Antiepileptic drug poisoning: Three-year experience

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ABSTRACT

Introduction: Antiepileptic drugs, which are also called anticonvulsants, are used in the therapy and prophylaxis of epileptic seizures. The purpose of this paper was to investigate the relevant epidemiological data and to determine which of these drugs was the most frequent cause of intoxication. Another purpose of this study was to determine the neurological, cardiac, and biochemical problems caused by antiepileptics.

Material and method: This retrospective study included 95 consecutive patients under 18 years of age with antiepileptic intoxication, presenting to and being followed-up in, the Toxicology Unit between January 2010 and February 2013. The data were obtained by screening the patient files.

Results: Of the cases, 67 (70.5%) were self-poisoned by first generation antiepileptics (FGAEs) and 28 (29.5%) by second generation antiepileptics (SGAEs). The Glasgow Coma Scale (GCS) scores and the serum lactate levels of the patients poisoned by FGAEs and SGAES on admission to emergency department were 15 (25th: 12; 75th: 15; 95th: 15; IQR: 3) and 1.9 (25th: 1.4; 75th: 3.1; 95th: 5.6; IQR: 1.7), and 15 (25th: 14.3; 75th: 15; 95th: 15; IQR: 0.75) and 1.07 (25th: 0.9; 75th: 1.6; 95th: 5.5; IQR: 0.71), respectively. The serum lactate levels of patients poisoned by FGAEs were significantly higher (p < 0.001). Among the cases poisoned by carbamazepine, the most frequent cause of intoxication, the GCS score was significantly lower and serum lactate level was significantly higher in the group with high serum levels of carbamazepine (p = 0.004 and p < 0.001, respectively). In cases poisoned by valproic acid (VPA), the second frequent cause of intoxication, there was neither a significant association between the serum VPA level and the GCS score, nor between the serum lactate level and the systolic blood pressure (p = 0.470, p = 0.897, and p = 0.088, respectively). However, there was a positive correlation between the serum VPA level and the serum ammonia level (kk = 0.742, p < 0.001).

Conclusion: First generation antiepileptics are more toxic than SGAES. In patients with serum carbamazepine level, particularly those over 30 mg/L, serious disorders of consciousness, cardiovascular toxicity, and metabolic disorders may occur. In VPA intoxication, there is a positive correlation between the serum VPA levels and ammonia levels. On account of this finding, one should be more careful about hyperammonemic hepatic encephalopathy as the serum VPA level rises.

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1. Introduction

Antiepileptic drugs, which are also referred to as anticonvulsants, are used in the treatment and prophylaxis of epileptic seizures. The first antiepileptics, which were introduced to clinical use in 1939, were phenytoin and phenobarbital. These drugs were followed by first generation antiepileptics (FGAEs), such as carbamazepine and valproic acid (VPA), and later, by second generation antiepileptics (SGAEs), namely gabapentin and lamotrigine. Overdose of FGAEs has the potential of causing serious intoxication. Due to their narrow therapeutic windows, they may cause intoxications even at therapeutic doses. Acute toxicity caused by these drugs can be due to unintentional or suicidal intake, as well as to chronic use for therapy [1,2]. The purpose of this study was to assess the relevant epidemiological data, to find which of the antiepileptics was the most frequent cause of intoxication, and to determine the neurological, cardiac, and biochemical problems caused by antiepileptics. Another purpose of the study was to assess in particular the correlation between the levels of carbamazepine and VPA and the clinical picture in antiepileptic intoxications, and to compare the efficacies of different therapeutic approaches.

2. Material and method

2.1. Study design and population

In the Toxicology Unit of our Emergency Department, patients presenting with unintentional or suicidal poisoning are hospitalized and followed-up by specialists and resident physicians of emergency medicine. This unit has intensive care beds for the follow-up of patients requiring mechanical ventilation. This retrospective study comprised 95 consecutive patients aged 18-year-old and older with antiepileptic intoxication, presenting to and being followed-up in our Toxicology Unit between January 2010 and February 2013. The data were obtained by reviewing the patient files.

