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Case Series

Pharmacology Section

Sodium Valproate Induced Hyperammonaemia without Hepatic Failure in Adults: A Series of Three Cases

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ABSTRACT

Valproate is an antiepileptic drug that is most commonly prescribed because of its wide spectrum of antiepileptic activity. It is used for the treatment of many psychiatric conditions such as bipolar disorder, schizoaffective disorder, social phobias etc. Valproate is associated with modest elevation of plasma ammonia levels. Some of the risk factors associated with this are poor nutritional intake, antiepileptic polypharmacy, febrile conditions which are thought to deplete L-carnitine levels. Hence, it is important to monitor the plasma ammonia levels at intervals before the patient could develop hyperammonaemic encephalopathy. We hereby report a series of three cases of patients who developed hyperammonaemia following the intake of Sodium Valproate.

Keywords: Adverse drug reaction, Anti-epileptic, Elevated ammonia, Naranjo's scale

CASE: 1

We report a case of 48-year-old male patient, without any comorbidities such as hypertension or diabetes, with a 10-year history of organic personality disorder with temporal lobe epilepsy. The patient came with a complaint of repeated seizures. There was no history of alcohol intake, smoking or addiction to any drug. There were no previous medical records available regarding his treatment. He was started on tablet sodium valproate 600 mg along with Risperidone 4 mg for temporal lobe epilepsy and organic personality disorder and Trihexyphenidyl 4 mg for prevention of extrapyramidal symptoms. After seven months, the patient came to Outpatient Department (OPD) complaining of lethargy and drowsiness. On examination, there was flapping tremors. Motor and sensory system examination revealed to be normal. There was no disturbance in gait. Patient was admitted with a differential diagnosis of encephalopathy for evaluation. Blood investigations revealed increased ammonia level to 274 mcg/dL (Normal: 16-60 mcg/dL). Other liver enzymes and laboratory parameters were within normal limits. Sodium valproate was stopped in view of possible development of encephalopathy, and a strict protein intake of 60-80 gm/day (which included mainly vegetables) was recommended. After one month, on his follow up visits there was decrease in level of serum ammonia (110 mcg/dL).

CASE: 2

A 24-year-old male patient visited the Psychiatry OPD, with complaints of increased talkativeness, insomnia, auditory hallucinations. Patient had four similar episodes in the past, each lasting for about 20-25 days with increased talkativeness, overfamiliarity, disruptive behaviour and decreased sleep. A complete physical examination revealed a body mass index of 33 kg/m^2, putting him in the obese category. Patient was a diabetic but non alcoholic and non hypertensive. Patient's guardian revealed no history of developmental delay in the patient in childhood. Considering specific symptoms and signs of mania and psychosis, a diagnosis of bipolar affective disorder was made as per DSM-V classification and patient was initiated on sodium valproate 1.5 gm along with lithium 800 mg, olanzapine 30 mg and lorazepam 2 mg [1]. After one week of treatment with the above medications, patient came back with complaints of increased lethargy, drowsiness and impaired consciousness. His vitals were pulse rate 60/minute, blood pressure 118/74 mmHg, temperature 98°F and SpO_2 99% on room air. The typical presentation of encephalopathy (in the form of impaired consciousness) was noted and laboratory investigations revealed an elevated plasma ammonia level and deranged metabolic profile as given in [Table/Fig-1] [2].

Parameters	Values	Normal range
Serum urea	13 mg/dL	10-40 mg/dL
Serum creatinine	0.8 mg/dL	0.4-1.2 mg/dL
Serum sodium	136 mmol/L	136-144 mmol/L
Serum potassium	3.9 mmol/L	3.6-5.1 mmol/L
Total cholesterol	156 mg/dL	140-200 mg/dL
Triglycerides	78 mg/dL	60-150 mg/dL
Total bilirubin	0.4 mg/dL	0.3-1.2 mg/dL
Direct bilirubin	0.1 mg/dL	0.0-0.4 mg/dL
Plasma ammonia	110 mcg/dL	16-60 mcg/dL
Fasting blood sugar	133 mg/dL	60-100 mg/dL

[Table/Fig-1]: Metabolic profile of patient after Sodium Valproate treatment.

Patient did not have any fever, and among the drugs which the patient was receiving, sodium valproate was the most common cause for hyperammonaemia. Considering this possibility, sodium valproate was stopped. Lithium was titrated to 1200 mg/day. Olanzapine, was stopped in view of abnormal metabolic profile and Quetiapine was started at a dose of 175 mg along with Metformin 500 mg. Symptoms improved gradually after five days, serum ammonia levels decreased to 72 mcg/dL and patient was discharged.

