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Electrocardiographic Abnormalities During and After Withdrawal in Patients Diagnosed with Opioid Use Disorder

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ABSTRACT

Introduction: Opioid withdrawal is one of the most critical complications of opioid use disorder. In this study, we aimed to examine the possible risk of ventricular arrhythmia and sudden cardiac death by calculating electrocardiography (ECG) changes, the markers of ventricular repolarization, in opioid withdrawal.

Methods: A total of 90 patients diagnosed with opioid withdrawal who met the inclusion and exclusion criteria were included in the study. QT, QTc, TPe/QT, and TPe/QTc ratios of patients with a Clinical Opiate Withdrawal Scale (COWS) score higher than five and a Framingham heart risk score lower than 10% were measured in 12-lead ECG.

Results: A significant difference was found between the patients' heart rate, QT, QTc, and TPe/QT values during withdrawal (entry-first) and after withdrawal (second) ($p<0.05$). Mean QT First Value (380.69±22.46) was significantly different and higher than Mean QT Second Value (372.82±19.998); Mean QTc First Value (435.41±16.22) was significantly different and higher than Mean QTc Second Value (418.03±17.79); Mean Tpe First Value (81.62±6.009) was significantly different and higher than Mean Tpe Second Value (79.93±5.524); and The Mean Tpe/QT First Value (0.221±0.005) was significantly different and higher than the Mean Tpe/QT Second Value (0.213±0.004) ($p<0.05$).

Conclusion: The findings of our study show that electrocardiographic QT, QTc, Tpe and Tpe/QTc values, which indicate the risk of sudden cardiac death and ventricular arrhythmia, are significantly higher during opioid withdrawal. In addition to the regulation of addiction treatment during opioid withdrawal, it should be considered that individuals may be at cardiac risk, and the patient should be monitored for cardiac arrhythmia during the withdrawal period.

Keywords: Arrhythmia, ECG, opiate, withdrawal

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INTRODUCTION

Substance use disorders are a growing health crisis worldwide. According to data from the World Health Organization, approximately 5% of the adult population (250 million) worldwide have used substances at least once, and 29.5 million people suffer from substance use disorder (1). Opioid use is also a serious problem in the United States, with opioid overdose death rates more than tripled from 1999 to 2016 (2). More than 11 million people abused opioid substances in 2017, about 15% of which were classified as opioid use disorders (3). Opioid use disorder is diagnosed by the existence of a pattern of opioid use that causes significant dysfunction and distress in an individual and according to the criteria defined in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (4). Opioid withdrawal syndrome manifests itself with clinical symptoms mostly resulting from increased sympathetic and parasympathetic response. Following abrupt opioid withdrawal, unwanted adrenergic hyperactivity occurs, which is responsible for withdrawal symptoms (5,6). Significant symptoms of opioid withdrawal syndrome include anxiety, irritability, insomnia, sweating, diarrhea, nausea/vomiting, thermal irregularity, and pain (7).

Opioid peptides play a role in controlling cardiac function by reflex mechanisms involving the central nervous system or by modulating neurotransmitter release from neurons within the heart (8). Previous studies in this area have shown that opioid withdrawal leads to marked hyperactivity in cardiac sympathetic neurons (9,10). This may be responsible for the increases in heart rate and elevation in arterial blood pressure during opioid withdrawal (11,12). One article reported a case of transient myocardial ischemia due to severe benzodiazepine and opioid withdrawal (13). It is known that abnormal sympathetic or vagal activity directly alters ventricular repolarization and prolongs the QT interval. The influence of the autonomic system on the QT interval is shown, with differences between day and night QT intervals recorded at

Highlights

- **QT, QTc, Tpe and Tpe/QTc values are higher during opioid withdrawal.**
- **Individuals are at risk for cardiac arrhythmias during opioid withdrawal.**
- **Patients in the detoxification process should be closely monitored for cardiac safety.**

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the same heart rates (14). Experimental models have shown in the past that cardiac sympathetic denervation causes prolongation of the QT interval (15). Many measurements in the ECG are used to estimate the risk of ventricular arrhythmias. Parameters such as QT interval, corrected QT interval (QTc), Tpeak-Tend (Tp-e), and Tp-e/QTc ratio are the most popular repolarization parameters because of their predictive role for ventricular arrhythmias (16).

