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Biochemical, Metabolic, and Hematological Alterations Associated with Serum Carbamazepine Levels in Adult Epileptic Patients: A Cross-Sectional Correlation Study

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Abstract

Background: Carbamazepine (CBZ) remains one of the most widely used first-line antiepileptic drugs for focal and generalized tonic–clonic seizures. However, chronic CBZ therapy may lead to hepatic, metabolic, and hematological disturbances due to enzyme induction and oxidative stress.

Objectives: To evaluate biochemical, metabolic, and hematological alterations in adult epileptic patients receiving CBZ monotherapy and to correlate these parameters with serum CBZ concentrations.

Methods: A cross-sectional study was conducted on 96 adult epileptic patients (aged 16–72 years) receiving CBZ 300–800 mg/day for at least 15 days. Serum CBZ levels were measured by High-Performance Liquid Chromatography (HPLC). Biochemical (liver enzymes, renal and lipid profiles, electrolytes) and hematological (hemoglobin, leukocyte, and platelet counts) parameters were assessed. Patients were categorized as subtherapeutic (<4 mg/L), therapeutic (4–12 mg/L), or supratherapeutic (>12 mg/L). Data were analyzed using ANOVA and Pearson's correlation ($p < 0.05$).

Results: Patients with supratherapeutic CBZ levels exhibited significantly higher AST, ALT, ALP, and bilirubin ($p < 0.05$) and elevated cholesterol, triglycerides, and LDL levels. Conversely, hemoglobin, leukocyte, platelet counts, and serum sodium decreased with rising CBZ concentration ($p < 0.05$). Positive correlations were observed between CBZ levels and hepatic/lipid parameters, and negative correlations with hematological indices and sodium.

Conclusion: Chronic CBZ therapy induces significant biochemical and hematological alterations, especially at supratherapeutic concentrations. Regular biochemical monitoring alongside therapeutic drug monitoring (TDM) is essential to ensure efficacy, detect toxicity early, and guide individualized dosing.

Keywords: Carbamazepine, Therapeutic Drug Monitoring, Liver Enzymes, Dyslipidemia, Hematological Changes, Hyponatremia, HPLC, Epilepsy.

Introduction

Epilepsy is a prevalent neurological disorder characterized by recurrent, unprovoked seizures resulting from abnormal electrical discharges in the brain. Long-

term use of antiepileptic drugs (AEDs) is the mainstay of therapy, often extending over several years or even lifelong. Carbamazepine (CBZ) remains one of the most widely prescribed AEDs, favored for its proven efficacy in focal and generalized tonic–clonic seizures, affordability, and well-established clinical profile.[1] Despite these advantages, chronic CBZ therapy has been associated with several biochemical, metabolic, and hematological alterations that can affect patient safety and treatment outcomes.

CBZ induces hepatic microsomal enzymes, particularly cytochrome P450 isoenzymes, which can alter lipid metabolism, liver function, and endocrine pathways. Several studies have reported elevations in serum cholesterol, triglycerides, and low-density lipoprotein (LDL) among patients on long-term CBZ therapy[2]. Similarly, CBZ has been linked to increased bone turnover and reduced bone mineral density due to altered vitamin D metabolism[3]. These biochemical derangements can predispose patients to metabolic syndrome, hepatic dysfunction, or skeletal fragility with prolonged exposure. Hematological changes are another significant concern. Studies have identified CBZ-induced leukopenia, thrombocytopenia, and anemia, likely due to dose-dependent bone marrow suppression or immunologic reactions.[4] Furthermore, hyponatremia and hypo-osmolality, possibly caused by inappropriate antidiuretic hormone secretion, have been observed in chronic CBZ users[5]. Such biochemical imbalances can exacerbate seizure control difficulties and increase the risk of adverse drug reactions.

Additionally, CBZ may increase oxidative stress by elevating free radical levels and reducing total antioxidant capacity, potentially contributing to cellular damage and hepatic dysfunction[6]. These multidimensional effects underscore the importance of evaluating not only drug levels but also biochemical and hematological profiles during long-term CBZ therapy.

