International Journal of Research in Medical Sciences
Barman B et al. Int J Res Med Sci. 2014 Nov;2(4):1765-1767
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012

DOI: 10.5455/2320-6012.ijrms201411107

Case Report

Valproic acid induced pancreatitis: a case report

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Received: 26 September 2014
Accepted: 10 October 2014

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ABSTRACT

Valproic acid is a commonly used antiepileptic drug. Apart from its common side effect there is definite association between valproic acid therapy and acute pancreatitis. Since 1979, many cases of acute pancreatitis induced by valproic acid have been published in medical literature. Here we are reporting a case of valproic acid induced acute pancreatitis in a 27 years old boy. The treatment is supportive, re-challenge is hazardous and should be avoided.

Keywords: Valproic acid, Epilepsy, Acute pancreatitis

INTRODUCTION

Valproic acid was approved in 1978 for the treatment of Absence seizure. Valproic acid (VPA) is a carboxylic acid used as anti-epileptic in idiopathic and symptomatic generalized epilepsies and in some cases of symptomatic focal epilepsies, as well as for trigeminal neuralgia, migraine and bipolar disorders.[1] Idiosyncratic reaction can take place in an unpredictable way by abnormal interaction between the drug and the organism, usually mediated by immunologic or cytotoxic effects triggered by the drug or its metabolites.[2] There are several VPA-related idiosyncrasies, being the most noteworthy alopecia, bone marrow aplasia, immune-mediated hepatotoxicity and pancreatitis.[2] Pancreatitis associated with valproic acid was first reported by Batalden et al in 1979.[3] The pancreatitis provoked by VPA is a rare entity, with estimated incidence of 1:400000.[4] Outcomes of the patients with valproic acid associated pancreatitis have ranged from full recovery after discontinuation of the drug to severe hemorrhagic pancreatitis and death. A survey of 364 physician found that 53(14.5%) reported seeing a case of pancreatitis associated with valproic acid.[5]

We report here a case of a young male who developed pancreatitis in direct association with valproic acid therapy.

CASE REPORT

A 22 year old boy with history of generalized tonic clonic seizure was being treated with valproic acid (500mg twice daily) since last 3 years. He was brought to consultation because he had severe pain abdomen over the epigastric region, nausea and mild fever for last 2 days, not relieved by medication. There was no history of alcohol abuse, abdominal trauma or recent infection. On physical examination, patient was febrile, hydrated, weight 54kg, pulse: 106/min, Blood pressure: 110/70 mmHg. The abdomen was soft with tenderness during deep palpation over the epigastrium. Respiratory, Cardiovascular and Neurological examination were normal. Laboratory tests showed the following results: Hb: 11.2gm%, Leucocytes: 16,700/cu mm, Neutrophil 75%, Lymphocyte 17%, Eosinophil 8%, ESR: 28 mm, Random Blood Sugar: 122.6 mg/dl, Serum Urea: 36.4 mg/dl, Serum Creatinine: 1.2 mg/dl, Serum Amylase: 924.7 U/L, Serum Lipase: 1460 IU/L, Serum Lactate Dehydrogenase: 896.7 IU/L, C Reactive Protein: 7.6 mg/dl, Serum Sodium: 137 meq/L, Serum Potassium: 4.26 meq/L, Serum Calcium: 8.21 mg/dl, Liver Function Test and Fasting Lipid Profile were within normal limit. HIV and Hepatitis serologic tests were negative. Sonography of abdomen revealed hypoechoic, swollen

and edematous suggestive of acute pancreatitis. There was no pancreatic calculi, calcification or mass lesion. All medications that the patient was getting was kept on withhold. Follow up investigations after 72 hours showed improvement with Serum Amylase: 225 IU/L and Serum Lipase: 196.5 IU/L. The patient gradually became asymptomatic, anti epileptic therapy with Lamotrigine was started with 50 mg twice daily and was tolerated well. Patient was discharged after 7 days in stable condition.

