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Epidemiological Study of Acute Poisoning for Antiepileptic Drugs: A 2-Year Retrospective Study in Cracow, Poland

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Abstract

The aim of this study was designed to examine the rate of occurrence of antiepileptic drug overdose in 2002 and 2012 in Cracow, Poland, and analyze the demographics and clinical features of the patients Antiepileptic drugs (AEDs) intoxication. A retrospective study included all the patients admitted in to the Toxicology Units in Cracow for AED intoxications in 2002 and in 2012. Patients were identified of discharge diagnoses (ICD-10). AED intoxication were 5.40% of the total admissions. Mean age of the patients was 35.88 ± 12.54 years. The female-to-male ratio was 1:1.7. The most frequent AED was carbamazepine ($n = 140$), followed by valproate ($n = 31$). The most frequent motivation was intentional intoxication ($n = 166$, 94.86%). Ethanol was coingested by 51 patients (29.14%). Most of the patients ingested other drugs (32%). Antiepileptic drugs intoxication accounted for only of 7.13% of all cases admitted to the abovementioned toxicology units in 2002 and 2012 in Cracow. Our studies show that most of the AED poisoning cases in those years were caused by drugs belonging to the old generation antiepileptic drugs, including carbamazepine and valproic acid. The majority of the intoxication cases was related to suicidal poisoning and commonest identified reason of self-intoxication were issues with self including attention-seeking behavior.

Keywords: antiepileptic drugs, acute intoxication, clinical manifestations, drug serum level, suicide attempts

1. Introduction

Antiepileptic drugs (AEDs) are mainly used in the treatment of epilepsy and treatment of some mental disorders. Patients suffering from it are at increased risk of suicidal ideation, suicide attempts, and completed suicides. The widespread use of AEDs resulted also in the fact that this group of drugs is frequently encountered as the cause of acute toxicity among patients treated at the toxicology unit around the world. Few data are available regarding the rate of AED overdose in individual countries. For example, AEDs are approximately 3% of the intoxication cases in the USA [1]. Other studies shows a 25% increase in the rate of occurrence of antiepileptic drug overdose between 2000 and 2006 [2, 3] in the USA. Annual Report of the American Association of Poison Control Centers Toxic Exposure Surveillance System states that AEDs comprise 3.2% of all causes of poisoning in adults (>19 years old) [4]. The Brazilian study by Bonilha et al. show that in Saõ Paulo and its outskirts in 2001, AED poisoning accounted for 16% of all the poisonings [5]. In Edinburgh (the UK, Scotland) for the period from 2000 to 2007, AED poisonings accounted for 3.4% of all poisonings [6]. In Marmara region (Uludag) in west Turkey for the period 1996–1999, 6.7% of medicinal intoxications was due to AEDs [7]. In France (Paris emergency departments), the prevalence of poisoning with AEDs for the period 1992–1993 was 2.9% and for 2001–2002 was 0.9% [8]. In Iran (studies conducted in the referral center for all cases of poisoning occurring in Tehran), AED poisoning accounted for 4.8% of all the pharmaceutical intoxications [9].

2. Aim

This study was designed to examine the rate of occurrence of antiepileptic drug overdose in 2002 and 2012 in Cracow, Poland, and to analyze the demographics and clinical features of the patients AED intoxication.

3. Material and methods

A retrospective study included all patients admitted for AED intoxications to Specialist Hospital Louis Rydgier's Co. o.o. in Cracow, in 2002 (in 2002, Cracow was the only toxicological unit), and all the persons were admitted for the same reason in to University Hospital in Cracow as well as Specialist Hospital Louis Rydgier's Co. o.o in Cracow in 2012. Patients were identified on the basis of discharge diagnoses (using International Classification of Diseases, ICD-10) with the code for poisoning by antiepileptic, sedative-hypnotic, and antiparkinsonism drugs (T42, excluded T42.0, T42.1, T42.3, T42.4, T42.8).

The data gathered included age, gender, mode of poisoning, reasons for attempt, and history of attempting suicide. The clinical spectrum of data analyzed consisted of serum level of AEDs, severity of poisoning, and effects of treatment.

The project was approved by the Ethics Committee, Medical University of Warsaw (No. AKBE/32/13).

3.1. Area of the survey

In Poland, there lives about 38 million people. Today's Poland consists of 16 provinces (voivodships), according to the last changes implemented in 1999. In Poland, toxicological units are located in nine large cities, which hospitalized patients with individual provinces. The University Hospital in Cracow and Specialist Hospital Louis Rydgier's Co. o.o in Cracow are responsible for all inhabitants of the Malopolskie (comprises 3.4 million of the country's population) and Swietokrzyskie provinces (comprises 1.26 million of the country's population) in Poland.

