



Study of Liver Enzymes Levels in Patients on Antiepileptic Therapy

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Abstract

Background: Antiepileptic drugs induce and increase production of hepatic enzymes. The adverse metabolic effects of antiepileptic therapy have become main concern. The routine screening of hepatic enzymes during the chronic use of antiepileptic drug is recommended. **Aim:** To determine the correlation between liver enzymes and antiepileptic drugs. **Methods:** The study includes 50 neurosurgery patients who took antiepileptics for more than 6 months, including patients with single drug regime and multi drug regime for seizure control. Single drug regime includes patients on phenytoin, multidrug regime includes patients on treatment with phenytoin, sodium valproate, levetiracetam and carbamazepine. Liver enzymes estimated by IFCC method. LFT samples run by fully auto analyser. **Results:** In this study, the AST and ALT levels were not found to be raised in study patient's group. ALP levels were raised in patients on multidrug regime. However, the levels were not significantly raised. **Conclusion:** Patients on Antiepileptic therapy should be regularly checked for LFT especially on patients with multi drug therapy. As early detection and treatment can prevent the further complications and will be helpful during the management of patients on Antiepileptic therapy.

Keywords: Antiepileptic drugs, Epilepsy, Hepatotoxicity, Liver enzymes

1. Introduction

Epilepsy is not a singular disease but rather a syndrome encompassing various cerebral disorders of the Central Nervous System (CNS), characterized by excessive and abnormal neuronal discharges¹. It is a highly disabling condition, particularly distressing due to its unpredictable nature, and remains one of the most common neurological disorders globally².

The liver plays a central role in the metabolism and elimination of many Antiepileptic Drugs (AEDs), making it particularly susceptible to drug-induced toxicity. Hepatotoxic responses can range from mild, transient elevations in liver enzymes to severe and potentially fatal hepatic failure³.

1.1 Aim

To evaluate the impact of antiepileptic drug therapy on liver enzyme levels in patients with epilepsy, comparing

those on monotherapy with those on multidrug regimens.

1.2 Objectives

1. To measure and compare serum levels of liver enzymes—AST, ALT, and ALP—in patients on single versus multiple Antiepileptic drugs.
2. To assess the association between Antiepileptic drug regimens and the risk of hepatic enzyme elevation.
3. To identify the need for routine liver function monitoring during Antiepileptic drug therapy.

1.3 Review of Literature

Liver enzymes serve as useful biomarkers of hepatic injury. Enzymes such as Aspartate Aminotransferase (AST) and Alanine Aminotransferase (ALT) indicate hepatocellular damage, while Alkaline Phosphatase (ALP) and Gamma-Glutamyl Transferase (GGT) are associated with cholestasis. However, elevations in

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these enzymes may not always signify liver pathology, as they can also result from enzyme induction triggered by certain medications⁴.

Among the commonly used AEDs—carbamazepine, valproic acid, and phenytoin have serious adverse effects, including hepatotoxicity, have been documented. Although less frequent compared to other well-known hepatotoxic agents, AED-induced liver injury can be life-threatening, potentially leading to acute liver failure and necessitating liver transplantation. The mechanisms underlying such toxicity may include the formation of reactive metabolites or immune-mediated hypersensitivity reactions^{5,6}.

These AEDs are often associated with mild elevations in liver enzymes, occurring in up to 50% of patients. Typically, these elevations are dose-dependent or transient and are not indicative of actual liver cell damage. However, hepatotoxicity is more likely when accompanied by signs of drug allergy, such as fever, rash, and eosinophilia—reactions often observed with carbamazepine and phenytoin. In contrast, valproic acid is known to cause idiosyncratic hepatotoxic reactions due to the production of toxic metabolites via abnormal metabolic pathways³.

A persistent increase about more than two- to threefold in liver enzyme levels during AED therapy should alert the clinician to the possibility of underlying liver disease. If enzyme levels continue to rise on follow-up, further evaluation for coexisting hepatic pathology is warranted, and a change in the antiepileptic medication may be necessary⁴.

In light of these concerns, the present study was undertaken to evaluate the effects of antiepileptic drugs on liver enzyme levels as in table 1.

2. Materials and Methods

2.1 Study Setting

A cross-sectional study was conducted in the Department of Neurosurgery and Biochemistry, Thanjavur Medical College, Thanjavur, Tamil Nadu over a period of three months from November 2024 to February 2025.

