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Original Article

The effect of smoking cessation with or without bupropion on p wave duration and amplitude

Duygu Ilke Yildirim[1], Mert Ilker Hayiroglu[2], Mehmet Ali Eryilmaz[3]

[1] Health Sciences University Konya Training and Research Hospital, Department of Family Medicine, Konya, Turkey
[2] Dr. Siyami Ersek Thoracic and Cardiovascular Surgery Training and Research Hospital, Department of Cardiology, Istanbul, Turkey
[3] Health Sciences University Konya Training and Research Hospital, Department of General Surgery, Konya, Turkey

Abstract

Aim: In the current study, the impact of smoking cessation with and without bupropion usage on p wave duration and p wave amplitude in lead I has been analyzed. Bupropion, which is an atypical antidepressant with effects on both dopaminergic and noradrenergic systems, is approved in the medical treatment of smoking cessation. Several cardiac side effects have been presented when bupropion is prescribed in smoking cessation.

Material and Methods: Our study has a prospective design which has planned to evaluate p wave amplitude in lead I and p wave duration changes of bupropion by comparing smoking patients (n=78) before and after bupropion usage. The patients prescribed bupropion were also compared to ex-smoker group (n=50) who quit smoking without bupropion usage in regard to p wave indices in lead I. Differences in the median values between groups were analyzed using Mann-Whitney U test. Categorical variables were analyzed by chi-square test or Fisher's exact test. For repeated measurements, paired sample t-test and Wilcoxon signed rank tests were used to evaluate the significance of the difference in parameters with normal and skewed distribution.

Results: The study included both seventy-eight (79.5% male) patients under bupropion treatment and fifty (88.2% male) patients stopped smoking without pharmacotherapy. P wave duration was notably higher when compared before and after smoking cessation with bupropion (99.0 ± 15.7 ms vs 96.2 ± 11.9ms; p<0.001). The frequency of the patients with P wave duration >120 ms was significantly higher in smoking patients. (p=0.014) The frequency of the patients with P wave duration <100 ms was significantly lower in smoking patients.(p=0.001). P wave amplitude in lead I was statistically lower in smoking patients. (p=0.001) The change in P wave duration and P wave amplitude in lead I were positively correlated with the smoking packet/year. (Rho: 0.512, p<0.001 and rho=0.408, p<0.001)

Conclusion: Smoking cessation with or without bupropion was demonstrated to shorten P wave duration and increase P wave amplitude in lead I. Smoking cessation with or without bupropion have an effect to reverse atrial electrical remodeling.

Keywords: Smoking cessation; bupropion, p wave morphology.

INTRODUCTION

Cigarette smoking is a worldwide-accepted risk factor for cardiovascular diseases by contributing to risk of coronary artery disease and atrial fibrillation (1,2). 33% of deaths from cigarette smoking are due to cardiac causes and %11.1 of these deaths occurs in patients with exposed to secondhand smoke (3). Moreover, smoking cessation that ends up with weight gain is linked to short-term risk of type 2 diabetes mellitus but still reduces the cardiovascular and all-cause mortality (4). Thus, pharmacologic treatment regimens play a considerable role in order to reduce smoking addicts. The antidepressant drug bupropion has been available as a part of pharmacotherapy for smoking cessation since 1997. Bupropion is an effective mono-therapy in smoking cessation under favor of increasing extracellular dopamine and noradrenaline levels in subcortical regions (5). The bupropion pharmacotherapy has been reported to be successful in helping smokers achieve abstinence in large randomized placebo controlled trials (6,7). Even though cardiovascular safety of bupropion has been tested several times, its effect on atrial depolarization parameters during smoking cessation has not been reported yet.

Atrial fibrillation is one of the cardiovascular side effects of cigarette smoking and electrocardiography is the

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Corresponding Author: Mert Ilker Hayiroglu, Dr. Siyami Ersek Thoracic and Cardiovascular Surgery Training and Research Hospital, Department of Cardiology, 34668 Kadikoy-Istanbul Turkey **E-mail:** mertilkerh@yahoo.com

worldwide used diagnostic modality of atrial fibrillation. Smoking has been also associated with inter-atrial electromechanical delay and p wave dispersion (8). Deep terminal negativity of P wave in V1, an electrocardiographic sign of left atrial abnormality, has been associated with serum cotinine levels (9). Furthermore, interatrial block and reduced P wave voltage in lead I have been closely associated with development of atrial fibrillation especially in patients with coronary artery disease (10,11). The effect of smoking and smoking cessation with or without bupropion therapy on P wave duration and P wave voltage in lead I have not been elucidated. The change in P wave duration and P wave voltage in lead I after smoking cessation with bupropion may help us to understand the atrial electrical remodeling of patients during smoking and after smoking cessation with bupropion. The aim of the current study was to assess the effect of smoking cessation with or without bupropion pharmacotherapy on the atrial depolarization parameters in healthy individuals.

