Levocarnitine for valproic-acid-induced hyperammonemic encephalopathy

CHRISTIE M. MOCK AND KRISTEN H. SCHWETSCHENAU

Purpose. The use of levocarnitine for the treatment of valproic-acid-induced hyperammonemic encephalopathy (VHE) is reviewed.

Summary. VHE is generally characterized by an acute onset of impaired consciousness, focal neurologic symptoms, and increased seizure frequency. The exact mechanism of VHE is unclear but relates to the accumulation of toxic valproic acid metabolites and elevated ammonia levels. Carnitine is an essential cofactor in the proper metabolism of valproic acid and ammonia elimination. A lack of carnitine is thought to contribute to hyperammonemia. Valproic acid is thought to increase renal metabolism of glutamate and may contribute to ammonia production. Levocarnitine, the active isomer of carnitine, has been used to treat VHE resulting from valproic acid overdose as well as usual dosages of valproic acid. A literature search of PubMed was conducted for all English-language articles published from 1948 to May 2011 regarding the use of levocarnitine for VHE. Search terms included *levocarnitine*, *l-carnitine*, *valproic acid*, and *hyperammonemia encephalopathy*. Although large, randomized controlled trials of levocarnitine treatment in VHE are lacking, levocarnitine has been shown to be generally safe and effective in retrospective trials and case reports. Overall, there is more literature supporting the use of levocarnitine in VHE associated with acute overdose than with short- or long-term treatment with usual dosages of valproic acid. No adverse events related to levocarnitine therapy were reported in any of the literature reviewed. Prospective trials are needed to further support the efficacy and safety of levocarnitine in the treatment of VHE.

Conclusion. Levocarnitine may be effective and appears to be safe in the treatment of VHE.

Index terms: Amino acids; Anticonvulsants; Dosage; Encephalopathy; Hyperammonemia; L-Carnitine; Metabolism; Toxicity; Valproic acid

Am J Health-Syst Pharm. 2012; 69:35-9

Valproic acid is used to treat various seizure disorders and psychiatric disorders. Serum valproic acid concentrations should be monitored to ensure that an appropriate target range is maintained (50–100 µg/mL for epilepsy and 85–125 µg/mL for mania).[1] Concentrations exceeding 200 µg/mL are considered toxic, but serum valproic acid concentrations correlate poorly with clinical effects, as toxicity can occur at lower serum concentrations.[1] Valproic acid toxicity can manifest as altered mental status, hepatotoxicity, pancreatitis, bone marrow suppression, metabolic acidosis, gastrointestinal upset, seizures, behavioral changes, extrapyramidal disorders, and hyperammonemic encephalopathy.[2,3]

Valproic-acid-induced hyperammonemic encephalopathy

Valproic-acid-induced hyperammonemic encephalopathy (VHE) is generally characterized by an acute onset of impaired consciousness, focal neurologic symptoms, and increased seizure frequency. Approximately half of patients treated with valproic acid develop asymptomatic hyperammonemia that does not require intervention.[2,3]

VHE risk factors. There are multiple risk factors for the development of VHE. Patients who are treated with multiple anticonvulsants (such as valproic acid combined with phenobarbital, phenytoin, or carbamazepine) have an increased risk of VHE.[4] While liver dysfunction can be a VHE risk factor, VHE also occurs in patients with normal liver function test results. The reason for this is not

CHRISTIE M. MOCK, PHARM.D., BCPS, is Clinical Specialist in Internal Medicine, Wishard Health Services, Indianapolis, IN; at the time of writing she was Postgraduate Year 1 Pharmacy Resident, Cincinnati Veterans Affairs Medical Center, Cincinnati, OH. KRISTEN H. SCHWETSCHENAU, PHARM.D., is Clinical Pharmacist, Cincinnati Veterans Affairs Medical Center.

Address correspondence to Dr. Mock at Wishard Health Services, 1001 West 10th Street, Indianapolis, IN 46202 (christina.mock@wishard.edu).

