Severe Carbamazepine Intoxication in Children: Analysis of a 40-Case Series

Authors' Contribution:
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Data Collection B
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Background: We compared the factors that might impact the severity and the prognosis of carbamazepine (CBZ) intoxication in children, as well as the efficacy levels of the treatment options.

Material/Methods: Demographic information and clinical and laboratory findings for 40 patients were evaluated retrospectively. Predictive parameters for the development of serious complications were studied.

Results: Median age of patients was 14 years; 65% of the patients were female. The most common pathological clinical finding and laboratory abnormality were inability to awaken the patient and hyperglycemia (45% and 60%, respectively). The incidences of convulsion, coma, and respiratory failure were 14 (35%), 10 (25%), and 3 (7.5%), respectively. The Glasgow Coma Scale (GCS) scores and pH levels at emergency service admission were significantly lower in the severe intoxication group and the ICU admission group, and body temperature and serum glucose and lactate levels were significantly higher in these groups. A significantly negative correlation was found between the serum CBZ level and the GCS score, but the serum CBZ level was found to be significantly positively correlated with the lactate level.

Conclusions: According to our study, the GCS score at admission to hospital, the serum CBZ, glucose, pH, and lactate levels, and body temperature might be useful in predicting serious CBZ intoxication and prognosis in pediatric cases. We conclude that invasive treatment methods, such as hemodialysis or albumin-enhanced continuous venovenous hemodialysis, should be used in patients who do not respond to supportive treatment.

MeSH Keywords: Carbamazepine • Drug-Related Side Effects and Adverse Reactions • Poisoning

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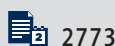
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Background

Carbamazepine (CBZ) is a first-generation anticonvulsant drug that has been commonly used to treat partial and generalized convulsions for many years. In addition, it is a mood stabilizer that has also been used to treat trigeminal neuralgia and neuropathic pain [1–3]. Because of its narrow therapeutic range, CBZ can cause serious acute or chronic intoxication if an excessive amount of the drug is accidentally ingested or taken in a suicide attempt [4]. According to data from the American Association of Poison Control Center, 3734 cases of CBZ overdose were reported in 2014. Of those cases 12.5% were children [5]. The mortality rate due to CBZ intoxication has been reported to range from 2% to 38% [6,7].

For most cases of CBZ poisoning, patients undergo supportive treatment and they are closely monitored; therefore, they do not experience any complications or sequela. Life-threatening complications and deaths due to CBZ intoxication are rare [4]. Although there are no antidotes for CBZ intoxication, treatment options include gastric lavage, administration of activated charcoal, hemodynamic support, and close monitoring. Recently, it has been reported that hemodialysis or hemoperfusion are effective ways to treat severe cases of CBZ intoxication [2,8–10]. It has been demonstrated that serum levels of CBZ in adults are correlated with the severity of the patient's neurological condition and prognosis [11]. However, prognostic age-related criteria for children are not yet clear.

Our objectives were to determine the clinical and demographic characteristics of pediatric patients who were monitored for CBZ overdose at our hospital and to compare the factors that might impact the severity of the intoxication and the prognosis.

Material and Methods

Ethical approval for this study was obtained from the Local Ethics Committee of Ondokuz Mayis University in accordance with the Helsinki Declaration. The medical records of 40 patients who were younger than 18 years of age and who were admitted to the Pediatric Emergency Service with a serum CBZ level >12 µg/mL (>50 µmol/L) were analyzed retrospectively.

The examined cases were reviewed for demographic and clinical characteristics, such as gender, age, past medical history, history of CBZ intoxication (ingestion time and cause), accompanying symptoms and clinical findings, Glasgow Coma Scale (GCS) scores, laboratory test results at admission, serum CBZ levels, electrocardiogram (ECG) findings, performed procedures, admission durations in a hospital ward and/or an intensive care unit (ICU), the need for endotracheal intubation and mechanical ventilation, and prognosis.

The patients were divided into two groups based on GCS scores as follows: patients with a GCS score <8 and patients with a GCS score >8.

Generally, serum levels of CBZ are used to assess or predict toxicity. Therapeutic and toxic levels of CBZ are 4–12 µg/mL and 20 µg/mL, respectively. We divided the CBZ poisoning patients into three groups according to serum CBZ levels as follows: between 12 and 20 µg/mL (mild), between 20 and 30 µg/mL (moderate), and over 30 µg mL associated with major toxicity symptoms such as apnea, seizures, and coma (severe) [6].

