VIA MEDICA
ORIGINAL ARTICLE
2015, Vol. 22, No. 5, 551–556
DOI: 10.5603/CJ.a2015.0038

ISSN 1897–5593

The effect of varenicline on Tp-e interval, Tp-e/QT ratio and Tp-e/QTc ratio in healthy smokers and nonsmokers

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Abstract

Background: *Varenicline could affect the T wave and QT interval. The interval from the peak to the end of the electrocardiographic (ECG) T wave (Tp-e) may correspond to the transmural dispersion of repolarization, and increased Tp-e interval and Tp-e/QT ratio are associated with malignant ventricular arrhythmias. In this study, we assessed the effects of varenicline on Tp-e interval, Tp-e/QT ratio and Tp-e/QTc ratio.*

Methods: *Thirty healthy volunteers (15 healthy non-smokers [NS] and 15 healthy smokers [S]) were included in the randomized, double-blind, placebo-controlled, crossover study. Varenicline (2 mg single dose) or placebo was administered in two different testing sessions (5 days after the first period, performed the second period). Tp-e interval, Tp-e/QT ratio and Tp-e/QTc ratio were assessed in the supine position and during handgrip exercise before and after the participants were given placebo or varenicline. Tp-e interval, Tp-e/QT ratio and Tp-e/QTc ratio were calculated from continuous ECG recordings and averages were used in the final analysis.*

Result: *There were no statistically significant differences among any of the Tp-e interval, Tp-e/QT ratio and Tp-e/QTc ratio before and after placebo administration in both groups (S and NS). In the S group, Tp-e and QTc interval, and Tp-e/QT and Tp-e/QTc ratio were significantly increased after varenicline administration (Tp-e: 64.28 ± 8.78 vs. 70.42 ± ± 13.12; p = 0.02, QTc: 409.57 ± 28.17 vs. 425.28 ± 32.79; p = 0.02, Tp-e/QT: 0.18 ± 0.02 vs. 0.19 ± 0.03; p = 0.04, Tp-e/QTc: 0.17 ± 0.02 vs. 0.19 ± 0.02; p = 001) but these parameters were not changed in the NS group.*

Conclusions: *Tp-e and QTc interval, and Tpe/QT and Tpe/QTc ratio were increased after varenicline administration in smokers.* (Cardiol J 2015; 22, 5: 551–556)

Key words: varenicline, Tp-e interval, QT interval

Introduction

Cigarette smoking is a major cardiovascular risk factor for atherosclerotic diseases [1]. Among smokers with coronary heart disease, smoking cessation is associated with a 36% reduction of the risk of mortality due to all causes, making smoking cessation fundamental to secondary prevention of cardiovascular disease [2, 3].

Pharmacotherapy is a standard component of evidence-based smoking cessation treatment [4]. One of the pharmacological agents used for

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Received: 09.04.2015 Accepted: 04.06.2015

smoking cessation treatment is varenicline. Varenicline is an $\alpha 4\beta 2$ nicotinic acetylcholine receptor (nAChR) partial agonist [5, 6]. As varenicline has this partial agonistic action, it may cause relief of the withdrawal and craving symptoms associated with nicotine.

Ventricular repolarization is commonly assessed using QT interval and T wave measurements. Recent studies indicated that the Tp-e interval, which is the interval between the peak and the end of the T wave on an electrocardiogram (ECG), can be used as an index of the total (transmural, apico-basal, global) dispersion of repolarization [7, 8]. Increased Tp-e interval might be also a useful index to predict ventricular tachyarrhythmias and cardiovascular mortality [9–11].

Changes in the autonomic tone modulate QT duration, and the prolonged QT interval is regarded as a marker of imbalanced distribution of sympathetic nervous system activity on the heart. Varenicline could affect the autonomic cardiovascular system by binding to $\alpha 3\beta 4$ nAChR and $\alpha 7$ nAChR. The effect of varenicline on QT interval and T wave measurements has not been studied. We have recently published a randomized, placebo controlled and crossover trial about the acute effects of varenicline on heart rate variability parameters [12], and we reanalyzed the study data to test the acute effects of varenicline on QT and Tp-e interval, and Tp-e/QT and Tp-e/QTc ratio in healthy smokers (S) and nonsmokers (NS). The goal of our study was to test hypothesis if administration of high dose of varenicline was (not) associated with changes in repolarization among healthy S and NS. Our secondary goal was to assess differences in varenicline induced repolarization changes between S and NS. Our tertiary goal was to assess for non-repolarization related (or non-cardiovascular) side-effect of administration of high dose varenicline.

