Original Article

Effects of Carbamazepine on liver markers of Epileptics in Ogun State, Nigeria

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ABSTRACT

Epilepsy is one of the commonest neurological diseases caused by an abnormal electrical discharge of brain neurons. Carbamazepine (CBZ) is widely used for the treatment of epilepsy. However, despite its use, it is not without effects on biochemical parameters. This study evaluated the effects of carbamazepine on plasma biochemical parameters in epileptics. Epileptics (n = 100) with different seizure types and age 18 – 50 years from Out Patient Clinic (OPC) in Neuropsychiatric Hospital, Abeokuta, Nigeria and sex-matched control (n = 100) from Federal University of Agriculture, Abeokuta were used. These epileptics were on CBZ for ≥ 6 months. Biochemical parameters such as Aspartate transaminase (AST), Alanine transaminase (ALT), Alkaline phosphatase (ALP), Lactate dehydrogenase (LDH) and Gamma Glutamyl Transferase (GGT) were determined in plasma. The results revealed that epilepsy is common in male than female subjects. By sex, AST, GGT and LDH increased significantly ($p<0.05$) by 18%, 30% and 2fold in male and 24%, 42% and 1fold in female epileptics compared to their respective controls. By age, GGT increased significantly ($p<0.05$) in subjects between 18 – 20years, and 31- 40 years as compared to the control. LDH activity also increased significantly ($p<0.05$) between 18 – 20 years in epileptics compared to control. Based on seizure types, ALT activity increased significantly in male with focal seizure (28. 15 ± 5.28 U/L) compared with male generalized seizure (22.47 ± 2.1.70 U/L) and unclassified seizure (19.58 ± 3.44 U/L). It is concluded that treatment with carbamazepine for at least six months causes an alteration in the plasma liver enzymes of epileptic subjects.

Keywords: Carbamazepine, Epilepsy, Hepatic Enzymes

INTRODUCTION

Epilepsy is one of the commonest neurological diseases. Any of the following conditions defines it: At least two unprovoked (or reflex) seizures occurring > 24 h apart, one unprovoked (or reflex) seizure and a probability of further seizure similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next ten years and diagnosis of an epilepsy syndrome[1]. It is a multifaceted neurological disease, characterized by recurrent spontaneous seizures arising from abnormal and uncontrollable electrical firings of a group of neurons appearing in the central nervous system[2]. Epilepsy occurs in all age groups, races, social classes, and geographical locations. It is connected with a burden of socio-economic, behavioral, psychiatric, and other medical issues for both the patient and their close ones [1,3]. Epileptogenesis is the process of structural modifications leading to seizure activity in a normal

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brain[4]. Several hypotheses have been proposed to explain the underlying etiopathogenesis of epilepsy, including neurodegeneration[5, 6], disturbance of the brain-blood barrier (BBB)[7], amygdala dysregulation, alterations of the glutamatergic system[8], oxidative stress [9], hypoxia [10], and the epigenetic modification of DNA[11].

There are various means adopted to manage and probably also cure epilepsy. Drugs used are termed antiepileptic drug (AEDs). The term antiepileptic is used synonymously with anticonvulsant to describe drugs that are used to treat "epilepsy" (which does not necessarily cause convulsions) as well as "non-epileptic" convulsive disorders [12]. Existing anti-epileptic drugs provide adequate seizure control in about two-thirds of patients, they exhibit similar pharmacokinetic properties including those with diverse structural and chemical properties because most have been selected for oral activity and all must enter the central nervous system. [13]

