

RESEARCH ARTICLE

Estimation of liver enzymes in patients taking antiepileptic drugs in a tertiary care center: A cross-sectional study

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Received: June 11, 2019; Accepted: July 05, 2019

ABSTRACT

Background: A number of antiepileptic drugs (AEDs) are used in the management of epilepsy. Almost all AEDs undergo hepatic biotransformation. Since drugs contribute a major part in causing liver injury, there is a need for identifying it. This study was designed to estimate the prevalence of liver enzyme elevation among patients treated with AEDs. **Aims and Objectives:** This study aims to estimate the prevalence of liver enzyme elevation and/or liver dysfunction in patients receiving AEDs. **Materials and Methods:** This cross-sectional descriptive study was conducted in the Department of Neurology, Tirunelveli Medical College Hospital for a period of 6 months. About 150 patients on AEDs, who met the inclusion and exclusion criteria, participated in the study. Demographic data, disease history, drug history, and history of any adverse drug reactions were recorded. Venous blood sample was collected to analyze complete blood count, serum aspartate aminotransferase (AST), and alanine aminotransferase (ALT). **Results:** Among 150 patients, 86 were male and 64 were female. Of these, 109 patients were on monotherapy with carbamazepine, sodium valproate, phenytoin, or phenobarbitone and rest 41 were on combination therapy. Serum AST levels were elevated in four patients treated with sodium valproate, phenytoin, or phenobarbitone as monotherapy, whereas ALT enzyme elevation was observed only in one male patient who was on sodium valproate as monotherapy. Serum alkaline phosphatase (ALP) was elevated in 14 patients and decreased in three patients. **Conclusion:** The magnitude of elevation in serum AST, ALT, and ALP levels with AEDs was found to be statistically insignificant. As such, there was no liver dysfunction in patients receiving AEDs as monotherapy or polytherapy.


KEY WORDS: Antiepileptics; Liver Enzymes; Epilepsy

INTRODUCTION

Epilepsy is a spectrum condition with a wide range of seizure types and control varying from person to person. It is the second most common neurological disorder and affects

people of all ages.^[1] About 70 million people have epilepsy worldwide and nearly 90% of them are found in developing countries.^[2] Antiepileptics form the mainstay of treatment for patients with epilepsy. Almost all antiepileptic drugs (AEDs) except few undergo biotransformation in the liver. Lipophilic AEDs need to be converted to a hydrophilic/water-soluble state for renal excretion.

Drugs are important cause of liver injury. More than 1000 drugs, toxins and herbs have been reported to cause hepatic injury^[3] and drugs account for 20%–40% of all the instances of fulminant hepatic failure. Approximately 75% of the idiosyncratic drug reactions result in liver transplantation

Access this article online	
Website: www.njppp.com	Quick Response code
DOI: 10.5455/njppp.2019.9.0723805072019	

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or death. In patients with acute liver injury, drugs are considered to be one among the differential diagnosis. In India, antituberculosis therapy (ATT) (58%), antiepileptics (11%), olanzapine (5%), and dapsone (5%) were the most common causes of drug-induced liver injury.^[4] The manifestations of drug-induced hepatotoxicity are highly variable, ranging from asymptomatic elevation of liver enzymes to fulminant hepatic failure. Physicians must be vigilant in identifying drug-related liver injury because early detection can decrease the severity of hepatotoxicity if the drug is discontinued.

Liver enzymes can serve as markers of hepatocellular injury (aspartate aminotransferase [AST] and alanine aminotransferase [ALT]). Although these enzymes are elevated in liver disease, the elevation may be secondary to enzyme induction in the absence of hepatic pathology. An elevated partial thromboplastin time or decrease in albumin along with elevated liver enzymes is a more specific marker of liver dysfunction.^[5] Monitoring for and recognition of drug-induced hepatotoxicity may prevent some cases of acute hepatic failure.^[6] Early diagnosis is the only way to reduce the harmful, potentially fatal effects of these adverse drug reactions.

