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Sodium Valproate Induced Hyperammonemia with Normal Liver Function: A Case Report

Teena C Abraham, Greeshma James, Anjana Thomas, Lakshmi R*
Department of Pharmacy Practice, Amrita School of Pharmacy,
Kochi, Amrita Vishwa Vidyapeetham, Amrita University, India.

Abstract

Sodium salt of valproic acid is a commonly used antiepileptic drug also used in the treatment of migraine headache prophylaxis, neuropathic pain, restless leg syndrome, dementia related agitation and social anxiety disorders. The most common adverse effects of sodium valproate are change in appetite, nausea, vomiting, diarrhea, dizziness, hair loss, gingival hyperplasia, abnormal liver function etc. Sodium valproic acid induced hyperammonemia are often seen in hepatic failure but it rarely occur with normal liver function and it is fatal. There is only less than 1% incidence rate for sodium valproate induced hyperammonemia. This is a case of sodium valproate induced hyperammonemia with normal plasma sodium valproate level (44.5mcg/ml) and with normal liver function. A 37 year old male who was admitted to the psychiatry department with reduced sleep for 4 days and anger. He had a history of Bipolar Affective Disorder, current episode mania with psychotic symptoms and Crohn's disease. Patient was on Tablet Sodium valproate 500mg Once Daily for the past one year as a mood stabilizer. He was admitted on 11-12-2015 in the psychiatry department and continued to take Tablet Sodium valproate 250 mg Twice Daily. After few days he was found to be disoriented. Hence ammonia levels was measured on 14 -12-2015 and it was found to be 100.3umol/L (normal range 10-48umol/L). Ammonia level returned to normal after the withdrawal of the sodium valproate. He also developed gingivial hyperplasia as a side effect of the sodium valproate. This case has the causality score of 5 (hyperammonemia) and 6 (gingivial hyperplasia) using NARANJO probability scale and causality of both Adverse Drug Reactions was found to be probable.

Keywords: Sodium valproate, Hyperammonemia, Epilepsy, Gingivial hyperplasia, Psychiatry.

INTRODUCTION

Sodium valproate is a broad spectrum antiepileptic drug that is used for the treatment of several types of seizures like, absence seizures, complex partial seizures, juvenile myoclonic epilepsy, tonic clonic seizures and the seizure associated with Lennox-Gasaut syndrome. Sodium valproate is also used for manic episodes associated with bipolar disorder. Sodium valproate increases the availability of GABA (Gamma amino butyric acid), an inhibitory neurotransmitter i.e., synthesised from glutamic acid by the enzyme glutamic acid decarboxylase (GAD). GAD is an enzyme that catalyzes the decarboxylation of glutamic acid to GABA. It acts on the GABA receptor and activate the receptor causing additional potassium channel to open thereby potassium ions flow out of the cell and due to this inside of the cell become more negative resulting in hyperpolarization and thus inhibits the action potential. This leads to the prevention of overstimulation and increases the calming activity of GABA in the brain, which stabilizes the electrical nerve activity and helps to prevent seizure[1].

The most common toxic effects of sodium valproate are change in appetite, diarrhea, dizziness, hair loss, gingivial hyperplasia, variation in liver function etc. Rarely, sodium valproate can cause blood dyscariasis, impaired liver function, jaundice, thrombocytopenia and prolonged coagulation time. Liver failure, high initial dose of valproate, extended sodium valproate therapy, administration of salicylates along with valproate, strict vegetarianism and disorder held with reduced albumin synthesis are the risk factors for developing sodium valproate induced hyperammonemia[2].

Valproic acid induced hyperammonemia are often less likely which can lead to brain damage and it is fatal. Hyperammonemia is a metabolic condition described by elevation of serum ammonia level above 40mmol/L which is manifested as disorientation, itching, vomiting, irritability and occasionally paradoximal seizures. Increased entry of ammonia to the brain also results in neurological disorders. The sodium valproate metabolises through mitochondrial oxidation which leads to the production of proponyl Co-A and valproyl Co-A which deplete N acetylglutamate by inhibiting N-acetylglutamate synthetase. This results in decreased removal of ammonia due to the inhibition of CPS1[3,4]. Another mechanism for hyperammonemia is sodium valproate causes defecit in carnitine. This results in decreased beta oxidation of fatty acids causing reduced level of acetyl Co-A and ultimately disrupts the urea cycle resulting in ammonia accumulation. Hyperammonemia are observed in 16-52% of patients receiving sodium valproate therapy. It is therefore recommended to monitor the serum ammonia level and serum valproate level[5].

