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Original Article

Risk factors and the outcome of therapy in patients with seizure after Carbamazepine poisoning: A two-year cross-sectional study

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ABSTRACT

Objective: We aimed to investigate the frequency of seizure after acute carbamazepine poisoning and the important risk factors related to the outcomes of therapy.

Methods: In this two-year cross-sectional study conducted in a University Hospital in Iran, 114 patients with acute carbamazepine poisoning were divided into two groups of with seizure (n = 8) and without seizure (n = 106) after intoxication. Demographic data, average amount of drug ingestion, time elapsed from ingestion to hospital admission, history of seizure before poisoning, mental status, visual disturbances and nystagmus, duration of hospitalization, the outcomes of therapy, arterial blood gas values and serum biochemical indices were compared between the two groups.

Findings: Patients with seizure had an estimated (Mean ± SD) ingestion of 14,300 ± 570 mg carbamazepine, which was significantly higher (P < 0.0001) than the seizure-free group (4600 ± 420 mg). The estimated average time between drug ingestion and hospital admission in patients with seizure and the seizure-free group were 515 ± 275 and 370 ± 46 minutes, respectively (P < 0.0001). In this study, 104 out of the total number of patients had recovered without any complication. Need for respiratory support, including airway support or intubation were the most recorded complication. One patient died after status epilepticus and aspiration pneumonia.

Conclusion: The ingested amount of carbamazepine and the time elapsed from the ingestion of drug to hospital admission may influence the occurrence of seizure after acute carbamazepine poisoning; however, the outcome of supportive care in these patients seems to be positive.

Keywords: Carbamazepine; outcome; poisoning; seizure

INTRODUCTION

Medical toxicologists commonly encounter poisoned patients who were exposed to neuro-psychoactive drugs, whereas seizure is considered as one of the most important clinical manifestations in these patients.[1] For therapeutic indications, carbamazepine may be prescribed for adults with a maximum dose of 1200 mg/day, and its overdose with higher doses is previously reported as a frequent nonbenzodiazepine cause of drug intoxication.[2,3] Acute carbamazepine intoxication can result in seizure in nonepileptic patients or may increase the frequency of seizure attacks in epileptic patients.[4,5] There are a limited number of published literature (which are mostly case reports) about the incidence of seizure after carbamazepine poisoning.[3,6-11] The mechanism of this seizure induction is not well defined yet and is just considered to be complex;[12-14] however, the metabolite of the drug is considered to be neurotoxic.[15,16] Carbamazepine induced dilutional hyponatremia is also a concern in patients with carbamazepine treatment, which may lead to seizure episodes.[17,18]

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In our clinical setting (Noor and Ali Asghar [PBUH] University Hospital, Isfahan, Iran), carbamazepine poisoning is one of the three most important causes of status epilepticus.[19] With regard to the serious complications of frequent seizure episodes and status epilepticus after carbamazepine poisoning (e.g., hypoxic brain damages in status epilepticus, sudden death with arrhythmia, rhabdomyolysis and aspiration pneumonia),[20,21] the evaluation of the associated risk factors for this type of seizure seems to be important. Therefore, this study was performed in order to increase the present knowledge about the frequency of seizure in carbamazepine poisoned patients and to define the important risk factors related to the outcomes of therapy, as well as the prognosis of these patients.

METHODS

This cross-sectional study was performed in the Department of Clinical Toxicology of Noor and Ali Asghar (PBUH) University Hospital (affiliated with the Isfahan University of Medical Sciences), which is the referral medical center for poisonings in the central part of Iran and is facilitated, staffed and designed for the management of poisoned patients, in which approximately 400 poisoned patients are admitted monthly.

During the 2 years study period, all intentionally and unintentionally carbamazepine poisoned patients with a positive and reliable history in whom drug poisoning was diagnosed clinically by the attending medical toxicologist[22] and confirmed by laboratory methods, were included in the study. These patients received the standard medical care (e.g., maintaining the airway, breathing and circulation, gastrointestinal decontamination with 1 g/kg of activated charcoal and other supportive measures as needed) according to the guidelines of the academic reference textbook of poisoning.[22]

Patients' blood samples were sent to the Noor hospital laboratory for the routine blood tests (e.g., complete blood counting [CBC], serum levels of sodium and glucose, blood urea nitrogen [BUN], serum creatinine and arterial blood gases [ABG]). The serum level of carbamazepine was determined by taking separate samples, and in a private laboratory setting outside the hospital using fluorescence polarization immunoassay method (TDx, Abbott Laboratories, IL, USA). These measurements were only confirmatory for the carbamazepine poisoning and were not used for pharmacokinetic-pharmacodynamic analysis.

