International Journal of Clinical Medicine, 2014, 5, 546-549
Published Online May 2014 in SciRes. http://www.scirp.org/journal/ijcm
http://dx.doi.org/10.4236/ijcm.2014.510075

Altered Mental Status and Hyperammonemia after Overdose of Valproic Acid with Therapeutic Valproic Acid Concentrations

Evan S. Schwarz[1], Mark Thoelke[2]

[1]Division of Emergency Medicine, Washington University School of Medicine, St. Louis, USA
[2]Department of Medicine, Washington University School of Medicine, St. Louis, USA
Email: schwarze@wusm.wustl.edu

Received 28 March 2014; revised 1 April 2014; accepted 28 April 2014

Abstract

Valproic acid is used in the treatment of multiple disorders. Adverse effects from valproic acid include hepatotoxicity, hypotension, metabolic acidosis, and decreased mental status. Valproic acid also causes hyperammonemia. Many physicians assume that this is due to a supratherapeutic valproic acid concentration; when in fact, it can occur with therapeutic valproic acid concentrations. This is because the hyperammonemia may be related to carnitine deficiency and disruption of the urea cycle, which can both occur with therapeutic valproic acid concentrations. We report a patient presented to the emergency department with alteration of mental status after ingesting valproic acid for recreational purposes, who developed hyperammonemia with a therapeutic valproic acid concentration.

Keywords

Valproic Acid, L-Carnitine, Levocarnitine, Overdose, Toxicity

1. Introduction

Valproic acid (VPA) is a medication used in the treatment of many disorders. Supratherapeutic ingestions can lead to altered mental status, respiratory depression, and hypotension. Metabolic derangements from VPA include hypernatremia, hypocalcemia, an anion gap metabolic acidosis, and hyperammonemia [1]-[4]. Hyperammonemic encephalopathy is characterized by altered mental status (AMS) and seizures [5]. Most importantly,

How to cite this paper: Schwarz, E.S. and Thoelke, M. (2014) Altered Mental Status and Hyperammonemia after Overdose of Valproic Acid with Therapeutic Valproic Acid Concentrations. *International Journal of Clinical Medicine*, **5**, 546-549.
http://dx.doi.org/10.4236/ijcm.2014.510075

hyperammonemic encephalopathy following ingestion of VPA can occur after ingestions resulting in therapeutic VPA concentrations. We report a case of hyperammonemic encephalopathy with a therapeutic VPA concentration.

2. Case

A 35 years old male with a history of alcoholism presented to the Emergency Department (ED) with AMS. He was at a party and was arrested. In jail, he was found unresponsive without any evidence of trauma or seizures. Emergency Medical Services administered naloxone 3 mg IV without a response. He was placed on oxygen and arrived at the ED at 2 am. On arrival, his vital signs (VS) were: heart rate 97 bpm, blood pressure 145/101 mmHg, respirations of 16/minute with oxygen saturations of 100% on a non-rebreather. His exam was remarkable for somnolence with brief, random arousals. His pupils were 2 mm and not reactive. He had moist mucous membranes, was not diaphoretic, had a soft abdomen with normal bowel sounds, and did not have rigidity or hyperreflexia. A bag of pills containing olanzapine 10 and 20 mg tablets, VPA 250 mg tablets, and rosuvastatin 10 mg tablets were found in his possession. The patient's mental status was deteriorated, and he was intubated with ketamine 80 mg and succinylcholine 100 mg. On the ventilator, he had normal VS: heart rate 88 bpm, blood pressure 114/72 mmHg, and saturating 100% on 40% oxygen.

A head CT and chest X-ray were unremarkable. Laboratory evaluation was remarkable for VPA 108 μg/ml (therapeutic 50 - 125), ammonia 128 μmol/L (normal 9 - 33), and a venous blood gas of pH 7.26/pCO_2 64/pO_2 30. An ethanol concentration was 139 mg/dL and a urine drug screen (UDS) was negative. Other laboratory testing was unremarkable. He was administered levocarnitine 6 grams IV, thiamine 100 mg IV, and lactulose 45 ml via a nasogastric tube, and admitted to the intensive care unit (ICU). Shortly after arrival to the ICU, he was extubated. Upon further questioning, he admitted to being prescribed clonazepam, aripiprazole, mirtazapine, and sertraline. He was not prescribed VPA, and admitted to receiving pills at a party for recreational purposes. He denied other medical conditions aside from chronic psychiatric disease (he was unsure of his official diagnosis) and denied prior ethanol withdrawal. L-carnitine was continued at 1050 mg IV every 4 hours and serial VPA and ammonia concentrations were obtained. The VPA concentration decreased to 67 μg/ml the following day. Repeat ammonia concentrations remained elevated at 136 and 145 μmol/L but decreased to 70 μmol/L by the following afternoon. He was given resources for substance abuse counseling and discharged.

