ORIGINAL ARTICLE

Prevalence and Outcomes of Carbamazepine Toxicity in the Emergency Department: A Single-center Retrospective Study

Darpanarayan Hazra[1], Nejah F Ellouze[2], Suad A Abri[3]

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Abstract

Background: Carbamazepine (CBX) is widely used for various medical conditions, but its associated toxicity poses significant clinical concerns. This study aims to provide insights into the clinical presentations, management strategies, and outcomes of CBX toxicity cases in an emergency department (ED) setting.

Methodology: This was a 10-year retrospective cohort chart review study, including all patients with elevated CBX levels. Data on clinical features, CBX levels, laboratory findings, electrocardiograms (ECGs), patient management, and outcomes were analyzed. Cases were categorized as acute or chronic toxicity.

Results: Out of the 1,965 medical charts reviewed, we included 70 patients with CBX levels above the therapeutic range (prevalence: 3.6%). Chronic CBX toxicity cases (55.7%) were predominant, with gastrointestinal (GI) symptoms being the most common. Most patients presented with isolated CBX overdoses (88.6%), while mixed overdoses (11.4%) were less frequent. Patients were categorized based on CBX levels: 44 had mild toxicity (>51 µmol/L), and 26 had moderate toxicity (>85 µmol/L). Within the mild group, 15 patients experienced acute toxicity, compared to 16 patients in the moderate group. Four patients who had mixed overdoses and low sensorium required intubation and mechanical ventilation. Three patients received activated charcoal (AC), and another 3 patients received multiple doses of AC to reduce drug absorption. The majority of patients (65.7%) required hospital admission, underscoring the seriousness of CBX toxicity. There were no fatalities among these 70 patients.

Conclusion: This study emphasizes the importance of a systematic approach to assessing and managing CBX toxicity, considering its diverse clinical presentations and variations in serum CBX levels.

Keywords: Carbamazepine, Carbamazepine toxicity, Emergency department, Toxicology.

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Highlights

This study highlights the diverse clinical presentations of CBX toxicity, which can affect the neurological, gastrointestinal (GI), and cardiovascular systems. Symptoms of CBX toxicity may range from mild to severe, necessitating tailored management for individual cases in the emergency department (ED).

Introduction

Carbamazepine (CBX) is commonly prescribed for various medical conditions such as focal epilepsy, neuropathic pain, schizophrenia, and bipolar disorder in both pediatric and adult patients.[1] Due to its extensive binding to plasma proteins and wide distribution throughout the body, a significant portion of CBX remains bound to these proteins, with the remainder circulating in tissue stores. Carbamazepine is primarily metabolized via oxidation mediated by enzymes like CYP 3A4 and, to a lesser extent, CYP 2C8, leading to the formation of carbamazepine-10,11-epoxide, an active metabolite associated with toxic effects.[2,3] Other metabolites, including the dihydroxy derivative of the epoxide, have also been identified. The metabolic pathway of CBX includes hydroxylation of its 6-membered aromatic rings and N-glucuronidation of the carbamoyl side chain.[2,3]

The occurrence of CBX toxicity following overdose was first documented in 1967 and continues to contribute significantly to life-threatening incidents associated with anticonvulsant toxicity.[4] Notably, CBX overdose is not uncommon, with 1,880 reported cases of toxic exposure in 2014 and 3,631 in 2016, according to data from the American Association of Poison Control Centers (AAPCC).[5,6] Clinically, CBX intoxication manifests with neurological, respiratory, and cardiac symptoms, including altered mental status, seizures, coma, respiratory depression, aspiration, tachycardia, hypotension, and, in severe cases, can even lead to death.[4,7] Carbamazepine toxicity has varying effects depending on the serum levels. The therapeutic range is typically from 8 to 12 mg/L (34–51 µmol/L). Signs and symptoms of CBX toxicity manifest at levels >12 mg/L (51 µmol/L), which are considered mild toxicity.[8] This can cause GI complaints such as nausea and vomiting, and mild central nervous system (CNS) symptoms mainly nystagmus and ataxia.[8,9] Moderate toxicity can be seen at levels >20 mg/L (85 µmol/L), which may result in significant CNS effects such as altered mental status and convulsions, as well as anticholinergic