Clinical and para-clinical symptoms of patients were evaluated by the attending medical toxicologist at the time of admission and during the next 48 h of supportive care/hospitalization. The outcome of treatment of patients was categorized on the basis of their clinical condition as recovery without complication, recovery with complication (aspiration pneumonia, renal failure, hypoxia, and encephalopathy, intubation with or without connection to the ventilator), and death. Diagnosis of complications was further confirmed by the relevant consultant (nephrologists, neurologists and anesthesiologist) physicians.

Patients were divided into two groups according to the eye-witnessed history of generalized tonic-clonic seizure after carbamazepine poisoning, before or after hospitalization. Demographic and clinical data of all patients (e.g., age, gender, estimated amount of carbamazepine ingestion, the time elapsed from taking drug to the hospital admission, duration of hospitalization, concurrent medication usage, past history of seizure, other clinical signs of carbamazepine poisoning, and blood biochemistry, e.g., blood glucose, BUN, serum sodium and serum creatinine, ABG values) were collected and recorded.

The study protocol was approved by the Institutional Board of Human Studies at the Isfahan University of Medical Sciences. In addition, after the study was accurately explained to each patient, informed consent was taken from them for inclusion to this study. If the patient was not able or had not the capacity for decision making (e.g., due to altered mental status conditions), informed consent for inclusion to this study were taken from the patients' first degree family member.

Descriptive analysis of the data was done on all baseline characteristics of the study patients. For continuous and quantitative variables, mean and standard deviation was calculated, and histograms were plotted to assess the distribution of these variables. In the case of categorical variables, frequencies were reported and tested. Mean values of continuous quantitative variables were compared between the two groups (with seizure and without a seizure) using Mann–Whitney U-test. For categorical variables that had cell counts <5 in the corresponding contingency table, the Fisher's exact test was used. All P values were based on two-sided tests and significance was set at a $P < 0.05$. Data processing was performed using SPSS statistical software (SPSS Inc., Chicago, IL, USA) version 15.

RESULTS

A total of 114 patients (43 males) with acute carbamazepine poisoning with a mean age of

25.4 years (range: 12–80 years) were completely studied during the 2 years period of study. Eight cases out of the total 114 patients had seizure episodes after poisoning and 106 patients were seizure-free. Statistical analysis of the median age in patients with and without the seizure manifestation, showed that there was no significant relationship between the age and occurrence of the seizure (P = 0.318, Mann–Whitney U-test). Patients with seizure episodes before or during the hospital admission had an estimated carbamazepine ingestion of 14,300 ± 570 mg while the seizure-free patients had ingested 4600 ± 420 mg (P < 0.0001, Mann–Whitney U-test); in both groups, patients had consumed a generic 200 mg tablet dosage form. The estimated average time between drug ingestion and hospital admission in patients with seizure and the seizure-free group were 515 ± 275 and 370 ± 46 min, respectively (P < 0.0001, Mann–Whitney U-test).

Sixty-four cases (60.4%) of seizure-free poisoned patients were female which was in contrast to the gender distribution in patients with seizure group in which seven out of all eight patients were female. Gender distribution in these groups (with or without seizure) was not statistically significant (P = 0.255, Fisher's exact test).

Fifty-nine patients (51.8%) had a history of carbamazepine alone intoxication, and the others had mixed poisoning mostly with antidepressants, antipsychotics, benzodiazepines and other anti-convulsants. Occurrence of seizure in these two groups of carbamazepine poisoned patients was not statistically significant (P = 0.152, Fisher's exact test).

Clinical manifestations of carbamazepine poisoned patients of both groups at the time of hospital admission are presented in Table 1. Among the all poisoned cases in this study, eight patients (7%) had seizure episodes before or during the hospital admission; of these cases, five had seizure before hospital admission, two cases had seizure during the hospitalization in the ward (isolated and generalized tonic-clonic seizure), and one of them had generalized tonic-clonic seizures both at the arrival time and also during the hospitalization time. Four out of the five patients who had a seizure attack before hospitalization had isolated seizure episodes, and one patient had two seizure episodes within a 10-min time interval. The presence or absence of previous history of seizure (before poisoning with carbamazepine) was not significantly different between the two groups (P = 0.437, Fisher's exact test).

Vital signs, biochemical indices and the ABG values of the studied patients are summarized in Table 2. Arterial blood pH was significantly lower in patients with seizure (P = 0.003, Mann–Whitney U-test) and other blood gas values were not statistically different in the two groups.

