Divalproex sodium-induced acute pancreatitis in a young patient of myoclonic seizures: A case report

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Abstract

Background: Acute pancreatitis affects 300-600 new patients per million populations per year and is most commonly caused by gall stone or alcohol, but there may be other causes and associations. Reports of drug-induced acute pancreatitis have been published since the early 1950s, and each year the list of drugs associated with pancreatitis increases. **Case report:** An 18-years-old male patient was prescribed Divalproex sodium tablets (500 mg) once daily for myoclonic seizures one year ago. He suddenly developed severe epigastric pain with gradually progressive worsening for the last five days, along with profuse vomiting. Serum lipase and computed Tomography (CT) scan of the patient suggested the presence of acute pancreatitis. The patient was hospitalized; the drug was stopped and he was treated symptomatically. A diagnosis of drug-induced pancreatitis was made following exclusion of other possible factors precipitating pancreatitis. **Conclusion:** This case report suggests that divalproex sodium can precipitate acute pancreatitis in some cases and clinicians must be vigilant about it. In the absence of re-challenge, it is probable that Divalproex sodium has a causative link with acute pancreatitis.

Keywords: Acute pancreatitis, Divalproex sodium, Myoclonic seizures, re-challenges

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Introduction

Acute pancreatitis typically presents as an acute inflammation of the pancreas that may or may not involve the surrounding tissues.[1, 2] There are many etiological risk factors for acute pancreatitis, including a

history of alcohol abuse, gallstones, procedures such as endoscopic retrograde cholangio-pancreatography (ERCP) and manometry, trauma or surgical interventions near the head of the pancreas, certain medications, hyperlipidemia, infections, and chronic hypercalcemia. [3] Drug-induced pancreatitis is less common, with an incidence of (2 - 5)% of the reported cases of acute pancreatitis in the general population.[1,2,3,4] The severity of drug-induced pancreatitis is variable; the majority of patients recover without any long-term morbidity, but 5%-15% of patients experience life-threatening complications.[5] People at risk of drug-induced pancreatitis include elderly patients taking multiple medications, patients who are HIV positive, patients who have cancer and patients receiving immunomodulatory agents.

Divalproex sodium consists of a compound of sodium valproate and valproic acid in a 1:1 molar relationship. It is used for the treatment of the manic episodes of bipolar disorder. In rare cases, it is also used as a treatment for major depressive disorder, and increasingly taken long-term for prevention of both manic and depressive phases of bipolar disorder, especially the rapid-cycling variant. It is also used for the treatment of epilepsy. The most severe side effect is a ten times higher-than-average incidence rate of serious, irreversible birth defects (teratogenic) such as births of anencephaly. Risk of birth defects such as spina bifida has also been demonstrated.

Life-threatening liver failure has occurred in patients taking Divalproex Delayed-Release Tablets. Children younger than 2 years old are at increased risk of developing life-threatening liver damage, especially those on more than one medicine to treat seizures, and those with metabolic disorders, severe seizure disorders accompanied by retardation, or organic brain disease.[6]

Case report

An 18 years old young male patient was on Divalproex sodium (500mg) once daily for the last one year, since he was diagnosed to be suffering from myoclonic seizures. He suddenly developed severe epigastric pain with gradually progressive worsening for the last five days, along with profuse vomiting. The pain was initially steady, dull & boring, waxing & waning in nature, penetrating in character & was intensified with intake of

