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THERAPEUTIC DRUG MONITORING OF CARBAMAZEPINE: A CROSS-SECTIONAL EVALUATION OF DOSE–CONCENTRATION RELATIONSHIP AND SERUM LEVEL VARIABILITY IN ADULT EPILEPTIC PATIENTS

Medical Science

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ABSTRACT

Background: Carbamazepine (CBZ) is a first-line antiepileptic drug widely used for focal and generalized tonic–clonic seizures. Due to its narrow therapeutic range and variable pharmacokinetics, serum levels may differ significantly among patients, making therapeutic drug monitoring (TDM) essential for optimizing therapy. Aim of study is to determine serum CBZ concentrations, assess dose–concentration relationships, and evaluate inter-individual variability among adult epileptic patients receiving CBZ monotherapy. **Methods:** A cross-sectional study was conducted on 96 newly diagnosed epileptic patients aged 18–72 years receiving CBZ 300–800 mg/day. Blood samples were collected at steady state (after 15 days of therapy), and serum CBZ levels were estimated using High-Performance Liquid Chromatography (HPLC). Data were analyzed using SPSS v25.0, and correlations were assessed using Pearson's test with a significance level of $p < 0.05$. **Results:** The mean age of participants was 38.4 ± 16.3 years; 52.1% were males. The mean daily CBZ dose was 535.4 ± 162.2 mg, and the mean serum concentration was 7.54 ± 3.50 mg/L (range 1.41–13.98 mg/L). 20 (20.8%) patients had subtherapeutic levels (<4 mg/L), 66 (68.8%) were within therapeutic range (4–12 mg/L), and 10 (10.4%) had supratherapeutic levels (>12 mg/L). A significant positive correlation was found between dose and serum concentration ($r = 0.62$, $p < 0.01$). Age and gender showed no significant influence. **Conclusion:** Considerable inter-individual variability in CBZ serum levels was observed despite uniform dosing. Routine TDM is recommended to guide individualized dosing, maintain efficacy, and prevent toxicity in epileptic patients.

KEYWORDS

Carbamazepine; Therapeutic Drug Monitoring (TDM); Epilepsy; Serum Drug Concentration; High-Performance Liquid Chromatography (HPLC)

INTRODUCTION

Epilepsy is one of the most common chronic neurological disorders, characterized by recurrent, unprovoked seizures due to abnormal, excessive electrical discharges in the brain. Effective long-term management typically requires the use of antiepileptic drugs (AEDs), which aim to suppress seizures and improve patients' quality of life.[1]

Among these, carbamazepine (CBZ) remains a widely used first-line AED for focal and generalized tonic–clonic seizures owing to its proven efficacy, affordability, and global availability, especially in resource-limited settings.[2] Despite its effectiveness, carbamazepine therapy presents considerable clinical challenges. It possesses a narrow therapeutic range (4–12 mg/L) and exhibits substantial inter- and intra-individual pharmacokinetic variability. Factors such as age, sex, hepatic function, genetic polymorphisms, drug interactions, and adherence significantly influence serum CBZ levels.[3] Moreover, CBZ undergoes auto-induction of its metabolism via cytochrome P450 enzymes, leading to increased clearance over time and fluctuating serum concentrations, even under steady dosing conditions.[4]

These pharmacokinetic complexities make standardized dosing unreliable and raise the risk of subtherapeutic exposure, breakthrough seizures, or drug toxicity. Therefore, Therapeutic Drug Monitoring (TDM) plays a crucial role in optimizing CBZ therapy by maintaining serum concentrations within the therapeutic window, guiding dose adjustments, and ensuring both efficacy and safety. TDM also helps identify drug interactions and poor adherence, especially in patients receiving polytherapy or with variable metabolic capacity.[5] Among analytical techniques, High-Performance Liquid Chromatography (HPLC) remains the gold standard for CBZ quantification due to its high sensitivity, specificity, and ability to detect both the parent compound and its active metabolite, carbamazepine-10,11-epoxide.[6] While CBZ is extensively prescribed across India, regional data on serum drug levels, dose–concentration relationships, and the extent of variability in clinical settings remain limited. Previous studies have reported wide variability even among patients on identical dosages, underscoring the need for individualized dose adjustment guided by TDM.[7]

Hence, the present study aims to evaluate serum carbamazepine concentrations among adult epileptic patients, to analyze the dose–concentration relationship, and to assess variability in serum levels. The findings are expected to reinforce the clinical importance of routine TDM in ensuring safe, effective, and individualized CBZ therapy in adult epilepsy management.

METHODS

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) from October 2024 to October 2025 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 epileptic patients (aged 18–65 years) of either sex, receiving carbamazepine (CBZ) therapy, were enrolled. Exclusion criteria included pregnant or lactating women, patients with hepatic or renal disorders, alcoholics, smokers, or those taking drugs known to interact with CBZ.

