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ARAŞTIRMA YAZISI / RESEARCH ARTICLE

TİP 2 DİABETES MELLİTUSLU HASTALARDA LİNAGLİPTİN'İN ARİTMİ ÜZERİNE ETKİSİ

THE EFFECT OF LINAGLIPTIN ON ARRHYTHMIA IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

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ÖZET

AMAÇ: Linagliptin, inkretin hormonlarının inaktivasyonunu engelleyen ve ayrıca glukoza bağımlı insülin salınımını uyaran bir dipeptidil peptidaz-4 (DPP-4) inhibitörüdür. P dalga dispersiyonu ve QT dispersiyonu, atriyal fibrilasyon ve ventriküler taşiaritmilerle ilişkili elektrokardiyografik bulgulardır. Bu çalışmadaki amacımız, Tip 2 diabetes mellituslu (Tip 2 DM) hastalarda linagliptin uygulamasının P dalga dispersiyonu ve QT dispersiyonu üzerine bir etkisinin olup olmadığını araştırmaktır.

GEREÇ VE YÖNTEM: Çalışmaya Ekim 2019 - Mayıs 2021 tarihleri arasında Eğitim ve Araştırma Hastanesi dahiliye polikliniğine başvuran ve linagliptin başlanan 60 rastgele hasta (28 kadın- %46,7, 18 hipertansiyon- %30, 16 sigara içen- %26,7) dahil edildi. Hastaların 6. ayın başında ve sonunda elektrokardiyogramları çekildi. Hastaların linagliptin başlandığı anda ve 6. ayda ekokardiyografileri yapıldı.

BULGULAR: Bazal ve 6. ay elektrokardiyogramları karşılaştırıldığında, P dalga dispersiyonu (0.0435 ± 0.014 - 0.0312 ± 0.011 p<0.01), QT dispersiyonu (0.0496 ± 0.01 - 0.0402 ± 0.01 p<0.01) ve QTc dispersiyonunda (0.051 ± 0.01 - 0.038 ± 0.14 p<0.01) anlamlı değişiklikler olduğunu saptadık.

SONUÇ: Bu çalışmada linagliptinin aritmi üzerine olumsuz bir etkisinin olmadığını gösterdik. Çalışmamız daha uzun soluklu çalışmalar için yol gösterici olacaktır.

ANAHTAR KELİMELER: Dipeptidil peptidaz-4 (DPP-4) inhibitörü, Tip 2 diabetes mellitus, P dalga dispersiyonu, QT dispersiyonu.

ABSTRACT

OBJECTIVE: Linagliptin is a dipeptidyl peptidase-4 (DPP-4) inhibitor that prevents the inactivation of incretin hormones and also stimulates the release of glucose-dependent insulin. Electrocardiographic abnormalities such as P wave dispersion and QT dispersion are associated with ventricular tachyarrhythmias and atrial fibrillation, respectively. In this study, we seek to determine if the introduction of linagliptin has any impact on the P wave dispersion and QT dispersion in individuals with Type 2 diabetes mellitus (Type 2 DM).

MATERIAL AND METHODS: The study included 60 random patients (28 females- 46.7 % , 18 hypertension- 30 %, 16 smokers- 26.7 %) who were admitted to the Training and Research Hospital internal medicine policlinic between October 2019 and May 2021 and who started linagliptin. The patients' electrocardiograms were taken at the start and the conclusion of the sixth month. Echocardiography was performed at treatment initiation and at the 6th month.

RESULTS: When basal and 6th month electrocardiograms were compared, significant changes were observed in P wave dispersion (0.0435 ± 0.014 - 0.0312 ± 0.011 p<0.01), QT interval dispersion (0.0496 ± 0.01 - 0.0402 ± 0.01 p<0.01) and QTc interval dispersion (0.051 ± 0.01 - 0.038 ± 0.14 p<0.01).

CONCLUSIONS: We demonstrated in this study that linagliptin had no detrimental effects on heart rhythm. Our study will be a guide for longer follow-up studies.

KEYWORDS: Dipeptidyl peptidase-4 (DPP-4) inhibitor, Type 2 diabetes mellitus, P wave dispersion, QT dispersion.

