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The Evaluation of Patients Admitted to the Emergency Department with Non-Benzodiazepine Antiepileptic Drug Poisoning

Non-Benzodiyazepin Antiepileptik İlaç Zehirlenmeleri ile Acil Servise Başvuran Hastaların Değerlendirilmesi

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Abstract

Objective: We aimed to determine the demographics, clinical findings and symptoms of the admissions of non-benzediazepine antiepileptic drugs patients (NBDAED) admitted to the University hospital Emergency Department (ED).

Material and Methods: The exposures above 18 years between 01.01.2006-01.01.2010 were included in this study. We evaluated the age, sex, kind of drug ingested, kind of poisoning, clinical finding and symptoms, and the results of the exposures to NBDAED.

Results: The exposures to NBDAED composed 3.2% of all the poisonings. 92.2% of the patients had ingested drugs intentionally, 67.1% were between 18-29 years and 64.1% were females. Patients ingested most frequently old generation drugs (81.3%); the most frequently ingested drugs were carbamezapine (34.4%) and valproic acid (29.7%); 72% of the patients ingested their own drugs and most frequently 39% of them admitted to ED within the first 2 hours.More clinical findings and symptoms developed in toxic dose ingestions and the mean hospital stay duration was longer than non-toxic dose ingestions.

Conclusion: Intentional drug exposures are at a high prevalence in NBDAED ingestions. It is mostly seen in the young adult group and females. The most frequently ingested drugs are the old generation drugs and the most frequently used drugs are carbamazepine and valproic acid.

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Key words: Antiepileptic drugs, poisoning, emergency department

Özet

Amaç: Üniversite hastanesi acil servisine başvuran non-benzodiyazepin antiepileptik ilaçlara (NBDAEİ) bağlı zehirlenme vakalarının demografik özelliklerini, klinik bulgu ve sonuçlarını ortaya koymaktır.

Gereç ve Yöntemler: 01.01.2006-01.01.2010 tarihleri arasında acil servise zehirlenme şikayeti ile başvuran 18 yaş üstü hastalar çalışmaya kabul edildi. Bu hastalardan antikonvülzan ilaçlara maruz kalan olgular; yaş, cinsiyet, alınan antikonvülzan ilaç, zehirlenme tipi, klinik belirti ve bulgular ve sonuç verileri değerlendirildi.

Bulgular: Non-benzodiyazepin antiepileptik ilaçlar ile zehirlenmeler tüm ilaç zehirlenmelerinin %3,2'sini oluşturmaktaydı. Hastaların %92,2'si istemli ilaç alımı, %67,1'i 18-29 yaş aralığında idi ve %64,1'i kadındı. Hastaların en sık eski kuşak (%81,3) ilaçlar ile zehirlendiği, en çok zehirlenilen ajanların karbamezapin (%34,4) ve valproik asit (%29,7) olduğu %72'sinin kendi ilacı ile zehirlendiği ve %39 ile en sık ilk 2 saat içinde hastaneye başvurduğu belirlendi. Toksik dozda ilaç alan hastalarda daha çok klinik bulgu ve belirti gelişmiş ve ortalama hastanede kalış süresi toksik dozda ilaç almayanlara göre daha uzun bulunmuştur.

Sonuç: Non-benzodiyazepin antiepileptik ilaç alımlarında istemli ilaç alımı yüksek oranda gözükmektedir. Hastaların büyük çoğunluğunu genç yetişkin grubu oluşturmaktadır. Kadınlarda antiepileptik ilaçlara maruziyet oranı erkeklerden fazladır. En sık maruz kalınan ilaçlar eski kuşak antiepileptik ilaçlar olup bunlar içinde en sık görülen ilaçlar karbamazepin ve valproik asittir.