3. Discussion

His AMS was likely multifactorial. His ethanol concentration was 139 mg/dl, which would likely cause some intoxication even in a tolerant individual. While his UDS was negative, these tests are notorious for being insensitive and do not exclude the possibility of drug use. Olanzapine, an atypical antipsychotic found in his possession, can cause AMS and miosis. The hyperammonemia likely also contributed to his AMS. Aside from VPA, none of the other medications that he regularly used, or that were found on him, are associated with hyperammonemia.

Physicians may believe that the VPA concentration must be supratherapeutic in order to develop hyperammonemia. In fact, there is not a correlation between the ammonia concentration and the measured serum VPA concentration [6] [7]. In a case series of ingestions, a patient with a VPA concentration of 133 μg/mL had an ammonia concentration of 204 μmol/L while patients with VPA concentrations of 870 μg/mL and 1,005 μg/mL had ammonia concentrations of 33 μmol/L and 53 μmol/L, respectively [8].

Hyperammonemia may be due to VPA-induced carnitine deficiency, interference with carbamoylphosphate synthase 1 (CPS 1), and failure to incorporate ammonia into the urea cycle [2]. The exact mechanism is unknown. VPA enters the mitochondria using L-carnitine as a co-factor [9]. VPA undergoes β-oxidation resulting in the depletion of both carnitine and acetyl CoA. Carnitine excretion is increased by the formation of valproyl-carnitine, which then inhibits the ATP-dependent carnitine transporter. The depletion of carnitine shifts valproate metabolism toward microsomal ω-oxidation [5] [10] [11]. Products of ω-oxidation interfere with CPS 1, an enzyme responsible for incorporation of ammonia into the urea cycle [1] [12]. Depletion of acetyl CoA stops the formation of N-acetylglutamate, a required CPS 1 co-factor [1]. Thus, hyperammonemic encephalopathy can occur with therapeutic VPA concentrations.

Hyperammonemia with therapeutic VPA concentrations is reported in other settings. In a series of psychiatric patients, 51% taking VPA developed hyperammonemia [13]. In a study of outpatients with bipolar disorder,

nearly 17% receiving VPA had hyperammonemia compared to no patients in the control group (p = 0.005) [14]. In a series of patients with epilepsy, patients receiving VPA had higher ammonia concentrations, including 16% with hyperammonemia, than the group that that received other antiepileptics [15]. The clinical relevance of the hyperammonemia is not known as many patients are not encephalopathic, [13]-[16] although some do develop hyperammonemic encephalopathy with therapeutic VPA concentrations [12] [17]. While treatment is controversial, administration of L-carnitine has generally been shown to be safe and can be considered in addition to general supportive care [18].

4. Conclusion

Patients with therapeutic VPA concentrations can develop hyperammonemia even with therapeutic VPA concentrations. While the clinical relevance is not entirely known, some become encephalopathic. Hyperammonemic encephalopathy should be considered in patients taking valproic acid that present with altered mental status even if they have therapeutic valproic acid concentrations.

References

[1] Sztajnkrycer, M.D. (2002) Valproic Acid Toxicity: Overview and Management. *Journal of Toxicology—Clinical Toxicology*, **40**, 789-801. http://dx.doi.org/10.1081/CLT-120014645

[2] Lheureux, P.E. and Hantson, P. (2009) Carnitine in the Treatment of Valproic Acid-Induced Toxicity. *Journal of Toxicology—Clinical Toxicology*, **47**, 101-111. http://dx.doi.org/10.1080/15563650902752376

[3] Dealberto, M.J. and Sarazin, F.F. (2008) Valproate-Induced Hyperammonemic Encephalopathy without Cognitive Sequelae: A Case Report in the Psychiatric Setting. *The Journal of Neuropsychiatry and Clinical Neurosciences*, **20**, 369-371. http://dx.doi.org/10.1176/appi.neuropsych.20.3.369

