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Valproate-Induced Severe Adverse Effects in Patients with Mania: A Case Series

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Abstract

Sodium valproate is widely used in the management of acute mania and bipolar disorder, but rare and serious adverse drug reactions may occur. We report a case series of three patients with bipolar affective disorder, current episode mania, who developed significant valproate-related adverse effects. A 22-year-old woman developed acute necrotising pancreatitis within two weeks of treatment initiation, confirmed biochemically and radiologically after exclusion of other causes. A 35-year-old woman developed progressive diffuse alopecia that resolved following valproate discontinuation. A 55-year-old man developed asymptomatic thrombocytopenia, with normalisation of platelet counts after drug withdrawal. In all cases, clinical and laboratory improvement occurred after cessation of valproate, and alternative mood stabilisers were successfully introduced. This case series highlights the spectrum of rare but clinically significant valproate-induced adverse effects and underscores the importance of vigilant monitoring, early recognition, and prompt intervention to prevent serious morbidity.

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Introduction

Sodium valproate is an eight-carbon branched fatty acid and a broad-spectrum antiepileptic approved for epilepsy, bipolar affective disorder, and migraine.[1] Approved by the US Food and Drug Administration in 1978, it is among the most commonly prescribed mood stabilisers due to its relative cognitive safety.[2,3] Common adverse effects include gastrointestinal symptoms and alopecia, while rare but serious reactions such as acute necrotising pancreatitis, hepatic failure, and thrombocytopenia may occur, with pancreatitis reported in approximately 1 in 40,000 cases.[4] Evidence of such severe adverse effects in psychiatric populations, particularly during acute mania, remains limited, underscoring the need for heightened clinical vigilance.

Case 1: Valproate-Induced Acute Necrotising Pancreatitis

A 22-year-old unmarried woman with no prior medical or psychiatric history presented with a first episode of mania without psychotic symptoms (YMRS score: 40). She was initially treated with lithium up to 1200 mg/day (serum lithium: 0.34 mmol/L) and olanzapine up to 30 mg/day, without adequate clinical response.

Sodium valproate was subsequently initiated at 500 mg/day and titrated to 1000 mg/day, along with modified electroconvulsive therapy.

Within two weeks of starting valproate, she developed nausea, recurrent vomiting, abdominal pain, and progressive abdominal distension. Laboratory investigations revealed markedly elevated serum lipase (643 U/L; reference range: 0–160 U/L) and lactate dehydrogenase (LDH: 512 U/L; reference range: 140–280 U/L), along with hypocalcaemia (7.4 mg/dL) and hypokalaemia (3.1 mEq/L). Common causes, including alcohol use, biliary pathology, trauma, metabolic abnormalities, and infection, were excluded.

Sodium valproate and olanzapine were discontinued. The patient was managed conservatively with bowel rest, intravenous fluids, analgesics, and empirical antibiotics (piperacillin–tazobactam) along with correction of electrolyte abnormalities. Clinical and biochemical improvement was observed, and pancreatic enzyme levels gradually returned to normal. She was subsequently started on oxcarbazepine for mood stabilisation and remained clinically stable on follow-up.

Case 2: Valproate-Induced Diffuse Alopecia

A 35-year-old woman diagnosed with bipolar affective disorder, current episode mania without psychotic symptoms, was treated with sodium valproate 1000 mg/day and risperidone 6 mg/day. Baseline haematological and biochemical parameters were within normal limits. Significant clinical improvement was noted within two weeks (YMRS reduction >50%).

Approximately three weeks after initiation of valproate, the patient reported progressive diffuse scalp hair loss with noticeable thinning. There was no prior history of dermatological disease, endocrine disorder, nutritional deficiency, or psychosocial stress. Dermatological evaluation did not identify an alternative cause. Investigations, including thyroid function tests, serum ferritin, vitamin B12 levels, and complete blood counts, were within normal limits, thereby excluding common metabolic or nutritional causes of alopecia. Given the temporal association and exclusion of other aetiologies, valproate-induced alopecia was suspected.

Valproate was discontinued while risperidone was continued, and the patient was monitored closely for relapse of mood symptoms. Gradual regrowth and improvement in hair density were noted at subsequent visits. She was later transitioned to lithium 900 mg/day and has remained euthymic without recurrence of alopecia.

Case 3: Valproate-Induced Thrombocytopenia

A 55-year-old man with bipolar affective disorder, current episode mania without psychotic symptoms, and no history of substance use or medical comorbidities, was started on sodium valproate 1500 mg/day and olanzapine 20 mg/day. Baseline complete blood counts were within normal limits. A reduction in manic symptoms (YMRS improvement >35%) was observed during inpatient care.

Routine laboratory monitoring revealed a progressive decline in platelet counts during hospitalisation. The patient remained asymptomatic, with no evidence of bleeding or bruising. Evaluation for

Table 1: Clinical characteristics of valproate-associated adverse events

Case	*Age/ Sex*	*Diagnosis*	*Valproate dose (mg/ day)*	*Time to onset (weeks)*	*Adverse event*	*Management*	*Outcome*	*Naranjo score*
1	22/F	Mania	1000	2	Acute necrotizing pancreatitis	Valproate stopped, supportive care	Complete recovery	7
2	35/F	Mania	1000	3–4	Diffuse alopecia	Valproate stopped	Reversal of alopecia	6
3	55/M	Mania	1500	2–3	Thrombocytopenia	Valproate tapered & stopped	Platelet normalization	6

alternative causes of thrombocytopenia, including infection, nutritional deficiencies, and systemic illness, was unremarkable. Based on the temporal relationship and exclusion of other causes, valproate-induced thrombocytopenia was considered.