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Anahtar kelimeler: Antiepileptik ilaç, zehirlenme, acil servis

Introduction

Today antiepileptic drugs (AED) are used to treat several neurological and psychiatric disorders such as epilepsy, prophylaxis of migraine, neuropathic pain, bipolar disorders and fibromyalgia (1). In recent years, both in our country and in the world, AED are increasingly prescribed since AED have been commonly used for different indications (2). Thus, the probabilities of overuse of these drugs have been increasing. In the group of adults, intentional drug intoxications are more common, whereas in the child group, unintentional drug ingestions are commonly seen (3-5). According to the 2011 annual report of American Association of Poison Control Centers'

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(AAPCC) National Poison Data System (NPDS), AED poisonings composed 3% of drug intoxications seen over the age of 20 (5). In a different study, the intoxication rate was reported as 3.4% (6).

In our country data about patients admitted to the emergency department (ED) due to AED poisonings are limited. The objective of this study is to analyze the demographics and clinical features of the patients of who are poisoned with nonbenzodiazepine antiepileptic drugs.

Material and Methods

Criteria of Inclusion and Exclusion

This study was approved by Ondokuz Mayıs University (OMU) clinical studies ethical committee. Between 01.01.2006-01.01.2010, all of the poisoning cases over 18 years old admitted to adult ED were identified. Those cases with AED poisonings were selected. All cases of misuse or suicide were included in this study regardless of drugs ingestion alone or combined with other toxic agents. Cases whose data records were limited were excluded from the study.

Data Records

A standard data form prepared beforehand was used for recording data. Admission time, demographics (age, gender, occupation), poisoning data (poisoning type, kind of drug, cause, duration after poisoning) clinical features, results of laboratory, treatment data ,and prognoses and duration of hospital stay were evaluated. According to Poisoning Severity Score (PSS), clinical features were scored as none (0), minor (1), moderate (2) and severe (3) (7).

Statistical analysis

Data was recorded in a standard program called 'Statistical Package for Social Sciences for Windows 15.0' (SPSS). The Kolmogorov Smirnov test was used to study the distribution of variables. All quantitative data were expressed as mean±Standard deviation (SD) and median (variables without normal distribution). The Mann-Whitney U test was used for two group comparisons and the Kruskall Wallis test was used to compare 3 or more groups. The Chi-square test was used to study categorical variables and $p<0.005$ were considered statistically significant.

Results

Of 1987 poisonings, patients admitted to the 19 Mayıs University Faculty of Medicine Emergency Department (19 MUFM ED) between 01.01.2006-01.01.2010, 64 (3.2%) were diagnosed with poisoning by non-benzodiazepine antiepileptic drugs (NBDAED). Of these cases, 41 (64.1%) were female (mean age 27.5±7.4), and 23 (35.9%) were male, (mean age 30.3±12.9). The mean age of total patients was 28.5±9.7 cases (average 18-66 years old). There was no statistically significant difference between age and gender (χ^2=6.071, p=0.194).

Of the cases, 92.2% (n=59) were suicide, whereas 4.7% (n=3) were not. The cause of poisoning in 2 cases (3.1%) couldn not be found. All of the poisoning patients without suicide were younger than 30 years old, but it was not statistically significant (p=0.95).

Of the patients, 39.1% (n=25) were admitted to the emergency department within 2 hours after drug ingestion. In this group, the clinical findings and symptoms were fewer than in those admitted to theemergency department later than 2 hours. The difference was statistically significant (χ^2=4.70, p=0.030).

The drugs taken by patients were classified according to their content; as old generation drugs [phenytoin, valproic acide (VPA), carbamazepine (CMZ), phenobarbital], new generation drugs [oxcarbazepine (OXCMZ), gabapentin (Gbt), lamotrigin, levotresetam, topiramate (Tmt), primidone] and combinations of these two groups. The admissions for old generation drugs poisoning were 52 (81.3%), those for new generation drugs poisoning were 11 (17.2%), and combinations of these two groups were only 1 (1.6%). When the cases were examined regarding whether they developed clinical findings or not at admission time according to new or old generations drug ingestion and clinical severity scoring, it was found that 23 of 26 patients (88.5%) with clinical findings in the admission time were poisoned with old generation drugs and only 3 patients with clinical findings poisoned with new generation drugs, but it was not statistically significant (χ^2=1.61, p=0.329). When the patients poisoned with new and old generation drugs were compared according to their hospital stay, the combined group was excluded, the median hospital stays of the two groups were quite similar (24 hours for old generation and 23.5 hours for new generation, $p>0.05$).