Tirunelveli Medical College is a tertiary teaching hospital where in the Department of Neurology approximately 300–400 old cases and 80–100 new cases of epilepsy are prescribed AEDs every month. Carbamazepine, sodium valproate, and phenytoin are the common AEDs prescribed in this center.

This study was planned to estimate the prevalence of liver enzyme elevation among patients treated with AEDs such as carbamazepine, phenobarbitone, phenytoin, or sodium valproate as monotherapy or combination therapy.

Aims and Objectives

This study aims to estimate the prevalence of liver enzyme elevation and/or liver dysfunction in patients receiving AEDs.

MATERIALS AND METHODS

Study Design

This was a cross-sectional descriptive study.

Study Center

This study was conducted at the Department of Neurology, Tirunelveli Medical College Hospital.

Study Duration

The study duration was 6 months.

Study Population

Epileptic patients receiving AEDs.

Sample Size

The sample size was 150.

Inclusion Criteria

Both male and female patients, in the age group of 18–60 years, diagnosed with epilepsy and receiving carbamazepine or sodium valproate or phenytoin or phenobarbitone as monotherapy or combination therapy at least for the past 6 months were included in the study.

Exclusion Criteria

Patients with a history of alcoholism, drug abusers, and those who were not willing to participate were excluded from the study. Patients who were on other hepatotoxic drugs such as statins, steroids, ATT, and antiretroviral agents were also excluded.

Study Procedure

The study commenced after getting approval from the Institutional Ethical Committee. The study subjects were recruited according to the inclusion and exclusion criteria. Written informed consent was obtained from every participant. Demographic data, disease history, drug history, and history of any adverse drug reactions were recorded. History for nausea, vomiting, and yellow-colored urine was elicited. Clinical examination of the patients for ascites and right hypochondrial tenderness has been done and recorded. Venous blood sample was taken to analyze complete blood count, serum AST, and ALT. The magnitude of serum aminotransferases and alkaline phosphatase (ALP) was obtained from the patient's venous blood sample to assess the liver function. It was planned to do ultrasonogram abdomen, serum hepatitis B surface antigen, and activated prothrombin time in patients whose liver enzymes were found to be elevated more than 3 times of normal. However, as there was no such elevation in any of the patients, they were not done. The results were statistically analyzed.

RESULTS

This study was conducted on 150 epileptic patients among them were 86 male and 64 female patients with their age ranging from 18 to 60 [Table 1].

Among these 36 patients were on carbamazepine therapy, 40 patients were on sodium valproate, 24 patients were on phenytoin therapy, and 9 patients were on phenobarbitone as monotherapy. As a whole, 109 patients were on

monotherapy and the rest 41 were on combination therapy with either of the following combinations – phenytoin, sodium valproate, phenobarbitone, and carbamazepine [Figure 1a and b].

Adverse drug reactions like loss of appetite were present in 17.3% and a history of yellow-colored urine was present in 19.3% of patients [Figure 2].

Table 1: Demographic profile of patients	
Demographic profile	n (%)
Age (years)	
18–20	11 (7.3)
21–30	30 (20)
31–40	41 (27.3)
41–50	34 (22.7)
51–60	34 (22.7)
Sex	
Male	86 (57.3)
Female	64 (42.7)

Table 2: Investigation reports: Complete blood count	
Parameters	n (%)
Anemia	
Mild	13 (8.6)
Moderate	3 (2)
Severe	2 (1.4)
Thrombocytopenia	Nil
Leukopenia	Nil
Leukocytosis	8 (5.3)

Table 3: Liver function

Enzyme alterations (number of patients) (%)								Serum albumin	Serum bilirubin
SGOT elevations			SGPT elevations			ALP			
1–2 times	2–3 times	>3 times	1–2 times	2–3 times	>3 times	Increased	Decreased		
4 (2.7)	Nil	Nil	1 (0.7)	Nil	Nil	14 (9.3)	3 (2)	Nil	Nil

SGOT: Serum glutamic-oxaloacetic transaminase, SGPT: Serum glutamate-pyruvate transaminase, ALP: Alkaline phosphatase

Blood investigations for anemia, leukopenia, leukocytosis, and thrombocytopenia were done which revealed mild anemia in 8.6% of patients [Table 2].

