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Suicide attempts with amitriptyline in adults: a prospective, demographic, clinical study

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Aim: There are several studies on tricyclic antidepressant (TCA) intoxication in the literature; however, there is no specific study on amitriptyline, a specific TCA, intoxication.

Materials and methods: Forty adult patients who had been admitted to the emergency department due to suicide attempts with amitriptyline were included. Medical and social histories of the patients were obtained. The estimated amount of amitriptyline ingested was determined. The psychiatric support and psychiatric diagnosis were all recorded. All patients were contacted by phone 6 months later.

Results: Main reason of suicidal attempt was family problems. The stated amount of ingested amitriptyline by the patient or parents was between 60 mg and 1250 mg. Mean cost of diagnosis and treatment were US$ 87.9 ± 83.5 and US$ 290.5 ± 164.8, respectively. Somnolence was the main complaint. Sinus tachycardia and hypocalcaemia were the most common findings. Seven and a half percent of the patients had a GCS score under 8. There was a significant negative correlation between mean arterial pressure and the estimated ingested amitriptyline dose. After discharge, 52.5% of the patients visited the psychiatry outpatient clinics. There was only 1 patient with recurrent suicidal attempt.

Conclusion: Amitriptyline was usually abused by young females in our region. Drowsiness, dizziness, and urinary retention were the most common clinical features. Family conflicts and communication problems were the most cited reasons of suicide attempts.

Key words: Tricyclic antidepressant, amitriptyline, suicide attempt, psychiatry

Yetişkinlerde amitriptilinle intihar girişimleri: İleriye dönük, demografik ve klinik bir çalışma

Amaç: Literatürde trisiklik antidepresan (TCA) zehirlenmeleriyle ilgili pek çok yayın vardır, fakat spesifik bir TCA olan amitriptilin zehirlenmesiyle ilgili özel bir çalışma yoktur.

Yöntem ve gereç: Amitriptilin zehirlenmesi yoluyla intihar girişiminde bulunan ve acil servise başvuran 40 yetişkin hasta çalışmaya dahil edildi. Hastaların tıbbi ve sosyal öyküleri alındı. Psikiyatrik tanı ve tedavileri kaydedildi. Tüm hastalar 6 ay sonra telefonla bağlantı kurularak yeniden değerlendirildi.

Bulgular: İntihar girişiminde temel neden aile problemleriydi. Ağızdan alındığı belirtilen amitriptilin dozu 60-1250 mg (ortalama: 293,6 ± 233,5 mg/doz) idi. Ortalama tanı ve tedavi maliyeti sırasıyla 87,9 ± 83,5 (dağılım: 64,9-147,9) ve 290,5 ± 164,8 (dağılım: 69,0-856,7) Amerikan dolarıydı. Uyku hali temel yakınmaydı. Sinüs taşikardisi ve hipokalsemi en sık görülen bulgulardı. Hastaların % 7,5'inde GKS 8 in altındaydı. Hastaların ortalama arteriyal kan basınçları ile tahmini alınan amitriptilin dozları arasında anlamlı negatif ilişki mevcuttu. Taburculuktan sonra, hastaların % 52,5'i psikiyatri polikliniğine başvurduklarını bildirdi. Tekrar intihar girişiminde bulunan yalnızca bir hasta vardı.

Sonuç: Bölgemizde amitriptilin sıklıkla genç bayanlar tarafından kötüye kullanılmaktadır. Uyuşukluk, sersemlik ve idrar retansiyonu en sık klinik bulgulardı. Belirtilen en sık intihar nedenleri aile içi çatışmalar ve iletişim problemleriydi.

Anahtar sözcükler: Trisiklik antidepresan, amitriptilin, intihar girişimi, psikiyatri

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Introduction

The incidence of suicidal attempt varies between 3.7 and 26.6 per 100,000 people based on the geographical and cultural characteristics (1,2). On the basis of the current trends, the WHO has estimated for the year 2020 that approximately 1.53 million people will die due to suicide and that 10–20 times more individuals will attempt suicide worldwide (3). Therefore, suicidal behavior is a serious public health problem that remains to be solved by healthcare systems in different countries.