Carbamazepine is an antiepileptic drug, chemically related to the Tricyclic Antidepressants. It is an iminostilbene -derivative with a carbamyl moiety at the 5th position of the molecule. [14]. CBZ is used for the treatment of epilepsy and non-epileptic seizures (e.g in multiple sclerosis, withdrawal of addictive drugs), for the treatment of certain pain conditions (e.g nerve pain due to trigeminal neuralgia or diabetic neuropathy) and for the treatment of certain mental illnesses (e.g, preventing manic phases in bipolar disorders) [15]. Its main function is reduction of sustained repetitive firing in neurons by blocking voltage-gated sodium channels [16]. The metabolism pathway of CBZ includes oxidation, deamination, hydroxylation, and esterification with glucuronic acid. The liver enzyme CYP_{450} 3A4 is the main enzyme that metabolizes it to its active metabolite carbamazepine-10,11-epoxide, which is further metabolized by the enzyme epoxide hydrolase. Along with Carbamazepine-10,11-epoxide, further identified metabolites are: 10,11 Dihydroxycarbamazepine, Carbamazepine 2,3-epoxide, 2 Hydroxycarbamazepine, 2 Hydroxyiminostibene, Carbamazepine-iminoquinon, 3-Hydroxycarbamazepine, 2,3-Dihydroxycarbamazepine and Carbamazepine-O-quinone. [15] This epoxide metabolite is thought to contribute to central nervous system toxicity and other untoward adverse effects. In addition, with chronic use, CBZ can induce its own metabolism (autoinduction), and it is a potent inducer of several of the cytochrome (CYP) P450 enzymes and uridine - glucuronyl transferases (UGT). [17,18,] CBZ exerts its therapeutic effects through the inhibition of brain neuronal activities, used for the treatment of seizure disorders and trigeminal and other neuralgias [19]. Severe liver failure is much less common in individuals using the drug, but has been reported with CBZ therapy [20].

MATERIALS AND METHOD

Study setting

The study was carried at Neuropsychiatric Hospital Aro, Abeokuta Along Lagos - Abeokuta Expressway. The study was conducted within the space of four months (May – August, 2017).

Chemicals

All chemicals and reagents were of analytical grade. Reagent Diagnostic Kits used for the determination of Aspartate Transaminase (AST), Alanine Transaminase (ALT), Alkaline Phosphatase (ALP), Lactate dehydrogenase (LDH) and Gamma Glutamyl Transferase (GGT) were obtained from Linear Chemicals (Cromatest), Montgat, Barcelona, Spain, Teco Diagnostics, California, U.S.A and Cypress Diagnostics, Langdorp, Belgium.

Subjects

One hundred (100) chronic epileptic patients (male = 64 and female = 36) with different seizure types (focal, generalized and unclassified) were included in this present study. The patients must have been on carbamazepine for at least 6 months. Epileptic patients were randomly recruited from the out - patient epilepsy clinic, Neuropsychiatric Hospital, Aro, Abeokuta, Ogun State, Nigeria. One hundred (100) normal healthy (age - and sex - matched) volunteers served as a control group. This study was accepted by the Ethical committee Department of Biochemistry, Federal University of Agriculture, Abeokuta Ogun State Nigeria. A consent form which contains comprehensive information on the study was given to each patient and all subjects gave their written consent to participate this study.

Study criteria

Inclusion criteria

1. All patients who participated in the study were diagnosed epileptic
2. Both sexes were involved ranging from 18 to 50 years of age
3. Patients had no other health problems or metabolic diseases,
4. All patients underwent electroencephalography (EEG) for a definitive diagnosis and must have been on carbamazepine for at least six months.

Exclusion criteria

1. Patients who were less than eighteen years,
2. Patients who were alcoholic,
3. Patients who had other chronic diseases as kidney, liver, heart or endocrine diseases
4. Patients who were receiving any drug that could alter lipid profile or liver function.

Pre - clinical assessment

Subjects included in this study were subjected to careful history taking, general and neurological examination "according to standardized neurological sheet" including the name, tribe, age, gender, weight of each epileptic patient, the duration of illness and therapy and type of seizure.

Blood sample collection

Subjects under this study were advised to fast overnight (12 hours) and sample was collected in fasting condition. Blood samples (10.0 ml) were collected between 08:00 am and 12.00 noon on each clinic day from the vein of the epileptic subjects and control. Blood samples were separated into plasma and erythrocytes by centrifuging the whole blood at 4000 rpm for 10 minutes. The plasma was then removed and stored in Eppendorf tubes for further analyses.