Given these findings, the present study aims to evaluate the biochemical, metabolic, and hematological alterations associated with serum CBZ levels in adult epileptic patients and explore their correlation with therapeutic ranges. This analysis supports the clinical need for integrated therapeutic monitoring combining drug concentration analysis with laboratory parameter assessment to ensure safe and effective management of epilepsy.

Materials and Methods

Study Design and Setting

This cross-sectional observational study was conducted in the Department of Medicine in collaboration with the Department of Pharmacology, J.L.N. Medical College, Ajmer (Rajasthan, India), after obtaining approval from the Institutional Ethics Committee (IEC). Written informed consent was obtained from all participants.

Study Population

A total of 96 newly diagnosed adult epileptic patients, aged 18–72 years, of either sex, receiving CBZ therapy were included. Patients were selected from the outpatient Medicine (neurology) department. Inclusion criteria were: (1) confirmed diagnosis of epilepsy, (2) treatment with CBZ for at least 30 days at doses ranging from 300–800 mg/day, and (3) no concurrent use of other antiepileptic or hepatotoxic drugs.

Exclusion criteria included: (1) pre-existing hepatic, renal, or hematological disorders; (2) pregnancy or lactation; and (3) poor treatment adherence or irregular dosing.

Sample Collection and Preparation

After an overnight fast, 5 mL of venous blood was drawn from each participant approximately 12 hours after the last CBZ dose (trough level).

- 2 mL of blood was collected in a plain vacutainer for biochemical and lipid assays.
- 2 mL in an EDTA tube for hematological analysis.
- 1 mL was centrifuged, and the serum stored at –20°C until CBZ estimation.

Serum Carbamazepine Estimation

Serum CBZ concentrations were measured using High-Performance Liquid Chromatography (HPLC) (YL 9100 HPLC system, YL instrument company limited Korea) with UV detection at 285 nm. Separation was achieved using a C18 column (250 × 4.6 mm, 5 µm particle size). The mobile phase consisted of methanol: water: acetic acid (65:34:1) at a flow rate of 1.0 mL/min. Calibration curves were linear in the range of 0.5–15 µg/mL. The intra- and inter-assay coefficients of variation were <5%.

Biochemical and Hematological Investigations

Biochemical analysis included

- Liver function tests – AST, ALT, ALP, and total bilirubin
- Renal function tests – serum urea and creatinine
- Electrolyte levels – sodium and potassium
- Lipid profile – total cholesterol, triglycerides, HDL, LDL, and VLDL
- Hematological parameters – hemoglobin, total leukocyte count (TLC), differential leukocyte count (DLC), platelet count, and erythrocyte indices (RBC, MCV, MCH, MCHC).

All assays were performed using automated analyzers (Erba Chem-7 Biochemistry Analyzer and Sysmex XN-1000 Hematology Analyzer) following standard laboratory protocols.

Statistical Analysis

Data were analyzed using SPSS version 25.0 (IBM Corp., USA). Continuous variables were expressed as mean ± standard deviation (SD). Patients were grouped according to serum CBZ levels as subtherapeutic (<4 mg/L), therapeutic (4–12 mg/L), and supratherapeutic (>12 mg/L). Comparisons among groups were made using one-way ANOVA followed by Tukey's post hoc test and Correlations between serum CBZ concentration and biochemical/hematological parameters were analyzed using Pearson's correlation coefficient. A p-value <0.05 was considered statistically significant.

