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Editorial

Değerli Okuyucular,

2020 yılının üçüncü ve son sayısını size ulaştırmaktan mutluluk duyuyoruz.

Bu sayımızda toksikoloji ile ilgilenen tüm okuyucularımıza katkı sağlayacak şekilde hazırlandı. Dört araştırma makalesi ve üç vaka sunumu ile toksikoloji literatürüne katkı sağlayarak kökleri çok eskilere dayanan bu bilim dalını geliştirmeye devam ediyoruz.

Dergimize katkıda bulunan değerli yazarlara ve derginin hazırlanmasında emeği geçen tüm paydaşlarımıza teşekkür ederiz.

Saygılarımızla.

Eurasian Journal of Toxicology Editörler kurulu adına,

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Original Article

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Retrospective Analysis of Possible Drug Interactions in Prescriptions Written by Branch and Emergency Physicians

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Abstract

Objectives: Drug-drug interactions may occur when more than one drug is taken by the same patient. These interactions can result in increasing, decreasing or preventing the effectiveness of drugs. In this study, prescriptions given by branch and emergency physicians were examined in terms of possible drug interactions.

Materials and Methods: Patients over 65 years of age who received a prescription from both the emergency department and the internal medicine or cardiology outpatient clinic were screened over a period of six months from July to December 2019. For the selected patients, information on the name and number of drugs prescribed, age, and gender were recorded. Then, the interactions between the drugs included in the prescriptions were investigated using Drug Interaction Checker-Medscape software.

Results: The study included 93 patients (57% females), with a mean age of 73.5 years. A total of eleven serious interactions, with the highest number belonging to the interaction of aspirin-ramipril were observed in the prescriptions given by branch physicians. Comparing the prescriptions of the branch and emergency physicians, 33 serious interactions, mostly that of ibuprofen-aspirin, were detected. Among the prescriptions of branch physicians, the majority of interactions were observed between aspirin and B blockers. For the emergency physicians, the highest number of interactions were seen in NSAID-NSAIDs. In the comparison of the prescriptions of the branch and emergency physicians, the highest number of interactions was 28, observed between NSAID and beta-blockers.

Conclusion: Emergency physicians should take a detailed history of elderly patients, especially concerning their regularly renewed prescriptions when prescribing NSAID-group drugs.

Key words: emergency, aspirin, drug interaction, NSAIDs

Özet

Amaç: Aynı hasta tarafından birden fazla ilaç aynı anda alındığında ilaç-ilaç etkileşimleri oluşabilir. Bu etkileşimler ilaçların etkinliğini arttırma, azaltma veya engelleme şeklinde olabilirler. Bu çalışmada, branş ve acil hekimlerinin yazdığı reçeteler incelenerek olası ilaç etkileşimleri incelendi.

Gereç ve Yöntem: Temmuz 2019 - Aralık 2019 arasını kapsayan 6 aylık sürede hem acil servisten hem de dahiliye veya kardiyoloji poliklinikten reçete düzenlenen 65 yaş üstü hastalar belirlendi. Belirlenen hastalara, yazılan ilaçların isimleri, ilaç sayısı, hastalara ait yaş, cinsiyet gibi bilgiler kaydedildi. Sonrasında Drug Interaction Checker- Medscape programı kullanarak yazılan reçetelerdeki ilaç etkileşimleri araştırıldı.

Bulgular: Çalışmaya 93 hasta dahil edildi. Dahil edilen hastaların yaş ortalaması 73,5 yıldı. Hastaların 57%'si kadındı. Branş hekimlerinin yazdığı reçetelerde aspirin-ramipril arasında en yüksek sayıda olmak üzere toplam 11 ciddi etkileşim görüldü. Acil ve branş hekimlerinin reçeteleri arasında en fazla ibuprofen-aspirin olmak üzere 33 ciddi düzeyde etkileşim tespit edildi. Branş hekimlerinin reçetelerinde en fazla aspirin-B bloker arasında etkileşim görüldü. Acil hekimlerinin reçetelerinde en fazla NSAID-NSAID arasında etkileşim vardı. Acil ve branş hekimlerinin reçeteleri arasında ise 28 etkileşim ile ne yüksek NSAID-B bloker arasında görüldü.

Sonuç: Acil hekimleri, ileri yaş hastalara özellikle NSAID grubu ilaçları yazarken hastanın kullandığı raporlu ilaçlarla ilgili ayrıntılı öykü almalıdır.

Anahtar kelimeler: acil, aspirin, ilaç etkileşimi, NSAID

Introduction

Polypharmacy, which is defined as the simultaneous use of multiple drugs by an individual, refers to the use of two or more drugs in some definitions while four or more drugs in others. The most important reason for polypharmacy is the need to prescribe drugs by more than one branch due to the increasing number of chronic problems with advancing age, such as diabetes, coronary artery disease, and hypertension. Another cause is the irregular and incorrect use of

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drugs due to the patient being elderly or negligent behavior of caregivers[1]. In studies conducted, the rate of polypharmacy in prescriptions has been reported to be 29% in the USA, mostly seen over the age of 75 years, 50% in Canada, and 53% in Italy[2].

Some patients need to use more than one drug at the same time, even if it is undesirable. In such cases, interactions between the two drugs can be seen. This interaction can sometimes be in the form of increasing the effect of one drug while at other times, a reduction or inhibition occurs. As the number of drugs used increases, the probability of interactions also increases. While the probability of developing an adverse effect is approximately 40% in patients using five drugs at the same time, this risk reaches 80% in those simultaneously taking seven or more drugs. In the literature, these interactions have been classified as serious, moderate, and minor. Being aware of these interactions in advance can prevent adverse effects by adjusting the dose or changing the drug if necessary[3,4].

In this study, drug-drug interactions were investigated by examining the prescriptions given by physicians working in internal medicine, cardiology and emergency clinics. Our aim was to raise awareness of drug-drug interactions and prevent adverse effects in elderly populations in which polypharmacy is frequently seen.

Materials and Methods

This retrospective study was carried out in the emergency medicine clinic of a tertiary hospital. Patients over 65 years of age who presented to our emergency department between July and December 2019 and received a prescription from an emergency physician for any reason were identified. Then, the previous year prescriptions of these patients were examined from the hospital system, and it was investigated whether the same patients had been given any prescription report by branch physicians in the internal medicine or cardiology outpatient clinic. Thus, patients who received a prescription from both the emergency department and an outpatient clinic within the past year were identified. In Turkey, branch physicians usually prepare prescription reports that cover a one to two year period. In our study, we limited the history of drugs prescribed for the duration of one year from the emergency presentation. In order to detect the interactions between the drugs prescribed by two physicians, we assumed that the patient was using the drugs that s/he had been given by the branch physician at the time that the emergency physician wrote a prescription for the same patient. Patients who were given three or more drugs in the same prescription were included in the study. Information on the names and numbers of the drugs, and patient age and gender was recorded.

After the prescriptions given to the patients were compiled, the presence of interactions between the drugs was investigated using Drug Interaction Checker, Medscape software. First, the presence and levels of interaction were investigated for each patient in the prescriptions written by the branch physicians. Then, the prescriptions written by emergency physicians were examined. Finally, all the drugs prescribed by the branch and emergency physician were entered into the software, and the number and level of interactions between the prescriptions of the two physicians were determined. In addition, drugs or drug groups that were involved in the interaction were identified.

According to the results of the software, the interaction levels were determined as serious, moderate (close follow-up), and minor. According to the software, an example of a serious drug-drug interaction is the use of aspirin and ibuprofen at the same time. In this situation, ibuprofen may increase the anticoagulant effect of aspirin and cause bleeding. An example of a moderate interaction is the use of candesartan-flurbiprofen, in which flurbiprofen may reduce the effect of candesartan through pharmacological antagonism. Lastly, an example of a minor interaction is that of diltiazem-aspirin, in which the former may increase the antiaggregant effect of the latter[5].

Statistical Analysis

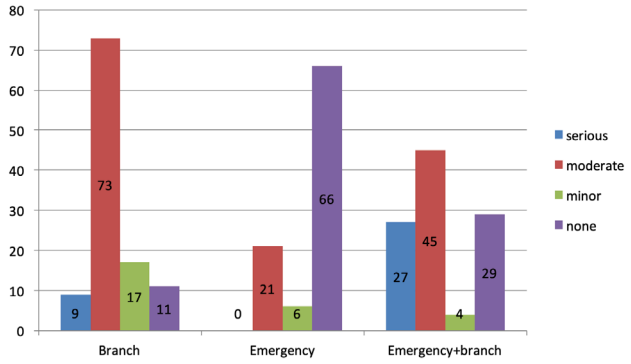
The study was carried out using SPSS v. 17.0. Descriptive statistics were given as mean ± standard deviation and percentages. For percentages, decimals were rounded to the nearest whole number where necessary.

Results

In this study, it was determined that a prescription containing three or more drugs was prepared for 157 patients in the emergency department over a period of six months. After examining these patients through the hospital system, 93 were determined to have also been prescribed drugs from the outpatient clinics within the past year, and thus were included in the study. The mean age of the patients was 73.5 years, and the majority were female (n = 53). When the prescriptions written by the branch physicians for these patients were examined, it was observed that there were 11 serious interactions in nine patients, 145 moderate interactions in 73 patients, 40 minor interactions in 17 patients, and no interaction in 11 patients. The prescriptions written by the emergency physicians revealed no serious interaction in any of the patients, 21 moderate interactions in 21 patients, six minor interactions in six patients, and no interaction in 66 patients. Examining the interactions of the drugs prescribed by two physicians, it was determined that there were 33 different serious interactions in 27 patients, 109 moderate interactions in 45 patients, and four minor interactions in

four patients, while 29 patients did not have any drug-drug interaction (Figure 1).

Figure 1. Number of patients receiving prescriptions according to the working area of physicians



The drug that caused the highest number of interactions in the prescriptions written by the branch physicians was aspirin (85 interactions), followed by beta-blockers (70 interactions) and angiotensin II receptor blockers (ARBs) (35 interactions). In the prescriptions of emergency physicians, flurbiprofen (n = 10), ibuprofen (n = 9) and etodolac (n = 3) mostly caused interactions. Drug-drug pairs with the highest number of interactions were aspirin-beta-blockers (n = 33) among the branch physicians, NSAID-NSAIDs (non-steroidal anti-inflamatory drug) (n = 15) among the emergency physicians, and beta-blockers-NSAIDs (n = 28) and aspirin-NSAIDs (n = 25) in the comparative evaluation of the branch and one emergency physicians (Table 1).

Table 1. Drug groups with the highest number of interactions

Physician	Number of interactions
Branch	
Aspirin-Beta-blockers	33
Aspirin-Clopidogrel	16
Aspirin-ARBs	15
Emergency	
NSAIDs-NSAIDs	15
Caffeine-Pseudoephedrine	5
Chlorpheniramine-Codeine	2
Brach + emergency	
NSAIDs-Beta-blockers	28
NSAIDs-Aspirin	25
NSAIDs-ARBs	21

ARB= angiotensin II receptor blockers, NSAID= non-steroidal anti-inflammatory drug

Considering the drug groups that caused serious interactions, aspirin-ramipril was the most common in the prescriptions of the branch physicians, while there was no serious interaction in those of emergency physicians. When the prescriptions of the branch and emergency physicians were comparatively evaluated, it was seen that the most common drug pair that created serious interactions was ibuprofen-aspirin (Table 2).