MATERIAL and METHODS

Patient and study design

This study carried out in Selçuk University Family Medicine Clinic between February 2018 and May 2018. 108 smoking patients at all ages were included in our investigation. All of the participants were included in the study if they agreed to use bupropion as they have taught by his/her physician. Exclusion criteria were known arrhythmias (both atrial and ventricular), start smoking after cessation, diagnosed with atherosclerosis, all types of cardiomyopathies, significant valvulopathies, bundle branch block, ECGs without a clearly assessable P wave, thyroid disease and taking any chronotropic medication such as atrioventricular node blockers. Among 108 patients, those with re-smoking (n=22), those with arrhythmias (n=4), those with bundle branch block (n=1), those with atherosclerotic vascular disease (n=2), those with cardiomyopathy (n=1) were excluded. Thus, 78 patients meeting the aforementioned criteria and 50 sex-, body mass index (BMI)-, and age-matched individuals who stopped smoking without any pharmacotherapy formed the study group. The patients obtained information about the study design and gave informed consents. The study protocol was certified by the Local Ethical Committee of our hospital.

Our team collected the baseline features and relevant clinical data of the patients at the time of patients' agreement to take part in the study. Blood values obtained from venous blood samples at hospital admission were recorded.

A standard 12-lead ECG (Schiller, Cardiovit AT-10 plus) (filter 150Hz, 25 mm/s, 10 mm/mV) was recorded from all patients before the bupropion prescription and after 3 months of bupropion treatment. ECGs were scanned at 300 DPI and images were augmented 10x. P waves were measures manually using a caliper in all 12 leads to acquire the longest P wave duration. The onset of P wave was determined as the point of initial up- or downward deflection from the baseline and the offset of P wave was determined as the returning point of the deflection to the baseline. P wave amplitude in lead I measured from the peak of the P-wave to the isoelectric line of the TP interval. This method has been previously described and validated with high levels of agreement in both inter-observer and intra-observer variability (12,13). Two of the authors measured all the aforementioned parameters. The intra-observer and inter-observer coefficients of variation (the SD of differences between two observations divided by the mean value and expressed as a percentage) were found to be 1.5% and 2.6% respectively.

Follow-up

The starting dose of bupropion was 150 mg once daily for three days. The dose was changed to 150mg twice daily after the first three days. Patients were followed up with 150 mg once daily in they were older than 65-year. Patients were also evaluated after six weeks of bupropion usage. They were excluded if they failed to quit smoking despite pharmacologic treatment. At the three-month visit, another assessment was performed. The venous blood samples and ECGs were also recorded in the final control.

Statistical analysis

Data were analyzed with Statistical Package for Social Sciences (SPSS) version 20.0 for Windows (IBM, Armonk, New York). Normality of distribution will be assessed using Kolmogorov-Smirnov test. Continuous variables will be defined as the mean ± standard deviation. Categorical variables will be presented as number and percentages. Differences in the median values between groups were analyzed using Mann-Whitney U test. Categorical variables were analyzed by chi-square test or Fisher's exact test. For repeated measurements, paired sample t-test and Wilcoxon signed rank tests were used to evaluate the significance of the difference in parameters with normal and skewed distribution, respectively. Spearman correlation analysis was used for the correlation between packet/year and change in P wave duration and amplitude. Statistical significance was defined as a p value < 0.05. The effect size (Cohen's d) and power value (1- β) for P wave duration, compared between smokers and after smoking cessation, were calculated using G*Power software (version 3.1.9.2.) The alpha level used for this analysis was <0.05. The effect size and power value were 0.521 and 0.953 for P wave duration. The minimum sample size was 42 to evaluate properly the change of P wave duration through the cessation process. 78 patients were enrolled in our study.

RESULTS

The study included both seventy-eight (79.5% males) patients under bupropion treatment and fifty (88.2% male) patients stopped smoking without pharmacotherapy. Patients were analyzed in terms of their change in the P wave duration and amplitude. Mean age of bupropion treatment group was 41.6 ± 12.8 years. Table 1 presented the laboratory and ECG features of the bupropion treatment group at the beginning and after smoking cessation

with bupropion. Hemoglobin level, TSH, free T3, free T4, sodium, potassium, calcium and magnesium levels did not differ before and after smoking cessation with bupropion. Regarding electrocardiographic parameters, the heart rate and QRS duration were similar before and after smoking cessation with bupropion. P wave duration was notably higher in smoking patients. (99.0 ± 15.7 ms vs 96.2 ± 11.9ms; p<0.001) The frequency of the patients with P wave duration >120 ms was significantly higher in smoking patients. (p=0.014) The frequency of the patients with P wave duration <100 ms was significantly lower in smoking patients. (p=0.001). P wave amplitude in lead I was significantly lower in smoking patients. (p=0.001) Our team did not encounter any arrhythmic event during the follow-up with bupropion.

