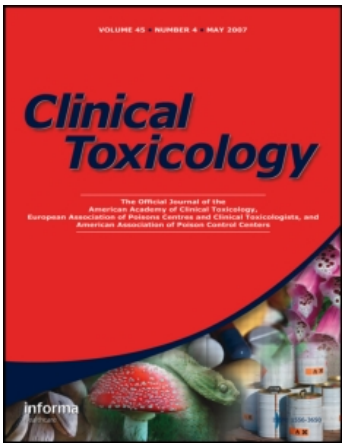

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REVIEW ARTICLE

Carnitine in the treatment of valproic acid-induced toxicity

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Introduction. Valproic acid (VPA) is a broad-spectrum antiepileptic drug that is now used commonly for several other neurological and psychiatric indications. VPA is usually well tolerated, but serious complications, including hepatotoxicity and hyperammonemic encephalopathy, may occur. These complications may also arise following acute VPA overdose, the incidence of which is increasing. Intoxication usually only results in mild central nervous system depression, but serious toxicity and death have been reported. *Valproic acid and carnitine.* As a branched chain carboxylic acid, VPA is extensively metabolized by the liver via glucuronic acid conjugation, mitochondrial β- and cytosolic ω-oxidation to produce multiple metabolites, some of which may be involved in its toxicity. Carnitine is an amino acid derivative that is an essential cofactor in the β-oxidation of fatty acids. It is synthesized endogenously from the essential amino acids, methionine and lysine. VPA inhibits the biosynthesis of carnitine by decreasing the concentration of α-ketoglutarate and may contribute to carnitine deficiency. It is postulated that carnitine supplementation may increase the β-oxidation of VPA, thereby limiting cytosolic ω-oxidation and the production of toxic metabolites that are involved in liver toxicity and ammonia accumulation. VPA-induced hepatotoxicity and hyperammonemic encephalopathy may be promoted either by a pre-existing carnitine deficiency or by deficiency induced by VPA *per se*. *Carnitine supplementation.* Some experimental and clinical data suggest that early intravenous supplementation with L-carnitine could improve survival in severe VPA-induced hepatotoxicity. Carnitine administration has been shown to speed the decrease of ammonemia in patients with VPA-induced encephalopathy although a correlation between ammonia concentrations and the clinical condition was not always observed. As it does not appear to be harmful, L-carnitine is commonly recommended in severe VPA poisoning, especially in children, although the clinical benefit in terms of liver protection or hastening of recovery from unconsciousness has not been established clearly. Prophylactic carnitine supplementation is also advocated during VPA therapy in high-risk pediatric patients. *Conclusion.* Further controlled, randomized, and probably multicenter trials are required to better delineate the therapeutic and prophylactic roles of L-carnitine and the optimal regimen of administration in the management of VPA toxicity.

Keywords Valproic acid; Carnitine; Hyperammonemia; Hepatotoxicity; Antidotes

Introduction

Valproic acid (VPA) is a broad-spectrum antiepileptic drug that has been used widely for more than 30 years in the treatment of several types of partial and generalized seizure. It is also increasingly prescribed to control bipolar and schizoaffective disorders, social phobias and neuropathic pain, as well as for prophylaxis or treatment of migraine headache.

Chemically, VPA is a branched chain carboxylic acid (2-propylpentanoic acid or di-*n*-propylacetic acid) and is therefore very similar to short-chain fatty acids, making VPA a substrate for the fatty acid oxidation pathways (1,2). VPA therapy is usually well tolerated, but serious complications, including fatal hemorrhagic pancreatitis, bone marrow suppression, hepatotoxicity, and hyperammonemic encephalopathy, may occur rarely. Some data suggest that hepatotoxicity and encephalopathy may be promoted either by a pre-existing carnitine deficiency or by a deficiency induced by VPA *per se*.

The incidence of acute VPA poisoning, whether resulting from intentional or accidental overdose, is increasing (3–6) probably as a consequence of the use of VPA in psychiatric disorders. Although VPA intoxication is most often mild and self-limiting, central nervous system (CNS) depression, serious toxicity, and even death may occur (3,7). Isolated reports suggest a potential role for carnitine supplements in this condition.

This article updates a previous review (8) on the clinical evidence regarding the potential role of carnitine in the management of these various aspects of VPA toxicity and will focus especially on VPA-induced hepatotoxicity, VPA-induced hyperammonemic encephalopathy, and acute VPA poisoning. The preventive value of carnitine supplementation in patients on chronic VPA therapy will also be discussed briefly.

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Carnitine

Carnitine (3-hydroxy-4-trimethylamino-butyric acid or β-hydroxy-gamma-*N*-trimethylamino-butyrate) appears to be essential in ensuring the proper metabolism of VPA and the metabolism of fatty acids. Sometimes referred to as vitamin BT, this water-soluble amino acid derivative is not a true vitamin because it is also biosynthesized endogenously from dietary amino acids (trimethyllysine), especially in the liver and in the kidneys (7,9,10). It is an important nutrient; approximately 75% comes from the diet, particularly from red meat and dairy products (7). A typical, well-balanced omnivorous diet contains significant amounts of carnitine (20–200 mg/day for a 70 kg person) as well as the essential amino acids and micronutrients needed for carnitine biosynthesis. Even in strict vegetarian diets (which contain as little as 1 mg/day exogenous carnitine for a 70 kg person), endogenous synthesis combined with the high tubular reabsorption rate is enough to prevent deficiency in otherwise healthy people. Thus, carnitine deficiency is an unusual problem in the healthy, well-nourished adult population (11).

