Review Article

Carnitine, Valproate, and Toxicity

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Abstract

Carnitine is an important nutrient that is present in the diet (particularly in meat and dairy products) and is synthesized from dietary amino acids. It functions to assist long-chain fatty acid metabolism and to regulate the ratio of free coenzyme A to acylcoenzyme A in the mitochondrion. Carnitine deficiency occurs in primary inborn errors of metabolism, in nutritional deficiency, and in various other disorders including antiepileptic drug therapy. Valproate therapy is often associated with decreased carnitine levels and occasionally with true carnitine deficiency. Some experimental and clinical evidence links valproate-induced carnitine deficiency with hepatotoxicity, but this evidence is limited and inconclusive. Carnitine supplementation has been useful in some studies, but these data are also limited. Young children with neurologic disabilities taking multiple antiepileptic drugs may have the greatest risk for carnitine deficiency. Measurement of carnitine levels appears warranted in these patients and in patients with symptoms and signs of possible carnitine deficiency. (*J Child Neurol* 1991;6:7–14).

The risk or occurrence of toxicity during antiepileptic drug therapy often influences the choice of drugs or limits the success of drug therapy. This is particularly true with valproate. Valproate is an extremely effective antiepileptic drug when used properly, but its use is limited by the risk of potentially fatal hepatotoxicity. Reducing this risk would greatly facilitate valproate treatment. The attempt to understand valproate toxicity has focused much attention on its biochemical effects. The purpose of this review is to examine the evidence concerning the effects of valproate on carnitine metabolism and to consider how these effects may relate to valproate toxicity. It is possible to develop a coherent hypothesis for which there is some empirical support, but another purpose of this review is to point out what is not known and what needs further study.

Carnitine Metabolism

Carnitine (β-hydroxy-γ-*N*-trimethylaminobutyric acid) was first reported to cause a deficiency syndrome in 1973.[1] Since then, numerous studies have shown that carnitine is an important nutrient and that carnitine deficiency may occur through a variety of mechanisms.

Carnitine is obtained from the diet in two ways. First, it is present as the intact, active molecule in certain foods and is absorbed as such from the intestine. Foods highest in carnitine content include red meat, milk, and milk products.[2] Second, it is synthesized from dietary lysine and methionine. Lysine provides the principal carbon chain of the molecule, and methionine provides the methyl groups. Ascorbic acid, niacin, pyridoxine, and ferrous iron are required cofactors for carnitine biosynthesis. Trimethyllysine is formed in the intestine and converted to γ-butyrobetaine there and in skeletal muscle, cardiac muscle, brain, liver and kidney.[2] γ-Butyrobetaine is hydroxylated to form carnitine only in brain, liver and kidney, however.[3] γ-Butyrobetaine hydroxylase, the enzyme necessary for final synthesis of carnitine, is relatively deficient in newborns and young infants.[4] Endogenously synthesized carnitine must be transported from these organs to skeletal muscle and cardiac muscle, where 98% of the total body content of carnitine is found. The rest of the body content of carnitine is in the liver and kidney.[5] Tissue concentrations of carnitine are as much as 10 times higher than plasma concentrations of carnitine,[6] so carnitine uptake in these tissues occurs against a concentration gradient by an active transport process.[4] Carnitine is excreted in the urine either as the intact molecule (free carnitine) or as an

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ester (acylcarnitine). The renal threshold for free carnitine is close to the serum concentration, suggesting that renal excretion regulates the serum concentration. The renal clearance of acylcarnitine is much higher than that of free carnitine, so excess acylcarnitine is rapidly cleared from the serum.[4] Free carnitine and acylcarnitine are reabsorbed at a common site,[7] and free carnitine may be reabsorbed at a separate site in the renal tubule,[8] which may help maintain carnitine status.

Carnitine has two principal functions in the body. One is to transport long-chain fatty acids into the mitochondrion. Carnitine palmityltransferase 1 at the outer surface of the inner mitochondrial membrane combines long-chain fatty acyl–coenzyme A (CoA) with carnitine. This acylcarnitine ester is then transported to the inner surface of the inner mitochondrial membrane, where carnitine palmityltransferase 2 releases the long-chain fatty acyl–CoA and carnitine. Long-chain fatty acyl–CoA is then metabolized through beta-oxidation to form acetyl-CoA, which enters the tricarboxylic acid cycle and is oxidized through the pathways of mitochondrial energy metabolism.[9]