The liver function was assessed by measuring the serum AST, ALT, and ALP levels with a reference range of 10–40 IU/L, 7–56 IU/L, and 44–147 IU/L, respectively. Serum bilirubin and albumin were also measured with a reference range of 0.1–1.2 mg/dl and 3.5–5.5 g/dl among the 150 patients, only 2.7% showed serum glutamic-oxaloacetic transaminase elevations 1–2 times above the normal value. ALP levels were increased in 9.3% of patients [Table 3].

DISCUSSION

This study which had been approved by the institutional committee was carried out as a cross-sectional study in a tertiary care center of South Tamil Nadu strictly on accordance with the exclusion and inclusion criteria. The study evaluated any impairment of liver function in patients who were on long-term treatment for epilepsy.

Demographic data showed a preponderance of male among 150 patients taking AEDs. About 27.3% of patients were in the age group between 30 and 40 years. Majority of the patients were on monotherapy and few were on combination therapy. Among those on monotherapy, sodium valproate was taken by maximum number of patients (26.7%). Sodium valproate and carbamazepine combination formed the major part among patients on combination therapy.

History on adverse drug reactions revealed yellow-colored urine in 19.3% and loss of appetite in 17.3% of patients. The

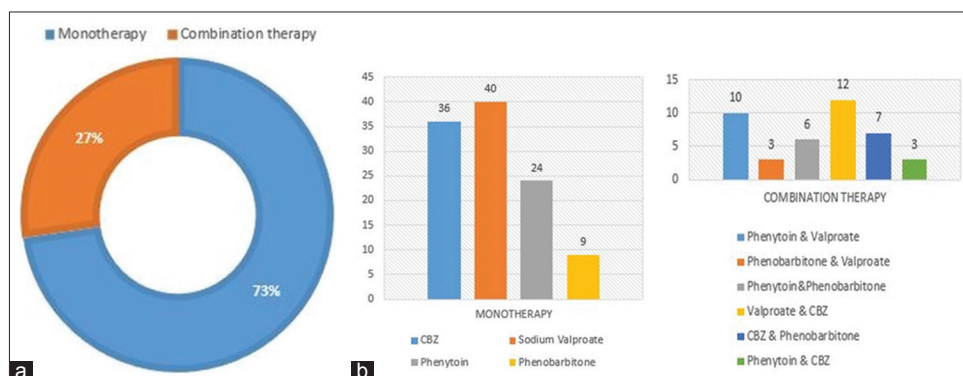


Figure 1: (a) Treatment given; (b) monotherapy and combination therapy

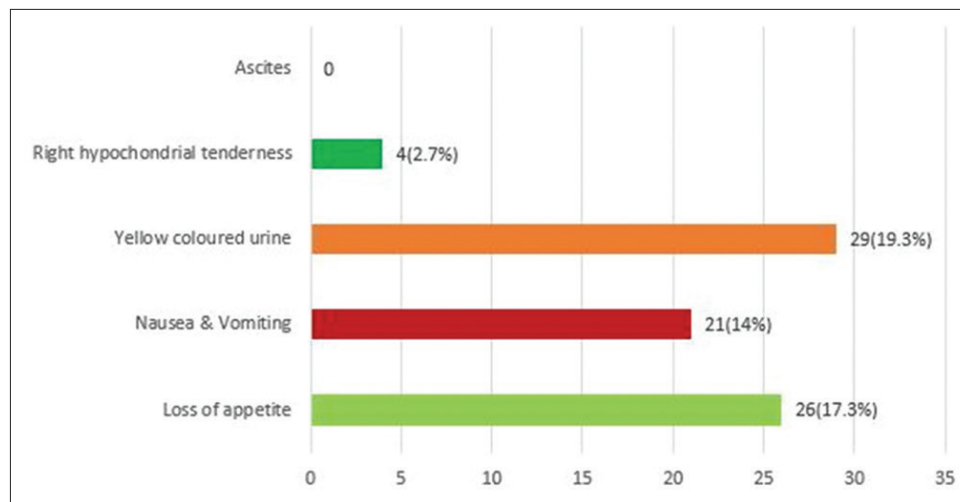


Figure 2: Adverse drug reactions profile

right hypochondrial tenderness was observed in only 2.7% of patients. The observation on complete blood count on 150 patients revealed apparently no thrombocytopenia or leukopenia, whereas anemia and leukocytosis were noted in few patients. Anemia was seen in eight patients. Mild, moderate, and severe anemia were observed in patients who were on monotherapy and combination therapy with sodium valproate and carbamazepine. As peripheral smear and other investigations such as serum iron, B12, or folic acid were not done, the causes of anemia in these individuals were not known. The incidence of mild anemia was higher in females as compared to males. Leukocytosis was observed in eight patients accounting about 5.3% of the total sample size. Serum bilirubin and albumin were normal in all the patients.

The serum AST levels were found to be elevated in four patients who were on monotherapy with sodium valproate^[7] or phenytoin or phenobarbitone which is in accordance with the study done by Verma and Haidukewych who showed a significant correlation between sodium valproate or phenobarbital and AST. AST elevations were about 1–2 times the normal values in this study and it is not significant which might be due to reduced dose used in these patients. ALT enzyme elevation was observed only in one male patient who was on sodium valproate^[8] as monotherapy, as seen with the study done by Hadzagic-Catibusic *et al.