Only the L-isomer is found endogenously and is active in metabolic functions. Most body carnitine is stored in skeletal muscle, but it is also found in other high-energy demanding tissues such as myocardium, liver, and adrenal glands (2.5–4 μmol/g tissue) (12). Plasma carnitine represents less than 0.6% of total body stores. Indeed, the total plasma concentration (free carnitine + acylcarnitine) is only 45–85 μmol/L.

L-carnitine has two main metabolic functions and thereby plays a central role in the metabolism of fatty acids and mitochondrial energy production: it facilitates fatty acyl group transport into mitochondria and it regulates the mitochondrial ratio of acyl-CoA to free CoA (13–15).

Transport of long-chain fatty acids

Carnitine facilitates the transport of long-chain fatty acids from the cytosol compartment of the muscle fiber into the mitochondria, where they undergo β-oxidation and produce acetyl-CoA, which enters the Krebs cycle (14). Indeed, esterification as acylcarnitine is required to allow this transport through the mitochondrial membrane (15). The transport process includes several steps and enzymes ("carnitine shuttle": carnitine palmitoyltransferase, carnitine acylcarnitine translocase) that are also used by VPA (Fig. 1) (8,16,17). VPA is extensively metabolized by the liver via glucuronic acid conjugation, mitochondrial β-oxidation, and cytoplasmic ω-oxidation (Fig. 2). In normal conditions, β-oxidation predominates and produces relatively nontoxic metabolites. Only a small amount of VPA is metabolized through ω-oxidation, a pathway that produces toxic metabolites, especially 2-propyl-4-pentanoic acid, 4-en-VPA, and propionic acid metabolites, that have been incriminated in the genesis of hepatotoxicity and hyperammonemia (8). During long-term or high-dose VPA therapy, or after acute VPA overdose, a greater degree of ω-oxidation occurs, potentially increasing the risk of toxicity.

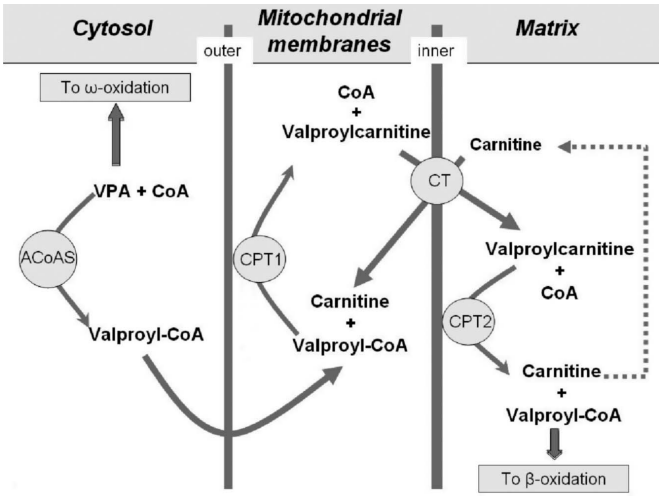

Fig. 1. The "carnitine shuttle." ACoAS, acyl-CoA synthetase; CoA, coenzyme A; CPT, carnitine palmityl transferase; CT, carnitine translocase.

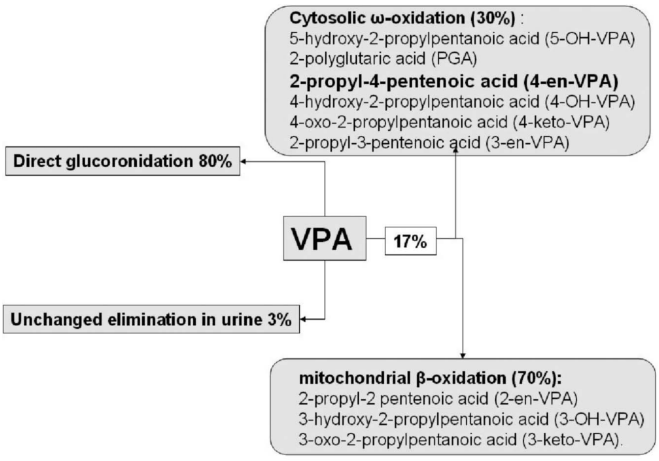

Fig. 2. Liver metabolism of valproic acid.

Carnitine depletion impairs the transport of long-chain fatty acids into the mitochondrial matrix, with subsequent decrease in β-oxidation, acetyl-CoA, and ATP production. Such impairment in mitochondrial β-oxidation also shifts the metabolism of VPA toward predominantly peroxisomal ω-oxidation, resulting in excessive production and accumulation of toxic products (8).