Data and Sample Collection

Clinical details such as age, sex, weight, type of seizure, dose, frequency, and duration of therapy were recorded in a case report form. Blood samples (3 mL) were collected after achieving steady-state concentration (approximately 15 days after treatment initiation). Serum was separated by centrifugation and stored at –20°C until analysis.

Estimation of Serum Carbamazepine

Serum CBZ concentration was estimated by 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). As per the validated method take 0.2 mL of the plasma sample or standard and add 0.2 mL of 1.0 M sodium acetate buffer (pH 5.5), followed by 3 mL of chloroform. Shake the mixture for one minute, then centrifuge at 3000 rpm for 10 minutes. Carefully transfer 2.8 mL of the chloroform layer into a clean test tube and evaporate the chloroform under a water bath at 50°C. Once the chloroform has evaporated, reconstitute the residue in 0.2 mL of mobile phase. Inject 20 µL of this reconstituted solution into the HPLC system for analysis.

Classification of Serum Levels

Participants were grouped according to serum CBZ concentration:

- Subtherapeutic: <4 mg/L
- Therapeutic: 4–12 mg/L
- Supratherapeutic: >12 mg/L

Statistical Analysis

Data were analyzed using SPSS version 25.0 (IBM Corp., USA). Continuous variables were presented as mean ± SD, and categorical data as percentages. The relationship between dose and serum concentration was assessed using Pearson's correlation, and group differences were evaluated by ANOVA. A p-value <0.05 was considered statistically significant.

Ethical Considerations

The study was conducted in accordance with the Declaration of Helsinki (2013) and ICMR Ethical Guidelines (2006).

RESULTS

The mean age of participants was 38.4 ± 16.3 years; 52.1% were males. The mean daily CBZ dose was 535.4 ± 162.2 mg, and the mean serum concentration was 7.54 ± 3.50 mg/L (range 1.41–13.98 mg/L). 20 (20.8%) patients had subtherapeutic levels (<4 mg/L), 66 (68.8%) were within therapeutic range (4–12 mg/L), and 10 (10.4%) had supratherapeutic levels (>12 mg/L). A significant positive correlation was found between dose and serum concentration ($r = 0.62$, $p < 0.01$). Age and gender showed no significant influence.

Table 1. Demographic Characteristics of the Study Participants (n = 96)

Parameter	Category	Frequency (n)	Percentage (%)
Age (years)	Mean ± SD	38.4 ± 16.3	—
Age group	<20	11	11.5
	21–40	42	43.8
	41–60	34	35.4
	>60	9	9.3
Gender	Male	50	52.1
	Female	46	47.9
Weight (kg)	Mean ± SD	59.2 ± 8.6	—

Table 1 summarizes the age distribution (mean 38.4 ± 16.3 years, with most participants aged 21–60 years), gender (slightly more males at 52.1%), and average weight (59.2 ± 8.6 kg) of 96 patients in a study on carbamazepine therapy.

Table 2. Carbamazepine Dosage Pattern Among Patients

Dose (mg/day)	No. of patients	Percentage (%)
300 mg	24	25.0
400 mg	28	29.2
600 mg	30	31.3
800 mg	14	14.6
Mean ± SD	535.4 ± 162.2	—

Above table show that daily carbamazepine doses administered to 96 patients, showing the most common dose at 600 mg (31.3% of patients), followed by 400 mg and 300 mg, with an overall mean dose of 535.4 ± 162.2 mg/day.

Table 3. Serum Carbamazepine Concentrations (mg/L)

Parameter	Value
Range	1.41 – 13.98
Mean ± SD	7.54 ± 3.50
Median	7.60
Therapeutic range	4 – 12

Above table no-3 presents the serum levels of carbamazepine in 96 patients, including a wide range (1.41–13.98 mg/L), mean concentration (7.54 ± 3.50 mg/L), median (7.60 mg/L), and the standard therapeutic reference range (4–12 mg/L).

Table 4. Distribution of Patients According to Serum CBZ Levels

Serum Level Range	Interpretation	No. of Patients (n)	Percentage (%)	Mean ± SD (mg/L)
<4 mg/L	Subtherapeutic	20	20.8	2.72 ± 0.81
4–12 mg/L	Therapeutic	66	68.8	8.17 ± 2.36
>12 mg/L	Supratherapeutic	10	10.4	12.97 ± 0.67

Table 4 categorizes 96 patients by serum carbamazepine levels: 68.8% in the therapeutic range (4–12 mg/L), 20.8% subtherapeutic (<4 mg/L), and 10.4% supratherapeutic (>12 mg/L), with corresponding mean concentrations for each group.

Table 5. Relationship Between Daily Dose and Serum CBZ Concentration

Dose (mg/day)	Mean Serum Level (mg/L)	r (correlation coefficient)	p-value
300	5.36 ± 2.4	r = 0.62	p < 0.01
400	7.41 ± 3.0		
600	8.69 ± 2.7		
800	9.94 ± 3.1		

This table no 5 examines the correlation between carbamazepine doses (300–800 mg/day) and mean serum levels (rising from 5.36 to 9.94 mg/L), demonstrating a positive linear relationship (correlation coefficient $r = 0.62$, $p < 0.01$) across dose groups.

