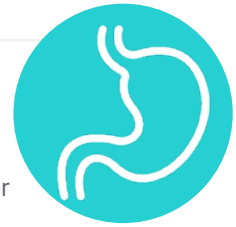
A Rare Complication of Valproate-Induced Acute Pancreatitis in an Adult Patient with Bipolar Disorder: A Case Report



Authors:	P. Kaur,[1] D. Bhasin,[2] H. Singh,[1] *T.S. Kundra[3] 1. Department of Critical Care, Max Super Speciality Hospital, Mohali, India 2. Department of Pulmonology and Critical Care, Max Super Speciality Hospital, Mohali, India 3. Department of Anaesthesiology and Intensive Care, Government Medical College, Patiala, India *Correspondence to tvskundra@yahoo.co.in

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Abstract

Background: Valproate-induced pancreatitis is an idiosyncratic reaction of the drug, commonly seen in the paediatric age group, between 1 week to 8 years of starting the drug.

Case: The authors present a case report of a 61-year-old patient who presented with acute pancreatitis. All common causes were ruled out. The patient had a significant treatment history of taking valproate for bipolar disorder for 12 years. The patient was resuscitated with intravenous fluids and analgesics. Sodium valproate was stopped. The patient was monitored to detect early symptoms of systemic inflammatory response syndrome or any organ dysfunction or failure. The patient was sent to the ward after 4 days. The patient had a good outcome due to early diagnosis and resuscitation.

Conclusion: Acute pancreatitis is a rare and potentially fatal complication in patients on valproate. After ruling out other common causes, a detailed medical and treatment history can lead to the diagnosis of this entity. Healthcare providers should be vigilant about the early signs and symptoms of pancreatitis, including acute abdomen, vomiting, and raised serum amylase and lipase.

Key Points

1. Valproate-induced pancreatitis is an idiosyncratic reaction of the drug, commonly seen in paediatric age group, between 1 week to 8 years of starting the drug.

2. This entity is a diagnosis of exclusion. After ruling out other common causes, a detailed medical and treatment history can lead to the diagnosis of this entity.

3. Even in adults, and beyond the 8-year window, healthcare providers should be vigilant about the early signs and symptoms of pancreatitis, including acute abdomen, vomiting, and raised serum amylase and lipase in patients who are taking this drug.

INTRODUCTION

Sodium valproate, or valproic acid (VPA), is a broad-spectrum antiepileptic drug, commonly used for the treatment of epilepsy, bipolar disorder, migraine headache, and diabetic-neuropathy related pain.[1] VPA was approved by the U.S. Food and Drug Administration (FDA) in 1978 for treating epilepsy and absence seizures.[2] Since then, it has been used either as monotherapy, or in combination with other anticonvulsant agents for the treatment of mixed and complex partial seizures, acute manic episodes in bipolar disorder, and for prophylaxis of migraine headache.[3] It is also the most prescribed mood stabiliser by far due to its little impact on cognitive function and central nervous system.[4] VPA is also effective in treating myoclonic, simple partial, and generalised tonic-clonic seizures.[5]

VPA is a simple eight-carbon branched-chain fatty acid, which is structurally unrelated to any other marketed drug. Several mechanisms of VPA's therapeutic effects have been reported, including increasing levels of γ-aminobutyric acid by decreasing reabsorption and catabolism, restraining neuronal repetitive firing via suppression of ion channels, and targeting the transcriptomic system to directly inhibit Class I histone deacetylases.[6-9]

However, serious complications may be associated with valproate. These effects include hepatotoxicity, teratogenicity, possible polycystic ovaries with a potential sterile effect, and acute pancreatitis.[10] These side effects need to be considered when prescribing this medication to certain susceptible populations, such as the paediatric age group and persons with intellectual disability and neurological deficits, including mental retardation, cerebral palsy, and developmental delay.[11-13]

Acute pancreatitis is a rare, but one of the most severe VPA-related toxic effects. It makes a total of around 100 cases reported in the literature from 1979 to the time of writing.[12,14-18] Necrotising pancreatitis is an extreme complication of acute pancreatitis.[19] Most of the cases are children with epilepsy; however, only one bipolar disorder patient with renal failure, who underwent haemodialysis and subsequently developed acute pancreatitis due to VPA treatment, has been reported.[20]

Herein, the authors present a rare case of adult valproate-induced acute pancreatitis, presenting 12 years after starting the drug, and who had a good outcome due to early diagnosis and resuscitation.

