

Valproate-induced Hyperammonaemia in a Bipolar Disorder Patient: A Case Report

INDUJA NAIR¹, SUVARNA JYOTHI KANTIPUDI²

ABSTRACT

Valproate is a widely used mood stabiliser in neurology and psychiatric practice. It can cause rare but serious adverse effects, including hyperammonaemia. Hereby, the authors present a case report of 40-year-old married male diagnosed with bipolar affective disorder, who presented with manic symptoms and subsequently developed hyperammonaemia after the initiation of Sodium Valproate. Despite normal liver function and no history of substance use, the patient exhibited excessive drowsiness and constipation five days after increasing the valproate dosage to 1500 mg/day. Serum ammonia levels were significantly elevated, prompting the cessation of all psychiatric medications and the initiation of lactulose treatment. Over six days, ammonia levels normalised, revealing the underlying manic symptoms. The patient was transitioned to Lithium for mood stabilisation while Valproate was not reintroduced. The case highlights the potential for hyperammonaemia in patients receiving valproate, even in the absence of liver dysfunction. The mechanisms behind this adverse effect may include Carnitine depletion and toxic metabolite accumulation from valproate metabolism. The report underscores the importance of vigilance in monitoring for hyperammonaemia, particularly in patients receiving rapid dose escalations of valproate. Limitations of the report include the absence of serum Valproate levels at the time of hyperammonaemia, which would have aided in understanding the dose-response relationship. It also highlights the need for early detection of hyperammonaemia and appropriate management.

Keywords: Adverse drug reaction, Ammonia, Mood disorder, Valproic acid

CASE REPORT

A 40-year-old married male was brought to the emergency room for admission with symptoms of elevated mood, excessive talk, increased irritability, inflated self-esteem, reduced need for sleep, and increased energy levels for one week. The patient was apparently normal until one week prior to admission, following which he was noticed to be getting into trivial fights with his family members, especially when they commented on his dressing, praying excessively, and talking only in English, which was unlike his usual self. The patient had two similar episodes in the past, one nine years ago and another four years back; however, the records of these episodes were not available with the family. He had been non compliant with his previous medication regimen and had lost contact with his psychiatrist. He had no known medical co-morbidities and no history of substance use. On general physical examination, the patient showed no abnormalities. On Mental Status Examination (MSE), he had increased psychomotor activity, labile affect, inflated self-esteem, and grade 1 insight. Based on his history and examination, he was diagnosed with Bipolar Affective Disorder- current episode mania without psychotic symptoms (F 30.1) as per International Classification of Diseases (ICD)-10 and had a Young Mania Rating Scale (YMRS) score of 27 [1].

The patient, upon admission, underwent routine blood investigations, including complete blood counts, renal and liver function tests, serum electrolytes, random blood sugar levels, and an electrocardiogram, all of which returned normal results. Tablet Sodium Valproate was initiated at 500 mg/day, which was increased to 1500 mg/day in divided doses after two days to optimise the dose for the patient's body weight of 60 kg, with the Indian Psychiatric Society (IPS) guidelines stating optimal doses of 20-30 mg/kg body weight of Valproate [2], and due to persisting symptoms. The patient was also prescribed Tablet Olanzapine, titrated up to 20 mg, and Tablet Clonazepam 0.5 mg at night for sleep.

Five days after the Valproate dose was increased to 1500 mg, the patient was noticed to be excessively drowsy during the morning

rounds and reported a two-day history of constipation. He remained oriented and obeyed commands, with no focal neurological deficits. All psychiatric medications were withheld, and serum ammonia levels were assessed and found to be 108.7 $\mu\text{mol/L}$, which was well above the upper limit of the normal reference range of the hospital laboratory levels (16-60 $\mu\text{mol/L}$). The patient was started on Syrup Lactulose 15 mL three times a day, with serial MSEs and regular monitoring of serum ammonia levels. Six days later, serum ammonia levels normalised, which could also be observed clinically in terms of improvement of drowsiness, in turn unmasking the patient's manic symptoms. The patient was restarted on Olanzapine 10 mg and Clonazepam 0.5 mg at night. Instead of reintroducing Tablet Sodium Valproate, the patient was started on Tablet Lithium sustained release 400 mg at bedtime and titrated to 800 mg over the next four days. The patient's affective symptoms gradually improved with a YMRS score reduction to 10, and he was discharged after two weeks with regular follow-up outpatient visits, during which he remained euthymic without any long-term or delayed adverse consequences of Valproate.