Early recognition of ECG findings (QT, QTc, TPe/QT, TPe/QTc ratios) and prompt intervention in possible cardiac arrhythmias are crucial during opioid withdrawal. This study aimed to compare ECG findings, which are markers of ventricular repolarization, during and after opioid withdrawal.

METHODS

Study Design and Participant

Our study is a prospective follow-up study. A total of 90 patients between the ages of 18 and 45 who met the criteria for DSM-5 opioid use disorder who were admitted to inpatient treatment at the Alcohol and Substance Addiction Treatment and Research Center (AMATEM) Clinic of Erenköy Mental Health and Neurological Diseases Training and Research Hospital with the diagnosis of opioid use disorder, who had been a regular and active user for the past month at the time of application for treatment, and had recently used it before hospitalization (to be confirmed by urinalysis), had no history of cardiac disease, whose Clinical Opioid Withdrawal Scale (COWS) score was higher than five and Framingham Heart Risk Score was higher than 10%, who accepted to participate in the study and gave written consent were included. Patients who had used buprenorphine in the last 14 days (to be confirmed by urinalysis), patients with a history of additional alcohol-substance use in the last six months with positive urine metabolites were excluded from the study.

Patients with the following possible risk factors reported to cause QT prolongation: 1) comorbid heart disease (heart failure, ventricular dysfunction, myocarditis, hypertrophy, arrhythmia, bradycardia, block, heart valve diseases), 2) abnormal laboratory findings that may affect the cardiovascular system (electrolyte, cholesterol, low density lipoprotein [LDL], very low density lipoprotein [VLDL], high density lipoprotein [HDL], triglyceride, fasting blood glucose levels that are off normal limits), 3) another medical disease that affects the cardiovascular system, 4) use of any pharmacological agent other than antipsychotic and antidepressant drug therapy, 5) systemic hepatic or renal disease, 6) hypothyroidism, 7) cerebrovascular accident, Parkinson's disease, or other central nervous system conditions were taken into account and not included in the study (17,18).

During the opioid withdrawal period, ECG was taken to measure the QT, QTc, TPe/QT, TPe/QTc ratios, and control ECGs were taken after the end of the abstinence period and clinical stabilization (approximately 7–14 days later), and all values were compared. An experienced cardiologist researcher evaluated ECGs. A 12-lead, 25 mm/min speed, and 10 mm/mV standard ECG were used. PR, R-R, QRS and QT intervals, QTc, heart rate, rhythm, axis and conduction, QRS, ST, and T wave abnormalities were measured for each ECG.

The Ethics Committee Report was obtained from Erenköy Mental Health and Neurogical Diseases Traning and Research Hospital Clinical Researches Ethical Committee.

Data Collection Tools

Sociodemographic Data Form:

It is the form in which sociodemographic variables such as age, gender, marital status, economic level, working life, additional medical disease status, and family history of the patient were evaluated. The researchers prepared it for this study.

Turkish Version of the Clinical Opioid Withdrawal Scale (COWS-COWS)

This scale is an 11-item scale in which the clinician evaluates and grades all objective and subjective findings of the patient in opioid withdrawal. The total score ranges from 0 to 47. A higher score indicates that the level of withdrawal is more severe. Scores between 5–12 points indicate mild, 13–24 points indicate moderate, 25–36 points indicate moderate-severe, and scores higher than 36 indicate severe withdrawal symptoms. This scale was developed by Wesson and Li, and the validity and reliability study of the Turkish version was conducted (19,20).

Framingham Heart Risk Score

Framingham risk score is used to calculate the 10-year risk of cardiovascular diseases such as myocardial infarction/coronary death and is calculated according to the age, gender, smoking status, blood pressure and lipoprotein cholesterol values of individuals. The Framingham scoring system is one of the most widely used measures in calculating risk in cardiological diseases. When calculating the 10-year risk, <10% is determined as low risk, 10–20% as medium risk, and >20% as high risk (21). The risk calculator on the web page of the Turkish Cardiology Association was used. The parameters asked in the risk calculator are among the blood tests routinely requested during the hospitalization of patients.