Result

Among the 96 adult epileptic patients on CBZ monotherapy, liver function parameters increased progressively with rising serum CBZ levels, with the supratherapeutic group showing significantly higher AST (42.6 ± 10.5 U/L), ALT (39.2 ± 9.1 U/L), ALP (121.7 ± 27.8 U/L), and total bilirubin (1.01 ± 0.23 mg/dL) compared with subtherapeutic and therapeutic groups (Table 1; $p < 0.05$). A similar dose-related metabolic trend was observed in the lipid profile, where total cholesterol, triglycerides, LDL, and VLDL were significantly higher in the supratherapeutic category (e.g., cholesterol 202.4 ± 36.5 mg/dL, triglycerides 165.3 ± 40.2 mg/dL) while HDL showed a non-significant decline across groups (Table 2). In contrast, hematological indices decreased with higher CBZ concentrations, as evidenced by lower hemoglobin (11.7 ± 1.3 g/dL), total leukocyte count (5.9 ± 1.2 $\times 10^9$/L), platelet count (208.3 ± 51.6 $\times 10^9$/L), and RBC count (4.1 ± 0.5 $\times 10^{12}$/L) in the supratherapeutic group (Table 3; $p < 0.05$). Electrolyte assessment revealed a significant decline in serum sodium with increasing CBZ level (138.6 ± 3.9 → 132.5 ± 3.0 mmol/L; $p = 0.004$), whereas potassium and renal parameters (urea, creatinine) showed no statistically significant differences among groups (Table 4). Correlation analysis further supported these findings by demonstrating positive correlations between serum CBZ and hepatic/lipid markers (AST r = +0.41; ALT r = +0.46; cholesterol r = +0.38; triglycerides r =

+0.36; all $p < 0.01$) and negative correlations with key safety markers including hemoglobin ($r = –0.31$, $p = 0.012$), sodium ($r = –0.44$, $p = 0.002$), and platelet count ($r = –0.29$, $p = 0.018$) (Table 5).

Table 1: Liver function parameters in relation to serum carbamazepine levels

Parameter	Subtherapeutic (<4 mg/L)	Therapeutic (4–12 mg/L)	Supratherapeutic(>12 mg/L)	p-value
AST (U/L)	29.4 ± 6.8	33.5 ± 8.2	42.6 ± 10.5	0.003
ALT (U/L)	27.1 ± 5.4	30.9 ± 6.7	39.2 ± 9.1	0.001
ALP (U/L)	98.5 ± 20.6	105.2 ± 24.1	121.7 ± 27.8	0.021
Total Bilirubin (mg/dL)	0.72 ± 0.14	0.81 ± 0.20	1.01 ± 0.23	0.014

Table 2: Lipid profile among patients with different serum CBZ levels

Parameter	Subtherapeutic	Therapeutic	Supratherapeutic	p-value
Total Cholesterol (mg/dL)	162.3 ± 28.4	178.6 ± 31.2	202.4 ± 36.5	0.012
Triglycerides (mg/dL)	122.7 ± 29.8	138.9 ± 33.6	165.3 ± 40.2	0.015
HDL (mg/dL)	48.5 ± 6.2	46.9 ± 7.1	42.8 ± 8.0	0.081
LDL (mg/dL)	91.8 ± 24.3	103.5 ± 27.6	120.1 ± 31.4	0.023
VLDL (mg/dL)	24.5 ± 6.2	27.7 ± 6.7	33.1 ± 8.0	0.019

Table 3: Hematological parameters in relation to serum carbamazepine levels

Parameter	Subtherapeutic	Therapeutic	Supratherapeutic	p-value
Hemoglobin (g/dL)	13.1 ± 1.0	12.9 ± 1.1	11.7 ± 1.3	0.026
Total Leukocyte Count ($\times 10^9$/L)	7.2 ± 1.1	6.8 ± 1.3	5.9 ± 1.2	0.017
Platelet Count ($\times 10^9$/L)	256.4 ± 45.3	238.6 ± 49.2	208.3 ± 51.6	0.029
RBC Count ($\times 10^{12}$/L)	4.6 ± 0.4	4.5 ± 0.5	4.1 ± 0.5	0.041

Table 4: Electrolyte and renal function parameters

Parameter	Subtherapeutic	Therapeutic	Supratherapeutic	p-value
Sodium (mmol/L)	138.6 ± 3.9	136.8 ± 3.2	132.5 ± 3.0	0.004
Potassium (mmol/L)	4.2 ± 0.4	4.1 ± 0.5	4.0 ± 0.5	0.294
Urea (mg/dL)	28.1 ± 6.1	30.2 ± 6.7	33.8 ± 7.4	0.082
Creatinine (mg/dL)	0.84 ± 0.14	0.89 ± 0.16	0.97 ± 0.18	0.067

