Original Article

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ECG Changes in Patients with Amitriptyline Intoxication; P, QT, QTC, T and PR Wave Dispersion: A Retrospective Study

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Abstract

Objective: Amitriptyline intoxication is a life-threatening condition as it can cause cardiac arrhythmias. This study aims to examine the ECG changes in patients with amitriptyline intoxications who were admitted to the emergency department and to compare the P-wave, T-wave, QT, QTC, and PR dispersions with healthy controls.

Material and Methods: The sample of the current retrospective study consists of only 46 patients with amitriptyline intoxication and 65 healthy controls. The 12-channel ECG recordings of the participants were evaluated by two experienced cardiologists. P wave, T wave, QT, QTC, and PR distance, minimum, maximum, and dispersion values were measured. The obtained data were recorded on the data set and subjected to statistical analysis.

Results: There was no significant difference in sociodemographic variables between patients with amitriptyline intoxication and the control group. The main symptoms of the patients were as follows: 28.3% (n=13) lethargy, 32.6% (n=15) nausea-vomiting, 21.7% (n=10) unconsciousness, and 17.4% (n=8) other. According to the analysis of amitriptyline intoxication and ECG parameters of healthy controls, P-wave, T-wave, QT, QTC, and PR dispersion were higher in the intoxication group than in the healthy controls (p0.05). The patient group had a higher heart rate than the control group (p=0.026).

Conclusion: The current study found that P-wave, T-wave, QT, QTC, and PR dispersion were higher in the amitriptyline intoxication group than in the control group, which is thought to play a role in cardiac arrhythmias. Clinicians should be on alert for any ECG changes in these cases.

Keywords: Dispersion; ECG; Amitriptyline; Tricyclic antidepressant; arrhythmia.

Introduction

Intoxication is a pathological condition of the organism caused by the excessive consumption of a toxic substance due to its chemical structure. It is a dynamic process that manifests its effects intensely in a short time, can deteriorate rapidly, disrupt functions, and lead to life-threatening complications. It is a global health issue that causes morbidity and mortality[1]. Drugs are among the most common intoxicating agents due to their ease of access and prevalence[2]. Tricyclic antidepressants (TCA), paracetamol, and nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most commonly used drug classes with toxic doses[3, 4]. Amitriptyline is the most commonly used drug in TCA intoxications[5]. Although its use has gradually declined, it is still widely used in clinical practice due to its high efficiency and low cost[6]. Therefore, this causes amitriptyline-related intoxications frequently in emergency departments[3, 7].

Cardiac side effects from drug intoxication play a significant role in morbidity and mortality. In drug-related intoxications that necessitate hospitalization, 15% of patients experience cardiovascular events that necessitate medical attention and may even result in death[8]. Besides vital symptoms, the most quickly obtained, easily accessible, and inexpensive test for detecting cardiac side effects is electrocardiography (ECG)[9]. Sodium channel blockage, slow calcium channel blockage, potassium channel blockage, and sodium-potassium ATPase blockage are the main mechanisms responsible for changes in ECG parameters[10]. Prolonged cardiac action potential and refractory period, as well as delayed atrioventricular node (AVN) conduction, can result in prolonged QRS, QTd, and PR times[11]. These effects are thought to be dose-independent, and QTd prolongation can be observed even at therapeutic doses. QTd prolongation is associated with mortality and arrhythmic events, and ECG is becoming more important in diagnosis and treatment management[9].

TCAs, commonly used in clinical practice, are known to increase the risk of sudden cardiac death due to adverse cardiac effects in intoxication cases. These drugs are thought to increase the risk of cardiac arrhythmia, which could lead to sudden cardiac death[12, 13]. As a result, ECGs are frequently used in cases of intoxication to assess the increased risk of arrhythmias. According to studies on ECG abnormalities, there may be pulse changes, arrhythmia, and transmission delays[14]. TCAs are known

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to have cardiac effects via voltage-dependent Na+ and K+ channel blockage, as well as postsynaptic inhibition of central and peripheral α-adrenergic receptors. Arrhythmias, depolarization delay, conduction abnormality, and ectopic heartbeats can all result from voltage-dependent Na+ channel blockage[15]. In this context, ECG monitoring is important in amitriptyline intoxication, a TCA. Furthermore, there is inconsistency in the literature regarding arrhythmia and other cardiac side effects in amitriptyline intoxications[16-19]. Furthermore, as far as we know, there have been limited studies on the dispersion of ECG waves[12]. Examining the ECG parameters of amitriptyline intoxications will be useful in clarifying the management of this risky process.