DISCUSSION

Valproate is a versatile medication with uses in the treatment of seizures, migraine prophylaxis, bipolar affective disorder, and schizoaffective disorder [3,4]. Although Valproate is generally a safe medication, it has many adverse effects, ranging from common ones like somnolence, weight gain, alopecia, constipation, tremors, petechiae, and rashes to severe adverse effects like hepatotoxicity, hyponatremia, Polycystic Ovary Syndrome (PCOS), erythema multiforme, hyperammonaemia, encephalopathy, and coma. Furthermore, antenatal exposure to the drug can cause foetal toxicities and neural tube defects [3,5].

Hyperammonaemic encephalopathy in response to treatment with Valproate, in the background of normal liver functioning, is rare and completely reversible but a severe and potentially life-threatening adverse reaction [6]. The present case report presents the clinical

presentation, investigations, and management of Valproate-induced hyperammonaemia in a tertiary care inpatient setting in India. The possible causes for Valproate-induced hyperammonaemia can be attributed to Carnitine deficiency or depletion. Valproate undergoes beta-oxidation in liver mitochondria, a process dependent on Carnitine, and chronic administration, overdose, or rapid dose escalation may deplete Carnitine, resulting in elevated blood ammonia levels [7,8]. A small amount of Valproate is also metabolised via omega-oxidation, which produces toxic metabolites that inhibit Carbamoyl Phosphate Synthetase (CPS), an enzyme that aids in the conversion of ammonia to Carbamoyl phosphate in the urea cycle [7,9]. Since, the reason and complete mechanism of the development of hyperammonaemia in different scenarios are not yet fully understood, it is difficult to determine the exact risk factors for its development [10].

The few existing case reports and case series do not provide adequate insight into the incidence of Valproate-induced hyperammonaemia and potential risk factors [6,9,11,12]. A study done in Cleveland, Ohio, in 2016 by Baddour E et al., on 347 inpatients in a psychiatric ward at a community teaching hospital showed the incidence of hyperammonaemia in patients on Valproate to be 36%, and lactulose was the commonly given treatment (48.7%), and discontinuation of the Valproate was the most effective treatment with a 56.3% success rate [13]. Though there are no established consensus on how a case of Valproate-induced hyperammonaemia needs to be managed, most case reports and series reported discontinuation of the offending agent, starting the patient on laxatives, and regular monitoring of serum ammonia levels [12,14,15] as the management. A high index of suspicion for the development of hyperammonaemia would be essential to identify this adverse effect. This requires vigilant clinical observation for any drop in sensorium, constipation in a drowsy patient, and monitoring the levels of ammonia and valproate when in doubt.

CONCLUSION(S)

The present case report emphasises the necessity for additional studies to investigate the risk factors and incidence of Valproate-induced hyperammonemia, particularly in developing countries where the drug is extensively utilised. Research into the temporal relationship between Valproate dosage and the rate of dose escalation is crucial. A limitation of present case report is the lack

of serum Valproate levels at the time of hyperammonemia, which could have offered insight into the dose-response relationship.