Electrocardiographic Evaluation

Standard 12-lead ECGs at rest were taken from the patients included in the study (25 mm/sec, 10 mm/mV). The QT interval was measured as the distance from the beginning of the Q wave to the end of the T wave (where it reaches the T-P line). Measurements were not made in the leads where the end of the T wave could not be determined. Heart rate corrected QT (QTc) was calculated using Bazett's formula [QT (ms)/RR (s)1/2]. P wave duration, RR interval, PR interval, QRS duration, QT interval and Tp-e interval were measured manually. Tp-e/QT ratio and Tp-e/QTc ratio were calculated from these measurements. The Tp-e interval was measured from the peak of the T wave to the end of the T wave. The end of the T wave was defined as the intersection of the tangent to the downslope of the T wave and the isoelectric line (22).

Statistical Evaluation

Statistical analysis was performed using Statistical Package for the Social Sciences version 22 program. The data conformity to the normal distribution was examined with the Single Sample Kolmogorov-Smirnov test. The t-test was used for independent groups to compare the quantitative data with the normal distribution between the groups, and the Mann-Whitney U test was used to compare data that did not fit the normal distribution. The chi-square test was used to compare categorical data, and the Quade's Rank ANCOVA test was used to compare the differences in change between the onset and end of abstinence. $P < 0.05$ was accepted as statistically significant in all tests.

RESULTS

The mean age of the study group was 29.4±6.741. Eighty-one were male (90%), and nine were female (10%). Fourteen (15.6%) of them were primary school graduates, 51 (56.7%) were secondary school graduates, 21 (23.3%) were high school graduates, four (4.4%) were university graduates. While 62 (68.9%) were single, 16 (39%) were married; 31 (34.4%) were working, 55 (61.4%) were not working, four (4.4%) were students. Ninety (100%) of them were smokers, nine (10%) had a history of additional medical disease, and 42 (53.3%) had a psychiatric disease. Seventeen (17.9%) of them had a family history of substance use, and four (4.4%) had a family history of psychiatric illness. Fourty-eight (53.6%) had a forensic history (Table 1).

Table 1. Sociodemographic information

Group	**Mean ± SD**		
Age (year)	29.42±6.741		
Opioid use duration (year)	8.70±5.347 (year)		
Opioid dosage (gram)	2.98±1.645 (gram)		
		n	**%**
Gender	Male	81	90.0
	Female	9	10.0
Education status	Primary school	14	15.6
	Middle school	51	56.7
	High-school	21	23.3
	University	4	4.4
Marital status	Single	62	68.9
	Married	16	17.8
	Divorced	12	13.3
Employement status	Working	31	34.4
	Not working	55	61.4
	Student	4	4.4
Smoking	No	0	0.0
	Yes	90	100.0
Additional medical illness	No	81	90.0
	Yes	9	10.0
Substance history in the family	No	73	81.1
	Yes	17	17.9
Mental illness	No	48	46.7
	Yes	42	53.3
Mental illness in the family	No	86	95.6
	Yes	4	4.4

There is a statistically significant difference between the Average Pulse First Value and the Pulse Second Value Average (p=0.01). The Mean Pulse Second Value (78.33±8.83) is significantly different and greater than the Pulse First Value Average (74.56±11.41) (Table 2).

There is a statistically significant difference between the QT First Value Mean and the QT Second Value Mean (p=0.008). Mean QT First Value (380.69±22.46) was significantly different and higher than the Mean QT Second Value (372.82±19.99) (Table 2).

There is a statistically significant difference between the Mean QTc First value and the Mean QTc Second value (p=0.001). Mean QTc First value (435.41±16.22) was significantly different and higher than the Mean QTc Second value (418.03±13.25) (Table 2).

There is a statistically significant difference between the Average Tpe First Value and the Average Tpe Second Value (p=0.027). Mean Tpe First Value (81.62±6.009) is significantly different and higher than the Mean Tpe Second Value (79.93±5.52) (Table 2).

There is a statistically significant difference between the Mean Tpe/QT First Value and the Mean Tpe/QT Second Value (p=0.000). The Mean Tpe/QT First Value (0.221±0.005) is significantly different and higher than the Mean Tpe/QT Second Value (0.213±0.004) (Table 2).