Methods

Subjects

Thirty healthy volunteers with a mean age of 28.23 ± 1.46 years (range 24–33 years, 16 male, 14 female) were studied in a randomized, double-blind, placebo-controlled, crossover design study. Fifteen healthy NS and 15 healthy S were included in the study after providing their written informed consent in accordance with the study protocol approved by the Ethical Committee of our hospital. All subjects had normal standard ECGs and no structural heart disease as documented by medical history, physical examination, and echocardiography. No subject was taking any medication or had any history of a chronic disease.

Study design and electrocardiographic measurements

All participants were asked to refrain from alcohol, cigarette smoking and caffeine-containing beverages as well as strenuous exercise for 24 h prior to each study session. All subjects had a light breakfast after an overnight period of fasting and were taken to a quiet, dimly lit room maintained at 22– 24°C. The studies were performed between 09:00 am and 02:00 pm to avoid circadian variations in ECG parameters. All participants were taken to the test room and allowed to rest in the supine position for at least 15 min on a comfortable bed to stabilize heart rate. After this resting period, continuous ECG recordings (ECGs were recorded at a sampling rate of 200 Hz using a Spiderview™ recorder) were performed in the supine position for 10 min. After this recording period, ECG recording performed at sitting position for 10 min during handgrip exercise. Participants performed isometric handgrip exercise at 25% of their predetermined maximum voluntary capacity by 45 s contraction and 15 s rest per minute using a Saehan hydraulic hand dynamometer (SH5001, Seoul, Korea). The 10 min handgrip exercise procedure repeated three times and the averages of total rest and handgrip exercise period were used in the final analysis. After baseline data were obtained, subjects were orally administered varenicline (2 mg) or placebo. The order of administration of test drug or placebo was randomized, and subjects were blinded to whether they received the test drug or the placebo. Three hours after use of varenicline or placebo, the participants once again underwent the same procedures described above. Blood pressure measurements were obtained from the left arm supported at heart level by a nurse using a sphygmomanometer prior to and after each period. Previously, it had been shown that the elimination half-life of varenicline is nearly 24 h [13]. Five days after (total varenicline elimination time) the first testing period, the participants were reassigned to the opposite group (varenicline or placebo group) and again underwent the same procedures described above.

Tp-e interval, Tp-e/QT ratio and Tp-e/QTc ratio were calculated from continuous ECG recordings (ECGs were recorded at a sampling rate of 200 Hz using a Spiderview™ recorder). Recordings were analyzed on a Synescope™ system. We

Table 1. Baseline characteristics of nonsmokers and smokers.

	Nonsmoker (n = 15)	Smoker (n = 15)	P
Age [year]	28.20 ± 2.67	28.26 ± 2.57	0.94
Gender (male/female)	8 (53.3%)/7 (46.7%)	8 (53.3%)/7 (46.7%)	1
BMI [kg/m^2]	24.33 ± 3.41	22.60 ± 2.10	0.10
Heart rate [bpm]	80.46 ± 6.79	82.01 ± 6.32	0.52
SBP [mm Hg]	113.33 ± 9.75	116.07 ± 11.83	0.50
DBP [mm Hg]	66.66 ± 6.17	69.33 ± 11.62	0.43
LVEF [%]	66.86 ± 1.18	67.33 ± 1.67	0.38
Cigarette smoking (pack-years)	10.2 ± 2.1	–	< 0.001

BMI — body mass index; DBP — diastolic blood pressure; SBP — systolic blood pressure; LVEF — left ventricular ejection fraction

measured the QT, RR and Tp-e intervals in lead II. We measured the QT interval from the beginning of the QRS complex to the end of the T wave and the Tp-e interval from the peak of the T wave to the end of the T wave, defined as the point of return to the T–P baseline. If U waves were present, we defined the end of the T wave as the nadir of the curve between the T and U waves. The QT intervals were corrected according to the formula of Bazett, where ($QTc = QT / \sqrt{RR}$) [14].

Statistical analysis

Statistical analyses were performed with the SSPS 10.0 software package (SPSS Inc., Chicago, IL). All numeric variables are expressed as the mean ± standard deviation, and categorical variables are expressed as percentages. The normal distribution suitability of the groups was assessed using the Shapiro-Wilk test. According to the Shapiro-Wilk test only the placebo period Tp-e (mean) value is not distributed normally, other parameters distribute normally. Because of the result we used nonparametric tests. Inter-group comparisons were made by the Mann-Whitney U test (for continuous variables), and categorical variables were compared by the χ^2 test or Fisher's exact test. The repeated measurements (before and after varenicline or placebo) were analyzed with the Wilcoxon signed rank test. A p-value < 0.05 was considered statistically significant.

