ORIGINAL ARTICLE

Seizure in Patients with Antiepileptic Drug Overdose: Study on Patients Admitted To Shoushtari Hospital in Shiraz

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Abstract

Background: Poisoning with non-barbiturate anti-epileptics (carbamazepine, sodium valproate and phenytoin) shows a growing trend. The objective of this study was to investigate clinical manifestations of poisoned patients with these medications.
Methods: This prospective study was conducted in the Shiraz Shoushtari Hospital during a two-year period from 2010 to 2012. Poisoning was confirmed according to patient's history and clinical examinations. Patients who consumed other anti-epileptics and those who consumed other medications (except anti-epileptics) were excluded from the study. Using the AVPU scale, level of consciousness was graded. Clinical manifestations and demographic features of patients were entered into a predesigned checklist.
Results: In total, 200 patients were studied, of which 36% were men. The mean (SD) age of patients was 26.2 (11.7). The most common overdosed medication was sodium valproate, followed by carbamazepine and phenytoin. Decreased consciousness was seen in 34.5% of patients. Sixty-three patients (31.5%) had metabolic acidosis, 15 patients (7.5%) had respiratory alkalosis and 4 patients (2%) had mixed acid-base disorders. Hypercalcemia was the most common electrolyte disorder (49%). Eighty-four patients (42%) had developed seizure. The highest proportion of seizure occurred in patients with multiple drug overdose (100%) followed by phenytoin overdose (60%), carbamazepine overdose (42%) and sodium valproate overdose (33%).
Conclusion: This is the first study that shows high rates of seizure in patients poisoned with antiepileptic medications. Due to the growing trend of poisoning with these medications, it is necessary to take appropriate preventive measures include restriction on sale of these medications in pharmacies, psychiatric counseling for the patients and medication safety training to the patients.

Keywords: Carbamazepine; Drug Overdose; Phenytoin; Seizures; Valproic Acid

INTRODUCTION

Non-barbiturate anti-epileptics including carbamazepine, sodium valproate, phenytoin are the most common medications used for treatment of seizure and epilepsy. These medications, in addition to the treatment of epilepsy, are used for the treatment of psychiatric and neurologic disorders such as bipolar disorder, migraine, trigeminal nerve pain, diabetic ulcers, wound healing and cardiac arrhythmia (1,2).

Besides, patients with epilepsy in the majority of cases are involved with mental disorders such as depression (3). Therefore, they are vulnerable to high risk behaviors. Considering these factors, these medications are widely consumed among patients with the underlying mental illnesses and thus the possibility of self-poisoning with them is very high (1-3). On the other hand, poisoning with these medications may occur accidentally as a result of unintended dose increase (2). Anti-epileptic drug overdose is only 1.1% of reported poisonings in Iran (4); however, recent reports show a growing trend of this type of poisoning (2).

Poisoning with antiepileptics mainly affects central nervous system. Consequently, loss of consciousness, hyperreflexia, hyporeflexia, ataxia, tremor, hallucinations, pupillary changes, dizziness, headache, insomnia, convulsions, and even death are the most expected symptoms (1-3,5).

Due to the relatively easy availability of these medications and the increasing trend of suicide with them, study on poisoning with these medications is essential. The aim of this study was to investigate clinical manifestations of poisoning with anti-epileptics (carbamazepine, sodium valproate and phenytoin), complications, morbidities and mortalities in poisoned patients admitted to the Shoushtari Hospital, Shiraz.

METHODS

This prospective study was conducted on all poisoned patients with carbamazepine, sodium valproate and phenytoin during a two-year period from 2010 to 2012. Poisoning was confirmed according to patient's history and clinical examinations. Patients who consumed other anti-epileptics and those who consumed other medications (except anti-epileptics) were excluded from the study. Using the AVPU scale, level of consciousness was graded (6). Based on this scale, patient alertness is determined as Alert (A), responsive to verbal stimuli (V), responsive to painful stimuli (P) and unresponsive (U). Clinical manifestations and demographic features of patients were entered into a

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predesigned checklist.

