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Case Study

VALPROIC ACID INDUCED TRANSAMINITIS

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ABSTRACT

Valproic acid (VPA) is a broad spectrum antiepileptic agent used in the treatment of absence, myoclonic, partial and tonic clonic seizure and also used in the treatment of bipolar disorder. Although VPA, a proven anticonvulsant agent thought to have relatively few side-effects, has been referred as the third most common xenobiotic suspected of causing death due to liver injury. VPA-induced hepatotoxicity can be identified through an abnormal liver function test mainly an abnormal elevation in hepatic enzymes which is called transaminitis. Here we report a case of 21 y old female presented with transaminitis which occurred after 3 y of taking VPA that was started in view of here seizure disorder. The hepatic enzyme levels came down once VPA was stopped and appropriate treatment measures using hepatoprotectives were initiated. Causality assessment using Naranjo probability scale indicated a probable relationship (score-7) between the patient's condition and the use of VPA. Clinicians prescribing VPA should go for careful liver function monitoring not only initially but throughout the time the drug is given.

Keywords: Valproic acid, Transaminitis, Hepatoprotectives.

INTRODUCTION

Valproic acid (VPA) is a branched chain carboxylic acid that is mainly used in the treatment of epilepsy and bipolar disorder. It is a broad-spectrum antiepileptic agent used in the treatment of absence, myoclonic, partial and tonic-clonic seizures [1]. It is also used to prevent migraine headaches. VPA acts by increasing the availability of gamma amino butyric acid (GABA), an inhibitory neurotransmitter, to brain neurons or may enhance the action of GABA or mimic its action at postsynaptic receptor sites [2].

The most common side effects of VPA are transient gastrointestinal side effects including anorexia, nausea and vomiting in approximately 16% of patients [3]. VPA toxicity has been steadily increasing in frequency since the FDA approved the drug in 1995 for acute mania. According to the 2008 Annual Report of the American Association of Poison Control Centres' National Poison Data Systems (NPDS), 8,705 acute exposures to VPA occurred. Of these cases, major adverse outcomes were reported in 404 patients of this cohort [4].

Hepatotoxicity due to VPA appears in two forms. The benign form exists as a mild, dose-related elevation of liver enzymes [5, 6] that appears with reduction in dosage or discontinuation of the drug. The other form is a less common non-dose related disorder characterized by hepatic failure [7, 8]. The mechanism of valproate hepatotoxicity is thought to be due to mitochondrial toxicity, may be from inhibition of beta-oxidation and subsequent loss of mitochondrial function.

Here we will be discussing a case of Drug-Induced Transaminitis. Transaminitis is one of the earlier signs of hepatotoxicity. Transaminitis is the elevation of transaminases in the liver, most commonly alanine transaminases and aspartate transaminases. These enzymes are normally present in high concentrations within the hepatocytes. The presence of elevated serum concentrations of one or more of these enzymes suggests hepatocytes have lysed in response to some noxious insult, resulting the cell contents to circulate in the blood. [9] Other causes of transaminitis include alcoholic liver disease, viral hepatitis and hemochromatosis. In the case of drug-induced transaminitis, the levels of transaminases usually come down after the offending drug is stopped. Other measures include administration of IV Carnitine and addition of hepato protective's [10].

CASE REPORT

A 21 y old female patient was admitted in our hospital due to complaints of high-grade intermittent fever and vomiting episodes after consuming food from outside 2 d prior to hospital admission. The patient had nausea and multiple episodes of vomiting associated with food particles. The patient is a known case of seizure disorder on antiepileptics since 3 y. She had 3 episodes of seizure in the past 3 y. She was treated with Tab. Sodium Valproate 200 mg 1-0-1. She was seizure free for the past 1 y.

On examination, the patient was hypotensive. Physical examination revealed icterus was present and right lumbar tenderness was also present. On admission, her routine laboratory investigations were performed that revealed transaminitis. The Aspartate aminotransferase (AST) was 7139 IU/l (normal: 5-35 IU/l) and Alanine aminotransferases (ALT) level was 7006 IU/l (normal: 5-45 IU/l). She also had an elevated INR value of 2.31. USG abdomen was performed that turned out to be normal. Causality assessment using Naranjo probability scale indicated a probable (score-7) relationship between the patient's condition and the use of VPA.

