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SERUM CARBAMAZEPINE CONCENTRATIONS AND THEIR ASSOCIATION WITH BIOCHEMICAL, METABOLIC, AND HEMATOLOGICAL CHANGES IN ADULT EPILEPTIC PATIENTS

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ABSTRACT

Background: Carbamazepine (CBZ) is one of the most commonly prescribed first-line antiepileptic drugs for the management of focal and generalized tonic–clonic seizures. However, prolonged CBZ therapy is known to cause hepatic, metabolic, and hematological disturbances, primarily due to hepatic enzyme induction and increased oxidative stress.

Objectives: To assess biochemical, metabolic, and hematological alterations in adult epileptic patients receiving CBZ monotherapy and to evaluate their correlation with serum CBZ concentrations.

Methods: This cross-sectional study included 96 adult patients with epilepsy (aged 16–72 years) receiving CBZ monotherapy at doses ranging from 300–800 mg/day for a minimum duration of 15 days. Serum CBZ concentrations were estimated using high-performance liquid chromatography (HPLC). Biochemical parameters (liver function tests, renal profile, lipid profile, and electrolytes) and hematological indices (hemoglobin, leukocyte count, and platelet count) were analyzed. Based on serum CBZ levels, patients were categorized into subtherapeutic (<4 mg/L), therapeutic (4–12 mg/L), and supratherapeutic (>12 mg/L) groups. Statistical analysis was performed using one-way ANOVA and Pearson's correlation, with p
< 0.05 considered statistically significant.

Results: Patients with supratherapeutic CBZ levels demonstrated significantly elevated liver enzymes (AST, ALT, ALP), total bilirubin, total cholesterol, triglycerides, and LDL cholesterol ($p < 0.05$). In contrast, hemoglobin levels, total leukocyte count, platelet count, and serum sodium levels showed a significant decline with increasing CBZ concentrations (p
< 0.05). Pearson's correlation analysis revealed positive correlations between serum CBZ levels and hepatic and lipid parameters, while negative correlations were observed with hematological indices and serum sodium levels.

Conclusion: Chronic CBZ therapy is associated with significant biochemical and hematological alterations, particularly at supratherapeutic concentrations. Regular biochemical surveillance in conjunction with therapeutic drug monitoring is essential to optimize efficacy, detect early toxicity, and individualize CBZ dosing in patients with epilepsy.

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

INTRODUCTION

Epilepsy is a common chronic neurological disorder characterized by recurrent, unprovoked seizures resulting from abnormal electrical discharges within the brain. Long-term administration of antiepileptic drugs (AEDs) remains the cornerstone of epilepsy management, often requiring prolonged or lifelong therapy. Carbamazepine (CBZ) continues to be one of the most widely prescribed AEDs due to its proven efficacy in focal and generalized tonic–clonic seizures, cost-effectiveness, and extensive clinical experience.[1]

Despite its clinical utility, chronic CBZ therapy has been associated with several biochemical, metabolic, and hematological abnormalities that may adversely affect patient safety and long-term treatment outcomes. CBZ is a potent inducer of hepatic microsomal enzymes, particularly cytochrome P450 isoenzymes, leading to altered lipid metabolism, hepatic function, and endocrine pathways. Previous studies have reported significant elevations in serum cholesterol, triglycerides, and low-density lipoprotein (LDL) levels among patients receiving long-term CBZ therapy.[2]

Additionally, CBZ has been implicated in increased bone turnover and reduced bone mineral density due to disturbances in vitamin D metabolism.[3] Hematological adverse effects such as leukopenia, thrombocytopenia, and anemia have also been reported, possibly resulting from dose-dependent bone marrow suppression or immune-mediated mechanisms.[4]

Electrolyte abnormalities, particularly hyponatremia and hypo-osmolality, are well-recognized complications of CBZ therapy and are thought to result from syndrome of inappropriate antidiuretic hormone secretion (SIADH).[5] Such disturbances may compromise seizure control and increase the risk of adverse drug reactions. Furthermore, CBZ-induced oxidative stress, mediated by increased free radical production and reduced antioxidant defenses, may contribute to hepatocellular injury and systemic toxicity.[6]

Given these multifactorial effects, it is imperative to evaluate not only serum drug concentrations but also the associated biochemical and hematological changes during CBZ therapy. The present study was undertaken to assess these alterations in relation to serum CBZ levels in adult epileptic patients, thereby emphasizing the clinical importance of integrated therapeutic drug monitoring combined with routine laboratory surveillance.

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 at Saveetha Medical College and Hospital, India, after obtaining approval from the Institutional Ethics Committee. Written informed consent was obtained from all participants prior to enrollment.