The second function of carnitine is to help regulate the intramitochondrial ratio of acyl-CoA to free CoA. Acylcarnitine transferase at the inner surface of the inner mitochondrial membrane combines acyl-CoA with carnitine to form acylcarnitine esters, which are then transported out of the mitochondrion. This reaction also releases free CoA back into the mitochondrion. This function of carnitine is important because it removes excessive (and potentially toxic) short- and medium-chain fatty acids from the mitochondrion, and because it maintains sufficient free CoA within the mitochondrion to support energy metabolism.[4]

Tissue (mitochondrial) carnitine deficiency impairs energy metabolism by restricting mitochondrial beta-oxidation of long-chain fatty acids and by permitting build-up of acyl-CoA within the mitochondrion (thereby limiting the amount of free CoA available). This results in dysfunction of those tissues most dependent on mitochondrial energy metabolism, brain and muscle. The symptoms and signs are those of an encephalopathy, a myopathy, or both. Hepatic dysfunction may also result from impaired mitochondrial metabolism in the liver or from the release of hepatotoxic metabolites into the circulation.[4]

TABLE 1
Carnitine Levels With Valproate Therapy

	Subjects on Valproate					Controls				
Source	Description	N	TC*	FC*	AC*	Description	N	TC*	FC*	AC*
Ohtani et al[10]	Age 3–21 yr	14	32.6†	28.6†	—	Epilepsy, other drugs	11	48.6	43.0	—
						Healthy	27	49.0	44.2	—
Murphy et al[11]	Age <10 yr	13	39.6	—	—	Not stated	—	50.0	—	—
Morita et al[12]	Age 1–30 yr	12	33.4‡	21.5‡	12.0	Epilepsy, other drugs	13	43.6	31.5	12.0
						Healthy	32	60.3	51.7	9.7
Laub et al[13]	VPA alone; age 3–21 yr	14	46.4	34.7	11.7	Epilepsy, other drugs	21	47.0	39.9	7.0
	VPA plus other drugs	7	36.4	28.9	7.5	Healthy	21	49.5	41.2	8.0
Melegh et al[14]	Children	11	24.3†	16.8†	—	Healthy	11	34.9	26.5	—
Rodriguez-Segade et al[15]	Age 17–65 yr	34	36.9	26.4	10.5	Epilepsy, other drugs	149	48.1	41.2	6.9
						Healthy	49	53.3	47.1	6.2
Beghi et al[16]	VPA alone; age 1–39 yr	54	49.4	36.2	13.1§	Epilepsy, other drugs	51	46.9	37.0	10.1
	VPA plus other drugs	55	44.2§	33.0§	11.2	Epilepsy, no drugs	53	50.8	41.4	9.2
Present study	Age 1–15 yr	6	41.3	27.5	13.8	Epilepsy, other drugs	2	73.7	47.1	26.6

*All carnitine values are mean levels in μmol/L.
†Significantly different ($P < .05$) compared to values of healthy control group in same study.
‡Significantly different ($P < .05$) compared to values for control group of epileptics given other drugs in the same study.
§Significantly different ($P < .05$) compared to values for control group of epileptics given no drugs in the same study.
TC = total carnitine; FC = free carnitine; AC = acylcarnitine; VPA = valproic acid.

Carnitine Deficiency

Prevalence in Epilepsy

In 1982, Ohtani, Endo, and Matsuda first reported carnitine deficiency in patients taking valproate.[10] These results were confirmed in numerous subsequent studies[11–16] summarized in Table 1. Compared to healthy controls, serum free and total carnitine levels were significantly decreased in patients taking multiple antiepileptic drugs including valproate. Patients taking valproate alone also had significantly decreased carnitine levels in one study[13] but not in another study.[16] Patients taking other antiepileptic drugs but not valproate had significantly decreased carnitine levels in one study[15] but not in another.[16] In another study (not included in Table 1 due to insufficient data), carnitine levels were lowest in patients taking phenobarbital and were also significantly decreased in patients taking other antiepileptic drugs including valproate.[17]

These studies compared mean carnitine levels in patients and controls. Although the mean levels were significantly lower in the patients as a group, one may reasonably ask whether clinically significant carnitine deficiency was present in individual cases. Carnitine deficiency (defined as a free carnitine level more than 2 standard deviations below the mean for controls) was found in 22% of patients taking valproate in two studies, but none of the patients was considered to be symptomatic.[10,11] Carnitine deficiency was more common in another study, affecting 76% of patients taking valproate and 22% of patients taking other antiepileptic drugs. No data on symptoms were reported in this study.[15] On the other hand, Beghi et al found carnitine deficiency in only 4% of patients taking valproate, and there was no apparent correlation between carnitine levels and adverse drug effects.[16]