In light of these data, and with the hypothesis that amitriptyline intoxication will result in lethal arrhythmia, the study aimed to reveal the ECG parameters of patients who were admitted to the emergency department with intoxication after taking only amitriptyline.

Materials & Methods

Participant

The clinical parameters and ECG findings of patients who were admitted to the Erzurum Region Training and Research Hospital emergency department between 6 February 2016 and 10 April 2020, due to excessive amitriptyline intake were analyzed retrospectively from the database and archive files in our study, which examined the relationship between amitriptyline intoxication and ECG findings. The control group consisted of 65 people who were admitted to the medical board for various reasons and did not differ in age or gender. The study included patients who were at least 18 years old. Patients with chronic diseases, those who use other medications or are suspected of using multiple medications, and patients whose biochemical parameters and electrolyte values are outside the normal reference range were excluded from the study due to the possibility of changes in ECG parameters. During the study period, 669 of 786 patients who presented to the emergency department with intoxication were excluded because they were taking medication other than amitriptyline, and 71 patients were taking other medications in addition to amitriptyline. Finally, the study included 46 amitriptyline intoxications and 65 healthy controls (Figure 1). Patients' sociodemographic information, their complaints when admitting to the emergency department, and the approximate dose of amitriptyline were all recorded. Before the study,

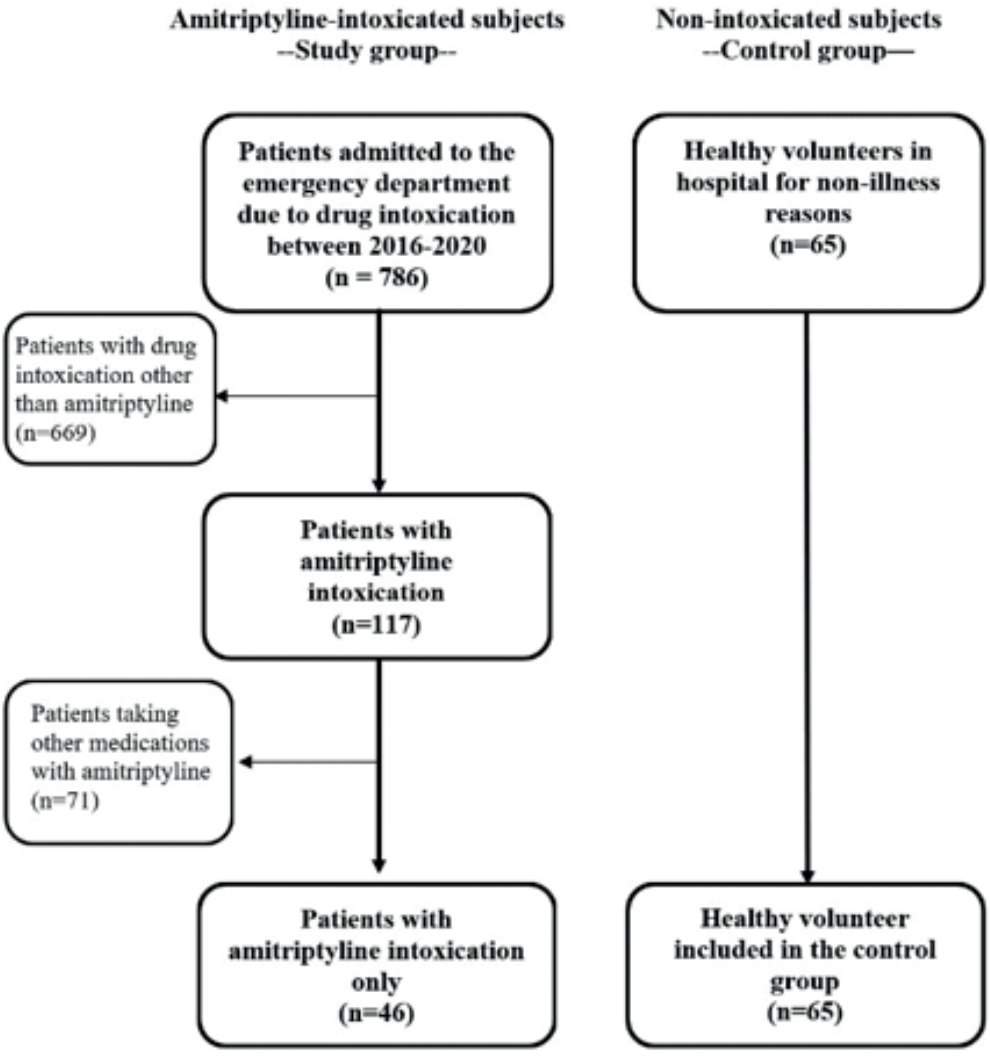

Figure 1: Flow chart of participants included in the study.

Table 1: Sociodemographic characteristics of the participants

Variable	Healthy Control Group (n=65)	Patient Group with Amitriptyline Overdose (n=46)	Statistic	d*f*	p
Age, years; mean±SD	25.06±7.10	25.47±3.50	t=0.363	60	0.718
Gender, n(%)			χ^2=0.530	1	0.467
Female	50 (76.9%)	38 (82.6%)			
Male	15 (23.1%)	8 (17.4%)			
Marital Status, n(%)			χ^2=1.447	2	0.485
Married	27 (41.5%)	24 (52.2%)			
Single	31 (47.7%)	19 (41.3%)			
Other	7 (10.8%)	3 (6.5%)			