According to our laboratory test limits for children, serum glucose levels <60 mg/dL and >110 mg/dL, a serum sodium level <135 mEq/L, a serum potassium level <3.5 mEq/L, an arterial blood gas pH <7.35, and serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels higher than twice the upper limit of normal for these enzymes were defined as hypoglycemia, hyperglycemia, hyponatremia, hypopotassemia, acidosis, and high AST and ALT levels, respectively.

Statistical analysis

All parameters were analyzed with IBM SPSS software, version 21.0 (SPSS Inc., Chicago, Illinois, USA). Control of normal distribution of data was made with the Shapiro-Wilk test. All categorical variables were represented as numbers and percentages, whereas continuous variables were given as median (minimum-maximum). The values for patients and controls were analyzed with Kruskal Wallis and Mann-Whitney U tests. Categorical data were analyzed with the Fisher chi-square test. Spearman's rho correlation test was used for assessing the relationships between variables. A value of $p < 0.05$ was considered statistically significant.

Results

The median age of the patients in the 40 analyzed cases was 14 years (1.5–18 years), and the male/female ratio was 1:1.85. Eighty-five percent of the CBZ poisonings occurred because of a suicide attempt. The median time between drug ingestion and hospital admission was 5 hours (0–24 hours), and the median estimated ingest amount was 60 mg/kg. The demographic and clinical features of the cases are presented in Table 1.

The most frequent reasons for emergency service admissions were inability to awaken the patient, vomiting, and convulsions (45%, 42.5%, and 35%, respectively). At admission, nine (22.5%) of the patients had a GCS score ≤8. The details regarding patients' GCS scores are shown in Table 1.

Table 1. Demographic and clinical findings.

Female gnder n (%)	26	(65.0)
Cause of poisoning n (%)		
Suicide	34	(85)
Accidental	6	(15)
Duration between exposure and first medical intervention (hour) (medain (min–max)	5	(0–24)
0–4 hour	19	(47.5)
5–8 hour	11	(27.5)
>8 hour	10	(25.0)
Estimated dose mg/kg [median (min–max)]	60	(20–224)
Signs and symptoms n (%)		
Drowsiness	18	(45)
Vomiting	17	(42.5)
Seizures	14	(35)
Tachycardia	8	(20)
Respiratory failure	3	(7.5)
Hypotension	5	(12.5)
Hypertension	3	(7.5)
Fever	3	(7.5)
Arrhythmia	3	(7.5)
Urinary retention	2	(5)
Bradycardia	1	(2.5)
Glaskow Coma Score n (%)		
GCS ≤8	9	(22.5)
GCS (9–12)	14	(35.0)
GCS (13–15)	17	(42.5)

Classification of CBZ toxisity according to the serum CBZ Levels n (%)		
Mild	11	(27.5)
Moderate	17	(42.5)
High	12	(30.0)
Complication n (%)	19	(47.5)
Convulsion	14	(35.0)
Coma	10	(25.0)
Distonik reaksiyon	9	(22.5)
Respiratory failure	3	(7.5)
Aritmia	3	(7.5)
Ataxia	3	(7.5)
Status epilepticus	1	(2.5)
Abnormal laboratory n (%)		
Hyperglycemia	24	(60)
Acidosis	17	(42.5)
Hyponatremia	13	(32.5)
Hypokalemia	10	(25)
Elevation of liver functions	1	(2.5)
Treatment n (%)		
Gastric lavage	32	(80)
Single dose activated charcoal	6	(15)
Multiple dose activated charcoal	26	(65)
Dialysis	1	(2.5)
Mechanical ventilation	3	(7.5)

According to the classification based on serum CBZ levels, the moderate intoxication group had the most patients (17); the severe and mild intoxication groups had 12 and 11 patients, respectively. The most frequent abnormalities detected by laboratory tests were hyperglycemia (60%) and hyponatremia (32.5%). Hypoglycemia, hypernatremia, or hyperkalemia were not found in any of the patients. The classification of the CBZ toxicity according to the serum CBZ levels, the complications secondary to CBZ toxicity, and abnormal laboratory tests are shown in Table 1.

The most common complications were convulsion, coma, and dystonic reaction. All complications are shown in Table 1. The median CBZ level of the group with complications was 26.4 (14.6–58) µg/mL; that value was 19.7 (12.5–35.0) µg/mL in the group without complications.

The GCS scores and pH levels at emergency service admission were significantly lower in the severe intoxication group (p=0.043, and p=0.016, respectively) and the ICU admission group, and body temperature and serum glucose and lactate levels were significantly higher in these groups (p=0.005, p<0.001, and p=0.016, respectively; Tables 2, 3).