3.2. Statistical analysis

The data were collected in a Microsoft Excel database. Data are presented as mean and standard deviation (SD). Statistical analysis was performed using Statistical Programme for Social Sciences (SPSS). We used Pearson's χ^2 test to evaluate the association (and its strength) of the frequencies of data distribution among the different drug groups. A value of $p < 0.05$ was considered to be statistically significant.

4. Results

Of all the poisoning cases ($n = 2455$ patients), 175 (7.13%) patients with AED intoxications were admitted to the Toxicology Unit in Cracow, Poland, in 2002 and 2012. Females accounted for 37.14% of the cases and males accounted for 62.86% with a female-to-male ratio of 1:1.7. The mean age of patients in the sample was 35.88 years (SD \pm 12.54). **Table 1** describes the demographic characteristics of the patients.

	2002	2012	Total N (%)
Gender			
Female	37	28	65 (37.14%)
Male	73	37	110 (62.86%)
Total	110	65	175 (100%)
Age			
Range	14–58 years	18–82 years	14–82 years
Mean \pm SD	34.93 \pm 11.,80	37 \pm 13.64	35.88 \pm 12.54

Table 1. Demographic characteristics of study population.

Out of 175 patients with AED intoxications, 170 took one of the antiepileptic drugs, while 5 patients received more than one AED (carbamazepine [CBZ] + valproic acid [VPA]). The majority of patients receiving AED took carbamazepine only ($n = 140$). Valproate ($n = 31$) was

the second most common (but 5 out of 31 have taken VPA in combination with CBZ). Smaller numbers were found for the remaining AEDs (<1% each): lamotrigine ($n = 1$), phenytoin ($n = 1$), and topiramate ($n = 2$)—see **Table 2**. Men were more likely to ingest carbamazepine than women (Person $\chi^2 = 11.7$, $p < 0.0001$).

Drug	2002	2012	Total N (%)
Carbamazepine	96	44	140 (80%)
Valproic acid	8	18	26 (14.86%)
Carbamazepine + Valproic acid	4	1	5 (2.86%)
Topiramate	0	2	2 (1.14%)
Lamotrigine	1	0	1 (0.57%)
Phenytoin	1	0	1 (0.57%)

Table 2. Characteristics of antiepileptic drugs associated with analyzed poisoning cases ($n = 175$).

The distribution of serum levels of AEDs was found as follows: 11 patients had therapeutic serum levels, 4 patients had subtherapeutic level of drugs, while in 141 cases, the drug concentrations were at the toxic level. AED concentrations in serum could not be measured in 23 patients (13.14%). **Table 3** shows the serum-level distributions for individual antiepileptic drugs.

Carbamazepine level	N (%)
Subtherapeutic level (<4 $\mu\text{g/ml}$)	1
Therapeutic level (4–12 $\mu\text{g/ml}$)	10
Toxic level (>12 $\mu\text{g/ml}$)	113
Toxicological analysis confirmed presence of CBZ in blood.	21
Range: 3.88–56.2 $\mu\text{g/ml}$. Mean: 26.94 \pm SD 11.59	
Valproic acid level	N (%)
Subtherapeutic level (<50 $\mu\text{g/ml}$)	3
Therapeutic level (50–100 $\mu\text{g/ml}$)	1
Toxic level (>100 $\mu\text{g/ml}$)	27
Range: 5–660 $\mu\text{g/ml}$. Mean: 263 \pm SD 174.17	
Topiramate level	N (%)
Toxicological analysis confirmed presence of TPM in blood.	1
Lamotrigine level	N (%)
Toxicological analysis confirmed presence of LTG in blood	1
Phenytoin level	N (%)
Subtherapeutic level (<10 $\mu\text{g/ml}$)	0
Therapeutic level (10–20 $\mu\text{g/ml}$)	0
Toxic level (>20 $\mu\text{g/ml}$)	1
Mean: 53 $\mu\text{g/ml}$	

Table 3. Serum levels of valproic acid ($n = 31$), carbamazepine ($n = 145$), topiramate ($n = 2$), lamotrigine ($n = 1$), phenytoin ($n = 1$) stratified by toxicological status of drug concentrations.