The case was diagnosed to be Drug Induced Transaminitis. After neurologist's consultation, tab sodium valproate was stopped on the first day of admission itself and Inj. Levipil (levetiracetam) IV 500 mg 1-0-1 was started. After stopping the drug, the AST and ALT levels were as follows:

Table 1: .Laboratory investigations during hospital stay

Test	1/5/2015 (Day of admission)	2/5/15	3/5/15	4/5/15	5/5/15	Normal level
AST	7136 ↑	2289 ↑	604 ↑	275 ↑	99 ↑	5-35 IU/l
ALT	7006 ↑	4278 ↑	2227 ↑	1712 ↑	1133.5 ↑	5-45IU/l

The patient was also observed to have deranged International Normalized Ratio (INR) level. Vitamin K injection was administered to correct the INR levels. After the injection the INR level came down within the normal range.

Table 2: INR Levels during hospital stay

Test	1/5/2015 (Day of admission)	2/5/2015	3/5/15	4/5/15	5/5/15	Normal level
INR	2.31 ↑	2.39 ↑	1.14	1.04	1.31	0.9-1.2

She responded to the above-mentioned treatment and remained asymptomatic. At the time of discharge, her issues were resolved, transaminitis subsided and INR was normalized. The patient was discharged on Tab Levipil (Levetiracetam) 500 mg 1-0-1 and other hepatoprotectives like Tab. Udiliv (ursodeoxycholic acid) 300 mg 1-0-1, Tab Heptral (ademetionine) 400 mg 1-0-1, Tab. Silymarin 140 mg 1-0-1, Tab. Rifagut (rifaximin) 400 mg 1-1-1.

The patient came on 22/5/2015 for follow-up, during which her lab investigations showed the following results:

Table 3: Laboratory investigations during follow-up

Test	Result	Normal level
AST	25.3 IU/l	5-35 IU/l
ALT	41.3 IU/l	5-45 IU/l
INR	0.91	0.9-1.2

DISCUSSION

VPA is said to be an effective and popular antiepileptic agent which is associated with only a very small number of patients who have had severe toxic effects from its use. In up to 44% of patients chronic dosing with VPA may be associated with elevations in the transaminases during the first months of therapy. [11] Prospective studies suggest that 5%-10% of persons develop ALT elevations during long term valproate therapy, but it has been said that these abnormalities are usually asymptomatic and can resolve even with continuation of the drug. Although the overall incidence is estimated at 1 in 5000 to 1 in 50000, the occurrence of fatal hepatotoxicity can be as high as 1 in 800 in high risk groups.

The various measures of management include

- Discontinuation of the possible offending drug
- Close laboratory monitoring
- Specific therapy may not be available, and most of the time, management is supportive.
- Liver biopsy may be helpful in excluding other causes of liver injury
- Addition of hepatoprotectives

In a study conducted by Koeing S A *et al.* in Germany from 1994 to 2003 reports that of the published cases of fatalities with sodium valproate, 61% occurred within the first 3 mo of valproic acid treatment, with the appearance of first symptoms between 4 w and 3 mo after starting valproic acid. In these patients, the hepatotoxicity was resolved after discontinuation of the drug and addition of IV carnitine supplementation [12]. In another study conducted by Ware S and Sadler G H M on five patients who developed the acute liver disease after treatment with sodium valproate reports that the liver disease began 3-6 mo after the start of treatment [13].

In contrast, in our case, the patient has developed transaminitis after 3 y of treatment with VPA. The drug was stopped as soon as an elevation in transaminases was observed. Currently, the patient has been put on Levetiracetam 500 mg as a replacement for VPA. The levels of transaminases started to decrease immediately as VPA was stopped. The patient was also given hepatoprotective like Tab. Udiliv (ursodeoxycholic acid) 300 mg 1-0-1, Tab. Heptral (ademetionine) 400 mg 1-0-1, Tab. Silymarin 140 mg 1-0-1, Tab. Rifagut (rifaximin) 400 mg 1-1-1. Vitamin K injection was given in view of deranged INR values after which the INR levels came down to normal levels.

CONCLUSION

Although sodium valproate is an effective antiepileptic agent, hepatotoxicity continues to be an important and severe side effect of VPA therapy.

Previously case reports have shown valproic acid-induced transaminitis which occurred in the initial months of initiation of therapy. But in this case, we have seen transaminitis that occurred after 3 y of therapy. In conclusion, physicians prescribing VPA should go for careful liver function monitoring not only initially but throughout the time the drug is given.

CONFLICT OF INTERESTS

Declared None

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