CASE REPORT

The patient was a 61-year-old male who was known to have diabetes and hypertension. They were diagnosed with bipolar disorder 12 years ago.

The patient presented to the hospital with a chief complaint of 3 days of abdominal pain, which was diffuse in nature. The patient had no history of duodenal or gastric ulceration and no other digestive system disease; they did not have metabolic syndrome or food poisoning. The pain was associated with multiple episodes of vomiting, containing partially-digested gastric contents, and was non-bilious and non-bloody in nature. These complaints were accompanied by decreased urine output for 2 days. The patient also complained of bloating and obstipation.

The patient's medication history showed that they were taking a 500 mg tablet of valproate thrice a day for 12 years. A complete list of medications being taken by the patient includes valproate 500 mg thrice a day; lorazepam 2 mg at bedtime; quetiapine at bedtime; glimepiride 2 mg once daily; and telmisartan 40 mg once daily.

The patient was a non-smoker and did not drink or partake in recreational drug use.

The patient had their first dose of the COVID-19 vaccination in early 2021, and was found negative for COVID-19 on testing. Bedside screening echocardiography was done to rule out any cardiac event, and it was suggestive of left ventricle diastolic dysfunction, preserved left ventricle systolic function, and no regional wall motion abnormality.

The patient was managed with intravenous fluids and analgesics. VPA was stopped, while lorazepam and quetiapine were continued in consultation with the psychiatrist. Abdominal distension was present. The patient was kept nil per oral. A Ryles tube was inserted, which yielded 300 mL aspirate. Patient was given a proctoclysis enema, after which the patient passed stool. An ultrasound of the abdomen was done, which showed bulky pancreas and mildly prominent common bile duct (CBD) at porta. Investigations revealed a raised serum amylase (861 U/L) and lipase (690 U/L). Serum calcium was 9.0 mg/dL and serum triglycerides were 175 mg/dL. The patient was managed conservatively and monitored to detect earliest signs of systemic inflammatory response syndrome or organ dysfunction or failure.

MRI cholangiography was done on the third day to rule out CBD stones. MRI cholangiography was suggestive of acute pancreatitis with minimal ascites and bilateral minimal pleural effusion. The right and left hepatic ducts, along with the CBD, were normal. There was no intra-luminal filling defect.

The patient had a form of mild acute pancreatitis, probably due to the prompt and early treatment (initiated by the intensive care doctors). There were no signs and symptoms of acute organ failure. There were no local or systemic complications. The patient was moved to the ward after 4 days.

DISCUSSION

The present patient presented to the hospital with acute abdomen. Clinically, after laboratory and radiological investigations, a diagnosis of acute pancreatitis was made.

After making this diagnosis, a search for the probable aetiology was made. A list of the causes of acute pancreatitis was made to reach the probable cause, as enumerated below:[21] gallstones, which were ruled out after an ultrasound; alcohol, but the patient did not drink alcohol; and hypertriglyceridemia, but serum triglycerides were borderline high and, at these levels, are highly unlikely to be cause the of acute pancreatitis.

The authors also considered drugs. Drug-induced pancreatitis (DIP) is a rare cause.[22] Drugs are responsible for only 0.1–2.0% of acute pancreatitis incidents.[23-25] According to a German retrospective study, the incidence of pancreatitis caused by drugs was 1.4%.[26] A nationwide survey conducted in Japan showed that 1.2% of all cases of acute pancreatitis were caused by drugs.[27] The list of drugs responsible for this complication has increased to about 500 agents.[28] A substantial number of drugs commonly prescribed for gastrointestinal disorders are known to cause acute pancreatitis.[22,27] Antiepileptics have been implicated as a cause of acute pancreatitis, though the incidence is rare.[29] The diagnosis is essentially a diagnosis of exclusion.

The patient was not subjected to endoscopy before presentation with features of acute pancreatitis, ruling out endoscopic retrograde cholangiopancreatography induced pancreatitis.

Other causes were also considered, including accidental damage or injury to the pancreas, but there was no such history in this patient; viruses like mumps or measles, but no such disease history was given by the patient; hypercalcaemia, but serum calcium was within normal limits; and autoimmune pancreatitis, but the patient had no such history of any autoimmune disease, and no history was present in their family.