One of the easiest methods of attempting suicide is drug overdose. Even though newer and safer antidepressants are introduced each year, the prescription of tricyclic antidepressants (TCA) is still widespread as they are inexpensive, and have high availability and efficiency (4). Amitriptyline is one of the most commonly prescribed and sold TCA agents; it is also an agent that is most commonly involved in suicide or suicide attempts in many countries (5). It is also the most common agent causing deaths due to antidepressant overdose (6-10). A cohort study of death rates per million prescriptions in Great Britain has shown TCAs, such as amitriptyline and imipramine, to be more toxic than other antidepressants (11).

There are several studies on TCA intoxication in the literature; however, there are only a few studies on amitriptyline intoxication. The aim of this prospective study was to assess the patients who used amitriptyline overdose for suicide in terms of demographics, causes of suicide attempt, symptoms and clinical signs, treatment attempts, and cost of diagnostic and therapeutic processes. In addition, we examined the previous and post-attempt psychological changes and prognosis of these patients 6 months later.

Patients and methods

Forty patients, admitted to the emergency department (ED) of the university hospital due to suicide attempts with amitriptyline between March 2007 and March 2008, were included in this study. The exclusion criteria were incorrect or inadequate information, patients <18 years of age, other medical conditions affecting consciousness (such as diabetic coma, epilepsy), or concurrent drug or alcohol use with amitriptyline.

After the initial assessment in the ED, medical and social histories were obtained from patients and/or relatives including demographic details, complaints, symptoms and signs, previous psychosocial status, the approximate time passed following the drug ingestion, the reason for ingestion, and the source of drug. The estimated amount of amitriptyline ingested was determined using the information obtained from relatives and from the patients after they gained consciousness. If adequate information could not be collected regarding the drug dose (number of tablets and doses), the ingested dose was recorded as the lowest dose (in 8 patients); however, it was accepted as the probable highest dose in the treatment approach. Vital signs and clinical findings, such as Glasgow Coma Score (GCS) and anticholinergic findings, were recorded. Electrocardiography (ECG) and analyses of the arterial blood gases, complete blood count, and biochemical parameters were performed. The reference ranges in our laboratory were as follows: pH: 7.35-7.45, pCO_2: 35-45 mmHg, pO_2: 83-108 mmHg, HCO_3: 22-26 mmol/L, BE (base excess): 0-5 mmol/L, sodium: 135-145 mEq/L, potassium: 3.5-5.5 mEq/L, calcium: 8.5-10.4 mg/dL, blood urea nitrogen: 8-23 mg/dL, creatinine: 0.5-1.3 mg/dL, glucose: 70-115 mg/dL, AST: 0-37 U/L, ALT: 0-41 U/L, gamma-glutamyl transferase: 0-49 U/L, lactic dehydrogenase: 0-250 U/L, creatinine kinase: 24-195 U/L, creatinine kinase-MB: 0-24 U/L, myoglobin: 25-72 μg/L, troponin-I: 0-0.16 μg/L, PT: 10-15.89 s, aPTT: 70-130 s, INR: 0.9-1.3. The patients were accepted as hypotensive if the mean arterial pressure (MAP) was <70 mmHg.

All patients with oral intoxication were treated using the standard intervention and treatment protocols (including nasogastric catheterization, gastric lavage, active charcoal with an initial dose of 1 g/kg, and 0.5 g/kg if needed again, fluid replacement, and oxygen administration). Cost of diagnosis (physical examination, gastric lavage with NG catheter, initial laboratory tests, and other diagnosing procedures) and cost of treatment (bed rate, laboratory tests during hospitalization, consultations, and medical treatments, such as active charcoal and fluid replacement and other applications) were

calculated for each patient. All the patients were contacted by phone 6 months later to assess if the problem causing the suicidal attempt had been solved, if the patient had any regrets about it, if there was any recurrent suicidal attempt, if the patient had any psychiatric support, and if the patient had any medical treatment for the suicidal attempt, and the answers were recorded.

Ethics and statistics

Informed consents were obtained from patients and ethical approval was obtained from the ethics committee of the hospital. The data were installed and analyzed using SPSS 13.0. The data were presented as number, percentage, mean, and standard deviation. The relationship of the approximate amitriptyline dose ingested with the clinical and laboratory parameters, and the relationship between the mean blood pressure and laboratory parameters, and the relationship between cost of diagnosis or cost of treatment and the clinical and laboratory parameters were analyzed using the Pearson correlation analysis. Statistical significance was set as $P < 0.05$.

