Levocarnitine for Valproic Acid Hyperammonemia and Hepatotoxicity

Question:
What is the role of levocarnitine in valproic acid/divalproex sodium induced hyperammonemia or hepatotoxicity?

Answer:
Levocarnitine (L-carnitine) has been shown to play an integral part in the management of hyperammonemia and hepatotoxicity associated with valproic acid (VPA) therapy. Retrospective reviews and case reports have demonstrated efficacy when using it in patients on therapeutic doses of VPA, and currently a guideline for use is available through the Georgia Poison Center. Patients who are demonstrating signs of encephalopathy with VPA levels >200 mcg/mL, have evidence of hepatotoxicity, or who have VPA levels >450 mcg/mL should be considered for L-carnitine therapy.

Dosing currently recommended:
- IV: L-carnitine 100 mg/kg (max. 6g) (initial dose) infused over 30 minutes, followed by 15 mg/kg Q4-6h infused over 10-30 minutes
- PO: L-carnitine 20-33 mg/kg/dose (maximum single dose 1g) q8h

Explanation:
Carnitine is an amino acid that is important for mitochondrial utilization of fatty acids and is necessary for the transport of valproic acid (VPA) into the mitochondria. The FDA has approved levocarnitine (L-carnitine) for primary or secondary carnitine deficiencies and use in hemodialysis. L-carnitine also has an orphan drug destination status for the prevention and treatment of secondary carnitine deficiency in VPA toxicity.1,2

VPA has been demonstrated to cause hyperammonemia (>80 mcg/dL or 35 µmol/L) without predictability for symptoms or hepatic dysfunction. This can occur with both therapeutic dosing or in acute overdoses, often with corresponding reductions in serum L-carnitine concentrations. Hyperammonemia results from the stimulation of glutaminase which increases glutamate uptake and ammonia release from the kidney. The reduction in serum glutamate then decreases the production of a co-factor that is necessary to convert ammonia to urea in the liver.2 Okamura and colleagues demonstrated that VPA combines with L-carnitine to form valproylcarnitine, thereby resulting in decreased β-oxidation of fatty acids and potentially inhibiting renal resorption of L-carnitine.3 VPA has also been shown to cause hepatotoxicity with elevated AST/ALT. L-carnitine deficiency inhibits mitochondrial β-oxidation of VPA and other fatty acids, which then cause hepatocellular accumulation.2

The most compelling evidence for use of L-carnitine in patients came from Bohen and colleagues who utilized the International Registry for Adverse Reactions to valproic acid to conduct a retrospective analysis using patients on chronic valproic acid/divalproex sodium therapy. The study compared patients with acute, symptomatic hepatic dysfunction who were not treated with L-carnitine (n=50) to patients treated with L-carnitine (n=42). A total of 10% of patients who were not treated with L-carnitine survived, while 48% of patients treated with L-carnitine survived. This was a statistically significant difference in overall survival between the two groups (p <0.001). The average doses of L-carnitine ranged from 50-100mg/kg/day with a statistically significant difference in survival for patients treated with IV vs. enteral L-carnitine (p<0.001) within the first 5 days of hepatotoxicity development.4
Glatstein et al performed a retrospective chart review that identified pediatric patients with valproic acid-induced hyperammonemic encephalopathy by looking at exposure history, clinical manifestations, physical exam, and laboratory values. Thirteen cases were identified in total, including patients taking VPA therapeutically (n=12) or who had a VPA overdose (n=1). VPA concentrations ranged from 68-600 mcg/mL, the maximum ammonia concentration was 557 µmol/L, and there was minimal or no evidence of hepatotoxicity. L-carnitine was given IV as 100mg/kg/day (n=12) or 200mg/kg/day (n=1) in 3 divided doses. All patients made a full recovery with no adverse events or toxicities reported to L-carnitine. Several case reports have also been published demonstrating the potential benefit of L-carnitine in acute overdoses of VPA. Papaseit et al described a 30-year-old man who intentionally ingested an estimated 35 g of extended-release VPA 15 hours prior to admission. An initial VPA plasma concentration was 391 mcg/mL with clinical evidence of hyperammonemic encephalopathy and no evidence of hepatotoxicity. L-carnitine (1 g 3 times per day) IV was administered for 24 hours. The patient’s level of consciousness improved, VPA levels decreased (to therapeutic range), and ammonia concentrations decreased approximately 13 hours later (28 hours post-ingestion). Borbath and colleagues discussed a 51 year old women who presented 10 days after starting VPA at 10mg/kg/day with severe hyperammonemic encephalopathy. L-carnitine was administered at 100 mg/kg IV, and blood arterial ammonia concentrations decreased from 234 to 35 mmol/L 10 hours post L-carnitine. Her neurologic condition improved within 18 hours. The Georgia Poison Center recommends the use of L-carnitine in patients who present with a valproate level >200-250mcg/mL and have signs of encephalopathy. L-carnitine can be considered for use in specific patients who have evidence of hepatotoxicity, valproate levels >450 mcg/mL, are <2 years in age or have a poor nutritional status.

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References:

8. Guideline for Management of Valproic Acid Ingestions [Internet]. Atlanta, GA: Georgia Poison Center; 2016 [cited 2018 May 3].
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Hyperammonemia results from the stimulation of glutaminase which increases glutamate uptake and ammonia release from the kidney. The reduction in serum glutamate then decreases the production of a co-factor that is necessary to convert ammonia to urea in the liver. VPA has also been shown to cause hepatotoxicity with elevated AST/ALT. L-carnitine deficiency inhibits mitochondrial β-oxidation of VPA and other fatty acids, which then cause hepatocellular accumulation.²

The most compelling evidence for use of L-carnitine in patients came from Bohan and colleagues who retrospectively compared patients with acute, symptomatic hepatic dysfunction who were not treated with L-carnitine (n=50) to patients treated with L-carnitine (n=42). Only 10% of patients who were not treated with L-carnitine survived, while 48% of patients treated with L-carnitine survived (p <0.001). There was also a statistically significant difference in survival for patients treated with IV vs. enteral L-carnitine (p<0.001) within the first 5 days of hepatotoxicity development.³ Glatstein et al performed a retrospective chart review of pediatric patients with valproic acid-induced hyperammonemic encephalopathy. Thirteen cases were identified in total, including patients taking VPA therapeutically (n=12) or who had a VPA overdose (n=1). VPA concentrations ranged from 68-600 mcg/mL, the maximum ammonia concentration was 557 µmol/L, and there was minimal or no evidence of hepatotoxicity. L-carnitine was given IV as 100mg/kg/day (n=12) or 200mg/kg/day (n=1) in 3 divided doses. All patients made a full recovery with no adverse events or toxicities reported to L-carnitine.⁴

The Georgia Poison Center recommends the use of L-carnitine in patients who are demonstrating signs of encephalopathy with VPA levels >200 mcg/mL, have evidence of hepatotoxicity, or who have VPA levels >450 mcg/mL should be considered for L-carnitine therapy. Patients who are <2 years in age or have a poor nutritional status should also be considered for L-carnitine therapy associated with VPA ingestions or usage. Intravenous therapy is more commonly utilized, however enteral therapy may be reserved for patients with less severe manifestations of VPA toxicity and at a Toxicologist’s discretion. The route of administration is also dependent on the patient’s ability to tolerate enteral therapy.

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