CASE: 3

A 45-year-old woman with more than 20 years' history of illness of schizoaffective disorder, episodic in nature with unsure treatment details, presented to our hospital with complaints of 2nd and 3rd person hallucination, inappropriate laughter and smiling to self, decreased sleep and poor socio-occupational functioning. A routine physical examination revealed a body mass index of 31 kg/m^2 putting her in the obese category with all other parameters within normal limits. Laboratory investigations revealed a high fasting blood sugar level of 140 mg/dL. Mental status examination revealed increased psychomotor activity, sad mood, inappropriate affect, avolition and attention not sustained. In view of the above signs and symptoms, patient was diagnosed as a case of schizoaffective disorder as per DSM-V/ICD-10 classification and was initiated on Quetiapine 150 mg, Risperidone 4 mg, Lithium 900 mg for her psychotic and maniac symptoms, and Lorazepam 2 mg for insomnia. However, she returned to psychiatric department in a period of two months with history of poor compliance to medication and relapse of her psychotic symptoms.

Hence, she was started on Valproate 100 mg and Clozapine 450 mg in May 2016. After five months of treatment with valproate, patient presented with history of lethargy, drowsiness and mental confusion. Patient was admitted with a differential diagnosis of encephalopathy for evaluation. She had no history of alcohol intake, no gait disturbances. Investigations revealed fasting blood sugar- 103 mg/dL, urea- 20 mg/dL, creatinine- 0.2 mg/dL, total bilirubin -0.6 mg/dL, direct bilirubin- 0.2 mg/dL and plasma ammonia raised to 135 mcg/dL. There were no other differentials to consider in the patient other than sodium valproate induced hyperammonaemia, hence drug was stopped and the dose of clozapine was increased to 650 mg along with Injection Zuclopenthixol 400 mg intramuscularly. Patient improved symptomatically and was discharged with the above medications. [Table/Fig-2] presents the summary of all the cases.

	Case 1	Case 2	Case 3
Age (years)	48	24	45
Sex	Male	Male	Female
Underlying disease	Organic personality disorder with temporal lobe epilepsy	Bipolar affective disorder	Schizoaffective disorder
Comorbidities	nil	Obesity, diabetes	Obesity High fasting blood sugar (140 mg/dL)
Duration of sodium valproate therapy	7 months	1 week	5 months
Initial serum ammonia level	274 mcg/dL	110 mcg/dL	135 mcg/dL
Ammonia level after stopping sodium valproate	110 mcg/dL	72 mcg/dL	85 mcg/dL
De-challenge	Done	Done	Done
Re-challenge	Not done	Not done	Not done
Naranjo's score	7 (probable)	7 (probable)	5 (probable)

[Table/Fig-2]: Summary of the above cases.

DISCUSSION

Sodium valproate is an antiepileptic drug that is most commonly prescribed because of its wide spectrum of antiepileptic activity. It is also used for the treatment of many psychiatric conditions such as bipolar disorder, schizoaffective disorder, and social phobias [3]. It is known to cause many adverse effects like hepatotoxicity, encephalopathy, coagulation disorder, pancreatitis, and bone marrow suppression [4].

Sodium valproate induced hyperammonaemia is common in children and young adults [5]. However in our case series, all patients were adults. The incidence of sodium valproate induced hyperammonemic encephalopathy is not known, but asymptomatic increases in serum ammonia are seen in 16–52% of patients receiving sodium valproate therapy [6]. Ammonia is by product of amino acid metabolism that is ultimately converted to urea and excreted through urine. Carbomyl Phosphate Synthetase-I (CPS-I) is an important enzyme that is involved in this process. Hyperammonaemia is a condition where the ammonia level in the blood is elevated to more than 40 mcg/dL. Hyperammonaemia is caused by many causes such as inborn errors of metabolism, portosystemic shunts, urinary tract infections with urea-splitting organism, liver diseases, malignancies, drugs such as 5-Fluorouracil, Salicylates, Acetazolamide, higher doses of the sodium valproate medication and concomitant use of other antiepileptics like topiramate. However, none of our patients had any of the above causes of hyperammonaemia. Previous case reports, and various cohort studies have recognised the following risk factor for this causation such as an increased sodium valproate dose, female gender and concomitant use of enzyme inducers [7].

In the first case hyperammonaemia developed seven months after starting Sodium Valproate treatment. Valproic acid is a short fatty acid, it is metabolised to valproic CoA. It forms complex with carnitine and enhances its excretion [8]. Chronic sodium valproate treatment in this case might have reduced the carnitine stores in the body subsequently leading to development of hyperammonaemia.

In the next two cases, hyperammonaemia has developed after one week of Sodium Valproate therapy. Here inhibition of enzyme N-acetyl glutamate synthase ultimately leading to inhibition of CPS-I enzyme thereby decreased ammonia clearance might be the underlying mechanism [9].

Temporal relationship between starting Sodium Valproate treatment and development of hyperammonaemia and reversal of the symptoms after stopping sodium valproate treatment confirms the diagnosis of valproate induced hyperammonaemia. As per Naranjo's scale in all the three cases hyperammonaemia and its symptoms are probably caused by Sodium Valproate [10].

CONCLUSION

Sodium Valproate is most commonly prescribed drug due to its wide range of activity in both neurological and psychiatric conditions. Treating physician should keep an eye on the symptoms of hyperammonaemia such as drowsiness, lethargy, poor seizure control in epileptic patients which can develop at any time during treatment and in any age group.

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