Prevention of the intramitochondrial accumulation of acyl-CoA

Carnitine helps to prevent intramitochondrial accumulation of acyl-CoA by transforming acyl-CoA into acylcarnitine. In this way, it protects the cell from the membrane-destabilizing effects of toxic acyl groups, as well as their restraining effects

on several enzymes that participate in intermediary metabolism and energy production in the mitochondria (α-ketoacid oxidation and gluconeogenesis, among others). Carnitine depletion can thus result in intracellular accumulation of toxic acyl-CoA, resulting in impairment in several enzymatic processes (15).

Carnitine is also indirectly required for proper functioning of the urea cycle. First, the ω-oxidation metabolite, 4-en-VPA, that accumulates when carnitine is lacking, inhibits carbamyl phosphate synthetase I (CPS I), the first mitochondrial enzymatic step of the urea cycle. Second, the synthesis of *N*-acetyl glutamic acid (NAGA), an important cofactor of CPS I, produced from acetyl-CoA and glutamate by NAGA synthetase, is decreased. The impairment of urea production results in ammonia accumulation (Fig. 3) (8).

Levocarnitine (L-Carnitine) is an orphan drug, available in some countries as an oral preparation (1 g/10 mL solution, 330 mg tablets) or as an injectable drug [intramuscular or intravenous, 1 g/5 mL solution; e.g., Levocarnil® (Sigma-Tau, Ivry-sur-Seine, France) and Carnitor® (Sigma-Tau, Gaithersburg, MD, USA)]. As bioavailability is limited by the oral route (about 15%), parenteral administration is recommended for therapeutic uses. Carnitine has been administered in senile dementia, inborn errors of metabolism, HIV infection, tuberculosis, zidovudine-induced mitochondrial myopathies, pediatric cardiomyopathies, renal failure on hemodialysis, anemia, and has been included in baby foods and milk (12).

Carnitine deficiency

Primary carnitine deficiency results from a rare inherited (autosomal and recessive) defect in membrane carnitine transporter in muscle and/or other organs. Secondary carnitine deficiency is associated with several inborn errors of metabolism and acquired medical conditions (9,11). Preterm neonates develop carnitine deficiency because of impaired proximal renal tubule carnitine reabsorption and immature carnitine biosynthesis. The final step in carnitine synthesis occurs in liver and kidney and depends on the enzyme γ-butyrobetaine hydroxylase, which may be deficient in children. An increasing number of problems are reported in relation to carnitine metabolism in preterm infants not receiving an exogenous source of carnitine. Children with various forms of organic acidemia have carnitine requirements that exceed their dietary intake and biosynthetic capability, so that they are unable to excrete accumulating organic acids.

Endogenous carnitine biosynthesis is impaired in cirrhosis and chronic renal failure. Patients with end-stage renal disease also lose carnitine via hemodialysis. Malabsorption, Fanconi syndrome, diabetes mellitus, heart failure, and Alzheimer's disease have also been associated with carnitine deficiency, as have conditions that involve increased catabolism, such as trauma, sepsis, and organ failure. Finally, several drugs, especially VPA but also anti-HIV nucleoside analogues, pivalic acid-containing antibiotics, and some chemotherapy agents (e.g., ifosfamide, cisplatin, and doxorubicin), are associated with decreased carnitine concentrations and occasionally with true carnitine deficiency (11,18).

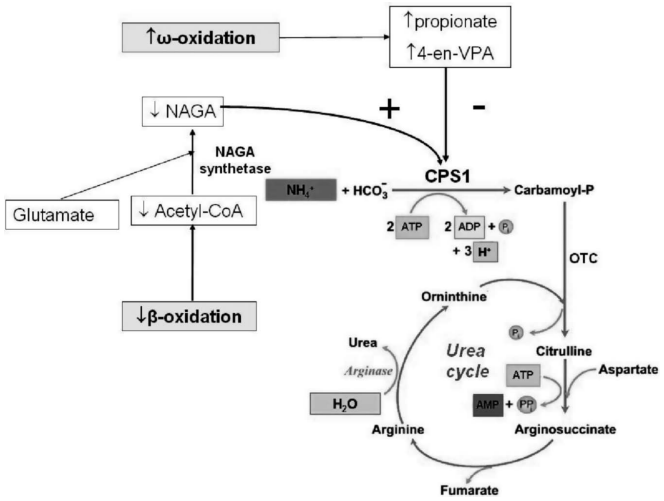

Fig. 3. Effects of decreased β-oxidation and increased ω-oxidation of fatty acids and VPA on the urea cycle. NAGA, *N*-acetyl glutamic acid; CoA, coenzyme A; CPS, carbamyl phosphate synthetase; OTC, ornithine transcarbamylase; 4-en-VPA, 2-propyl-4-pentanoic acid.