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INTRODUCTION

Globally, the number of Type 2 DM patients is rising daily, worsening the situation, particularly in low- and middle-income nations (1). Due to the increased loads of Type 2 DM, effective and well-tolerated medications are required, and there are many alternatives for managing hyperglycemia. However, some of the treatments commonly used for Type 2 DM are contraindicated in patients with hypoglycemia and excess weight (Sulphonylurea, thiazolidinedione, and insulin), the possibility of gastrointestinal side effects (metformin, α-glucosidase inhibitors), or in patients with severe or moderate renal impairment (metformin, sulfonylureas) (2). According to population-based studies, DM is a separate risk factor for atrial fibrillation.

Linagliptin, a novel oral antidiabetic that has recently begun to be widely used, has strengthened our hand against Type2 DM. Linagliptin is an effective oral antidiabetic (3) that selectively inhibits dipeptidil peptidaz-4 (DPP-4) and is used once a day. DPP-4 prevents the dysfunction of glucagon-like peptide-1 (GLP-1) and gastric inhibitory peptide (GIP) which are incretin hormones and secreted by enteroendocrine cells in response to hyperglycemia. DPP-4 inhibitors extend the half-lives of GLP-1 and GIP, as well as inactivate various substrate hormones, chemokines, neuropeptides, and growth factors. These effects happen separately from how they affect blood sugar levels. They benefit heart health in this manner as well. Linagliptin is a powerful, long-acting, and highly specialized DPP-4 inhibitor in this situation. The absence of problems occurring in the kidneys caused by its excretion from the body and its direct strong effects on the vessels are the primary reasons to prefer it for the patients with Type2 DM (4, 5). Some drugs act on the atrium conduction, causing the arrhythmia. This has also been associated with P-wave dispersion on electrocardiography (ECG) (6). Some drugs also have the effect of bringing out ventricular arrhythmia by acting on the ventricular conduction system, which has been associated with QT dispersion on ECG. Electrocardiography's P-wave represents atrial depolarization, and the QT interval is the entire amount of time between the ventricles' depolarization and repolarization. Simple and affordable tests that indicate the spatial heterogeneity of atrial and ventricular repolarization, respectively, are P-wave and QT dispersions. Prolongation in QT dispersion leads to inhomogeneous transmission rates in different regions of the ventricles or to severe ventricular arrhythmias through the re-entry mechanism of repolarization, thus leading to sudden cardiac death. P wave dispersion is an index reflecting the risk of atrial fibrillation (7, 8). In this research, we studied the effect of linagliptin, a very new and commonly used oral antidiabetic drug, on P wave dispersion and QT dispersion and investigated its effect on arrhythmia.

MATERIAL AND METHODS

We conducted a randomized, prospective, open-ended study showing the effect of linagliptin, a DPP-4 inhibitor, on cardiac arrhythmia in patients with Type 2 DM.

Study Population

We included patients with Type 2 DM who were admitted to the Internal Medicine outpatient clinic of Educational Research Hospital between October 2019 and May 2021 and started to receive linagliptin 5 mg in the last 2 weeks. A total of 75 patients were followed up, and after these patients were informed about the subject, objective, and method of the study, the patients' written consents were obtained. Information forms were filled out face-to-face.

Criteria For Participation In The Study

The patients with Type 2 DM, who were between the ages of 30-65, without changes in DM drugs in the last 8 weeks and in antihypertensive drugs in the last 8 weeks, without cardiac intervention performed in the last 8 weeks, with body mass index (BMI) below 45 kg m^2, HbA1c value between 6.5% and 8.5%, and who gave a written consent form stating that the patient voluntarily participated in the study were included in the study.

Exclusion Criteria From The Study

The patients with Type 1 DM, receiving insulin therapy, using of another DPP-4 inhibitor or similar oral antidiabetic drug, having atrial fibril-

lation and a similar arrhythmia, the ejection fraction below 50 %, uncontrolled hyperglycemia, uncontrolled hypertension, drug dose changes during the study, interventional coronary angiography due to acute coronary syndrome and similar reasons, dose change in hypertension drugs, dose change in thyroid drugs, stroke in the last 3 months, acute liver disease and impaired liver function, alcohol and drug use, current corticosteroid use, former or planned bariatric surgery, and anti-obesity medication within the last 3 months were excluded from the study.

