Antiepileptic drug poisoning: Three-year experience

Yahya Kemal Günaydın [a,*], Nazire Belgin Akıllı [a], Zerrin Defne Dündar [b], Ramazan Köylü [a], Ekrem Taha Sert [a], Bora Çekmen [a], Emine Akıncı [c], Başar Cander [a]

[a] Konya Training and Research Hospital, Department of Emergency Medicine, Konya, Turkey
[b] Necmettin Erbakan University, Faculty of Medicine, Department of Emergency Medicine, Konya, Turkey
[c] Keçiören Training and Research Hospital, Department of Emergency Medicine, Ankara, Turkey

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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.

* Corresponding author. Tel.: +90 05058658089.
E-mail address: gsykg@yahoo.com (Y.K. Günaydın).

1. Introduction

Antiepileptic drugs, which are also referred to as anti-convulsants, 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

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

normally distributed. Descriptive variables are expressed as mean $\pm$ 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 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)