VPA-induced carnitine deficiency

VPA depletes carnitine stores through several synergistic mechanisms, especially during long-term or high-dose therapy (19,20–23). First, VPA combines with carnitine to form valproylcarnitine, which is excreted in urine (24). This represents only a minor route of elimination (25) so that it is unlikely that it is sufficient to produce significant carnitine deficiency in well-nourished patients (26). Second, a reduction in tubular reabsorption of both free carnitine and acylcarnitine has been reported during VPA treatment (27,28). Third, VPA reduces endogenous synthesis of carnitine by blockade of the enzyme γ-butyrobetaine hydroxylase (29). Fourth, valproylcarnitine inhibits the membrane carnitine transporter, thereby decreasing the transport of extracellular carnitine into the cell and the mitochondria. VPA also induces reversible inhibition of plasmalemmal carnitine uptake *in vitro* in cultured human skin fibroblasts (30). Fifth, VPA metabolites combine with mitochondrial CoA-SH. The pool of free CoA-SH decreases, so that free mitochondrial carnitine stores cannot be restored from acylcarnitine (including valproylcarnitine) under the action of carnitine palmitoyl transferase II (CPT II). Finally, the mitochondrial depletion of CoA-SH impairs β-oxidation of fatty acids (and VPA) and ATP production. ATP depletion further impairs the function of the ATP-dependent membrane carnitine transporter.

Studies have shown a significant decrease in carnitine concentrations and changes in the ratio of acylcarnitine to free carnitine in patients treated with VPA for both neurologic or

psychiatric indications (31). Although systematic assessment of carnitine status has been sometimes recommended in VPA-treated patients (9,14), hypocarnitinemia has not been confirmed in all studies. For example, in a cross-sectional surveillance study (32) conducted in 43 paediatric patients taking VPA, only two were found to have carnitine concentrations below the normal limit, suggesting that routine checking of carnitine concentrations is not justified. Indeed, VPA-treated patients may be carnitine depleted despite having normal carnitine serum concentrations (33). Measurement of the serum carnitine concentration is probably warranted in those patients who are actually at risk of carnitine deficiency to identify those who need carnitine supplementation: children less than 24 months, those patients with concomitant neurological or metabolic disorders, those receiving multiple anticonvulsants, patients with marked reduction of liver or kidney function (8).

Carnitine supplementation in VPA-induced toxicity

As VPA-induced hyperammonemia and hepatotoxicity could be mediated at least in part by carnitine deficiency, it has been hypothesized that L-carnitine supplementation could prevent, correct, or attenuate these adverse effects.

VPA-induced hepatotoxicity

Elevation in transaminases, alkaline phosphatase, and bilirubin may develop in up to 44% of patients receiving VPA, particularly during the first months of therapy (34,35), but these abnormalities are usually reversible with time or when the drug is discontinued. Severe VPA-induced hepatotoxicity in association with hepatic failure is rare (36–41). It may develop as an idiosyncratic reaction, is often associated with fatal liver failure, and is not always preceded by minor elevation in transaminases. Histological changes are similar to those observed in the Reye's syndrome, with early production of microvesicular steatosis followed by development of centrilobular necrosis (34,35,39–41). The most common clinical presentation consists of fatigue, lethargy, jaundice, nausea, vomiting, hemorrhage, worsening seizures, and anorexia (33,34,42).

Certain risk factors for severe VPA-induced hepatotoxicity have been identified and include young age (especially under 24 months and those with organic brain disease), developmental delay, congenital metabolic disorders (such as mitochondrial enzyme deficiencies), coincident history of previous liver dysfunction, severe epilepsy treated with polytherapy, ketogenic diets, or stressful conditions such as infections (34,35,37,38,43). Some of these risks factors may be linked (42). Although the overall incidence is estimated at 1/5,000–1/50,000, the occurrence of fatal hepatotoxicity could be as high as 1/800–1/500 in these high-risk groups (44). Early reports of severe VPA-induced hepatotoxicity mainly concerned children less than 2 years (45). However, fatalities have also been reported in older children and adults (42). Authors agree that fatalities most often occur within the first 3–6 months of therapy (42,45). Hence, VPA should be avoided in patients with known or suspected metabolic disorders.

The mechanisms underlying VPA-induced hepatotoxicity remain incompletely understood, but it has been believed since the early 1980s, based on limited experimental and clinical evidence (46–49), that carnitine depletion, subsequent imbalance between β-oxidation and ω-oxidation, and accumulation of 4-en-VPA are involved. Additionally, carnitine deficiency may result in disruption of mitochondrial functions due to depletion in CoA-SH (14,34,37,50). Reduced serum-free carnitine as well as reduced concentrations of 3-keto-VPA, the main metabolite of β-oxidation of VPA, was first reported in 1982 by Bohles and coworkers (46) in a 3-year-old girl who developed acute liver disease with typical features of Reye's syndrome after treatment with VPA for 6 months. Reduced free carnitine and increased serum and urine acylcarnitine concentrations were also demonstrated in patients with VPA-induced Reye-like syndrome (27). In a patient with fatal VPA-induced hepatotoxicity, Krahenbuhl and coworkers (51) demonstrated a reduction in free and total carnitine concentrations in plasma and liver.