Valproate was gradually tapered and discontinued, after which platelet counts steadily improved towards normal levels. The patient was then switched to lithium 900 mg/day and has maintained clinical stability with normalised haematological parameters on follow-up.

Discussion

Sodium valproate is widely used in the management of acute mania and bipolar disorder due to its broad therapeutic efficacy and relative cognitive safety. However, despite its long-standing use, rare but serious idiosyncratic adverse drug reactions continue to pose significant clinical challenges, particularly in psychiatric populations where routine systemic monitoring may be less stringent than in neurological settings.

In this case series, we describe three clinically significant adverse events temporally associated with valproate exposure – acute necrotising pancreatitis, diffuse alopecia, and thrombocytopenia – each demonstrating improvement following drug withdrawal, thereby supporting a probable causal relationship.

Most cases reported with valproic acid-induced acute necrotising pancreatitis are in the 5 to 20-year age group diagnosed with epilepsy, indicating the need for vigilance.[4] Evans *et al*. reported a case of a 31-year-old woman with cerebral palsy, intellectual disability, and seizures treated with valproic acid 84 mg/kg to control seizures. After three weeks of exposure, she began to experience nausea, vomiting, and breathlessness, and was diagnosed with valproate-induced acute pancreatitis after other causes were excluded.[4] Case reports of acute necrotising pancreatitis associated with valproic acid were first published in 1979 by Bataladen *et al*. and Camfield *et al*., in a child with absence seizures.[7]

A study by Gerstner T *et al*. showed that the mortality rates of acute pancreatitis in children and adults are 15.4 and 21.4%, respectively. Acute pancreatitis is a rare but potentially fatal side effect of valproic acid, occurring in approximately 1 in 40,000 cases. The risk of developing acute pancreatitis is multifactorial. Other conditions such as alopecia and thrombocytopenia have also been reported, with the incidence of drug-induced cases estimated at 0.1 to 2%.[5] The development of conditions such as acute pancreatitis, alopecia, and thrombocytopenia is mostly attributed to idiosyncratic reactions that generate free radicals. Genetic factors, age, initial dose, and titration rate increase the risk of these idiosyncratic reactions. Studies have also shown that drug allergies do not occur at low doses or with slow titration. Previous studies suggest that sodium valproate-induced pancreatitis can also occur in patients with end-stage renal disease and liver failure.[5]

Kaur P *et al*., reported a case of valproate-induced acute necrotising pancreatitis in a 61-year-old who was taking valproate 500 mg three times daily for bipolar disorder for 12 years. The patient developed haemodynamic instability with abdominal distension and pain, and was diagnosed with valproate-induced pancreatitis after other causes were excluded.[6]

Barbosa *et al*. published a case report of valproic acid-induced necrohaemorrhagic pancreatitis. In this report, the authors discussed the diagnostic approach and noted that it is advisable to consider drug-induced (such as valproic acid) acute pancreatitis in patients without a clear causative agent.[7]

For the treatment of acute mania, sodium valproate is typically initiated at 500 to 750 mg/day and titrated according to clinical response and tolerability. The usual therapeutic dose range is 1000 to 2500 mg/day, aiming for a serum valproate concentration of approximately 50 to 125 µg/mL, which is considered the therapeutic range for mood stabilization. In the present case series, the patients received doses between 1000 and 1500 mg/day, which fall within standard therapeutic limits[8] In our cases, there was no identifiable cause, as the patients had no alcohol use, history of trauma, or overeating, and were free of biliary or hepatic disorders. Similar to previous case reports, our patient developed acute necrotising pancreatitis, alopecia, and thrombocytopenia at a dose of 1500 mg of valproic acid. After stabilisation, the doses were

adjusted during follow-up visits for mood stabilisation and monitoring for adverse effects. Although routine pancreatic enzyme monitoring is not universally recommended, clinicians should maintain a high index of suspicion for pancreatitis during the early weeks of valproate therapy, particularly when patients develop gastrointestinal symptoms. [8] Several reports and reviews have emphasized prompt evaluation with serum amylase or lipase when abdominal pain, nausea, or vomiting occur during valproate therapy. Early detection and drug discontinuation are critical to prevent severe complications.

Conclusion

Valproate can induce acute, potentially fatal conditions such as acute pancreatitis, alopecia, and thrombocytopenia; the mechanism remains unclear. The incidence of drug-induced acute pancreatitis has been reported to be 0.1 to 2%. Most reported cases have occurred in children and the elderly with epilepsy and renal failure, respectively. Only a few cases have been reported in the current literature involving patients with psychiatric illness, highlighting the need for thorough vigilance by healthcare professionals for early diagnosis and management of this potentially fatal condition. Early recognition and prompt discontinuation can be lifesaving.

Limitation

Serum valproic acid levels could not be obtained due to a lack of laboratory infrastructure.

Declaration of Patient Consent

Patient consent statements were obtained from each patient as per institutional ethics committee approval, along with consent for participation in the study and for publication of the scientific results/ clinical information, or images without revealing their identity, name, or initials. The patient is aware that, though confidentiality would be maintained, anonymity cannot be guaranteed.

Authorship Contribution

Corresponding and first author 1: Conceptualization; Methodology; Investigation; Data curation; literature review; Writing – original draft; Supervision. Co-author 2: Clinical data acquisition; Investigation; Writing – review & editing.

Ethics Compliance

Patient consent statement was taken from each patient as per institutional ethics committee approval, along with consent taken for participation in the study and publication of the scientific results/ clinical information/image without revealing their identity, name, or initials.

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Conflict of Interest

None

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