Reversible Encephalopathy due to Valproic Acid Induced Hyperammonemia in a Patient with Bipolar I Disorder: A Cautionary Report

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ABSTRACT ~ Valproic acid (VPA) is an FDA-approved medication widely prescribed for seizures, migraines, and mixed or manic episodes in bipolar disorder. Hyperammonemia is a rare complication of VPA use, which can result in high morbidity and occasionally fatal encephalopathy. The scant literature on Valproate Induced Hyperammonemic Encephalopathy (VIHE) is characterized by acute onset of decreasing level of consciousness, drowsiness, lethargy which in rare instances can lead to seizures, stupor, coma, and persistent morbidity and cortical damage. Below we describe a case report of a patient with Bipolar I Disorder with no primary evidence of hepatic dysfunction that was initiated on VPA and olanzapine to address manic and psychotic symptoms. This patient subsequently developed elevated ammonia (NH₄) levels that led to a reversible encephalopathy. This cautionary case report highlights the potential for a rare but serious complication from VPA, a medication increasingly used in both neurologic and neuropsychiatric settings. It is imperative that clinicians perform a thorough physical, neurological and diagnostic evaluation, routinely check NH₄ and VPA levels when prescribing these agents and exercise caution when VPA is concomitantly prescribed with antipsychotics and cytochrome P450 inducing antiepileptic medications.


INTRODUCTION

Valproic acid (VPA) is an FDA-approved medication widely prescribed for seizures, migraines, and bipolar disorder. Compared to Europe where Lithium...
is more commonly prescribed for bipolar disorder, VPA usage is more common in the US. The use of VPA increased by 22.6% in North America between 1995 and 2009.¹

A rare complication of VPA use, hyperammonemia, can result in encephalopathy that is occasionally fatal.² Valproate Induced Hyperammonemia (VIH) is characterized by acute onset of reduced level of consciousness, drowsiness, and lethargy which can progress to seizures, stupor, and coma with persistent cortical damage.³⁻⁶ The pathogenesis of this adverse effect is likely caused by VPA disruption of aminogenesis and ammonia disposal via the urea cycle. The inhibition of N-acetyl glutamate, the active metabolite of the urea cycle, and activation of valproyl-CoA increases blood ammonia levels. This adverse effect may be further exacerbated by genetic defects in the urea cycle system.⁷

The literature exploring the association between VPA and Hyperammonemic encephalopathy is limited.⁸ We describe a patient with bipolar disorder-I, started on Valproic acid that developed elevated NH₄ levels and secondary encephalopathy.

**CASE HISTORY**

A 48 year-old Caucasian female with congestive heart failure, hypertension, degenerative joint disease and bipolar disorder presented to the ER complaining that family members were putting E.coli in her home for the past 2 weeks. On psychiatric assessment, the patient reported increasing depressive symptomatology since her VPA treatment was discontinued 3-months prior. The patient’s husband reported a past history of manic episodes characterized by high energy, lack of sleep, and frequent shopping. She had a previous history of addiction with 15-years of sobriety. Active daily medications included: paroxetine 40 mg qd, Atenolol 25 mg qd, pregabalin 300 mg TID, Ropinirole 1 mg qhs (restless leg syndrome), diazepam 10 mg qd, OxyContin 20 mg TID, and Roxicodone 15 mg BID (back pain). Mental status exam on admission was significant for a dysphoric mood, tangential and circumstantial speech with increase spontaneity, auditory and visual hallucinations, and persecutory delusions. The urine drug screen was positive for opioids. Brain imaging, basic metabolic panel and complete blood count were reported normal.