Study Population

A total of 96 newly diagnosed adult patients with epilepsy, aged 18–72 years, of either sex, receiving CBZ monotherapy were included in the study. Patients were recruited from the outpatient neurology services of the Medicine Department. Inclusion criteria were:

1. Confirmed diagnosis of epilepsy
2. Treatment with CBZ for at least 30 days at doses between 300–800 mg/day
3. Absence of concomitant antiepileptic or hepatotoxic medications

Patients with pre-existing hepatic, renal, or hematological disorders, pregnant or lactating women, and those with poor treatment adherence were excluded.

Sample Collection and Preparation

After an overnight fast, 5 mL of venous blood was collected from each participant approximately 12 hours after the last CBZ dose to obtain trough serum levels. Of this:

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

Serum Carbamazepine Estimation

Serum CBZ concentrations were measured using high-performance liquid chromatography (HPLC) 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 in the ratio of 65:34:1 at a flow rate of 1.0 mL/min. The calibration curve was linear over a concentration range of 0.5–15 µg/mL, and both intra- and inter-assay coefficients of variation were below 5%.

Biochemical and Hematological Investigations

Biochemical parameters included liver function tests (AST, ALT, ALP, total bilirubin), renal function tests (serum urea and creatinine), electrolytes (sodium and potassium), and lipid profile (total cholesterol, triglycerides, HDL, LDL, and VLDL). Hematological evaluation comprised hemoglobin, total and differential leukocyte counts, platelet count, and erythrocyte indices (RBC count, MCV, MCH, and MCHC). All analyses were performed using automated analyzers following standard laboratory protocols.

Statistical Analysis

Data were analyzed using SPSS version 25.0. Continuous variables were expressed as mean ± standard deviation. Patients were categorized into subtherapeutic (<4 mg/L), therapeutic (4–12 mg/L), and supratherapeutic (>12 mg/L) groups based on serum CBZ concentrations. Intergroup comparisons were performed using one-way ANOVA followed by Tukey's post-hoc test. Pearson's correlation coefficient was used to assess the relationship between serum CBZ levels and laboratory parameters. A p-value <0.05 was considered statistically significant.

RESULTS

Among the 96 adult epileptic patients receiving CBZ monotherapy, liver function parameters showed a progressive increase with rising serum CBZ concentrations. The supratherapeutic group exhibited significantly higher mean values of 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 to the subtherapeutic and therapeutic groups ($p < 0.05$).

A similar dose-dependent pattern was observed in metabolic parameters, with significantly elevated total cholesterol (202.4 ± 36.5 mg/dL), triglycerides (165.3 ± 40.2 mg/dL), LDL, and VLDL levels in patients with supratherapeutic CBZ concentrations. HDL levels showed a non-significant declining trend across groups.

In contrast, hematological parameters demonstrated a significant decline with increasing serum CBZ levels. Patients in

the supratherapeutic group had lower hemoglobin (11.7 ± 1.3 g/dL), total leukocyte count (5.9 ± 1.2 ×10⁹/L), platelet count (208.3 ± 51.6 ×10⁹/L), and RBC count (4.1 ± 0.5 ×10¹²/L) compared to other groups ($p < 0.05$).

Electrolyte analysis revealed a statistically significant reduction in serum sodium levels with increasing CBZ concentration (138.6 ± 3.9 to 132.5 ± 3.0 mmol/L; $p = 0.004$), while serum potassium, urea, and creatinine levels did not differ significantly among the groups.

Correlation analysis further confirmed these findings, demonstrating significant positive correlations between serum CBZ levels and hepatic and lipid parameters (AST $r = +0.41$; ALT $r = +0.46$; cholesterol $r = +0.38$; triglycerides $r = +0.36$; all $p < 0.01$). Conversely, significant negative correlations were observed between serum CBZ concentrations and hemoglobin ($r = –0.31$), serum sodium ($r = –0.44$), and platelet count ($r = –0.29$).

Table 1. Liver function parameters according to serum carbamazepine (CBZ) 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

Values expressed as mean ± SD. Statistical significance determined using one-way ANOVA.

Table 2. Lipid profile parameters in relation to serum carbamazepine 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

HDL showed a declining trend that did not reach statistical significance.

Table 3. Hematological parameters across serum carbamazepine concentration groups

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 (×10⁹/L)	7.2 ± 1.1	6.8 ± 1.3	5.9 ± 1.2	0.017
Platelet count (×10⁹/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

Progressive decline in hematological indices observed with increasing CBZ levels.

