Journal of Neonatal and Pediatric Medicine

ISSN: 2572-4983

Nguyen et al., Neonat Pediatr Med 2017, 3:S1
DOI: 10.4172/2572-4983.1000S1016

Case Report Open Access

Valproate Acid (Depakote) Induced Hyperammonemic Encephalopathy in the Pediatric Populations

Hoang Nguyen[1*], **Joseph P Kitzmiller**[1], **Ferdnard Osuagwu**[2], **Vijay Chandran**[3] **and Pooja Khungar**[4]

[1]*Department of Biological Chemistry and Pharmacology, College of Medicine, The Ohio State University, Columbus, Ohio, USA*

[2]*Department of Psychiatry, School of Medicine, University of Michigan, Michigan, USA*

[3]*Department of Psychiatry, Bronx-Lebanon Hospital, Bronx, NY, USA*

[4]*Advocate Illinois Masonic Medical Center, Chicago, Illinois, USA*

[*]**Correspondence author**: Hoang Nguyen, Department of Biological Chemistry and Pharmacology, College of Medicine, The Ohio State University, Columbus, Ohio, USA, Tel: 1-213-446-2519; E-mail: Hoang.Nguyen@osumc.edu

Received date: July 27, 2017, **Accepted date**: August 07, 2017, **Published date**: August 15, 2017

Copyright: © 2017 Nguyen H, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Abstract

Valproate acid (Depakote) (VPA) is very effective in the treatment of various illnesses including: seizure disorders, migraine headache prophylaxis, neuralgia, and bipolar disorder. The use of VPA frequently results in elevated plasma levels of ammonia. This is seen despite normal baseline liver function test results in such patients.

In this case report, we describe two instances of VPA-induced hyper ammonemic encephalopathy in patients who had supra therapeutic levels of VPA. Family physicians, Child Neurologists, Child Psychiatrists and Pediatricians should be aware of this potential complication, and it is highly recommended to check ammonia levels in patients taking VPA who present with a change in mental status. With a rise in off-label use it is even more important that physicians are made aware of this potential complication. Treatment of VPA-induced hyperammonemic encephalopathy is still under investigation. As of yet, administration of L-carnitine is postulated to have a potential benefit in some cases.

VPA has numerous drug interactions and toxicities, including pancreatitis, thrombocytopenia, hepatitis and hyperammonemia. Here are we list two case reports of VPA induced hyperammonemic encephalopathy both occurring in patients with no history of any underlying liver pathologies. In both two cases, both patients were under stable conditions, no comatose. In both 2 cases of patients we described, they all have normal or sub therapeutic level of VPA. Because of the wide spectrum of symptoms associated with Valproate Acid induced Hepatic Encephalopathy (VHE), clinician should be aware of hyperammonenia in differential diagnosis with other common symptoms.

Keywords: Seizure disorders; Migraine headache prophylaxis; Child neurologists; Neuralgia

Case Report 1

A 6 year old girl is brought to the physician due to recent altered mental status. Her immunizations are up to date. The patient's past medical history is unremarkable except for generalized seizure, and she has been generally healthy. The girl has no fever, vomiting or joint pains. She has had no travel, animal exposures or sick contacts. Her medications include Topiramate and Depakote for seizure. Topiramate and Depakote were given within the normal dosing, and both under regular formulation. In the ER, she was nonresponsive to verbal or painful stimuli, her vital signs were normal. Her pupils were equal at 5 mm and her ammonia level was 230 mmol/L (normal value is 10-47), her VPA level was 120 mcg/mL (normal value is 50-100), her AST=18 IU/L, and ALT=20 IU/L. Both level of VPA and Ammonia were performed by high-performance liquid chromatography method (HPLC) with ultraviolet-visible (UV-Vis). The remainder of lab test including hematology panel and urinalysis were normal. For the first 24 hours, the patient remained nonresponsive, after discontinuing VPA and maintenance IV fluid, Ammonia level dropped to 160 mmol/L. Generalized Tonic-Clonic Seizure (GTC) is the diagnosis. Accordingly, EEG showed generalized spikes or sharp waves. Pediatrician was notified and L-carnitine 50 mg/kg/day of was administered once daily via NG tube. Ammonia level was monitored, the next day it was 54 mmol/L, and her VPA level lowered at 55 mcg/mL, and she began to respond to verbal stimuli. Pediatrician decided to keep her in hospital and continue to monitor her for the next 4 days. Her Ammonia level was in the range of 30-50 mmol/L, and she was discharged home with instructions to discontinue VPA, continue Topiramate, and to continue the L-carnitine for 7 to 10 days at 50 mg/kg/day.