Table 1: Clinical characteristics of carbamazepine poisoned patients with and without seizure at the time of hospital admission

Clinical characteristics	Frequency in patients with seizure (n=8)	Frequency in patients without seizure (n=106)	P*
Co-ingestion of other drugs			0.152
Yes	6	49	
No	2	57	
Previous history of seizure			0.437
Yes	4	34	
No	4	72	
Level of consciousness			0.340
Conscious	1	17	
Lethargic	3	61	
Stupor	2	20	
Coma	2	8	
Ataxia			0.467
Present	2	45	
Absent	6	61	
Vomiting (after admission)			0.444
Yes	1	30	
No	7	76	
Vision disturbances (blurred vision/diplopia)			1.000
Present	2	27	
Absent	6	79	
Nystagmus			0.598
Present	0	16	
Absent	8	90	
Outcome of therapy			0.085
Recovery without complication	7	97	
Recovery with complication	0	9	
Death	1	0	

*Fisher's exact test

The total hospitalization time period in patients who had seizure and in seizure-free cases were 2.75 ± 0.7 and 2.4 ± 0.1 days, respectively, which was not statistically different (P = 0.420, Mann–Whitney U-test). In this study, 104 out of the total number of 114 patients had recovered without any complication [Table 1]. Need for respiratory support including airway support or intubation were the most recorded complication. One patient died after status epilepticus and aspiration pneumonia.

DISCUSSION

In this two-year cross-sectional study, we aimed to assess some probable risk factors in the course of hospitalization for patients who had a seizure after

Table 2: Vital signs, serum biochemical indices and arterial blood gas values of carbamazepine poisoned patients with and without seizure at the time of hospital admission

Variables	Patients with seizure (*n*=8)	Patients without seizure (*n*=106)	*P**
Vital signs			
Respiratory rate (/min)	17.3±3.5	16.2±4.6	0.549
Pulse rate (/min)	88.3±6.9	84.3±8.1	0.177
Systolic blood pressure (mmHg)	92±15	101±13	0.064
Serum biochemical indices			
Serum sodium level	139.8±1.6	137.8±0.47	0.323
Blood glucose level	107.3±13.1	123.0±5.8	0.583
BUN (mg/dl)	13.8±2.267	10.56±0.313	0.019
Creatinine (mg/dl)	1.12±0.124	0.94±0.026	0.096
Arterial blood gas			
pH	7.28±0.025	7.39±0.063	0.003
$PaCO_2$ (mmHg)	36.25±5.543	38.68±9.597	0.659
HCO_3– (mEq/L)	19.48±3.746	23.09±4.350	0.207
O_2 saturation (%)	78±15	92.44±7.113	0.061

Data presented as mean±SD. *Mann-Whitney U-test. $PaCO_2$=Arterial carbon monoxide pressure, BUN=Blood urea nitrogen, SD=standard deviation

carbamazepine poisoning. Since seizure is dangerous and can lead to some serious and permanent complications for patients, thus having some insights about the factors, which may be related to the final outcome and prognosis of these patients seems necessary for emergency medicine practitioners and medical toxicologists.[12]

Our patients were predominantly female which may be due to the more prevalent depression and suicidal gesture actions in women in the Middle East region.[23] It also seems that using the tablet ingestion method for suicide in women is more common which is consistent with previous studies.[13] The average age of the patients was 25.4 years and the most prevalent age class was 20–29 years, which could be due to more prevalent prescription of carbamazepine for the youth as an anticonvulsant drug, here in Iran.[24]

In this study, the average estimated amount of ingested carbamazepine in the all patients in both groups was 4900 ± 470 mg (approximately 24–25 of 200 mg tablets) and the difference between the amounts of carbamazepine ingestion was statistically significant between the two groups. This may indicate that this seizure is not an idiosyncratic complication, but it is dose-dependent. Higher dosage consumption in poisoning with this drug may increase the seizure probability, which may be due to the production of more neurotoxic metabolite.[25]

In comparison of concurrent drug consumption in seizure patients and nonseizure patients, it was observed that the percentage of patients using concurrent medications with carbamazepine was higher in seizure patients than in nonseizure patients (75% vs. 46.2%). It can be justifiable because most concurrent drugs consumption can result in seizure in high doses like tramadol, lamotrigine, tricyclic antidepressants, antipsychotics, phenytoin, etc. However interestingly, there was no statistically significant relationship between concurrent consumption of other drugs and the occurrence of seizure episodes. The mean duration of hospital stay was 2.42 days. Since the ingested carbamazepine was a controlled-release formulation, serum levels often peak between 6–24 h after consumption.[2] The average days of hospitalization in patients with seizure was more than nonseizure patients (2.75 vs. 2.40), which is justified by the fact that the seizure is a complication that needs more care and patient monitoring. Meanwhile, we have not found any statistically significant relationship between duration of hospitalization and occurrence of seizures.

