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Case Report

# Non-hepatic Hyperammonemia with Loading Dose of Perampanel in a Case of CNS Lupus Presenting with Non-Convulsive Status Epilepticus

**Rahul Ghiya*, Sanghita Layek and A Shobana**

*Department of Neurocritical Care, Institute of Neurosciences, Kolkata, West Bengal, India*

***Corresponding Author:** Rahul Ghiya, Department of Neurocritical Care, Institute of Neuroscience, Kolkata, West Bengal, India.

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## Abstract

Hyperammonemia manifests clinically as mild cognitive impairment to coma and even death. It happens due to both hepatic metabolic disorders or non-hepatic causes. Perampanel is an antiepileptic drug metabolized by hepatic enzymes.We here report a patient of CNS lupus who presented with NCSE and developed hyperammonemia after receiving the loading dose of perampanel. No definite mechanism has been able to explain the correlation between perampanel and hyperammonemia. The blood ammonia levels came down to the normal range after stopping the medication. However, even after the stoppage of perampanel and normalization of ammonia, her condition and NCSE remains the same. We suggest serum ammonia levels should be done before starting perampanel in any patient with a constant monitoring of ammonia levels at regular intervals. However, more cases are required to understand the mechanism of action, risk factors and establish monitoring protocols in patients for perampanel therapy.

**Keywords:** Hyperammonemia; Perampanel; NCSE; Neurological Manifestations

## Introduction

Hyperammonemia is a metabolic disorder characterized by the raised levels of ammonia, a nitrogen-containing compound [1]. Hyperammonemia, where ammonia is the principal toxin, can result from various congenital and acquired conditions [1].

The clinical presentation of hyperammonemia mainly includes neurological signs and symptoms due to its neurotoxic effects and can vary from mild, cognitive and psychomotor changes to altered level of consciousness and neuromuscular dysfunction. Hyperammonemia is a life-threatening condition and should be addressed rapidly for intervention [2].

Hyperammonemia may occur as a part of hepatic disorders that involve various metabolic abnormalities, inborn errors of metabolism or other non-hepatic causes include infective causes, Reye's syndrome, drug toxicity.

Sodium valproate is commonly prescribed to treat mood disorders, epilepsy and migraine. Valproate has been reported to have caused hyperammonemia in 27% of patients, most of whom are asymptomatic. In patients developing encephalopathy, even coma and death may occur if the cause is not recognized and valproate is not stopped [3].

Perampanel is a novel antiepileptic drug (AED) approved in 2012 in Europe and the United states for the treatment of partial (focal) seizures, and as adjunctive treatment for primarily generalized tonic-clonic seizures. Perampanel is metabolized by CYP3A4 and CYP3A5 oxidation, followed by glucuronidation [4]. Clearance rate is reduced in patients with renal and hepatic impairment [4]. Limited data is available on the role of Therapeutic Drug Monitoring (TDM) in perampanel therapy, thus a therapeutic range has not yet been established.

We here report a patient of CNS lupus who presented with NCSE and developed hyperammonemia after receiving the loading dose of perampanel.

## Case Report

A fifty two year old female presented to our OPD with a history of

blurring of vision, gait instability and speech difficulty for 21 days. She was a known case of hypothyroidism and hypertension. She had no other significant past medical or surgical history. The patient underwent routine investigations with MRI brain which showed diffuse restriction in the left caudate nucleus and periventricular region and diffuse abnormality in the left hemispheric cerebral cortex.

As the symptoms worsened the patient got admitted in our hospital on 12th may. All routine investigations were done and were within normal limits. CSF examination was normal. [CSF study: Cell-1 (lymphocyte), Protein- 16 mg%, Glucose- 84 mg%]. CSF autoimmune panel, ANA profile and ANA Hep-2 profile were also sent. Anti TPO antibody - normal.

On 17 May 2021, the patient was confused with altered sensorium so EEG was done which showed Non convulsive status epilepticus (NCSE). She was given lorazepam and loaded with levetiracetam 1gm followed by 500 mg BD, even then the NCSE did not subside. So, she was shifted to ICU and intubated. Thereafter, midazolam infusion @ 0.3mg/kg/hr was started and the dose of levetiracetam was increased to 1gm BD.

The patient was started on pulse therapy of methyl prednisolone 1 gm daily for 5 days. On 20 May, she was still on midazolam infusion and the NCSE continued, therefore, injection lacosomide 200 mg was loaded followed by 100mg BD. Midazolam infusion was changed to propofol infusion and intravenous immunoglobulin was started.

On 22 May 2021, the patient continued having NCSE, so perampanel 12 mg was given as loading dose followed by 6 mg OD. Baseline metabolic and liver function investigations were done on 22 May 2021 - all were within normal limits (serum sodium -147 meq/l, serum potassium - 3 meq/l and ammonia (NH3) - 29 ug/dl.).

Next day, as the patient was still having NCSE, propofol was changed to ketamine infusion and tablet clobazam (10mg BD) was added. On the following day, burst suppression was achieved on EEG, therefore, ketamine was tapered off.

CSF autoimmune panel- Negative, Serum Paraneoplastic Profile- Negative, ANA Profile- Anti SSA/ SSB- Strongly positive, Anti Phospholipid Antibody IgG and IgM- Negative, C3 level- 121 mg%. So she was finally diagnosed to have been suffering from CNS Lupus with NCSE.