To evaluate the influence of VPA on carnitinemia, as well as the possible etiological role of carnitine in fatal VPA-induced hepatotoxicity, Laub and coworkers (52) prospectively measured total carnitine, free carnitine, and acylcarnitine concentrations in the serum of 21 paediatric patients receiving VPA therapy, 21 healthy matched control individuals, and 21 patients receiving various anticonvulsants other than VPA. The free carnitine concentrations were the lowest ($p < 0.05$) and the short-chain acylcarnitine/free carnitine ratio was the highest ($p < 0.01$) in the VPA group. Moreover, patients receiving polytherapy including VPA had lower total carnitine concentrations than did patients receiving VPA monotherapy ($p < 0.05$). However, carnitine deficiency is probably not the only reason for fatal VPA-induced hepatotoxicity. Indeed, a 3.5-year-old girl developed hepatic failure during VPA therapy even though her serum carnitine concentration was normal, and she died despite oral L-carnitine supplementation.

VPA-induced lipid peroxidation and glutathione depletion are other mechanisms that could also contribute to VPA-induced hepatotoxicity (53). Rat studies have suggested that 4-en-VPA is transformed through β-oxidation to reactive intermediates such as 2-propyl-2,4-pentadienoic acid (2,4-dien-VPA) that deplete mitochondrial GSH (54). While VPA itself failed to induce discernible liver lesions at near lethal doses, unsaturated VPA metabolites (4-en-VPA and 2,4-dien-VPA) are potent inducers of microvesicular steatosis in rats (54). Sequestration of CoA-SH and direct inhibition of specific enzymes in the β-oxidation sequence by CoA esters (especially 4-en-VPA-CoA) are other mechanisms also suggested by rat studies (55).

Role of carnitine in VPA-induced hepatotoxicity

The common mild elevation in aminotransferases is usually reversible with time, or when VPA therapy is discontinued or the dose reduced. Even in severe VPA-induced hepatotoxicity, the prognosis seems to be improved if VPA therapy is promptly discontinued (7).

No animal study has evaluated the effect of L-carnitine when hepatotoxicity has already developed. More than 20 years ago, Sugimoto and coworkers (56) had demonstrated that chronic administration of VPA in rats was associated with significantly lower concentrations of serum-free and total carnitine and higher concentrations of acylcarnitine and acyl to free ratio than those of the controls. The coadministration of phenobarbital further decreased free carnitine concentrations in serum and liver of the rats as compared with rats treated with either VPA or phenobarbital alone. An experimental study in rats treated with therapeutic and toxic doses of VPA showed that carnitine supplementation was able to prevent fatty infiltration and liver necrosis induced by VPA (57).

Although human-controlled studies are lacking, some experimental and clinical evidence suggests that the early administration of intravenous L-carnitine could improve survival in severe VPA-induced hepatotoxicity. Intravenous rather than oral supplementation is usually recommended because it is likely to ensure higher concentrations of carnitine in the blood. Indeed, carnitine has a poor gastrointestinal bioavailability, which is further compromised by digestive dysfunction. Among cases of severe hepatotoxicity occurring during VPA therapy, survival has been reported mainly in those patients treated with carnitine (58–62). This approach is likely to be biased and failures of carnitine therapy have occasionally been reported (52).

In a retrospective series of 92 patients identified by a registry of adverse reactions to VPA (most of whom had chronic illness or were malnourished children) with severe, symptomatic VPA-induced hepatotoxicity, Bohan and coworkers (63) observed an improvement in survival (48%) in 42 patients treated with L-carnitine, as compared with only 10% of the 50 (historical) patients treated solely with aggressive supportive care ($p < 0.001$). Moreover, the 10 patients who were diagnosed within 5 days and treated with intravenous L-carnitine survived. Although these observations are interesting, the comparison with historical control individuals is a serious limitation in the interpretation of these results and such a benefit is not observed in all cases (52,65).

VPA-induced hyperammonemic encephalopathy

VPA-induced hyperammonemia was reviewed recently (64,66). The chronic use of VPA may result in elevated plasma ammonia, even in patients with normal liver tests, and seems therefore to result from underlying mechanisms that are independent of hepatotoxicity (65,66). Hyperammonemia can develop after both acute overdose and acute on therapeutic overdose, as well as during chronic VPA therapy (20,67–75).

The prevalence of hyperammonemia in prospective studies ranged from 70 to 100% (64). Although it remains asymptomatic in almost 50% of cases (21), hyperammonemia can, however, produce clinically significant encephalopathy, which may even be severe. Symptoms of VPA-induced hyperammonemic encephalopathy can appear only a few days after initiation of VPA therapy, or after several months or years of treatment, even in those with normal liver function, despite normal therapeutic doses and serum VPA concentrations, and without any enzymatic disorder of the urea cycle. VPA-induced hyperammonemic encephalopathy occurs almost equally in both genders and in a large range of age, but it is a rather rare phenomenon in adults, especially when VPA is used as monotherapy.

VPA-induced encephalopathy is characterized typically by acute onset of impaired consciousness, disorientation, cognitive slowing, delirium, and sometimes focal neurologic deficits (64,76). Vomiting and seizures or increased seizure frequency may also occur (77). Very high ammonia concentrations have been reported, even with normal liver function tests (78), but there is no clear relationship between clinical severity and blood ammonia concentrations (64,79). The EEG is characterized commonly by a continuous generalized slowing with predominance of theta and delta activity. Occasional bursts of frontal intermittent rhythmic delta activity, and triphasic waves, may be observed suggesting severe encephalopathy (80). Clinical manifestations of VPA-induced hyperammonemic encephalopathy, as well as EEG findings and hyperammonemia, tend to normalize rapidly when VPA therapy is discontinued.