The distribution of anticonvulsant drug content was examined and the first three were only CMZ 34.4% (n=22), only VPA 29.7% (n=19) and only OXCMZ 9.4% (n=6). The groups poisoned with CMZ and VPA causing most poisoning were compared with each other and with the group poisoned with other AED agents according to clinical finding and symptoms. One patient who had ingested CMZ and VPA together and 2 patients who had ingested these two agents with other agents were excluded for this reason. When the groups were compared, 14 of 22 patients (63%) poisoned with only CMZ had higher clinical findings and symptoms (51.9%) than the total of patients poisoned with only VPA and other AED agents (n=13, 49.1%). The difference was statistically significant (χ^2=6.22, p=0.045). When the groups were compared in pairs, the clinical findings and symptom development rate of the group poisoned with only CMZ was higher than the group poisoned with only VPA and the group poisoned with other AED agents, which was statistically significant ($p<0.05$). There was no statistically significant difference between the groups poisoned with only VPA and other AED agents ($p>0.05$).

There was a statistically significant difference between the groups in terms of hospital stay. The median hospital stay of the groups are as following: 38 hours for only VPA ingestion, 17 hours for only CMZ ingestion, 26 hours for other agents ingestion and the median hospital stay of all the admissions was 24 hours. The hospital stay of the group poisoned with only CMZ had significantly shorter hospital stay than groups poisoned with only VPA and other AED agents ($p<0.05$). There was no statistically significant difference between the group that ingested only VPA and the group poisoned with other agents ($p>0.05$).

The number of patients with only AED exposure (n=35, 54.7%) was greater than those who ingested AED together with other agent groups (n=29, 45.3%). Antidepressant and antipsychotic agents (n=8) came first in the distribution of the agents taken together. Six patients poisoned with multiple agents composed 9.4% of all patients and 20.6% of combined drug ingestion.

It was found that 46 patients were poisoned with their own drugs (72%), 11 patients were poisoned with drugs that did not belong to themselves (17%), yet it was not determined whether 7 patients ingested their own or not. 27 of the patients (42.2%) poisoned with their own drugs had been using these drugs for neuro-

logical disorders and 18 of them (28.1%) had been using their drugs for psychiatric disorders. It was not obvious why1 patient who was poisoned with his own drug had been using it (1.5%).

After excluding the case group whose reason for using NBDAED could not be determined (n=8, 12.5%), there was a statistically significant difference between the case group who had not use AEDpreviously , the other group who used drugs for psychiatric disorders and another group who used drugs for neurological disorders in terms of the rates of poisoning with using different kinds of drugs together with AED (χ^2=7.12, p=0.028) (Table 1). When the case groups were compared in pairs, the rate of taking different kinds of drugs together with AED of the case group who used these drugs for psychiatric disorders was significantly higher than the case group who used drugs for neurological disorders (p<0.05).

The cases admitted to ED for exposure to NBDAED were classified as toxic or non-toxic according to therapeutic values determined in the laboratory. When the serum drug level is above the therapeutic values, it is classified as toxic, yet when it is between or below the therapeutic values, it is classified as non-toxic and when the drug level could not be determined, it is classified as unknown. The serum drug level of CMZ, VPA, phenytoin and phenobarbital could be measured. The serum therapeutic values and distribution of patients are presented in Table 2.

Most of the patients ingested drugs at toxic doses according to their serum drug levels (n=28, 43.8%). The numbers of patients who ingested drugs at non-toxic doses and patients whose serum drug level could not be measured were equal (n=18, 28%).