Table 2. Number of interactions for drug pairs causing serious interactions

Physician	Number of interactions
Branch	**11**
Aspirin-ramipril	8
Valsartan-ramipril	3
Emergency + branch	**33**
Ibuprofen-aspirin	10
Ibuprofen-ramipril	6
Clarithromycin-clopidogrel	5
Ketoprofen-ramipril	3
Moxifloxacin-indapamide	3
Prednol-silodosin	2
Aspirin-ramipril	2
Clarithromycin-rosuvastatin	1
Clarithromycin-atorvastatin	1

Discussion

Drug-drug interactions and their side effects are important reasons for hospital admission and mortality. Farooqui et al. determined that an average of 4.6 drugs were given per prescription, and most were prescribed for diabetes at a rate of 28.4%[3]. In the literature, the results concerning the number of drugs included in one prescription vary, with one study reporting 7.8 drugs[6] while another observing 9 drugs[7] per prescription. In another study examining drug-drug interactions among the elderly, it was determined that 39% of the prescriptions written included 11 or more drugs[8]. In our study, the number of drugs per prescription was 3.9 among the branch physicians and 3.35 among the emergency physicians.

The geriatric population and patients with depression, HIV positivity, diabetes and hypertension constitute the groups in which polypharmacy is most commonly seen[9]. In a study by Obreli-Neto et al., it was stated that drugs were mostly prescribed due to hypertension and diabetes. In the same study, the drugs that caused the highest number of interactions were reported to be warfarin, NSAID, digoxin, and diuretics [10]. In another study, aspirin, NSAIDs, diuretics, and beta-blockers were identified as the drugs that most caused interactions[4]. In our study, we observed that aspirin, beta-blockers and the ARB-group drugs were most commonly prescribed by branch physicians and the NSAID-group drugs by emergency physician. Beta-blockers and NSAID also had the highest number of adverse effects in the prescriptions comparatively evaluated between the branch and emergency physicians. It was also seen that most prescriptions were for cardiovascular diseases.

Limitations

In this study, only the information on the prescriptions was used and it was assumed that the patients used all the prescribed drugs. In addition, it was not investigated whether the patients presented to the hospital again after an adverse reaction and needed treatment. A multi-center study that will cover all health institutions in a city and examine hospital admission after adverse effects can yield more valuable results.

Conclusion

It was determined that the prescriptions of branch physicians had more drug-drug interactions than those of emergency physicians. The drug that caused the highest number of interactions was aspirin among the branch physicians and NSAIDs among the emergency physicians. Before prescribing NSAID-group drugs to patients on regularly renewed prescriptions, emergency physicians should investigate possible drug-drug interactions to significantly reduce the number of adverse effects.

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Original Article

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Evaluation of the Changes in T Peak-T End Interval and T Peak-T End/QT Ratio in Tricyclic Antidepressant Intoxication

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Abstract

Objectives: Tricyclic antidepressant (TCA) intoxication can affect various systems including cardiovascular system. In recent years, the transmiyocardial repolarization parameters including T peak-Tend (Tp-Te) interval, Tp-Te dispersion and Tp-Te/QT have been shown to be associated with increased cardiac arrhythmia risk. The aim of this study was to evaluate the effect of TCA intoxication on transmyocardial repolarization parameters.

Materials and Methods: This study was a cross-sectional study including 124 patients (43 male and 81 female) who were followed up and treated for TCA intoxication and 37 volunteer controls. At admission, 6th hour and 24th hour, the electrocardiogram of the patients were evaluated and Tp-Te and QT interval were measured manually and Tp-Te/QT ratio was calculated.

Results: The mean age of the study group was 27.95±7.72. There were statistically significant difference in terms of Tp-Te ($p<0.001$), Tp-Te mean ($p<0,05$) and dispersion ($p <0,05$) in V2-6 derivations between patient and control groups. There were significant difference in the Tp-Te/QT values in V2-5 derivations ($p<0,05$). We found a statistically significant difference in maximum and minimum QT values, prolonged QTc, prolonged QTc dispersion and prolonged mean Tp-Te/QT values between patient and control groups ($p <0.05$); prolonged mean Tp-Te values were similar between groups ($p = 0,117$). In the ROC analysis performed to investigate the diagnostic value of Tp-Te and Tp-Te/QT data in predicting disease, we found that all leads except V2 derivation were diagnostic ($p <0.05$).

Conclusion: TCA intoxication significantly increased the transmiyocardial repolarization parameters compared to the healthy population.

Key words: tricyclic antidepressant intoxication, Tp-Te interval, QT interval, Tp-Te/QT ratio, electrocardiography

Özet

Giriş: Trisiklik antidepresan (TSA) zehirlenmesi, kardiyovasküler sistem dahil olmak üzere çeşitli sistemleri etkileyebilir. Son yıllarda, Tp-Te aralığı, Tp-Te dispersiyonu ve Tp-Te / QT gibi transmiyokardiyal repolarizasyon parametrelerinin artmış kardiyak aritmi riski ile ilişkili olduğu gösterilmiştir. Bu çalışmanın amacı, TSA intoksikasyonunun transmiyokardiyal repolarizasyon parametreleri üzerindeki etkisini değerlendirmektir.

Gereç ve Yöntem: Bu çalışma, TSA intoksikasyonu için izlenen ve tedavi edilen 124 hasta (43 erkek ve 81 kadın) ve 37 gönüllü kontrolü içeren kesitsel bir çalışmadır. Başvuru anında, 6. saat ve 24. saatte hastaların elektrokardiyogramları değerlendirilerek Tp-Te ve QT intervali manuel olarak ölçülerek Tp-Te / QT oranı hesaplandı.

Bulgular: Çalışma grubunun yaş ortalaması 27.95 ± 7.72 idi. Hasta ve kontrol grupları arasında V2-6 derivasyonlarında Tp-Te ($p <0.001$), Tp-Te ortalaması ($p <0,05$) ve dağılımı ($p <0,05$) açısından istatistiksel olarak anlamlı fark vardı. V2-5 derivasyonlarında Tp-Te / QT değerlerinde anlamlı farklılık vardı ($p <0,05$). Hasta ve kontrol grupları arasında maksimum ve minimum QT değerleri, uzamış QTc, uzamış QTc dispersiyonu ve uzamış ortalama Tp-Te / QT değerlerinde istatistiksel olarak anlamlı fark bulundu ($p <0,05$); uzamış ortalama Tp-Te değerleri gruplar arasında benzerdi ($p = 0,117$). Tp-Te ve Tp-Te / QT verilerinin hastalığı öngörmedeki tanısal değerini araştırmak için yapılan ROC analizinde V2 derivasyonu dışındaki tüm derivasyonların tanısal olduğunu bulduk ($p <0.05$).

Sonuç: TSA intoksikasyonu, transmiyokardiyal repolarizasyon parametrelerini sağlıklı popülasyona göre anlamlı olarak artırmaktadır.

Anahtar kelimeler: Trisiklik antidepresan zehirlenmesi, Tp-Te aralığı, QT aralığı, Tp-Te / QT oranı, elektrokardiyografi

Introduction

Intoxication cases are among the most common reasons for admission to emergency services. In USA, the most common reason for drug intoxication at the age of 20 and above were analgesic drugs (13.1%), followed by sedative, hypnotic, antipsychotic drugs (11.2%) and antidepressant drugs with a rate of 6.2%. In the same report, sedative, hypnotic and antipsychotic drugs were the most common with 14.2% and antidepressant drugs were the fifth reason with 6.5% for drug intoxication-related deaths[1].

Tricyclic antidepressants (TCAs) show their therapeutic

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effects as negative allosteric modulators of neurotransmitter (serotonin and noradrenaline) reuptake[2]. It is reported that deaths caused by TCAs are most commonly seen with dotiepin and amitriptyline[3-4]. In Turkey, one of the most preferred TCA is amitriptyline (40-58%)[5].According to a review conducted in England and Wales death rate per 100.000 for all TCAs is 0.33 and for amitriptyline is 0,12[6]. TCAs are the most commonly prescribed antidepressants in the US after selective serotonin reuptake inhibitors and according to the report of the American Association for Poison Control Centers in 2003, among 12710 TCA intoxications, 0.6 % of them resulted in death while 64.7% of the patients had to be hospitalized[7].

The rate of life-threatening arrhythmia in TCA intoxications is known as 2.3% to 6% [8]. In these cases, electrocardiography (ECG) changes lead us to determine the severity of intoxication[9]. It has been reported that most patients develop major signs of TCA intoxication within 3 hours and severe rhythm disorders are seen in the first 6 hours[10]. The most common ECG change in these patients is sinus tachycardia. Also PR, QRS and QT prolongation, right axis deviation, right bundle branch block, AV blocks, changes that mimic acute myocardial infarction and Brugada syndrome, supraventricular tachycardia, premature ventricular extrasistoles, ventricular tachycardia, ventricular fibrillation, nonspecific ST-T changes and bradyarrhythmias can be seen in these patients[11]. T wave is the ECG finding of ventricular repolarization. In recent studies, transmyocardial repolarization parameters including T peak-Tend interval, Tp-Te dispersion and Tp-Te / QT ratio have been shown to be associated with increased risk of cardiac arrhythmias[12].

The aim of this study was to evaluate the effect of TCA intoxication on transmyocardial repolarization parameters and whether there is a relationship between these parameters and cardiac damage.

Materials and Methods

One hundred and twenty four patients who were admitted to our hospital between September 2011 and November 2015 and followed up and treated with TSA poisoning and thirty seven healthy control patients without any history of drug use were included to the study. The study was a cross-sectional clinical study.

Pregnant women, lactating women, those who were under 18 years of age, those with known or detected cardiac disease and those with additional diseases, those with electrolyte disorder, those with chronic medication use, patients whom the multidrug test was not performed were excluded from the study. Informed consent was taken from all study population. Ethical approval was obtained from the local ethics committee.

Age, gender, pulse, blood pressure, Glasgow coma scale (GCS), urea, creatinine, lactate and ECGs of all patients at the 6th and 24th hours were evaluated. In ECGs; QRS distance, ST elevation, ST depression, at aVR derivation R wave positivity, QT interval and corrected QT interval were measured and Tp-Te and Tp-Te/QT ratios were calculated. ECG recordings were measured by two experts who were completely blind about the condition of the patients. Prolonged QRS duration was defined as ≥100 msec. Tp-Te interval was measured by the tail method in the precordial leads. According to this method, the distance between the projection of the peak point of T wave on the isoelectric line and the point where the T wave ends was measured and defined as Tp-Te time. The QT interval was measured from the beginning of the QRS complex to the end of the T wave. In addition, corrected QT interval was calculated with the Bazett formula when the heart rate was not within normal range. In this way, abnormalities in heart rate were prevented from affecting the Tp-Te/QT ratio. The Tp-Te/QT ratio was calculated in the lead at which the Tp-Te interval was measured.

In the statistical evaluation, Chi-square or Fisher (in cases where the values observed in the cells did not provide the Chi-square test assumptions) was used. In the comparison of normal scattered numerical data between patient and control group, Student t test was used and Mann-Whitney U test was used for non-normal distribution. The change in rates in the data collected at the arrival, 6th and 24th hours was compared using the Cochran's Q test. Diagnostic characteristics of Tp-Te value and Tp-Te / QT ratio in chest leads were evaluated by ROC curve analysis. Sensitivity, specificity, positive predictive and negative predictive values of these limits was calculated in the presence of significant limit values. In the evaluation of the area under the curve, the cases with Type-1 error level below 5% were interpreted as statistically significant.

Results

The study included 124 patients who were followed up with TSA intoxication and 37 healthy volunteers as the control group.

The mean age of the patients was 27.95 ± 7.72 years and the mean age of the control group was 29.65 ± 6.76 years. There was no statistically significant difference between the age of the patients and the control group (p = 0.230). 43 (34.7%) of the males were in the patient group and 17 (45.9%) were in the control group. 81 (65.3%) of the females were in the patient group and 20 (54.1%) were in the control group. There was no statistically significant difference in terms of gender between the patient and control groups (p = 0.213).