The assistance of Jason Heitt, Pharm.D., BCPS, and Dan Knight, Pharm.D., is acknowledged.

The authors have declared no potential conflicts of interest.

DOI 10.2146/ajhp110049

The Clinical Consultation *section features articles that provide brief advice on how to handle specific drug therapy problems. All articles are based on a systematic review of the literature. The assistance of ASHP's Section of Clinical Specialists and Scientists in soliciting* Clinical Consultation *submissions is acknowledged. Unsolicited submissions are also welcome.*

completely understood.[2-4] Metabolic abnormalities (e.g., carnitine deficiency), congenital defects in the urea enzymatic cycle, a protein-rich diet, and hypercatabolic states may also increase ammonia production.[2-4]

Mechanism of VHE. The exact mechanism of VHE is unclear but relates to the accumulation of toxic valproic acid metabolites and elevated ammonia levels. Valproic acid is a branched-chain carboxylic acid that has a chemical structure similar to that of short-chain fatty acids. It undergoes extensive hepatic metabolism through glucuronidation, mitochondrial beta-oxidation, and, to a lesser extent, cytosolic omega-oxidation.[2] Carnitine is an essential cofactor in mitochondrial beta-oxidation. It is thought that depletion of carnitine stores during long-term or high-dosage valproic acid therapy results in a shift from mitochondrial beta-oxidation to increased omega-oxidation. This increases the production of toxic metabolites from omega-oxidation, including 2-propyl-2-pentenoic acid (a possible cause of cerebral edema), 2-propyl-4-pentenoic acid (a possible cause of hepatotoxicity), and propionic acid. The propionic acid metabolite inhibits mitochondrial carbamyl phosphate synthetase I, an enzyme involved in ammonia elimination. This decrease in ammonia elimination results in greater levels of ammonia in the blood, which can cause encephalopathy.[2-6] Overall, ammonia concentrations are directly correlated with the dosage and serum concentrations of valproic acid and inversely correlated with serum concentrations of carnitine.[7-9]

The effects of valproic acid on the kidneys may also contribute to hyperammonemia. It is theorized that valproic acid causes more glutamine to be transported across the mitochondrial membrane in the kidneys. As this additional glutamine is metabolized to glutamate, more ammonia is produced.[10]

Carnitine deficiency and levocarnitine

Carnitine is both synthesized endogenously and obtained from dietary sources. It is an essential cofactor in the metabolism of fatty acids into acyl-carnitines and aids in their transport into the mitochondrial matrix, where they are used for energy production in the Krebs cycle.[2-9] Carnitine deficiency can occur from both primary and secondary causes. Primary causes include autosomal recessive diseases in which the renal or gastrointestinal transport of carnitine is impaired or endogenous synthesis of carnitine is lacking.[2-9] Secondary causes include organic acidurias, intermittent hemodialysis, and long-term total parenteral nutrition.[11] Finally, carnitine is thought to be depleted in valproic acid metabolism.[2-9]

Levocarnitine, the active isomer of carnitine, is used to treat carnitine deficiency. The time to reach maximum serum carnitine concentrations during oral levocarnitine use is approximately 3–5 hours.[6,11,12] The half-life of levocarnitine in healthy volunteers ranges from 2 to 15 hours. The metabolism and excretion of levocarnitine have not been fully elucidated. Higher percentages of i.v. versus oral doses have been found unchanged in urine (70–100% versus 7–34%, respectively); this difference has been attributed to metabolism by intestinal flora after oral administration. The amount of drug administered also may affect metabolism and excretion. The drug is primarily excreted in the urine, with less than 2% eliminated in the feces.

Transient nausea and vomiting are the most common adverse effects of levocarnitine.[6,11,12] Rare but more serious adverse effects include hypertension, hypotension, tachyarrhythmias, chest pain, headache, hypercalcemia, anemia, and seizures (in patients with and without a history of seizures). Desired effects of levocarnitine have been reported at plasma levocarnitine concentrations of 35–60 μmol/L.