The patients admitted for NBDAED poisoning were classified as toxic, non-toxic and not measured, and then they were compared on the basis of their median values of hospital stay. The median value of hospital stay duration of the patients with toxic dose drug ingestion was 30 hours, it was 18 hours for patients with non-toxic dose drug ingestion and 24 hours for the patients whose serum drug level could not be measured. There was no statistically significant difference between the case groups in terms of their hospital stay durations (p>0.05).

The clinical features of patients were examined according to poisoning severity score and it was found that 38 cases (59.4%) had no clinical findings or symptoms, 18 cases (28%) had minor, 5 cases (7.8%) had moderate, 3 cases (4.7%) had severe clinical findings and symptoms. As expected, the possibility of developing clinical findings and symptoms of the cases with toxic dose drug ingestion was higher than the case group with non-toxic dose drug ingestion and the group whose serum drug level could not be measured (χ^2=12.8, p=0.046) (Table 3).

The clinical outcomes of the patients after their follow-up were determined as complete recovery, recovery with sequellae, and death. The clinical outcome of 6 (9.4%) out of 64 cases could not be determined because they left the ED voluntarily before their follow-up finished. All of the remaining 58 cases (90.6%) had a complete recovery.

Table 1. The Frequency of Taking Different Kinds of Drugs Together with NBDAED*

	The Reason for Using Drugs			
Different Kind of Drug (Other than AED)	**Neurological n (%)**	**Psychiatric n (%)**	**No Reason n (%)**	**Total n (%)**
Not Used	18 (66.7)	5 (27.8)	7 (64)	30 (53.6)
Used	9 (33.3)$^{++}$	13 (72.2)$^{++}$	4 (36)	26 (46.4)
Total	27 (100)	18 (100)	11 (100)	56 (100)

* The reason of using drugs couldn't be determined for 8 patients.
$^{++}$p<0.05; between psychiatric and neurological disorders.

Table 2. The distributions of patients according to serum drug levels

Drugs	**Therapeutic Value**	**Sub- Therapeutic n (%)**	**Therapeutic n (%)**	**Toxic n (%)**	**Total n (%)**
Carbamazepine*[a]	4-12 µg/mL	6 (26)	4 (17)	13 (57)	23 (100)
Valproic acide*[b]	50-100 µg/mL	5 (25)	2 (10)	13 (60)	20 (100)
Phenytoin	10-20 µg/mL	2 (50)	-	2 (50)	4 (100)
Phenobarbital	15-45 g/L	2 (66)	-	1 (33)	3 (100)

*A patient's serum level of both VPA and CMZ were above therapeutic value
[a]: The serum CMZ level of 10 cases who had toxic drug level was 20 mcg/mL
[b]: The VPA level of 8 cases with toxic drug levels was 150 mcg/mL and only 1 of these cases was > 800 mcg/mL

Table 3. The distribution of clinical findings and symptoms according to the serum drug level

Serum Drug Level	**Clinical Finding and Symptoms**				
	No Finding n (%)	**Minor n (%)**	**Moderate n (%)**	**Severe n (%)**	**Total n (%)**
Toxic	10 (35.7)	12 (42.9)	4 (14.3)	2 (7.1)	28 (100)
Non-toxic	14 (77.8)	3 (16.7)	1 (5.6)	-	18 (100)
Not Measured	14 (77.8)	3 (16.7)	-	1 (5.6)	18 (100)
Total	38 (59.4)	18 (28.1)	5 (7.8)	3 (4.7)	64 (100)

Discussion

Antiepileptic drugs affect the central nerve system using different mechanisms. They are used for a wide range of disorders such as epilepsy, mood disorders and neuropathic pain syndromes, so they are used commonly worldwide (1). Since AED are drugs types which are used frequently, their misuse is frequently encountered with side effects and overdose ingestion. Overdoses of AED may result in severe clinical findings and symptoms which have a life- threatening effect.