The median GCS at the arrival of the patients was 15. The most common used drug was amitriptyline and followed by opipramol, imipramine and clomipramine, in the specified order. The median amount of drug taken by the patients was determined as 500 mg. The most common symptom was nausea and vomiting. The other commons symptoms were tachycardia, agitation, confusion, secretion,

Table 1. Comparison of mean arterial pressure, pulse, pH and lactate values of the patient group with the 6th hour and 24th hour data

	Admission	6th hour	24th hour	p
MAP,mean±SD, mmHg	83.19±13.64	81.03±12.69	84.40±10.75	0.009
Pulse, mean±SD	100.5±28.78	90.98±12.73	83.69±8.83	<0.001
pH, mean±SD	7.372±0.458	7.394±0.032	7.390±0.018	<0.001
Lactate,median(IQR)	1.15(0.93)	0.91(0.34)	0.85(0.49)	<0.001

Abb. IQR, interquartile range; MAP, mean arterial pressure; SD, standart deviation

dry mouth, hypertension, hypotension, tremor, mydriasis, seizure, delirium, coma, and myositis, respectively. All patients underwent gastric lavage, activated charcoal and fluid treatment. 79 (63.7%) patients underwent NaHCO3 treatment and 26 (20.9%) patients underwent other treatments. Median duration of hospitalization was 2 days. 121 (97.6%) patients were discharged with cure, 3 (2.4%) patients were transferred to another service and no patient died.

Mean arterial pressure, pulse, pH and lactate parameters were recorded at admission, the 6th hour and 24th hours. There was a statistically significant difference in the follow-up values of mean arterial pressure, pulse, pH and lactate values of the patients (p <0.05). (Table 1)

ECG findings were recorded at admission, the 6th hour and 24th hours. There was a statistically significant difference in the follow-up of the ratio of ECG parameters like normal sinus rhythm, sinus tachycardia, QRS complex enlargement, R wave at aVR derivation, supraventricular tachycardia, ST segment changes and ventricular extra systole (p <0.05). There was no statistically significant difference in QTc prolongation, right bundle branch block, right axis deviation, first degree atrioventricular block, Wolf Parkinson White and Brugada syndrome findings (p> 0.05).

There was no statistically significant difference between the Tp-Te values at V1 derivations at admission, the 6th hour and 24th hours of ECG (p = 0.289); There was a statistically significant difference in Tp-Te values in V2-6 derivations (p <0.001). There was also a statistically significant difference in the mean and dispersion of Tp-Te values (p <0.05) (Figure 1).

There was a statistically significant difference in Tp-Te / QT values in V1-5 derivations at admission, the 6th hour and 24th hour ECGs of the patients (p <0.05). There was no statistically significant difference in the follow-up of Tp-Te / QT at V6 derivation (p = 0.163) (Figure 2).

Figure 1. Tpeak - Tend intervals of the patient group at admission, 6th hour and 24th hours

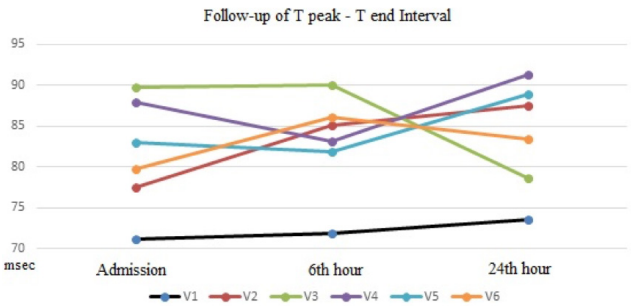
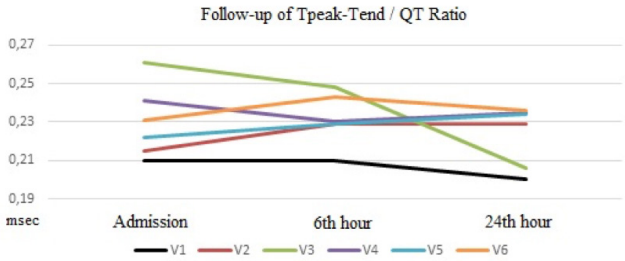


Figure 2. Tpeak - Tend / QT ratio of the patient group at admission, 6th hours and 24th hours



There was a statistically significant difference in the maximum and minimum QT values of the patients' ECGs at admission, the 6th hour and 24th hours (p <0.001); There was no statistically significant difference in QT dispersion, maximum and minimum QTc, QTc dispersion values (p> 0.05).

There was a statistically significant difference between prolonged QTc, prolonged QTc dispersion and prolonged mean Tp-Te / QT values between the patient and the control groups (p <0.05). There was no statistically significant difference between prolonged mean Tp-Te values between the groups (p = 0,117).

The patients were divided into 4 groups according to the active ingredient of the drugs they received. Prolonged QTc was seen in 66 (71.7%) patients, prolonged QTc dispersion in 45 (48.9%), prolonged mean Tp-Te in 8 (8.7%) and prolonged mean Tp-Te / QT was seen in 26 (28.3%) patients receiving amitriptyline. Prolonged QTc was seen in 18 (100%) patients, prolonged QTc dispersion in 13 (72.2%) patients, prolonged mean Tp-Te / QT was seen in 2 (11.1%) patients receiving opipramol. No prolonged mean Tp-Te / QT were detected in opipramol patients. Prolonged QTc was detected in 12 (100%) patients, prolonged QTc dispersion in 10 (83.3%), prolonged mean Tp-Te / QT in 3 (25%) patients and prolonged mean Tp-Te was seen in none of the patients who received imipramine. Prolonged QTc and prolonged mean Tp-Te / QT were detected in 2 (100%) patients receiving clomipramine. No prolonged QTc dispersion and prolonged mean Tp-Te was detected in clomipramine patients.

According to the comparison of the chest derivations of the ECGs taken at admission, the 6th hour and 24th hours;

there was a statistically significant difference in Tp-Te, the mean Tp-Te, the Tp-Te dispersion and the Tp-Te / QT (except the value of Tp-Te / QT at V3 derivation at the 24th hour) values between patient and control groups ($p < 0.05$). Only in V3 derivation at 24th hour, there was no statistically significant difference between the Tp-Te / QT values of the patient and control groups ($p = 0.236$).

In the ROC analysis performed to investigate the diagnostic value of Tp-Te data in chest derivations, all derivations except V2 were found to be diagnostic for predicting the pathology ($p < 0.05$). The highest AUC value was present in V4 derivation. The cut-off value for V4 derivation was ≥ 73.5 msec, the sensitivity 83.1% specificity was 78.4%, the positive predictive value was 92.8% and the negative predictive value was 58% (Figure 3).

In the ROC analysis performed to investigate the diagnostic value of T peak-T end / QT data in chest derivations, all derivations except V2 were considered to be diagnostic for predicting the pathology ($p < 0.05$). The highest AUC value was present in lead V6. The cut-off value for the V6 diversion was ≥ 0,216, the sensitivity was 71.8%, the specificity was 86.5%, the positive predictive value was 94.7% and the negative predictive value was 47.8% (Figure 4).

Discussion

Intoxication is one of the most common causes of emergency service admissions and it constitutes 0.07-0.7 % of all patients admitted to emergency clinics[13]. The studies conducted in Turkey showed this ratio to be in the range from 0.7 to 1.5%[14-17]. GCS is widely used to determine the severity of the patient's condition during the initial evaluation and follow-up of patients brought for intoxication. Arranto et al.[18] reported that they had an average GCS score of 11 in antidepressant intoxications. In another study, the mean GCS of patients was found to be 14[19]. In our study, GCS median was 15.

In the USA, amitriptyline (40%) is the most common cause of intoxications with TCAs. Imipramine second and doxepin have been reported in the third place[11]. In our study, it was found that most common cause for TCA intoxications were amitriptyline (74.2%), the second most frequent opipramol (14.5%), then imipramine and clomipramine. Amitriptyline, which is known as a sleep pill among the population, is frequently seen in intoxication cases because it is cheap in our country and widely prescribed by physicians.

There are few studies showing the rate of high dose drug intake in suicidal attempts. In a study performed by Makk et al., 498 (79.3%) of the 628 patients received high dose medication, and 130 (20.7%) received non-high dose medications[20]. The median value of the drug taken in our study was 500 mg.

Clinical signs and symptoms of TCA intoxication are altered state of consciousness, meaningless speech, mydriasis, and decrease in bowel sounds, nausea, vomiting, dry mouth, ataxia, and tachycardia[11]. The fact that the clinical findings of TCA poisoning are variable and the absence of specific findings cause difficulties in diagnosis and follow-up. However, the most common disturbed organs are heart and brain and especially central nervous system depression and cardiovascular findings are important so it is important to follow-up these findings[21]. In our study, nausea, vomiting, tachycardia, agitation, confusion, dry mouth and mydriasis were common symptoms and findings consistent with the literature. One of the clinical conditions of anticholinergic drugs due to the effects of postsynaptic muscarinic receptor antagonism is seizure. In some studies, the rate of convulsion has been reported to be 4 - 24% in severe antidepressant intoxication[22]. Several studies stated that the percentage of seizures in anticholinergic drug intoxications is 3.5-25 %[19, 21-23]. In our study, seizures were observed in 2 patients (2.4%).

There is no special antidote to be used in the treatment of anticholinergic intoxications[24]. TCAs show their primary cardiotoxic effects by blocking sodium and potassium chan-

Figure 3. ROC curve of Tpeak-Tend data at chest derivations

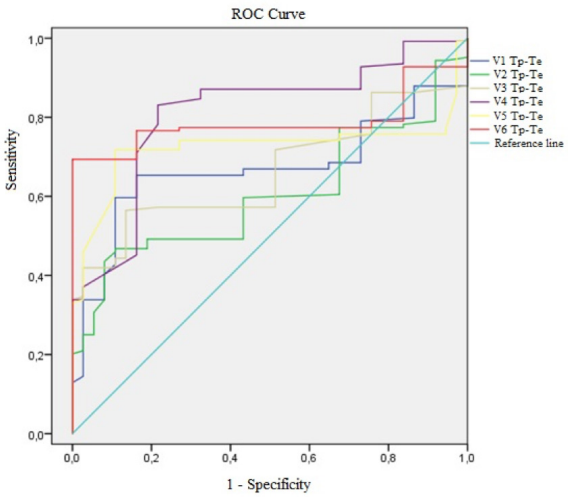
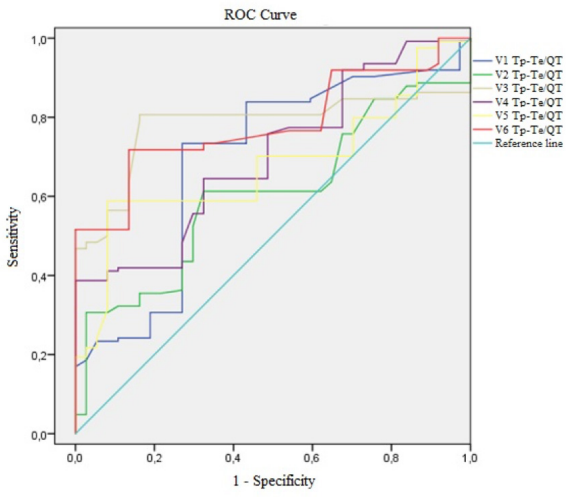


Figure 4. ROC curve of Tpeak-Tend / QT ratio at chest derivations



nels[25, 26]. NaHCO3 has been shown to regulate the conduction, increase cardiac contraction and suppress ventricular ectopia. Therefore, it is recommended that patients with QRS duration of longer than 100 msec, fluid therapy resistant hypotension and ventricular arrhythmias should be treated with NaHCO3[10]. Unverir et al.[27] reported that 6.5% of their patients were treated with sodium bicarbonate, 2.2% with diazepam and 1.6% had dopamine. In our study, 100% of the patients were treated with fluid and 63.7% of them were treated with sodium bicarbonate. The reason for these high rates is the fact that the patients were hospitalized in intensive care and most of the patients had cardiac involvement.

The duration of hospital stay is also an important factor. Graudins et al.[19] reported an average length of stay of 14 hours in antidepressant intoxication. In a study conducted in our country, the duration was reported as 0.7 days[14]. In another study, patients with antidepressant, intoxication had a mean stay of 1 day in the intensive care unit[18]. In our study, the median duration of stay in intensive care unit was 2 days. Considering the patients in our study were serious intoxication cases with cardiac involvement, the duration of hospitalization of our patients were similar with the previous studies.