The median serum CBZ level was higher in the group of patients with convulsions than the group of patients without convulsions. However, the difference between these two groups was not statistically significant (27.5 µg/mL and 22.5 µg/mL, respectively; p=0.180). The CBZ level of the patient group with a GCS score <8 was statistically significantly higher than that in the patient group with a GCS score >8 (32 µg/mL and 20 µg/mL, respectively; p<0.001). The patient group with a GCS score <8 also demonstrated statistically significantly higher serum lactate and glucose levels (p=0.001, and p=0.005, respectively); however, the pH levels of that patient group were statistically significantly lower than the pH levels of the patient group with a GCS score >8 (p<0.001). A significantly negative correlation was found between the serum CBZ level and the

Table 2. Comparison of clinical and laboratory findings in all patients according to the classification of carbamazepine toxicity.

	Mild (n=11)		Moderate (n=17)		Severe (n=12)		p
Demografic findings							
Age* (year)	13.8	(6–18)	14	(1.5–17)	15.5	(11–17)	0.376
Male/Female (ratio)	4/7		8/9		2/10		0.238
GCS*	13	(9–15)^A	11.5	(4–15)^{AB}	8	(3–15)^B	0.043
SBP* (mmHg)	100	(80–120)	112	(80–140)	110	(57–120)	0.056
Body temperature* °C	36.0	(36–37.4)^A	36.5(36–38)^B		36.6	(36–40)^B	0.005
Laborotory findings							
Lactate level* mmol/L	10.5	(8–30)^A	18	(6–98)^{AB}	27	(15–136)^B	0.016
WBC Count* (cells/mm³)	9000 (6400–14900)		9920 (7170–24600)		10300 (6400–32100)		0.666
Blood Glucose* (mg/dL)	93	(80–142)^A	115	(91–170)^B	133	(104–540)^B	<0.001
Sodium* (mEq/L)	137	(133–142)	134	(128–142)	135	(128–138)	0.108
Potassium* (mEq/L)	4.3	(3.3–4.6)	3.8	(3.2–5.0)	3.4	(2.5–5.1)	0.054
pH*	7.36	(7.32–7.41)^A	7.35	(7.21–7.42)^{AB}	7.28	(6.93–7.40)^B	0.016

* Median (min–max); GCS – Glasgow Coma Scale, SBP – systolic blood pressure; WBC – white blood cell

Table 3. Comparison of the clinical and laboratory findings, according to whether the need for intensive care.

	Intensive Care Unit (n=18)		Emergency Service (n=22)		p
Demografic findings					
Age* (year)	15	(6–17)	14	(1.5–18)	0.916
Male/Female (ratio)	6/12		8/14		0.842
GCS*	8.5	(3–15)	14	(11–15)	<0.001
SBP* (mmHg)	110	(57–140)	100	(80–130)	0.402
Body temperature* °C	36.9	(36–40)	36.2	(36–37.4)	0.001
Laborotory findings					
Serum CBZ level* (µg/dl)	30.5	(14.6–58)	19.7	(12.5–35)	<0.001
Lactate level* mmol/L	26.5	(6–136)	11.5	(8–128)	0.008
WBC Count* (cells/mm³)	10910 (6400–32100)		9920 (6400–23660)		0.663
Blood Glucose* (mg/dL)	121	(89–540)	107	(80–170)	0.105
Sodium* (mEq/L)	135	(128–139)	135	(130–142))	0.150
Potassium * (mEq/L)	3.6	(2.5–4.6)	4	(3.2–5.1)	0.126
pH*	7.30	(6.93–7.40)	7.36	(7.28–7.42)	0.008

* Median (min–max); GCS – Glasgow Coma Scale, SBP – systolic blood pressure; CBZ – carbamazepine, WBC – white blood cell.

GCS score, but the serum CBZ level was found to be significantly positively correlated with the lactate level (r=−0.501 [p=0.001] *vs.* r=0.558 [p=0.002], respectively).

No statistically significant difference was found between the severe intoxication group and the mild and moderate intoxication groups with respect to blood pressure, white blood cell count, and sodium levels at admission (p=0.056, p=0.666, and

p=0.108, respectively). Similarly, with respect to these parameters, no statistically significant difference was found between the patient groups with complications and the groups that either required ICU admission or did not require ICU admission (p=0.109, p=0.279, and p=0.628; Table 3).

