ORIGINAL ARTICLE

Acute effects of synthetic cannabinoids on ventricular repolarization parameters

Sentetik kanabinoidlerin ventrikül repolarizasyon parametrelerine akut etkileri

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ABSTRACT

Objective: An association between ventricular repolarization parameters (VRPs) and ventricular arrhythmias has been demonstrated in previous studies. However, there are limited data related to a relationship between synthetic cannabinoids (SCs) and VRPs. The aim of this study was to analyze the acute effects of SCs on VRPs using electrocardiogram (ECG) measurements of the T-peak to T-end interval (Tp-e), Tp-e/QT ratio, and Tp-e/corrected QT (QTc) ratio.

Methods: The present study included 58 patients who were admitted to the emergency department who used SCs (SC +) between 2014 and 2016, and 50 healthy control subjects (SC -). The QT and QTc intervals, Tp-e interval, Tp-e/QT, and Tp-e/QTc ratios were measured from a 12-lead ECG. These parameters were compared between groups and correlation analysis was performed.

Results: The Tp-e and QTc intervals were significantly higher in SC + patients when compared with the SC- group (92.2±10.0, 77.4 ±9.3, p<0.001; 434.5±30.8, 410.9±27.3, p<0.001, respectively). Tp-e/QT and Tp-e/QTc ratios were greater in SC + patients in comparison with SC – participants (0.26±0.02, 0.22±0.02, p<0.001; 0.21±0.02, 0.18±0.02, p<0.001, respectively). Significant correlations were found between the use of SCs and the Tp-e interval (r=0.610; p<0.001), Tp-e/QT (r=0.655; p<0.001) and Tp-e/QTc ratios (r=0.437; p<0.001).

Conclusion: The Tp-e interval, Tp-e/QT and Tp-e/QTc ratios were greater in subjects who used SCs. Therefore, SC users might have an increased risk of ventricular arrhythmia.

ÖZET

Amaç: Önceki çalışmalarda ventriküler aritmi ve ventriküler repolarizasyon parametreleri (VRP) arasındaki ilişki gösterildi. Ancak, VRP ile sentetik kanabinoidler (SK) arasındaki ilişkiyi gösteren sınırlı sayıda veri bulunmaktadır. Bu çalışmada, T-peak to T-end (Tp-e) aralığı, Tp-e/QT ve Tp-e/QTc oranlarının kullanılmasıyla, SK'lerin VRP'ye akut etkilerini analiz edilmesi amaçlandı.

Yöntemler: Mevcut çalışma, 2014–2016 yılları arasında, SK kullanmış ve acil servise kabul edilmiş 58 hasta (SK +), ve 50 sağlıklı kontrol olgularını içerdi (SK -). Tp-e aralığı, Tp-e/QT ve Tp-e/QTc oranlarını içeren VRP'ler tüm olgularda 12 derivasyonlu elektrokardiyografiden ölçüldü. Sonra, bu parametreler gruplar arasında karşılaştırıldı ve korelasyon analizi yapıldı.

Bulgular: The Tp-e ve QTc aralıkları anlamlı olarak, SK - grup ile karşılaştırıldığında SK + grupta daha yüksekti (sırasıyla, 92.2±10.0, 77.4±9.3, p<0.001; 434.5±30.8, 410.9±27.3, p<0.001). Tp-e/QT ve Tp-e/QTc oranları SK - grup ile karşılaştırıldığında SK + grupta artmıştı (sırasıyla, 0.26±0.02, 0.22±0.02, p<0.001; 0.21±0.02, 0.18±0.02, p<0.001). SK kullanımı ile Tp-e aralığı (r=0.610, p<0.001), Tp-e/QT (r=0.655, p<0.001) and Tp-e/QTc oranları (r=0.437, p<0.001) arasında anlamlı korelasyon saptandı.

Sonuç: Mevcut çalışma, SK kullanmış olgularda Tp-e aralığı, Tp-e/QT ve Tp-e/QTc oranlarının arttığını gösterdi. Bu yüzden, SK kullanmış genç olgular, artmış ventriküler aritmi riskine sahip olabilirler.