Table 4. Electrolyte and renal function parameters according to serum CBZ levels

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

Significant hyponatremia noted in the supratherapeutic CBZ group; renal parameters remained comparable.

Table 5. Correlation between serum carbamazepine concentration and laboratory parameters

Variable	Correlation coefficient (r)	*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

Positive correlations indicate increasing values with higher CBZ levels, while negative correlations indicate declining trends.

DISCUSSION

The present study evaluated the biochemical, metabolic, and hematological alterations associated with varying serum carbamazepine (CBZ) concentrations in adult patients with epilepsy. The findings demonstrate that increasing serum CBZ levels are significantly associated with hepatic enzyme elevation, dyslipidemia, mild hematological suppression, and hyponatremia. These observations reinforce the concept that chronic CBZ therapy, although clinically effective, exerts clinically relevant multisystem effects that necessitate routine laboratory surveillance in addition to therapeutic drug monitoring (TDM).

Elevation of hepatic transaminases observed in patients with supratherapeutic CBZ levels is consistent with the established enzyme-inducing property of CBZ. Chronic exposure to CBZ enhances cytochrome P450 activity, leading to increased oxidative stress, disruption of glutathione homeostasis, and subsequent hepatocellular injury.[7] Experimental studies have demonstrated dose-dependent hepatotoxicity, which can be attenuated by antioxidant agents such as pentoxifylline and grape seed extract, highlighting the role of oxidative mechanisms in CBZ-induced liver injury.[8–9] Furthermore, recent clinical evidence has shown normalization of gamma-glutamyl transferase levels following substitution of CBZ with lacosamide, underscoring the hepatic burden imposed by prolonged enzyme induction.[10]

With respect to lipid metabolism, our findings of elevated total cholesterol, LDL, and triglyceride levels parallel earlier long-term studies reporting CBZ-associated dyslipidemia.[11]

Retrospective analyses have demonstrated that CBZ exerts a stronger adverse effect on lipid metabolism when compared with structurally related antiepileptic agents such as oxcarbazepine and eslicarbazepine.[12] The underlying mechanism is believed to involve increased hepatic synthesis of cholesterol and lipoproteins mediated by cytochrome P450 induction.[13] Additionally, dyslipidemia in CBZ-treated patients has been linked to hyperhomocysteinemia, suggesting a potential increase in long-term cardiovascular risk.[14]

Hematological evaluation in the present study revealed mild anemia, leukopenia, and thrombocytopenia, particularly

among patients with higher serum CBZ concentrations. These findings are concordant with both clinical and experimental reports of CBZ-induced hematopoietic suppression.[15] Bone marrow toxicity may result from immune-mediated mechanisms or direct oxidative injury, reinforcing the importance of periodic hematological monitoring during long-term therapy.

A significant decline in serum sodium levels was observed in patients with supratherapeutic CBZ concentrations. This finding aligns with well-documented reports of CBZ-induced hyponatremia, most commonly attributed to syndrome of inappropriate antidiuretic hormone secretion.[16] Persistent hyponatremia is clinically relevant, as it may worsen seizure control, increase fall risk, and contribute to cognitive impairment, thereby complicating epilepsy management.

Experimental evidence has further elucidated CBZ's role in promoting oxidative stress and lipid peroxidation through reactive oxygen species generation, leading to compromised hepatic and cellular integrity.[17–18] Interindividual variability in CBZ metabolism, partly explained by genetic polymorphisms involving CYP3A4 and CYP3A5 isoenzymes, may account for the heterogeneous biochemical responses observed among patients.[19] Although renal parameters in the present study did not show statistically significant alterations, experimental models have demonstrated potential CBZ-induced nephrotoxicity mediated by inflammatory and oxidative pathways. Notably, matricin has been shown to attenuate CBZ-induced renal injury through down-regulation of MEK–JAK2–STAT3 signaling and pro-inflammatory cytokines.[20]

Collectively, the findings of this study indicate that chronic CBZ therapy can induce clinically significant multisystem effects, including hepatic enzyme elevation, dyslipidemia, mild bone marrow suppression, and hyponatremia, particularly at supratherapeutic serum concentrations. The enzyme-inducing nature of CBZ, combined with interindividual metabolic variability, underscores the importance of individualized therapy.

CONCLUSION

In conclusion, this study confirms dose-dependent biochemical and hematological alterations in epileptic patients receiving chronic CBZ therapy. Integration of therapeutic drug monitoring with routine biochemical and hematological assessment can enhance patient safety, facilitate early detection of subclinical toxicity, and support optimized, individualized dosing strategies.

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