Study Protocol

Patients who did not achieve the desired blood sugar level despite following the prescribed diet, exercise, and oral antidiabetic medications for at least 8 weeks prior to the study's commencement were still included in it. After giving information about the study and obtaining written consent from the patients, blood was taken for baseline blood values, routine biochemistry, urea, creatinine, electrolytes (potassium, sodium, calcium), lipid profile, alanine aminotransferase (AST), aspartate aminotransferase (ALT), hemogram values, hemoglobin a1c (HbA1c) value, and the results were recorded.

Electrocardiography

A three-channel Nihon Kohden electrocardiography (ECG) equipment was used to measure the ECG at a speed of 25 mm/sec, an amplitude of 10 mm/mV, and a standard 12 derivations, each of which contained at least three QRS complexes. During the measurements, the patients breathed freely but were not allowed to speak.

P wave times were measured manually in all derivations. The P wave's intersection with the isoelectric line was determined to be at its onset.

The junction of the isoelectric line and the P wave's endpoint was chosen as the point of completion. The longest atrial conduction time was acknowledged to be the greatest P wave time, which was regarded as the longest P wave. The P dispersion was defined as the distance between the longest and shortest P waves (9, 10).

The distance between the start of the QRS complex and the end of the T wave was referred to as QT dispersion. Measurements could not be made in the derivations where the T wave could not be selected. When the T wave had a double peak, if the second peak was less than 50% of the first peak, the point at which the extension of the first wave reached the isoelectric line was considered the end of the T wave. When calculating QT dispersion, three QT distances were measured for each derivation and their averages were taken. QT dispersion (QTd) was determined by the difference between the largest and smallest average QT dispersion from the obtained QT and QTc values, and QTc dispersion (QTcd) was determined by the difference between the average of largest and smallest QTc. Bazzet's formula ($QTc=QT/\sqrt{RR}$) was used to calculate QTc values (11).

Echocardiography

The same doctor used a Philips EPIQ 7 transthoracic echocardiography device while placing patients on their left side to perform a routine echocardiogram in accordance with the American Society of Echocardiography's guidelines. We assessed the left atrial size, valve function, interventricular septum thickness, posterior wall thickness, left ventricular systolic diameter, diastolic diameter, ejection fraction, and systolic pulmonary arterial pressure. Patients' biochemical blood levels, ECG, and echo results were mostly recorded on the first day of the trial and again at the end of the sixth month.

Ethical Committee

Before starting the research, Antalya Training and Research Hospital Clinical Research Ethics Committee received the necessary approvals (reference number-2019-272).

Statistical Analysis

The Statistical Package for Social Sciences (SPSS) version 16.0 for Windows was used for the statistical analysis. The Kolmogorov-Smirnov test was used to assess if the data had a normal distribution. It was demonstrated that numerical variables follow a normal distribution. Categorical variables were specified as numbers and percentages. The paired sample t-test was preferred for independent samp-

les in the analysis of numerical variables with the normal distribution. P<0.05 value was considered significant in statistical analyses.

RESULTS

In the follow-up of 75 patients included in the study, we completed our study with 60 patients because 3 patients had acute coronary syndrome, 1 patient had a temporary ischemic stroke, 6 patients' hypertension medications were changed, and 5 patients started to receive insulin treatment. Of these patients, 28 were female (46.7%), 32 were male (53.3%). Eighteen of them had hypertension (30 %) and were using at least one antihypertensive agent, no drug dose changes were made throughout the study. Sixteen of the patients used to smoke (27%). Five of the patients (8%), who had previously undergone coronary angiography and had a stent implanted, had coronary artery disease. These individuals had not begun taking any new medications for cardiology in the previous six months. Baseline clinical characteristics of the patients are shown in **Table 1**.

Table 1: Baseline characteristics of patients

Gender (Female)	n(%)	28 (60)	46.7 %
Hypertension	n (%)	18 (60)	30 %
ARB	n (%)	7 (18)	39 %
ACE-I	n (%)	3 (18)	17 %
Calcium channel bloker	n (%)	2 (18)	11 %
ARB + Calcium channel bloker	n (%)	6 (18)	33 %
Smoking	n (%)	16 (60)	26.7 %
CAD	n (%)	5 (60)	8.3 %
Age, (years)	55.86 ± 5.39		
BMI (Kg/m2)	26 ± 3.4		
HbA1c (%)	8.35 ± 1.24		
Fasting glucose (mg/dl)	122 ± 33		
Hemoglobin (g/dl)	13.67 ± 1.87		
Creatinine (mg/dl)	1.03 ± 0.32		
Potassium (mmol/L)	4.12 ± 0.52		
Sodium (mmol/L)	139.10 ± 3.40		
Calcium (mg/dl)	8.66 ± 0.49		
Heart rate (HR)	74.10 ± 11.81		
Pr distance /msec)	0.15 ± 0.017		
Qrs distance (msec)	93.75 ± 9.63		
QT dispersion (msec)	0.49 ± 0.10		
QTc dispersion (msec)	0.051 ± 0.01		