2.2. Study protocol

The patients were evaluated in terms of gender, age, the drugs they were exposed to or took, the serum drug levels, the route and reason for taking the drugs (unintentional or suicidal), the clinical picture, the therapeutic methods applied, complications, the length of hospitalization, and mortality.

2.3. Collection of data and statistical analysis

In this retrospective study, the data were obtained by reviewing the patients’ files. The study included all patients between the ages of 18 and 80 with antiepileptic intoxication who had been hospitalized in the Toxicology Unit for at least 24 h for examination and therapy.

Statistical analysis was performed using SPSS v.15.0 for Windows. Both visual (histogram and probability graphs) and analytical (Kolmogorov–Smirnov and Shapiro–Wilk tests) methods were used to determine if the data were normally distributed. Descriptive variables are expressed as mean ± SD for data that are normally distributed and as median and interquartile range (IQR) for variables that are not normally distributed. Clinical and laboratory characteristics were evaluated via Mann–Whitney U test for variables without normal distribution. Patients were divided into three groups according to their level of drug. Comparison of these three groups by the Kruskal–Wallis test was used. When necessary, the Mann–Whitney U test with the Bonferroni correction was used to compare variables. The Spearman’s rho correlation test was performed for correlations. A p value of <0.05 was accepted as statistically significant with 95% confidence interval.

The study protocol was approved by the local ethics committee and conducted in accordance with the Declaration of Helsinki and Good Clinical Practices.

3. Results

3.1. Demographic data

The median age of the 95 patients included in the study was 21 (25th: 19; 75th: 31; 95th: 48.6; IQR: 12) years. Of 95 patients, 24 (25.3%) were male and 71 (74.7%) were female, with a male:female ratio of 1:3. The median age of males was 25.5 (25th: 20; 75th: 35; 95th: 71.6; IQR: 15) years and that of females was 20 (25th: 19; 75th: 29; 95th: 49.2; IQR: 10) years. The cause of intoxication in 91 (95.8%) patients was taking an excessive amount of the drug for suicidal purpose, and in 4 (4.2%), the cause was a side-effect of the drug used for therapy.

All of the cases were self-poisoned by the oral route. Apart from the patients with intoxication as the side-effect of the drugs, all patients self-poisoned for suicide administered gastric lavage and activated charcoal. Of the cases, 67 (70.5%) were poisoned with FGAEs and 28 (29.5%) with SGAES. Carbamazepine and VPA poisonings were the most frequent intoxications, in 40% (n = 38) and 27.4% (n = 26) of the patients, respectively. The demographic data of the patients have been summarized in Tables 1 and 2, and the

| Table 1: Age distribution of patients. |
|---------------------------------------|
| Age group (years) | Number (n) | Percent (%) |
|-------------------|------------|-------------|
| 18–20             | 44         | 46.3        |
| 20–30             | 25         | 26.3        |
| 30–40             | 15         | 15.8        |
| 40–50             | 7          | 7.4         |
| 50–60             | 2          | 2.1         |
| 60–70             | 1          | 1.1         |
| 70–80             | 1          | 1.1         |
| Total             | 95         | 100.0       |

| Table 2: Age and gender distribution of patients. |
|-------------------------------------------------|
| Gender  | Number (n) | Median age (years) |
|---------|------------|--------------------|
| Male    | 24(25.3%)  | 25.5 (25th: 20; 75th: 35; 95th: 71.6; IQR: 15) |
| Female  | 71(74.7%)  | 20 (25th: 19; 75th: 29; 95th: 49.2; IQR: 10) |
| Total   | 95 (100%)  | 21 (25th: 19; 75th: 31; 95th: 48.6; IQR: 12) |
distribution of intoxicating drugs has been presented in Tables 3 and 4.