The average estimated time elapsed from carbamazepine ingestion and the first therapeutic intervention for the whole 114 patients was 380 min (6 h and 20 min). In patients with seizure after carbamazepine poisoning, this elapsing time was significantly higher, which may indicate that the delay before hospitalization may increase the chance of poisoning complications including seizures.

In our study, most of the carbamazepine poisoned patients were lethargic at the time of hospital admission, which is justifiable with the fact that lethargy is a known side-effect of carbamazepine. We have not found any statistical significance between the consciousness status (e.g., conscious, lethargic, stupor, and coma) of the two groups of patients with seizure and without it. Paradoxical behavior of carbamazepine at high and toxic doses may probably justify this finding.

Interestingly, history of seizure before carbamazepine poisoning was not a risk factor for presenting seizure after consuming toxic amounts of this drug, whereas 50% of patients with seizure had not any previous convulsive history. This is in contrast to a previous study.[14]

Outcomes study of the patients showed that the most frequently outcome was recovery without complications, which may also depend on the quality of care in this medical center. Higher percentage of discharge or recovery without complication in nonseizure patients may indicate a better prognosis in this group. Furthermore, higher percentage of discharge with complications or death in patients with seizure may show poor prognosis in this group of patients, despite

we have not found any statistical relationship between seizure occurrence and the prognosis in our patients.

Arterial pH of blood in patients with seizure was more acidic than the other group which may be due to the increased oxygen consumption and hypoxia associated with seizure producing anaerobic metabolism of body tissues and production of lactic acid, which may increases the chance of metabolic acidosis.[6] The mean serum sodium level in the seizure group was higher than in the nonseizure group but this difference was not statistically significant. According to a previously published study, we were expecting a below normal level of sodium in the group of patients with seizure;[17] but in fact the mean serum sodium level in both groups was in the normal range. However, this is not consistent with the probable dilutional hyponatremia, which is expected after chronic use of carbamazepine. Mean serum glucose level in patients with seizure was less than nonseizure patients, which may be due to higher consumption of glucose followed by muscle spasms, which is caused by convulsion and the increased energy consumption in the brain following seizure. Despite the non-significance of the p value, the higher number of heart rate and respiratory rate in patients with seizure comparing to seizure-free cases, is justifiable following seizure attacks..[2]

The mean blood pressure was lower in seizure patients than nonseizure patients. This can be justified by considering that patients with seizure consumed higher drug doses than nonseizure patients and hypotension is one of the known probable complications after carbamazepine poisoning.[2]

Over all 27.2% of the whole 114 poisoned patients had vomiting before or after hospitalization. The frequency of vomiting was higher (near to twice) in the nonseizure patients group than patients with seizure, which can be explained by the fact that vomiting can reduce the acute clinical manifestations of poisoning by displacing the ingested drug out of the body. These are despite the fact that vomiting can also increase the chance of seizure through stimulating the nervous system.[2] Finally, a significant relationship between the incidence of vomiting and seizures was not observed.

About 25.4% of admitted patients suffered from vision disorders, including diplopia and blurred vision, which shows that vision disorders following carbamazepine poisoning are a relatively common problem. The frequency of vision impairment in both groups of seizure and nonseizure patients were almost equal, which may show that the vision disorder may not have a prognostic value for the occurrence of seizure episodes.

The most important limitation for our study was the fact that despite the 2 years period of the study, the sample size of patients with seizure was quite small which prevented us from performing more relevant statistical analysis like logistic regression. This may make us to consider the results more conservatively and avoid forthright extrapolation of them.

In conclusion, it seems that the ingested amount of carbamazepine and the time elapsed from the ingestion of drug to the first medical care facility or hospital admission are important factors that may partially influence the occurrence of seizure in carbamazepine poisoned patients. According to our results, the prognosis of these patients with normal supportive therapy is not poor. Further studies with larger sample size are recommended.

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AUTHORS' CONTRIBUTION

AY, NEM, AMS and GM contributed in designing and conducting the study. MS collected the data and NEM did the data analysis. AMS and LZ rechecked the statistical analysis and prepared the manuscript. All authors have assisted in the preparation of the manuscript and have read and approved its content and are accountable for all aspects of the work.

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