[1–3]Department of Emergency Medicine, Sultan Qaboos University Hospital, Muscat, Sultanate of Oman

Corresponding Author: Suad A Abri, Department of Emergency Medicine, Sultan Qaboos University Hospital, Muscat, Sultanate of Oman, Phone: +96899878005, e-mail: ghammari@squ.edu.om

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effects like agitation and hallucinations.[8,9] Severe toxicity cases are considered at levels >40 mg/L (170 µmol/L), which can lead to coma, seizures, and cardiac conduction abnormalities, and can even lead to death.[8,9] Larger doses have a higher likelihood of causing more anticholinergic symptoms before coma.[8,9]

Evaluating patients with suspected CBX toxicity in the emergency department (ED) requires a comprehensive and systematic approach. This includes a thorough assessment of the patient's history, the intent of ingestion (intentional or accidental), dosage consumed, form of CBX, and potential co-ingestants.[10,11] A comprehensive physical examination should evaluate neurological and cardiovascular symptoms, as well as any underlying medical conditions that could exacerbate toxicity.[4,7,10] Diagnostic investigations play a crucial role in confirming CBX toxicity, including electrocardiograms (ECGs) and measurement of CBX concentrations, with special attention to possible co-ingested substances.[4,9] In cases of acute ingestion with an unknown quantity, tailored treatment strategies should be used, considering the patient's CBX use.[4,10] Collaboration with a toxicologist is essential for guidance on decontamination procedures, which may involve the administration of activated charcoal (AC), multiple-dose activated charcoal (MDAC) or extracorporeal therapies in moderate to severe cases.[12,13] Ongoing care includes observation of mild symptoms for at least 8 hours, and possibly longer for controlled-release formulations, with potential admission for patients with persistent moderate to severe symptoms.[9,12] Discharge decisions are based on criteria such as normal sensorium, neurological examination, ECG findings, and symptom-free status post-observation.[4,9]

This retrospective observational study, conducted at an academic tertiary care center in the Sultanate of Oman, includes both acute and chronic CBX toxicity cases. The study aimed to provide valuable insights into ED presentations, complication probabilities, and overall outcomes, thereby contributing to the existing body of knowledge on CBX toxicity.

Methodology

Study Design and Setting

This retrospective observational cohort chart review study was conducted within the ED of a tertiary care teaching hospital in Muscat, Sultanate of Oman.

Research Duration and Participants

We reviewed charts of all patients whose CBX levels were tested over a 10-year period from January 1, 2011 to January 1, 2021. We included patients with CBX levels above the therapeutic range and excluded charts with incomplete or missing data or CBX levels below or within the therapeutic range. Acute CBX toxicity cases involved patients who presented with complaints of deliberate self-harm or accidental ingestion of many carbamazepine tablets (and/or mixed overdoses), resulting in significantly elevated CBX levels. In contrast, chronic toxicity cases involved patients who had been on long-term carbamazepine therapy for an underlying medical condition, where the accumulation of the drug over time had led to high CBX levels. By collecting all the CBX-level data, we ensured that no severe cases were missed.

Variables

We reviewed and documented patients' clinical presentation, and relevant lab results including CBX levels, and ECG findings. Additionally, we recorded details of patient management in the ED and the final ED outcome.

Statistical Analysis

The data were entered into Microsoft Excel for Mac (version 16.73) for further evaluation. Continuous variables were described using mean and standard deviation to indicate central tendency and variability. Conversely, categorical variables were summarized using frequencies and percentages to illustrate the proportion and distribution of various categories in our study cohort.