Results

During the study period, 166 intoxicated patients were observed and 67 of them were due to antidepressants. Of these 67 cases, 40 patients (24.1% of all intoxications) who ingested 'only amitriptyline' were assessed. The demographic details of the patients are presented in Table 1. The stated amount of ingested amitriptyline was between 60 mg and 1250 mg (mean: 293.6 ± 233.5 mg/dose). The duration between intoxication and hospitalization was between 20 min and 10.5 h (mean: 5.08 ± 2.51 h). The mean length of hospitalization for intoxication was 1.8 ± 1.7 days (range: 1-10 days). The mean cost of diagnosis was Turkish Liras (TL) 131.8 ± 125.3 (range: 97.4-221.8) [US$ 87.9 ± 83.5 (range: 64.9-147.9)] and the mean cost of treatment was TL 435.8 ± 247.2 (range: TL 103.5-1285.3) [US$ 290.5 ± 164.8 (range US$ 69.0-856.7)]. There was a moderately positive correlation between the estimated ingested amitriptyline dose and the cost of treatment ($r = 0.4$; $P = 0.012$), and there was no correlation between the estimated ingested amitriptyline dose and the diagnostic cost ($r = 0.3$; $P = 0.076$).

Table 1. The general characteristics of the patients.

Characteristics	N (%) or mean ± SD (Range)
Gender	
Female	37 (92.5)
Male	3 (7.5)
Age	25 ± 9.5 (16-54)
Marital status	
Married	19 (47.5)
Single	19 (47.5)
Widowed	1(2.5)
Engaged	1 (2.5)
Educational status	
Illiterate	5 (12.5)
Basic writing-reading skills	3 (7.5)
Primary school	15 (37.5)
High school	11 (27.5)
University	6 (15)
Occupation	
Yes	4 (10)
No	29 (72.5)
Student	7 (17.5)

Table 2 shows the frequency of complaints related to high dose amitriptyline ingested. Somnolence (92.5%) was the main complaint. In the initial evaluation, most patients had GCS scores of 15 (35%, n = 14), and 7.5% of the patients (n = 3) had a score of ≤8. Of the cases, 65% (n = 26) had abnormal ECG. Sinus tachycardia (22/40; 55%) was the most common finding (Table 2).

There was a moderately significant negative correlation between MAP and the estimated ingested amitriptyline dose ($r = -0.4$; $P = 0.009$), and there was a moderately significant positive correlation between MAP and blood calcium levels ($r = 0.4$; $P = 0.008$). We found a moderately significant negative relationship between the estimated ingested amitriptyline dose and calcium levels ($r = -0.4$; $P = 0.031$). As the time between ingestion of amitriptyline and admission to hospital prolonged, the levels of lactate dehydrogenase and creatine kinase-MB significantly increased ($r = 0.5$; $P = 0.002$, $r = 0.3$; $P = 0.038$, respectively).

Table 2. The symptoms and signs of the patients.

Symptoms and signs	Total N (%)
-Drowsiness	37 (92.5)
-Fatigue	28 (70)
-Dizziness	19 (47.5)
-Urinary retention	17 (42.5)
-Agitation	15 (37.5)
-Headache	14 (35)
-Nausea and/or vomiting	14 (35)
-Dry skin	5 (12.5)
-Hypotension	2 (5)
ECG findings	
-Sinus tachycardia	22 (55)
-ST-T changes	6 (15)
-Widened QRS	6 (15)
-Right Bundle Branch Block	5 (12.5)
- I° AV block	3 (7.5)
-Long QT	1 (2.5)

The results of the arterial blood gases in the initial assessment were pathological in 85% of the cases (acid-base disequilibrium). These were respiratory alkalosis (50%), respiratory acidosis (15%), metabolic acidosis (5%), and mixed (respiratory acidosis and metabolic acidosis) (15%). The other abnormal laboratory results are presented in Table 3.

Table 3. The laboratory findings of the patients.