food & positional changes. The pain was not associated with distension, borborgymi & gastrointestinal bleeding. The patient was exclusively on liquid diet for the fear of pain. He was neither alcoholic nor smoker, had no past history of jaundice or gall stones or any major surgery in the recent past. Along with Divalproex sodium, he was concomitently receiving pantroprazole and multivitamins in the recent past. Physical examination showed temperature 39.5^{o}C, pulse -110/minute, anaemia, epigastric tenderness and fullness. Complete haemogram revealed Hb-9.5 gm/dl;T.C.-8,200/cumm with neutrophil count-65%, platelet count, B.T, C.T was normal. Liver Function Test (LFT) showed ALP->300u/ml; reduced albumin level, serum lipase ->650 U/L & Serum amylase->700U/L. Inflammatory markers like ESR>100mm/hr; CRP >4 mg(normal-0.2-0.6mg). Blood sugar & renal function tests were within normal limits. Blood calcium<20mmol/l. Arterial blood gas analysis revealed normal pH with a Spo_2 86mmof Hg. Glassgow severity score [7] was 4 out of 7, indicating severe acute pancreatitis. CT scan of abdomen revealed enlarged liver with normal outline with hypoechoeic ecotexture, diffuse pancreatic swelling, fluid collection & change in the density of the gland. An abdominal ultrasound demonstrated a common bile duct, measuring 0.5 cm in diameter, without cholelithiasis. Other abdominal organs were normal. A diagnosis of acute pancreatitis with pseudocyst was made. The patient was immediately hospitalized and was shifted to intensive care unit (ICU). Offending drug was withdrawn, but in order to control the seizures another antiepileptic drug lamotrigine was started. The sign & symptoms gradually subsided after initial resuscitation & all the parameters became normal within a week. There were no other confounding factors. Causality assessment of the adverse drug event by WHO causality assessment scale and Naranjo algorithm showed that a 'Probable' adverse drug reaction has occurred in this case.

Discussion

The most common causes for pancreatitis in adults are cholelithiasis and excessive alcohol use, accounting for 35-40% and 30% of cases, respectively. Other causes include anatomic variants of the pancreas,

mechanical obstruction to pancreatic juice, hypertriglyceridemia, hypercalcaemia, toxins, trauma, ischemia, infections and autoimmune conditions [7]. Many medications also have been identified as a probable cause of acute pancreatitis. The first to report a case of drug-induced acute pancreatitis was Zion *et al*. in 1955; they described a case of hemorrhagic pancreatitis associated with cortisone therapy. [8] Drug-induced pancreatitis is rare, although more than 100 drugs have been implicated in causing this condition. [9] Definite association of drugs with acute pancreatitis include aminosalicylates, L-asparaginase, azathioprine, didanosine, estrogen, furosemide, pentamidine, sulfonamide, tetracycline, thiazides, valproic acid, vinca alkaloids and 6-mercaptopurine. [9] A detailed history and physical examination along with routine radiological evaluation consisting of ultrasound and/or CT of the abdomen can detect the underlying etiology of acute pancreatitis in approximately 80% of patients. If this initial investigation is unrevealing, the patient is classified as having idiopathic acute pancreatitis. [10] In this case, cholelithiasis, alcoholism, hypertriglyceridemia, infection and trauma were ruled out as other possible causes of acute pancreatitis.

An association between acid suppressing drugs and acute pancreatitis has not been clearly supported by cohort and case control studies. Since our patient was receiving pantoprazole for gastro-esophageal reflux for the last few months and also the condition subsided on withdrawal of the drug, the possibility of it to be the offending agent seems to be unlikely. The mechanisms of action for drug-induced acute pancreatitis are based on theories extracted from case reports, case-control studies, animal studies and other experimental data. In general, some potential mechanisms of action for drug-induced acute pancreatitis include pancreatic duct constriction, cytotoxic and metabolic effects, and accumulation of a toxic metabolite or intermediary and hypersensitivity reactions. [11]

Conclusion

Current evidence reveals that the risk of drug-induced acute pancreatitis is low (2 - 5%) and it is imperative to rule out more common causes before attributing the event

to a certain medication. Even with a relatively safe profile as shown by studies on patients taking Divalproex sodium, the risk of having an adverse reaction exists and warrants immediate withdrawal of the drug and further investigation to prevent serious consequences. Except for the fact that this patient was on Divalproex sodium, there was no established cause of his acute pancreatitis. In summary, we document a clinical case of acute pancreatitis. The patient had no significant past medical history and no other risk factors for the development of acute pancreatitis. He had no other causes of acute pancreatitis as were excluded by the clinical history, serum toxicology and abdominal imaging. In the absence of re-challenge, therefore it is probable that Divalproex has a causative link with acute pancreatitis.

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