CASE REPORT

We hereby report a case of sodium valproate induced hyperammonemia. A 37 year old male who was admitted to the psychiatry department of a tertiary care hospital on 11-12-2015 with complaints of reduced sleep for 4 days and anger and also refused to take medicines properly. He had a history of BPAD, current episode mania with psychotic symptoms and Crohn's disease for past 10 years. Patient was on Tablet Sodium valproate 500mg OD, Clonazepam 2mg BD and Haloperidol 2mg TID. These medications were prescribed for mood stabilizing, anxiety and Haloperidol was started for impulsivity. Trihexyphenydyl was also started to prevent extrapyramidal side effects and infliximab for the

management of crohn's disease. During hospital stay sodium valproate was continued with a dose of 250 mg BD and all other medication continued with same dose. After few days of the admission he was found to be disoriented. So all laboratory investigations were done and lab reports showed low blood counts, elevated eosinophills and normal renal and liver functions including creatinine, SGPT, SGOT, ALP etc. Later, on examination patient was found to have itching all over the body and also had vomiting. For this he was started on symptomatic management with tablet ondansetron 40 mg OD. As the symptoms persist the physician recommended to measure the ammonia level on 14 -12-2015 and it was found to be very high i.e 100.3umol/L. The normal ammonia level ranges between 10-48umol/L. Further serum valproate level was also measured, but it was within therapeutic range i.e 44.5mcg/ml. So physician adviced to withhold the sodium valproate due to hyperammonemia inspite of its normal serum concentration and after few days patient relieved from all this symptoms and ammonia level attained within normal range (39umol/L). He also developed gingival hyperplasia as a side effect of the sodium valproate. After the withholding of sodium valproate the patient manic symptoms get worsened. So decided to start sodium valproate with decreased dose of 250 mg OD and continued the monitoring of serum ammonia level. His manic symptoms improved well with this treatment and he was discharged in a stable condition.

DISCUSSION

Sodium valproate is a broad spectrum antiepileptic drug that is approved for the treatment of several types of seizures[6]. There is only few reported case of sodium valproate induced hyperammonemia with normal liver functions.

Aiyer et al reported a case of patient on long term sodium valproate for management of bipolar affective disorder. During hospital stay serum ammonia level was measured and found to be very high even though the patient is asymptomatic. For the management of hyperammonemia, dual therapy of lactulose and carnitine was given and valproic acid was not stopped. This case shows that patients with hyperammonemia need not be symptomatic and prolonged use of valproic acid can result in high ammonia levels[7]. Sumant et al describes a case of 11year old girl with complex seizures was on clonazepam and ethosuximide, in addition to it sodium valproate was added. Thereafter she developed hyperammonemia that get worsened by protein load. Hperammonemia improved and resolved on discontinuation of the sodium valproate and no changes in serum bilirubin or transaminases were not observed[8].

Naresh et al report a case of 15 year old female, who was on phenytoin and carbamazepine for the management of seizure disorder. She was admitted in the hospital due to fever and she was diagnosed with pulmonary Tb and was initiated on antitubercular treatment. Phenytoin was gradually withdrawn and substituted with sodium valproate 50 mg BD due to interaction between phenytoin and rifampicin. After 20 days she admitted with complaints of headache, altered sensorium and unsteadiness and found high levels of ammonia level and sodium valproate, so that valproate was discontinued immediately. As a result of this patient's complaints improved[1]. Charles et al evaluated all individuals taking valproate therapy in an institution for hyperammonemia. Out of these 19 developed hyperammonemia, 6 had intermittent and 5 other had persistent and all these 19 patients are asymptomatic. He also found that sodium valproate induced hyperammonemia is more common in younger adults and in patients treated with multiple anticonvulsants especially phenytoin[9].

CONCLUSION

Sodium valproate induced hyperammonemia is rare and usually reversible with discontinuation of sodium valproate. Discontinuations of valproate, hemoperfusion, haemodialysis, symptomatic and supportive measures, withdrawl or adjusting the dose of valproate are the treatment options for hyperammonemia. The causality of sodium valproate induced hyperammonemia was probable and special caution should be used in patients with mental retardation. Physician should be aware of the possibility of hyperammonemia while prescribing sodium valproate and regular monitoring of blood ammonia level is required.

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