2.2 Study Population

The study participants were divided into two Groups - 1 and 2 patients on antiepileptics with multi drug and single

Table 1. Metabolism of antiepileptic drugs

Table 1 Metabolism of AEDs		
Predominantly metabolized by the liver	Partially metabolized by the liver	Extrahepatic metabolism or excretion
Benzodiazepines	Leviteracetam	Gabapentin
Carbamazepine	Topiramate	Vigabatrin
Ethosuximide	Zonisamide	
Felbamate		
Lamotrigine		
Oxcarbazepine		
Phenobarbital		
Phenytoin		
Tiagabine		
Valproate		

drug regime respectively. In Group 1, 25 patients on multi drug regime persons without any comorbidity of both genders were included in the study. In Group 2, 25 patients on single drug regime persons without any comorbidity of both genders were included. Patients with associated, liver diseases, cancer, pregnancy or alcoholism and drugs causing elevation of liver enzymes such as antibiotics, anti-rheumatic drugs, statins and non-steroidal anti-inflammatory drugs were excluded from the study.

2.3 Study Methodology

The blood samples were collected from both the group patients who were on multi drug and single drug regime antiepileptics respectively who attended Neurosurgery OPD, Thanjavur Medical College Hospital Thanjavur. About 2 mL of venous blood was taken from antecubital vein, serum transaminases (AST and ALT) and Alkaline Phosphatase were estimated in serum. Liver transaminases (AST, ALT) and ALP were analyzed by IFCC method in fully automated general chemistry ERBA XL-640 analyzer.

2.4 Statistical Analysis

Continuous variables like age, serum AST, ALT, ALP levels were expressed in terms of mean and standard deviation. A comparison of these parameters between the two groups was done using the independent samples two-tailed t-test. IBM SPSS software version 21 was used for the analysis and P value of less than 0.05 was considered to be statistically significant.

3. Results

The data was obtained from a total of 50 study participants. They were divided into two Groups – 1

Table 2. Biochemical parameters among the study population

S. No	Biochemical Parameters	Group 1 (Multi Drug Regime Therapy) Mean (SD)	Group 2 (Single Drug Regime Therapy) Mean (SD)	P Value
1	AST	21.280±6.75	23.560±5.88	0.209
2	ALT	24.560±8.71	27±10.93	0.387
3	ALP	155.00±67.92	82.56±24.64	0.000*

*Significant P value

and 2. Group 1 had 25 patients with multi antiepileptic regime therapy and group 2 had 25 patients with single antiepileptic regime therapy respectively. All the study participants who were approached agreed to take part in this study and the response rate was 100%.

In this study, the AST and ALT levels were not found to be raised in study patient's group. In Group 1*mean (SD) of serum AST 21.280±6.75 and in Group 2* it was 23.560±5.88 and the p value was not significant. In Group 1*mean (SD) of serum ALT 24.560±8.71 and in Group 2* it was 27±10.93 and the p value was not significant. In Group 1*mean (SD) of serum ALP 155.00±67.92 and in Group 2* it was 82.56±24.64 and the p value was significant as in table 2.

*Group 1- patients on multi antiepileptic drug regime

*Group 2- patients on single antiepileptic drug regime

On observing correlation using Pearson's correlation coefficient, it is found that ALP levels showed highly significant positive correlation with patients on multi drug antiepileptic regime ($p < 0.001$).

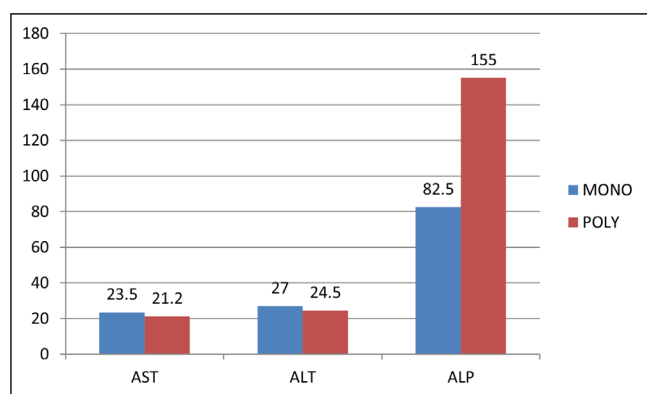


Figure 1. Distribution of serum liver enzymes among multi and single antiepileptic drug regime.

