Case Report

Valproic Acid Induced Pancreatitis in an Arab Male

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Abstract

Valproate, a commonly used antiepileptic, is known to cause pancreatitis, which may present days to years after initiation of therapy. A 20-year-old Arab male patient with electroencephalogram (EEG) confirmed epileptiform activity over the left posterior head region was initiated with tablet carbamazepine 400 mg twice daily in the year 2015 and based on subsequent EEG findings (suggestive of more of generalized myoclonic seizure) carbamazepine was withdrawn gradually and started with sodium valproate 500 mg twice daily and levetiracetam 1 g twice daily. During treatment, the patient had status epileptics, treated with diazepam and lamotrigine 50 mg was added. Laboratory data indicated low valproate level, 47 μg/mL (normal range: 50–125 μg/mL) resulting in two episodes of myoclonic jerks necessitating lamotrigine dose escalation (100 mg twice daily). A month later, the patient developed nystagmus and tremors, and lamotrigine dose was deescalated to 75 mg twice daily. Patient was brought to the emergency with severe abdominal pain and vomiting since the day before and valproate level was 179 μg/mL (>150 μg/mL μg/mL is considered toxic), a diagnosis of acute pancreatitis due to valproate was made and the patient was treated in the intensive care unit. The causality assessment of the adverse drug reaction was "probable" (Naranjo score 8), and severity was "Severe" (Level 5; Modified Hartwig and Siegel scale), and the adverse reaction was "Not preventable" (Modified Schumock and Thornton scale). This report suggests the need for constant clinical monitoring and the need for therapeutic drug monitoring for patients undergoing valproate therapy.

Keywords: Antiepileptic, pancreatitis, side effect, valproic acid

Introduction

Valproic acid (Valproate) is approved by the United States Food and Drug Administration (US FDA) for absence seizure (simple and complex), and complex partial epileptic seizure.[1] It is a commonly prescribed medication for use in epilepsy, migraine, and bipolar disorder.[2] It is considered as the anti-epileptic drug of the first choice in idiopathic and symptomatic generalized epilepsies and one of the most frequently-prescribed antiepileptic drugs worldwide.[3] Like any other antiepileptic drug valproate is also associated with many adverse reactions (ADRs). The common ADRs associated with valproate are dermatologic (injection site pain, 2.6%; injection site reaction, 2.4%), gastrointestinal (nausea, 3.2%), and neurologic (dizziness, 5.2% to 7.1%; headache, 2.7% to 4.3%, somnolence, 1.7% to 10.7%).[4] Among the serious side effects associated with valproate are metabolic (hyperammonemia), gastrointestinal (pancreatitis), hematologic (myelodysplastic syndrome, thrombocytopenia (27%), hepatic (liver failure), immunologic, (drug reaction with eosinophilia and systemic symptoms), neurologic (hyperammonemic encephalopathy).[4]

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Pancreatitis due to valproate is reported in 1% to 5% of the cases.[4] It is reported that valproate-coincident pancreatitis is uncommon and is usually idiosyncratic.[5] Acute pancreatitis occurs due to several etiologies and is sometimes associated with the use of medications.[6] The authors herein report a case of valproate-induced pancreatitis with established causality, severity, and preventability assessments using Naranjo algorithm,[7] Modified Hartwig and Siegel Scale,[8] and Modified Schumock and Thornton scales,[9] respectively.

Case Report

A 20-year-old young unmarried Arab male weighing 37 kg was admitted to the Security Forces Hospital, Makah, Saudi Arabia for the first time in October 2015 with a complaint of

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behavioral changes, involuntary smile and grimace, and history of nocturnal myoclonic jerks. Work-up tests with magnetic resonance imaging (MRI) and electroencephalography (EEG) were carried out. The MRI report was normal while EEG showed epileptiform activity over the left posterior head region; the plan was to repeat sleep deprived EEG. The patient was started on tablet carbamazepine 400 mg twice daily.