Ethical Considerations

Before commencing this study, we obtained ethical approval from the Institutional Review Board (IRB) under Reference No: SQU-EC/638/2021; MREC #2668, dated February 13, 2022. Since the research was retrospective, the IRB granted a waiver of consent. To protect patient confidentiality and ensure data security, we anonymized patient information using unique identifiers and employed password-protected data entry software, restricting access to authorized personnel only.

Results

A total of 1,965 patients had their serum CBX levels measured, but only 70 met the inclusion criteria (Fig. 1). The mean age of the participants was 27.97 (±25.02) years, with an age range of 2–70 years. The majority were males at 58.6%, while females made up the remaining 41.4% (Table 1). The most common past medical history was seizure disorder, noted in 85.7% of patients (Table 1). Isolated CBX overdoses were seen in 62 (88.6%) cases, while mixed overdoses involving opioids, benzodiazepines, lithium, and ethanol were found in 8 (11.4%) of cases.

Mild toxicity was seen in 62.8% of cases, whereas moderate toxicity was seen in 37.2% of cases. No cases had severe toxicity. Table 2 compares the clinical characteristics, presenting complaints, and mental status in mild vs moderate toxicity cases. Among patients with mild toxicity, nausea, vomiting, and abdominal pain were more common, affecting 70.5% of cases, compared to 76.9% in those with moderate toxicity. Abnormal neurological findings at presentation were more commonly seen in moderate toxicity cases, accounting for 80.8%, compared to 56.8% in the mild toxicity group. One patient in the moderate toxicity group presented with convulsions, with a CBX level of 61.9 µmol/L.

Laboratory investigations and 12-lead ECG results are presented in Tables 3 and 4. The mean CBX level at presentation was 82.2 (SD: 51.5) µmol/L, while mean repeated CBX levels were 52.9 (SD: 6.6) µmol/L.

Emergency resuscitation, including intubation and mechanical ventilation, was performed for 5.7% (4 patients), all due to very low sensorium associated with mixed overdoses. Single-dose activated charcoal (AC) was administered to 4.3% (3 patients), while an additional 4.3% (3 patients) received multiple doses of AC. Forty-six patients (65.7%) required admission to the hospital, either in monitored or non-monitored beds, while 24 (34.3%) were managed conservatively and discharged in stable condition by the ED physician. No fatalities occurred among these 70 patients.

Discussion

Carbamazepine toxicity, whether resulting from acute overdose or chronic use, remains a significant concern in clinical practice.

