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Case Report

Psychiatry Section

Valproate Induced Delirium due to Hyperammonemia in a Case of Acute Mania: A Diagnostic Dilemma

SIDDHARTH DIXIT[1], MAYANK NAMDEO[2], SUDIP AZAD[3]

ABSTRACT

Divalproex sodium is commonly used drug to treat variety of psychiatric and neurological disorders. Hyperammonemia is infrequent adverse affect of treatment with divalproex sodium. It needs high degree of clinical suspicion or else can lead to delirium of non hepatic origin in some group of patients and to medication errors or even death. We hereby report a case of mania who developed hyperammonemia with normal sodium valproate levels and liver function tests where delirium lead to diagnostic and medication errors. Withdrawal of divalproex sodium led to clinical recovery but delirium prolonged his hospital stay. This case report cautions the clinicians about hyperammonemia as the uncommon side effects and emphasizes the need of doing blood ammonia testing in patients treated with divalproex sodium where recovery is halted or clinical condition worsens despite normal liver function test and EEG.

Keywords: Bipolar disorder, Encephalopathy, Non hepatic hyperammonemia, Valproic acid

CASE REPORT

A 31-year-old male with no past history of any significant medical illness manifested with acute onset of behavioural problems of seven-eight days duration in form of increased psychomotor activity, elated mood, verbosity, distractibility, enhanced self esteem, hyper-religiosity, delusion of grandiosity, impaired biodrives (sleep, appetite and libido) in absence of any perceptual disturbance and with intact sensorium. There was no history of fever, altered sensorium, neurological deficit and significant weight loss prior to onset of behavioural abnormalities. There were no developmental issues. Physical examination revealed pulse 82/min, BP 130/82 mm of Hg, afebrile, respiratory rate was 16/min, no digital tremors or hyperhydrosis. Lab investigations including heamogram, LFT, urea, creatinine, blood sugar, lipid profile, serum electrolyte, X-ray chest, CT Scan Brain, T3, T4, and TSH was within normal limits and HIV status was negative. He was diagnosed as a case of mania with psychotic symptoms as per International Classification of Diseases 10 (ICD10) [1] and started on mood-stabilizer tab divalproex sodium 500 mg BD and olanzapine 5 mg BD. Patient started showing improvement. By 10th day his symptoms remitted to about 40% however his hyper-religiosity, self esteem and grandiose manners though less severe persisted, however on 13th day patient complained of headache right hemi-cranium lasting for half hour to one hour accompanied by nausea and vomiting. His pulse, BP and temp were normal. MRI brain and fundoscopy revealed no abnormality. A neurophysician referral resulted in prescription of tab topiamate 25 mg BD in view of vascular headache and the same evening (15th day of admission) after receiving tab topiramate patient developed disorientation, confusion, unsteadiness of gait, irrelevant talks and agitation which continued for next three-five days. His topiramate was stopped immediately. His MMSE score was 13/30. Subsequently divalproex sodium was increased to 1500 mg along with 15 mg of olanzapine by 22nd day. EEG revealed normal bilateral symmetrical 9-12 Hz posteriorly dominant alfa rhythms. Patient did not show any improvement and continued to remain puzzled, dazed, confused and disoriented during day time with irrelevant talk and exhibited more hyperactivity towards evening with altered sleep-Wake schedule. His physical examination revealed pulse 88/min, BP 136/88 mm of Hg, respiratory rate 18/min. There were no menningeal, cerebellar or extra pyramidal signs. His neurological examination was non contributory. His repeat liver function, electrolyte, urea, creatinine and CPK levels were within normal range. A pre-anesthetic check up was done and after taking appropriate consent of patient and relatives, he was taken up for electroconvulsive therapy (ECT) on 29th day suspecting it to be a case of Delirious mania. ECT was planned twice a week. Before starting ECT dose of divalproex sodium was reduced to 250 mg BD to achieve sufficient seizure duration suspecting interference in seizure activity by antiepileptic action of divalproex sodium. Patient responded well to first two ECT with disappearance of day time confusion, hypo activity, hyperactivity, irrelevant talks and restoration of sleep wake schedule. Slowly divalproex sodium dose was increased to 1500 mg in divided doses over couple of days and antipsychotic was changed to tab aripiprazole 15 mg. Once again patient deteriorated with irrelevant talks, headache, disorientation, hypo activity mixed with hyperactivity. On 46th day after five ECT and not finding desired improvement ECT was stopped and on clinical suspicion of hyperammonemia venous blood was sent for estimation. His serum valproate levels were 65 mg/l (therapeutic range 60 -100 mg/l). His serum ammonia levels were deranged at 98 umol/l (n=11-35 umol/l). Thereafter divalproex sodium was stopped. Further investigation for underlying urea cycle enzyme abnormality was not evaluated in this patient as there was no history of failure to thrive, protein intolerance or hematological disease that could lead to hyperammonia. On stopping divalproex sodium patient started showing dramatic improvement with disappearance of headache, nausea, confusion, lethargy and disorientation. His serum ammonia level was 30 umol/l on 5th day. His MMSE score improved to 27/30. He was well stabilized with tab oxcarbazepine 900mg and tab aripripazole 15 mg in divided doses. By 70th day of admission patient was asymptomatic and was discharged on maintenance medication.