The incidence of ECG abnormalities in TCA intoxications was reported to be 37%[28]. These ECG findings include: heart rate changes, rhythm disturbances and conduction delays[29]. Unverir et al.[27] evaluated the ECG findings after TCA intake in their study and normal sinus rhythm was observed in 41% of patients, sinus tachycardia in 40.7%, right axis deviation in 10.7%, prolongation of QRS in 7.9%, R> S in aVR was observed in 7.3% of the patients. In addition, it has been reported that right bundle branch block, prolongation of QT duration, left bundle branch block, left axis deviation, premature atrial contraction, sinus bradycardia, ST depression, second degree atrioventricular block, atrial tachycardia, ventricular fibrillation and asystole were also seen in these cases. In our study, 29.8% of patients had normal sinus rhythm, 33.1% had sinus tachycardia, 8.9% had right axis deviation and 47.6% had +R wave in aVR derivation.

One of the most important signs of heart involvement in TCA intoxications is the arrhythmias. The rate of ventricular arrhythmias in TCA intoxications was reported to be 2.7% and 6% in previous studies[8, 30]. In another study, the rate of life-threatening arrhythmias in TCA intoxications was reported to be 2.3%[31]. According to Foulke et al.[22], the rate of arrhythmias in antidepressant intoxications was 57% and by Arranto et al. the rate was 15%[32]. In our study, supraventricular tachycardia was found to be 8.1% and ventricular extra systoles were detected in 9.7% of the patients. All of these arrhythmias were completely recovered after treatment with NaHCO3 without any use of antiarrhythmic drugs. This shows that NaHCO3 treatment may alone be enough for arrhythmias caused by TCA intoxications since it suppresses ventricular ectopic beats.

The prolongation of QRS duration is an important parameter indicating cardiac influences in TCA intoxications. In the studies conducted by Bosch et al.[33], the rate of prolongation of QRS in TCA intoxications was 19% and Arranto et al. reported as 18%[32]. In our study, the rate of QRS prolongation was found to be 76.6%. The high rate of QRS prolongation in our study can be explained by the fact that we included intoxication patients with cardiac involvement and in need for intensive care.

It is known that antipsychotic drugs cause A-V block, PR-QRS-QT and T wave changes in ECG by suppressing contraction of heart with especially quinidine-like effects[13]. Of the patients included in the study, 2.4% had first degree AV block, 37.9% had right bundle branch block, 79% had QTc prolongation, 47.6% had +R wave in aVR, 3.2% had nonspecific ST changes and 1.6% had Brugada syndrome. This suggests that there may be a wide variety of ECG findings in anticholinergic drug intoxications and that the clinician should be alert to the development of almost all kinds of ECG findings in such intoxications.

It is known that TCA drugs can increase the risk of sudden cardiac death in intoxication patients due to the adverse cardiac effects[34]. These drugs are thought to lead to sudden cardiac death by increasing cardiac arrhythmogenicity[35]. The ECGs are often used to evaluate the increased arrhythmia risk. In surface ECG, QT interval, QTc interval, QT dispersion measurements show the heterogeneity of cardiac repolarization and are the parameters used to identify patients with increased risk of cardiac arrhythmia. In our study, maximum and minimum QT, QT dispersion, maximum and minimum QTc, QTc dispersion values were calculated at admission, the 6th and 24th hours. There was a statistically significant difference in maximum and minimum QT values and there was no statistically significant difference in QT dispersion, maximum and minimum QTc, QTc dispersion values.

In the ECG, the range from the top to the end of the T wave (Tp-Te) corresponds to the repolarization dispersion and the increase in the Tp-Te interval and Tp-Te / QT ratio has been shown to be related to life-threatening ventricular arrhythmias like in QT dispersion[36]. There are a limited number of studies in the literature about the Tp-Te / QT ratio in TCA drug intoxications.

The importance of Tp-Te as an indicator in the prediction of Torsades de Pointes (TdP) in patients with long QT syndrome (LQTS) was highlighted by Yamaguchi et al[37]. These investigators concluded that Tp-Te is more valuable than QTc and QT dispersion as a predictor of TdP in patients with acquired LQTS. Shimizu et al. showed that not QTc but Tp-Te predicts sudden cardiac death in patients with hypertrophic cardiomyopathy[38]. Topilski et al. showed that QT, QTc and Tp-Te are strong predictors of TdP. They also stated that the elongated Tp-Te alone was the best indicator [39]. Also Watanabe et al. reported that the long Tp-Te interval was associated with the development of spontaneous and inducible ventricular tachycardia in individuals with organic heart disease[40].

The ratio of Tp-Te / QT was significantly increased in patients with risk for arrhythmic events such as LQTS, Brugada syndrome, short QT syndrome, and organic heart diseases such as acute myocardial infarction. Functional reentry is the underlying mechanism in arrhythmias associated with an increased Tp-Te / QT ratio. Gupta et al. reported that Tp-Te / QT ratio is more sensitive than Tp-Te is an arrhythmogenic indicator[41]. Tp-Te duration and Tp-Te / QT ratio have been investigated in many diseases, but there are few studies on Tp-Te duration and Tp-Te / QT ratio in TCA drug intoxications. In our study, in the follow-up of Tp-Te values in V2-V6 leads, in Tp-Te mean and dispersion follow-up, Tp-Te / QT values in leads V1-V5 were found to be statistically significant as a result of the comparison between TCA intoxication patient group and control group. Similarly, there was a statistically significant difference between prolonged QTc, prolonged QTc dispersion and prolonged mean Tp-Te / QT values between the groups. In the ROC analysis to investigate the diagnostic value of Tp-Te / QT data in predicting the disease, other leads except V2 derivation were found to be valuable in predicting the disorder. These findings have also shown that Tp-Te and Tp-Te / QT have a high diagnostic value in TCA intoxications.

Conclusion

In conclusion, according to our study; there is significant prolongation in transmyocardial repolarization parameters in TCA intoxication cases compared to healthy population. These group of patients should be hospitalized, monitored carefully for life threatening arhytmias and cardiac injury.

Conflict of Interest

The authors declare that that have no conflict of interest. No funding was taken for the study. All authors participated in data collection, data analysis, writing and final manuscript control processes of the study. Informed consent was taken from all study population. Ethical approval was obtained from the local ethics committee.

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Original Article

Eurasian Journal of Toxicology

Demographic Characteristics of Patients Taking Single and Multiple Medications for Suicidal Purposes and Evaluation by Beck Anxiety Scale

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Abstract

Objectives: Anxiety appears as a normal reaction to life events such as life-threatening events, disappointment, separation from a loved one or environment, and physical illnesses. If the defense mechanisms in people are mentally healthy, they can cope by controlling the feeling of anxiety, but if the individuals are not fully mentally healthy, the feeling of anxiety can become chronic. This may cause undesirable situations in patients.

Materials and Methods: Our research; This is a prospective study conducted in Atatürk University Medical Faculty Hospital Emergency Service. The study was conducted in accordance with the descriptive research model that aims to compare patients who took single and multiple drugs for suicide purposes according to their demographic characteristics and the value they received from the beck anxiety scale. Our study was conducted on patients who applied to the emergency department in April (01.04.2019) -May (31.05.2019) in 2019.

Results: Our study was conducted on 111 patients in total, 56 of whom were taking multiple drugs, and 55 of whom were taking single drugs. The demographic data of the patients and the values they obtained from the beck anxiety scale were not found to be statistically significant between the patients taking single and multiple drugs.

Discussion: Patients with many psychiatric disorders due to organic or psychiatric reasons use drugs and these patients generally use these drugs for suicidal purposes. In our study, we investigated whether there was an underlying cause of single or multiple drug use. In our study, it was investigated whether multiple drug intake was related to a more severe anxious condition. However, in our study, no relationship was found between the amount of medication taken and the depressive state of the patient who committed suicide. In our study, no relationship was found between patients who took single or multiple drugs for suicide and their anxiety levels.

Key words: suicide, beck anxiety, toxicology

Özet

Amaç: Kişide, hayatı tehdit eden durumlar, kişide hayal kırıklığı yaratan nedenler, sevilen birinden veya ortamdan ayrılma, fiziksel hastalıklar gibi yaşamsal olaylara normal bir tepki olarak ankisyete oluşabilir. Eğer kişi, savunma mekanizmaları normal yani ruhsal olarak sağlıklı ise anksiyete hissini kontrol altına alarak kaygı ile baş edebilir fakat bireylerin ruhsal sağlığı tam olarak yerinde değilse anksiyete hissi kronikleşebilr. Bu da hastalarda istenmeyen durumların ortaya çıkmasına neden olabilir.

Gereç ve Yöntem: Bu araştırma, Atatürk Üniversitesi Tıp Fakültesi Hastanesi Acil Servisinde prospektif olarak yapılmıştır. Araştırma, öz kıyım amaçlı tekil ve çoklu ilaç alan hastaların demografik özelliklerini saptamaya ve Beck Anksiyete ölçeğinden aldıkları değere göre karşılaştırılmayı amaçlayan tanımlayıcı araştırma modeline uygun olarak yapılmıştır. Çalışmamız 01.04.2019-31.05.2019) tarihleri arasında acil servise başvuran hastalar üzerinde yapılmıştır.

Bulgular: Çalışmaya, çoklu ilaç alan 56, tekil ilaç alan 55 olmak üzere toplam 111 hasta dahil edilmiştir. Hastaların demografik verileri ile Beck Anksiyete ölçeğinden aldıkları değerler tekil ve çoklu ilaç alan hastalar arasında istatistiksel olarak anlamlı bulunmadı.

Sonuç: Organik veya psikiyatrik nedenlere bağlı olarak birçok psikiyatrik rahatsızlığı bulunan hasta ilaç kullanmaktadır ve bu hastalar genellikle bu ilaçları öz kıyım amaçlı kullanmaktadır. Bizde çalışmamızda tekil veya çoklu ilaç kullanımının altta yatan bir nedeninin olup olmadığını araştırdık. Araştırmamızda çoklu ilaç alımının daha şiddetli bir anksiyöz duruma bağlı olup olmaması araştırılmıştır. Ancak çalışmamızda alınan ilaç miktarı ile intihar eden hastanın depresif durumu arasında bir ilişki bulunamamıştır. Araştırmamız ile intihar amaçlı tekil veya çoklu ilaç alan hastalar ile bu hastaların anksiyete seviyeleri arasında bir ilişki tespit edilemedi.

Anahtar kelimeler: intihar, beck anksiyete, toksikoloji

Introduction

Anxiety is separated from other forms of emotion by its unpleasant properties. Anxiety can be briefly defined as distress. The anxious person may develop physical symptoms such as palpitations, shortness of breath, tachypnea, tremors in the hands and feet, excessive sweating, while psychological symptoms such as distress, excitement, feeling

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or doubt that suddenly a bad event will happen can be seen. The difference between anxiety from fear is that the source of anxiety is mostly unclear. Mild anxiety accelerates the adaptation process to new conditions in people, supporting their spiritual development[1,2].

Anxiety appears in the person as a normal response to life-threatening events such as causes of frustration in the individual, separation from a loved one or environment or physical illnesses. With anxiety, autonomic and somatic symptoms are seen in individuals at the same time. This is a protective mechanism. In some cases, stimuli that come from the internal world of the individual without any external stimuli can automatically cause the development of anxiety sensations in individuals.

If the people are spiritually healthy, they can deal with the feeling of anxiety by controlling it through defense mechanisms, but if the individuals are not fully spiritually healthy, the feeling of anxiety can become chronic. Anxiety disorders have a higher prevalence in women (30%) than in men (19%)[3]. Anxiety conditions, in which bodily symptoms such as muscle tension, dry mouth, palpitations and tremors usually occur, which reduce the professional function of chronic individuals and cause deterioration in inter-people ties, should be treated pathologically[4]. A high level of anxiety can lead people to unwanted events. In our study, we aimed to compare the demographic data of patients taking multiple medications and the scores they received from the Beck anxiety scale.

