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RESEARCH

Investigation of the effects of tadalafil on the myocardium via electrical and isometric contractions and cardiac markers in Wistar rats

Wistar sıçanlarda tadalafilin miyokard üzerindeki etkilerinin elektriksel ve izometrik kasılmalar ve kardiyak belirteçler yoluyla araştırılması

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Abstract

Purpose: Tadalafil, a long-acting phosphodiesterase-5 (PDE-5) inhibitor, is commonly used in the treatment of erectile dysfunction. This study investigates the contribution of tadalafil in cardiac function by measuring isometric and electrical contractions of myocardium in rats.

Materials and Methods: Thirty rats were divided into five groups. Basal electrical contractions were recorded via electrocardiogram (ECG) for intervals PR (ms), QRS (ms), QT (ms), Tp (ms), Te (ms), pathological Q and heart beats/min. Then group 1 received saline for 7 days (control); group 2 received tadalafil 1 mg/kg; group 3 received tadalafil 10 mg/kg; group 4 received tadalafil 1 mg/kg for 7 days; group 5 received tadalafil 10 mg/kg for 7 days. After treatments, electrical contractions were re-performed to analyze the differences in ECG. For isometric contractions, hearts were connected to isometric power transducer to determine myocardial contractile forces (g), durations (ms) and frequencies (Hz). Serum samples were collected for cardiac creatine kinase (CK-MB) and cardiac troponin I via ELISA.

Results: We found a significant decrease in CK-MB in Group 2 (395.56±124.38 pg/ml) and 3 (377.81±79.61 pg/ml), compared to Group 1 (575.32±83.54 pg/ml). The differences in cardiac contractile forces, contraction durations or frequencies were not statistically significant.

Conclusion: Tadalafil did not exert obvious distruption on myocardial electrical or isometrical contractions. It is noteworthy that tadalafil 1 and 10 mg/kg reduced serum CK-MB. Shortening in QT and decrease in heart rate may have important implications on myocardial functions.

Keywords: Tadalafil, Muscle contraction, Myocardium, Electrocardiography

Öz

Amaç: Uzun etkili bir fosfodiesteraz-5 (PDE-5) inhibitörü olan tadalafil, erektil disfonksiyon tedavisinde yaygın olarak kullanılmaktadır. Bu çalışma, sıçanlarda miyokardın izometrik ve elektriksel kasılmalarını ölçerek tadalafilin kalp fonksiyonuna katkısını araştırmaktadır.

Gereç ve Yöntem: Otuz sıçan beş gruba ayrıldı. Bazal elektriksel kasılmalar elektrokardiyogram (EKG) aracılığıyla PR (ms), QRS (ms), QT (ms), Tp (ms), Te (ms), patolojik Q ve kalp atım/dakika aralıklarında kaydedildi. Daha sonra grup 1'e 7 gün boyunca salin verildi (kontrol); grup 2'ye 1 mg/kg tadalafil verildi; grup 3'e 10 mg/kg tadalafil verildi; grup 4'e 7 gün süreyle 1 mg/kg tadalafil verildi; grup 5'e 7 gün süreyle 10 mg/kg tadalafil verildi. Tedavilerden sonra EKG'deki farklılıkları analiz etmek için elektriksel kasılmalar yeniden gerçekleştirildi. İzometrik kasılmalar için kalpler, miyokardiyal kasılma kuvvetlerini (g), sürelerini (ms) ve frekanslarını (Hz) belirlemek için izometrik güç dönüştürücüye bağlandı. ELISA yoluyla kardiyak kreatin kinaz (CK-MB) ve kardiyak troponin I için serum örnekleri toplandı.

Bulgular: CK-MB değerlerinde Grup 2'de (395,56±124,38 pg/ml) ve Grup 3'te (377,81±79,61 pg/ml), Grup 1'e (575,32±83,54 pg/ml) göre anlamlı bir azalma bulduk. Kardiyak kasılma kuvvetleri, kasılma süreleri veya frekanslarındaki farklılıklar istatistiksel olarak anlamlı değildi.

Sonuç: Tadalafil, miyokardın elektriksel veya izometrik kasılmaları üzerinde belirgin bir bozulma yaratmadı. Tadalafil 1 ve 10 mg/kg'ın serum CK-MB'yi azalttığı dikkat çekicidir. QT'deki kısalma ve kalp hızındaki azalmanın miyokardiyal fonksiyonlar üzerinde önemli etkileri olabilir.