DISCUSSION

Valproate is widely used drug in various neuropsychiatric and neurological conditions. It is considered quite safe with wide therapeutic window. Rarely valproate induced hyperammonemia produces delirium like state of non hepatic origin and if not timely suspected may also lead to valproate induced encephalopathy or even death [2]. Hyperammonemia could be asymptomatic [3] or

may progress to focal neurological deficit, seizure, marked sedation, coma, due to encephalopathy [4].

Our case was young adult who had hyperammonemia due to divalproex sodium use despite therapeutic blood levels of drug and normal LFT and EEG. Co-administration of topiramate worsened his clinical state as it is a risk factor for hyperammonemia [5]. Withdrawal of valproate lead to prompt recovery. The Naranjo adverse drug reaction probability scale [6] of this case scored nine on this scale which was categorized as definite adverse drug reaction. Valproate induced hyperammonemia can baffle the treating psychiatrist and confuse the case with psychosis or worsening of mania and can induce improper management [2,3] as happened with us when delirium due to hyperammonemia in mania was mistaken for delirious mania and treated with ECT.

Majority of literature reported on valproate induced hyperammonemic encephalopathy (VIHE) is from neurology or pharmacological case studies. VIHE was first reported from psychiatric side in 1995 [7] and uptill now about 36 cases of VIHE have been reported from psychiatric arena [8]. Our case differed from others as valproate induced hyperammonemia did not progress to encephalopathy (seizure, focal neurological deficit, coma or death) [7,9-11]. Secondly valproate induced hyperammonemia developed while on monotherapy with valproate and there was neither polypharmacy [8] nor known medical comorbidity [8,9]. Lastly stoppage of divalproex sodium for few days lead to prompt recovery and no other treatment measure like carnitine, lactulose, heamodylysis [12,13] were required.

The mechanism of valproic acid and its derivatives causing hyperammonemia is multifactorial. Besides topiramate other anti epileptic drugs like phenobarbitone, phenytoin and carbamazapine, urea cycle disorders, low plasma carnitine levels, rich protein diet and fasting are known risk factors for VHE [9,14]. VHE pathogenesis is related to urea cycle defect mostly in form of carbamoyl phosphate synthetase-1inhibition leading to decreased utilization of ammonia followed by a hyperammonemic state [15]. Valproate also reduces the hepatic synthesis of carnitine and increases its renal excretion thereby causing hyperammonemia [16]. Hyperammonemic encephalopathy can lead to edema of astrocytes via glutamate uptake inhibition, which may produce cerebral oedema and neuronal injury [14]. There is apparently no link between the development of VHE and serum levels and doses of valproic acid [9,14].

This case is reported to caution the psychiatrist that there should be high index of suspicion for VPA induced hyperammonemia if any patient shows deterioration in clinical recovery or develops delirium while on treatment with VPA as hyperammonemia is potentially a reversible condition.

CONCLUSION

There should be high index of suspicion for valproate induced hyperammonemia if any patient shows deterioration in clinical recovery or develops delirium while on treatment with valproic acid or its derivatives as it is potentially fatal but reversible condition.

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PARTICULARS OF CONTRIBUTORS:

1. Classified Specialist, Department of Psychiatry, Base Hospital Delhi Cantt, New Delhi; Assisstant Professor, Department of Psychiatry, Army College of Medical Sciences, New Delhi, India.
2. Resident, Department of Psychiatry, Base Hospital Delhi Cantt, New Delhi, India.
3. Resident, Department of Psychiatry, Base Hospital Delhi Cantt, New Delhi, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:

Dr. Siddharth Dixit,
Classified Specialist, Department of Psychiatry, Base Hospital Delhi Cantt. New Delhi 110010, India.
E-mail: sid68sify@gmail.com

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