Finding	Total N (%)
Hypokalemia	5 (12.5)
Hypocalcemia	11 (27.5)
Hyperglycemia	9 (22.5)
Aspartate aminotransferase ↑	3 (7.5)
Alanine aminotransferase ↑	4 (10)
Gamma glutamyl transferase ↑	3 (7.5)
Lactate dehydrogenase ↑	8 (20)
Creatine kinase ↑	10 (25)
Creatine kinase-MB fraction ↑	17 (42.5)
Myoglobin ↑	6 (15)
Prothrombin time ↑	14 (35)
INR (international normalized ratio)↑	9 (22.5)
Respiratory alkalosis	5 (12.5)
Metabolic acidosis	2 (5)
Respiratory acidosis + Metabolic alkalosis	21 (52.5)
Respiratory acidosis + Metabolic acidosis	1 (2.5)

It was found that 22.5% of the patients had previous visits to the psychiatry outpatient clinics prior to the admission to the ED for intoxication. The reasons for suicide attempt and the psychiatric characteristics of the patients are presented in Table 4. Six months later, the patients were contacted by phone and only 4 patients (10%) could not be reached. In 61.1% of patients, the ingested drug was the patient's prescribed medication; in 30.6% of patients, the drug was someone else's; and in 8.3%, the patient had bought it from pharmacy. After discharge from the ED, 52.5% of the patients had visited the psychiatry outpatient clinics. There was only 1 patient with recurrent suicidal attempt. No patient died due to amitriptyline overdose during the study period.

Table 4. The psychiatric characteristics of the patients.

Characteristics	N (%)
Previous psychiatric diagnosis	9 (22.5)
Previous suicidal attempt	7 (17.5)
Visit to psychiatry outpatient clinic in the last six months	7 (17.5)
Positive family history for psychiatric disorders	5 (12.5)
Stated causes of suicidal attempt	
-Family	6 (15)
-Communication problems	5 (12.5)
-Loneliness	5 (12.5)
-Other	4 (20)
-Domestic violence	3 (7.5)
-Death/missing	3 (7.5)
-Economic problems	3 (7.5)
-Alcohol and substance abuse	2 (5)
-Chronic disease	2 (5)
-Parental conflicts	2 (5)
Diagnosis after psychiatry consultation	
-Impulsive suicide	20 (50)
-Psychiatric disease diagnosis	20 (50)

Discussion

Amitriptyline is an easily-accessed and easily prescribed drug in our country. We tried to outline demographic and clinical characteristics and reasons of suicide attempts with amitriptyline. Our findings suggest that the severity and the level of laboratory

changes after ingestion of amitriptyline at toxic doses may provide indirect information on the amount of drug ingested and the time of drug ingestion.

TCAs clearly have a price advantage over more recently introduced antidepressant agents. Therefore, amitriptyline is widely prescribed in our region. However, the apparent cost advantage of prescribing a less expensive drug may be nullified by the cost associated with adverse consequences (12). Comparison of the relative hospital costs of the cases of overdose of tricyclics with those of selective-serotonin re-uptake inhibitors (SSRIs) shows that TCAs incur substantially greater hospital costs than SSRIs (13). It was reported in a study from England that those taking SSRIs had a shorter (1.96 vs. 2.59 days) and less expensive (£ 330 vs. £ 567) stay (14). Same results were obtained also in America: the cost of hospital treatment for patients who overdosed on TCAs was 4 times greater than that for patients who overdosed on SSRIs (US$ 22,923 vs US$ 5379) (12). In our study, 67 patients, out of 166, were admitted due to TCA overdose, and of these, 59.7% were due to amitriptyline. Mean cost of diagnosis and treatment were US$ 87.9 ± 83.5 and US$ 290.5 ± 164.8, respectively. We believe that the cost of overdose is often ignored and should be considered in future analyses of the cost effectiveness of different antidepressant prescribing policies in primary care.

The patients who ingested amitriptyline for suicide in our study were usually young female patients. A gender discrepancy in terms of suicide attempt was obvious in our results compared to the literature (15,16). Suppression of personal freedom by parents was also a major risk factor for suicidal attempts of female adolescents in Greece, a neighboring country (17). Family conflicts and parental disagreement played important roles in suicidal attempts in our region (18). Oppressive attitude of the husband towards the wife, marriage at young age, and being a housewife (not working) have impacts on suicide attempts of women (19,20). Fifty percent of the patients who committed suicide with amitriptyline did not have any psychiatric diagnoses in the present study. Impulsive suicides are generally motivated by anger, the desire to get even, the wish to frighten or punish others, or the need to avoid intense shame.