### 3.2. Primary results

The median GCS score of the patients on admission to emergency department was 15 (25th: 13; 75th: 15; 95th: 15; IQR: 2). The electrocardiograms of the patients at the time of presentation demonstrated normal sinus rhythm in 74 (77.9%), sinus tachycardia in 18 (18.9%), sinus bradycardia in 2 (2.1%), and left branch block in 1 (1.1%). As therapy, 58 (61.1%) patients received general treatment of poisoning and supportive therapy. Of the patients, 22 (23.2%) patients received hemoperfusion, 7 (7.4%) received carnitine, 6 (6.3%) received carnitine and hemoperfusion, and 2 (2.2%) received NaHCO₃. Only 5 (5.3%) patients required mechanical ventilation, and 1 (1.1%) patient died. Of the 5 patients who underwent mechanical ventilation, 2 had disorder of consciousness due to carbamazepine, 2 had ammonemic hepatic encephalopathy and lactic acidosis due to VPA, and 1 had disorder of consciousness, lactic acidosis, and consequently, pneumonia due to gabapentine intoxication. One patient, who had a disorder of consciousness and lactic acidosis caused by gabapentine intoxication received mechanical ventilation, but died of the consequently developing pneumonia and septic shock (Table 5).

The Glasgow Coma Scale (GCS) scores and the serum lactate levels of the patients poisoned by FGAEs and SGAEs on admission to emergency department were 15 (25th: 12; 75th: 15; IQR: 3) and 1.9 (25th: 1.4; 75th: 3.1; IQR: 1.7), and 15 (25th: 14.3; 75th: 15; 95th: 15; IQR: 0.75) and 1.07 (25th: 0.9; 75th: 1.6; 95th: 5.5; IQR: 0.71), respectively. The serum lactate levels of patients poisoned by FGAEs were significantly higher ($p < 0.001$). There was no significant difference among the patient groups poisoned by FGAEs and SGAEs in terms of age, GCS score, and the length of hospitalization ($p = 0.459$, $p = 0.055$, and $p = 0.774$, respectively) (Table 6).

### 3.3. Secondary results

We assessed the cases poisoned by carbamazepine, the most frequent cause of intoxication in our study, in terms of association between the serum carbamazepine level and the age, the GCS score and also between the serum lactate level and the systolic blood pressure on admission to emergency medicine. We divided the carbamazepine poisoning patients into 3 groups according to serum carbamazepine levels as follows: under 15 mg/L (Group 1, $n = 12$), between 15 and 30 mg/L (Group 2, $n = 13$), and over 30 mg/L (Group 3, $n = 13$). We observed that in the group with high levels of carbamazepine levels, GCS score was significantly lower, and the serum lactate level was significantly higher ($p = 0.004$ and $p < 0.001$). When the cause

### Table 3
Classification of antiepileptic drugs.

| Drugs         | Number (n) | Percent (%) |
|---------------|------------|-------------|
| First generation | 67         | 70.5        |
| Second generation | 28         | 29.5        |

### Table 4
The distribution of patients poisoned drugs.

| Drugs         | Number (n) | Percent (%) |
|---------------|------------|-------------|
| Carbamazepine | 38         | 40.0        |
| Valproic acid | 26         | 27.4        |
| Gabapentin    | 10         | 1.5         |
| Topiramate    | 5          | 5.3         |
| Levetiracetam | 7          | 7.4         |
| Pregabalin    | 3          | 3.2         |
| Lamotrigine   | 2          | 2.1         |
| Fenobarbital  | 1          | 1.1         |
| Phenytoin     | 1          | 1.1         |
| Clonazepam    | 2          | 2.1         |
| Total         | 95         | 100.0       |

### Table 5
Patients’ characteristics.

| Number (n)         | Age (median) | Glasgow Coma Score (median) | First electrocardiography | Treatment methods | Hemoperfusion | Mechanical ventilation requirements |
|--------------------|--------------|-----------------------------|---------------------------|-------------------|---------------|------------------------------------|
|                    | 21 (25th: 19; 75th: 31; 95th: 48.6; IQR: 12) | 15 (25th: 13; 75th: 15; 95th: 15; IQR: 2) | Normal sinus rhythm 74 (77.9%) | General intoxication treatment 58 (61.1%) | 22 (23.2%) | No 90 (94.7%) Yes 5 (5.3%) Discharged with healing 94 (98.9%) Died 1 (1.1%) |