VHE treatment

Treatment of VHE includes discontinuing valproic acid therapy and correcting other potential causes of encephalopathy, such as electrolyte disorders, drug overdoses, acid-base disorders, sepsis, and Wernicke's encephalopathy. Otherwise, VHE management includes general supportive care to protect the airway and maintain hemodynamic stability. Case reports have described the use of lactulose to treat VHE,[3-5] though lactulose has not specifically been studied for that indication. Lactulose lowers the gastrointestinal pH and favors the conversion of ammonia to ammonium in the gut. Ammonium, a polar molecule, cannot be reabsorbed through the colon membrane and is therefore excreted.

In several case reports, naloxone has reversed somnolence and respiratory depression in acute valproic acid toxicity not associated with opioid intoxication.[13-16] Conversely, some case reports have described naloxone as being ineffective in treating valproic acid toxicity. Decontamination with activated charcoal is often used in an acute overdose; in severe cases, hemodialysis is performed.[3-5]

The evidence supporting the abovementioned therapies for VHE is limited; however, levocarnitine remains a potential treatment option for hyperammonemic encephalopathy in patients on valproic acid therapy.

A literature search of PubMed was conducted for all English-language articles published from 1948 to May 2011 regarding the use of levocarnitine for VHE. Search terms included *levocarnitine*, *l-carnitine*, *valproic acid*, and *hyperammonemia encephalopathy*. Although large, randomized controlled trials of levocarnitine treatment in VHE are lacking, levocarnitine has been shown to be generally safe and effective in retrospective trials and case reports.[4,6,17-24] Overall, there is more literature supporting the use of levocarnitine in VHE associated with acute overdose than with short- or long-term treatment with usual dosages of valproic acid.

VHE secondary to acute valproic acid overdose

Several review articles have described the use of levocarnitine for VHE secondary to acute valproic acid overdose.[4,6,17,18] The authors of these reviews have generally concluded that while extensive published evidence is lacking, levocarnitine could be considered in the treatment of VHE, as acute valproic acid overdoses can be life threatening. These conclusions are based on the effectiveness documented in case reports and the general safety of levocarnitine. All reviews mentioned the need for future studies to further evaluate safety and efficacy and to establish appropriate dosing regimens. The authors also discussed that reducing a patient's ammonia level does not always result in clinical improvement of consciousness and that levocarnitine has not been shown to hasten the reversal of general central nervous system depression related to valproic acid overdose.

The safety of levocarnitine administration in overdoses, including valproic acid overdoses, was evaluated in a retrospective study.[19] More than 300,000 charts from a poison center were reviewed to determine if patients who received levocarnitine sustained any adverse events. Adverse events were defined as hypotension or allergic reactions. Of the 674 patients who ingested valproic acid, 19 patients had isolated valproic acid ingestions with elevated ammonia levels. These 19 patients received a total of 55 doses of levocarnitine with no adverse events. An unreported number of patients with mixed overdoses including valproic acid who also had elevated ammonia levels received 196 doses of levocarnitine with no adverse events. The authors concluded that levocarnitine can safely be administered in patients with valproic acid toxicity who have hyperammonemia. Limitations of the study included its retrospective nature and the evaluation of only two adverse events (i.e., hypotension and allergic reactions), which are not the most commonly occurring or the most serious with levocarnitine use. In addition, the doses of levocarnitine were not reported, and there was no statistical analysis of the data. It is also uncertain if the same results would be found in VHE associated with usual dosages of valproic acid. The results of the study supported the safety of levocarnitine use in valproic acid toxicity, but prospective studies are needed to further investigate the safety and efficacy of this treatment.

VHE associated with usual dosages of valproic acid

VHE can also occur in patients receiving usual valproic acid dosages for short- or long-term treatment, but data on the use of levocarnitine in these patients are limited.