The difference in the prevalence of carnitine deficiency in these studies undoubtedly reflects the nature of the population studied. Carnitine deficiency was more common in studies that included mostly patients with multiple disabilities such as cerebral palsy.[10,15] Our patients included in Table 1 all had multiple disabilities, and carnitine deficiency was present in two of the six taking valproate. Carnitine deficiency appears to be much less common in patients with epilepsy who are otherwise healthy,[16] although further studies are needed to confirm this idea.

Etiology

Carnitine deficiency in patients with epilepsy may result from a variety of causes. The three principal categories are primary deficiency states (inborn errors of metabolism), nutritional deficiency states, and deficiency states induced by antiepileptic drugs. Multiple factors may be present in some patients.

Primary carnitine deficiency may be confined to muscle and present as a myopathy[1] or may be widespread (systemic) and present as brain, muscle, heart, or liver dysfunction.[18] Many cases of systemic carnitine deficiency are actually secondary to inborn errors of metabolism, however. These include acyl-CoA dehydrogenase deficiencies, organic acidemias (propionic acidemia, methylmalonic acidemia, isovaleric acidemia, and others), mitochondrial respiratory disorders (Kearns-Sayre syndrome, cytochrome *c* oxidase deficiency, and others), and urea cycle disorders.[4] Seizures may occur in some of these inborn errors of metabolism and may be treated with antiepileptic drugs including valproate. Thus, it is possible that carnitine deficiency in some patients taking antiepileptic drugs may be caused (at least in part) by an underlying primary inborn error of metabolism.

Nutritional carnitine deficiency is known to occur in premature infants, in children and adults receiving long-term intravenous nutrition lacking supplemental carnitine, and in severely malnourished children and adults.[2,5] Serum carnitine level was significantly correlated with arm circumference in a group of institutionalized patients with multiple disabilities including epilepsy who were taking antiepileptic drugs.[12] This suggests that decreased lean body mass in patients with epilepsy may be a risk factor for carnitine deficiency. Since dietary carnitine is obtained primarily from red meat and milk, and endogenous carnitine is synthesized from dietary protein containing lysine and methionine, it is reasonable to hypothesize that patients with epilepsy whose diet is deficient in these foods may be at risk for carnitine deficiency. In particular, patients with oral motor disorders and those on tube feedings may have the greatest risk for carnitine deficiency.[19] Most of the studies summarized in Table 1 either did not report dietary carnitine intake or indicated only that the patients' diet was normal. Nutritional inadequacy may cause or contribute to the low carnitine levels reported in these patients with epilepsy, but this remains unproven. Further studies are needed that include quantitative measures of dietary protein and carnitine intake.

It is not clear how antiepileptic drugs other than valproate might induce carnitine deficiency, and it is possible that the carnitine deficiency observed in patients taking these drugs (Table 1) may not be

caused directly by the drugs. Valproate does have a direct effect on carnitine metabolism, however. Valproate, a fatty acid, combines with carnitine within the mitochondrion. The resulting valproylcarnitine ester is then transported out of the mitochondrion and is excreted in the urine.[20] Several studies have reported an increased ratio of acylcarnitine to total carnitine in the urine of patients taking valproate, although total urinary carnitine excretion was not increased.[14,21] Urinary carnitine excretion was markedly increased in one patient with valproate-induced hepatotoxicity, however.[22] During long-term valproate therapy, continued urinary excretion of valproylcarnitine might gradually deplete total body stores of carnitine and result in a deficiency state. In addition, increased acylcarnitine excretion might interfere with tubular reabsorption of free carnitine.[22] If the ability to replenish tissue carnitine were also reduced by some other mechanism, this urinary depletion of carnitine might become significant. This hypothesis remains unproven.

It appears that no studies have investigated the effect (if any) of valproate on carnitine absorption, transport, endogenous biosynthesis or tissue uptake.

