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Case Report

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Valproic Acid Induced Acute Pancreatitis – A case report

***N.S Neki ,**Jaswinder Singh, ** Narendra Kumar Meena,**Deepali Kaushal, **Aaarti Vaid, **Amandeep Singh Dhanju,** Ajay Jolly,**Bhoj Raj , **Rohit Kumar, **Jithesh G**

*Professor, **Junior Resident, Dept. of Medicine, Govt. Medical College and Guru Nanak Dev Hospital, Amritsar, 143001, India.

Corresponding Author: **DR. N.S. Neki,** Professor of Medicine, Govt. Medical College and Guru Nanak Dev Hospital, Amritsar, India.

*Corresponding author: *drneki123@gmail.com*

Abstract

Valproic acid is most widely used antiepileptic drug and known to cause potentially fatal complication of acute pancreatitis. The patient may recover completely after its discontinuation or may develop severe acute pancreatitis and death. We report a case of 18 year school going girl suffering from generalised tonic clonic seizures on treatment with valproic acid. The treatment is supportive while re-challenge is dangerous and must be avoided.

Keywords: Valproic acid; Acute pancreatitis.

Introduction

Valproic acid (VPA) was approved in the United States in the year 1978 for the treatment of absence seizures. Since then it is being commonly used either as monotherapy or in combination with other antiepileptic agents for the treatment of primary and secondary generalised seizures, simple partial and complex partial seizures, trigeminal neuralgia, bipolar disorders and migrane[1]. Idiosyncratic reactions to drugs occur by abnormal interaction between the drug and organism, usually mediated by immunologic or cytotoxic effects triggered by the drug or its metabolites[2]. The toxic effects can be dose dependent or idiosyncratic. The mechanism is probably associated with the metabolism of the neurotransmitter GABA. There are so many VPA related idiosyncratic reactions and the most common include alopecia, bone marrow aplasia, hepatotoxicity and pancreatitis[2]. VPA induced pancreatitis was first reported by Batal den et al in 1979 [3] and it is rare in incidence ie 1:40000 [4]. VPA induced pancreatitis occurs mainly during the first year of treatment or after increase in dose, with higher incidence in young individuals, in polypharmacy (mainly with carbamazepine, phenytoin, phenobarbitone, benzodiazepines), with chronic encephalitis and in delayed treatment [5,6]. Acute pancreatitis is commonly caused by choledocholithiasis, trauma, ethanol abuse, drugs including statins, thiazide, diuretics, furosemide,

antiretroviral agents and anticonvulsants, tetracycline, acetaminophen, propoxyphene, clonidine, rifampicin, azathioprine, oral contraceptives, corticosteroids and ACTH [5,6]. The treatment is mainly immediate withdrewl of drug, supportive measures and specific treatment of the possible complications. We report a case of 18 year old school going girl, suffering from generalised tonic clonic seizures, taking treatment with VPA ultimately resulting in drug induced (VPA induced) acute pancreatitis.

