemia.

A CLINICAL PERSPECTIVE ON CARNITINE SUPPLEMENTATION

Unfortunately, scientific data on the effects of carnitine therapy in patients with epilepsy are limited. There is a compelling need for controlled clinical trials. Only one such trial has been reported. Freeman et al. (66) examined the effects of carnitine therapy in 37 children with epilepsy between the ages of 3 and 17 years. There were 17 children taking VPA alone, five taking VPA with another AED, and 15 taking CBZ alone. Thirteen of the children were developmentally delayed.

The patients' blood total and free carnitine and acyl/free carnitine ratios were measured at the start of treatment and after 4 weeks. The well-being of these patients was assessed by their parents before treatment with carnitine, weekly during treatment, and after the end of treatment. After receiving carnitine or placebo for 4 weeks, the 37 children showed similar but statistically insignificant improvement in their well-being. The investigators concluded that prophylactic administration of L-carnitine to alleviate common, nonspecific symptoms in children who are taking AEDs is not warranted.

The findings of the trial should be interpreted with caution. The small sample size may have limited the power of the study to detect a statistically significant difference; there was no clear description of the population with respect to risk factors for carnitine deficiency; and the subjects' baseline carnitine levels were not low. No information about the severity of the subjects' epilepsy was obtained. The seizure types represented in the study are often the most easily controlled and occur in otherwise normal children. Only a few of the subjects were taking multiple medications, and AED levels were not provided. As for the administration of L-carnitine, the 1-week washout period was probably too brief. The prestructured scale that was used to collect the well-being data was unvalidated, and no other measure of effect was used. The carnitine measurements did not include tissue carnitine levels; thus the conclusions of Freeman et al. must be viewed as preliminary. The results of the study do not preclude a beneficial effect for carnitine supplementation in symptomatic patients and in those at risk for carnitine deficiency.

An unblinded, uncontrolled study of carnitine supplementation in 20 children with epilepsy who had two or more risk factors for carnitine deficiency suggests that supplementation may be beneficial (67). Clinical improvement was noted in more than half of the children who exhibited symptoms such as apathy, listlessness, lethargy, anorexia, and gastrointestinal complaints (nausea, vomiting, and constipation). In some children, symptoms of weakness and hypotonia were reduced, as was the frequency of seizures (67). This study suffers from its poor design, and like the Freeman study, the conclusions are preliminary at best.

SUMMARY: L-CARNITINE SUPPLEMENTATION IN PEDIATRIC EPILEPSY

Well-designed studies of specific and general uses of L-carnitine replacement therapy in children with epilepsy are needed. However, looking specifically at the issue of hepatotoxicity, the rarity of this complication makes execution and statistical analysis of such a study an unlikely possibility. In the absence of more specific information, clinical practice must be based on empiric observation, clinical experience, and theory. Collectively, available evidence provides a reasonable argument for the role of L-carnitine supplementation in certain cases of childhood-onset epilepsy. The panelists summarized key points about the diagnosis and treatment of carnitine deficiency in childhood epilepsy, which follows.

Diagnosis

- Carnitine deficiency is defined as a free blood carnitine value of <20 μM.
- Carnitine insufficiency is defined as an acylcarnitine/free carnitine ratio >0.4.
- A beneficial clinical response to L-carnitine supplementation supports the diagnosis of symptomatic carnitine deficiency.
- Muscle carnitine levels can be measured to assess tissue carnitine levels and are a more accurate measure of carnitine deficiency.

- Carnitine deficiency can be suspected clinically and confirmed biochemically.

Rational use of L-carnitine supplementation

- The benefits of L-carnitine for patients with some inborn errors of metabolism, such as the primary plasmalemmal carnitine-transporter defect, have been documented.
- L-Carnitine supplementation for most children with epilepsy has not been studied satisfactorily, and the possible value of this treatment is based on an understanding of the pathophysiologic processes associated with carnitine deficiency.
- Intravenous, high-dose L-carnitine treatment may be life-saving in cases of VPA-associated hepatoxicity.
- The judicious use of L-carnitine supplementation requires consideration of the formulation, dosage, route of administration, and measure of response.