Diagnosis of VPA-induced hyperammonemic encephalopathy in the psychiatric setting (68,78,79,81,82) or in geriatric patients (83,84) may be especially challenging, due to the multiple possible etiologies of mental status changes.

The pathogenesis of hyperammonemic encephalopathy is still incompletely understood. Ammonia readily crosses the blood–brain barrier and is thought to inhibit glutamate uptake, thereby increasing extracellular glutamate concentrations in the brain and resulting in activation of NMDA receptors. NMDA receptor activation is associated with a decrease in phosphorylation by protein kinase C, activation of Na^+-K^+ ATPase, and ATP depletion. Activation of the NMDA receptors is a major factor in the pathogenesis of hyperammonemic encephalopathy and is probably the cause of seizures.

Hyperammonemia associated with VPA therapy has been mainly related to carnitine deficiency. Matsuda and coworkers (27) demonstrated markedly reduced free carnitine concentrations in serum in five hyperammonemic patients (of whom three had a Reye-like syndrome). Various authors have suggested a direct correlation between serum ammonia concentrations and the dose or serum concentrations of VPA, and an inverse correlation with serum concentrations of carnitine (19–21). Actually, in children younger than 2 years of age, who have increased susceptibility for the development of

hyperammonemia, ammonia concentrations seems to be mainly linked to VPA dose or concentrations (69). Lokrantz and coworkers (85) reported the case of an elderly woman on VPA monotherapy in whom VPA-induced hyperammonemic encephalopathy was precipitated by treatment for a urinary tract infection with pivmecillinam – an antibiotic known to decrease the serum concentration of carnitine. Also, metabolites of VPA ω-oxidation (including propionic derivatives and 4-en-VPA) inhibit the mitochondrial CPS I, the first enzymatic step of ammonia elimination via the urea cycle in the liver (8,72,73). This effect appears related to the dose of VPA (86). As acetyl-CoA stores are depleted, the synthesis of NAGA, an important cofactor of CPS I, produced from acetyl-CoA and glutamate by NAGA synthetase, is decreased.

Besides carnitine deficiency, congenital defects of the urea enzymatic cycle (77), a protein-rich diet (21,87), or catabolism induced by fasting (88,89) also promote hyperammonemia. An increase in ammonia production by the kidneys could also contribute to hyperammonemia (77,86), as suggested by both animal (88) and human (89) studies. Indeed, VPA promotes the transport of glutamine through the mitochondrial membrane, thereby enhancing glutaminase activity; ammonia is released as a result of the transformation of glutamine into glutamate (90,91).

Factors other than ammonia may be involved in the pathogenesis of VPA-induced hyperammonemic encephalopathy, including accumulation of lactate, pyruvate, glutamine, and free glucose, and depletion of glycogen and ketone bodies. For example, Verrotti and coworkers (77) demonstrated that VPA-induced hyperammonemic encephalopathy is also associated with an increase in glutamine production in astrocytes, whereas glutamine release was inhibited. Glutamine accumulation increases intracellular osmolarity, promoting an influx of water with resultant astrocytic swelling, cerebral edema, and increased intracranial pressure (62).

Finally, some VPA metabolites could also play a role. For example, the β-oxidation metabolite 2-en-VPA can promote cerebral edema when it accumulates in brain and plasma. This metabolite has a prolonged elimination half-life. Even when β-oxidation is impaired in the setting of VPA toxicity, accumulation of 2-en-VPA could be responsible for prolonged coma despite return of plasma VPA to therapeutic concentrations (69,70). Conversely, effects of VPA in the CNS seem independent of the formation of valproyl-CoA that does not accumulate in brain tissue (92). The development of cerebral edema is not clearly correlated with the dose of VPA (93).

Role of carnitine in VPA-induced hyperammonemic encephalopathy

Administration of exogenous carnitine is thought to help normalization of elevated plasma ammonia concentrations by binding to VPA, thereby enhancing the β-oxidation process and production of acetyl-CoA, and relieving the inhibition of urea synthesis.

Several studies or reports suggest that L-carnitine supplements can be associated with a favorable clinical response (21,23,78,94–98). Carnitine supplementation (52 mg/kg/day) for 4 weeks was shown to correct both carnitine deficiency and hyperammonemia in 14 VPA-treated patients (20). Bohles and coworkers (94) investigated the effects of carnitine supplementation in 69 children and young adults treated with VPA monotherapy. Their mean plasma ammonia concentration was within the normal range, but 24 patients (35.3%) with ammonia concentrations above 800 μg/L (46 μmol/L) were considered hyperammonemic and 15 of these 24 (22.1%) had ammonia concentrations above 1,000 μg/L (58 μmol/L). Total plasma carnitine concentrations were determined in 48 out of 69 patients and were found to be rather low, as was the percentage of free carnitine. Fourteen hyperammonemic and one normoammonemic patients were supplemented with L-carnitine (500 mg/m^2, twice daily). Prolonged L-carnitine supplementation was associated with normalization in plasma ammonia concentrations and marked increase in carnitine concentration in all 15 patients. The plasma ammonia concentrations were significantly correlated with the percentage of free plasma carnitine in plasma ($r = -0.67$, $p < 0.0001$).