Serum Biochemical Examination

Alkaline Phosphatase (ALP) Activity, Phenolphthalein monophosphate method for the in vitro determination of alkaline phosphatase in plasma using Labkit (LBK) test kit. Alanine Aminotransaminase (ALT) activity was determined by the Reitman-Frankel [21] colorimetric method Persijn and van der Slik[22] for invitro determination of GPT ALT in plasma using Randox test kit. Alanine aminotransaminase also called glutamic-pyruvate transaminase (GPT) catalyses the transfer of α-amino group from alanine to α-ketoglutarate with the release of pyruvate and glutamate. Aspartate Aminotransaminase (AST) activity was determined by the Reitman-Frankel colorimetric method [21] for invitro determination of AST in plasma using Randox test kit. AST was measured by monitoring the concentration of oxaloacetate hydrazone formed with 2,4-dinitrophenylhydrazine which is proportional to its concentration at 505nm.

Statistical analyses

Values were expressed as mean ± standard error mean deviation (SEM). The level of homogeneity among the results of groups was tested using analysis of variance (ANOVA) and $p < 0.05$ was considered significant. Where heterogeneity occurred, the groups were separated using Duncan and Tukey's Multiple Range Test (DMRT). All analyses were done using Statistical Package for Social Sciences (SPSS) version 17

RESULTS

Effects of carbamazepine on plasma liver of epileptics based on gender

From the result in table 1, there was a significant ($p < 0.05$) increase in the activity of AST, LDH and GGT of both male and female epileptics when compared with their respective control. The changes in the activity of AST in male epileptics was not significantly ($p > 0.05$) different from the female epileptics. There was no significant ($p > 0.05$) difference in the activity of ALP in both male and female epileptics when compared with their control

Effects of carbamazepine on plasma liver of epileptics based on age

Table 2.0 results showed that there were no significant ($p > 0.05$) differences in the activity of AST, ALT and ALP in all the age groups when compared with their respective control. There was a significant ($p < 0.05$) increase in the activity of LDH in age group 18 – 20 in epileptics when compared with the control. GGT activity increase significantly

($p < 0.05$) across all the age groups when compared with the control.

Effects of carbamazepine on plasma liver epileptics based on seizure types

Classifying the epileptics based on their seizure types, results showed that there was a significant ($p < 0.05$) difference in the activity of ALT in male epileptics with focal seizure when compared with the female epileptics with the same seizure type. There was no significant ($p > 0.05$) difference in the activities of AST, ALP, LDH and GGT in all the seizure group (Table 3).

Table 1: Effects of Carbamazepine on liver markers of epileptic subjects based on gender

	Control male (n = 50)	Epileptic male (n = 64)	Control female (n = 55)	Epileptic female (n = 36)
AST	42.15±1.51^{a}	50.10±2.08^{bc}	45.32±1.65^{ab}	56.03±3.27^{c}
ALT	26.33±1.63^{b}	20.08±0.97^{a}	25.33±1.31^{b}	22.91±1.57^{ab}
ALP	36.00±1.02^{a}	34.12±1.34^{a}	32.60±1.12^{a}	32.61±1.82^{a}
LDH	149.05±6.27^{a}	193.68±9.38^{b}	135.93±3.11^{a}	193.09±11.03^{b}
GGT	2.22±0.10^{a}	7.41±0.42^{b}	2.18±0.88^{a}	6.15±0.47^{b}

Table 2: Effects of Carbamazepine on liver markers of epileptic subjects based on age