Antiepileptic drug overdose accounted for only a small proportion of all overdose admission. According to the 2011 Annual Report of the AAPCC, AED poisoning occupies the 12th place of all the poisonings (1.86%) (5). In our study, poisoning with AED composed of all poisonings, which was similar to a study carried out by Nixon et al and another study from Iran (6, 8).

Most studies have shown that female exposure to poisoning was much higher than that of males in the sex distribution of the adult age group (3, 6, 9-11). Similar to the literature, the admissions of females were greater than males in our study (F/M=41/23). According to the 2011 Annual Report of the AAPCC, 58% of all the poisonings over the age of 20 were females and 41% were males (5).

Poisonings with drugs are more frequent in the young adult groups in our country as it is all over the world (3, 9, 11-13). In a study from Iran, which included all age groups, it is reported that 43.2% of the patients who were poisoned with NBDAED were between the ages of 20-30 (8). In our study, patients were mostly between the ages of 18-29 (68%), but the young age group was more than stated in the literature. Contrary to our study, according to the 2011 Annual Report of the AAPCC, poisonings in the adult age groups were mostly between the ages of 30-39 (5). Nixon et al. (6) found that the median age value was 34 and the age group mostly exposed to poisoning was between the ages of 30-39.

In our country, Akkas et al. (14) reported that 52% of the patients poisoned with drugs were admitted to ED in the first 2 hours. Likewise in our study, the patients were admitted to the ED mostly in the first 2 hours (39.1%) even if this has a lower percentage.

In our study of cases, 92.2% ingested AED overdose via suicide. In similar studies it is seen that intentional drug ingestions are higher even if the rates show differences (3, 10, 11, 15). However in our study, this rate is a little higher than it is in other studies. Similarly, in a study from Iran which included all poisonings from all age groups, poisonings with drugs were 60% of all poisonings and 90.2% of them were suicide or abuse poisonings (9).

On the other hand, there are studies which associate psychiatric disorders and epilepsy with a high risk of suicides (16-18). In a meta-analysis by Jones et al. the risk of suicidality is 1.1-1.2%, and for epilepsy this rate is 12% (17). Besides, depression is frequently seen in epilepsy patients which is a significant risk factor for suicide (17, 18). In a study by Jones et al. (17) mood disorders are 12% in the healthy population, however this rate is 20-22% in the epilepsy patients.

Another debate about the relation between AED and the idea of suicide is issued in the 2008 American Food and Drug Administration (FDA) report which suggests that antiepileptics might double the suicidal risk in a meta-analysis (19). In contrast, Arana et al. (20) reported that the use of AED was not associated with an increased risk of suicide-related events among patients with epilepsy, but it was associated with an increased risk of such events among patients with depression and among those who did not have epilepsy, depressions or bipolar disorder. Supporting Hesdorffer et al. (21) many authors stated that the report of FDA was exaggerated and thus it would be more dangerous not to start treatment or to delay treatment of epilepsy than the increase in the suicidal risk. Our study is in line with these studies in terms of the fact that 66% of the patients examined by psychiatrists had mood disorders like depression. However, it should be noted that most of the case groups in our study (92.2%) had the intentional attempt of suicide and they were admitted to ED for only poisoning. Because of the lack of a control group and the limited number of the cases (n=64), it would not be a realistic statement to say that there is an increased suicidal risk in patients with epilepsy and psychiatric disorders.

In our study, together with the combined drug ingestions, CMZ took the first place (n=24, 37.5%) VPA took the second place (n=22, 34%) and OXCMZ took the third place (n=6, 9.5%). In the literature when the two important studies and the 2011 Annual Report of AAPCC about AED poisoning are taken into account, there are differences in the antiepileptics that the patients were mostly exposed to (5,6,8). In the study from UK (6) the first three were CMZ, VPA and Phenytoin; on the other hand, in a study from Iran (8) the first three were CMZ, Phenobarbital, and VPA. This difference might result from the fact that the study from UK included only an adult population, however the study from Iran included child population for which Phenobarbital is preferred (6, 8). According to the 2011 Annual Report of AAPCC in the population above the age of 20 the first three were VPA, CMZ and analogs, Phenytoin (5). Our study is in line with the study from UK since the first two are CMZ and VPA.

