

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

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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 hyperammonemia 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 Carboxyphosphate 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 hyperammonemia 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].

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