Case Report 2

A 16 year old girl brought in by police to ER department with chief complaint of altered mental status. Upon asking for identification, patient mumbles incoherently. She is not oriented for time and place. The patient complained of diminished short-term memory, confusion, disorientation, hypersomnia and blurred vision for 2 to 3 weeks. Lab results are unremarkable. Her past medical history was significant for Obsessive compulsive disorder and bipolar disorder. She denied any recent alcohol intoxication. Her prescribed medications included VPA

1,500 mg/day, Fluvoxamine 400 mg BID, and clonazepam 1 mg qhs. Patient was on VPA 8 months prior to this admission. Patient reports one month before this admission, her VPA was increased from 1,000 mg to 1,500 mg and her PCP was not aware of this increase. Physical exam is unremarkable while she is in ER, except her speech was slurred and her responses were sluggish. Topiramate and Depakote were given within the normal dosing, and both under regular formulation. Diagnosis during admission is bipolar disorder. No EEG was ordered by ER physician. In the ER comprehensive metabolic panel and hepatic panel were within normal limits. Both level of VPA and Ammonia were performed by high-performance liquid chromatography method (HPLC) with ultraviolet-visible (UV-Vis). Her VPA level was 120 mcg/mL (normal is 50 to 100), and her ammonia level was 186 mcg/L (normal is 10 to 47). Emergency physician decided to keep her couple days for monitoring her VPA and Ammonia level, VPA was discontinued, and the next day her VPA level was 110 mcg/mL, and her ammonia level was 82 mcg/L. And the next day, her VPA level normalized to 36 mcg/mol and her ammonia normalized to 42 mcg/mol, and her mental status improved. And the next day after, her mental status totally improved. In-house psychiatrist decided to discharge her, and VPA was discontinued and replaced with Gabapentin and Topiramate and followed up as outpatient at her PCP office.

Summary

Clinical findings

Patients with VHE present with varying degrees of cognitive and behavioral dysfunction. With respect to drug-drug interactions, other anticonvulsants may potentiate the effects of VPA. Phenobarbital and phenytoin may increase ammonia levels in patients taking VPA, mechanism will be discussed under Pathophysiology. Topiramate has been shown to inhibit the urea cycle and glutamine synthetase activity, both attributed into development of VHE [1-3].

Laboratory findings

VPA levels may be normal and don't necessarily correlate with the degree of hyperammonemia or the severity of the symptoms. Patients with VHE may have no other laboratory derangements other than elevated serum ammonia.

Treatment

L-carnitine has shown to reduce mortality in patients with severe VPA-induced hepatotoxicity, and also in reducing ammonia levels, improving symptoms of hyperammonemia. It may be given orally or IV at the dose of 50 to 100 mg, and is generally safe [4-7]. Mechanism of action of L-Carnitine, when L-Carnitine level is low it results in diminished mitochondrial function which results in inhibition of urea cycle in the liver. The first step of management of VHE is discontinuation of VPA. Partial recovery occurs over a period of 1 to 2 days, and complete recovery occurs usually within 3 days.