Amitriptyline dose, mg; mean±SD (min-max)		465.76±189.61 (175-875)			
Main Symptoms and signs, n (%)					
Lethargy		13 (28.3%)			
Nausea-vomiting		15 (32.6%)			
Unconsciousness		10 (21.7%)			
Other		8 (17.4%)			

t: Student t test, χ^2:Chi-square test

consent was obtained from the Erzurum Region Training and Research Hospital Ethics Committee (Date: February 1, 2021, Decision no:2021/03-48).

Design

12-channel ECG recordings were obtained from healthy controls and patients while they were at rest at the time of admission to the emergency department (Cardiofax V; Nihon Kohden Corp., Tokyo, Japan). ECGs of all participants were transferred to a personal computer via scanner and analyzed using Adobe Photoshop software. In order to reduce the error rate, measurements were made by two experienced cardiologists using the electronic, digital measurement method. The P-wave, which expresses the atrial depolarization time, was measured in many different derivations and the difference between the longest and shortest time was defined as P-wave dispersion[20]. The QT interval was calculated as the time between the first QRS complex deflection and the end of the T-wave. QT intervals were measured in as many derivations as possible and corrected for heart rate using Bazett's formula (QTc=QT/√(R-R interval)[21]. The difference between the maximum and minimum QT intervals was defined as QT dispersion. The difference between the maximum and minimum QRS intervals was defined as QRS dispersion. The difference between the maximum and minimum PR intervals was defined as PR dispersion. The difference between the maximum and minimum T intervals was defined as T dispersion[22]. The obtained data were recorded on the data set and subjected to statistical analysis.

Statistical Analysis

SPSS 22.0 package program was used to perform statistical analyses on study data. Descriptive statistics were made with frequency and percentage for categorical variables and mean and standard deviation for continuous variables. Parametric assumptions were tested first in the comparison of continuous variables between the case and control groups, then the Student-T test was used, and the Chi-square test was used in the comparison of categorical variables. $p < 0.05$ values were considered statistically significant in all analyses.