On 25th May 2021, the patient again developed NCSE on EEG, ketamine infusion was started. All the routine investigations were repeated on which ammonia (NH3) was found to be 116 ug/dl. Serum sodium was 143 meq/l and serum Potassium was 2.7 meq/l. Anti-ammonia measures were given.

Next day on 26/05/2021 her ammonia further rose to 175 ug/dl. However, Liver function tests were within normal ranges (SGPT-31U/L, SGOT- 31U/L). Abdominal imaging and hepatitis screening were also done and found to be normal. Perampanel was stopped and the patient was started on phenytoin. As the patient was still having NCSE, ketamine infusion was again started and pulse therapy of cyclophosphamide (1gm) was given on 27th May.

On subsequent days, ammonia levels started decreasing (79ug/dl on 27th May, 76 ug/dl on 28thMay) which finally came to normal on 31st May (ammonia- 55ug/dl). Subsequent values of ammonia were within limits, but the patient's general condition remained the same and NCSE continued for which the patient was again subjected to MRI, MR angiogram and MR venogram of brain on 1st June. Reports revealed ischemic foci in subcortical and periventricular white matter. Diffusion weighted imaging showed diffusion restriction in the head of caudate nucleus and also in the lentiform nucleus. In MR angiogram, narrowing was noted in bilateral supraclinoid internal carotid artery (ICA), left A1 anterior cerebral artery (ACA) was not visualized and middle cerebral artery (MCA) was narrow with paucity of middle cerebral artery branches. Distal subtraction angiography was done which revealed narrowing in bilateral ICA, ACA, MCA in A1 and M1 segment. A final impression of CNS vasculitis was made. Ultimately, the patient died from septic shock on 21st June.

## Discussion

Ammonia is a normal constituent of all body fluids, and the body excretes excess ammonia as urea following synthesis in the liver by the urea cycle enzymes [5].

Primary causes of hyperammonemia are congenital enzymopathies in the urea and secondary hyperammonemia occurs commonly in the presence of hepatic disorders leading to portosystemic encephalopathy, but can occur even in the absence of hepatic dysfunction in disorders like Reye's syndrome, ureterosigmoidostomy, and infection in a neurogenic bladder. Drug toxicity due to drugs like cyanide, carbamazepine, valproic acid, iron which disrupt mitochondrial pathways and cytotoxins can also cause secondary hyperammonemia, thus this is the main mechanism by which non-hepatic or noncirrhotic

hyperammonemia occurs in people exposed to these drugs [3,5-7].

If ammonia accumulates in the blood, it can cross the blood-brain barrier and result in the neurological manifestations due to hyperammonemia [5,8]. Symptoms include irritability, headache, vomiting, ataxia, and gait abnormalities in the milder cases [1]. Seizures, encephalopathy, coma, and even death may occur in cases with ammonia levels greater than 200 micromol/L [1].

One of the most common cause of non-hepatic hyperammonemia is drug toxicity, of which valproate is a documented common cause. It has been reported that there is a positive correlation between the dose of valproate and the development of hyperammonemia and also between plasma levels of sodium valproate and ammonia [9]. Thus therapeutic drug monitoring of Valproic acid (VPA) is essential to prevent toxicity, but the correlation between plasma ammonia level and serum VPA concentration remains unclear [9].

Other AEDs have rarely been associated with HE. Levetiracetam (LEV), Phenobarbital (PB) or Topiramate (TPM) when administered to a patient already taking VPA has been reported to trigger HE [10-12]. Especially TPM may increase that risk 10-fold [10]. Cases have been reported describing HE in patients taking Carbamazepine (CBZ) either as a single drug or in combination with other AEDs [13] and with TPM monotherapy [10].

Our patient underwent all the investigations to rule out all these causes and there is no other AED drug history.Also, in our case hepatic function test and arterial ammonia levels were normal before starting perampanel.

Perampanel is a noncompetitive antagonist at AMPA-type glutamate receptors on postsynaptic neurons [14].

Perampanel has a rapid absorption after oral administration with maximal serum concentrations attained within 0.5-1.5 h. The $C_{max}$ is delayed by 2 hours when taken with food [4]. The bioavailability is about 100%. The volume of distribution is 77 L and protein binding is 96% [4]. Perampanel is metabolized by enzymatic oxidation through CYP3A4, and the elimination half-life is 70-110 h [4,14]. Perampanel is affected by concomitant enzyme-inducing AEDs, and its clearance is increased by 4 times.

A similar case of 27 year male patient with young onset history of seizures, where one month after adding PER, he had collapsing episodes and showed increased levels of ammonia: 139 umol/L was described [15]. In our patient we observed the highest ammonia level between 72-96 hours of administration. As our patient was constantly in NCSE, so the assessment of clinical presentation and symptoms worsening after hyperammonemia was not possible. The blood ammonia levels came down to the normal range after stopping the medication. However, even after the stoppage of perampanel and normalization of ammonia, her condition and NCSE remains the same.

## Conclusion

VPA and TPM are well documented causes of hyperammonemia. We suggest serum ammonia levels should be done before starting perampanel in any patient with a constant monitoring of ammonia levels at regular intervals. However, more cases are required to understand the mechanism of action, risk factors and establish monitoring protocols in patients for perampanel therapy.

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