DISCUSSION

The present study assessed the relationship between carbamazepine (CBZ) dosage and serum concentrations in adult epileptic patients under monotherapy and demonstrated a statistically significant positive correlation ($r = 0.62$, $p < 0.01$). Despite this association, substantial inter-individual variability was observed even at similar doses, reaffirming the need for Therapeutic Drug Monitoring (TDM) to guide dose adjustments and optimize therapeutic outcomes.

Comparable findings have been reported in a Peruvian cross-sectional study by Alvarado et al., who demonstrated a strong positive correlation ($r = 0.544$, $p = 0.002$) between CBZ daily dose and serum concentration, while nearly 10% of patients exhibited supratherapeutic levels and 2% subtherapeutic concentrations despite similar dosing regimens.[8] Such observations are consistent with the current study's results, where 20.8% of patients were below and 10.4% above the therapeutic range (4–12 mg/L). These results emphasize inter-patient variability due to metabolic differences, autoinduction, and adherence factors.

Carbamazepine exhibits a narrow therapeutic window and autoinduction of hepatic enzymes, primarily CYP3A4, which increases clearance over time.[9] Tolou-Ghamari et al. reviewed 60 years of CBZ pharmacokinetic data and confirmed that autoinduction, hepatic impairment, and comorbid conditions contribute significantly to variable plasma concentrations and shortened half-life[9]. Likewise, Punyawudho et al. described in elderly epilepsy patients an apparent clearance (CL/F) of 3.59 L/h with 18.1% variability and a volume of distribution (V/F) of 102 L with 74.7% variability.[10] These findings underscore that even in well-controlled dosing regimens, CBZ levels fluctuate widely among individuals.

In Singaporean epileptic patients, Chan et al. reported that age, gender, and race had no significant influence on CBZ clearance, whereas concomitant phenobarbital therapy increased clearance by 44% .[11] This is similar with our study, where neither age nor gender significantly affected serum CBZ concentrations, suggesting that metabolic induction and genetic polymorphisms may play a more dominant role.

Pharmacogenetic variability has been recognized as a crucial determinant of CBZ pharmacokinetics. Lu et al. found that the UGT2B72 variant was associated with reduced dose-normalized CBZ concentrations and greater dose requirements, while CYP3A53 had minimal effect.[12] Such genetic polymorphisms can alter enzyme activity, explaining why some patients remain subtherapeutic despite adequate dosing. Hence, integrating pharmacogenetic profiling with TDM may improve individualized therapy.

Our findings further align with the results of Chbili et al., who demonstrated that both CBZ and its active metabolite, carbamazepine-10,11-epoxide, influenced therapeutic response; specifically, patients with metabolite levels around 0.8 µg/mL and CBZ levels near 5.5 µg/mL achieved optimal seizure control.[13] This indicates that measuring only the parent drug may be insufficient for accurate therapeutic evaluation and that metabolite quantification enhances TDM accuracy.

Methodologically, Tuchilă and Baconi emphasized that due to CBZ's narrow therapeutic index and complex metabolism, high-performance liquid chromatography (HPLC) remains the gold standard for precise quantitation in serum.[14] Our use of HPLC for CBZ estimation followed this standard, providing reliable and reproducible results consistent with other studies.

Ding et al. explored the pharmacokinetic consequences of missed or delayed CBZ doses using Monte Carlo simulations and observed a marked increase in subtherapeutic exposure, especially at higher daily doses.[15] Their findings confirm that compliance strongly affects serum levels—supporting our interpretation that part of the observed

variability may be due to adherence issues. Furthermore, Eshiet et al. identified that only 3.7% of patients receiving CBZ in Nigerian clinics underwent routine hematologic or hepatic monitoring, underscoring the global underutilization of TDM in real-world practice.[16]

From a clinical perspective, maintaining CBZ concentrations within the therapeutic range is essential not only for seizure control but also to prevent cognitive and neuropsychological side effects. Gillham et al. found that rising CBZ and CBZ-epoxide concentrations were significantly correlated with decreased psychomotor performance and cognitive function.[17] This supports the present study's recommendation that regular TDM is vital for maintaining efficacy while minimizing neurotoxicity. However time period was only limitation of this study.

CONCLUSION

In summary, CBZ therapy requires individualized monitoring because of its non-linear pharmacokinetics, autoinduction, and genetic variability. Routine TDM supported by precise HPLC analysis should be standard practice to ensure therapeutic efficacy and avoid adverse effects. Additionally, future protocols integrating pharmacogenetic screening may further enhance the safety and precision of CBZ dosing.

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Declarations

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Conflict of Interest: None declared

Ethical Approval: The study was approved by the Institutional Ethics Committee.

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