REFERENCES

- [1] Lukasiwicz M, Gerard S, Besnard A, Falissard B, Perrin E, Sapin H, et al. Young Mania Rating Scale: How to interpret the numbers? Determination of a severity threshold and of the minimal clinically significant difference in the EMBLEM cohort. *Int J Methods Psychiatr Res.* 2013;22:46-58. Available from: <https://doi.org/10.1002/mpr.1379>.
- [2] Shah N, Grover S, Rao GP. Clinical practice guidelines for management of bipolar disorder. *Indian J Psychiatry.* 2017;59:S51-S66. Available from: <https://doi.org/10.4103/0019-5545.196974>.
- [3] Rahman M, Awosika AO, Nguyen H. *Valproic Acid.* StatPearls, Treasure Island (FL): StatPearls Publishing; 2024.
- [4] Carr RB, Shrewsbury K. Hyperammonemia due to valproic acid in the psychiatric setting. *Am J Psychiatry.* 2007;164:1020-27. Available from: <https://doi.org/10.1176/ajp.2007.164.7.1020>.
- [5] Stahl SM. *Stahl's Essential Psychopharmacology: Neuroscientific Basis and Practical Applications.* 5th ed. Cambridge: Cambridge University Press; 2021. Available from: <https://doi.org/10.1017/9781108975292>.
- [6] Sousa C. Valproic acid-induced hyperammonemic encephalopathy- a potentially fatal adverse drug reaction. *SpringerPlus.* 2013;2:13. Available from: <https://doi.org/10.1186/2193-1801-2-13>.
- [7] Vázquez M, Fagiolino P, Maldonado C, Olmos I, Ibarra M, Alvariza S, et al. Hyperammonemia associated with valproic acid concentrations. *Bio Med Res Int.* 2014;2014:217269. Available from: <https://doi.org/10.1155/2014/217269>.
- [8] Krishna V, Thomson SR, Chogtu B, Soundarajan GP, Sharma P. Sodium Valproate induced hyperammonaemia without hepatic failure in adults: A series of three cases. *J Clin Diagn Res.* 2018. Available from: <https://doi.org/10.7860/JCDR/2018/30892.11221>.
- [9] Segura-Bruna N, Rodríguez-Campello A, Puente V, Roquer J. Valproate-induced hyperammonemic encephalopathy. *Acta Neurol Scand.* 2006;114:01-07. Available from: <https://doi.org/10.1111/j.1600-0404.2006.00655.x>.
- [10] Duman B. Risk factors for valproic acid induced hyperammonemia and its association with cognitive functions. *Gen Hosp Psychiatry.* 2019.
- [11] Qayyum W, Yousafzai ZA, Iqbal MS, Khan S, Amin QK, Shafiqs I. Valproate Induced Hyperammonemic Encephalopathy. *J Ayub Med Coll Abbottabad JAMC.* 2022;34(Suppl 1):S1038-39. Available from: <https://doi.org/10.55519/JAMC-04-S4-10190>.
- [12] Wadzinski J, Franks R, Roane D, Bayard M. Valproate-associated hyperammonemic encephalopathy. *J Am Board Fam Med JABFM.* 2007;20:499-502. Available from: <https://doi.org/10.3122/jabfm.2007.05.070062>.
- [13] Baddour E, Tewksbury A, Stauner N. Valproic acid-induced hyperammonemia: Incidence, clinical significance, and treatment management. *Ment Health Clin.* 2018;8:73-77. Available from: <https://doi.org/10.9740/mhc.2018.03.073>.
- [14] Shah S, Wang R, Vieux U. Valproate-induced hyperammonemic encephalopathy: A case report. *J Med Case Reports.* 2020;14:19. Available from: <https://doi.org/10.1186/s13256-020-2343-x>.
- [15] Lewis C, Deshpande A, Tesar GE, Dale R. Valproate-induced hyperammonemic encephalopathy: A brief review. *Curr Med Res Opin.* 2012;28:1039-42. Available from: <https://doi.org/10.1185/03007995.2012.694362>.

PARTICULARS OF CONTRIBUTORS:

1. Junior Resident, Department of Psychiatry, Sri Ramachandra Institute of Higher Education and Research (SRIHER), Chennai, Tamil Nadu, India.
2. Associate Professor, Department of Psychiatry, Sri Ramachandra Institute of Higher Education and Research (SRIHER), Chennai, Tamil Nadu, India.

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

Dr. Suvarna Jyothi Kantipudi,
Associate Professor, Department of Psychiatry, Sri Ramachandra Institute of
Higher Education and Research (SRIHER), Chennai-600116, Tamil Nadu, India.
E-mail: suvarna.srmc@gmail.com

AUTHOR DECLARATION:

- Financial or Other Competing Interests: None
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. NA

PLAGIARISM CHECKING METHODS: [Jain H et al.]

- Plagiarism X-checker: Aug 28, 2024
- Manual Googling: Sep 23, 2024
- iThenticate Software: Oct 08, 2024 (3%)

ETYMOLOGY: Author Origin

EMENDATIONS: 6

Date of Submission: **Aug 27, 2024**

Date of Peer Review: **Sep 21, 2024**

Date of Acceptance: **Oct 09, 2024**

Date of Publishing: **Nov 01, 2024**