Borbath and coworkers (98) reported the case of a 51-year-old woman who received 10 mg/kg VPA daily to prevent seizures after a neurosurgical procedure. She developed VPA-induced hyperammonemic encephalopathy [ammonia concentration 3,980 μg/L (234 μmol/L)] without any sign of hepatic dysfunction. VPA was stopped and L-carnitine supplementation (100 mg/kg) was administered intravenously. Although the initial plasma carnitine concentration was normal in this patient, ammonemia rapidly decreased within 10 h to 600 μg/L (35 μmol/L), her neurological condition improved, and the triphasic waves on the EEG disappeared.

Unfortunately, normalization of ammonia concentrations is not always associated with an improvement of the clinical condition. Hantson and coworkers (99) reported the case of a 47-year-old epileptic man in whom parenteral VPA therapy was associated with a severe hyperammonemic encephalopathy [peak ammonia concentration 7,000 μg/L (411 μmol/L)] without any biological signs of hepatotoxicity. VPA treatment was discontinued and L-carnitine supplementation (100 mg/kg/day) was initiated. Although subsequent normalization in the blood arterial ammonia concentration was observed within 4 days, the patient remained comatose for 3 weeks. The clinical course was correlated with magnetic resonance imaging and multimodal evoked potential findings, but not with ammonia concentrations.

Acute valproic acid poisoning

Acute VPA poisoning is an increasing problem that has been reviewed (5). The clinical and biological features and complications that may be encountered reflect both exaggerated therapeutic effect and impairment in metabolic pathways. In

a series of six severe VPA poisonings, for example, Eyer et al. (67) demonstrated signs of impaired mitochondrial β-oxidation with increase of medium- and long-chain acyl-carnitines in serum as well as hyperammonemia in all six patients. CNS depression is the most common manifestation of toxicity, ranging in severity from mild drowsiness to profound coma and fatal cerebral edema (36,67,93). Severely poisoned patients may develop respiratory and multiorgan failure (67). However, the majority of patients only experience mild to moderate lethargy and recover uneventfully with only supportive care (5,100,101). Although there is no close relationship between plasma VPA concentrations and the severity of CNS toxicity (44,102), patients who ingest more than 200 mg/kg VPA and/or have plasma concentrations greater than 450 mg/L usually develop severe CNS depression (3). In such severe cases, cerebral edema becomes clinically apparent 12 h to 4 days after the overdose (35,66,88,103) although CNS depression may be delayed if a slow-release preparation has been ingested (36,104).

Other clinical findings include respiratory depression, nausea, vomiting, diarrhea, hypothermia or fever, hypotension, tachycardia, miosis, agitation, hallucinations, tremors, myoclonus, and seizures. In contrast to poisoning with phenytoin or carbamazepine, nystagmus, dysarthria, and ataxia are rarely noted following VPA poisoning. Other recognized but rare complications of overdose include heart block, pancreatitis, acute renal failure, alopecia, leucopenia, thrombocytopenia, anemia, optic nerve atrophy, and acute respiratory distress syndrome (36,70). Acute VPA poisoning is associated rarely with a minor and reversible elevation in transaminases (69,70). Hyperammonemia, anion gap metabolic acidosis, hyperosmolality, hypernatremia, and hypocalcaemia may also develop (36,70,93).

Management of acute VPA poisoning is largely supportive. Patients who present early may benefit from gastrointestinal decontamination with a single dose of activated charcoal. Other interventions may involve blood pressure support with intravenous fluids and vasopressors, and correction of electrolyte abnormalities or acid–base disorders (commonly an anion gap metabolic acidosis). Mechanical ventilation may be necessary in patients who require airway protection or who develop cerebral edema or respiratory depression (67).

In patients with renal dysfunction, refractory hypotension, severe metabolic abnormalities, recurrent seizures, or persistent coma, extracorporeal removal by hemodialysis or hemofiltration may be considered although there are no controlled trials that demonstrate an improvement in outcome with these measures (67,105–107).

Role of carnitine in VPA poisoning

Data in this setting remain scattered and consist only of anecdotal case reports. Carnitine supplementation has been shown to reverse metabolic abnormalities and to hasten the resolution of hyperammonemia (5). As far as CNS depression is concerned, clinical observations do not suggest that carnitine is able to hasten the recovery of consciousness (19,75). For example, a healthy, nonepileptic, 16-month-old child was admitted in a deep coma after ingestion of a overdose (~4 g) of VPA (19). Very high serum and urinary concentrations of VPA were documented. Urinary concentrations of the β-oxidation metabolites of VPA were low, whereas concentrations of ω-oxidation metabolites were high. Moreover, the hepatotoxic compound 4-en-VPA was detected in urine. Gastric lavage and general supportive measures were undertaken, including intravenous infusion of saline to increase urine output. Oral L-carnitine was administered for 4 days to correct hypocarnitinemia. Subsequently, the β-oxidation metabolites increased, the ω-oxidation metabolites decreased, and 4-en-valproate was no longer detected in urine. However, the child only regained consciousness on day 4, when his serum VPA concentration reached therapeutic concentrations.