Long-term valproic acid therapy. Barrueto and Hack[20] reported the case of a 41-year-old man who arrived at the emergency department in an unconscious state with hyperammonemia (serum ammonia concentration, 377 µmol/L), normal hepatic function, and a serum valproic acid concentration within the target range (73.5 µmol/L). He had been taking valproic acid for more than 3 years, and no recent dosage changes were noted. His valproic acid was discontinued, and levocarnitine 10 g (100 mg/kg) i.v. over one hour was administered. Within seven hours, his serum ammonia concentration dropped to 47 µmol/L, and he was alert and oriented. Valproic acid was not resumed in this patient.

In another case report, Raby[21] described a 38-year-old woman who had been treated with valproic acid 1000 mg daily for six months and reported increasingly frequent periods of slowing cognition and lethargy. She had normal liver function test values, a serum valproic acid concentration of 73 µmol/L, and a serum ammonia concentration of 101 µmol/L. Valproic acid was continued, and levocarnitine 1 g orally twice daily was initiated. Her lethargy diminished over the next two weeks, and her serum ammonia concentration decreased to 22 µmol/L.

Short-term valproic acid therapy. Raby[21] reported the case of a 24-year-old woman who was a strict vegetarian and developed fatigue, lethargy, and nausea 10 days after initiating valproic acid. Her dosage had been increased to 500 mg twice daily, and her serum ammonia concentration was 101.5 µmol/L. The valproic acid dosage was subsequently decreased to 250 mg every morning and 500 mg every evening. Her lethargy persisted, and further testing revealed normal liver function test values, a serum valproic acid concentration of 89.9 µmol/L, and a serum ammonia concentration of 51 µmol/L. The valproic acid was continued at 250 mg daily, and levocarnitine 1 g orally twice daily was initiated. Ten days later, her symptoms resolved, and her serum ammonia concentration decreased to 28 µmol/L. It was postulated that her strict diet may have caused carnitine deficiency and contributed to VHE.

Borbath et al.[22] described the successful use of levocarnitine in a 51-year-old woman who developed

VHE after receiving valproic acid 10 mg/kg i.v. daily to prevent seizures after neurosurgery. She had a valproic acid level within the target range, normal liver function test values, and an elevated serum ammonia concentration (234 µmol/L). After discontinuation of valproic acid and initiation of levocarnitine 100 mg/kg i.v., her serum ammonia concentration decreased to 35 µmol/L. Her neurologic status improved within 18 hours.

Another case report described a 33-year-old woman who became lethargic and developed changes in mental status after two days of treatment with divalproex sodium (equivalent to valproic acid 1500 mg) orally at bedtime. The woman, who was taking multiple psychotropic medications, had a serum ammonia concentration of 283 µmol/L and a serum valproic acid concentration of 120 µmol/L.[23] Her mental status improved several hours after withholding all psychiatric medications and administering levocarnitine 3 g i.v. Levocarnitine 990 mg orally three times daily and lactulose 30 mL orally every six hours were administered for seven days. Factors that likely contributed to this patient's altered mental status included a high starting dosage of valproic acid, not dividing the dose of valproic acid, and polypharmacy.

In contrast, one case report revealed no clinical benefit when ammonia levels normalized after administering levocarnitine for the treatment of VHE.[24] A 47-year-old man with a history of generalized seizures (for which his outpatient regimen included phenytoin and carbamazepine) arrived in the emergency department with acute generalized seizures. He was given a loading dose of valproic acid 10 mg/kg (as valproate sodium), followed by valproic acid 1 mg/kg/hr i.v. When the seizures subsided, he remained unconscious. Status epilepticus was ruled out through continuous electroencephalogram monitoring during the first 24 hours. By day 7, he developed hyperammonemic encephalopathy, with a serum ammonia concentration of 411 µmol/L, a serum valproic acid concentration within the target range (91.5 µmol/L), and no signs of hepatotoxicity. Valproic acid was discontinued, and levocarnitine 100 mg/kg i.v. daily was administered. The patient's serum ammonia concentrations returned to normal within four days, yet the patient remained in a coma for three weeks. His neurologic status on discharge was poor (Glasgow Outcome Scale score of 2). Electroencephalogram, head computed tomography, and magnetic resonance imaging results and multimodal evoked potentials were followed closely in this patient, showing progression to brain atrophy. Brain stem abnormalities on imaging correlated with his clinical status. The pathophysiology related to seizures likely contributed to his continued coma, making it difficult to ascertain whether this was a true clinical failure of levocarnitine. The use of concomitant antiepileptic medications may have increased the patient's risk of hyperammonemia.

