INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA): IJPS00]
Journal Homepage: https://www.ijpsjournal.com

Case Study

Valproic Acid Induced Hyperammonemia: A Case Report

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ARTICLE INFO

Published: 27 Mar. 2025
Keywords:
Valproic Acid, Hyperammonaemia, Epilepsy
DOI:
10.5281/zenodo.15091651

ABSTRACT

Valproic acid (VPA) is a widely used antiepileptic and mood-stabilizing drug, but its administration is associated with various adverse effects, including hyperammonaemia. Valproic acid-induced hyperammonaemia (VPA-IH) is a potentially serious metabolic disturbance that can lead to encephalopathy, cognitive dysfunction, lethargy, vomiting, and, in severe cases, coma. The underlying mechanisms of VPA-IH are multifactorial and may include inhibition of carbamoyl phosphate synthetase I (CPSI) in the urea cycle, increased mitochondrial toxicity, and disruption of glutamine metabolism. Risk factors for VPA-IH include polypharmacy, especially with other antiepileptic drugs, underlying urea cycle disorders, liver dysfunction, and genetic predisposition. While some patients with VPA-IH remain asymptomatic, others develop valproate-induced encephalopathy (VIE), necessitating prompt recognition and management. Diagnosis involves measuring plasma ammonia levels, especially in patients with unexplained neurological symptoms while on VPA therapy. Management strategies include discontinuation or dose reduction of VPA, administration of alternative anticonvulsants, and use of ammonia-lowering agents such as L-carnitine, sodium benzoate, or lactulose in severe cases. Monitoring of ammonia levels and liver function tests is crucial in patients on long-term VPA therapy. Awareness of VPA-IH among clinicians can facilitate early diagnosis and prevent serious complications. Future research should focus on identifying genetic markers for susceptibility and optimizing treatment strategies for affected individuals.

INTRODUCTION

Valproic acid (VPA) is a widely used antiepileptic drug (AED) for the treatment of epilepsy, bipolar disorder, and migraine prophylaxis. It is known for its broad-spectrum anticonvulsant properties, making it an effective option for various seizure disorders. Despite its efficacy, VPA is associated with several adverse effects, including hepatotoxicity, thrombocytopenia, pancreatitis, and metabolic disturbances. Among these, valproic acid-induced hyperammonaemia (VPA-IH) is a significant yet often underrecognized complication that can lead to serious neurological consequences, including encephalopathy.

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Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Hyperammonaemia occurs due to the interference of VPA with the urea cycle. The drug inhibits carbamoyl phosphate synthetase I, a key enzyme responsible for ammonia detoxification in the liver, leading to increased systemic ammonia levels. Additionally, mitochondrial dysfunction and carnitine depletion further impair ammonia metabolism, exacerbating the condition. While some patients may remain asymptomatic, others can develop symptoms such as confusion, lethargy, vomiting, ataxia, cognitive decline, and, in severe cases, coma. The presentation of VPA-IH can be subtle and may be mistaken for medication side effects or disease progression, highlighting the importance of clinical vigilance. This case report describes a 54-year-old patient with epilepsy who has been on long-term VPA therapy (500 mg daily) for ten years and subsequently developed hyperammonaemia. The patient presented with progressive cognitive impairment, lethargy, and episodes of altered mental status, raising concerns for VPA-IH. This case underscores the necessity of early recognition, routine ammonia level monitoring, and appropriate management strategies, including dose adjustment, L-carnitine supplementation, or switching to an alternative AED. Increased awareness among clinicians is essential to prevent severe complications and optimize treatment outcomes for patients on long-term VPA therapy. Given the potential severity of VPA-IH, timely intervention is crucial. Management typically involves discontinuation or dose reduction of VPA, administration of ammonia-lowering agents such as sodium benzoate or lactulose, and supplementation with L-carnitine to enhance mitochondrial function. In cases of severe hyperammonaemia with neurological impairment, hospitalization and intensive supportive care may be required. Genetic predisposition, underlying liver disease, polypharmacy, and prolonged VPA use increase the risk of developing hyperammonaemia, emphasizing the need for personalized treatment plans. Further research is needed to identify predictive markers and optimize therapeutic approaches for individuals at risk of VPA-IH.

