Case Report

The Menacing Side of Valproate: A Case Series of Valproate-induced Hyperammonemia

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ABSTRACT

Valproate (VPA) is a well-tolerated and commonly used drug to treat variety of psychiatric and neurological disorders. VPA-induced hyperammonemic encephalopathy is a rare adverse effect which can commonly occur in the background of normal liver function and therapeutic serum levels. Any delay in treatment of VPA-induced hyperammonemic encephalopathy can lead to life-threatening coma thus a strong clinical suspicion, fair understanding of the pathophysiology, and management of this drug-related complication can prevent fatal outcome. We hereby report a series of cases admitted to a tertiary care center that developed hyperammonemia and all patients recovered on stopping VPA. This case series cautions the clinicians about hyperammonemia as an uncommon but highly plausible life-threatening side effect, emphasizing astute observation, and high degree of clinical suspicion to prevent mortality and limit morbidity. Early recognition of subtle gastrointestinal, cognitive, and behavioral signs can lead to immediate intervention with satisfying results.

Key words: *Encephalopathy, valproate, hyperammonemia*

INTRODUCTION

Valproate (VPA) is an antiepileptic drug which is extensively used in psychiatry for many disorders.[1] VPA has a wide therapeutic window and is considered relatively safe. VPA-induced hyperammonemic encephalopathy (VHE) is a rare adverse effect of VPA which commonly occurs in the background of normal liver function and therapeutic serum VPA levels[2] presenting with nonspecific gastrointestinal (GI) and cognitive symptoms.[3] Literature reported on VHE is from neurological cases, with scarce representation from psychiatry. The first case in psychiatric patients was reported in 1995,[4] and less than fifty cases have since been reported.[3] We discuss a series of four cases with VHE from a tertiary care center, admitted during April-September 2015 outlining the early warning signs and management of VHE.

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CASE REPORTS

Case 1

A 52-year-old male diagnosed with bipolar affective disorder (BPAD) for 20 years, presented with an

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episode of mania with psychotic symptoms of 1-month duration precipitated by nonadherence. The patient was started on VPA, which was increased to 1500 mg in a week. The patient started complaining of constipation 2 days after the dose increase, followed by altered sensorium. Serum ammonia levels were elevated at 148 mcg/dl (30–86 mcg/dl), with normal VPA level of 56.2 mg/L (50–100 mg/L). VPA was promptly discontinued and gastroenterology consult taken. The patient was started on lactulose and his condition improved within 2 days.

Case 2

A 26-year-old female with schizoaffective disorder presented with mania of 1-month duration. She was on levothyroxine 25 μg. The patient was started on VPA increased to 800 mg in a week, with risperidone and benzodiazepines to contain her agitation. On the 2nd day of receiving 800 mg VPA, she appeared drowsy and had four episodes of vomiting. Serum ammonia levels were raised at 291 mcg/dl and VPA level was slightly high (120 mg/L). All psychotropics were immediately stopped, and patient was kept under observation. Her level of consciousness gradually improved in 3 days.

Case 3

A 18-year-old male with diagnosis of BPAD, rheumatic heart disease, and cannabis dependence syndrome for 2 years presented with an episode of mania. He was started on VPA which was gradually increased to 1500 mg (levels 100 mg/L). After a week on the same dose, the patient had sedation and three episodes of vomiting. He was disoriented, and serum ammonia levels were increased (204 mcg/dl). VPA was stopped and significant improvement was achieved within 2 days.

Case 4

A 20-year-old male presented with mania of 6 months duration with cannabis and tobacco intake independent pattern and alcohol intake in harmful pattern. The patient was started on VPA which was increased to 1000 mg with serum levels of 56 mg/L. Following day after increase in the dose, patient complained of constipation. On the 3rd day, he appeared drowsy with slurring of speech and had two episodes of vomiting. His serum ammonia levels were increased at 122 mcg/dl. VPA was immediately stopped, and the patient's level of consciousness improved.

DISCUSSION

Hyperammonemia has emerged as an important adverse reaction of VPA. 51.2% of patients receiving VPA in a psychiatry unit had asymptomatic hyperammonemia.[5] For a diagnosis of VHE to be made, the serum ammonia level should be raised, and the clinical picture should improve with VPA withdrawal or dose adjustment.[6] In all the cases discussed above serum ammonia levels were raised, and there was improvement on stopping VPA. Naranjo *et al*. probability score[7] was 6 establishing hyperammonemia as a probable adverse reaction of VPA.

In a review of thirty cases of VHE in psychiatric patients, mean serum ammonia level was 174 ± 184 μmol/L and mean VPA level was 91 ± 23 μg/ml. The majority of the patients recovered completely in a month after discontinuation of VPA, and some received additional treatment with L-carnitine, lactulose, and neomycin.[3]

Six cases of VHE in the psychiatric setting have been reported from India. All the patients were of BPAD and received VPA as a monotherapy or in addition to benzodiazepines, antipsychotics, and topiramate.[8] The dose of VPA ranged between 600 and 1500 mg, and they improved drastically on stopping the drug.[9,10]

In this case series, there were three males and one female subject, presenting in mania, with a lifetime diagnosis of BPAD in three and schizoaffective disorder in one. Two cases had medical morbidity (hypothyroidism and rheumatic heart disease) and two had cannabis dependence. All four cases presented with GI symptoms (constipation and vomiting) preceding altered sensorium. Ammonia levels were found to between 122 and 291 mcg/dl. Gastroenterology consult was taken in all cases, and only the first case required lactulose considering his age and severity of symptoms, with rest improving spontaneously. Underlying protein deficiency or urea cycle enzyme deficiency was not evaluated as none of them had any prior history suggestive of protein intolerance, hematological disease, or failure to thrive.

Several putative risk factors for the development of VHE have been proposed with foremost being urea cycle enzyme deficiency. Polypharmacy, complicated medical condition, mental retardation, dietary restrictions, and carnitine deficiency due to genetic abnormalities, and infancy have been proposed.[2]

These cases highlight the need of early diagnosis of VHE as it is a potentially fatal but reversible condition which is seen not only in the acute phase but also later in the treatment. The inpatient setting of our case series may increase the presence of certain risk factors such as poor oral intake, dehydration, and polypharmacy. We were unable to rule out the urea cycle disorders and inferred their absence historically which may be inconclusive.

A high index of suspicion is warranted in patients on VPA presenting with confusion, altered sensorium, gastric disturbance, or a sudden deterioration. Polypharmacy should be avoided and VPA should be used judiciously in patients with underlying inborn errors of metabolism and mental retardation. Systematic research targeting identification of risk factors, pathogenesis, therapeutic, and prophylactic agents for VHE is the need of the hour for safer use of VPA.

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Conflicts of interest
There are no conflicts of interest.

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