There is no statistically significant difference between the Mean Tpe/QTc First Value and the Mean Tpe/QTc Second Value (p=0.378) (Table 2).

DISCUSSION

In this study, ECG findings (QT, QTc, TPe/QT, TPe/QTc ratios), which are markers of ventricular repolarization, were compared during and after opioid withdrawal. Understanding cardiac physiology during opioid use and withdrawal guides our interpretation of the findings of our study.

Chronic opioid use is known to induce adaptation of noradrenergic neurons in the brainstem locus coeruleus. Most of the withdrawal symptoms that occur with abrupt discontinuation of the opioid result in noradrenergic hyperactivity (5,6). In addition, it has been reported that the QTc interval is prolonged by blocking cardiac potassium channels through opioid use and some genes such as hERG (human Ether-à-go-go-Related Gene) (23). In a study on 511 opioid addicts; the most common ECG abnormalities were determined as ST abnormalities, QTc prolongation, and prolonged R– and/or S waves (24). Methadone and buprenorphine, two opioid-agonist drugs approved by the Food and Drug Administration (FDA), are widely used throughout the world in opioid treatment programs (25). In a study with methadone; the QT duration was found to be significantly higher in the methadone group than in the control and buprenorphine groups, regardless of the dose (26). Methadone has been associated with significant QTc increases even at therapeutic doses and has been shown to cause torsades de pointes, a ventricular arrhythmia that can be lethal (27). In another study; QTc interval was found to be 460 and 386 ms between two opioid user and non-user groups, respectively. Prolonged QTc interval was not detected in 59.3% of the cases and any of the non-users. In terms of dose and duration of opioid use, no difference was observed between QTc times (28). Lofexidine is also the first non-opioid drug approved by the FDA for the treatment of opioid withdrawal (29). An increase in QTc was detected with lofexidine, a molecule used during opioid withdrawal. However, while an increase in QTc was detected on the 1st and 2nd days of starting lofexidine treatment, the QTc level decreased below the basal level on the 7th day (30). In a study on cardiomyocytes (cardiac muscle cells); only methadone was found to affect QTc by blocking hERG channels among methadone,

Table 2. ECG Changes during (first) and after (second) opioid withdrawal.

	N	Mean	Mean difference	SD	t	df	p
Pulse First	90	74.56	-3.79	11.407	-2.630	89	0.01*
Pulse Second	90	78.33		8.834			
QT First	90	380.69	7.87	22.460	2.727	89	0.08*
QT Second	90	372.82		19.998			
QTc First	90	435.41	17.38	16.22	14.339	89	0.001*
QTc Second	90	418.03		17.79			
Tpe First	90	81.62	1.69	6.009	2.256	89	0.027*
Tpe Second	90	79.93		5.524			
Tpe/QT First	90	0.221	0.008	0.005	11.236	89	0.000*
Tpe/QT Second	90	0.213		0.004			
Tpe/QTc First	90	0.188	-0.001	0.016	-0.887	89	0.378
Tpe/QTc Second	90	0.189		0.013			

*p<0.05; df: degree of freedom; QTc: Corrected QT interval; SD: Standard deviation.

buprenorphine, norbuprenorphine, naltrexone, and naloxone (31). In our working group; buprenorphine was used during withdrawal, but ECG evaluation was done before treatment initiation. There are also studies in which buprenorphine was not associated with QT interval prolongation and torsades de pointes ventricular arrhythmias (32,33). For this reason, there are publications stating that buprenorphine is a safer alternative for cases that develop QTc prolongation during methadone treatment (34,35). It is also stated that, unlike methadone, buprenorphine has no effect on QTc in the commonly used dose range (36). In the treatment of opioid use disorder, it is widely stated that the dose of buprenorphine should be determined individually and daily doses should be an average of 8–16 mg (37). These are consistent with the buprenorphine/naloxone doses used in our patients included in our study.

Considering the pre- treatment and post-treatment QTc values, QTc, Tpe, Tpe/QTc rates are higher at the beginning of withdrawal. Based on the data of our study, it seems complicated to determine whether opioid agonists given during the withdrawal period or chronic intake of opioids cause QTc prolongation. However, in our study, the QTc rate was higher especially during the withdrawal period compared to the post-withdrawal period.