Results

One hundred eleven participants in the study had a mean age of 25.30±5.27 years, with 79.3% being female. In terms of age (p=0.718), gender (p=0.467), and marital status (p=0.485), there was no statistically significant difference between the patients with amitriptyline intoxication and the control group (Table 1). The intoxication group received a mean dose of 465.76±189.61 (175-875) mg of amitriptyline. Furthermore, 28.3% (n=13) of those who were admitted to the emergency department with amitriptyline intoxication reported lethargy, 32.6% (n=15) nausea-vomiting, 21.7% (n=10) unconsciousness, and 17.4% (n=8) other symptoms (Table 1).

The ECG parameters of the participants are shown in Table 2. When the two groups were compared, the amitriptyline intoxication group (83.90±18.26) had a statistically higher heart rate than the control group

(91.58±16.83) (p=0.026). When the P-wave parameters of the study groups were compared, P_{max} (p0.001), P_{min} (p0.001), and P_{dis} (p=0.023) were statistically significantly higher in the amitriptyline intoxication group than in the control group. When the QT intervals were compared, it was observed that QT_{max} (p=0.012), QT_{dis} (p=0.002), and QTc_{dis} (p=0.002) were statistically significantly higher in the amitriptyline intoxication group than in the control group. When T-wave parameters were compared, T_{max} (p0.001), T_{min} (p0.001), and T_{dis} (p0.001) were found to be statistically significantly higher in the amitriptyline intoxication group than in the control group. When the QRS intervals were compared, it was found that QRS_{max} (p<0.001) and QRS_{min} (p<0.001) were statistically significantly higher in the amitriptyline intoxication group than in the control group. When the PR intervals were compared, it was observed that PR_{max} (p=0.008) and P_{dis} (p<0.001) were statistically significantly higher in the amitriptyline intoxication group than in the control group (Table 2).

Discussion

The most important result of the current study comparing amitriptyline intoxication with the case-control design and ECG parameters of healthy controls is that the intoxication group had higher P-wave, T-wave, QT, QTC, and PR dispersions than the healthy controls. We believe that the results of this study are significant because they can help in the development of treatment strategies for amitriptyline intoxications.

We evaluated the minimum, maximum, and dispersion (maximum-minimum difference) parameters of P-wave,

Table 2: Electrocardiography results of the groups.

Variable	Healthy Control Group (n=65)	Patient Group with Amitriptyline Overdose (n=46)	Statistic	d*f*	p
Heart rate, beat/m, mean±SD	83.90±18.26	91.58±16.83	t=-2.253	109	**0.026***
P wave, ms, mean±SD					
$P_{maximum}$	84.78±17.98	118.64±20.00	t=-9.156	109	**<0.001***
$P_{minimum}$	69.78±21.54	98.41±17.26	t=-7.761	109	**<0.001***
$P_{dispersion}$	15.00±14.71	20.23±9.07	t=-2.139	109	**0.023***
QT wave, ms, mean±SD					
$QT_{maximum}$	341.30±34.35	361.73±50.23	t=-2.545	108	**0.012***
$QT_{minimum}$	321.73±33.15	330.18±42.80	t=-1.121	109	0.265
$QT_{dispersion}$	19.56±23.66	31.55±15.35	t=-3.237	109	**0.002***
QTc wave, ms, mean±SD					
$QTc_{maximum}$	417.26±31.79	420.24±35.68	t=0.452	109	0.652
$QTc_{minimum}$	393.86±37.26	384.17±33.68	t=1.428	109	0.156
$QTc_{dispersion}$	23.40±27.32	36.07±15.54	t=-3.098	109	**0.002***
T wave, ms, mean±SD					
$T_{maximum}$	147.39±27.76	206.70±38.05	t=-9.494	108	**<0.001***
$T_{minimum}$	129.34±25.85	162.63±33.06	t=-5.944	107	**<0.001***
$T_{dispersion}$	18.04±17.59	44.07±16.49	t=-7.969	109	**<0.001***
QRS wave, ms, mean±SD					
$QRS_{maximum}$	74.78±12.95	103.03±17.23	t=-9.391	109	**<0.001***
$QRS_{minimum}$	53.91±17.31	85.52±17.20	t=-9.510	109	**<0.001***
$QRS_{dispersion}$	20.86±13.95	17.50±7.58	t=1.486	63	0.142
PR wave, ms, mean±SD					
$PR_{maximum}$	150.00±25.21	162.78±24.39	t=-2.682	109	**0.008***
$PR_{minimum}$	141.30±24.36	139.26±22.79	t=0.452	109	0.652
$PR_{dispersion}$	8.69±13.76	23.52±6.11	t=-7.691	109	**<0.001***