Table 5: Correlation between serum CBZ concentration and key laboratory parameters

Variable	Correlation Coefficient (r)	Significance (p-value)
AST	+0.41	0.001
ALT	+0.46	0.001
Total Cholesterol	+0.38	0.003
Triglycerides	+0.36	0.004
Hemoglobin	–0.31	0.012
Sodium	–0.44	0.002
Platelet Count	–0.29	0.018

Discussion

The present study evaluated the biochemical, metabolic, and hematological alterations associated with varying serum carbamazepine (CBZ) concentrations in adult epileptic patients. Our findings demonstrated that higher CBZ levels were significantly correlated with elevations in hepatic enzymes (AST, ALT, ALP), dyslipidemia, mild hematological suppression, and hyponatremia. These results reaffirm that chronic CBZ therapy, despite its proven efficacy, has considerable systemic effects requiring routine biochemical surveillance.

Our data showing elevated hepatic transaminases in supratherapeutic CBZ users align with previous evidence that CBZ is a potent hepatic enzyme inducer. Prolonged CBZ exposure increases oxidative stress and disrupts glutathione homeostasis, contributing to hepatocellular injury[7]. Experimental studies confirmed dose-dependent hepatotoxicity, which can be mitigated by antioxidants such as pentoxifylline or grape seed extract[8;9]. Similarly, a 2024 clinical report showed normalization of gamma-glutamyl transferase (GGT) after switching CBZ to lacosamide, underscoring the hepatic burden induced by CBZ enzyme induction[10].

Regarding Lipid Metabolism and Atherogenic Potential, our observation of increased total cholesterol, LDL, and triglycerides parallels long-term human studies reporting CBZ-induced dyslipidemia.[11] In a retrospective study, CBZ exhibited a stronger impact on lipid metabolism compared to oxcarbazepine and eslicarbazepine.[12] Chronic CBZ therapy increases hepatic synthesis of cholesterol and lipoproteins via cytochrome P450 induction[13]. Furthermore, dyslipidemia has been positively correlated with hyperhomocysteinemia in CBZ-treated patients, suggesting potential cardiovascular risks[14].

We observed mild anemia, leukopenia, and thrombocytopenia, particularly among patients with higher CBZ levels. These findings are consistent with both human and animal studies reporting CBZ-induced hematopoietic suppression[15]. Bone marrow toxicity may result from immune-mediated mechanisms or direct oxidative damage, emphasizing the need for periodic hematologic assessment. A significant decline in serum sodium was found in the supratherapeutic group, consistent with previous clinical findings of CBZ-induced hyponatremia due to inappropriate antidiuretic hormone secretion.[16] Persistent hyponatremia can exacerbate seizure frequency, further complicating epilepsy management.

Experimental studies have highlighted CBZ's role in generating oxidative stress and lipid peroxidation through reactive oxygen species, compromising hepatic and cellular integrity[17,18]. This oxidative mechanism, involving CYP3A4 and CYP3A5 isoforms, explains much of the hepatocellular and metabolic variability seen among patients[19]. Although our renal indices were largely unaltered, experimental studies indicate potential nephrotoxicity through inflammatory and oxidative pathways. Co-administration of matricin was found to attenuate CBZ-induced nephritis by down regulating MEK–JAK2–STAT3 signaling and inflammatory cytokines[20]

Our findings collectively indicate that chronic CBZ therapy can induce multisystem effects — hepatic enzyme elevation, dyslipidemia, mild bone marrow suppression, and hyponatremia — especially at supratherapeutic serum levels. The enzyme-inducing nature of CBZ, along with interindividual metabolic polymorphisms, may explain the variability observed among patients. Regular biochemical and hematological

monitoring should therefore accompany therapeutic drug monitoring (TDM) to prevent subclinical toxicity.

The study confirms significant biochemical and hematological alterations among epileptic patients on chronic CBZ therapy, with clear dose–response associations. Integration of TDM with laboratory monitoring can enhance patient safety, detect toxicity early, and guide individualized dosing strategies.

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