At the conclusion of the sixth month, transthoracic echocardiography and baseline were compared. When ejection fraction (EF), interventricular septum (IVS), ventricular posterior wall (VPW), left ventricle systolic diameter (LVSD), left ventricle diastolic diameter (LVDD), isovolumetric relaxation time (IVRT), deceleration time (DT), E/A, E/E', septal E' values were compared **(Table 2)**, it was seen that they had no significant differences (EF, IVS, VPW, LVSD, LVDD). A significant difference was observed between the measurements between diastolic functions (IVRT, DT, E/A, E/E', E'). Comparing the ECGs of the first day to those of the end of the sixth month, significant difference was found in P wave dispersion (0.043 ± 0.14 - 0.031 ± 0.11- p <0.01), QT dispersion (0.49 ± 0.10 - 0.40 ± 0.10 - p <0.01) and QTc dispersion (0.051 ± 0.01-0.038 ± 0.014 -p <0.01)**(Table 3)**.

Table 2: Comparison of echocardiography values (Before medication and 6th-month of medication)

	Baseline	6th-month
EF (%)	62.7 ± 2.56	62.2 ± 2.37 (p=0.58)
Diastole (mm)	47.5 ± 3.35	47.46 ± 2.60 (p=0.40)
Systole (mm)	28.3 ± 2.18	28.82 ± 1.69 (p=0.49)
IVS (mm)	11.0 ± 0.82	10.85 ± 0.49 (p=0.32)
PW (mm)	10.5 ± 0.43	10.62 ± 0.54 (p=0.78)
IVRT (msec)	108.46±9.17	100.34±11.57 (p<0.01)
DT (msec)	224.94±25.44	219.52±29.58 (p<0.01)
E/A	0.81±0.19	0.96±0.19 (p<0.01)
E/e'	9.73±1.82	9.25±1.85 (p<0.01)
E' (cm/sec)	6.14±1.49	7.10±1.38 (p<0.01)
Left Atrium (mm)	37.05± 2.50	26.96± 2.32 (p=0.64)
Aortic root (mm)	35.46± 2.44	35.43± 2.39 (p=0.47)

Table 3: Comparison of electrocardiography values

	Baseline	6th-month
P Dispersion (msec)	0.043 ± 0.14	0.031 ± 0.11 (p<0.01)
QT Dispersion (msec)	0.49 ± 0.10	0.40 ± 0.10 (p<0.01)
QTc Dispersion (msec)	0.051 ± 0.01	0.038 ± 0.014 (p<0.01)

A decrease in P wave dispersion, QT, and QTc dispersion was observed in the ECGs of the patients. This was also thought to be beneficial for both atrial and ventricular arrhythmias. Comparisons between P, QT, and QTc dispersion before and after the sixth month reveal a propensity for no detectable arrhythmia. When we contrast baseline values with 6th month end values in **Figure 1**, this is more obvious.

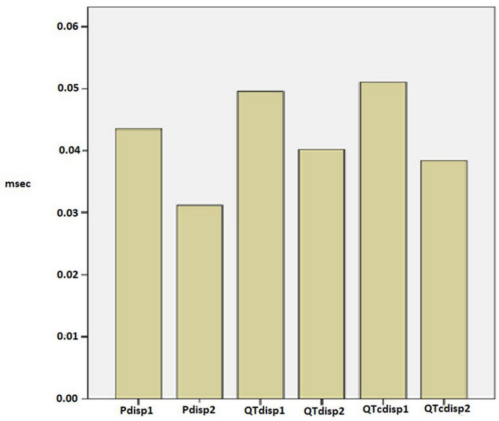

Figure 1: Comparison P wave dispersion, QT dispersion and QTc dispersion basal values and 6th months of linagliptin treatment.
Pdisp1: P wave dispersion at baseline ECG
Pdisp2: P wave dispersion at 6th month ECG
QTdisp1: QT dispersion at baseline ECG
QTdisp2 : QT dispersion at 6th month ECG
QTcdisp1: QTc dispersion at baseline ECG