During the second visit, the MRI was normal, and the EEG finding was suggestive of generalized myoclonic seizure. The plan was to withdraw carbamazepine gradually, i.e., 400 mg twice daily for 2 weeks and then 400 mg once daily for 2 weeks and to start sodium valproate 500 mg twice daily with levetiracetam 1 g twice daily. Patient came after 6 days with status epilepticus and was treated with diazepam. He was sedated, not in distress, vitally stable, no fits, and laboratory investigation, i.e., complete blood count, liver function test, and biochemical parameters tests were all normal. When patient had status epilepticus, he developed pneumonia and meropenem and levofloxacin were given; meanwhile, lamotrigine 50 mg was added. The impression was that the patient suffered from hospital-acquired pneumonia and aspiration pneumonia with nonconvulsive status epilepticus. The plan was to continue the treatment and started physiotherapy. Patient was shifted from the intensive care unit (ICU) to the ward when he stabilized. For epilepsy treatment, the patient received levetiracetam 1.5 g twice daily, valproic acid acid 500 mg twice daily. Pneumonia improved markedly after taking full course of antibiotic.

The laboratory investigation showed valproate level of 47 μg/mL which is considered low (normal range is 50–125 μg/mL), but no change to the dose was made because the patient was well controlled. After 2 weeks, he developed two episodes of myoclonic jerks; thus, the lamotrigine dose was escalated to 100 mg twice daily. A month after increasing lamotrigine dose, he started to have nystagmus and tremors; the lamotrigine dose was deescalated to 75 mg twice daily.

In April 2016, the patient was brought to the emergency department complaining of severe abdominal pain with vomiting since the day before and valproate level was 179 μg/mL (>150 μg/mL is considered toxic). The impression was that the patient had experienced acute pancreatitis due to valproate; he was given nothing orally and started on dextrose normal saline 250 ml/hour. Several laboratory tests were requested, and the patient was shifted to the ICU with daily laboratory tests, i.e., complete blood count, C-reactive protein, renal function tests, liver function tests, prothrombin time, calcium level, magnesium levels, and venous blood gases. The patient had no social history of alcohol abuse, no history of accident or illnesses that could affect the pancreas. Multi-slice CT (computed tomography) scan of the abdomen and pelvis after IV contrast administration was carried out. The pancreas appeared bulky with homogenous enhancement surrounded by fluid densities in the lesser sac and pararenal spaces. Moderate ascites was also observed throughout the peritoneal recesses. There were no definite masses or collections, bilateral moderate pleural effusion associated with passive lower lung lobes collapse, intra-hepatic or extra-hepatic biliary radicles dilatation. The liver was of average size with homogenous CT texture, no focal lesions or contour irregularities. Other findings were patent homogenously enhancing portal vein (main branches as well as its main tributaries), normal size and parenchymal texture of the spleen with no focal lesions, normal sized both kidneys with no stones or back-pressure changes, normal appearance of aorta, inferior vena cava and both suprarenal, smooth filling of the urinary bladder with no filling defects or diverticular out pouching. Based on the clinical opinion, the CT findings were concurrent with interstitial pancreatitis.

Since the patient had a previous history of status epilepticus which was difficult to control, to try to prevent new seizures in the presence of valproate-induced pancreatitis, valproate was put on hold and lamotrigine was reduced to 50 mg twice daily since it is known that lamotrigine increases valporic acid level. He was continued on intravenous levetiracetam 1500 mg bid, clonazepam 0.5 mg orally once. Hypokalemia was treated with calcium gluconate 2 g IV thrice daily; phosphorous, calcium, and magnesium levels were continuously monitored. Two days later, the patient experienced frequent generalized myoclonic jerks and was started on diazepam IV and phenytoin 100 mg thrice daily. To control the seizures, the patient was given the following: lamotrigine increased to 100 mg bid, continued with levitracetam 1500 mg; phenytoin level was measured, and after 4 days, the phenytoin dose was tapered. On discharge, the patient was prescribed lamotrigine 100 mg twice daily, clonazepam 1 mg thrice daily, and the initial dose of ethosuximide 10 mg/kg/day (increased to 20–30 mg/kg/day, if required with a discussion with family).

The causality assessment was carried out using a commonly used algorithm "Naranjo algorithm"[7] and was found to be "probably" associated with the drug (Naranjo score 8), the severity assessment as per Modified Hartwig and Siegel scale[8] categorized the ADR to be "severe (Level 5)" in nature and the preventability assessment as per the Modified Schumock and Thornton scale[9] categorized the ADR to be "Not preventable."