Results

Baseline characteristics of the S and NS groups are shown in Table 1. Echocardiographic examination revealed no significant cardiac disorder and normal left ventricular ejection fraction.

There were no statistically significant differences among any of the QT, QTc and Tp-e interval, Tp-e/QT and Tp-e/QTc ratio before and after placebo or varenicline administration, between the S and NS group ($p > 0.05$) (Table 2). In the S group QTc (409.57 ± 28.17 vs. 425.28 ± 32.79; $p = 0.02$), Tp-e interval (64.28 ± 8.78 vs. 70.42 ± 13.12; $p = 0.02$), Tp-e/QT (0.18 ± 0.02 vs. 0.19 ± 0.03; $p = 0.04$) and Tp-e/QTc ratio (0.17 ± 0.02 vs. 0.19 ± 0.02; $p = 0.01$) were significantly increased after varenicline administration but these parameters were not change in the NS group (Table 3).

Adverse events

Nausea and vomiting (NS: 7 [46.7%] vs. S: 1 [6.7%]; $p = 0.01$), dizziness (NS: 6 [40%] vs. S: 1 [6.7%]; $p = 0.03$) and hypotension (NS: 4 [26.7%] vs. S: –; $p = 0.03$) were significantly more frequent in the NS group than in the S group. The palpitation rate and the incidence of sweating were similar in both the S and NS groups ($p > 0.05$). At the Holter recording ventricular extrasystole was significantly more frequent in the NS group than in the S group (NS: 4 [26.7%] vs. S: –; $p = 0.03$), however supraventricular extrasystole was similar in both groups (Table 4).

Discussion

The principal findings of the analysis are; first, the repolarization parameters were not different before and after the administration of high dose of varenicline in between healthy S and NS, second, the repolarization parameters were significantly changed before and after the administration of high dose of varenicline in S however it was not significantly changed in NS, third, non-cardiovascular side-effects were significantly higher in the NS than in the S with a single high dose of varenicline.

A single high dose of varenicline did not affect the QT and Tp-e interval, Tp-e/QT and Tp-e/QTc

Table 2. Tp-e, QT parameters in nonsmokers and smokers with placebo and varenicline.

	Nonsmokers (n = 15)	Smokers (n = 15)	P	Nonsmokers (n = 15)	Smokers (n = 15)	P
	Before placebo			Before varenicline		
QT	363.28 ± 19.12	374.50 ± 44.27	0.61	367.00 ± 23.66	357.57 ± 20.75	0.41
QTc	421.00 ± 12.51	446.83 ± 60.82	0.31	422.63 ± 12.05	409.57 ± 28.17	0.36
Tp-e (mean)	69.71 ± 5.21	65.83 ± 10.14	0.15	72.45 ± 7.82	64.28 ± 8.78	0.07
Tp-e/QT	0.19 ± 0.02	0.17 ± 0.09	0.19	0.19 ± 0.08	0.18 ± 0.02	0.41
Tp-e/QTc	0.17 ± 0.05	0.15 ± 0.08	0.39	0.18 ± 0.09	0.17 ± 0.02	0.21
	After placebo			After varenicline		
QT	379.71 ± 33.97	387.66 ± 49.68	0.66	357.18 ± 23.24	357.14 ± 21.62	0.92
QTc	442.42 ± 55.30	452.50 ± 74.01	0.52	423.09 ± 15.28	425.28 ± 32.79	0.71
Tp-e (mean)	66.02 ± 13.87	63.00 ± 7.64	0.24	71.43 ± 14.11	70.42 ± 13.12	0.55
Tp-e/QT	0.17 ± 0.03	0.16 ± 0.02	0.39	0.20 ± 0.02	0.19 ± 0.03	0.44
Tp-e/cQT	0.15 ± 0.06	0.14 ± 0.05	0.31	0.20 ± 0.03	0.19 ± 0.02	0.29

Table 3. Tp-e, QT parameters in nonsmokers and smokers before and after varenicline.