4. Discussion

The present study was conducted on 50 patients, 25 patients on multi antiepileptic drug regime and 25 patients on single antiepileptic drug. All patients were submitted to through history, medical and neurological examination, measurement of serum liver enzymes. Patients using multi drug therapy had significantly higher ALP than those using phenytoin, but there was no statistically significant difference between the two groups regarding AST or ALT.

Christiansen *et al.*, and O'Hare *et al.*, attributed the alterations in liver enzyme levels to the enzyme-inducing properties of carbamazepine, which stimulate hepatic microsomal enzyme activity^{7,8}. Deda *et al.*, reported a statistically significant positive correlation between serum carbamazepine concentrations and serum Alkaline Phosphatase (ALP) levels⁹. Sonmez *et al.*, suggested that inconsistencies among study findings may be due to variations in patient characteristics such as age, gender, and ethnicity; differences in methodologies; and disparities in study protocols¹⁰. Additionally, the administered doses of antiepileptic drugs may have been insufficient to produce notable elevations in liver enzyme levels.

Moreover, Spiller *et al* reported that valproic acid mediated hepatic injury is associated with dose dependent rise in serum liver enzymes¹¹. Sussman *et al.*, noted that valproic acid-associated hepatotoxicity is distinct from the form of dose-related liver enzyme elevation that appears to be reversible with a reduction in dosage or discontinuation of the drug¹².

Patients receiving phenytoin exhibited significantly lower ALP levels compared to those treated with carbamazepine or sodium valproate. However, no statistically significant differences were observed between the groups in terms of AST or ALT levels. Additionally, findings indicated no significant

correlation between the duration of phenytoin use and liver enzyme levels. Craig *et al.*, reported no significant association between serum phenytoin levels and the risk of hepatotoxicity¹³. In contrast, Perucca *et al.*, suggested a dose-dependent induction of hepatic enzymes in epileptic patients treated with therapeutic doses of phenytoin¹⁴. Similarly, Spielberg *et al.*, demonstrated a dose-dependent hepatotoxic effect of phenytoin¹⁵.

The present study demonstrated that patients on a multidrug antiepileptic regimen had significantly higher ALP levels compared to those receiving phenytoin monotherapy. Additionally, liver enzyme elevations were observed during the initial phase of antiepileptic treatment, likely due to the enzyme-inducing effects of these drugs. This was particularly evident within the first six months of therapy, as our study included patients who had been on antiepileptic medication for at least six months. Over time, however, liver enzyme levels may normalize despite continued drug use, possibly due to hepatic adaptation—an observation supported by Bjornsson. This adaptive response may explain the statistically significant negative correlation found between the duration of antiepileptic drug use and AST and ALT levels.

5. Conclusion and Recommendations

Our findings indicate that multi drug regime exhibits greater hepatotoxicity compared to single drug (phenytoin). Therefore, it is strongly recommended to perform baseline liver function tests prior to initiating antiepileptic therapy. Routine monitoring of hepatic enzyme levels should be conducted, especially in patients with risk factors for liver damage.

Special precautions must be taken when prescribing antiepileptic drugs to individuals with pre-existing liver conditions, those concurrently taking other potentially hepatotoxic medications, or in cases where clinical signs of hepatic impairment emerge.

6. Summary

Epilepsy is a neurological syndrome characterized by abnormal neuronal discharges, often managed with Antiepileptic Drugs (AEDs). Many AEDs are

metabolized in the liver, which increases the risk of hepatotoxicity. This study evaluated liver enzyme levels in 50 epilepsy patients on either phenytoin monotherapy or multidrug antiepileptic regimens. While AST and ALT levels showed no significant difference between the groups, ALP levels were significantly elevated in the multidrug group, indicating increased hepatic stress.

Literature supports that AEDs like carbamazepine and valproic acid can induce liver enzymes or cause hepatotoxicity. Phenytoin was associated with lower ALP levels and minimal hepatic impact. Findings highlight the need for baseline liver function tests and regular monitoring during AED therapy. Special caution is advised for patients with existing liver conditions or those on other hepatotoxic medications.

6.1 Limitations

The main limitation is shorter follow up period and prolonged follow up is necessary to determine long term side effects of antiepileptic therapy.

7. References

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