	2002	2012	Total N (%)
Mode of poisoning			
Suicidal	106	60	166 (94.86%)
Accidental	3	3	6 (3.43%)
Not available	1	2	3 (1.71%)
Poisoning Severity Score (PSS)			
Minor	60	33	93 (53.14%)
Moderate	45	26	71 (40.57%)
Severe	4	6	10 (5.71%)
Fatal	1	0	1 (0.57%)
No. of suicide attempts			
Not available	65	43	108 (61.71%)
Another	41	18	59 (33.71%)
Not applicable	4	4	8 (4.57%)
Treatment effect			
Cured	62	57	119 (68%)
Psychiatric ward	32	1	33 (18.9%)
Death	1	0	1 (0.57%)
Discharged from hospital at his own request	15	7	22 (12.57%)
Ethanol			
N	36	15	51 (29.14%)
Range	0–3, 59‰	0–2, 92‰	
Mean ± SD	0.43 ± 0.081	0.42 ± 0.85	
Reason for attempting suicide			
Person to person conflicts	0	22	22 (12.57%)
Reason not identified or not recorded	82	25	107 (61.14%)
Issues with school/work	1	4	5 (2.86%)
Issues with self-including attention-seeking behavior	22	6	28 (16%)
Mentally challenged	5	8	13 (7.43%)
Comorbidity			
Depression	29	14	43 (24.57%)
Alcohol dependence syndrome	42	24	66 (37.71%)
Personality disorder	14	13	27 (15.43%)
Bipolar disorder	1	3	4 (2.28%)
Schizophrenia	1	6	7 (4%)
Other mental disorder	23	15	38 (21.71%)
Somatic disease	3	12	15 (8.57%)
Epilepsy	41	23	64 (36.57%)
Other drugs			
Antipsychotics	12	9	21 (12%)
Antidepressants	6	5	11 (6.28%)
Barbiturates	4	1	5 (2.86%)
Benzodiazepines	17	3	20 (11.43%)
Nonsteroidal anti-inflammatory drugs	1	2	3 (1.71%)
Opioids	0	2	2 (1.14%)

Table 4. Characteristics of suicide attempts.

Severity of intoxication was classified according to Poisoning Severity Score (PSS). The PSS grades severity as (0) none—no symptoms or signs related to poisoning; (1) minor—mild, transient, and spontaneously resolving symptoms, (2) moderate—pronounced or prolonged symptoms, (3) severe—severe or life-threatening symptoms, and (4) fatal poisoning—death [10].

The PSS was minor in 93 patients, moderate in 71 patients, severe in 10 patients, and fatal in 1 patient. Alcohol was involved in 29.14% of cases. An alcohol consumption did not differ significantly depending on the gender (Pearson's $\chi^2 = 0.1$, $p = 0.745$).

It is noteworthy that of the 56 ($n = 36$ in 2002, $n = 20$ in 2012) patients (32%), one patient took 1 or >1 antiepileptic drug and more than one (i.e., antiepileptic only) drug, including antipsychotics (12%), benzodiazepines (11.43%), antidepressants (6.28%), barbiturates (2.86%), nonsteroidal anti-inflammatory drugs (1.71%), and opioids (1.14%).

One-third of the patients (33.71%) had at least one suicide attempt before hospitalization; however, no information was available regarding the severity of these suicide attempts. Two patients (1.14%) had attempted suicide during hospitalization.

Suicidal and accidental poisoning, respectively, represented 94.86% and 3.43% of acute intoxications cases. The cause of poisoning in three cases (1.71%) could not be found. The most frequent reason of intoxication was issues with self—including attention-seeking behavior (16%), followed by person to person conflicts (12.57%). The frequency of poisoning cases between different circumstances did not differ significantly depending on the gender (Pearson's $\chi^2 = 0.5$, $p = 0.920$). There was no association between previous history of parasuicide, gender, and AED intoxication ($p > 0.05$).

Nearly half of the poisoned patients (44.57%) described in this report were treated with AEDs because of epilepsy or psychotic disorders prior to the poisoning.

More than half of the patients had a diagnostic history of psychiatric disorders, and 66 (37.71%) a diagnostic history of alcoholism.

Most patients (68%, $n = 119$) were discharged to homes in good condition, 33 (18.9%) were transferred to a psychiatric ward. As many as 22 patients (12.57%) did not complete hospitalization because they left the hospital at their own request.

The characteristics of the suicide attempts are shown in **Table 4**.

5. Discussion

Our results show a lower probability of AED intoxication in women than in men (37.1% vs. 62.9%). However, most studies observe that women were more likely than men to undergo drugs intoxications, including antiepileptic drugs [7, 11–14]. In Poland, women more often than men attempted suicide; however, men tend to be more successful than women in actual lethality. Other studies have confirmed this result [15–17]. In Poland, according to the data by

the Police Headquarters the most common way to commit suicide is hanging (72%), other popular methods often include: jumping from a height (6.9%) and poisoning (4.6%) [18]. The Polish study by Bolechała et al. show that in Cracow, in 1991–2000, suicidal poisoning was in the male-to-female ratio of 1.8:1 [19].