The clinical presentations in amitriptyline overdose include antimuscarinic symptoms (tachycardia, dryness of the mouth and skin, and pupillary dilatation), severe cardiotoxicity (hypotension), respiratory depression/insufficiency, impaired consciousness, convulsions, and rarely, adult respiratory distress syndrome and death (21-25). Among these, mental state changes were the most common (21). In the present study, drowsiness, dizziness, and urinary retention were the most common clinical features (Table 2). Fatigue and agitation were also major symptoms.

Cardiac arrhythmias and ECG changes due to blockage of sodium and potassium channels are common in amitriptyline intoxication and usually develop within the first 2–6 h after admission and resolve generally in 12-36 h (26,27). Sinus tachycardia due to anticholinergic activity and/or inhibition of norepinephrine uptake is the most common dysrhythmia in 70% of symptomatic cases (21,28). Rarely, ECG changes, such as ventricular arrhythmias and wide QRS, may be seen in more serious cases (21,28). The most common ECG changes in our study were sinus tachycardia (55%), long QRS (15%), and non-specific ST-T changes (15%) (Table 2). Additionally, ECG changes were present on admission and no further ECG changes occurred on follow up, and all changes improved within 12-24 h.

Although the laboratory parameters of the patients may change with clinical progress, and early intervention and treatment, they are not directly related to the clinical manifestations. In a study carried out by Caksen et al., 44 children with accidental amitriptyline intoxication were reviewed. The most commonly observed clinical and laboratory findings were lethargy (45%), tachycardia (48%), convulsion (11%), hyperglycemia (32%), and leukocytosis (16%) (23). Hypokalemia is the most common electrolyte disorder in TCA overdose. In a study, 9% of patients with TCA intoxication had potassium concentrations of <3.0 mmol/L (29). Although this change in potassium levels may be secondary to $NAHCO_3$ therapy, hypopotassemia (12.5%) may develop before the initiation of $NAHCO_3$ therapy, as it was the case in our study. We found a moderately significant positive correlation between MAP and blood calcium levels ($r = 0.4$; $P = 0.008$). A

correlation between serum calcium levels and blood pressure was described previously especially for hypertensive patients. Essential hypertension was associated with perturbations in calcium metabolism. Hypertensive subjects had lower mean serum levels of ultrafilterable calcium, ionized calcium, and complexed calcium, and higher levels of protein-bound calcium (30). It was attributed to decreased active transport of Ca^{2+} across isolated plasma membrane vesicles from large and small arteries (31).

Amitriptyline is metabolized in the liver via glucuronic acid conjugation and is then excreted through the kidneys (21,32). Thus, monitoring the renal and liver functions is important. We found that the increase in the liver function tests did not correlate with dose and clinical progress in the present study (Table 3). Further pharmacological studies about lactate dehydrogenase and creatine kinase-MB levels may help estimate the time of amitriptyline ingestion in patients who are known to have taken amitriptyline, but the time the drug was taken is unknown.

The most common acid-base disorder after amitriptyline over-dosage is acidosis (33). It is usually of mixed type. As the admission times of our cases were different, their arterial blood gas results were also different (Table 3). At the early period, when there is no disorder of consciousness yet, most of our cases displayed normal arterial blood gas results, or they had respiratory alkalosis due to hyperventilation. In the late period, especially in patients with stupor, we observed mild hypoxia and respiratory acidosis. This suggested that respiratory functions might be affected by serious sedation after intoxication.

The frequency of endotracheal intubation in antidepressant intoxication is 23%-68%. Clinical progress, hemodynamic instability, and GCS are important parameters in decision-making. Though the coma in amitriptyline intoxication is usually short-term, a GCS of <8 was the most sensitive predictor of serious complications (24,34). We had patients with a clinical presentation of coma in relation with GCS, but as a result of close follow-up and monitoring, none of the patients required an invasive intervention, such as intubation, and none suffered any serious complication.

The main limitation of this study was the accuracy of the estimated dose, as the TCA was not prospectively administered and the dose information relied on historical data from a witness, parent, or the patient.

In conclusion, we outlined demographic, clinical and laboratory characteristics and causes of suicide attempts with amitriptyline. It was usually abused by young females in our region. Drowsiness, dizziness, and urinary retention were the most common clinical features. Family conflicts and communication problems were the most cited reasons of suicide attempts with amitriptyline.

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