*:p<0.05, t: Student t test

T-wave, QRS-wave, QT, QTC, and PR distances in our study, which we believe may be predictors of cardiac arrhythmia in amitriptyline intoxication. We compared them to healthy controls because there is no clear information or data about the normal ranges of dispersion times in the literature[23]. As a result, we found that, with the exception of the QRS-wave, dispersions were higher in amitriptyline intoxications than in healthy controls. This result suggests that an overdose of amitriptyline causes dispersion in ECG parameters and may play a role in arrhythmia mechanisms. These results suggest that amitriptyline intoxication causes heterogeneity in cardiac electrical activity[24]. There are a few studies in the literature examining dispersion parameters in TCA excess intakes that have found that QT dispersion is higher in intoxication patients than in controls, which is consistent with our results[12]. The P-wave is a non-invasive ECG finding that indicates atrial depolarization. Atrial dysrhythmias, such as particularly atrial fibrillation, have been linked to increased P-wave dispersion[25]. QT dispersion is a ventricular repolarization time variability parameter that is thought to be an indicator of cardiac arrhythmia. In this context, our results provide important indicators for understanding lethal arrhythmias in amitriptyline intoxication.

It is also critical to monitor clinical signs in intoxication cases. However, in TCA intoxications, including amitriptyline, the clinical findings are variable and the symptoms are not specific, making diagnosis and follow-up difficult[12]. In general, symptoms such as changes in consciousness, agitation, confusion, drowsiness, nausea, and vomiting are observed in a dose-dependent manner[26]. The most common symptoms in our study, are consistent with the literature. These were lethargy, nausea-vomiting, and changes in consciousness. Because the central nervous system and cardiovascular system are more affected, it is critical to monitor the symptoms.

Another significant finding in our study is that, while multiple medication intakes play an important role in intoxication cases, they were excluded from the study to clearly see the effect of amitriptyline and to reduce confounding factors. When all of the results are considered together, we conclude that there may be a wide range of ECG findings in amitriptyline intoxications and that clinicians should be cautious about the development of almost any ECG finding in such intoxications. Furthermore, as far as we know, no other study in the literature examines ECGs, including dispersion, in amitriptyline intoxications as thoroughly as the current study.

The results of our study can be evaluated within some limitations. First of all, the retrospective design of the study and the limited sample size are important limitations. Furthermore, although only amitriptyline intoxication cases were included in our study, multiple medication uses, and drug doses were based on the declaration. On the other hand, the lack of follow-up of the clinical results of the patients is another important limitation. In addition, the inability to analyze the time elapsed between taking medication and applying to the hospital was another shortcoming for the study.

Conclusion

The current study found that amitriptyline intoxication increased P-wave, T-wave, QT, QTC, and PR dispersions more than controls. Because this difference may play a role in cardiac arrhythmias, clinicians should be careful about any type of ECG change in these severe intoxications. It would be beneficial to confirm the current study's findings with future animal trials and prospective studies.

Disclosure statement

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Conflict of Interest: The authors declare that there is no conflict of interest.

Ethics. Authorization was obtained from the local ethics committee (Date:01.02.2021, IRB: 2021/03-48), the study was conducted in accordance with the Helsinki Declaration Guidelines.

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