Data analysis was done with the SPSS for windows, version 11.5 (SPSS Inc., Chicago, IL, USA). The graphs were plotted using the Microsoft Excel (Microsoft Corp., Redmond, WA, USA). Results are shown with mean and standard deviation (SD) for normally distributed variables and with median and interquartile range (IQR) for non-normally distributed variables. Categorical data are shown with frequency and percentage.

RESULTS

Demographic features

In total, 200 patients were studied, of which 36% were men. The mean (SD) age of patients was 26.2 (11.7). Most patients were among the 20-25 years age group (Figure 1). Forty-eight patients (26%) had a previous suicidal attempt. Median (IQR) of the time interval between overdose and presentation to emergency department was 5.2 (1-24) hours. The reason of poisoning was suicide in 141 cases (70.5%) followed by unintentional consumption of the medication in excess of normal dosage in 53 cases (26.5%) and accidental consumption of antiepileptics instead of other medications in 6 cases (3%).

Clinical manifestations

The most common overdosed medication was sodium valproate, followed by carbamazepine and phenytoin (Figure 2). Clinical manifestations of patients are summarized in table 1. Decreased consciousness was seen in 34.5% of patients. Considering the size of pupil, mydriasis was present in 34% and mid-size pupil in 32% of patients. Regarding acid-base disturbances, 63 patients (31.5%) had metabolic acidosis (22 cases with carbamazepine, 31 cases with sodium valproate, 3 cases with phenytoin and 7 cases with co-ingestion of all 3 medications), 15 patients (7.5%) had respiratory alkalosis (4 cases with carbamazepine, 10 cases with sodium valproate and 1 case with co-ingestion of all 3 medications) and 4 patients (2%) had mixed acid-base disorders (2 cases with phenytoin and 2 cases with sodium valproate).

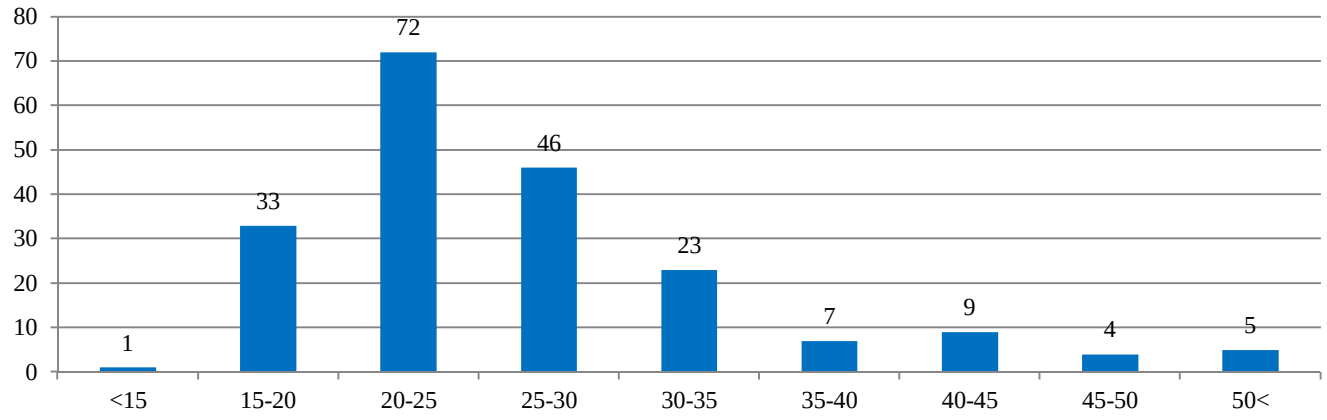

Figure 1. Age distribution of patients (n = 200)