In 2002, 5100 people died by suicide in Poland. According to the data, the vast majority of the suicides were committed by males ($n = 4215$). Whereas, in 2012, in Poland 4177 people committed suicide, including 3569 men [18]. In our study, twofold more men in 2002 committed suicide than in 2012.

In our study, the most commonly encountered drug was carbamazepine which generally corresponded with community prescribing patterns. It is also compatible with reports from Edinburgh [6], Iran (Tehran) [9], and São Paulo [5]. Another frequently used drug in our study was valproic acid. It is known from the literature that the number of overdose cases of sodium valproate is steadily increasing in civilized countries [20, 21]. Carbamazepine and sodium valproate were the most frequently used AEDs. In the present study, men were more likely to use carbamazepine than women ($p < 0.0001$). However, in a study by Nixon et al. (data from Edinburgh, the UK), women were more likely to ingest lamotrigine than men ($p < 0.0001$) and less likely to ingest sodium valproate ($p = 0.0234$) [6].

In our study, a higher than expected proportion of patients had coingested other (taken for reasons other than epilepsy) drugs (32%), which was in concordance with a previous report from Turkey [22]. However, this proportion was higher in the study by Nixon et al. in Edinburgh (65.4%) [6]. In our study, the most frequently taken drug types were antipsychotics (12%) as in the study by Çelenk et al. (12.5%) [22] concerning 1987 patients admitted to the Mayıs University Faculty of Medicine Emergency Department (Samsun, central Black Sea Region, Turkey). In Poland, in 2002, 211 people died by an overdose of hypnotics drugs, in 2012—193 people [18].

The suicide risk in patients with epilepsy is significantly higher than in the general population. Standardized mortality ratio for suicides among epileptic patients is estimated at 3.5–5.8 in comparison with the general population [23, 24]. In a review of 21 studies, a mean of 11.5% (range: 0–67%) of the deaths of patients with epilepsy were attributed to suicide [25]. The proportion of deliberate self-poisoning was 94.86% in our study. Suicide attempt was the most frequent circumstance observed in Brazil (São Paulo) [5] and Iran (Tehran, 98.9%) [9], too.

In a study by Harris et al., suicide attempt among patients with epilepsy increases future suicide risk to 38.4% compared with the general population [26]. Similar results were obtained in the Swedish study (data from Stockholm county area), where that percentage was 46.2% [17]. Our study show that every third patient had a history of previous parasuicide. Our findings are consistent with those of Hassanian-Moghaddam et al. [9]. Previous suicide attempt is a risk factor for suicide attempts in future.

The most important reasons for suicide attempts in epileptic patients are common to general population and other chronic disease. Some authors suggest that concomitant depression and other psychiatric disorders are the main risk factors of suicidal thoughts [27]. Danish study confirmed that 2.32% ($n = 492$) individuals who committed suicide had epilepsy compared

with 0.74% ($n = 3140$) controls. In case of comorbid psychiatric disease, overall risk of suicide in epileptic patients appears to be nearly 14-fold higher, including 32-fold for affective disorders and 12-fold for anxiety disorders [28], and it is almost twice higher in the case of those with previous mental disorders and 12.5-fold for schizophrenia [29]. Similarly, Swedish study showed that epilepsy concomitant with psychiatric disorders is associated with ninefold higher risk of suicide [23]. Logistic regression analysis in a study by Hassanian-Moghaddam et al. revealed that the presence of medical disorders and history of psychiatric events is associated with AED intoxication [9]. In the present study, most patients had a history of psychiatric disorders (i.e., depression, personality disorders, bipolar disorder, and schizophrenia) or somatic disorders.

The mental illness (including depression, bipolar disorder, schizophrenia, and others) was the cause for the vast majority of suicides in Poland, in both 2002 and 2012 (respectively, $n = 1017$ and $n = 808$) [18].

On the other hand, Buljan et Santić demonstrated that among hospital-treated epilepsy patients, beside psychiatric comorbidity, difficult family situation is a significant factor of higher suicide risk. Study results showed that 14.6% of the epileptic patients treated at one hospital in Zagreb (Croatia) have attempted suicide [30]. This study revealed that person-to-person conflicts were reasons for attempting suicide for 12.57% of the patients. In our study, in 107 of the cases, the cause of suicide is unknown because some patients discharged from hospital at their own request refused to answer the question on the reason for attempting suicide.