DISCUSSION

In recent years, the number of patients with Type 2 DM has been steadily increasing worldwide. Our healthcare systems are currently under a lot of strain as a result of the rise in Type 2 DM prevalence. In connection to myocardial infarction or cardiac arrhythmias, type 2 diabetes has been demonstrated to reduce cardiac morbidity (12). Among supraventricular arrhythmias in patients with DM, the most reported arrhythmia is paroxysmal AF (13).

One of the earliest studies on the subject, the Framingham heart study, concluded after 38 years of follow-up that type 2 DM is a significant independent risk factor for AF (14). While developing a risk score for AF, the Framingham Heart Study includes DM as an important predictor of AF (15). One study found that db/db mice's sinoatrial recovery time was prolonged, which resulted in sinoatrial node malfunction. It was demonstrated that neither the transmission ranges nor wave amplitudes of these mice nor control mice differed noticeably (16). In previous studies, sudden cardiac deaths in patients with Type 2 DM were associated with underlying ventricular arrhythmias (12, 17). The development of DM in patients can also trigger intracardiac and extracardiac predisposing factors. It has effects on myocardial remodeling as an intracardiac factor and, on metabolic disorders and the remodeling of the neural pathway as extracardiac factors. As a result, insulin and glucose disorders directly impact the atrial and ventricular myocardium. Therefore, a study conducted in 2013 found that increased glucose concentration in cardiomyocytes significantly increased CaMKII-induced spontaneous sarcoplasmic reticulum Ca21 activation, causing cardiac mechanical dysfunction and arrhythmias. However, it was found in the NICE-SUGAR study that silent hypoglycemia causes cardiac arrhythmias and rapid mortality from arrhythmias (18). Moreover, severe hypoglycemia increased arrhythmia-related fatalities by 77%, according to the Outcome Reduction with Initial Glargine Intervention (ORIGIN) research (19). Studies showed that hypoglycemia increases sensitivity to arrhythmias in patients with Type2 DM. Unusual repolarization and altered cardiac autonomic tone are probable contributory factors. Other mechanisms that cause arrhythmias by acting directly on the ether-a-go-go-related gene (hERG) ion channel of hypoglycemia are leading to hypokalemia and prolongation of cardiac repolarization through the release of catecholamines, thus increases the risk of early depolarization and ventricular arrhythmia. (20, 21). Extracardiac abnormalities, such as remodeling of the neural pathway, lead to more arrhythmias (12). Patients with DM frequently experience autonomic neuropathy, which has been linked to an increased risk of arrhythmia (22). Autonomic neuropathy can cause sympathetic dis- and hyper-innervation (23, 24), increasing nor-epinephrine release, causing ventricular sensitivity (25), and prolonging the QT interval (26, 27). Numerous case reports detail spontaneous ventricular fibrillation in people with diabetes mellitus either by itself or in conjunction with hypoglycemia (28). Although these studies generally demonstrate that hypoglycemia causes arrhythmias, numerous research have also demonstrated that type 2 diabetes causes coronary artery disease and secondary or direct arrhythmia (29). The effect of linagliptin on hypoglycemia, when taken with food, is very little. Because there aren't enough studies on arrhythmia in people who have previously taken linagliptin, we decided to make a contribution to this field of study with this one. Although our study was limited in patient number and duration, the results we received were satisfactory. Comparisons between P, QT,

and QTc dispersion before and after the sixth month reveal a propensity for no detectable arrhythmia. When we contrast baseline values with 6th month end values, this is more obvious. Since there is no need for kidney dose adjustment and it is an efficient oral antidiabetic, linagliptin is a highly favored medication. This study has demonstrated that it can be used safely, particularly in the treatment of arrhythmia.

Our research demonstrated that, by blocking DPP4, linagliptin successfully controls blood sugar and has no detrimental effects on arrhythmia. Because of this, we think that our study will inform future research with more patients and longer follow-up.

If we were to list the variables that restricted our study, the first would be the small number of patients, the second would be the little follow-up period, and the third would be the fact that it was a single-center study and we were unable to enroll patients of other races.

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