The patient was diagnosed with Bipolar disorder, manic, severe, with psychotic features. She was restarted on VPA 500 mg BID on day 1 of admission for mood stabilization, olanzapine 10 mg daily for psychosis, and Oxycontin for back pain. Paroxetine and Ropinirole were discontinued to prevent aggravation of mania and psychosis respectively.
Diazepam was discontinued. On day 6 after starting VPA, the patient appeared sedated and was difficult to arouse. When awake, she was oriented to person, place, and time. She reported dizziness and fatigue, but denied nausea and vomiting. Laboratory evaluation revealed an elevated ammonia level (NH4) of 188 umol/l (normal range 12–60 umol/l). No symptoms of liver disease or abnormalities in liver function panel were noted. Comprehensive metabolic panel reported normal. Abdominal ultrasound, Urinalysis and complete blood count were negative. The patient was diagnosed with valproic acid induced hyperammonemic encephalopathy (VIHE). VPA was discontinued on day 6 and lactulose (30 ml TID) was initiated. A repeat NH4 level on day 7 showed dramatic reduction to 77 (normal range 12–60 umol/l). On day 8, the patient’s symptoms of somnolence, fatigue, and dizziness had dissipated.

On day 13, due to the persistence of the patient’s manic symptoms VPA was re-challenged at 500 mg daily, with careful monitoring for signs and symptoms of hyperammonemia and encephalopathy. On day 14, olanzapine was increased to 20 mg/d to address manic symptoms. As no signs of somnolence, ataxia, or confusion developed, VPA was titrated up to 500 mg BID on day 15. Assessment on day 18 revealed elevated NH4 and VPA levels: NH4 88 umol/l and VPA 112 microgram/ml (normal range 50–100). Symptoms of nausea/vomiting developed and lactulose (30 ml TID) was restarted to clear the ammonia. VPA was discontinued. At day 19 the NH4 level had normalized at 36. The patient was told to report VPA as an allergy due to recurrence of symptomatic hyperammonemia. Manic and psychotic symptoms were eventually stabilized on Olanzapine 20 mg nightly and the patient was discharged on day 22.

**DISCUSSION**

We describe a case of VPA-induced hyperammonemic encephalopathy on a therapeutic dose of VPA in the absence of hepatic dysfunction which recurred on re-challenge. On both occasions, the encephalopathy promptly resolved once the VPA was discontinued and lactulose implemented. Previous case reports, 9 a large cohort study of adult patients (2724) and pediatric patients (1753), recognize the following risk factors for VPA-induced Hyperammonemia: VPA dose, female gender and concomitant use of enzyme inducers.10,11 Concomitant use of VPA with antipsychotics, especially risperidone, is considered a risk factor for VPA induced hyperammonemia through competition for protein binding sites in the blood.12 Olanzapine could have predisposed valproate-induced Hyperammonemia by this same mechanism in the case described above.
Between 1985 and 2007, 11 case reports of symptomatic Hyperammonemia due to VPA in a psychiatric setting were published. Onset was heralded by symptoms of lethargy, confusion, mania, and most fatally coma. Four patients required intubation and medical intensive care. 11 of the 14 reported cases completely recovered from their encephalopathy usually within days with cessation of VPA; however 2 cases requiring maintenance therapy with carnitine due to probable urea cycle disorder, required 10–14 days to recover, and one had other medical complications. Our patient’s encephalopathy resolved within few days of cessation of VPA and initiation of lactulose. Although our patient was not tested for urea cycle disorders, there was no indication to evaluate the patient for these deficiencies, as patient had no prior symptoms of malnutrition.

CONCLUSION

We describe a patient on combination VPA and olanzapine that required discontinuation of VPA following two challenges due to NH4 elevation and encephalopathy in the context of normal hepatic functioning. The patient’s encephalopathy resolved shortly after discontinuation of VPA as seen in previously reported studies. This cautionary report highlights the potential for a rare but serious complication. It is imperative that clinicians have a high index of suspicion for this adverse effect in the context of mental status change, drowsiness and lethargy and exercise caution when VPA is concomitantly prescribed with anti-psychotics and enzyme-inducing antiepileptic medications.

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DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Drs. Patel, Landry, Fargason and Birur have no conflict of interest to disclose in the preparation of this manuscript.

REFERENCES

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