Materials and Methods

Research Design and Ethical Considerations

Our research is a prospective study conducted in the Emergency Department of Ataturk University Medical Faculty Hospital. This study was conducted on a voluntary basis on patients taking suicidal drugs admitted to Ataturk University Medical Faculty research hospital Emergency Department. The research was conducted in accordance with the descriptive research model aimed at comparing patients taking singular and multiple medications for suicide based on their demographic characteristics and the score they receive from the Beck anxiety scale.

The patients who would participate in the research were given information about the purpose of the research, the method and the time they were asked to spend for the research before starting the research. It was explained to patients that participating in the research did not carry any risk, that the participation was purely voluntary, that they could leave the research at any time. Their permission was received orally and in writing. The working protocol was carried out in accordance with the Helsinki Declaration.

The Context of the Study

The research was conducted prospectively at the Emergency Medicine Clinic at Ataturk University Medical Faculty Research Hospital in Erzurum province. Participants who accepted participation in the study were taken to a private room in the emergency room and their treatment was arranged.

Criteria for inclusion in the study:
- Being 18 years of age or older
- Having taken drugs for suicidal purposes
- Volunteering to participate
- Being literate
- Not being unable to comprehend what is being told

Criteria for Exclusion from the Study:
- Having a chronic disease
- Disorder of vital findings
- Being unable to give consent to the study
- Having injuries in addition to drug use (falls or trauma)
- Refusing to participate in the study
- Being pregnant
- Being under the age of 18

All our patients were also informed about the objectives of the study, the way it was implemented and the benefits of the results to be obtained. Then, all patients were interviewed face-to-face and the study was first explained and the informed consent form was signed by all accepting patients and those who did not accept were not included in the study.

Data Collection

Our study was carried out on patients admitted to the emergency department between April 2019 (01.04.2019)-May (31.05.2019). During this time, it was completed on 111 patients who were admitted to the emergency room and agreed to participate in the study. The study forms of the patients who accepted participation in the study were filled out by face-to-face interview method. In the study, patients who used a single drug (such as antibiotic analgesics) were included in the single-drug group of patients. The multiple-drug group, on the other hand, included patients taking drugs from at least 2 different groups. The patient who took antibiotics alone was included in the single-drug group, while the patients who took antibiotics and analgesia together were included in the multiple-drug group.

Data Collection Instruments

Beck Anxiety scale was applied to all patients who were taken to the study.

Beck Anxiety Scale

It's a self-evaluating test. It is used to investigate the frequency of anxiety symptoms experienced by individuals. It has been accepted by conducting confidence and validity studies in our country. The test consists of 21 items. For each

item, the participant is asked to score between 0-3. According to the answers given, the severity of anxiety experienced by people is determined[5].

For the study, patients' age, gender, systolic blood pressure, diastolic blood pressure, pulse, respiratory count, fingertip saturation, fever and Beck anxiety scale score were recorded.

Statistical Analysis:

The variables were divided into categorical and continuous. Categorical data were shown in number and percentage, compared with the Chi-square test. Whether the continuous variables were distributed normally was calculated by the Kolmogorov-Smirnov test. Continuous variables were shown with average and standard deviation. Normally distributed continuous variables were compared with paired sample T-test, while variables that were not distributed normally were compared with Related simple test. Statistics were made with SPSS 20.0 (SPSS Inc., Chicago, IL, United States) on the Windows operating system and $p<0.05$ was considered statistically significant.

Results

Our study was carried out on a total of 111 patients, including 56 patients taking multiple medications and 55 patients taking single medications. The gender distribution of these patients is shown in Table-1. There was no statistically significant difference between groups by gender (p=

Table 1. Drug intake by gender

	Single drug	Multiple drugs	Total
Female	37	39	76
Male	18	17	35
Total	55	56	111

Demographic data of patients by groups are shown in Table 2.

The demographic data of the patients and the values they received from the Beck anxiety scale were not statistically significant.

Discussion

Anxiety is a useful state of emotion for individuals that also contributes to the development of the ability to adapt to the new environment in which people live for certain periods[6]. However, it is inevitable to define exaggerated responses to internal or external stimulants and any condition that damages the self-integrity of individuals, that affect negatively socially and even impair body physiology as pathological[1,2]. There are some common clinical symptoms of depression and anxiety; emotional (frequent crying dysphoria, irritability) behavioral (poor social skills, decrease in activity and low energy level), bodily (sleep disorders and panic attacks), cognitive (anxiety, helplessness, self-confidence reduction). Situations more specific to depression can be listed as anhedonia, psychomotor retardation, sexual reluctance, decreased SSS alertness, decreased appetite, apathy, reluctance, severe grief and despair. More common conditions in anxiety are increased activity, premature ejaculation, hypervigilance, sense of uncertainty, increased alertness, agitation, fear and tension (86). Anxiety in individuals occurs in the period between encountering danger and ending danger, causing additional autonomic dysfunction in many people[7]. These autonomous changes can be listed as constricted sensation in the stomach, enlargement of pupils, shortness of breath, hypertension, fever, frequent urination, tremors, sweating, palpitations[2].

The word suicide comes from the Latin word suicidium, which derives from the root "sui caedere", which means that someone kills oneself. A Suicide attempt is defined as dest-

Table 2. Demographic data of patients and Beck Anxiety Scale score

	Parameter	n	Average	Standard Deviation	Minimum	Maximum	p
Single drug	Age	55	29,27	7,60	19	61	0,246
Multiple drugs	Age	56	31,55	8,67	20	62	
Single drug	Systolic Blood pressure (mmHg)	55	122,64	11,67	100	150	0,950
Multiple drugs	Systolic Blood pressure (mmHg))	56	122,77	10,37	100	140	
Single drug	Diastolic Blood Pressure (mmHg)	55	78,04	9,30	51	90	0,918
Multiple drugs	Diastolic Blood Pressure (mmHg)	56	77,86	9,07	51	90	
Single drug	Fingertip saturation (%)	55	95,82	1,17	93	98	0,355
Multiple drugs	Fingertip saturation (%)	56	95,59	1,41	93	98	
Single drug	Number of Respirations (min)	55	19,78	1,89	17	24	0,330
Multiple drugs	Number of Respirations (min)	56	20,14	1,99	16	24	
Single drug	Pulse(min)	55	97,60	19,29	60	142	0,464
Multiple drugs	Pulse(min)	56	100,30	19,45	60	142	
Single drug	Temperature(^{0}C)	55	36,92	0,42	36	38	0,749
Multiple drugs	Temperature(^{0}C)	56	36,94	0,38	36	38	
Single drug	Beck Anxiety Scale	55	17,98	3,08	11	25	0,797
Multiple drugs	Beck Anxiety Scale	56	17,82	3,46	11	25	

ructive behavior towards ending a person's own life[8] Suicide behavior is a serious health problem and is one of the major causes of reference in psychiatric emergencies. Many studies have shown that patients who attempt suicide have high levels of anxiety and depression[9,10]. The presence of an accompanying psychiatric disease was found to be the strongest determinant for suicide risk[11]. It has been reported that many patients who have attempted suicide exhibit depressive symptoms and 60% are diagnosed with emotional disorder[12].

Accordingly, suicidal patients and patients with many psychiatric conditions use medications. Due to organic or psychiatric reasons, many patients use drugs and these patients usually use these drugs for suicidal purposes. In our study, we investigated whether there is an underlying cause of single or multiple drug use. In our research, we thought that multiple drug intake would be due to a more severe anxious condition, but the result of our study did not support this assumption. In our study, no relationship was found between the amount of medication taken and the depressive status of the patient who committed suicide. Patients who commit suicide do not make multiple or single drug selections in suicide and attempt suicide with the drugs they reach most easily by making instant decisions.

Conclusion

With our research, no relationship was detected between patients taking single or multiple medications for suicide and the anxiety levels of these patients.

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Original Article

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Demographic Characteristics of Patients Applied to The Emergency Service with Drug Intoxications

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Abstract

Objectives: The term poisoning is quite old. Poisoning; It is the situation that stops vital functions where a substance enters the living organism through mouth, skin, respiration, circulation, and damages its function. Poisoning has been one of the important health problems throughout human history. The term "poisoning" was first used by the British in 1230. According to the first report of Turkish National Poison Control Center on the application by poisoning in Turkey is located medical drugs (69.74%). Poisoning caused by pesticides is in second place (8.34%) and poisoning with household chemicals is in third place (7.57%).

Materials and Methods: Patients who applied to Erzurum Regional Training and Research Hospital emergency service with drug intoxication between 07.04.2018 and 07.04.2020 were retrospectively screened and analyzed from the medical records.

Aim: It was aimed to examine the demographic characteristics of the patients who applied to Erzurum Regional Training and Research Hospital Emergency Service between 07.04.2018 and 07.04.2020 with drug intoxication in a period of two years.

Results: 96 patients admitted to the emergency departmant with drug intoxication beetween 07.04.2018 and 07.04.2020. Patients presenting with intoxication are 4.1% of all admitted patients. 79.3% of the patients presenting with intoxication are drug intoxication. The average age of these patients is 29,7 years old. 69 (71.8%) of the patients were female 67.7% of patients admitted to the emergency departmalet with drug intoxication are married.

Conclusion: Woman were intoxicated with a higher rate of drug intake than male. The lower socio-economic level of female in our geography may cause female to hold on to life less and want to end their lives. By increasing the socioeconomic status of female, the rate of suicide can be reduced. In our geography, as the marriage of female puts more psychological burden on themselves, drug intoxication may be more common among female who are married. Drug intoxication may be reduced in those who are married in male, perhaps because their lives are regulated. Since our study was conducted retrospectively, it is not certain what the purpose of poisoning was. Working prospectively in larger groups will provide us with more accurate and broader data.

Key words: drug intoxications, demographic, poisoning

Özet

Amaç: Zehirlenme; bir maddenin canlı organizmaya ağız, deri, solunum, dolaşım yoluyla girip zarar vererek işlevini bozmasıdır. 2008 yılı Ulusal Zehir Danışma Merkezi raporuna göre Türkiye'de zehirlenme ile başvurularda ilk sırada medikal ilaçlar yer almaktadır, tarım ilaçları ile oluşan zehirlenmeler ikinci ev kimyasalları ile olan zehirlenmeler ise üçüncü sıradadır.

Gereç ve Yöntem: Erzurum Bölge Eğitim ve Araştırma Hastanesi acil servisine 07.04.2018 - 07.04.2020 tarihleri arasında ilaç intoksikasyonu ile başvuran hastaların tıbbi kayıtları retrospektif olarak tarandı ve analiz edildi.

Bulgular: Araştırma dönemi boyunca acil servise toplam 2943 hasta başvurmuştu. Bu hastalardan 121'nin geliş şikayeti zehirlenmeydi. Bunlardan 96 tanesi ilaç intoksikasyonu ile acil servise başvurmuştur. İntoksikasyon ile başvuran hastalar tüm başvuran hastaların %4,11'idir. Zehirlenme ile başvuran hastaların %79,33 ü ilaç zehirlenmesidir. Bu hastaların yaş ortalaması 29,73 dir. İlaç intoksikasyonu ile gelen 96 hastanın 69 tanesi kadındı ve 65 (%67,7). İlaç intoksikasyonu ile gelen 96 hastanın 69 tanesi kadındı.

Sonuç: Kadınlar erkeklere göre daha yüksek oranda ilaç içerek intoksikasyona uğruyor. Coğrafyamızda kadınların sosyoekonomik düzeyinin daha düşük olması, kadının hayata daha az tutunmasına ve hayatına son vermek istemesine sebep oluyor olabilir. Kadınların sosyoekonomik düzeyinin artırılması ile özkıyım oranı azaltılabilir. Coğrafyamızda kadınların evli olmaları kendi üzerlerine daha fazla psikolojik yük yüklediğinden kadınlarda evli olanlarda ilaç intoksikasyonu daha fazla görülüyor olabilir.