In terms of AED taken in our study, old generation AED (81.3%) are more common in the case group than the new generation AED (17.2%). There are many articles which focus on the potential harm of the old generation AED (22-24). Previous articles stated that new generation AED are more advantageous than the old generation AED, since new generation AED have fewer side effects and they are tolerated better (25, 26). A study by Sukumaran et al. (27) which compared old and new generation AED poisonings stated that old generation AED poisonings were more common. Similar to our study, in the study by Sukumaran et al. (27) there was no case of mortality or sequel. Although there are no cases of mortality either in the study of Sukumaran et al. (27) or in our study, Sukumaran et al. (27) concluded that new generation AED are safer as they result in less severe toxicity and less mortality than the old generation AED because in the literature there are cases of mortality resulting from old generation AED (27). It is a compelling fact that there was no statistically significant difference between the old and new generation drugs in terms of the sex, hospital stay duration and clinical findings and symptoms. Surely we are not trying to say that there are differences between old and new generations drugs in terms of safety. As there are limited studies in the literature about this issue, we think that this issue needs further research to obtain more realistic data.

In our study, it was found that the rate of taking different kinds of drug together with AED was 45.3%, and in a study from Iran (8) this rate was 42% which is close to our study. However, it was higher in the study by Nixon et al. (6) (65.4%). In our study, the most frequently taken drug types were anti-psychotics (12.5%) and antidepressants (12.5%) yet in the study by Nixon et al. (6) the most frequently taken kinds of drug were antidepressants (23.8%) and benzodiazepines (22.8%). In the study by Nixon et al. (6) although the hospital stay duration was not stated, only 25.4% of the patients were dis-

charged from hospital on the same day they were poisoned with AED. In the same study, the hospital stay duration of the case group who were poisoned with NBDAED was longer than the control group who were poisoned with other kinds of drugs. Similarly in the study from Iran, the median hospital stay duration of the case group who were poisoned with NBDAED was 24 hours, in line with our study, however the median hospital stay duration of the group who were poisoned with other kinds of drug was 12 hours (8).

Study Limitations

The major limitation of our study was a retrospective research.

Conclusion

Antiepileptic drug poisoning accounted for only a small proportion of all overdose admissions (3.2%) and it is more common in the female and young adult groups. Mostly patients were admitted to ED in the first 2 hours after ingestion and the clinical findings and symptoms were fewer in this group than the patients admitted to ED later than 2 hours. The drugs with which the patients mostly poisoned themselves were old generation AED and the first two drugs were CMZ and VPA. The majority (92.2%) of the cases were suicide and most (72%) patients took their own drugs. The rate of taking another kind of drug together with AED was 45.3% and the mostly commonly ingested drug types were antidepressants and antipsychotics. Of the patients, 59.4% developed no clinical finding or symptoms, yet 4.7% of them developed severe clinical findings and symptoms. Total of the case groups had completed recovery.

Conflict of Interest

No conflict of interest was declared by the authors.

Peer-review: Externally peer-reviewed.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Ondokuz Mayıs University School of Medicine.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Author Contributions

Concept - Y.Ç., C.K., K.B.; Design - Y.Ç., C.K.; Data Collection and/or Processing - Y.Ç., L.D., H.U.A.; Analysis and/or Interpretation - K.B.; Literature Review - L.D., H.U.A.; Writer - Y.Ç., C.K.; Critical Review - K.B., L.D.

Çıkar Çatışması

Yazarlar herhangi bir çıkar çatışması bildirmemişlerdir.

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