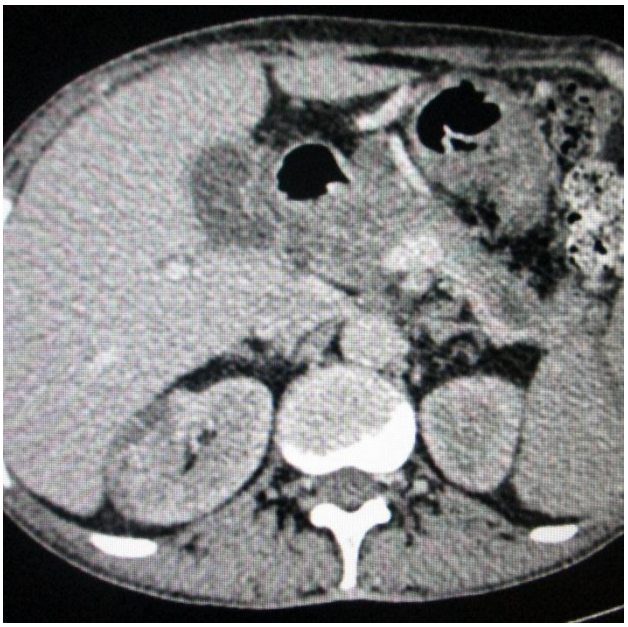

Figure 1: Contrast enhanced CT scan of the abdomen showing multiple hypodense areas within the head of the pancreas and tail with bulky appearance of head and peripancreatic fat stranding suggestive of acute pancreatitis.

DISCUSSION

Valproic acid has been used as an anti-epileptic drug for over 20 years. In addition to its usefulness in treating a wide variety of seizure type, it has become a first line agent in treatment of psychiatric disorders like acute mania and in prophylaxis of Bipolar disorder and Migraine.

Acute pancreatitis is a serious condition with multiple causes. Gall stone and alcoholism accounts for 80% of cases, while 10% remains idiopathic. Other miscellaneous causes includes abdominal trauma, metabolic, infection (mumps, hepatitis, rubella, HIV), ischemia, inherited diseases, vasculitis, toxins and drugs.[6] Approximately 2 % of acute pancreatitis in the general population is caused by drugs.[7] The first reported drug causing pancreatitis was published in 1954. Since then more than 85 drugs have been accused of causing pancreatitis. Apart from valproic acid other drugs associated with pancreatitis include thiazide diuretics, furosemide, , acetaminophen, propoxyphene, clonidine, tetracycline, ethacrynic acid, chlorthalidone, rifampin, azathioprine, asparaginase, oral contraceptives, corticosteroids, and ACTH hormone.[8] Other than valproic acid the patient reported here had taken none of these drugs. The mechanism by which valproic acid induces pancreatitis is unknown. However, it has been said that depletion of the free radical scavengers superoxide dismutase (SOD), catalase and glutathione peroxidase occurs in patients receiving valproic acid.[9] Depletion of the free radical scavengers lead to an excess of superoxide radical (O_2^-), hydrogen peroxide (H_2O_2) and hydroxyl free radical (OH-) that results in increase endothelial permeability and lipid peroxidation leading to tissue damage which in turn causes pancreatitis. Another theory that has been proposed for valproic induced pancreatitis is on mitochondrial-b-oxidation. It has been established that valproic acid is metabolized through mitochondrial-b-oxidation. Those patients with genetic deficiency in the enzyme involved in mitochondrial-b-oxidation of valproic acid may experience an increase in toxic metabolites. There is no specific recommendation for monitoring pancreatic enzyme in patients taking valproic acid. Consideration should be given before giving recommendation regarding routine measurement of pancreatic enzyme in patients taking valproic acid because of their very low occurrence. Mild, asymptomatic elevation of pancreatic enzyme occur frequently with no progression to pancreatitis in due course of treatment. Our patient is having clinical symptoms, laboratory markers and sonographic evidence suggestive of acute pancreatitis and was resolved after withdrawal of valproic acid, feature consistent with valproic acid induced pancreatitis.

CONCLUSION

Pancreatitis is well documented, life threatening toxicity associated with valproic acid. Pancreatitis should be considered, in patients complaining of nausea, vomiting and pain abdomen during valproic acid therapy. Those reporting their symptoms should have pancreatic enzyme checked as part of evaluation, however routine monitoring of pancreatic enzyme is not necessary in all patients receiving valproic acid. The withdrawal of valproic acid in patients who have pancreatitis is mandatory, and use of the drug must not be resumed once the patient has recovered.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

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DOI: 10.5455/2320-6012.ijrms201411107
Cite this article as: Barman B, Kalotia N, Ete T. Valproic acid induced pancreatitis: a case report. Int J Res Med Sci 2014;2:1765-7.