### Table 6
The resulting differences in terms of severity of poisoning between two generations.

|                       | First generation (n = 67) | Second generation (n = 28) | p       |
|-----------------------|---------------------------|---------------------------|---------|
| Age (years)           | Median (25th; 75th; 95th; IQR) | 20 (19; 28; 62.9; 9.75) | 0.459*  |
| Lactate (mmol/L)      | 1.9 (1.4; 3.1; 5.6; 1.7)     | 1.07 (0.9; 1.6; 5.5; 0.71) | <0.001* |
| GKS                   | 15 (12; 15; 15; 3) | 15 (14.3; 15; 15; 0.75) | 0.055*  |
| Length of stay in hospital (days) | 3 (2; 3; 5.6; 1) | 3 (2; 3; 4; 1) | 0.774*  |

GCS, Glasgow Coma Score.

* Mann–Whitney test.
of these differences was evaluated, we found a statistically significant difference between Group 3 and Group 1 in terms of GCS score ($p = 0.001$). There was also a significant difference between Group 1 and Group 3, as well as, between Group 2 and Group 3 in terms of the serum lactate level ($p < 0.001$ and $p < 0.001$, respectively). There was no difference in terms of age and systolic blood pressure between the groups ($p = 0.142$ and $p = 0.081$) (Table 7). Likewise, there was a significant positive correlation between the serum carbamazepine level and the serum lactate level, and a significant negative correlation between the serum carbamazepine level and GCS score ($kk = 0.602; p < 0.001$; and $kk = -0.568; p < 0.001$, respectively) (Table 9).

We assessed the cases poisoned by VPA, the second most frequent cause of intoxication in our series, in terms of the association between serum VPA level and age, the GCS score, and also between the serum lactate level and the systolic blood pressure at the time of presentation. We divided the VPA poisoning patients into 3 groups according to serum VPA levels as follows: under 100 mg/L (Group 1, $n = 7$), between 100 and 125 mg/L (Group 2, $n = 10$), and over 125 mg/L (Group 3, $n = 9$). There was no significant difference between the serum VPA level and GCS score, nor between the serum VPA level and the serum lactate level and the systolic blood pressure ($p = 0.470$, $p = 0.897$, $p = 0.888$, respectively) (Table 8). Likewise, there was no significant correlation between the serum VPA level and the serum lactate level, nor between the serum VPA level and the GCS score, the systolic blood pressure, and age ($kk = 0.132; p = 0.520$; $kk = -0.185; p = 0.130$, $kk = -0.286; p = 0.156$, $kk = 0.171; p = 0.404$, respectively) (Table 9). However, there was a significant positive correlation between the serum VPA level and the serum ammonia level ($kk = 0.742; p < 0.001$).

### 3.4. Study limitations

The most important limitation of our study was that it was a single-center study including relatively few cases. Another limitation was that it was retrospective with data collected from the patients’ files.

### 4. Discussion

In the United States, intoxications due to antiepileptic drugs comprise 3% of all intoxications. Among antiepileptic drug intoxications, most are caused by FGAEs, namely VPA, carbamazepine, phenytoin, and phenobarbital.

### Table 7

Between the serum carbamazepine level and the mean GCS and also between the serum lactate level and the systolic arterial pressure.

| Serum levels of carbamazepine (mg/L) | p |
|--------------------------------------|---|
| <15 ($n = 12$) | 15–30 ($n = 13$) | >30 ($n = 13$) |
| Age (years) | 20 (18; 23.5; 32.7; 5.5) | 33 (19.5; 44; 52.2; 24.5) | 24 (18.5; 35.5; 55; 17) | 0.081* |
| Lactate (mmol/L) | 1.6 (1.2; 1.9; 2.3; 0.67) | 1.5 (1.3; 1.8; 2.9; 0.57) | 2.8 (1.9; 3.8; 5.4; 1.9) | <0.001* |
| GKS | 15 (13.2; 15; 15; 1.75) | 15 (12.5; 15; 15; 2.5) | 10 (10; 13; 15; 3) | 0.004* |
| Blood pressure (mmHg) | 112.5 (106.3; 120; 128; 13.7) | 110 (95; 117.5; 146; 22.5) | 90 (90; 124; 140; 34) | 0.142* |

GKS, Glasgow Coma Score; blood pressure, mean systolic blood pressure value.