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Abbreviations:

ECG	*Electrocardiogram*
QTc	*Corrected QT interval*
QTd	*QT dispersion*
SC	*Synthetic cannabinoid*
TDR	*Total dispersion of repolarization*
Tp-e	*T-peak to T-end interval*
VRP	*Ventricular repolarization parameters*

Natural cannabis (Δ9-THC, tetrahydrocannabinol) is derived from the hemp plant (Cannabis sativa). The chemical structure of synthetic cannabinoids (SCs) is quite different from that of natural cannabis; the activity and affinity to cannabinoid receptors are greater than that of natural cannabis.[1] SCs are known by different brands and generic names in different regions of the world; in the USA, these products may be known as "K2," in Europe as "Spice," and in other countries as "Bonsai," "Black Mamba," or "Jamaica."[2] SCs are manufactured from herbal or chemical substances and have different effects on various organs by binding to the cannabinoid receptors 1 and 2 (CB-1 and CB-2) in the human body.[3,4] The most common route of administration of SCs is inhalation.[5] The effects, duration of action, and potency differ, as the composition varies. Therefore, it is difficult to identify the systems that SCs act on or to measure their effects or the duration of action once they are consumed.[6] SCs can lead to emergency medical problems that require urgent intervention, including cardiovascular events, psychosis, nephrotoxicity, respiratory depression, acute cerebral ischemia, and sudden loss of consciousness.[6–11] SCs bind to cardiac cannabinoid receptors, and may cause conduction disorder and myocardial depression.[12] Moreover, SCs may affect myocardial repolarization due to their cardiac effects. Impaired myocardial repolarization is an important predictor of malignant ventricular arrhythmias and cardiovascular mortality.[13] Previous studies have reported that the interval between the peak and end of the T-wave (Tp-e), the QT interval, corrected QT interval (QTc), QT dispersion (QTd), and Tp-e/QT ratio recorded on an electrocardiogram (ECG) are markers of total (transmural, apicobasal, and global) dispersion of repolarization (TDR). In particular, Tp-e has been accepted as an index of TDR.[14,15] It is well known that cardiovascular effects of SCs can include bradycardia, tachycardia, hypotension P-wave dispersion, prolonged QTc interval, and Mobitz type II atrioventricular block.[16–18] Despite known cardiac proarrhythmic effects, data regarding the cardiac side effects and ECG parameters are limited. There is a need for easily accessible and reliable ECG parameters that illustrate the acute effect of SCs on the cardiovascular system. The objective of the present study was to evaluate the acute effects of SCs on the TDR index ECG markers of Tp-e, Tp-e/QT ratio, and Tp-e/QTc ratio in patients who used SCs.

METHODS

A total of 58 patients who were said to have used SCs (SC + group) and who had been admitted to the emergency department at Şişli Hamidiye Etfal Training and Research Hospital between July 1, 2014 and March 31, 2016 due to impaired consciousness were enrolled. All of the patients had reportedly consumed a SC known generically as bonsai and had no acute cerebrovascular event according to hospital records. The use of a SC was determined by the medical history provided by patient relatives. Urine or blood tests for SC use were not available. All of the patients were treated in the emergency room with supportive care and intravenous fluids to treat electrolyte and fluid disturbances. A group of 54 healthy, age- and sex-matched individuals who were referred to the cardiology outpatient clinic for cardiac evaluation were included as a control group (SC – group). The control group did not demonstrate evidence of pathologies affecting VRPs in laboratory and noninvasive cardiac examinations (ECG, echocardiography, and treadmill exercise tests). Patient data that included an abnormal ECG (n=9), electrolyte disturbances (n=5), intubated patients (n=22), exitus (n=1), myocardial infarction (n=1), a history of a heart disease (n=2), or the use of drugs or alcohol or other substances known to change ECG parameters (n=43) were excluded from the study. The physical examination findings, medical history, resting 12-lead ECG results, and laboratory characteristics of the study groups were recorded. The study was approved by the local ethics committee on Human Research and was conducted according to the Helsinki Declaration.

Assessment of electrocardiogram

A standard 12-lead surface ECG recording with a paper speed of 25 mm/second and an amplitude of 10 mV/mm was performed. All of the surface ECG recordings were scanned and transferred to a computer. An electronic caliper (Cardio Calipers, version 3.3 software; Iconico.com, Philadelphia, PA, USA) was used under magnification to record the measurements. All

of the ECG recordings were analyzed by physicians SS and KK. The RR interval, QT interval, QT dispersion, and QTc interval were measured in all leads. The QT interval was defined as the time from the beginning of the QRS complex until the end of the T-wave (Fig. 1). Three consecutive QT interval measurements were performed in all leads, and the mean value was recorded for analysis. QTd was defined as the difference between the maximum and minimum QT intervals of the 12-lead findings. The QT interval was corrected for heart rate using Bazett's formula. The Tp-e interval was defined as the distance between the peak of the T-wave and the end of the T-wave (Fig. 1). All Tp-e intervals were measured using the best available T-wave in lead V5.[19] When the lead V5 result was not suitable for analysis, the V4 and V6 were used. The Tp-e/QT interval and Tp-e/QTc interval ratios (Tp-e divided by QT and Tp-e divided by QTc) were also calculated as the repolarization index. For each Tp-e, Tp-e/QT ratio, and Tp-e/QTc ratio, measurements were made from 3 consecutive beats, and the average of these measurements was recorded for analysis.