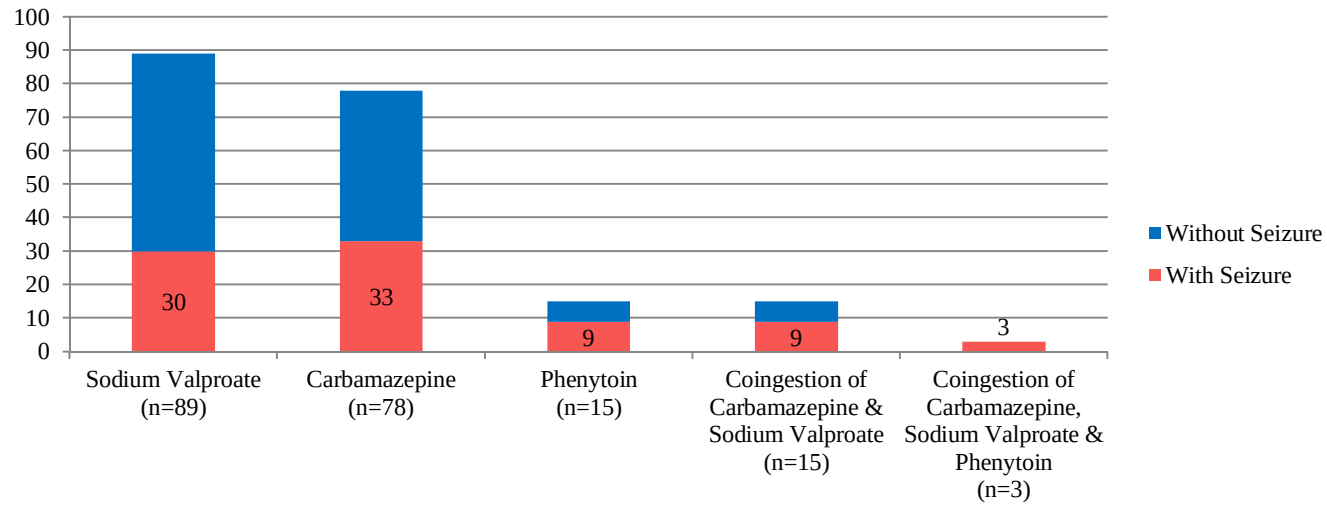

Figure 2. Frequency of seizures occurred in patients with antiepileptic drug overdose (n = 200)

In terms of electrolyte disorders, the most frequent disorder was hypocalcemia which was seen in 49% of patients (56 cases with carbamazepine, 52 cases with sodium valproate). Hypercalcemia was observed in only one patient who overdosed phenytoin. Twenty-five patients including 12 cases with carbamazepine overdose and 13 cases with sodium valproate developed hyponatremia, while one patient who was poisoned with carbamazepine developed hypernatremia. Hypokalemia was detected in 27 patients (15 cases with carbamazepine, 11 cases with sodium valproate, and 1 case with phenytoin) and hyperkalemia in 6 patients (2 cases with carbamazepine, 2 cases with sodium valproate and 1 case with phenytoin).

Eighty-four patients (42%) had seizure which 57 of them had generalized tonic colonic seizure and 27 had focal seizure. The highest proportion of seizure occurred in patients with multiple drug overdose (3 out of 3 patients (100%) with co-ingestion of all 3 medications and 9 out of 15 patients (60%) with co-ingestion of carbamazepine and sodium valproate) followed by phenytoin overdose (9 out of 15 patients (60%)). In the next ranks, rate of seizure was 42% in carbamazepine overdose (33 out of 78 patients) followed by 33% in sodium valproate overdose (30 out of 89 patients) (Figure 2).

Treatment and outcomes

Eleven patients (5 cases with carbamazepine, 5 cases with sodium valproate and 1 case with phenytoin overdose) were hospitalized in intensive care unit due to reduced consciousness, aspiration pneumonia and low O2 saturation. Gastric lavage was performed in 100% of cases. Ninety percent of patients were treated with multiple dose activated charcoal and 10% with single dose activated charcoal. Other treatments included sodium bicarbonate (58.5%), L-carnitine (13%) and calcium gluconate (10.5%). For 11 patients (5.5%) mechanical ventilation was instituted and for 6 patients (3%) hemodialysis was done. Benzodiazepines (diazepam and midazolam) were used for treatment of all patients with seizure attacks. Only two patients (1%) died (one case with carbamazepine and one case with sodium valproate overdose) which was due to status epilepticus and aspiration pneumonia.