Anahtar kelimeler: ilaç intoksikasyonu, demografik, zehirlenme

Introduction

The term poisoning is quite old. Poisoning is the situation that stops vital functions where a substance enters the living organism through mouth, skin, respiration, circulation, and damages its function. Poisoning has been one of the important health problems throughout human history. The term "poisoning" was first used by the British in 1230 [1, 2].

Paracelsus described poision as "All matter is poison. It is the dose that separates the drug from the poison. " He said and emphasized the amount of poison. In 1959, Du Bois and Geilling published their first toxicology book. Although poi-

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sonings are not common diseases such as stroke and heart diseases in emergency medicine, they are important disease groups. They constitute 5 percent of emergency applications in Germany[4]. Although it is close to this in France, there is no exact data on poisoning for Europe in general[5]. In studies of patients admitted to the emergency departmant in Turkey, 0.7-5% of patients admitted to the emergency constitutes intoxication[6, 7]. Drug-related poisoning can occur as a result of suicidal or accidental substance ingestion. According to first report of Turkish National Poison Counseling Center in 2008, it is located in applicants with medical drug poisoning in Turkey (69.74%). Poisoning caused by pesticides is in second place (8.34%) and poisoning with household chemicals is in third place (7.57%)[3]. The number of female patients admitted with poisoning in 2008 in Turkey (58.38%) male patients (38.1%) is greater than the number[3].

In this study, we aimed to the poisoning cases admitted to our emergency department with medication to harm themselves; evaluate it retrospectively in terms of demographic characteristics, cause of poisoning, treatment characteristics and duration and to contribute to the poisoning data of our country.

Materials and Methods

Patients who applied to Erzurum Regional Training and Research Hospital Emergency Service with drug intoxication between 07.04.2018- 07.04.2020 were retrospectively screened and analyzed from the medical records.

Results

Between 07.04.2018-07.04.2020, 2943, patients applied to Erzurum Regional Training and Research Hospital Emergency Service, among which 121 patients applied with intoxication. Ninety-six of them applied to the emergency departmalet with drug intoxication. Patients presenting with intoxication are 4.1% of all admitted patients. 79,3% of patients presenting with intoxication have drug intoxication. The average age of patients presenting with drug intoxication is 29,7. Out of a total of 96 patients, 69 were female and the remaining 27 were male. The rate of female patients is 71.87%. The rate of male patients is 28.13%. (Table.1) The oldest female patient is 57 years old. The youngest female patient is 16 years old. The average age of female is 29,9. 65 of 96 patients were married and 31 of them were single. 67.7% of the patients presented to the emergency departmalet with drug intoxication were married, and 32.3% were single. Fifty-four of the female patients are married, and 15 of them are single. Married patients are 67.7% compared to the total number of patients, while single patients are 32.3%. (Table 2) Of the female patients admitted to the emergency departmalet with drug intoxication, 78.26% were married, and 21.7% were single. The number of married female was 54, and the number of single female was 15. 40.7% of male patients admitted to the emergency departmalet with drug intoxication are married, and 59.26% are single. The number of married male patients was 11, and the number of single male patients was 16. (Table 3)

25 (15.9%) patients had medication from more than one group. The distribution of drugs taken by the patients is shown in Table-4. Specific antidote was given to 28% of the patients in addition to supportive therapy. N-Acetylcysteine (NAC) was started in 59.1% of the patients receiving specific treatment. Apart from NAC, atropine, PAM, vitamin K, fresh frozen plasma, desferrioxamine were other specific antidotes. The mean discharge time of the patients was 3.26 ± 1.67 days.

Table 1. Gender distribution of patients who presented to the emergency department with drug intoxication

	Number of patients (%)
Female	69 (%71.8)
Male	27 (%28.1)
Total	96 (%100)

Table 2. The ratio of married and single patients who presented to the emergency department with drug intoxication

	N (%)
Married	65 (%67.7)
Single	31 (%32.3)
Total	96 (%100)

Table 3. Married and single rates of male and female admitted to the emergency departmalet with drug intoxication

Female		**Male**	
Married	**Single**	**Married**	**Single**
n (%)	n (%)	n (%)	n (%)
54 (%78.2)	15 (%21.7)	11 (%40.7)	16 (%59.2)

Table 4. Demographic distribution of drugs causing intoxication

Medicines	**% (n)**
Parasetamol	%24.2(23)
Soğuk algınlığı ilaçları	%19.1 (19)
NSAI ilaçlar	%18.5 (18)
Triksiklik antidepresanlar	%12.1 (11)
SSRI	%8.3 (8)
Antihipertansifler	%5.7 (5)
Diğer*	%40.1 (38)

* Antibiotics, anticoagulant drugs, psychotic drugs, digestive system regulators, drugs affecting the cardiovascular system, drugs used in rheumatological diseases were classified in the other group.

Discussion

Özyapar et al. study in patients admitted to the emergency departmalet with intoxication in Turkey was found to account for 0,46-1,57's% of patients admitted to the emergency room. In our study, It constitutes 4.11% . The high rate may be due to the lower socioeconomic status in our region[8]. Poisoning is a significant health problem that has been going on since the beginning of human history. In our study, it has been shown to parallel in Turkey according to data from our data. In our study; According to the NPCC's (national poison counseling center) data of 2008, the rates of male and female patients are 38.1% and 58.38%, respectively. Our study 71.87 %% female, the male gender distribution is similar to that specified 28,13't% average in Turkey. The high proportion of female may be due to the lower socio-economic status of female. In studies conducted in other centers in Turkey, medication intake of female patients showed that men more than the rate of patient-related poisoning. In our study, the rate of female patients was similarly higher than the rates of male patients[1, 9-12]. In the study of NA Buckley et al.; Women have a higher rate of intoxication after taking medication than men. The results obtained in our study are similar[13].

Similar to Avınca O. et al., The number of female patients is higher than the number of male patients. In our study, when the marital status of the patients was examined, the majority of the cases who came to our emergency department with drug intoxication were married individuals[15].

In our study, drug-related intoxication cases were found to be the most common type of intoxication by the literature. We think that the reason for this is that the drugs and other substances are more comfortable to reach, and the drugs not used at home are easily accessible. In some exercises, women constitute the majority of applications for suicide[16].

As a conclusion women are intoxicated by drinking a higher rate of medication than men. Married women experience higher rates of drug intoxication. Single male patients suffer more drug intoxication. The lower socio-economic level of women in our geography may cause women to hold on to life less and want to end their lives. By increasing the socioeconomic level of women, the rate of intoxication can be reduced. In our geography, the psychological responsibility arising from the fact that women are mostly married and their higher responsibility may cause drug intoxication to be seen more in women, especially in those who are married. Drug intoxication may be reduced among married men, perhaps because their lives are regulated. Since our study was carried out retrospectively, the purpose of poisoning is not known precisely. Conducting a larger group of prospective studies will increase the accuracy of the data.

Paracetamol is the most common cause of drug intoxications both in the world and in our country, as it is available without a prescription. Paraetamol was the most common cause of intoxications in our patient group. In our study, anti-flu drugs were the second cause of intoxication, while NSAI drugs were in the third place. In many studies in the literature, antidepressant drugs are shown as one of the first three drugs that cause poisoning. Although this situation is seen relatively differently in our results, when TCA and SSRI group drugs are evaluated together in our study, it stands out that antidepressants (20.4%) are the second most common cause of intoxication. In our study, while most of the patients were discharged with supportive therapy, some of them received a specific antidote. Among the specific antidotes, NAC treatment leads, but K-vitamin, FFP, atropine and PAM are other specific substances. It would be appropriate to have these antidotes in emergencies so that patients can be treated as soon as possible. The mean discharge time of the patients included in the study was similar to previous studies in the literature.

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Nadir Görülen Bir İntoksikasyon Vakası: İzoniazid İntoksikasyonu

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Özet

Antitüberküloz ilaçlar ile zehirlenmeler günümüzde yok denecek kadar azdır. İzoniazid yüksek dozlarda alındığında, dozla ilişkili olarak, konvülsiyon, metabolik asidoz, laktik asidoz, rabdomiyoliz, koma ve hatta uygun tedavi edilmediği takdirde ölümle sonuçlanabilmektedir. 26 yaşındaki erkek hasta hastanemiz acil servisine bilinç değişikliği ile getirildi. Yaklaşık 15 dakika önce evde baygın halde bulunmuştu. İlk muayenesinde glaskow koma skalası 10, pupiller izokorik, IR:+/+ olarak saptandı. Yakınlarından ilaç aldığı öğrenilen hastanın mide lavajı yapıldı ve aktif kömür tedavisi uygulandı. Ancak ne ilaç aldığı yakınlarından öğrenilemedi. Hasta gözetim altında iken nöbet geçirdi. Hastanın nöbetini durdurmak için intravenöz diazepam yapıldı. Nöbetin önce agresyonu hafifledi daha sonra nöbeti durduruldu. Takip esnasında tekrar nöbeti olan hastanın nöbetine yönelik bu sefer intravenöz midazolam yapıldı ve nöbeti durduruldu. Klinik şüphe üzerine yakınlarından ayrıntılı anamnez alındı ve hastanın izoniazid aldığı öğrenildi. 50 mg/kg/gün dozunda intravenöz piridoksin tedavisi yavaş infüzyon şeklinde başlandı. Yaklaşık 30 dakika sonrasında hastanın bilinci açıldı. İzoniazid zehirlenmesi erken müdahale edildiği ve tek tedavi seçeneği olan piridoksin verildiği takdirde başarı ile tedavi edilebilmektedir.

Anahtar kelimeler: izoniazid intoksikasyonu, koma, piridoksin

Abstract

Poisonings with antituberculosis drugs are almost nonexistent but rarely seen. When isoniazid is taken in high doses, it may result in convulsions, metabolic acidosis, lactic acidosis, rhabdomyolysis, coma or even death if not treated appropriately. A 26-year-old male patient with no known systemic disease and history of drug use was admitted to the emergency department of our hospital with a change of consciousness. According to the anamnesis taken from relatives, it was learned that he was unconscious at home about 15 minutes ago. In the first examination of the patient, the glaskow coma scale (GCS) was 10, and the pupillary isochoric and IR: + / + were determined. It was learned that the patient was taking medication from relatives and gastric lavage was performed and activated charcoal treatment was applied. However, the relatives did not know what medication he was taking. The patient had a seizure while in custody. Intravenous diazepam was administered to stop the seizure. Aggression of the seizure first decreased and then seizure was stopped. During the follow-up, the patient had a seizure again, and this time intravenous midazolam was administered and the seizure was stopped. Upon clinical suspicion, a detailed anamnesis was obtained from the relatives and the patient was admitted to take INH medication. Intravenous pyridoxine (50 mg / kg / day) was started as a slow infusion. Approximately 30 minutes later, the patient regained consciousness. Isoniazid poisoning can be successfully treated with early intervention and pyridoxine, the only treatment option.

Key words: isoniazid intoxication, coma, pyridoxine

Giriş

İzoniazid (INH) hem ucuz hem de tedavide etkin rol oynadığı için tedavide uzun zamandır kullanılmaktadır. Antitüberküloz ilaçlar ile zehirlenmeler günümüzde yok denecek kadar azdır ancak nadiren görülebilmektedir. Dozla ilişkili olarak, INH fazla miktarda alındığında, metabolik asidoz, dirençli konvülsiyon, rabdomiyoliz, derin laktik asidoz, koma ve hatta ölümle de sonuçlanabilmektedir[1]. INH zehirlenmesinde konvülsiyonun tedavisinde en iyi yol, piridoksin (B6 vitamini) uygulanmasıdır. Bu olguda, yüksek anyon açıklı metabolik asidozu ve tekrarlayan dirençli konvülsiyonları olan akut INH zehirlenmesi nedeniyle acil servise getirilen olgu tartışılmıştır.