The laboratory and ECG data of the control group and bupropion prescribed group were presented in Table 2. The two groups were similar in terms of age, gender, body mass index, laboratory values and heart rate. P wave duration, the frequency of patients with P wave >120ms, 100 – 119ms, <100 ms and P wave amplitude in lead I were similar between the control group and smoking cessation with bupropion group. Figure 1 presents mean P wave duration and P wave amplitudes in lead I in bupropion prescribed patients and in smoking patients. Figure 2 indicates scatterplot of the correlation between packet/year and ΔP wave duration, ΔP wave amplitude in lead I. (Rho:0.512, p<0.001 and rho=0.408, p<0.001) Throughout the bupropion treatment for three months, 20 patients (25.6%) reported insomnia and 7 patients (8.9%) reported dry mouth.

Table 1. Laboratory and electrocardiography findings of the bupropion prescribed patients

	Smoking (n=78)	Smoking cessation with Bupropion (n=78)	P value
Hemoglobin, (g/dl)	15.4 ± 1.8	15.4 ± 1.6	0.287
TSH	2.28 ± 3.17	2.58 ± 2.47	0.264
Free T3	3.33 ± 0.44	3.37 ± 0.37	0.328
Free T4	1.29 ± 0.28	1.25 ± 0.16	0.168
Sodium, (mEq/L)	140.3 ± 9.1	138.5 ± 13.0	0.240
Potassium, (mEq/L)	4.49 ± 0.34	4.50 ± 0.33	0.764
Calcium, (mg/dl)	9.58 ± 0.44	9.57 ± 0.41	0.956
Magnesium, (mg/dl)	2.02 ± 0.19	2.03 ± 0.14	0.408
Heart rate	76.4 ± 13.0	74.3 ± 12.3	0.098
P wave duration, ms	99.0 ± 15.7	96.2 ± 11.9	<0.001
P wave > 120ms	9 (11.5)	3 (3.8)	0.014
P wave 100 – 119ms	35 (44.9)	28 (35.9)	0.127
P wave < 100ms	34 (43.6)	47 (60.3)	0.001
P wave amplitude, mV	0.104 ± 0.015	0.111 ± 0.014	0.001
QRS, ms	88.1 ± 8.7	87.8 ± 8.2	0.634

Continuous variables are presented as mean ± SD
Nominal variables presented as frequency (%)

Table 1. Baseline characteristics, laboratory and electrocardiography findings

	Control group (n=50)	Smoking cessation with Bupropion group (n=78)	P value
Age, year	40.9 ± 11.5	41.6 ± 12.8	0.830
Male gender	45 (88.2)	62 (79.5)	0.196
Body mass index (kg/m2)	25.4 ± 4.3	25.5 ± 5.9	0.816
Hemoglobin, (g/dl)	15.5 ± 1.6	15.3 ± 1.9	0.704
TSH	1.95 ± 2.13	2.26 ± 3.51	0.252
Free T3	3.33 ± 0.45	3.37 ± 0.46	0.471
Free T4	1.24 ± 0.17	1.30 ± 0.34	0.418
Sodium, (mEq/L)	138.5 ± 4.0	139.0 ± 3.42	0.838
Potassium, (mEq/L)	4.52 ± 0.39	4.44 ± 0.29	0.346
Calcium, (mg/dl)	9.47 ± 0.32	9.55 ± 0.41	0.394
Magnesium, (mg/dl)	2.05 ± 0.19	2.01 ± 0.16	0.559
Heart rate (per minute)	75.2 ± 12.8	73.3 ± 12.0	0.386
P wave duration, ms	95.3 ± 11.2	96.2 ± 12.0	0.554
P wave > 120ms	1 (2.0)	3 (3.8)	1.000
P wave 100 – 119ms	13 (26.0)	28 (35.9)	0.242
P wave < 100ms	36 (72.0)	47 (60.3)	0.175
P wave amplitude, mV	0.111 ± 0.013	0.110 ± 0.013	0.907
QRS, ms	86.5 ± 12.6	87.8 ± 8.2	0.343

Continuous variables are presented as mean ± SD
Nominal variables presented as frequency (%)