Valproate Toxicity

The Carnitine Hypothesis

Valproate was toxic to rat liver mitochondria in vitro[23] and in vivo.[24] Thirty minutes after injecting mice with valproate, hepatic concentrations of CoA and free carnitine decreased, and the concentration of acylcarnitine increased.[25] This valproate-induced deficiency of CoA within the mitochondrion explained most of the observed biochemical effects, including decreased fatty acid oxidation and decreased formation of ketone bodies such as β-hydroxybutyrate. These metabolic effects were prevented by giving L-carnitine.[26] The morphologic swelling of rat liver mitochondria exposed to valproate was also prevented by giving L-carnitine simultaneously.[24]

Valproate may inhibit mitochondrial beta-oxidation of long-chain fatty acids by two mechanisms. One is by formation of valproyl-CoA, which sequesters free CoA so that less is available for fatty acid metabolism. This effect is somewhat transient however,[27] and may not be sufficient to explain the observed inhibition. A more potent and long-lasting effect is the inhibition of those enzymes involved in beta-oxidation by certain valproate metabolites, particularly 4-en valproate.[28] The protective effect of L-carnitine supplementation might occur through formation of carnitine esters with these metabolites, which would then be transported out of the mitochondrion. This hypothesis seems plausible but is unproven.

The carnitine hypothesis of human valproate hepatotoxicity was first proposed in 1984.[19] The data in Table 1 clearly document that valproate treatment is associated with reduced serum levels of free carnitine and, in some patients, with true carnitine deficiency. Carnitine deficiency interferes with metabolism of long-chain fatty acids and also permits accumulation of potentially toxic short-chain fatty acids by reducing the amount of available free CoA. These effects could explain the morphologic and biochemical evidence of hepatic dysfunction associated with valproate treatment. Mild tissue carnitine deficiency might result in mild or reversible hepatotoxicity, while more severe tissue carnitine deficiency might result in more severe illness such as a Reye-like syndrome or progressive and often fatal hepatotoxicity. Tissue carnitine levels are much higher than serum levels, so it is possible that tissue carnitine deficiency (or relative insufficiency to meet metabolic demands) might exist even when serum carnitine levels appear to be normal.

Patients at greatest risk for valproate hepatotoxicity are young children with neurologic disabilities who are taking multiple antiepileptic drugs.[29] Each of these risk factors may actually represent a risk factor for carnitine deficiency. Young children have a reduced capacity for carnitine biosynthesis, which may limit their ability to compensate for valproate-induced carnitine depletion. Children with neurologic disabilities may have an underlying primary carnitine deficiency due to an unrecognized inborn error of metabolism. In addition, these children may have oral motor disorders that limit dietary intake of carnitine-rich foods, or may have a dietary preference for carnitine-poor foods, or may receive tube feedings that do not contain sufficient carnitine. In these children, undernourishment might cause metabolic energy demands to be met primarily through fatty acid oxidation, which would be impaired by valproate-induced carnitine deficiency. The combination of phenobarbital and valproate caused greater mitochondrial injury in rats than either drug alone.[30] Treatment of humans with multiple antiepileptic drugs including valproate resulted in increased amounts of potentially hepatotoxic valproate metabolites,[31] which might exacerbate carnitine deficiency.

According to the carnitine hypothesis, patients with the greatest risk for symptomatic carnitine defi-

ciency would be the same patients presently thought to be at greatest risk for hepatotoxicity. Carnitine deficiency should be suspected if the patient is young, neurologically impaired, consuming a diet low in protein and carnitine, and taking multiple antiepileptic drugs including valproate for a long time. These risk factors were present in all six of our patients taking valproate included in Table 1, and two were found to have carnitine deficiency. The available data are very limited, however. This hypothesis would also predict that L-carnitine supplementation might prevent or reverse symptomatic hepatotoxicity in these patients at risk for carnitine deficiency.

Hepatotoxicity

Valproate treatment is often associated with mildly increased liver transaminase levels.[29,32,33] No symptoms are associated with this finding and the levels return to normal when the dosage is reduced or sometimes even if the dosage is maintained. There is no evidence that this phenomenon is related to carnitine deficiency, although it appears that no studies have investigated the question directly. Exposure of rat hepatocytes to valproate in tissue culture resulted in increased cellular leakage of transaminases and lactic dehydrogenase into the culture medium,[34] which could be an experimental model of the human phenomenon. This leakage of liver enzymes was prevented by adding carnitine to the culture medium.