Table 1. Clinical manifestations of patients (n=200)

Feature	No. (%)
Level of consciousness (Based on AVPU scale)	
Alert	131 (65.5)
Responsive to Verbal stimuli	20 (10)
Responsive to Painful stimuli	38 (19)
Unresponsive	11 (5.5)
Pupil size	
Midsize	64 (32)
Mydriasis	68 (34)
Miosis	40 (20)
Pin point	28 (14)
O_2 Saturation	
<60%	7 (3.5)
60-90%	127 (63.5)
>90%	66 (33)
Acid-Base disturbances	
None	118 (59)
Acidosis	63 (31.5)
Alkalosis	15 (7.5)
Mixed	4 (2)
Electrolyte disturbances	
Hyponatremia (<133 mEq/L)	25 (12.5)
Hypernatremia (>145 mEq/L)	1 (0.5)
Hypokalemia (<3.5 mEq/L)	27 (13.5)
Hyperkalemia (>5mEq/L)	6 (3)
Hypocalcemia (<8.5 mg/dL)	98 (49)
Hypercalcemia (>10 mg/dL)	1 (0.5)
Seizure	
None	116 (58)
Generalized tonic colonic seizure	57 (28.5)
Focal seizure	27 (13.5)

DISCUSSION

In this study, 200 patients with carbamazepine, sodium valproate and phenytoin overdose that were admitted to Shiraz Shoushtari Hospital were studied. The majority of patients were women which is similar to the study by Nixon et al. (7). Also, in their study, poisoning with carbamazepine poisoning was more common similar to our findings (7). In the present study, a high percentage of patients had an episode of seizure which was proportionately higher in poisoning with sodium valproate and carbamazepine. This finding is contrary to previous studies that showed seizure as an uncommon feature after poisoning with non-barbiturate anti- epileptics (8,9). In a study by Isbister et al. seizure was seen in 2% of patients poisoned with sodium valproate (8). Spiller and Carlisle reported status epilepticus in 2 poisoned patients with high dosage of carbamazepine (10). Regarding carbamazepine overdose, it has been shown in numerous studies that a history of seizure and poisoning with high doses are the major risk factors for seizure (9-11).

In study on 50 patients who were poisoned with phenytoin, Stilman et al. showed seizure in 14 patients (28%) (12). It has been shown that blood phenytoin concentration of higher than 30-50 mg/L may increase the risk for seizure and coma (12,13). Except this reason, other possible causes of seizure with antiepileptic

medications are hypocalcemia, infection, head injury or withdrawal syndrome in patients who are simultaneously opioid abusers (13). In this regard, in the present study, hypocalcemia was one of the most common clinical presentations.

In this study, metabolic acidosis was a very common finding especially in sodium valproate poisoned patients. Hypocalcemia was the most common electrolyte disorder in our study; whereas, in the study by Spiller et al, hypokalemia was the commonest (9). In the present study, loss of consciousness was present in approximately one third of patients which was similar to the findings of Isbister et al.'s study (8), and less than findings of Behnoosh et al. (44.5%) (14). Hypokalemia was found in 13.5% of our patients which was almost similar to the findings of Behnoosh et al. (11.8%) (14).

In the present study, we found that patients with multiple drug overdose developed more complications. Moreover, case fatality rate in our study was 1% which was lower than study of Isbister et al. (2%) and Behnoosh et al. (2%) (8,14).

LIMITATIONS

In this study, serum level of medications was not measured and also there was no history about the amount of medication ingested by the patients. Also, some patients had concomitantly ingested multiple types of the antiepileptic medications which can affect the interpretation of results.

CONCLUSION

This is the first study that shows high rates of seizure in patients poisoned with antiepileptic medications (carbamazepine, sodium valproate and phenytoin). Due to the growing trend of poisoning with these medications, it is necessary to take appropriate preventive measures include restriction on sale of these medications in pharmacies, psychiatric counseling for the patients, medication safety training to the patients and educating the patients that consumption of these medications with more than prescribed dosage not only does not control seizure, but also expose them to risk of seizure.

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