Gastric lavage was performed on 32 (80%) patients who were admitted to the hospital with in the first hour following CBZ intoxication, and they were administered activated charcoal. A single dose of activated charcoal was administered in 6 (15%) cases, and 26 (65%) patients received repeated doses of activated charcoal. Activated charcoal was not administered in eight (20%) cases. Hemodialysis were administered to one (2.5%) patient.

The mean hospital stay of the patients was 3 days (1–7 days). The mean admission duration in the pediatric ICU was 3 days (1–5 days). One case (2.5%) was fatal; in that patient, death occurred 12 hours after oral intake. The serum CBZ level of this patient was 58 µg/mL. The patient, who had serious hypotension and lactic acidosis at admission, died because of cardiac arrhythmia.

Discussion

Acute intoxication is an important cause of morbidity and mortality during childhood [1]. Acute CBZ overdose is an emergency situation that occurs relatively more frequently in the pediatric population, and it carries the potential risk of mortality [12]. Serious complications and death can be prevented by applying an appropriate supportive treatment and undertaking close monitoring [4].

Clinical symptoms due to CBZ intoxication usually occur within 1–3 hours. This duration may extend up to 30 hours when sustained-release CBZ tablets are ingested [4]. Patients that suffer from CBZ intoxication usually present with symptoms that impact their neurological, cardiovascular, and respiratory systems. Disorders of the gastrointestinal and urinary systems, hypotension, hypothermia-hyperthermia, vomiting, and impaired electrolyte balance are rare [4,9,13,14].

The severity of clinical presentation is associated with the amount of the ingested dose and the serum CBZ level [15]. Tibbals et al. [16] reported that the serum CBZ level is correlated with the severity of the patient's coma, convulsions, or hypotension, and the need for mechanical ventilation. Therapeutic and toxic levels of CBZ are 4–12 µg/mL and 20 µg/mL, respectively.

A serum CBZ level >40 µg/mL in adult patients is usually associated with coma, convulsions, breathing disorders, and cardiac complications [4]. Serious symptoms can appear in pediatric patients with lower serum CBZ levels (27–35 µg/mL) [17–19]. This situation is due to the relatively higher production of 11-epoxide as a toxic metabolite in pediatric patients in comparison with adult patients [11,20]. Therefore, according to our study, patients with serum levels of carbamazepine between 12 and 20 µg/mL (mild), between 20 and 30 µg/mL (moderate), and over 30 µg/mL (severity) were divided into three groups.

The neurological system is primarily affected in cases of acute CBZ intoxication [17]. It has been reported that convulsions occurred in 7–24% of CBZ overdose cases [11,18,21–23]. Norten and Robertson [21] reported that mean peak serum CBZ levels in patients with convulsions were higher than those in patients without convulsions (mean 33 *vs.* 21.3 µg/mL). Venci et al. [24] reported a positive correlation between increased levels of serum CBZ and convulsion risk. In the present study, the convulsion risk was found to be 35%. One patient was admitted with a clinical status of epilepticus. In the present study, the serum CBZ levels of the patient group with convulsions were higher than they were in the patient group without convulsions; however, the difference was not statistically significant (27.5 µg/mL and 22.5 µg/mL, respectively; p=0.180).

Altered levels of consciousness, which are considered to be the result of a sodium channel block, are the most common finding in cases of CBZ intoxication [11]. The frequency of coma due to CBZ overdose was reported to be 20–48% [6,11]. Studies have demonstrated a positive correlation between development of the risk of coma and serum CBZ levels. In the present study, we found a 25% risk for coma. There was a significant positive correlation between the serum CBZ level and the coma (r=0.454, p=0.003).

Brahmi et al. [6] and Günaydin et al. [2] reported a significantly negative correlation between serum CBZ levels at emergency service admission and concurrent GCS scores (r=-0.580 and r=−0.568; p=0.010 and p<0.001, respectively). With respect to the GCS score, Günaydin et al. [2] also detected a statistically significant difference between the group with a serum CBZ level >30 mg/L and the group with a serum CBZ level <30 mg/L. In this present study, a significantly negative correlation was found between the serum CBZ level and the GCS score that was similar to the findings reported in the literature (r=−0.501, p=0.001). This present study also found that the group with a GCS score <8 had statistically significantly higher serum CBZ, lactate, and glucose levels and statistically significantly lower pH levels than the group with a GCS score >8.

Cardiovascular toxicity due to CBZ overdose is rare [19,25]. Hypotension is a serious indicator of intoxication [11]. Apfelbaum et al. [25] reported that there is no correlation between the ECG findings and the serum CBZ level. In the present study, arrhythmia occurred in four (7.5%) cases, bundle

branch block occurred in two cases, and bradyarrhythmia occurred in one case. Sinus tachycardia, hypotension and hypertension developed in eight (20%), five (12.5%), and three (7.5%) cases, respectively.