In another child who accidentally ingested 400 mg/kg VPA, decreased β-oxidation and markedly increased ω-oxidation were also observed, and the concentration of 4-en-VPA was markedly increased although there was neither hyperammonemia nor signs of liver dysfunction (75). After L-carnitine supplementation for 3 days, VPA metabolism returned to normal. Once again, the child remained comatose until day 3.

Minville and coworkers (108) also reported a case of severe VPA poisoning in a 36-year-old man. Despite hemodialysis initiated to decrease the high serum VPA concentration and L-carnitine therapy (50 mg/kg/day for 4 days), cerebral edema appeared on the 3rd day. With the usual neuroprotective measures, the patient improved after 4 days and finally recovered without sequelae. Several other cases of VPA poisoning have been reported recently in which IV carnitine supplementation was part of the treatment and was associated with a favorable outcome, but the actual role of carnitine in the evolution is difficult to define (109,110). Severe hepatotoxicity is rare after acute VPA overdose and the lack of transaminase elevation following prophylactic carnitine administration does not necessarily demonstrate any hepatoprotective action.

Carnitine is generally considered safe and well tolerated: an unpleasant fishy odor and mild gastrointestinal upset after oral administration are the only side effects commonly reported. No cases of allergic or other severe adverse reactions have been reported in association with carnitine administration in patients with acute isolated VPA poisoning or mixed overdose including VPA (111,112). Although the benefit of L-carnitine supplementation on clinical outcome has not been demonstrated, the lack of significant adverse effects following its use, the relatively affordable cost of this agent, and the need for its availability for other indications (especially in the management of urea cycle disorders in neonates) has led to recommendations for its administration in VPA poisoning. In 1996, a Paediatric Neurology Consensus Conference (113) recommended carnitine supplementation for children with VPA overdoses. Subsequently, more restrictive

recommendations have limited carnitine supplements to severe overdose (> 400 mg/kg). Now, carnitine administration (preferably IV) is commonly recommended for documented severe VPA toxicity in both children and adults, especially in patients who present with coma, hyperammonemia, or high VPA concentrations [e.g., more than 450 mg/L (111,112)].

Prevention of VPA toxicity

Raskind and El-Chaar (23) extensively reviewed the pathophysiology and significance of VPA-induced carnitine deficiency and evaluated the literature pertaining to carnitine supplementation during VPA therapy in children. Despite the lack of prospective randomized clinical trials, a few studies have shown carnitine supplementation in patients receiving VPA to result in subjective and objective improvements and to prevent VPA-induced hepatotoxicity, in parallel with increases in carnitine serum concentrations. The Paediatric Neurology Consensus Conference in 1996 (113) and some textbooks and manuals (15,114) strongly recommended carnitine supplementation (50–100 mg/kg/day) during VPA therapy for children at risk of developing a carnitine deficiency, in VPA poisoning and in VPA-induced hepatotoxicity. Carnitine supplementation has been classified "grade C" (may be useful) in patients treated with VPA for seizure disorders (115). There is no clear evidence that appreciable toxic effects are associated with the use of carnitine. Moreover, when it is used to prevent carnitine deficiency, carnitine did not seem to alter the anticonvulsant properties of VPA in an experimental model in mice (116).

Until further data become available, L-carnitine supplementation may be recommended to those children on VPA therapy at greatest risk of hepatotoxicity (<2 years of age, more than one anticonvulsant, poor nutritional status, ketogenic diet). In older children or adults, it may be considered if there are clinical symptoms suggestive of carnitine deficiency (hypotonia, lethargy), a significant decrease in the serum-free carnitine concentrations, an impairment in hepatic function tests, or hyperammonemia, even in the absence of VPA-induced hyperammonemic encephalopathy.

Conclusions

Intravenous L-carnitine supplementation does not appear to be harmful and could be beneficial in patients with VPA-induced hepatotoxicity or hyperammonemia, regardless of whether the exposure to VPA was acute, chronic, or both. An improvement of liver function is, however, not always observed, and the decrease of ammonia concentrations is not always associated with an improvement of consciousness in VPA-induced hyperammonemic encephalopathy.

Although carnitine appears to normalize the metabolic pathways of VPA in acute VPA poisoning, the few clinical data that are available do not support the use of carnitine to hasten recovery in patients with VPA-induced CNS depression. However, its use should be considered in high-risk patients (especially children or those who have ingested large amounts of VPA) and those with VPA-induced hyperammonemia or hepatotoxicity.

The potential value of prophylactic oral L-carnitine supplementation in preventing adverse effects due to VPA-induced dysfunction of β-oxidation is suggested by several studies and isolated observations, especially in patients at risk of carnitine deficiency. A better delineation of the therapeutic and prophylactic value of L-carnitine in each of these conditions is still needed and would require further clinical investigations in controlled randomized multicenter trials.

Competing interests

The authors declare that they have no competing interests.

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