Valproate treatment may rarely cause acute hepatic failure[35] or a Reye-like syndrome.[36] Several reported patients with the Reye-like syndrome caused by valproate were found to have carnitine deficiency,[11,22,37] but others were not.[13] Although some cases of hepatic failure or Reye-like syndrome may actually have had an underlying primary carnitine deficiency due to an inborn error of metabolism,[38] this does not explain all such cases.[11,13] When hepatic failure occurred in a child with normal serum carnitine levels, treatment with up to 100 mg/kg/day of L-carnitine did not prevent death.[13] Several physicians have also informed the author that L-carnitine supplementation failed to reverse acute hepatic failure in their patients. In most cases, the patients' carnitine status prior to the onset of hepatic failure was unknown. Thus it remains unclear whether a preexisting carnitine deficiency (either primary or secondary) may cause or contribute to hepatic failure. The available evidence suggests that it could, and careful study of future cases is needed. Since L-carnitine treatment is relatively safe, it is probably warranted in cases of hepatic failure but may not be effective or prevent death.

Some patients who develop less severe hepatotoxicity will recover when valproate is discontinued.[29] Two children taking valproate in combination with other antiepileptic drugs developed lethargy and increased serum levels of transaminases and ammonia. Both recovered when valproate was discontinued. After other antiepileptic drugs failed to control seizures, valproate was reinstituted as part of a protocol that emphasized monotherapy and concomitant treatment with L-carnitine. Seizure control improved on this protocol and there was no clinical or biochemical evidence of recurrent hepatotoxicity.[39] Although the specific contribution of carnitine supplementation in these cases was unclear, the complete protocol might be considered in comparable cases to prevent recurrence of less severe valproate hepatotoxicity.

It should be noted that there is no evidence that carnitine treatment of high-risk patients taking valproate, such as young children with neurologic disabilities, will prevent the emergence of severe irreversible hepatotoxicity or prevent death due to acute hepatic failure or Reye-like illness. Patients who recover from less severe episodes (such as those described above) may be different from those who die and thus already "selected" in terms of their potential response to carnitine prophylaxis. There is no evidence that carnitine treatment will reduce the risk of death from severe hepatotoxicity.

Hyperammonemia

Hyperammonemia occurs during episodes of hepatic failure or Reye-like illness caused by valproate. It may also occur without any evidence of hepatic injury or elevation of serum transaminase levels. Following the initial report of hyperammonemia without hepatic failure,[40] numerous subsequent reports indicated that this phenomenon was not uncommon.[41–46] These reports are summarized in Table 2. Symptoms of lethargy, stupor, ataxia, or nausea were associated with elevated ammonia levels. These symptoms cleared and the ammonia level returned to normal when valproate was discontinued. The development of symptoms was related to the degree of hyperammonemia in one study,[47] but other studies have emphasized the lack of symptoms attributable to hyperammonemia.[16,44,45] Ammonia levels were not reported in two patients with asterixis who were taking multiple antiepileptic drugs including valproate, but the asterixis disappeared when valproate was stopped.[48] Whether

TABLE 2
Ammonia Levels With Valproate Therapy

Source	No. of Subjects		Symptoms	VPA Level*	Ammonia Level*	
	Total	VPA Alone			Subjects	Controls
Coulter & Allen[41]	8	0	Lethargy, hypotonia	67.4	145.0	24.3
Rawat et al[42]	1	0	Lethargy	33.0	190.0	(18–48)†
Zaret et al[43]	3	0	Lethargy, ataxia, nausea	42.3	114.0	(15–32)†
Batshaw & Brusilow[44]	28	0	None	11.5	33.6	23.6
Murphy & Marquardt[45]	55	16	None	No data	45.8	25.0
Ohtani et al[10]	14	0	None	No data	143.8	46.7
Williams et al[46]	19	2	Lethargy	63.1	62.4	30.5
Beghi et al[16]	55	—	None	No data	62.5	36.5
	—	54	None	No data	56.1	36.5

*VPA (mg/L) and ammonia (μmol/L) levels are mean values. Ammonia values are venous (references 41, 45, 10, 46, 16), arterial (reference 43), or unspecified (references 42, 44)
†Values in parentheses are laboratory normal ranges.
VPA = valproic acid.

symptomatic or not, hyperammonemia is apparently always completely reversible when valproate is discontinued.