Treatment recommendations

The panelists summarized the conditions in which L-carnitine supplementation is either indicated because of clinically proven benefits or recommended because of probable benefits. Table 3 lists these specific recommendations. The panelists' consensus derived from a critical review of published research findings and their clinical experience. The panel strongly recommended carnitine supplementation for neonates receiving total parenteral nutrition and patients undergoing dialysis, each of which may involve secondary carnitine deficiency. The immature metabolic pathways of preterm infants are unable to synthesize sufficient carnitine. In the absence of carnitine-supplemented parenteral formulations, carnitine deficiency may occur (68). In patients undergoing hemodialysis, excessive clearance of carnitine derivatives may occur, leading to disordered lipid and protein metabolism (1,69).

The panel noted the favorable risk–benefit ratio associated with L-carnitine. The main side effects are nausea, diarrhea, and a fishy body odor at large doses. Diluting the oral drug attenuates the gastrointestinal complaints. The expense of medication also was acknowledged. The panelists thought that cost reimbursement was more likely if the indications for L-carnitine supplementation were more widely publicized. The panelists also discussed the need for further research to clarify the risks and benefits of L-carnitine as treatment for specific long-chain fatty acid oxidation defects. With the important exception of the primary plasmalemmal carnitine-transporter defect, in which carnitine therapy is critical and life-saving, some circumstantial evidence suggests that carnitine administration may have deleterious effects in the other long-chain fatty acid oxidation disorders (Fig. 1). Clinically, these defects [e.g., long-chain acyl-CoA dehydrogenase (LCAD), very-long-chain acyl-CoA dehydrogenase (VLCAD), trifunctional protein, and the severe form of carnitine palmitoyltransferase (CPT) II deficiency] are associated with lipid-storage myopathy, recurrent myoglobinuria, and hypertrophic or dilatative cardiomyopathy (70–73).

Carnitine dosage recommendations

The existing literature about optimal dosing is limited; thus only general guidelines on dosing strategies are offered by the panelists. In general, oral carnitine should be administered in three or four divided doses. The daily dose should be 100 mg/kg/day, or 2 g/day, whichever is less. These recommendations are within the prescribing information guidelines for oral carnitine, which specify a dose of 50–100 mg/kg/day, up to 3 g per day. When attempting "metabolic rescue" of acutely ill patients, the panelists recommend intravenous administration of L-carnitine in higher doses of 150–500 mg/kg/day. These treatment guidelines are based on current knowledge of anecdotal reports, clinical experiences, and apparent safety of the agent.

DEDICATION

This article is dedicated to the memory of our esteemed colleague and co-author, Fritz Dreifuss, M.D., who died on October 18, 1997, in Charlottesville, Vir-

TABLE 3. *Recommendations for carnitine administration*

Carnitine clearly indicated	Carnitine strongly recommended
• VPA-induced hepatoxicity (i.v. administration) • VPA overdose (i.v. administration) • Primary plasmalemmal carnitine-transporter defect	• Specific secondary carnitine deficiency syndromes[a] • Symptomatic VPA-associated hyperammonemia • Renal-associated syndromes • Infants and young children receiving VPA, especially those younger than 2 years with a complex neurologic disorder who are receiving multiple anticonvulsants • Patients who have multiple risk factors for hepatotoxicity (e.g., neurologic impairments, poor nutrition, failure to thrive, chronic illness, multiple anticonvulsants) • Epileptic patients on the ketogenic diet who have hypocarnitinemia • Premature infants who are receiving total parenteral nutrition (TPN) • Patients who are receiving dialysis

VPA, valproate.
[a] Exception: long-chain FAO disorders.

ginia. Dr. Dreifuss made significant contributions to this manuscript, both as panel member and reviewer. His insightful knowledge about the use of antiepileptic drugs and their effects on the liver was invaluable to our discussion. We are honored to have served on this panel with him.

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