Age		AST	ALT	ALP	LDH	GGT
18-20 years	Control (n = 49)	47.53±1.99^{a}	22.26±1.36^{a}	34.10±1.18^{a}	140.56±5.03^{a}	2.31±0.11^{a}
	Epileptic (n = 11)	48.54±4.73^{a}	19.93±2.63^{a}	35.19±2.86^{a}	225.6 ±2.00^{b}	6.34±0.45^{b}
21-30 years	Control (n = 56)	41.46±1.39^{a}	24.74±1.70^{a}	35.12±1.27^{a}	141.78±4.55^{a}	2.08±0.83^{a}
	Epileptic (n = 30)	51.55±2.99^{a}	22.03±1.93^{a}	34.37±2.05^{a}	163.76±7.22^{ab}	1.95±0.17^{a}
31-40 years	Control (n =5)	37.83±7.39^{a}	19.32±3.31^{a}	35.13±1.62^{a}	165.70±14.70^{ab}	1.95±0.17^{a}
	Epileptic (n = 27)	43.90±2.47^{a}	22.15±1.57^{a}	31.62±1.54^{a}	177.68±12.50^{ab}	7.62±0.63^{b}
41-50 years	Control (n = 3)	45.22±7.48^{a}	28.30±12.97^{a}	37.01±0.86^{a}	141.79±0.00^{a}	1.86±0.46^{a}
	Epileptic (n = 6)	41.45±9.68^{a}	20.11±2.27^{a}	29.02±2.42^{a}	181.44±24.30^{ab}	4.95±0.91^{ab}

Table 3: Effects of Carbamazepine on liver markers of epileptic subjects based on seizure types

	Focal Seizure		Generalized Seizure		Unclassified Seizure	
	Male (n =11)	Female (n = 6)	Male (n = 31)	Female (n = 23)	Male (n= 24)	Female (n = 7)
AST	53.57±4.94[a]	59.67±9.88[a]	47.16±3.11[a]	55.29±4.33[a]	51.51±3.73[a]	61.44±7.20[a]
ALT	20.47±2.14[a]	28.51±5.28[b]	21.44±1.50[ab]	22.47±1.70[ab]	18.69±1.74[a]	19.58±3.26[a]
ALP	36.15±3.82[a]	40.36±5.50[a]	34.82±2.42[a]	30.66±1.62[a]	32.99±1.62[a]	27.87±3.44[a]
LDH	225.75±22.39	171.63±10.29[a]	172.64±12.82[a]	196.93±15.13[a]	208.25±17.82[a]	199.44±27.88[a]
GGT	7.01±0.61	5.20±1.09[a]	7.06±0.57[a]	5.91±0.39[a]	7.64.0.81[a]	7.62±1.86[a]

DISCUSSION

The primary organ of drug metabolism and elimination, including anti-epileptic drugs (AEDs) is the liver and it is subjected to drug-induced toxicity from mild and transient elevations of the hepatic enzymes to fatal hepatic failure. CBZ has been evaluated to be potent enzyme inducers and induce cytochrome P450 system [23,24]. The hepatotoxicity caused by carbamazepine may either be as a result of the production of reactive active metabolites (carbamazepine-10,11-epoxide), immune-allergic reactions or obstruction in bile flow, cholestasis [25]. Results from this study show an elevation of AST in male epileptic subjects (50.10 ± 2.08 U/L) compared to the control (42.15 ± 1.51 U/L). Female epileptic subjects also experienced elevation (56.03 ± 3.27 U/L) in AST level when compared with the control (45.32 ± 1.65 U/L). This finding agrees with the report of Mathew *et al.*, (2016) [26] and Maghoub *et al.* [27] who reported a significant increase in AST level ($P < 0.001$) of 96 % in epileptic subjects. Serum levels of GGT is determined by several factors: alcohol intake, body fat content, plasma lipid/lipoproteins, glucose levels, and various medications. GGT is cleared from the plasma by liver uptake. It is well-known that administration of carbamazepine may cause the elevation of serum levels of AST, ALT, and GGT in adults. Present investigation witnessed a significant increase in GGT, a 2fold increase was noticed in male epileptics, while a 1.8-fold increase was observed in female epileptics. It has been established that most patients on CBZ therapy will develop mild-to-moderate elevations in GGT level that are likely indicative of hepatic enzyme induction as opposed to liver injury[28,29,30]. However, a marked increase in aminotransferase (> 5-fold increase) occurs less frequently and is indicative of hepatotoxicity or an alternative type of liver injury [31].