Based on the above, and a thorough literature search, the treating physicians made the probable diagnosis of valproate-induced pancreatitis, which is essentially a diagnosis of exclusion.

VPA is a broad-spectrum antiepileptic, which is commonly prescribed for seizures, epilepsy,

and bipolar disorder. Commonly reported side effects of VPA include congenital anomalies, infection, abdominal pain, asthenia, drowsiness, nausea, tremor, vomiting, alopecia, diarrhoea, dizziness, flu-like symptoms, thrombocytopenia, and anorexia. Rare side effects include fulminant hepatitis, pancreatitis, encephalopathy, and pedal oedema.[30] Acute pancreatitis is one of the rare complications of this drug.

Santos et al.[31] published about VPA-induced pancreatitis in an adult in less than 2 months of treatment.They discussed about the history of the entity. The first cases of acute pancreatitis associated to VPA were reported in 1979 by Bataladen et al.[32] and Camfield et al.,[33] with several sporadic cases being published subsequently. There are two cases described in Brazil, the first in 1986 by Barros et al.[34] and the other in 1998 by Munhoz et al.[35]

Barbosa et al.[36] published a case report of VPA-induced necrohaemorragic pancreatitis. The authors discussed the diagnostic approach in this uncommon pancreatitis, and mentioned that it is convenient to consider medication (such as VPA) induced acute pancreatitis in patients without a clear causative agent.

Huang W et al.[4] published a case report of VPA-induced acute pancreatitis in a patient with bipolar disorder presenting within 1 year of starting the drug. The authors mentioned acute pancreatitis to be considered as one of the idiosyncratic adverse reactions to antiepileptic drugs. Idiosyncratic reactions to drugs are adverse effects that are not directly related to pharmacodynamic mechanisms of the drug, and they take place by abnormal interaction between the drug and the organism in unpredictable manner, usually mediated by immunologic or cytotoxic effects triggered by the drug or its metabolites.[37]

The risk of idiosyncratic drug reactions is affected by several factors. The first factor is genetic determinants. If a patient has reacted to an immune-mediated aromatic antiepileptic drug, there is a 25% chance that their siblings will experience similar responses when exposed to the same class of drugs. The second factor is age. Many idiosyncratic reactions are typically age-dependent, in which age influences the metabolism of drugs.[38] Specifically, the decreased glucuronide conjugation is commonly seen in young babies. The younger age group is at higher risk of idiosyncratic drug effects and increased reactive metabolite production.[39] The third factor is initial dose and titration rate. Allergic reactions are generally regarded as not relative to drug dosage. However, allergic reactions may occur when the drug level reaches a certain threshold. Drugs with low effective doses (below 10 mg/day) are less likely to trigger immune-mediated reactions.[40] The titration speed is also a matter of great importance. Generally, the allergic reactions may not occur at low initial dose and slow titration rate, giving time for the body to become desensitised. Additionally, other factors include the similar responses to prior treatment, or disease-related factors such as patients with metabolic disorder and sodium valproate-related liver toxicity.[37]

Other valproate-related idiosyncratic reactions reported are alopecia, bone marrow aplasia, and immune-mediated hepatotoxicity.[37]

Werlin et al.[41] published about the spectrum of VPA-associated pancreatitis in paediatric patients, and mentioned that VPA-associated pancreatitis does not depend on VPA serum level and may occur any time after the onset of therapy. In most cases reported in the literature, the serum VPA level was within the normal range, again pointing towards idiosyncratic nature of this side effect.[13]

Gerstner et al.[12] published about VPA-induced pancreatitis in 16 patients, the average age of whom was 11.3 years (median age: 10.3 years). The authors estimated the incidence of VPA-induced pancreatitis to be 1:40,000. Similar data was presented by Genton et al.[42] The authors mention that pancreatitis is an unusual reaction to VPA therapy, approximately seen in one out of 40,000 patients.[42]