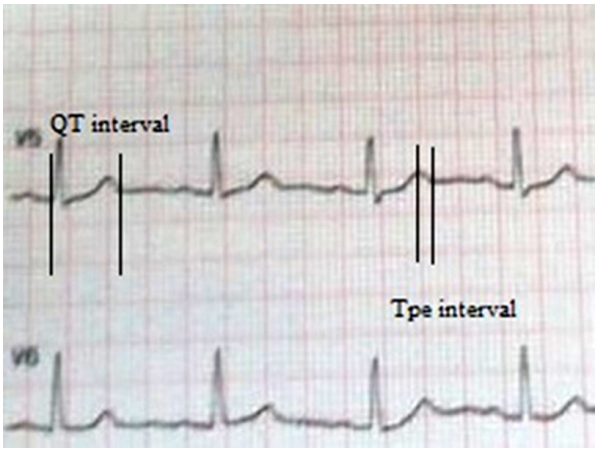

Figure 1. Comparison of the T-peak to T-end (Tp–e) interval, Tp-e/QT ratio, and Tp–e/corrected QT ratio of users of synthetic cannabinoids and a non-user control group.

ECG measurements were performed by 2 experienced cardiologists who were blinded to the clinical data of the study groups. Intraobserver and interobserver variabilities in the QT and Tp-e intervals were 1.2% and 1.7%, and 2.5% and 3.7%, respectively.

Table 1. Baseline demographic, laboratory, and clinical characteristics of the study population

	SC (+) group (n=58)			SC (–) group (n=54)			*p*
	n	%	Mean±SD	n	%	Mean±SD	
Age (years)			29.6±6.5			31.5±6.0	0.280
Men	50	86.2		42	84.0		0.829
Smoking	55	94.8		45	90.0		0.126
Systolic blood pressure (mm Hg)			116.8±15.4			106.8±9.7	<0.001
Diastolic blood pressure (mm Hg)			68.0±10.5			71.0±7.5	0.086
Heart rate (beat/min)			93.8±12.5			82.5±13.2	<0.001
Glucose (mg/dL)			112.0±21.2			92.1±9.3	<0.001
Creatinin (mg/dL)			0.81±0.17			0.76±0.15	0.08
Sodium (mmol/L)			140.3±2.7			139.9±1.2	0.383
Potassium (mmol/L)			4.07±0.50			4.15±0.26	0.282
Oxygen saturation (%)			95.4±3.0			–	–
pH			7.33±0.15			–	–
Partial pressure of oxygen (mm Hg)			86.0±12.8			–	–
Partial pressure of carbon dioxide (mm Hg)			41.2±3.6			–	–
Bicarbonate (mEq/L)			23.4±1.5			–	–
Body temperature, °C			36.6±0.02			–	–
Endotracheal intubation	0	0		–	–		–

Data are shown as mean±SD or numbers and percentages, as appropriate. SC: Synthetic cannabinoid; SD: Standard deviation.

Statistical analysis

Data were reported as the mean±SD for continuous variables and, as appropriate, compared using an independent sample t-test or the Mann-Whitney U test. Categorical variables were reported as percentages and numbers and, if appropriate, compared using a chi-square test or Fisher's exact test. The normality assumption was evaluated with the Kolmogorov-Smirnov test. Pearson correlation analysis was performed to assess possible associations between the use of SCs and ventricular repolarization parameters. The power analysis of this study was determined to be 90% (accepted for alfa: 0.05, beta: 0.1). Intra- and interobserver variabilities for ventricular repolarization parameter measurements in all subjects were estimated according to the Bland-Altman method. For all statistical tests, a p-value <0.05 was considered statistically significant. The statistical analysis was performed using IBM SPSS Statistics for Windows, version 21 (IBM Corp., Armonk, NY, USA).