In addition to short-term treatment of VHE, the use of levocarnitine supplementation during long-term valproic acid therapy has been postulated as a way to enhance carnitine stores and promote mitochondrial beta-oxidation of valproic acid, therefore preventing VHE. A complete discussion of levocarnitine for VHE prevention is beyond the scope of this review, but it is an area for further research.

Dosing and administration of levocarnitine for VHE

The appropriate dosage of levocarnitine for VHE is not well defined. Levocarnitine's indication in the Food and Drug Administration-approved labeling is for short- and long-term treatment of patients with an inborn error of metabolism resulting in secondary carnitine deficiency.[12] The labeled dosage for this indication is 50 mg/kg/day in divided doses every three to six hours. Doses can be given as i.v. push over two to three minutes or as i.v. infusions. In severe metabolic crises, an i.v. loading dose of 50 mg/kg can be administered. The maximum dose per the package insert is 300 mg/kg. Dosing in severe renal disease and end-stage renal disease has not been established. Levocarnitine is available as a 200-mg/mL i.v. solution, a 330-mg oral tablet, and a 100-mg/mL oral solution.

A recent review recommended the following dosing strategy for acute valproic acid overdose: levocarnitine 100 mg/kg i.v. once, followed by 50 mg/kg i.v. (maximum 3 g per dose) every eight hours thereafter, continuing until serum ammonia levels decrease, clinical improvement is seen, or adverse effects are evident.[17] Similarly, most of the published case reports and reviews described the use of a 50–100-mg/kg i.v. dose, followed by 50–100 mg/kg/day i.v. or 250–990 mg orally three times daily. The Pediatric Neurology Advisory Committee has recommended 150–500 mg/kg i.v. per day (maximum, 3 g/day) as rescue therapy for valproate-induced hepatotoxicity.[18] Another review recommended the following for acute valproic acid ingestion in children: a loading dose of 100 mg/kg i.v. over 30 minutes (maximum, 6 g) followed by a maintenance dose of 15 mg/kg i.v. over 10–30 minutes every four hours.[25]

Discussion

The literature suggests that levocarnitine may be effective for VHE as part of general supportive therapy, with no adverse events reported with its use. However, these data are mostly from case reports. Prospective studies would be beneficial to further support or refute the efficacy and safety of levocarnitine in VHE. Future trials should also seek to

establish standardized dosing recommendations for different clinical situations (i.e., short-term overdose versus VHE secondary to usual dosages). Until those studies are performed, levocarnitine 100 mg/kg i.v. followed by 50 mg/kg/day i.v., with a maximum of 3 g/day i.v., may be considered as part of the treatment regimen for VHE secondary to overdoses or usual dosages of valproic acid.

Conclusion

Levocarnitine may be effective and appears to be safe in the treatment of VHE.