Pathophysiology

Ammonia is a by-product of the conversion of amino acid to alpha-ketoacids, and primarily its metabolism occurs in the urea cycle. In the liver (in mitochondria) carbonyl phosphate synthetase one is the first step in the urea cycle, this enzyme plays a role in deamination of Glutamine or Glutamate to produce Ammonia which then attaches to Carboxyphophate to produce Carbamoyl Phosphate [8]. VPA inhibits the activity of carbonyl phosphate synthetase one, thus hindering the excretion of ammonia and raising plasma ammonia level. Mechanism of mental status change associated with hyerammonemia is very understandable [9,10]. Hyperammonia will stimulate increased glutamine synthetase activity, causing increased levels of glutamine in astrocytes. And, Glutamine in astrocytes will cause an osmotic shift of fluid into astrocytes, producing astrocyte swelling and cerebral edema.

Conclusion

The use of VPA will often cause VHE, physicians and clinician should be aware of possible cause of changes in mental status in patients treated with VPA. Severe mental status could occur if secondary anticonvulsant agents are added. L-Carnitine supplements decrease ammonia levels, improve symptoms and primary treatment still is discontinuation of VPA. In term of drug-drug interaction, using Topiramate (TPA) together with Valproic Acid (VPA) may increase the risk of hyperammonemia, or elevated ammonia levels in the blood [8].

Acknowledgement

The authors are grateful to all medical staffs, volunteer patients, and statistician for assistance with data analysis. Special thanks to scientists and professors at The Ohio State University, College of Medicine, Department of Biological Chemistry and Pharmacology, Columbus, Ohio, USA for re-evaluate, recommend and validate important basic intellectual concepts correlate to clinical. Department of Psychiatry of University of Michigan at Ann-Arbor, Michigan; Department of Psychiatry of Bronx-Lebanon Hospital, Bronx, New York; and Department of Pediatrics at Advocate Illinois Masonic Medical Center, Chicago, Illinois. All have been acknowledged on this article. The authors are also thankful for the oversight of all aspects of this research but the Internal Review Boards (IRB).

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

1. Yehya N, Saldarini CT, Koski ME, Davanzo (2004) Valproate-induced Hyperammonemic Encephalopathy. J Am Aca Child Adolesc Psychiatry 43: 926-927.
2. Hamer HM, Knake S, Schombur U, Rosenow (2000) F. Valproate-induced Hyperammonemic Enchepalopathy in the presence of Topiramate. Neurology 54: 230-232.
3. Raskind JY, El-Chaar GM (2000) The Role of Carinitine Supplementation During Valproic Acid Therapy. Ann Pharmacother 34: 630-638.
4. Triggs WJ, Gilmore RL, Milington DS, Cibula J, Bunch TS, et al. (1997) Valproate-Associated Carnitine Deficiency and Malignant Cerebral Edema in the absence of Hepatic Failure. Int J Clin Pharmacol Thera 35: 353-356.
5. Ohtani Y, Endo F, Matsuda I (1982) Carnitine Deficiency and Hperammonemia associated with Valproic Acid Therapy. J Pediatr 101: 782-785.
6. Bohan TP, Helton E, McDonald I (2001) Effect of L-Carnitine treatment for Valproate-Induced Hepatotoxicity. Neurology 56: 1405-1409.
7. Bohles H, Sewell AC, Wenzel D (1996) The effect of Carnitine Supplementation in Valproate-Induced Hyperammonaemia. Act Paediatr 85: 446-449.

8. Verrotti A, Trotta D, Morgese G, Chiarelli F(2002) Valproate-Induced Hyperammonemic Encephalopathy. Metab Brain Dis 17: 367-373.
9. LoVecchio F, Shriki J, Samddar R (2005) L-carnitine was safely administered in the setting of valproate toxicity. Am J Emerg Med 23: 321-322.
10. Brusilow SW, Maestri NE (1996) Urea cycle disorders: diagnosis, pathophysicology, and therapy. Adv Pediatr 43: 127-170.

This article was originally published in a special issue, entitled: **"Pediatric Neurological Disorder"**, Edited by Eman Ahmed Zaky