

## Rapid Rescue from Hyperammonemic Coma After Valproic Acid Poisoning: Dual Therapy with Continuous Renal Replacement Therapy and L-carnitine Supplementation

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### Abstract

Acute hyperammonemia following valproic acid poisoning is a medical emergency which can lead to irreversible neurological damage, metabolic derangements, and liver failure. Although treatment with renal replacement therapy and L-carnitine supplementation is well documented, scant literature is available in using both modalities together.

**Case details:** We report a case with rapid rescue from life threatening hyperammonemic coma secondary to intentional valproic acid overdose by using dual therapy of continuous veno-venous hemodialysis in combination with L-carnitine supplementation. The patient presented with rapid decline in mental status requiring intubation. The patient's condition rapidly improved upon initiation of treatment, and there were no apparent sequelae from his overdose at the time of discharge.

**Discussion:** Treatment of life threatening valproic acid toxicity must clear valproic acid and ammonia from serum, curb the production of ammonia, control fluid balance, and maintain appropriate serum electrolyte levels. Prompt initiation of dual therapy with renal replacement therapy and L-carnitine supplementation facilitated a swift and complete recovery in this patient.

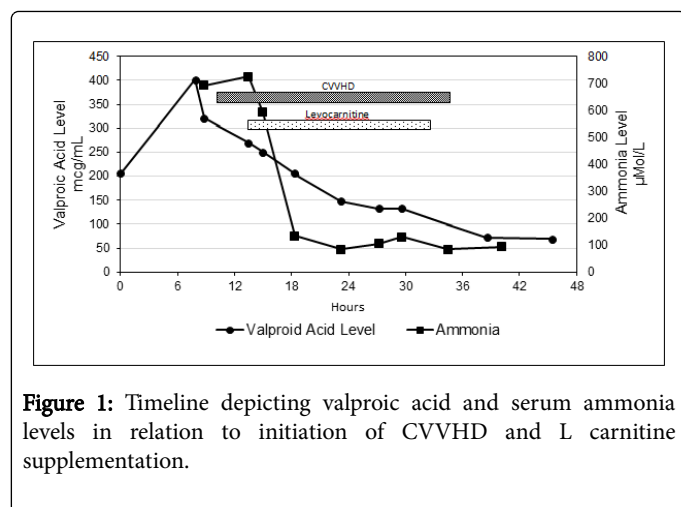
**Keywords:** Hyperammonemic coma; Renal replacement therapy; L-carnitine; Valproic acid tablets

### Introduction

Valproic acid is a carboxylic acid initially approved by the FDA in 1978. It is used in its various formulations to treat complex partial seizures, absence seizures, bipolar mania, and prophylaxis of migraine headaches. It is thought to work by increasing gamma-aminobutyric acid (GABA) levels in the brain. Therapeutic serum concentrations are usually between 50 to 100 mcg/mL depends on the condition being treated [1]. Life threatening complications of valproic acid toxicity such as CNS depression, respiratory depression, metabolic acidosis, hyperammonemia, and liver failure can occur across a wide range of serum concentrations but are strongly associated with serum concentrations >450 mcg/mL [2]. Valproic acid leads to hyperammonemia by increasing serum propionic acid levels, which inhibits carbamoyl phosphate synthase, a rate limiting enzyme in the metabolism of ammonia *via* the urea cycle [3]. Although the optimal treatment of valproic acid toxicity is unknown, treatment modalities previously shown by retrospective analysis to be helpful include carnitine supplementation, activated charcoal, and renal replacement therapy [4,5]. We describe the use and role of dual therapy with renal replacement therapy and L-carnitine for rapid rescue of acute valproic acid toxicity induced hyperammonemic coma following an intentional medication overdose.