References

1. Lexi-Drugs Online. Valproic acid. www.crlonline.com/crlonline (accessed 2009 Sep 21).
2. Verrotti A, Trotta D, Morgese G et al. Valproate-induced hyperammonemic encephalopathy. *Metab Brain Dis.* 2002; 17:367-73.
3. POISINDEX Management. Valproic acid. www.thomsonhc.com (accessed 2009 Sep 21).
4. Lheureux P, Hantson P. Carnitine in the treatment of valproic acid-induced toxicity. *Clin Toxicol.* 2009; 47:101-11.
5. Burns MJ, Palmer BF. Valproic acid poisoning. http://uptodateonline.com (accessed 2009 Sep 21).
6. Lheureux P, Penaloza A, Zahir S et al. Science review: carnitine in the treatment of valproic acid-induced toxicity—what is the evidence? *Crit Care.* 2005; 9:431-40.
7. Ishikura H, Matsui N, Matsubara M et al. Valproic acid overdose and l-carnitine therapy. *J Anal Toxicol*. 1996; 20:55-8.
8. Ohtani Y, Endo F, Matsuda I. Carnitine deficiency and hyperammonemia associated with valproic acid therapy. *J Pediatr*. 1982; 101:782-5.
9. Gidal BE, Inglese CM, Meyer JF et al. Diet- and valproate-induced transient hyperammonemia: effect of L-carnitine. *Pediatr Neurol*. 1997; 16:301-5.
10. Mallet L, Babin S, Morals JA. Valproic acid-induced hyperammonemia and thrombocytopenia in an elderly woman. *Ann Pharmacother*. 2004; 38:1643-7.
11. Goa KL, Brogden RN. L-carnitine: a preliminary review of its pharmacokinetics, and its therapeutic use in ischemic cardiac disease and primary and secondary carnitine deficiencies in relationship to its role in fatty acid metabolism. *Drugs*. 1987; 34:1-24.
12. Carnitor (levocarnitine) package insert. Gaithersburg, MD: Sigma-Tau Pharmaceuticals, Inc.; 2004.
13. Steiman GS, Woerpel RW, Sherard ES Jr. Treatment of accidental sodium valproate overdose with an opiate antagonist. *Ann Neurol.* 1979; 6:274.
14. Alberto G, Erickson T, Popiel R et al. Central nervous system manifestations of a valproic acid overdose responsive to naloxone. *Ann Emerg Med.* 1989; 18:889-91.
15. Montero FJ. Naloxone in the reversal of coma induced by sodium valproate. *Ann Emerg Med.* 1999; 33:357-8.
16. Espinoza O, Maradei I, Ramírez M et al. An unusual presentation of opioid-like syndrome in pediatric valproic acid poisoning. *Vet Hum Toxicol.* 2001; 43:178-9.
17. Perrott J, Murphy NG, Zed PJ. L-carnitine for acute valproic acid overdose: a systematic review of published cases. *Ann Pharmcother.* 2010; 44:1287-93.
18. Raskind JY, El-Chaar GM. The role of carnitine supplementation during valproic acid therapy. *Ann Pharmacother*. 2000; 34:630-8.
19. LoVecchio F, Shriki J, Samaddar R. L-carnitine was safely administered in the setting of valproate toxicity. *Am J Emerg Med*. 2005; 23:321-2.
20. Barrueto F, Hack JB. Hyperammonemia and coma without hepatic dysfunction induced by valproate therapy. *Acad Emerg Med*. 2001; 8:999-1001.
21. Raby WN. Carnitine for valproic acid-induced hyperammonemia. *Am J Psychiatry*. 1997; 154:8-9.
22. Borbath I, de Barsy TH, Jeanjean A et al. Severe hyperammonemic encephalopathy shortly after valproic acid prescription and rapid awakening following levocarnitine. *J Toxicol Clin Toxicol*. 2000; 38:219-20.
23. Eubanks AL, Aquirre B, Bourgeois JA. Severe acute hyperammonemia after brief exposure to valproate. *Psychosomatics*. 2008; 49:82-3.
24. Hantson P, Grandin C, Duprez T et al. Comparison of clinical, magnetic resonance and evoked potentials data in a case of valproic-acid-related hyperammonemic coma. *Eur Radiol*. 2005; 15:59-64.
25. Russell S. Carnitine as an antidote for acute valproate toxicity in children. *Curr Opin Pediatr*. 2007; 19:206-10.