[4] Verrotti, A., Trotta, D., Morgese, G., *et al*. (2002) Valproate-Induced Hyperammonemic Encephalopathy. *Metabolic Brain Disease*, **17**, 367-373. http://dx.doi.org/10.1023/A:1021918104127

[5] Hamer, H.M., Knake, S., Schomburg, U., *et al*. (2000) Valproate-Induced Hyperammonemic Encephalopathy in the Presence of Topiramate. *Neurology*, **54**, 230-232. http://dx.doi.org/10.1212/WNL.54.1.230

[6] Itoh, H., Suzuki, Y., Fujisaki, K., *et al*. (2012) Correlation between Plasma Ammonia Level and Serum Trough Concentration of Free Valproic Acid in Patients with Epilepsy. *Biological and Pharmaceutical Bulletin*, **35**, 971-974. http://dx.doi.org/10.1248/bpb.35.971

[7] Laub, M.C. (1986) Hyperammonemia in Valproate Therapy in Children and Adolescents. *Der Nervenarzt*, **57**, 314-318.

[8] Spiller, H.A., Krenzelok, E.P., Klein-Schwartz, W., *et al*. (2000) Multicenter Case Series of Valproic Acid Ingestion: Serum Concentrations and Toxicity. *Journal of Toxicology—Clinical Toxicology*, **38**, 755-760. http://dx.doi.org/10.1081/CLT-100102388

[9] Raskind, J.Y. and El-Chaar, G.M. (2000) The Role of Carnitine Supplementation during Valproic Acid Therapy. *Annals of Pharmacotherapy*, **34**, 630-638. http://dx.doi.org/10.1345/aph.19242

[10] Li, J., Norwood, D.L., Mao, L.F., *et al*. (1991) Mitochondrial Metabolism of Valproic Acid. *Biochemistry*, **30**, 388-394. http://dx.doi.org/10.1021/bi00216a012

[11] Mackay, F.J., Wilton, L.V., Pearce, G.L., *et al*. (1997) Safety of Long-Term Lamotrigine in Epilepsy. *Epilepsia*, **38**, 881-886. http://dx.doi.org/10.1111/j.1528-1157.1997.tb01252.x

[12] Shan, J.C., Hsieh, M.H., Liu, C.C., *et al*. (2010) Clinical Alertness to Valproic Acid-Induced Hyperammonemia—Two Case Reports. *Journal of Psychopharmacology*, **24**, 943-945. http://dx.doi.org/10.1177/0269881109102635

[13] Raja, M. and Azzoni, A. (2002) Valproate-Induced Hyperammonaemia. *Journal of Clinical Psychopharmacology*, **22**, 631-633. http://dx.doi.org/10.1097/00004714-200212000-00019

[14] Bocchetta, A., Siddu, A., Sardu, C., *et al*. (2012) Ammonemia in Bipolar Patients on Maintenance Treatment with Valproic Acid. *Journal of Clinical Psychopharmacology*, **32**, 148-150. http://dx.doi.org/10.1097/JCP.0b013e318240a4a7

[15] Thom, H., Carter, P.E., Cole, G.F., *et al*. (1991) Ammonia and Carnitine Concentrations in Children Treated with Sodium Valproate Compared with Other Anticonvulsant Drugs. *Developmental Medicine and Child Neurology*, **33**, 795-802. http://dx.doi.org/10.1111/j.1469-8749.1991.tb14963.x

[16] Hung, C.C., Li, T.M., Wei, I.H., *et al*. (2011) The Real Mechanism of VPA-Induced Hyperammonemia Remains Unknown. *General Hospital Psychiatry*, **33**, e83-e84.

[17] Young, L. and Coffey, B.J. (2010) Bipolar Disorder and Valproate-Induced Hyperammonemic Encephalopathy in an Adolescent with Diabetes. *Journal of Child and Adolescent Psychopharmacology*, **20**, 449-452. http://dx.doi.org/10.1089/cap.2010.2052

[18] Mock, C.M. and Schwetschenau, K.H. (2012) Levocarnitine for Valproic-Acid-Induced Hyperammonemic Encephalopathy. *American Journal of Health-System Pharmacy*, **69**, 35-39. http://dx.doi.org/10.2146/ajhp110049