Olgu Sunumu

İlaç kullanım anamnezi ve bilinen sistemik bir hastalığı olmayan 26 yaşındaki erkek hasta acil servise bilinç değişikliği ile getirildi. Yakınlarından alınan anamneze göre yaklaşık 15 dakika önce bayılmış halde bulunduğu öğrenildi. Hastanın yapılan ilk muayenesinde GKS puanı 10 olup, IR:+/+ ve pupilleri izokorik olarak saptandı. Vital değerleri TA:121/63 mmHg, nabız:114 /dk, parmak ucu saturasyon: %91 idi. Yakınlarından ilaç aldığı öğrenilen hastanın mide lavajı yapıldı ve aktif kömür tedavisi uygulandı. Ancak ne ilaç aldığı yakınlarından öğrenilememişti. Hasta gözetim altında iken nöbet geçirdi. Hastanın nöbetini durdurmak için intravenöz diazepam yapıldı. Nöbetin önce agresyonu hafifledi daha

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sonra nöbeti durduruldu. Takip esnasında tekrar nöbeti olan hastanın nöbetine yönelik bu sefer intravenöz midazolam yapıldı ve nöbeti durduruldu. Hastada bakılan kan parametrelerinde Glukoz: 149 mg/dl, üre: 26 mg/dl, kreatinin: 0,86 mg/dl, Na: 140 mEq/l, K: 3,4 mEq/l, Cl: 102 mEq/l, Ca: 9,7 mg/dl, AST: 28 U/L, ALT: 31 U/L, WBC: 17800 µ/L; venöz kan gazında pH: 7,22, pO2:47, pCO2: 38, HCO3: 15.3, BE:-12,2, SO2: 76, COHb: %4,2, lac:7,9 idi. Hastanın ayırıcı tanısı için beyin BT çektirildi BT'de akut patolojik görüntü yok idi. Madde kullanımı şüphesi ile idrarda madde analizi yapıldı ancak herhangi bir madde kullanmadığı tespit edildi. Yüksek anyon açıklı metabolik asidozu olan, tekrarlayan generalize tonik klonik tarzda konvülsiyonları başlayan hastada daha önceki tecrüberimize dayanarak INH intoksikasyonu düşünüldü ve tedavisi başlandı. Klinik şüphe üzerine yakınlarından ayrıntılı anamnez alındı ve hastanın yaklaşık 4,5g INH (300mg INH – 15 tablet) ilaç aldığı itiraf edildi. 50 mg/kg/gün dozunda intravenöz piridoksin tedavisi yavaş infüzyon şeklinde başlandı. Yaklaşık 30 dakika sonrasında hastanın bilinci açıldı. Acil serviste 2 saatlik takibi sonrası yoğun bakım ünitesine takip amaçlı sevk edildi. Yoğun bakım ünitesinde 24 saat daha takibi sonrası klinik olarak tamamen normale dönmüş, kontrol kan parametrelerinde anormal bir değere rastlanmaması sonucu şifa ile taburcu edilmiştir.

Tartışma

INH fazla miktarlarda alındığında, dozla ilişkili olarak, metabolik asidoz, dirençli konvülsiyon, rabdomiyoliz, derin laktik asidoz, koma ve uygun tedavi edilmediği zaman ölümle sonuçlanabilmektedir. Tedavi INH alım miktarına eş miktarda parenteral verilen yüksek doz piridoksin ve destek tedavisinden oluşmaktadır. Akut dönemde 20 mg/kg alındığında nonspesifik, hafif zehirlenme bulguları oluşturabilir. Jeneralize konvülsiyon 30 mg/kg' dan fazla alımlarda gelişebilir. 80 mg/kg ve daha fazla alımlar antikonvülsanlara dirençli ve tekrarlayan nöbete, laktik asidoza ve komaya yol açabilir, uygun tedavi düzenlenmezse mortal dahi seyredebilir.

Akut toksisite klinik bulguları alımdan sonraki 30 ile 120 dakika içinde gözlenen bulantı, kusma, taşikardi, ürtikeryal döküntü, motor disfazi, vertigo, grand-mal nöbetler ve komadır[2]. Hastamızda akut toksisite bulgularından taşikardi, yüksek anyon açıklı metabolik asidoz, tekrarlayan konvülsiyonlar, laktik asidoz mevcut olup bilinci kapalı ve GKS:10 idi.

INH zehirlenmesinde tedaviye dirençli konvülsiyonlar; santral sinir sisteminde gama amino bütirik asit (GABA) düzeylerinin azalması sonucu konvülsiyon eşiğinin düşmesi sonucu olduğu düşünülmektedir. Nöbetler antikonvülsanlara dirençlidir. Nöbetin tedavisinde antikonvülsanlara ek olarak pridoksin uygulaması, tek başına antikonvulsan kullanımına göre daha yüksek etkinliktedir[3]. Biz de olgumuza midazolama ek olarak piridoksin de vererek konvülsiyonları kontrol altına aldık.

INH zehirlenmelerinde konvülsiyon esnasındaki şiddetli kas hareketlerinin yıkımı sonucu olan rabdomiyoliz de nadir görülür, ancak ölümcül olabilen bir komplikasyondur ve INH yıkımı esnasında beta-hidroksi bütirikasit metabolizmasını azaltarak da metabolik asidoza katkıda bulunduğu ileri sürülmüştür[4].

Sonuç

Ülkemizde hâlâ tüberküloz vakalarına rastlanıldığından hem proflakside hem de tedavide kullanılan INH ile olan zehirlenme olguları da görülebilmektedir. INH zehirlenmesi uygun ve hızlıca tedavi edilmezse mortal seyredebilmektedir. Bu nedenle, nedeni açıklanamamış anyon açığı fazla olan metabolik asidoz, klasik antikonvülsanlarla durdurulamayan nöbetler ile acil servise getirilen hastalarda INH zehirlenmesi de akılda tutulmalıdır. Tedavide spesifik antidot sadece parenteral olarak verilen piridoksin olduğu unutulmamalıdır.

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Case Report
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Siklosporin Kullanımına Bağlı Nadir Bir Yan Etki: Nöbet

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Özet

Siklosporinin en önemli klinik endikasyonu; transplantasyon sonrası organ reddinin profilaksisidir. immunosupresan etkinliğinin yanı sıra ayrıca; romatoid artrit, psöriazis, nefrotik sendrom, atopik dermatit, üveit gibi bazı otoimmun hastalıkların tedavisinde de kullanılmaktadır. 62 yaşında kadın hasta baygınlık geçirme ve nöbet şikayetiyle acil servise başvurdu. Genel durum orta, apatik, uykuya meyilli olan hasta postiktal olarak değerlendirildi. Vital bulguları normal olarak değerlendirilen ve muayene sırasında generalize tonik klonik nöbet görülen hastaya 10 mg i.v. diazepam tedavisi verildi. Levotirasetam 20 mg/kg intravenöz infüzyonu başlandı. Beyin BT (bilgisayarlı tomografi), Difüzyon MR(manyetik rezonans) ve MR(manyetik rezonans) çekilen ve nöroloji ile konsülte edilen hastada acil nörolojik patoloji saptanmadı. Özgeçmişinde hastanın lösemi tanısı olduğu, siklosporin tedavisi aldığı ve birkaç gün önce kür sağlandığı öğrenildi. Takip amaçlı yoğun bakım yatışı yapıldı. Olgu Çalışmamız nörotoksik etkisi olduğu bilinen siklosporinin yalnızca nöbet şikayetiyle de karşımıza çıkabileceğini ve etki mekanizması ile ilgili yeni araştırmalara ihtiyaç olduğunu göstermeyi hedeflemiştir.

Anahtar kelimeler: siklosporin, nöbet, malignite

Abstract

The most important clinical indication of cyclosporine is the prophylaxis of organ rejection after transplantation. Besides immunosuppressant activity; used in the treatment of some autoimmune diseases (rheumatoid arthritis, psoriasis, nephrotic syndrome, atopic dermatitis, uveitis) It was aimed to show that seizures may occur due to cyclosporine use in patients diagnosed with cancer. 62-year-old female patient was admitted to the emergency service with complaints of fainting and seizure. The general condition was moderate, apathy and the patient was evaluated postictal. During the examination, a generalise tonic clonic seizure was seen. The patient whose vital signs were evaluated to be normal and who had generalized tonic-clonic seizure during examination was given 10 mg i.v. diazepam treatment was given. Levotiracetam 20 mg / kg intravenous infusion was started. No immediate neurological pathology was detected in the patient, who underwent brain CT (computed tomography), diffusion MRI (magnetic resonance) and MR (magnetic resonance) and was consulted with neurology. We was informed that the patient had leukemia diagnosis, received cyclosporine treatment, and was cured a few days ago. Follow-up intensive care hospitalization was performed. Our aim was to show that cyclosporine, known to be a neurotoxic effect, may be confronted with only a seizure complaint and that new research on the mechanism of action is needed.

Key words: cyclosporine, seizure, malignancy

Giriş

Siklosporin; tedavide oral, intravenöz ve oftalmik yollar ile uygulanmaktadır. Oral çözelti ve yumuşak jelatin kapsül formlarının yanı sıra, intravenöz infüzyon için konsantre çözelti formu da bulunmaktadır. Siklosporinin en önemli klinik endikasyonu; transplantasyon sonrası organ reddinin profilaksisidir[1,2]. Oral formülasyondan siklosporin absorpsiyonu; gastrointestinal kanaldaki safra tuzlarının varlığına ve pankreatik enzimler tarafından sindirilmeye bağlıdır. Bu nedenle formülasyonda siklosporin biyoyararlanımı düşüktür ve birey içi/bireyler arası değişkenlik göstermektedir[1,3].

1980 yılında immunosupresiyon etkinliğinin bulunması ile; organ reddi hızında ciddi bir azalma, başarı ile sonuçlanan nakiller ve artmış hasta uyumu görülmüştür[1,4,5,6].

İmmunosupresan etkinliğinin yanısıra ayrıca; romatoid artrit, psöriazis, nefrotik sendrom, atopik dermatit, uveit gibi bazı otoimmun hastalıkların tedavisinde de kullanılmaktadır[1,7]. Kuru göz sendromu[1,8], vernal konjuktivit[1,9], atopik keratokonjuktivit gibi pek çok oküler hastalığın tedavisinde yaygın kullanımı bulunmaktadır[1,10].

Siklosporinin terapötik kullanımında karşılaşılan en önemli sorun; böbrekler üzerinde ciddi toksik etkilerin (nefrotoksisite) görülmesidir. Karşılaşılan diğer yan etkiler arasında; nörotoksisite, hepatotoksisite, hiperlipidemi, hirsutizm, gingivalhiperplazi, lenfoproliferatif tümör oluşumu, bulantı, kusma ve tremor bulunmaktadır[1,11,12]. Bu olgu sunumunda kanser tanısı olan hastalarda, siklosporin kullanımına bağlı nöbet görülebileceğini göstermek amaçlandı.