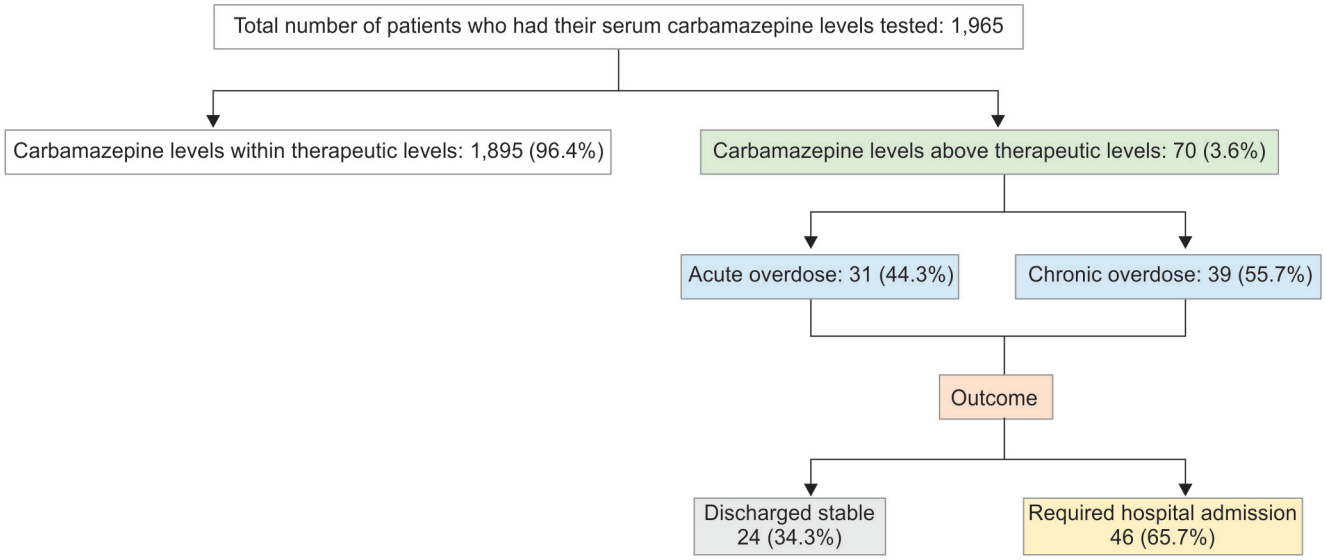

Fig. 1: Strengthening the reporting of observational studies in epidemiology (STROBE) diagram

Table 1: Demographics, past medical histories, and vital signs at presentation to the ED

Variables	*Frequency 70 (%)*
Age (SD*) years	27.97 (SD*: 25.02)
Male gender	41 (58.6)
Female gender	29 (41.4)
Preexisting illnesses (one or more)	
Seizure disorder	60 (85.7)
Psychiatry disorder	9 (12.9)
Hypertension	14 (20.0)
Diabetes mellitus	9 (12.9)
Others#	5 (7.2)
Abnormal vital signs at presentation	
Systolic blood pressure ≤90 mm Hg	2 (2.9)
Pulse rate ≥100 beats/minute	26 (37.2)
Respiratory rate ≥22/minute	15 (33.3)
O_2 saturation <88% in room air	9 (12.9)

SD*, standard deviation; Others#, chronic kidney disease, chronic liver disease, reactive airway disease, underlying brain malignancy

Table 2: Characteristics and clinical presentations in cases of carbamazepine toxicity

Variables	*Mild (51–84 µmol/L) (n = 44, 62.8%)*	*Moderate (85–170 µmol/L) (n = 26, 37.2%)*
Acute toxicity	15 (34.1)	16 (61.6)
Chronic toxicity	29 (64.9)	10 (38.4)
Most common clinical presentations (usually more than one symptom)		
GI manifestations: Nausea, vomiting, and abdominal pain	31 (70.5)	20 (76.9)
Neurological manifestations	21 (47.7)	20 (76.9)
• Altered mental status	11 (25.0)	12 (46.2)
• Dizziness and ataxia	10 (22.7)	7 (26.9)
• Convulsion	0	1 (3.9)
Mental status at presentation to the ED		
Normal mental status at presentation	19 (43.2)	5 (19.2)
Abnormal mental status at presentation	25 (56.8)	21 (80.8)

Table 3: Laboratory findings at presentation to the ED

Variables	*Frequency 70 (%)*
Initial carbamazepine levels (IQR$) (µmol/L)	82.2 (51.5, 150.9)
Repeated carbamazepine levels (IQR$) (µmol/L)	52.9 (6.6, 113.7)
Abnormal renal function*	20 (28.6)
Abnormal liver function*	8 (11.4)

*Abnormal function, Gross change from their baseline; IQR$, Interquartile range

Chronic CBX toxicity is particularly concerning as it can arise from prolonged therapeutic use or intentional misuse of the medication. According to the American Association of Poison Control Centers' 2014 report, 37% of cases involved intentional overdose, while 57% were unintentional and 4% were adverse effects that could represent chronic toxicity.[4,5] A similar trend was observed in our study, with 55.7% of CBX overdoses involving chronic toxicity. This underscores the importance of monitoring patients on long-term CBX therapy for signs of toxicity, especially when treating conditions such as neuropathic pain or mood disorders.