Case Report

An 18 year old school girl, strictly vegetarian, presented with severe pain abdomen in the epigastrium, nausea, vomiting and fever since 3 days and not relieved by medication. She was a known case of generalised tonic-clonic seizures on 500mg twice daily dose of valproic acid for the last 2 years. She was not receiving any other drugs, she had no history of alcohol abuse, abdominal trauma or recent infection. Her menstrual history was normal. She had no family history of convulsions, she was non hypertensive, non diabetic. On physical examination her vitals were BP 110/70 mmHg, Pulse 108 beats/min, Temp 99.2^{o} F, Respiratory rate 18/min. The abdomen was soft with tenderness over the epigastrium. Examination of the cardiovascular, neurological and respiratory system was unremarkable. Laboratory investigations revealed Hb 10.3 g%, Total leucocyte count 15800/mm3, Differential cell count P 76, L 18, E 6, B 0; ESR 25mm at the end of first hour; Random blood sugar 120 mg/dl; Blood urea 35 mg/dl, Serum creatinine 1.3 ng/dl; Serum amylase 850 IU/L; Serum lipase 1380 IU/L; Serum lactate dehydrogenase 770 IU/L, Serum Potassium 4.5 meq/L, Serum Calcium 9mg/dl. Liver function tests and fasting lipid profile were within normal limits. X ray chest was non contributory. ECG showed tachycardia. She was negative for HIV and viral markers of Hepatitis A,B,C and E. Arterial blood gas analysis was normal. Studies for cytomegalovirus and herpes virus analysis could not be done due to financial constraints. Based on history and laboratory investigations, she was suspected to be a case of acute pancreatitis. Ultrasound abdomen revealed hypoechoic, swollen pancreas suggestive of acute pancreatitis. There was no pancreatic calculi, calcification and mass lesion. CT abdomen revealed multiple hypodense areas within the head and tail of pancreas with swollen head and presence of peripancreatic fat stranding suggestive of acute pancreatitis. Keeping in view history, laboratory investigations and radiological studies, a diagnosis of VPA induced pancreatitis was made. Immediately VPA was discontinued and she was treated with Ryle's tube aspiration, nothing orally, intravenous (IV) broad spectrum antibiotics, IV fluids, laboratory investigations repeated after 3 days showed greater improvement in serum amylase tto 210 IU/L and serum lipase 180 IU/L. there was clinical improvement also with resolution of fever, pain abdomen and vomiting. Ryle's tube was removed on 7th day and oral diet was gradually reintroduced with good acceptance and no worsening of symptoms. She was started on tablet lamotrigine 50mg BD, which was very well tolerated by the patient. She was discharged on 8th day of hospitalisation with control of seizures.

Discussion

Valproic acid (VPA) is commonly used antiepileptic drug for over 20 years. The mechanism of VPA induced pancreatitis is unknown. However various theories have been put forward. According to one theory, it is postulated to be due to depletion of free radical scavengers (FRS), superoxide dismutase, catalase and glutathione peroxidase. Depletion of FRS can result in excessive production of free radicals which may lead to endothelial permeability and lipid peroxidation resulting in tissue damage.

Second theory is that VPA can cause reduction of carnitine, which may further induce pancreatic damage [7.] Second theory states that mitochondrial b-oxidation plays a role in the elimination of VPA. This enzyme system is involved in branched chain amino acid metabolism. VPA inhibits mitochondrial b-oxidation enzymes as in genetic deficiency resulting in excess toxic metabolites [8.] But this mitochondrial b-oxidation enzyme deficient theory was challenged by other workers who did not find any change in amino acid levels responsible for VPA induced

pancreatitis [9]. The diagnosis of pancreatitis is made on clinical findings [10] as well as increase in serum amylase and lipase values [11]. Abdominal ultrasound is useful in the preliminary evaluation of patients suspected of having acute pancreatitis and it should be done in the first 24-48 hours from the onset of the clinical symptoms [12] as was done in the present case. Abdominal CT scan must be performed on every patient of acute pancreatitis in order to evaluate extent of inflammatory process, evidence of necrosis and other local complications as was done in this patient. Many cases of VPA induced pancreatitis have also been reported in individuals with cerebral palsy, mental retardation and developmental delay [4]. The use of VPA must be avoided in patients who had acute pancreatitis associated with its use on account of high relapse rate and complications [13]. Our patient had clinical features, laboratory markers and sonographic and CT evidence suggestive of acute pancreatitis and was resolved after withdrawl of VPA. Valproic acid related acute pancreatitis is basically a diagnosis of exclusion and should be entertained after ruling out other reasonable causes of pancreatitis. In our case, we ruled out all other possible causes of pancreatitis. There was no evidence of gall stones, serum levels of calcium and triglycerides were normal. There was no family history of pancreatitis and the patient was not receiving any other medication except VPA.

Conclusion

Acute pancreatitis is potentially a life threatening fatal complication in those taking sodium valproic acid. Pancreatitis must be considered in those patients complaining of nausea, vomiting and pain abdomen during valproic acid therapy. As this drug is commonly used in epilepsy, incidence of pancreatitis may be much higher than reported in the literature due to under notification or lack of awareness on the part of treating practitioner/physicians prescribing this drug on a daily basis. The withdrawl of valproic acid in patients with acute pancreatitis is mandatory and this drug should not be used again once the patient has recovered.

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