RESULTS

The demographic characteristics, clinical features, and laboratory findings of all of the study participants are shown in Table 1. There were no significant differences between the groups with respect to age, gender, diastolic blood pressure, creatinine or electrolyte level, or smoking status (p>0.05 for all; Table 1). Systolic blood pressure, heart rate, and glucose level were significantly higher in the SC+ group compared with the control group (116.8±15.4, 106.8±9.7, p<0.001; 93.8±12.5, 82.5±13.2, p<0.001; 112.0±21.2, 92.1±9.3, p<0.001, respectively, Table 1). Arterial blood gas parameters (oxygen saturation, bicarbonate, partial pressure of oxygen and carbon dioxide, pH) were normal in the SC+ group (Table 1). No subject was intubated in in the emergency room in the SC+ group.

Table 2 illustrates that the QT intervals were similar between the groups (348.4±19.0, 353.4±30.7; p=0.301). The QTc intervals were significantly longer in the SC+ group than in the SC- group (434.5±30.8, 410.9±27.3; p<0.001). The Tp-e interval was also significantly longer in the SC+ group than in the SC- group (92.2±10.0, 77.4±9.3; p<0.001). The Tp-e/QT ratio and the Tp-e/QTc ratio were significantly higher in the SC+ group compared with the SC- group (0.26±0.02, 0.22±0.02, p<0.001; 0.21±0.02, 0.18±0.02, p<0.001, respectively).

Table 2. Electrocardiographic findings in the SC + group and the SC – group

	SC (+) group (n=58)	SC (–) group (n=55)	*p*
QRS duration (ms)	92.6±8.2	90.1±7.9	0.492
QT (ms)	348.4±29.0	353.4±30.7	0.301
QTc (ms)	434.5±30.8	410.9±27.3	<0.001
Tp-e (ms)	92.2±10.0	77.4±9.3	<0.001
TPe/QT ratio (ms)	0.26±0.02	0.22±0.02	<0.001
TPe/QTc ratio (ms)	0.21±0.02	0.18±0.02	<0.001

QT: QT interval; QTc: Corrected QT interval; Tp-e: T peak and T end; SC: Synthetic cannabinoid; Values are presented as mean±SD.

Table 3. Correlation analysis of ventricular repolarization parameters and synthetic cannabinoid use

Parameters	r	*p*
QT interval	0.09	0.378
QTc interval	0.378	<0.001
Tp-e	0.610	<0.001
Tp-e/QT	0.655	<0.001
Tp-e/QTc	0.437	<0.001

QT: QT interval; QTc: Corrected QT interval; Tp-e: T peak and T end; SC: Synthetic cannabinoid.

Correlation analysis indicated that the use of SCs was significantly correlated with the QTc interval (r=0.378; p<0.001), Tp-e interval (r=610; p<0.001), Tp-e/QT ratio (r=655; p<0.001), and Tp-e/QTc ratio (r=0.437; p<0.001) (Table 3). No significant correlations were found between the use of SCs and QT interval (r=0.08; p=0.626).

DISCUSSION

The present study revealed several major findings. First, prolonged Tp-e and QTc intervals and increased Tp-e/QT and Tp-e/QTc ratios were observed in subjects who consumed SCs compared with healthy control participants. Second, the QT interval did not markedly differ between groups. Finally, the results indicated that use of SCs was significantly correlated with the QTc interval, Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc ratio. To the best of our knowledge, this

is the first study to evaluate acute changes in VRPs in SC users admitted to the emergency department.

Although pathophysiological causes of malignant ventricular arrhythmias and sudden cardiac death are widely understood based on advanced cardiac electrophysiological techniques, the 12-lead surface ECG is still the first-line noninvasive diagnostic tool. The absence of a normal recovery of ventricular myocardial function after systole is known to predispose the patient to ventricular arrhythmias.[20] Prolongation of the QT and QTc intervals on a surface ECG, which provide information about ventricular repolarization, has been associated with an increased risk of cardiovascular diseases, such as ventricular tachycardia/fibrillation, torsades de pointes, and sudden cardiac death.[14,21] However. high rates of erroneous readings of these repolarization parameters have necessitated the search for other ECG-related repolarization parameters.[14] Experimental studies involving intracardiac measurements have reported that the end of epicardial and mid-myocardial action potentials corresponded to the T-wave peak and the end of the T-wave, respectively, indicating completion of repolarization. Therefore, the Tp-e interval was regarded as a reflection of TDR.[22] Xia et al.[23] reported that Tp-e was not just a measure of transmural ventricular repolarization, but also a measure of global (apico-basal) dispersion of ventricular repolarization in precordial leads. Furthermore, compared with the total duration of ventricular repolarization, the Tp-e/QT and Tp-e/QTc ratios have been suggested to provide more information about the transmural and spatial dispersion of repolarization and regarded as more reliable predictors of torsades de pointes.[24,25] Various causes have been suggested for a prolonged Tp-e interval and increased Tp-e/QT and Tp-e/QTc ratios in cardiac or noncardiac diseases involving the ventricular myocardium. Yayla et al.[26,27] reported that microvascular dysfunction, fibrosis, and apoptosis appeared to be responsible for an increased Tp-e interval and Tp-e/QT ratio in patients with systemic sclerosis and aortic stenosis.