CASE PRESENTATION:

A 54-year-old female patient with a known history of epilepsy, well-controlled on valproic acid (VPA) therapy for the past ten years, presented with progressive neurological and systemic symptoms. She had been taking VPA 500 mg daily with good seizure control but recently began experiencing increasing fatigue, confusion, and episodes of drowsiness. Her family reported a decline in cognitive function over the past few weeks, along with intermittent difficulty concentrating, forgetfulness, and episodes of disorientation. On examination, the patient appeared lethargic and had a slowed response to verbal stimuli. Neurological assessment revealed mild dysarthria, impaired coordination, and slight tremors in the upper limbs. No focal neurological deficits were identified, and deep tendon reflexes were normal. The patient exhibited signs of altered mental status, including fluctuating levels of alertness, irritability, and occasional agitation. There were no new seizure episodes, fever, or signs of infection. Routine laboratory investigations showed normal liver function tests and kidney function. However, serum ammonia levels were significantly elevated, confirming a diagnosis of valproic acid-induced hyperammonaemia (VPA-IH). An arterial blood gas analysis did not indicate metabolic acidosis, and other potential causes of hyperammonaemia, such as liver dysfunction or urea cycle disorders, were ruled out. On the routine blood examinations, the serum ammonia level was found to be highly elevated (103µg/dL). Hyperammonaemia was managed by the gradual cessation of T. VALPROIC ACID and the epileptic episodes were managed by initiation T. LEVETIRACETAM 500mg BD and other supportive care. On further observations the patient's serum ammonia level started to decline and showed impressive neurological improvement.

DISCUSSION:

Valproic acid-induced hyperammonaemia (VPA-IH) is a significant metabolic disturbance that can lead to serious neurological consequences if left unrecognized. VPA interferes with ammonia metabolism by inhibiting carbamoyl phosphate synthetase I, a key enzyme in the urea cycle, leading to impaired ammonia clearance. Additionally, VPA disrupts mitochondrial function and depletes carnitine levels, further contributing to the accumulation of ammonia in the bloodstream. The clinical presentation of VPA-IH is often nonspecific, ranging from mild cognitive impairment, lethargy, and confusion to severe encephalopathy and coma. In this case, the patient's progressive cognitive decline and altered mental status were initially subtle, making early recognition challenging. Since symptoms of VPA-IH can overlap with medication side effects or seizure-related cognitive issues, clinicians must maintain a high index of suspicion in patients receiving long-term VPA therapy. The diagnosis of VPA-IH is primarily confirmed through elevated plasma ammonia levels, with normal liver function tests helping to exclude hepatic causes of hyperammonaemia. Management involves discontinuation or dose reduction of VPA, administration of ammonia-lowering agents such as sodium benzoate or lactulose, and supplementation with L-carnitine to support mitochondrial function. Most patients show clinical improvement once VPA is withdrawn or adjusted, emphasizing the need for close monitoring in patients on chronic therapy. This case underscores the importance of regular screening for hyperammonaemia in at-risk individuals and highlights the necessity of considering alternative antiepileptic drugs in patients prone to metabolic disturbances.

CONCLUSION:

Valproic acid-induced hyperammonaemia (VPA-IH) is a critical yet often underdiagnosed adverse effect of long-term valproic acid therapy. It can present with a wide range of neurological symptoms, from mild confusion and lethargy to severe encephalopathy. Due to its nonspecific clinical presentation, VPA-IH can be misattributed to other causes, delaying appropriate intervention. This case highlights the importance of early recognition and regular monitoring of ammonia levels in patients receiving chronic VPA therapy. Identifying VPA-IH promptly allows for timely management, preventing severe complications and improving patient outcomes. Management of VPA-IH requires a multifaceted approach, including dose reduction or discontinuation of VPA, supplementation with L-carnitine, and the use of ammonia-lowering agents when necessary. Clinicians should maintain vigilance in patients on long-term VPA therapy and consider alternative antiepileptic drugs in those at higher risk of metabolic disturbances. Further research is needed to better understand the risk factors and optimize treatment strategies for VPA-IH. By increasing awareness and implementing proactive monitoring strategies, the risk of VPA-induced complications can be minimized, ensuring safer long-term epilepsy management.

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HOW TO CITE: Keziah Elizabeth Dona, Shaiju S Dharan, Drishya L.*, Valproic Acid Induced Hyperammonemia: A Case Report, Int. J. of Pharm. Sci., 2025, Vol 3, Issue 3, 2633-2636. https://doi.org/10.5281/zenodo.15091651