Discussion

Valproic acid, sodium valproate, and divalproex sodium are the same generic form of the drug with different formulations. Divalproex sodium is the enteric coated form of valproic acid[10] containing sodium valproate and valproic acid which dissociates to valproate ion in the gastrointestinal tract.[11] Sodium valproate is the sodium salt form of valproic acid. Although all these three preparations are almost completely bioavailable, they differ in terms of absorption and dissolution rates, with the sustained-release formulations having less fluctuations in serum drug concentrations.[12] The US FDA approved valproic acid and divalproex sodium for seizure disorders in 1986 and 1978, respectively. Valproic acid is

generally considered economic and less safe compared to divalproex sodium.[10]

Pancreatitis is the inflammation of the pancreas and can be acute or chronic in nature. The etiologies of both acute and chronic pancreatitis are the same and nearly 80%–90% of the cases are caused due to alcohol abuse and gallstones (about 35%–45% for each) followed by drugs, chemicals, trauma, hereditary disorders, infections, surgeries, hyperlipidemia, and genetic abnormalities of pancreas and intestine.[13] The incidence of drug-induced pancreatitis ranges from 0.1% and 2% of the total pancreatitis cases.[14] In one study, based on the data obtained from the US National Library of Medicine/ Pubmed, for reported cases of drug-induced pancreatitis (DIP) from 1966 to 2004, valproate accounted for at least 20 reported cases of acute pancreatitis with at least one documented case following reexposure.[15] In Denmark, DIP made up 0.1% of all the reports to the Danish Committee on Adverse Drug Reactions from 1968 to 1999.[16] During our literature review, we found only one case of valproate-induced pancreatitis from Saudi Arabia in a 19-year-old male patient. Authors reporting the case noticed this case after 12 years of the start of the drug and recommended watchfulness throughout the use of the drug. Early withdrawal may minimize high fatalities.[17]

There are multiple risk factors for DIP and include alcohol intake, hyperlipidemia, infection and concomitant medications use,[18] female gender, and younger age.[19] In the present case, the patient was on lamotrigine, a commonly used concurrent drug, at the time of valproate therapy. Concurrent use of these two drugs is known to result in an increased elimination half-life of lamotrigine leading to toxic symptoms of fatigue, drowsiness, ataxia, and skin rashes in a dose-dependent manner.[20] Thus, it is important for patients on valproate to be on regular monitoring. It is recommended to reduce the lamotrigine dose by 50% of the normal while used in combination with valproate. On the other hand, valproate should be started at a low dose and increased incrementally based on serum concentration.[21,22]

Patients should be advised of valproate-induced pancreatitis which may occur soon after starting the drug as well as many years after use. They should know the common signs of pancreatitis such as abdominal pain, fever, diarrhea and vomiting.[23] A systematic evaluation of a suspected ADR can be a valuable tool in the prevention of similar ADRs in the future. In the present case, the causality was established as "probable" using the Naranjo algorithm.[7] In a published review consisting of 45 cases of valproic acid-induced pancreatitis, 3 were found to be definite (by the Naranjo ADR probability scale), 32 probable, and 10 possible. There was no correlation between valproic acid dosage or plasma concentration and the development of pancreatitis.[24] In the present case, the ADR was confirmed by the treating physician and the presence of toxic concentration of the drug in the blood. The severity assessment as per Modified Hartwig and Siegel scale,[8] categorized the ADR to be "severe" (Level 5) suggesting the need for intensive care admission for treatment. In general, pancreatitis caused by valproate is severe and hence patients need counseling early during hospital visits in case of any suspected reactions. The preventability of this ADR was identified as per the Modified Schumock and Thornton scale[9] to be "Not preventable." However, a proper prescribing and dose escalation strategy, drug therapy monitoring, and patient education can be helpful in minimizing the occurrence of valproate-induced pancreatitis.

Conclusion

There might be more cases as such that were under-reported. Physicians who prescribe antiepileptic medications should be aware of the possibility of drug-induced pancreatitis. Regular monitoring (both clinically and drug levels) is mandatory for early identification and mitigation of the ADR. Patients should be educated to recognize the early signs of the problem. Early discontinuation of valproate is encouraged to prevent any serious reactions.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for his images and other clinical information to be reported in the journal. The patient understands that names and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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