Günaydın et al. [2] reported a positive correlation between serum CBZ levels and serum lactate levels, and the serum lactate level can be used as a prognostic indicator in patients with CBZ intoxication. Agulnik et al. [26] reported that serious lactic acidosis developed in a 15-year-old female patient with a serum CBZ level of 138 μg/mL. In the present study, we found a significantly positive correlation between serum CBZ levels and serum lactate levels (r=0.558, p=0.002).

Hyperglycemia can accompany CBZ intoxication [7,22,27,28]. Seymour [23] stated that the incidence of hyperglycemia is associated with high drug doses. In the present study the rate of hyperglycemia was 60%. In fact, a significantly positive correlation between serum CBZ levels and serum glucose levels (r=0.616, p<0.001) was found. The glucose level of the moderate-severe intoxication group was found to be significantly higher than the glucose level of the mild intoxication group. The serum glucose level of the group that was admitted to the ICU was higher than the group that did not need to be admitted to the ICU; however, the difference was not statistically significant.

Hyponatremia, hypokalemia, acidosis, and elevated liver enzyme levels rarely develop [4]. In the present study, hyponatremia, hypopotassemia, and elevated levels of liver function tests were detected in 13 (32.5%) cases, 10 (25%) cases, and 1 (2.5%) case, respectively. We also determined a significantly negative correlation between serum CBZ levels and pH levels (r=−0.665, p<0.001). The baseline pH value was found to be significantly lower in the severe intoxication group and the group that needed to be admitted to the ICU.

Hyperthermia can be due to the effects of an anticholinergic agent or it can a consequence of convulsive activity [11,29]. Some studies have reported case presentations in which body temperature is elevated in patients with CBZ intoxication [14,24]. Other case presentations have reported a correlation between CBZ intoxication and hypothermia [30]. In the present study, we found a significantly positive correlation between serum CBZ levels and body temperature (r=0.424, p=0.010). Moreover, body temperature at admission was found to be significantly high in the severe CBZ intoxication group and the ICU admission group.

The management of CBZ intoxication is almost always supportive treatment. It has been shown that gastric lavage and treatment using activated charcoal are useful therapies [2,9,14]. A single dose of activated charcoal can be administered by preserving the airway in cases in which patients with CBZ intoxication are admitted within two hours after acute overdose ingestion [19,31,32]. In the present study, six (15%) cases received a single dose of activated charcoal. It has been reported in the literature that administration of multiple-dose activated charcoal therapy is beneficial in cases of serious CBZ intoxication [6,14,33,34]. Studies conducted in the United States and Mexico have suggested that administration of multiple-dose activated charcoal therapy accelerates healing in patients that have ingested too much CBZ [4]. Several studies have also demonstrated that multiple-dose activated charcoal therapy provides effective outcomes, as do hemodialysis and hemoperfusion [35]. In the present study, multiple-dose activated charcoal was administered in 26 (65%) cases. The median serum CBZ levels in the groups that were administered single- and multiple-dose activated charcoal were 21.25 μg/mL and 27.85 μg/mL, respectively.

Despite significant improvements in hemodialysis technology and continuous venovenous hemofiltration, evidence supporting extracorporeal removal of a CBZ overdose is limited to case series studies [10,12,36–39]. The Extracorporeal Treatments in Poisoning Workgroup recommends extracorporeal removal of CBZ for severely intoxicated cases that progressively worsened despite administration of maximum supportive care (such as patients with multiple refractory seizures, hemodynamic imbalances requiring vasopressors, or life-threatening arrhythmias) [8]. In the present study, hemodialysis was administered in one (2.5%) case.

The incidence of mortality due to CBZ intoxication has been reported to be 1–38% [4,7,12]. The deaths were stated to be secondary to heart failure, aspiration, pneumonia, and septicemia [9]. In a study of 427 CBZ overdose cases, convulsion was reported to be the only clinical parameter associated with fatal outcome [15]. In the present study, only one case (2.5%) of exitus was found.

Study limitations

This present study had some limitations, the most important of which were its single-center design and its retrospective nature.

Conclusions

The present study's outcomes indicate that the GCS score at admission to hospital, the serum CBZ, glucose, pH, and lactate levels, and body temperature might be useful in predicting serious CBZ intoxication and prognosis in pediatric cases. Further prospective studies on this subject utilizing a larger case series are needed.

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