Olgu Sunumu

62 yaşında kadın hasta baygınlık geçirme ve nöbet şikayetiyle acil servise başvurdu. Genel durum orta, apatik, uyku-

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ya meyilli olan hasta post iktal klinik olarak değerlendirildi. TA(tansiyon):134/79 mmhg, Nabız:117/dk, satürasyon:85 %, ateş:36,7, glukoz:316 mg/dl, EKG(elektrokardiyogram) normal sinüs ritmi olarak değerlendirildi. Hastane başvurusundan 10 dakika sonra ilk muayenesi sırasında tekrar nöbet geçiren hastanın kan gazı analizinde PH:7.4, PCO2:38.6 mmhg, HCO3:27.2, WBC (white blood cell):11 10^3/µl, hemoglobin:12.6 g/dl, platelet:195 10^3/µl. Karaciğer ve böbrek fonksiyon testleri normal idi. Muayene sırasında hastada görülen nöbet generalize tonik klonik nöbet idi. 10 mg i.v. Dizepam verildi. Levatirasetam 20 mg/kg intravenöz serum fizyolojik içinde 30 dk infüzyon yapıldı. Sonra idame 20 mg/kg/gün intravenöz dozda levatirasetam infüzyonu başlandı. Nöbet sonrası TA:230/110 mmhg olarak belirlendi. Esmolol tedavisi intravenöz başlandı. Hastanın çekilen beyin BT (bilgisayarlı tomografi), difüzyon MR (manyetik rezonans) ve MR görüntülemeleri normal olarak değerlendirildi. Beta bloker (esmolol) tedavi sonrası TA:150/70 mmhg'a geriledi. Nöroloji ile konsülte edilen hastada acil nörolojik patoloji düşünülmedi. Özgeçmişinde hastanın lösemi tanısı olduğu, siklosporin tedavisi aldığı ve birkaç gün önce kür sağlandığı öğrenildi. Takip amaçlı yoğun bakım yatışı yapıldı.

Tartışma

Nöronal ağların elektriksel aktivitesinde aşırı artışlara bağlı olarak nöbet görülür[13,14]. Daha önce epilepsi tanısı almamış hastada görülen nöbetlerin %6'sı; status epilepticusun ise %9'unun ilaçlara bağlı olarak ortaya çıktığı düşünülmektedir[14,15].

Nöbete neden olabilecek ilaç grupları; analjezikler (meperidin), anestezik ajanlar (propofol), anti bakteriyel ajanlar (florokinolanlar), antidepresanlar (bupropion, maprotilin, trisiklik antidepresanlar), antineoplastik ajanlar (klorombusil), antipsikotik ajanlar (klozapin), kontrast madde, immünsüpresanlar ve immünmodülatörler idi. (interferonlar)[16,17] Hastamızda siklosporin dışında nöbete neden olabilecek farklı bir ajan kullanımı bulunmamakta idi.

1-18 yaş arası 206 vakanın incelendiği retrospektif bir çalışmada siklosporin başlanan 17 vakanın altısında (%35.3) siklosporine bağlı yan etkiler görüldü. En fazla görülen yan etkiler hipertansiyon, hirsutizm, gingival hiperplazi, monoliasis ve anemiydi[18].Hastamızda nöbetle birlikte hipertansiyon da görüldü fakat ilk geliş muayenesinde tansiyon ölçümü normal sınırlarda olarak değerlendirildi.

Mendosa ve Tune[15,16] siklosporin verdikleri hastalarında kreatinin yüksekliği, Kari ve ark.[18,20] gingival hipertrofi ve böbrek tutulumu saptamışlar ve ilacın kesilmesiyle bu etkilerin düzeldiğini bildirmişlerdir. Hirano ve ark.[18,21] %45,5 oranında kronik nefrotoksisite saptamışlardı. Hastamızın böbrek fonksiyon testleri normal sınırlardaydı. Chen LW ve arkadaşları 18 yaş altı hastalarda yaptıkları retrospektif bir çalışmada siklosporinin kronik kullanımının daha küçük yaşlarda daha fazla ensefolapatiye neden olduğunu göstermişlerdi[22]. Nöroloji tarafından da değerlendirilen hastada ensefolapati düşünülmedi. Handreck A ve arkadaşları siklosporinin parenteral kullanımının ratlarda nöbet eşiğinde değişiklik yapmadığını göstermişlerdi[23].

Bizim vakamızda 2 kez nöbet gözlenmiş ve nöbet etyolojisinin araştırılmasında siklosporin yan etkisi dışında herhangi bir organik paterni olan nöbet düşünülmemiştir. Hastanın santral sinir sistemi görüntülemelerinde herhangi bir patolojiye rastlanılmadı. Rutin labaratuvar tetkiklerinde serum glukozu, serum Na'u normal sınırlarda idi, tekrarlayan tetkiklerde de değişim olmadı. Hastanın hipoksi öyküsü, akciğer hastalığı bulunmamakta idi. Siklosporinin 36 saate kadar uzayan yarı ömrünün olduğu belirtilmekte fakat bireysel farklılıklar gösterdiği bilinmekte idi.

Sonuç

Çalışmamız nörotoksik etkisi olduğu bilinen siklosporinin sadece nöbet şikayetiyle de karşımıza çıkabileceğini göstermiştir. Hem acil hekimleri hem de nöroloji hekimleri tarafından nöbet etyolojisini belirlerken, santral nedenler ile birlikte ilaç yan etkileri de düşünülmeli; bazı ilaçların, toksik olmayan dozlarda da olsa nöbete neden olabilecekleri unutulmamalıdır.

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Case Report
Eurasian Journal of Toxicology

Metotreksat Kullanıma Bağlı Pansitopeni

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Özet

Metotreksat; folik asit analoğu ve antagonisti olup, sık kullanılan immunsupresif ajandır. Romatoid artrit hastalarında uzun süreli ve düşük dozlu olarak kullanılmaktadır. Düşük doz MTX tedavisinin hematolojik toksisitesinde anemi, trombositopeni veya lökopeni durumları az görülmesine rağmen pansitopeni çok daha nadir olarak karşımıza çıkmaktadır. Biz burada, MTX kullanımına bağlı pansitopeni gelişen olguyu sunmayı amaçladık.

Anahtar kelimeler: pansitopeni, metotreksat, acil

Abstract

Methotrexate; Folic acid analogue and antagonist, commonly used immunosuppressive agent. It is used as long-term and low-dose in patients with rheumatoid arthritis. Although anemia, thrombocytopenia or leukopenia are rare in hematological toxicity of low-dose MTX therapy, pancytopenia is rarely encountered. Herein, we aimed to present a case with pancytopenia due to MTX use.

Key words: pancytopeni, methotrexate, emergency

Giriş

Metotreksat (MTX); otoimmün hastalıklar, maligniteler, dermatolojik hastalıklar ve gebeliğin sonlandırılmasında kullanılan folik asit analoğu ve antagonistidir[1]. Pürin ve primidin sentezinde rol oynayan dihidrofolat redüktazı inhibe eder[1,2]. Romatoid artrit (RA) hastalarında MTX kullanımı malignite tedavisindeki kullanıma göre uzun süreli ve düşük dozlu olarak verilmektedir. MTX'ın tipik olarak RA tedavisi için kullanılan dozlarda en sık gözlenen yan etkileri, malignitelerin tedavisinde kullanılan yüksek dozların aksine, nadiren yaşamı tehdit edicidir[2].

Olgu Sunumu

59 yaşında erkek hasta, halsizlik şikayeti ile acil servise başvurdu. Özgeçmişinde RA dışında ek hastalık yoktu. Hastanın RA tanısı nedeniyle metotreksat 2.5 mg tablet haftada 1 gün, folbiol tablet haftada 1gün, deltakortil tablet günde 1 kez kullandığı öğrenildi. Hastanın ilaç kullanımı sorgulandığında son zamanlarda deltakortil ve folbiol tableti kullanmadığı, metotreksat tableti ise günde 1-2 sefer kullandığı öğrenildi. Fizik muayenesinde genel durumu orta, oryantasyon ve kooperasyon kısıtlı, bilinç uykuya meyilli, sklera soluk ve ağız mukozası kuru saptandı. Tansiyon: 80/40mmhg, nabız:100/saat, saturasyon: %90, ateş: 36.2°C idi. Dudakta ve ağız içinde mukozit mevcuttu. Hastanın laboratuar tetkiklerinde beyaz küre 3.8x10^9/L, hemoglobin 2.6 gr/dl, trombosit 16.6 x10^9/L, üre 83 mg/dl, kreatinin 1.14 mg/dl saptandı. Hasta metotreksat zehirlenmesine ikincil pansitopeni nedeniyle dahiliye bölümü ile konsülte edildi. Acil yoğun bakım ünitesine yatırıldı. Kalsiyum folinat 50 mg yükleme, 6 saat ara ile 15 mg idame olarak tedavisi acil serviste başlandı. Hemogram takipleri ile 3 ünite eritrosit ve 1 ünite trombosit süspansiyonu replasmanı uygulandı. Replasman sonrası hemoglobin: 7.8gr/dl, trombosit: 25x10^9/L, beyaz küre: 3.05x10^9/L saptandı, sonrasında dahiliye servisine yatışı yapılan hasta 8. gününde salah ile taburcu edildi.

Tartışma

MTX'ın farmakokinetiği oldukça değişkendir. Oral uygulamadan sonra hızla emilir, bir saat sonra serum üst seviyelerine ulaşır ve %50 oranında albümine bağlanır[2]. Böbrekler, karaciğer ve sinovyal sıvı da dahil olmak üzere ekstravasküler kompartmanlara dağılır[3]. Karaciğerde kısmen daha az

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aktif bir metabolit olan 7-hidroksi-metotreksata oksitlenir ve esas olarak böbreklerden ve daha az miktarda karaciğerden atılır[2]. Eliminasyon yarı ömrü 5 ila 8 saattir, ancak özellikle ileri evrelerde böbrek yetmezliği varlığında bu süre belirgin şekilde artar[3]. Romatoid artritli ve normal böbrek fonksiyonu olan hastalarda, önerilen doz haftada 5-7.5 mg ile 15 mg arasındadır[3].

MTX; DNA ve timidilat sentezi üretimini azaltarak özellikle oral mukoza, kemik iliği ve gastrointestinal sistem gibi hızlı çoğalma özelliği olan dokuları etkiler[4]. MTX kullanımına bağlı mukozit düşük dozlarda dahi ortaya çıkabilmektedir, doz arttırıldığında ise görülmesi daha olasıdır. Mukozit ilaç dozu azaltılması, folik asit ve lökoverin takviyesi ile kontrol altına alınmaya çalışılır[4].

Pansitopeni, tüm periferik kan hücre miktarlarının düşmesidir ve üç hücre grubunun tamamı normal referans aralığının altında olduğu durumdur. Pansitopeni, hayatı tehdit eden çok sayıda hastalık durumu ile ilişkilendirilebilir[5]. Tanı koyabilmek ve uygun tedaviyi seçmek için ayrıntılı anamnez, sistemik fizik muayene ve laboratuar değerleri gereklidir. RA tedavisinde kullanılan düşük doz MTX'a bağlı pansitopeni görülme oranı %1-2 gibi düşük olmasına rağmen mortal seyredebilmektedir[6]. Düşük doz MTX ile miyelosupresyon oluşması, genellikle akut bir hastalığın araya girmesi, nonsteroid-antiinflamatuar bir ilacın eklenmesi veya değiştirilmesi gibi böbrek fonksiyonunun bozulması sonucu ile gerçekleşmektedir[7]. MTX alan hastalar, tam kan sayımı ve trombosit sayımı ile periyodik olarak izlenmelidir. Kronik olarak düşük doz MTX alan tüm hastalarda folik asit ile tedavi önerilmektedir. Semptomlarına göre 5 mg/gün'e kadar doz artırılabilir[7]. Lökoverin ise yalnızca folik aside yeterli yanıt vermeyen hastalarda kullanılmaktadır[8]. Bizim hastamızda ise hasta uzun süredir MTX kullanımı olmasına rağmen poliklinik takiplerine gitmemesi ve folik asit tedavisine devam etmemesi nedeniyle pansitopeni tablosunun oluştuğu düşünülmüştür.

Sonuç

Pansitopeni görülen hastada onkolojik aciller, kanama, enfeksiyon durumları mutlaka ekarte edilmelidir. Acil servise başvuran MTX kullanan hastalarda pansitopeni ve benzeri toksik etkilerin ortaya çıkabileceği göz önüne alınmalı ve rutin kan parametrelerinin kontrol edilmesi gerektiğini düşünmekteyiz. Bu hasta gruplarını erken tanımak, erken tedavi başlamak mortalite ve morbidite üzerinde etkili olabilir.

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