Despite the serious potential adverse effects on the central nervous and cardiovascular systems, including loss of consciousness, hallucinations, tachycardia, bradycardia, hypotension, hypertension, resistant ventricular arrhythmias, and even mortality, the use of SCs has continued to increase, particularly in the young population, mainly due to cheap and easy accessibility worldwide.[2–4,9,10,12] While the underlying mechanism of atrial and ventricular rhythm disorder has not been completely elucidated, it is thought to involve inhibitor effects on myocardial ion channels independent of the cannabinoid CB-1 and CB-2 receptors.[28] Clark et al.[29] suggested that the use of SCs induces tachycardia by increasing sympathetic activity, which in turn, triggers coronary ischemia and may have a proarrhythmic effect. Aydin Sunbul et al.[17] reported that increased P-wave dispersion in young chronic users of SCs caused atrial fibrillation.

The present study consisted of young patients who were admitted to the emergency department due to loss of consciousness and confusion. Previously published studies and case reports have described cardiovascular and other system complications, including hypertension, tachycardia, and hyperglycemia (blood glucose level ≥140 mg/dL) in the acute phase after SC consumption, especially via the CB-1 receptors.[1,6,16,18,30] Similarly, elevated blood pressure (17%) and blood glucose level (22%), as well as tachycardia (48%) were found in patients who used SCs in our study. These complications appear to have been caused by the acute effects of SCs. All of the patients with tachycardia had sinus tachycardia. Only one individual had sinus bradycardia. No patient had ventricular arrhythmia or complete atrioventricular block when the ECG was performed in the emergency department. In the present study, users of SCs were found to have a prolonged Tp-e interval and high Tp-e/QT and Tp-e/QTc ratios, which are regarded as TDR indices. Therefore, our findings demonstrated that the use of SCs may lead to an increased risk of cardiovascular events through prolongation of TDR. In addition, we speculate that sympathetic overactivity and tachycardia can occur as an acute effect after the use of SCs, and as a result, this may lead to coronary ischemia and impaired TDR. Unlike cardiac or noncardiac chronic diseases affecting the ventricular myocardium, we think that SCs affect ventricular repolarization parameters, including the Tp-e interval, Tp-e/QT, and Tp-e/QTc ratios, at initial exposure. Because TDR indices predict ventricular arrhythmias, we recommend that an ECG be performed with at least a measurement of the Tp-e in the precordial V5 leads in all patients admitted to the emergency department due to the use of SCs.

Limitations

The present study has several limitations. The number of SC users included was relatively small and this was a retrospective analysis of electrocardiographic parameters. We had no usable data related to the dose and time of SC consumption. Associations between ventricular arrhythmias and the Tp-e interval, Tp-e/QT ratio, or Tp-e/QTc ratio were not evaluated in patients who used SCs. ECG data that would provide a follow-up comparison with the acute period were unavailable since the SC patients requested an immediate discharge once they regained normal consciousness. In addition, coronary ischemia in patients who used SCs was not investigated. The use of SCs was based only on the medical history taken from patient's relatives who brought them to the emergency department because evaluation of SCs in urine or blood is not routinely performed in our hospital.

Conclusion

A prolonged Tp-e interval and high Tp-e/QT and Tp-e/QTc ratios might enhance ventricular arrhythmias in users of SCs. Therefore, electrocardiographic repolarization parameters should be carefully evaluated in users of SCs in the emergency department. An ECG is an easily accessible and inexpensive method to detect and assess the pro-arrhythmic risk in patients suspected of using SCs. Further prospective studies are required to detect the exact pathophysiological mechanisms and the clinical importance of impaired VRPs in users of SCs.

Ethics Committee Approval: The study protocol was approved by Şişli Hamidiye Etfal Training and Research Hospital Ethics Committee (date: 20/11/2018, no: 2175).

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