Several possible explanations for hyperammonemia have been proposed. Valproate may inhibit hepatic carbamyl phosphate synthetase directly or by reducing synthesis of *N*-acetyl glutamate, which activates carbamyl phosphate synthetase.[49] A patient with a partial deficiency of carbamyl phosphate synthetase developed symptomatic hyperammonemia while taking valproate.[44] Valproate may interfere with beta-oxidation of long-chain fatty acids, which would result in decreased amounts of acetyl-CoA and limit the synthesis of *N*-acetyl glutamate.[46] Carbamyl phosphate synthetase is the first enzyme in the urea cycle, so decreased activity of this enzyme might interfere with the removal of ammonia through urea synthesis. Renal vein ammonia concentration increased after valproate administration, indicating that hyperammonemia may have a renal origin.[50] Hyperammonemia during valproate treatment most likely results from the combination of increased renal production of ammonia and decreased hepatic urea synthesis.[51] Both of these effects were significantly greater in patients treated with phenobarbital and valproate,[52] which may explain in part why hyperammonemia is more frequent in patients on multiple antiepileptic drug therapy (see Table 2).

Fourteen children taking multiple antiepileptic drugs including valproate had increased levels of ammonia and decreased levels of carnitine, which were significantly correlated.[10] Serum carnitine levels were not correlated with ammonia levels in other human studies, however.[13,16,21] Carnitine administration prevented valproate-induced hyperammonemia in rats in vivo[24] and in cultured rat hepatocytes.[53] Carnitine administration restored elevated ammonia levels to normal[10] and restored hepatic and neurologic function[54] in valproate-treated children. Carnitine treatment might improve beta-oxidation of long-chain fatty acids and increase production of acetyl-CoA, which could increase *N*-acetyl glutamate synthesis and thereby facilitate removal of ammonia through the urea cycle,[53] but this mechanism is unproven.

Measurement of serum carnitine levels seems warranted in patients with valproate-induced hyperammonemia. If carnitine deficiency is found, L-carnitine supplementation might be considered. Valproate monotherapy might also be considered if the patient is taking multiple antiepileptic drugs. Whether treatment with L-carnitine will relieve symptoms or restore ammonia levels to normal remains unclear, since the data are limited, and more studies of this therapeutic approach are needed.

Carnitine Treatment

Pharmacologic doses of L-carnitine are absorbed in the duodenum and ileum by an active transport process. Two percent is excreted in feces. The volume of distribution is approximately 26% using a two-compartment model. Maximum concentration in the blood is reached 3 to 5 hours after administration. The half-life in healthy adult volunteers ranges from 2 to 15 hours. Metabolism is primarily by formation of acylcarnitine esters, and excretion is in the urine. Recommended dosage for primary or secondary carnitine deficiency is 50 to 100 mg/kg/day in children and 1 to 3 g/day in adults, divided into two or three doses per day. Studies of valproate-induced carnitine deficiency that have reported the effects of

treatment have generally used these dosage regimens and have not described significant adverse effects. Minor gastrointestinal side effects such as nausea or diarrhea may occur.[55] Although serious adverse effects have apparently not been described, euphoria and increased platelet aggregation were reported in uremic patients on dialysis receiving L-carnitine. D-Carnitine is biologically inactive and D,L-carnitine may cause a myasthenialike syndrome, so only L-carnitine should be used in treatment.[2]

Conclusions

Valproate therapy is associated with a significant decrease in serum free carnitine levels. The magnitude of this decrease is small in most patients and actual free carnitine deficiency is uncommon. The symptoms and signs associated with valproate-induced free carnitine deficiency are not well defined. Based on experience with other carnitine deficiency syndromes, dysfunction of brain, liver, heart, or muscle might be anticipated. The hypothesis that carnitine deficiency is related to valproate hepatotoxicity is supported by some studies but not by others. Carnitine deficiency may be one cause, but not the only cause, of valproate hepatotoxicity.

Carnitine deficiency in patients with epilepsy may result from preexisting metabolic disorders, nutritional inadequacy, pharmacologic effects, or a combination of these factors. It is also observed in patients taking antiepileptic drugs other than valproate. Patients at greatest risk for carnitine deficiency may be young children with neurologic disabilities who are taking multiple antiepileptic drugs. Tissue carnitine deficiency or insufficiency might exist in the presence of normal serum levels, but tissue biopsy would be needed to confirm this.

Carnitine deficiency may be suspected in patients with epilepsy at greatest risk, in those with unexplained symptoms of lethargy, weakness, or hypotonia, and in those with evidence of hepatic dysfunction or hyperammonemia. If carnitine deficiency is documented, treatment with L-carnitine will correct the deficiency and seems warranted. Carnitine treatment might also be considered when serum levels are within the normal range, but symptoms and signs suggest possible tissue deficiency. The precise clinical benefit to be expected with carnitine treatment has not yet been defined, and more studies are needed. There is no evidence that carnitine treatment will prevent death due to valproate hepatotoxicity.

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