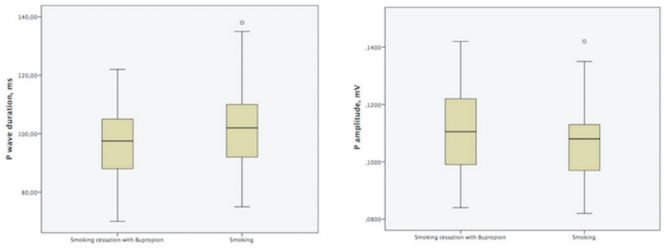

Figure 1. Presents mean P wave duration and P wave amplitudes in lead I in bupropion prescribed patients and in smoking patients

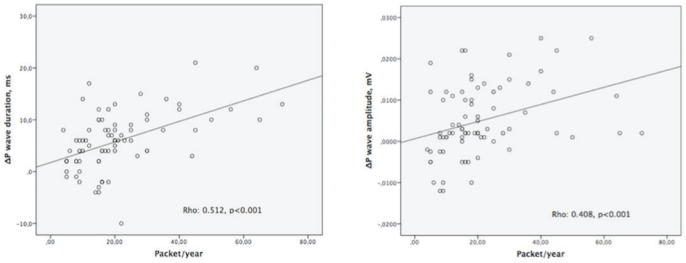

Figure 2. Indicates scatterplot of the correlation between packet/year and ΔP wave duration, ΔP wave amplitude in lead I. (Rho:0.512, p<0.001 and rho=0.408, p<0.001)

DISCUSSION

Our study is the first study presenting bupropion administration to shorten P wave duration and increase P wave amplitude in lead I after smoking cessation compared to the same patients' smoking status. There was no difference in terms of P wave duration and P wave amplitude in lead I when compared to healthy controls. Positive correlation was also determined between smoking packet/year and the change in P wave duration and P wave amplitude in lead I after bupropion usage.

Bupropion has been investigated several times accordingly its cardiovascular side effects after it has been approved as a pharmacotherapy in smoking cessation. When compared to placebo, bupropion has been reported to increased cardiovascular adverse effects despite statistical insignificance (14,15). Moreover, a large meta-analysis has shown that bupropion administration is not associated with cardiac diseases (16). Cardiovascular side effects, mainly tachycardia and conduction delays have been reported after bupropion overdose (17). The side effects of bupropion overdose have been considered due to dopaminergic and adrenergic activity of the active metabolite. On the other hand smoking may lead to atrial fibrillation and ventricular arrhythmias by altering ion channel permeability of the myocytes (8,18). P wave duration and P wave amplitude in lead I have been considered to be a strong predictor of atrial fibrillation in patients with coronary artery disease (11,19). P wave indices have been reported as an accepted marker of atrial electrical remodeling (20). Therefore we examined the reverse atrial electrical remodeling effect of smoking cessation with or without bupropion by the help aforementioned parameters. Re-smoker patients were especially excluded in order to remove the arrhythmic effect of smoking. The atrial electrical remodeling effects of smoking were observed to return after use of bupropion for three months. Bupropion appeared to be safe in smoking cessation after compared to the P wave parameters of ex-smoker patients who quitted smoking without pharmacotherapy. In our study, another important issue was the change in P wave duration and P wave amplitude in lead I were both correlated to the smoking packet/year. This correlation signified the cumulative effect of smoking on the P wave duration and P wave amplitude in lead I from a different perspective. Bupropion was successful to be effective in the reversal of the cumulative atrial electrical remodeling effect of smoking by the help of the changes in these electrocardiographic parameters.

Hormonal disorders and electrolytes imbalances have been already linked to changes in the predisposition to atrial fibrillation (21). The similarity of these parameters in our patients gave us a valuable opportunity to make these inferences.

Study Limitations

We have several limitations in our study. Firstly; this was a single center and observational study; however it was conducted in a high volume smoking cessation clinic and all consecutive patients who met the criteria were included, thus limiting selection bias. Secondly, we excluded the patients who started smoking to clarify the effect of bupropion on atrial depolarization parameters.

CONCLUSION

Smoking cessation with or without bupropion usage was demonstrated to shorten P wave duration and increase P wave amplitude in lead I. Bupropion may also has an effect to reverse atrial electrical remodeling effect of smoking. Smoking cessation with bupropion treatment may raise the anti-arrhythmic effect of smoking cessation. It appears to be safe to quit smoking with bupropion in terms of atrial rhythm disturbances.

Duygu Ilke Yildirim ORCID: 0000-0002-3893-5173
Mert Ilker Hayiroglu ORCID: 0000-0001-6515-7349
Mehmet Ali Eryilmaz ORCID: 0000-0002-5280-3943

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