LDH shows in a significant increase in all the groups. The increase was more significant in the age specific group where epileptic subjects within the age range (18-20) experience a mark elevation (225.63 ± 28.00 U/L) when compared with the control (140.56 ± 5.03 U/L). Aliyu *et al.* (2013) [32] reported an increase in LDH in CBZ polytherapy which was in accordance with the findings of this research. ALT and ALP remained unchanged in all the groups.

In contrast to this present study was the report of Ahmed *et al*. (2006) [33] who conducted a study on "anti-epileptic drugs and liver disease" to assess liver functions and hepatotoxicity during anti-epileptic drug therapy. A few weeks to a month's therapy with carbamazepine, there was a modest elevation of ALT and ALP. In the research of Amhimmid *et al.* (2024)[34] an increase in AST, GGT, and LDH was observed in the research. Anti-epileptic drugs such as CBZ, PHT and VPA

are commonly associated with mild elevations of liver enzymes. These elevations are usually transitory or dose-related and do not appear to be associated with hepatocellular injury [35]. This agrees with the findings from this research. Various researchers have related the elevation of liver enzyme levels either to the induction property of hepatic enzymes of some AEDs as CBZ and PHT, or to the high doses used of AEDs during their study. In addition, some of the patients might receive their treatment for a long period, since this study included patients who received their treatment for at least 6 months. The results could also be affected by the age of participants, as this study included both adults, and perhaps some of them had liver dysfunction or other metabolic diseases. Naithani *et al.* (2010) [36] conducted a comparative study that had similar results to ours. They correlated serum concentration of CBZ, PHT and PB with liver enzymes in epileptic patients as monotherapy or combination therapy of two or three of the aforementioned AEDs. Their study included 123 epileptic patients and 60 healthy controls. In the CBZ-treated group, their results showed a significant positive correlation between serum CBZ concentrations and serum levels of AST and ALT (Naithani *et al.,* 2010) [36]. This dose related hepatic injury caused by CBZ was not observed in this present research. This could account for the probably polytherapy medication as observed in some subjects. Epileptic subjects whose medication has been exhausted might decide to use any available similar medication when in danger of seizure, this will alter the plasma carbamazepine level in the subjects, thereby resulting in variation. Bjornson, (2008) [37] observed in his report that during the first 6 months of subject on carbamazepine, the biomarkers increase significantly when compared with the control which could be termed to be an hepatic injury but with time, the plasma level or concentration of AEDs (CBZ) tends to normalize and hence this was concluded to be an adaptation of the subjects to the drug. This correlates with the findings of this study as the subjects recruited for the research had been on CBZ for at least 6 months; this means that some of the subjects recruited might have been on CBZ therapy for more than a year. This could be a major factor with respect to the un- alter level of ALT, ALP. Variations in these results can also be attributed to other factors, such as the age of the subjects, history of metabolic disorder, error in CBZ metabolism, unknown polytherapy lifestyle of the subjects, infections, and several underlying diseases, which may contribute to this variation. Increase in ALP has been linked to bone malformation and in this present study there was no increase in the activities of ALP in both epileptic subject and the control. In contrast to this report was the findings of Merete, (2005) [38] in which increase in ALP activity was observed in epileptic subjects on CBZ therapy.

CONCLUSION

This study which investigated the effects of carbamazepine on liver biomarkers, shows an increase in AST, GGT and LDH which did not result to hepatocellular damage but might be caused by the drug (CBZ) due to the auto induction of the CBZ metabolism enzymes. LDH was found to increase in all the groups. LDH has multiple biomarkers specificity for heart, muscle, therefore the increase in the activity as seen in the epileptic subjects especially in subjects with age ranges between 18 - 20 years might be associated with cardiac malfunction considering the age range.

RECOMMENDATION

From the studies, anti- epileptic drug (carbamazepine) does not induce hepatocellular injury in epileptics. Further studies should be carried in which the liver markers of the epileptic subject should be measured before treatment with carbamazepine.

Conflict of Interest

The authors declared no potential conflict of interest with respect to the research, authorship or publications of this article. We received no financial support for the research and /or publication.

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