Smokers (n = 15)	Before varenicline	After varenicline	P
QT	357.57 ± 20.75	357.14 ± 21.62	0.93
QTc	**409.57 ± 28.17**	**425.28 ± 32.79**	**0.02**
Tp-e (mean)	**64.28 ± 8.78**	**70.42 ± 13.12**	**0.02**
Tp-e/QT	**0.18 ± 0.02**	**0.19 ± 0.03**	**0.04**
Tp-e/QTc	**0.17 ± 0.02**	**0.19 ± 0.02**	**0.01**
Nonsmokers (n = 15)	**Before varenicline**	**After varenicline**	**P**
QT	367.00 ± 23.66	357.18 ± 23.24	0.28
QTc	422.63 ± 12.05	423.09 ± 15.28	0.62
Tp-e (mean)	72.45 ± 7.82	71.43 ± 14.11	0.88
Tp-e/QT	0.19 ± 0.08	0.20 ± 0.02	0.44
Tp-e/QTc	0.18 ± 0.09	0.20 ± 0.03	0.29

Table 4. Adverse events in nonsmokers and smokers with varenicline.

	Nonsmokers (n = 15)	Smokers (n = 15)	P
Nausea and vomiting	7 (46.7%)	1 (6.7%)	0.01
Dizziness	6 (40%)	1 (6.7%)	0.03
Sweating	3 (20%)	–	0.06
Palpitation	1 (6.7%)	1 (6.7%)	1
Hypotension	4 (26.7%)	0 (0%)	0.03
Supraventricular extrasystole	1 (6.7%)	2 (13.3%)	0.54
Ventricular extrasystole	4 (26.7%)	0 (0%)	0.03

ratio in the NS group and increased QTc and Tp-e interval, Tp-e/QT and Tp-e/QTc ratio in the S group.

Tp-e interval and Tp-e/QT ratio have been used as new ECG markers of the increased dispersion of ventricular repolarization, prolongation of the Tp-e interval is related with ventricular arrhythmia and sudden cardiac death [7–11]. Electrophysiological studies showed that a prolonged Tp-e interval was associated with ventricular tachycardia induction and the spontaneous occurrence of ventricular tachycardia [9, 10]. However, the Tp-e/QT ratio is considered to be a more sensitive index of arrhythmogenesis compared with the sole use of either the Tp-e or QT intervals, as it is not affected by variations in body weight and heart rate [7]. This improves the signal-to-noise ratio, and provides more distinctive information to predict arrhythmogenesis [7]. Higher Tp-e/QT ratio has been associated with arrhythmic events in many clinical conditions, such as Brugada syndrome, hypertrophic cardiomyopathy, and acute myocardial infarction [7, 9–11].

In our study, we showed that single high dose (2 mg) varenicline increased Tp-e interval, and Tp-e/QT, Tp-e/QTc ratio in the smokers. On the other hand, smoking is one cause of the increased Tp-e, QT interval and Tp-e/QT, Tp-e/QTc ratio [15]. When considered from this point of view, when varenicline is usedto make smokers quit smoking, they should evaluate if they had a prearrhythmic state or not.

Experimental studies showed that high dose of varenicline could decrease or not change the QT and QTc duration [13, 16]. In our study, the QT duration was not changed significantly with single dose of varenicline, however QTc duration increased significantly. However, in that study, QTc was measured with the Fridericia's formula [17]. The different evaluation formula could explain the differences.

However, recent studies and meta-analysis showed that the cardiac effect of varenicline was similar with placebo but Tp-e, Tp-e/QT and Tp-e/QTc parameters were not evaluated in that analysis [18]. In our study, Tp-e interval and QTc duration were significantly increased. This result could be associated with a single high dose of varenicline administration, on the other hand, smoking cigarettes and exercise itself could prolong the QTc duration [15, 19]. For smoking cessation, the drug started with low dose and increased to 1 mg twice a day, not single 2 mg dose. Tp-e and QT parameters were not significantly changed before and after placebo and the baseline parameters were similar in both groups except for cigarette smoking so the combination effect of cigarette smoking and varenicline could explain the electrocardiographic changes.

Limitations of the study

This study is a sub-study of the "The effect of varenicline on heart rate variability in healthy smokers and nonsmokers". The present study included only a small number of healthy volunteers, and only short-term records were obtained. The patients were all young males and females, and most of the people using varenicline for treatment of smoking cessation are older than the participants in our study. Therefore, our results do not reflect the overall effects of the varenicline on ECG interval, and the results may not be completely generalized to all smoking patients. We administered only a single high dose of the drug, so we could not evaluate the long-term and the standard dose effects of varenicline.

Conclusions

Our study showed that Tp-e interval, Tp-e/QT ratio and Tp-e/QTc ratio increased after varenicline administration in smokers. The association between parameters of ventricular arrhythmogenesis and varenicline treatment needs to be confirmed by larger-scale studies.

Conflicts of interest: None declared

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