Carbamazepine toxicity can manifest with a wide range of clinical symptoms, often affecting GI and neurological systems, and rarely involving the cardiovascular system.[1,4,14] The predominant complaints in our cohort were GI symptoms (72.9%), followed by neurological symptoms (58.6%). Acute altered mental status was observed in 32.9% of cases. The majority of patients in our study experienced mild toxicity (62.8%), consistent with findings in previous literature.[8]

Management of CBX toxicity primarily involves supportive and symptomatic care.[9–11,13] Definitive airway protection should be considered for patients with severely depressed sensorium. In our study, only 4 patients required intubation and mechanical

Table 4: 12 Leads ECG findings at presentation to the ED

Variables	*Frequency 70 (%)*
Wide QRS complex	6 (8.6)
Sinus tachycardia	2 (2.9)
Left axis deviation	6 (8.6)
Right axis deviation	13 (18.6)

ventilation. Cardiac manifestations, a rare complication in severe toxicity, include a widening of the QRS interval on ECG, which can be managed with intravenous sodium bicarbonate.[9,15,16] In our cohort, 8.6% of patients had QRS widening, while 30% exhibited non-specific ECG changes.

A significant treatment for CBX poisoning is multiple-dose activated charcoal (MDAC), which, according to Brahmi et al.'s prospective study, has demonstrated greater effectiveness compared to single doses.[17,18] This method facilitates a consistent decrease in blood CBX half-life without causing rebound effects, potentially improving patient outcomes by reducing coma duration and hospital stays.[12,18] However, in our study, only 3 patients received MDAC, while 3 received a single dose of activated charcoal. We observed that patients who received MDAC showed a relatively faster reduction in drug levels compared to those who did not, though this difference was not statistically significant due to the small sample size, indicating underutilization of MDAC. Severe cases may require extracorporeal treatments such as intermittent hemodialysis; however, none of our cases necessitated hemodialysis.[19,20] The majority of our patients (65.7%) required hospital admission for observation and symptomatic management.

Limitations of Our Study

While our study offers valuable insights, it is essential to acknowledge several inherent constraints. Firstly, the retrospective nature of our research raises the possibility of selection bias and data limitations due to incomplete medical records. Secondly, the relatively modest sample size of our study prevented us from detecting significant relationships through sophisticated statistical analyses. Lastly, it is worth noting that our study was exclusively conducted at a single tertiary care center, potentially limiting the generalizability of our results to a broader population.

Conclusion

Our study provides valuable insights into the clinical presentation and management outcomes of CBX toxicity presented to the ED. It reveals a predominance of mild toxicity cases, with GI symptoms being notably prevalent. The wide age range from 2 to 70 years highlights the diverse demographic affected by CBX toxicity. Hospital admission was required for a majority of patients, yet reassuringly, no fatalities occurred. Despite evidence supporting its effectiveness, MDAC appears underutilized in our management practices. Further emphasis on the use of MDAC in cases of CBX toxicity is recommended to optimize treatment outcomes and patient care.

Declarations

Authors' Contribution Statement Using CRediT

DH: Conceptualization. data curation, methodology, resources, writing—original draft, writing—review and editing. NE: Conceptualization, data curation, resources, writing—original draft, writing—review and editing. SA: Conceptualization, investigations, methodology, project administration, supervision, writing—review and editing.

Research Quality and Ethics Statement

This study was approved by the Institutional Review Board/Ethics Committee at Sultan Qaboos University Hospital, Muscat, Sultanate of Oman: Reference numbers SQU-EC/638/2021; MREC #2668, dated 13th February 2022. The authors followed the applicable EQUATOR Network (http://www.equator-network.org/) guidelines, specifically the STROBE guidelines, during the conduct of this research project. We also certify that we have not plagiarized the contents in this submission and have done a plagiarism check.

Orcid

Darpanarayan Hazra https://orcid.org/0000-0002-5941-0587
Nejah F Ellouze https://orcid.org/0009-0005-8634-7498
Suad A Abri https://orcid.org/0009-0002-8561-4249

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