* Kruskal–Wallis test.

### Table 8

Between serum VPA level and the mean GCS, and also between the serum lactate level and the systolic arterial pressure.

| Serum levels of valproic acid (mg/L) | p |
|--------------------------------------|---|
| <100 ($n = 7$) | 100–125 ($n = 10$) | >125 ($n = 9$) |
| Age (years) | 20 (19; 20; 32.5; 1) | 23.5 (18.7; 26.5; 32.5; 7.7) | 28 (19; 29.5; 32.5; 10.5) | 0.431* |
| Lactate (mmol/L) | 2.95 (1.4; 4.2; 6.8; 2.82) | 2.03 (1.6; 4.8; 6.8; 3.21) | 3.1 (2.2; 3.6; 6.8; 1.39) | 0.897* |
| GKS | 15 (13; 15; 15; 2) | 15 (14.5; 15; 15; 0.5) | 15 (10.5; 15; 15; 4.5) | 0.470* |
| Blood pressure (mmHg) | 120 (110; 130; 119; 20) | 110 (103.7; 110; 119; 6.25) | 110 (75; 110; 119; 45) | 0.088* |

GKS, Glasgow Coma Score; blood pressure, mean systolic blood pressure value.

* Kruskal–Wallis test.

### Table 9

Correlations.

| Serum level of valproic acid | Serum level of carbamazepine |
|-----------------------------|-----------------------------|
| kk | p | kk | p |
| Age (years) | 0.171 | 0.404* | 0.145 | 0.386* |
| Lactate (mmol/L) | 0.132 | 0.520* | 0.602 | <0.001* |
| GKS | −0.185 | 0.130* | −0.568 | <0.001* |
| Blood pressure (mmHg) | −0.286 | 0.156* | −0.365 | 0.024* |
| Ammoniac (µg/dl) | 0.742 | <0.001* |

GKS, Glasgow Coma Score; blood pressure, mean systolic blood pressure value.

* Spearman’s rho.
Intoxications with new generation antiepileptics (such as lamotrigine, topiramate, felbamate, gabapentin) are rarely seen, and the data on their toxicity is limited by case reports [1–3]. In the study including 1028 patients, Bonilha et al. had showed that the most frequent cause of antiepileptic intoxication is phenobarbital, that is the drug of poisoning in 250 patients [4]. In another study including 652 patients, Nixon et al. had reported that carbamazepine is the leading cause of poisoning, that is the drug of poisoning in 306 patients [5]. In our study, we found that carbamazepine is the most frequent cause of antiepileptic poisoning. Bonilha et al. [4] found that antiepileptic poisoning was most frequently seen in the 25–29 age group. Nixon et al. [5] found that antiepileptic poisoning was most frequently seen in the 30–39 age group, whereas we found that it was most frequently seen in the 18–20 age group with a rate of 46.3%.

The serum lactate levels patients poisoned by FGAEs on admission to emergency department were significantly higher than the levels of patients poisoned by SGAEs. Accordingly FGAEs are metabolically more toxic than SGAEs.

In 2002, The American Association of Poison Control Centers has reported 5645 cases of intoxication caused by carbamazepine, which was the most frequent cause of intoxication in our study [6]. The main symptoms of carbamazepine poisoning are ataxia, nystagmus, ophthalmoplegia, dystonia, mydriasis, and sinus tachycardia. In severe intoxications, myoclonus, seizures, hyperthermia, coma, arrhythmias, and respiratory depression may also be observed. Due to having a structure similar to tricyclic antidepressants, carbamazepine may cause QRS and QT interval prolongation. The mortality rate, which is generally due to cardiovascular toxicity, is about 2% [1]. In our study, there was no mortality caused by carbamazepine intoxication.