### Case Report

A 57-year-old with a history of bipolar disorder presented to the Emergency Department after reportedly consuming 2 handfuls of his prescribed 500 mg delayed-release valproic acid tablets approximately 30 minutes prior to arrival. The patient had a brief period of alertness in the Emergency Department followed by drowsiness, combativeness, and progressive deterioration of mental status. Despite prompt treatment with gastric decontamination, the valproic acid level increased to >450 mcg/mL, and the ammonia level reached >700 umol/L. The patient developed hyperammonemic coma requiring endotracheal intubation for airway protection. Considering the patient's ongoing risk for cerebral edema from hyperammonemia, prompt initiation of dual therapy with L-carnitine and renal replacement therapy using CVVHD was started in the intensive care unit. L-carnitine 2000 mg IV administration was implemented followed by weight based approach of 1625 mg IV every four hours. After initiation of L-carnitine and CVVHD, there was a rapid decline in ammonia levels and valproic acid levels (Figure 1) and dramatic improvement in mental status. CVVHD and L-carnitine were discontinued after approximately 24 hours. He was then given lactulose and rifaximin for hyperammonemia maintenance therapy which was later tapered down and discontinued. He was extubated on hospital day 3. He was subsequently transferred to a general floor where his condition continued to improve. Psychiatry was consulted for his bipolar disorder and medication overdose. He was discharged home on hospital day 9.



**Figure 1:** Timeline depicting valproic acid and serum ammonia levels in relation to initiation of CVVHD and L carnitine supplementation.

## Discussion

Acute intoxication due to valproic acid most often results in mild CNS depression, but it can occasionally lead to coma and/or cerebral edema. Progression of CNS depression is usually rapid and unpredictable as the serum concentration of valproic acid does not correlate well with clinical severity. When it occurs, cerebral edema secondary to valproic acid overdose can result in early herniation and ischemia. Likewise, the serum concentration of ammonia is known to correlate poorly with neurologic symptoms; however, serum ammonia levels >150-200  $\mu\text{Mol/L}$  are associated with increased ICP and brain herniation [6]. For these reasons, providers should not hesitate to pursue rapid rescue of patients with elevated ammonia levels in the setting of valproic acid toxicity.

L-carnitine is an essential cofactor for the metabolism of both valproic acid and ammonia. Omega oxidation of valproic acid increases when the body is depleted of carnitine. The products of this omega oxidation further inhibit carbamoyl phosphate synthase causing increased accumulation of serum ammonia. Replacement of carnitine, therefore, should decrease the accumulation of ammonia in the setting of valproic acid overdose [7].

In cases of life-threatening hyperammonemia, renal replacement therapy should be considered as a method for rapidly decreasing serum ammonia concentration and improving clinical symptoms. Ammonia is a small molecule that does not exist in a significantly protein-bound state, which makes it amenable to dialysis. In contrast to intermittent hemodialysis, CVVHD provides continual clearance of ammonia while its production is ongoing. CVVHD also provides the benefit of continuous control of serum sodium, pH, and fluid balance

which are of utmost importance in a patient with cerebral edema [8]. Theoretically, CVVHD and L-carnitine supplementation used simultaneously helps decrease ammonia levels, clear valproic acid, and concurrently curbs the production of ammonia.

There are several other minimally invasive treatments used as adjunct therapies in the treatment of hyperammonemia and cerebral edema. Hypothermia may decrease some of the metabolic effects of ammonia by decreasing free radical formation, astrocyte swelling, and inflammation. Mannitol is known to be useful in reducing cerebral edema and improving mortality. Lactulose may or may not help in the setting of acute hyperammonemia, but it is a relatively low-risk treatment option. Additionally, sodium phenyl acetate and sodium benzoate are thought to help eliminate serum ammonia by alternate metabolic pathways [6].

## Conclusion

We have presented a case in which the acute intentional overdose of valproic acid led to life-threatening hyperammonemic coma. Successful treatment with both L-carnitine supplementation and prompt initiation of CVVHD resulted in a rapid decline in serum ammonia levels. The patient was ultimately discharged home and has suffered no known sequelae from this treatment. Although additional studies are needed to determine the optimal treatment regimen for acute valproic acid toxicity, early initiation of dual therapy with L-carnitine can facilitate rapid improvement.

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