Alcoholism is associated with a high risk for suicidality, suicide attempts, and completed suicides [31, 32]. Up to 40% of the persons with alcoholism attempt suicide at some time or other, and 7% end their lives by committing suicide [33]. Alcohol dependence syndrome was diagnosed in 37.71% of our patients. Ethanol was coingested by 51 patients (29.14%) in this study and by 94 patients (15.3%) in a study by Nixon et al. [16]. Alcohol use is associated with risk behaviors [34, 35]. People who are under the influence of alcohol are more likely to attempt suicide. Alcohol intoxication increases suicide risk up to 90 times in comparison with abstinence [34].

In Poland, in 2002 and in 2012 among the suicides, the vast majority was under the influence of alcohol (respectively, $n = 1069$ and $n = 1438$) [18].

In 2008, the FDA issued an alert contained a warning against an increased risk of suicidality (suicidal ideation or behavior) for antiepileptic drugs [36]. The FDA analyzed the reports of suicidality from placebo-controlled clinical studies of 11 antiepileptic drugs. In this analysis, patients receiving antiepileptic drugs had approximately twice the risk of suicidal behavior or ideation (0.43%) compared with patients receiving placebo (0.22%). In the present study, 44.57% of the patients described in this report were treated with AED because of the epilepsy or psychotic disorders prior to the poisoning. The number of cases of AED overdose is less in 2012 than in 2002, almost half. Some explanation for this may be that currently, there is a widespread use of drugs in the new generation. These newer drugs are more efficacious and have a better safety as compared with conventional (older) AED.

The patients' clinical condition was evaluated according to PSS and measuring serum level of AEDs. It was found that 93 persons (53.14%) had minor, 71 (40.57%) moderate, and 10 patients (5.71%) had severe clinical findings and symptoms. Only one patient (0.57%) died due to CBZ poisoning. A 56-year-old man reportedly poisoned intentionally was admitted to Toxicology Department. History from family members revealed that patient had ingested together 320 tablets of carbamazepine and clomipramine. His carbamazepine serum concentration was 56.2 microg/mL. Urine analysis revealed clomipramine presence. Serum levels of other drugs and ethanol were all negative. He had a history of psychiatric illness, including depression. During whole hospitalization the patient was unconscious, unresponsive to the pain (Glasgow Coma Scale, GCS = 3). His pupils were broad in size with no reaction to light. His vital signs were as follows: pulse rate 70 beats/min, blood pressure 90/40 mmHg, temperature 36.4 C, and respiratory insufficiency. He was immediately intubated, and gastric lavage was performed to give a small amount of tablet. Patient was shifted to intensive care unit. Despite intense treatment and decrease of carbamazepine level to therapeutic values, there were no signs of patient recovery. Despite intensive resuscitation, in the third day of treatment the patient died. The corpse was transferred for investigation to the Forensic Medicine Department, the section was performed. In literature, CBZ serum level of 37 mcg/ml has been potentially lethal [37], but death due to CBZ overdose has been observed at lower concentrations [38–40].

Celenk et al. reported that 38 of the cases (59.4%) had no clinical symptoms, 18 cases (28%) had minor, 5 cases (7.8%) had moderate.

In our study, most of the patients had toxic serum drug levels ($n = 141$, 80.57%). In the above-mentioned study from north Turkey, 28 patients (43.8%) had toxic serum AED level [22]. The knowledge of concentration range is significantly useful in clinical practice.

After treatment in the Toxicology Unit, a higher proportion of overdose patients discharged to go home (68%), whereas 18.9% of the patients required transfer to a psychiatric facilities. One death occurred in this study. Like our observation, Nixon et al. reported in the UK study that 14% of antiepileptic drug-overdose patients required transfer to a psychiatric facility, and 78.3% were discharged home [6].

6. Conclusion

Antiepileptic drugs intoxication accounted for only of 7.13% of all the cases admitted to the abovementioned toxicology units in 2002 and 2012 in Cracow, Poland, and AED poisoning is more common among males. Our studies show that most of AED poisoning cases in those years were caused by drugs belonging to the old generation antiepileptic drugs, including carbamazepine and valproic acid. The majority of intoxication cases were related to suicidal poisoning (94.86%), and commonest identified reason of self-intoxication were issues with self-including attention-seeking behavior (16%). Second leading established cause of suicide attempts were person-to-person conflicts (12.57%). Drugs combinations (AED + other drugs) were recorded in 32% of the cases and in 29.14% there occurred combinations between AEDs and alcohol.

Our study was a university hospital-based study, so these results may not be representative of the general population. However, these data still provide important information on the characteristics of the poisoning in this part of Poland. Further work is required to determine the rate of occurrence of antiepileptic drug overdose.

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