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Valproate Induced Hyperammonemic Encephalopathy in a Patient with Phenytoin Toxicity: A Case Report

Juneja H[1*], Dabla S[1] and Pahuja I[2]

[1]Department of Neurology, Pt. B D Sharma PGIMS Rohtak, Haryana, India
[2]Department of Gastroenterology, Pt. B D Sharma PGIMS Rohtak, Haryana, India

Abstract

Valproate is an antiepileptic drug which is commonly used for the treatment of focal and/or generalized epilepsy and mood disorders. Valproate is one of the safest first line antiepileptic drug, but like any other drug, it has adverse effects such as nausea, vomiting, drowsiness, tremors, alopecia, menstrual irregularities, polycystic ovarian disease, hepatotoxicity, pancreatitis, thrombocytopenia and rarely hyperammonemia etc. We have reported a case of 22-years-old female of idiopathic generalized epilepsy admitted with eptoin toxicity and subsequently she developed valproate induced non-hepatic hyperammonemia encephalopathy during her hospital stay. Valproate was withheld immediately, and her symptoms resolved after 48 hours.

Keywords: Valproate; Encephalopathy; Hyperammonemia; L-Carnitine

Introduction

Valproate is generally used in epilepsy and psychiatric disorders. Hyperammonemic encephalopathy is a rare adverse effect of valproate. Possible differentials in a patient with acute or subacute onset altered mental status on valproate could be drug overdose, valproate induced hepatic encephalopathy (VHE) and hyperammonemia in the absence of liver failure also known as valproate induced non-hepatic hyperammonemia encephalopathy (VNHE). Here we have presented a case of VNHE in a patient admitted in neurology ward with phenytoin toxicity.

Case Report

A 22-years-old female known case of IGE for the last 15-years with uncontrolled seizures on tab. phenytoin 200 mg once daily (weight 46 kg), presented in neurology outpatient department with complaints of vertigo, vomiting and difficulty in walking for the last one week. Patient admitted in neurology ward with a provisional diagnosis of phenytoin toxicity. A detailed past and treatment history revealed that patient was taking tab. phenytoin 600 mg from the last 2 weeks. Patient gave history that, dose of phenytoin was increased to 300 mg after she had one episode of seizure 2 weeks back. When we review the medicines that patient was taking, we came to know that patient was taking a total of 600 mg of phenytoin daily, 300 mg extra from government pharmacy in strip packing which she received from hospital when she visited last time in addition to 300 mg from a private pharmacy in glass bottle packing which she was taking previously. On examination, patient was conscious, oriented to time/place/person. Her vitals were stable and general physical examination was normal except for presence of gum hypertrophy. Nervous system examination revealed a horizontal bidirectional nystagmus, with positive finger to nose, positive heel to shin test and dysdiadochokinesia with a staggering gait. Rest of nervous system and systemic examination was normal. Phenytoin was immediately stopped, and injection valproate 500 mg I/V twice daily was started after giving loading dose of valproate. Routine blood investigations i.e., complete hemogram and biochemistry were normal. Her blood sugar levels were 114 mg/dl. Her serum sodium and potassium levels were 140 meq/L & 3.8 meq/L respectively. Serum phenytoin levels were found to be raised 29.36 ng/ml (normal 10-20 ng/ml). MRI brain was normal. On day 4th after admission, she was free of her symptoms. On day 5th, she became drowsy and was partially following verbal commands. Her vitals were stable (PR-88/min, blood pressure -110/60 mm Hg, afebrile). Higher mental functions were not assessible. Pupils were equal middilated sluggishly reactive to light. She was moving her all four limbs. DTR were 2+ in all four limbs. Plantares were bilateral extensor. Rest of systemic examination was normal. Repeat complete hemogram, liver function tests, renal function tests and serum electrolytes were normal. Her Blood sugar level was 101 mg/dl. EEG revealed diffuse slowing but no epileptiform discharges. Her serum valproate levels were 54.1 ug/ml (normal range 50-100 ug/ml). In view of normal liver enzymes and serum bilirubin possibility of hyperammonemia was kept. Blood ammonia levels were found to be raised 119 umol/l (normal range 9-30umol/l). So, a diagnosis of valproate induced non-hepatic hyperammonemic encephalopathy was made. Valproate was withheld and injection levetiracetam was started. In addition, syrup lactulose 30 cc (through ryles tube) and injection L-carnitine 500 mg I/V every eight hourly was given. Her symptoms resolved completely after 72 hours. She was discharged on day 12th on tablet levetiracetam 500 mg twice daily.

Discussion

Valproate is associated with many neurological adverse effects such as headache, unsteadiness, dizziness, blurred vision and tremor being the most common. Valproate frequently cause slight asymptomatic increase in blood ammonia levels. Symptomatic hyperammonemia in patients on valproate could be due to hepatotoxicity (VHE, incidence 1 in 20,000) and rarely hyperammonemia with normal liver functions tests (VNHE) [1]. VNHE is characterized by acute or subacute onset of impaired cognition, drowsiness, disturbed sleep-wake cycle and loss of appetite. It is an idiosyncratic reaction and does not correlate with serum valproate levels. In most of cases of VNHE valproate levels are found within normal range [2]. The pathophysiology behind VNHE is inbition of metabolism of ammonia which is metabolized into urea through Kreb-Henseleit urea cycle in liver. Carbamyl phosphate synthetase I (CPS I) enzyme is

***Corresponding author:** Juneja H, Department of Neurology, Pt. B D Sharma PGIMS Rohtak, Haryana, India, Tel: +919728208283; E-mail: himanshu_talkin@planetmail.net

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rate limiting enzyme in urea cycle and requires N-acetylglutamate for its activation. Valproate when metabolized by mitochondrial oxidation in liver produces propionyl Co-A and valproyl Co-A which inhibits N-acetylglutamate and leads to reduced activity of CPS I hence raised ammonia levels. Also, valproate inhibits fatty acid beta oxidation in mitochondria especially in the presence of l-carnitine deficiency which results in decreased production of acetyl Co-A which acts as substrate for N-acetylglutamate. Deficiency of N-acetylglutamate reduces CPS I activity thus ammonia metabolism [3]. Risk factors for VNHE are polypharmacy (leading to drug interactions), poor nutritional state, L-carnitine deficiency, febrile state, inherited susceptibility and urea cycle disorders. Diagnosis is made by temporal relationship i.e., that onset of encephalopathy after administration of valproate and resolution after its withdrawal. EEG shows diffuse slowing with predominant theta or delta waves. Triphasic waves also known as metabolic waves can also be seen in some patients. EEG must be done in these patients to rule out non-convulsive status epilepticus as seizure threshold is reduced in these patients [4]. Blood ammonia levels should be assessed in every patient on valproate who develops altered mental status, increased seizure frequency with normal valproate levels.

Treatment is supportive. Valproate should be discontinued. L-carnitine supplementation may attenuate ammonia levels, especially in patients with poor nutritional states. Recommended dose of L-carnitine is 100 mg/kg IV over 30 minutes followed by 15 mg/kg IV given every four to six hourly, continued until symptoms resolved [5].

Conclusion

In this case report, we can conclude that VNHE should be considered in a patient who develops new onset altered sensorium while being treated with valproate even when the valproate levels are in normal range and liver functions are normal.

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