Gerstner et al.[12] mention the proposed mechanism of action of valproate-induced acute pancreatitis as a direct toxic effect of free radicals on the pancreatic tissue and a depletion of superoxide dismutase, catalase, and glutathione peroxidise. Similarly, Sanfey et al.[43] and Pellock et al.[44] theorised that the depletion of the free radical scavengers, superoxide dismutase, catalase, and glutathione peroxidase occurs in patients receiving VPA. It has also been suggested that the reduction of carnitine brought

about by the use of VPA has an important role in the damage caused to the pancreas.[45]

Previous literature mentions that the incidence of valproate-induced acute pancreatitis is higher in paediatric and young patients.[46] According to earlier reports (Hamad et al.),[13] such adverse effects can occur after prescribing this medicine for 1 week to 8 years. Yazdani et al.[47] have also mentioned pancreatitis to develop as an idiosyncratic reaction within 1 week to 8 years of exposure to VPA, with no association between dosage and serum levels of valproate.

Despite appropriate treatment, DIP demonstrated severe complications and high mortality.[48] The onset can be a slight asymptomatic hyperamylasaemia up to a fatal necrohaemorragic pancreatitis, with many complications in the non-lethal cases (pseudocysts, infections, septic shock, chronic pancreatitis, and endocrine pancreatic insufficiency).[49] Some cases show rapid progression in bleeding from the initial symptoms until death; some are observed after the initial medication; and some appear after few years of medication.[50] The mortality rates of acute pancreatitis in children and adult patients are 15.4% and 21.4%, respectively.[12]

A pharmacological research has recommended the maximum daily VPA dose of 2,500 mg, and the authors' patient was taking 1,500 mg of VPA a day.[51] Furthermore, there was no identifiable cause of acute pancreatitis, as the patient had no history of trauma, no overeating or drinking, no history of drug sensitivity, and was free of biliary system disorders, such as gallstones.[52]

In this study, the patient exhibited abdominal pain, accompanied by nausea and vomiting. Laboratory findings indicated that the levels of amylase elevated sharply to 861 U/L and lipase to 690 U/L, while other laboratory indices were within the normal range. In addition, ultrasound was used to confirm the abnormality of their pancreas. The patient presented with symptoms while receiving sodium VPA, a Class I medication associated with acute pancreatitis. Quetiapine-induced acute pancreatitis has been reported in few cases, which is difficult to distinguish from VPA-induced pancreatitis because they share similar symptoms.[53-55] Moreover, there is limited existing evidence to support the assumption that quetiapine is combined with VPA to react against the pathogenesis of this disease.

During the follow-up period, the patient remained symptom-free under the treatment of quetiapine. Taken together, the authors assumed that the cause of acute pancreatitis in this patient was VPA treatment.

The novelty of the authors' case is the age of the patient and the duration after which the entity developed. The patient was an adult and not from the most affected paediatric age group, the disease developed after 12 years of taking the drug, while commonly it is reported in up to 8 years of taking the drug. Valproate induced adult pancreatitis is rare; only a few cases have been reported and, hence, this case adds to the knowledge on the topic.

Acute pancreatitis can be fatal. Although DIP is rare, physicians should bear in mind its possibility. To prevent DIP, the latest knowledge of medicines connecting their use to the occurrence of pancreatitis is required.[23]

Physicians should be aware of drug allergy history and a patient's comorbid conditions, while maintaining vigilance against the signs of severe toxic reactions. To prescribe VPA as bipolar disorder treatment, patients need to be closely monitored in order to prevent severe adverse effects, including acute pancreatitis. Physicians must be vigilant about this diagnosis even after many years of starting the implicating drug.

CONCLUSION

Valproate-induced acute pancreatitis is a rare and potentially fatal complication in patients on valproate. This is a diagnosis of exclusion, and is labelled only after the other common causes of pancreatitis have been ruled out.

The authors' patient had a good outcome because of early diagnosis and resuscitation. Though the complication is most commonly seen in paediatric patients up to 8 years after starting the drug, caregivers should be vigilant about the early signs and symptoms of pancreatitis, including acute abdomen, vomiting, and raised serum amylase and lipase, even in adult patients taking valproate for more than 8 years. Patients

on long-term valproate should be counselled to make them aware, so that patients seek immediate medical attention if any of these symptoms develop. Prompt blood investigations for acute pancreatitis (serum amylase and lipase tests) and radiological imaging must be done in patients on VPA who present at a healthcare setting with features of acute abdomen.

A case series that combines the published cases until the time of writing, would improve understanding of the association.

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