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Case Report Open Access

Valopric Acid Intoxication Induced Hyperammonemic Encephalopathy in a Setting of a Normal Liver Function

Mohammed Salhab*, Omair Tahir, Abdullah Quddus, Adil Bhutta and Taro Minami

The Warren Alpert Medical School of Brown University, Memorial Hospital of Rhode Island, USA

***Corresponding author:** Mohammed Salhab, The Warren Alpert Medical School of Brown University, Memorial Hospital of Rhode Island, 111 Brewster street, Pawtucket, RI 02860, USA, Tel: 4016634669; E-mail: Mohammed_salhab@brown.edu

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Abstract

We present a case of acute valoproic acid intoxication induced hyperammonemia encephalopathy and coma in a young man with a remarkably normal liver function test. L-Carnitine was used in addition to supportive management. Patient's mental status improved within 24 hours and VPA and ammonia levels were declining until normalized. Serial liver function tests, including the synthetic functions, were performed and they were only remarkable for mildly elevated aspartate aminotransferase on presentation and were normal throughout the admission course.

Keywords: Valoproic acid; Ammonia; Liver function; L-Carnitine

Abbreviations

LFT: Liver Function Test; VPA: Valoproic acid.

Introduction

Valproic acid (VPA, valproate), has been used as an anticonvulsant and mood-stabilizing drug, mainly in the treatment of epilepsy and bipolar disorder. Patients who ingest greater than 200 mg/kg of VPA and/or have serum concentrations greater than 180 mg/L (1260 μmol/L) usually develop some degree of central nervous system depression. Other complications caused by VPA toxicity include nausea, vomiting, mild toxic hepatitis, anion gap metabolic acidosis, hypernatremia, agitation and hyperammonemia. The blood half-life of VPA is fairly short (8-20 hours) [1].

Multiple syndromes of VPA hepatic injury have been described. VPA-related hyperammonemic encephalopathy is one of them and sometimes occurs without affecting the liver function test [2].

The use of L-canitine is reasonable and advisable in such cases based on experimental and clinical data in acute symptomatic overdose of VPA as it may prevent and attenuate the adverse effects [3-5].

Case Presentation

A 35 year old man with depression and bipolar disorder presented after ingestion of unknown amount of VPA with a suicidal intent. Patient presented with nausea, vomiting and abdominal pain. On examination, the temperature was 98.1°F, the blood pressure was 100/56 mm Hg, the pulse 109 beats per minutes and respiratory rate was 18. He was lethargic on neurological exam with no neurological deficits. His abdominal exam did not reveal any tenderness with positive bowel sounds. His cardiopulmonary exam was significant for tachycardia, normal heart sounds and clear to auscultation bilaterally. Laboratory data were significant for elevation of serum VPA level to 1400 μg/ml (normal 50-100 μg/ml), ammonia level was 40 μmol/liter, mildly elevated aspartate aminotransferase (44 U/L) and severe hypokalemia (2.4 mEq/L) with anion gap metabolic acidosis. Liver and kidney function tests were otherwise within normal ranges. Electrocardiogram showed a QT interval prolongation. Computed Tomography scan of the head showed no acute pathology. Urine and serum toxicology screen were otherwise negative. Supportive management with activated charcoal (50 grams), intravenous fluids and potassium repletion were initiated. A dose of Naloxone was given without significant outcome. His mental status worsened over the next 4 hours, subsequently ended in coma while an elevation in his ammonia level to 89 μmol/L was noted. Endotracheal Intubation was performed once a decrease in Glasgow Coma Scale was appreciated and L-carnitine was started. 6 grams were given IV over 30 minutes as a bolus, followed by 3 grams given every four hours for a total of 24 hours. Other causes for altered mental status were unlikely depending on imaging and cultures results.

Patient's mental status improved dramatically hours after intubation and VPA and ammonia levels were declining until normalized (Figure 1). Subsequent liver function tests remained normal. Anion gap was closed and potassium level was corrected. QT segment interval was back to normal. Patient was successfully extubated within 24 hours.

Discussion

VPA hepatotoxicity is believed to be mediated by either an inhibitory effect of VPA on the mitochondrial β-oxidation pathway, which gives rise to microvesicular steatosis, or by VPA-induced metabolic effects. VPA intoxication has been associated with hyperammonemia in both chronic and acute overdose setting [2,3].

The accumulation of toxic levels of VPA metabolites inhibits the activation of the mitochondrial enzyme Carbamoyl Phosphate synthase–I in urea cycle, thereby blocking the first step of the urea cycle [2].

Treatment of VPA-related hyperammonemic encephalopathy includes discontinuing VPA therapy as the elimination of the drug is the mainstay therapy. Supportive care including air way protection, intravenous fluid hydration, activated charcoal and L-carnitine should be considered. Hemodialysis and hemoperfusion should be considered

in cases refractory to the above mentioned management. Although VPA is mostly protein bound and the dialysis might be limited but it's still the last resort [3-5].

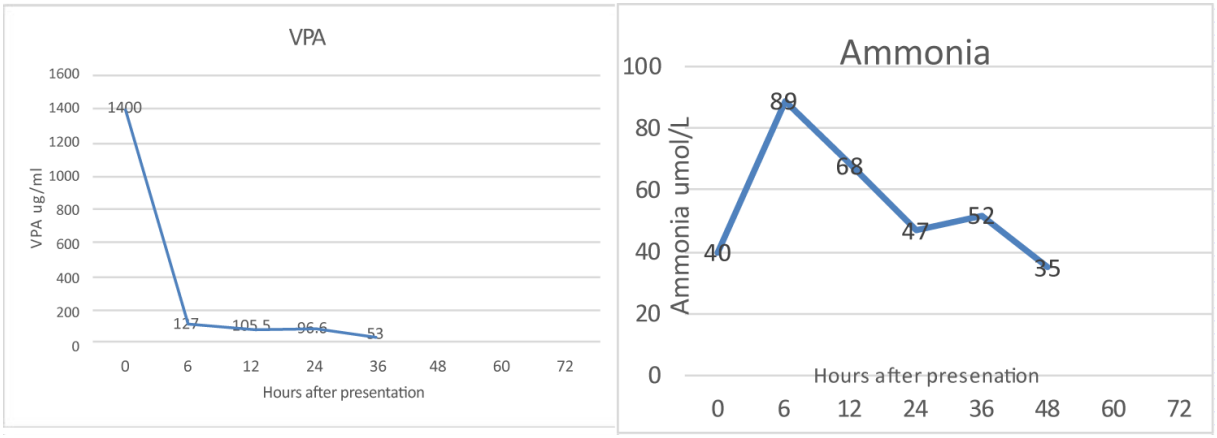

Figure 1: VPA and Ammonia levels during the hospital course.

Carnitine is thought to be depleted in VPA metabolism, so supplementation with L-carnitine in a setting of acute toxicity plays as a co-factor in beta oxidation which helps to reverse the inhibition Carbamoyl Phosphate synthase–I in urea cycle, thus decreasing the ammonia levels [3,4].

In conclusion, we present a case of a young man with acute VPA toxicity which induced hyperammonemic encephalopathy in a setting of a normal liver function test. L-carnitine was successfully used in the management and helped improving his mental status and ammonia level.

Conflicts of interest

No potential conflicts of interest relevant to this article were reported.

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