Although the correlation between the serum carbamazepine level and the clinical findings is weak, severe intoxication occurs at carbamazepine levels of >20 mg/L. Cardiovascular toxicity may occur at serum carbamazepine levels of >40 mg/L and death may occur at 120 mg/L [7]. In our study, the minimum, maximum, and average serum levels of carbamazepine were 5.2 mg/L, 69.6 mg/L, and 24.4 mg/L, respectively. There were serious intoxication findings, particularly in Groups 2 and 3. (Group 2: serum carbamazepine levels from 15 to 30 mg/L, the Group 3: 30 mg/L is above.)

The main therapeutic approach to carbamazepine intoxication is supportive therapy. In order to eliminate the drug, recurrent doses of activated charcoal are given, and charcoal hemoperfusion is carried out. High-flow hemodialysis is also an effective method of therapy. Furthermore, plasmapheresis was found to be effective both in reducing serum levels of carbamazepine and in clinical improvement [8]. Sodium bicarbonate is recommended in cases with QRS interval of >10 s [1]. In our study, out of 38 cases with carbamazepine intoxication, 15 received hemoperfusion and 2 patients received sodium bicarbonate treatment.

Some authors have reported that there is a correlation between the serum carbamazepine level and the neurological symptoms, and that the frequencies of seizures and coma increase at serum carbamazepine levels of 20–40 mg/L [9–12]. In his study on 82 cases of carbamazepine intoxication, Tibbals [13] has reported that serum carbamazepine level is correlated with coma, confusion, severity or depth of hypotension, and the need for mechanical ventilation. He has also reported deaths due to cardiac insufficiency, aspiration pneumonia, and septicemia in carbamazepine intoxication [13]. Brahmi et al. [14] have found a significant negative correlation between the serum carbamazepine level and GCS score ($r = -0.58; p = 0.01$). In our study, we also determined a significant negative correlation between carbamazepine and GCS score. We also observed a closer association with GCS score and a higher incidence of central nervous system depression findings when carbamazepine levels were over 15 mg/L. Ciszowski et al. [15] have reported a positive correlation ($r = 0.68; p < 0.001$) between the carbamazepine level and the systolic and diastolic blood pressure. In our study, we saw no association or correlation between the serum carbamazepine level and the systolic blood pressure.

As far as we know, there is no study in the literature demonstrating the positive correlation between the serum carbamazepine level and the serum lactate level. In our study, we determined a significant positive correlation between the serum carbamazepine level and the serum lactate level. Furthermore, we observed a closer association between the serum carbamazepine levels of over 15 mg/L and the serum lactate level. These data indicate that the serum lactate level can be used as a prognostic biomarker in carbamazepine intoxications.

In the year 2000, The American Association of Poison Control Centers has reported over 5000 cases of intoxication caused by VPA, which was the second most frequent cause of intoxication in our study [16]. The most frequent findings in VPA intoxication are coma and central nervous system depression, which can lead to respiratory depression. Tachycardia and hypotension are rare in VPA poisoning. Pupillary miosis may occur, mimicking opiate poisoning. Moreover, pancreatitis, hyperammonemia, metabolic and hematological disorders, and cardiopulmonary arrest can occur. In cases with severe VPA poisoning, optic nerve atrophy, brain edema, non-cardiogenic pulmonary edema, anuria, and pancreatitis can be observed as late sequelae [7].

Although there is a weak correlation between the serum VPA level and the clinical findings, numbness can be observed in patients with serum VPA level of >500 mg/L, and in patients with serum VPA levels of >1000 mg/L, metabolic disorders and coma may be seen [7]. In our study, the minimum, maximum, and average levels of serum VPA were 65 mg/L, 1005 mg/L, and 164.3 mg/L, respectively. We observed severe intoxication symptoms, particularly in Group 3. (Group 3: VPA serum level of 125 mg/L above.)

The main treatment modality in antiepileptic poisoning is supportive therapy. Naloxone is recommended for some patients who show symptoms of central nervous system depression [17]. Seizure cases can be treated with intravenous diazepam with a dosage of 0.1–0.3 mg/kg [18]. To decrease the serum drug level, extracorporeal methods such as hemofiltration and also carnitine are used.
Conflicts of interest

No conflict of interest was declared by the authors.

Transparency document

The Transparency document associated with this article can be found in the online version.

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