* who showed a significant elevation in ALT in patients on valproate. However, the elevated values in this study were not statistically significant which could be attributed to the dose and reduced duration of treatment, as we included all patients who were on AEDs for a minimum duration of 6 months.

Altered levels of serum ALP were observed in 17 patients and the levels were both increased and decreased. Fourteen of them showed increase in serum ALP and the rest showed decrease in the levels of ALP. Although the altered values were not statistically significant, the serum ALP levels were comparatively more elevated in the patients who were on

phenytoin^[9] as monotherapy than that of other drugs. This is in contrary as seen with the observation by Hussein *et al.* who showed that ALP elevation was more statistically significant with the administration of carbamazepine than other drugs. Patients on sodium valproate as monotherapy and carbamazepine^[10] or phenytoin^[11] as combination therapy showed leukocytosis. This was seen with the study done by Allam *et al.* and Gungor *et al.* Thus, compared to other drugs, sodium valproate and phenytoin have more negative correlation with the liver enzymes though levels being statistically insignificant.

Strength of the Study

All the patients included in the study were analyzed for the liver enzymes making the analyses completely comparable. The magnitude of the elevation of liver enzymes was obtained to assess the liver function.

Limitations

We included all patients taking AEDs for a minimum period of 6 months. We did not categorize patients on how long they were on AEDs and also the dosage pattern of each patient. If the data on dosage and duration were known, we could have correlated it to the rise in liver enzymes noted in few patients in this study.

CONCLUSION

To conclude, only a mild elevation of AST levels were seen in patients on sodium valproate, phenytoin and phenobarbitone. Comparatively, mild serum ALT levels were raised in patients who were on sodium valproate than any other drugs. Serum ALP levels were raised in patients taking phenytoin. Leukocytosis was seen in few patients on AEDs. The alteration in the levels was statistically insignificant.

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How to cite this article: Radha M, Rani A, Meenakshi B, Raj I. Estimation of liver enzymes in patients taking antiepileptic drugs in a tertiary care center: A cross-sectional study. *Natl J Physiol Pharm Pharmacol* 2019;9(10):950-954.

Source of Support: ICMR-STs, **Conflict of Interest:** None declared.