Studies in morphine-dependent rats have not determined whether the changes observed in the heart during morphine withdrawal are of peripheral or central origin. In one study, morphine-dependent rats were investigated by electrochemical sensing high-performance liquid chromatography during abstinence by administering naloxone, methiodide, and N-methyl levallorphan, and a significant increase in catecholamines in the right ventricle was observed (38). In a similar study on rats addicted to morphine which were deprived with the opioid blocker naloxone; it was observed that there was an increase in noradrenaline and dopamine turnover, an increase in hyperactivity of catecholaminergic neurons, and an increase in cAMP in the cardiac cells. Thus, changes were observed in cardiac functions during abstinence (9). Possible mechanisms of increased hyperactivity of catecholaminergic neurons during withdrawal were determined as a decrease in coronary flow reserve, microvascular dysfunction, direct effects of catecholamines on cardiac myocytes via cyclic AMP-mediated calcium overload, free radicals derived from oxygen, contractile band necrosis as an interstitial mononuclear inflammatory response, the formation of thrombosis at the junction of atherosclerotic vessels, increased blood pressure and ventricular contractility (39,40). In addition, during the opioid withdrawal period; decreased subendocardial perfusion, pulmonary edema, and cardiac arrhythmias have been reported to be associated with catecholamine release (41,42). Similarly, in a study consisting of a control group, a stable group using buprenorphine, and an opioid withdrawal group; it was observed that subendocardial perfusion decreased significantly in the abstinence group (41). According to the literature and the data of our study, we can say that the increase in catecholamines affects cardiac functions during the withdrawal period, and cardiac perfusion decreases, so cardiac risks such as ventricular arrhythmia may increase.

There are some limitations in our study. Since the majority of the sample consisted of chronic substance users and patients with severe withdrawal symptoms, it was not possible to investigate whether there was a relationship between the echocardiographic changes during the withdrawal period and the severity of withdrawal. It will be important to plan a detailed examination of the relationship between low-moderate-severe withdrawal findings and echocardiographic changes in future studies. There was no control group in our study, and additional medical drugs were used during the opioid withdrawal treatment of the patients. Quetiapine is the most common one among these drugs. In studies conducted with psychiatric patients, it is stated that they may be at higher risk for cardiovascular complications such as prolongation of the QT interval, and particularly, the use of quetiapine contributes to this situation (43,44). Mirtazapine is the most commonly used additional drug after quetiapine due to its sedative effect during detoxification. Studies show that mirtazapine does not affect OTc (45,46). However, it is essential to determine that the OTc intervals of the 1st ECGs are longer than the 2nd, despite the potential of QT prolongation of quetiapine used during the withdrawal period.

It is known that one of the symptoms of opioid withdrawal syndrome is tachycardia and this may cause echocardiographic changes, but it is also known that the QT interval shortens in faster heartbeats (47). Bazett's square root formula, which is the most commonly used formula to correct the QT interval, was used in our study (22). Torsades de Pointes (TdP), a ventricular tachycardia occurring in the setting of a prolonged QTc interval, is a malignant arrhythmia that is usually asymptomatic but associated with syncope and sudden death (48). Large, prospective,

population-based studies have associated QTc prolongation with increased mortality, and an initial prolonged QTc interval is a risk factor for life-threatening arrhythmia (49). Detection and follow-up of prolonged QTc occurring during opioid withdrawal are essential.

In conclusion, in our working group; although factors causing QT prolongation, which is a risk determinant of cardiac arrhythmia and low coronary heart disease scores, were excluded, ventricular repolarization markers were observed to be significantly higher during opioid withdrawal. The fact that adrenergic activity increases during opioid withdrawal and the risk of ventricular arrhythmia increases compared to the post-withdrawal period shows that more attention should be paid to cardiac risks during opioid withdrawal. In this context, it is important to consider cardiac safety while planning drug treatments during the withdrawal period of opioid use disorder.

Ethics Committee Approval: The Ethics Committee Report was obtained from the University of Health Sciences İstanbul Erenköy Mental Health and Neurological Diseases Training and Research Hospital Clinical Researches Ethical Committee (Date: 22.06.2020, No: 24).

Informed Consent: Informed consent was obtained from each participant included in the study.

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