Anahtar kelimeler: Tadalafil, Kas kontraksiyonu, Miyokard, Elektrokardiyografi

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INTRODUCTION

Tadalafil inhibits phosphodiesterase type-5 (PDE-5) in smooth muscles which degrades cyclic guanosine monophosphate (cGMP). As a result of PDE-5 inhibition, cGMP concentration increases and tissue relaxation is achieved[1,2]. Along with PDE-5 inhibition, nitric oxide (NO) exerts its physiological effects largely on cGMP via soluble guanylyl cyclase (sGS). Subsequently, cGMP acts mainly through the protein kinase G (PKG), a serine-threonine kinase that triggers or inhibits the functioning of target molecules such as channels, receptors, transporters or pumps by phosphorylating the functional proteins of the cell. Thus, phosphorylation by protein kinases works like an on-off switch for cell functions[3].

PDE-5 inhibitors target cGMP which is regulated by NO in the penile vasculature. In this way, it allows the vascular smooth muscle to relax and blood flow to increase. The physiological effects of PDE-5 inhibition are presented in many organ systems, significantly affecting the cardiovascular system, including pulmonary, systemic vasculature and myocardium. It has been observed that PDE-5 inhibitors have protective effects on cardiomyocytes, in addition to its vasodilatory effect on the systemic and pulmonary blood vessels, considered as positive developments for overcoming cardiovascular disorders. Previous human and animal studies have shown that PDE-5 inhibitors are effective for management of heart failure, as well as myocardial damage and cardiac remodeling[4].

There is ample evidence investigating the safety profile of the class of PDE-5 inhibitors and demonstrating supportive results in pre- and post-clinical studies[5-8]. The PDE inhibitors, proven as vasodilators and venodilators in the cardiovascular system, plays a regulatory part in myocardial contraction[9]. There are no sufficient studies in the literature on the myocardial functions, protection of myocardial cell integrity and electrophysiological effects of tadalafil. In this study, we planned to investigate the effect of tadalafil on myocardial cell contraction and electrical functions. We hypothesized that treatment with tadalafil may benefit cardiac parameters. We aimed to examine the effects of tadalafil on the myocardium, to investigate the contributions of tadalafil treatment to cardiac function of Wistar rats by measuring electrical and isometric contractions of the myocardium.

MATERIALS AND METHODS

The study was conducted in Kahramanmaraş Sütçü İmam University Medical Faculty, Department of Pharmacology. A number of thirty male Wistar rats were kept in stainless steel cages, at 22°C and 60±5% humidity with a 12-hr light/dark cycle, and access to water/food ad libitum. All conditions of the rats, such as the baseline health status, their diet, or environmental conditions, were standardized before the study to avoid any confounding factors that could affect the status of the study. All experiments were conducted in accordance with the National Institute of Health Guidelines for the Care and Use of Laboratory Animals. Experimental protocols were approved by Kahramanmaraş Sütçü İmam University Local Animal Experimentation Ethics Committee (File No: 2019/01/04, Approval date: 19.02.2019).

Animals and procedure

Tadalafil (Departon®), supplied from Abdi Ibrahim (Istanbul, Turkey), was homogenously dissolved in tap water. Tadalafil, which dissolves homogeneously in tap water, was given to the rats via orogastric lavage without wasting time. It was observed that the stability of tadalafil dissolved during this process was not impaired. The dissolution process in tap water was carried out separately for each animal. To maintain its stability, the dissolution process was done freshly and it was not stored. It was administered 1 mg/kg or 10 mg/kg per oral (p.o) with orogastric gavage, for 1 or 7 days in accordance to the experimental protocols. In previous rat studies, tadalafil doses for the treatment of erectile dysfunction were administered as 0.45-1.6 mg/kg (equals 5-20 mg in adult human). In our study, we administered tadalafil in doses of 1 mg/kg up to 10 mg/kg, based on previous studies[10,11].

Thirty male rats were randomly divided into five groups (n=6 per). Basal electrical contractions of hearts were recorded by electrocardiogram (ECG) in all groups to determine PR, QRS, QT, Tp, Te intervals, pathological Q and heart beats/min. Subsequently, drugs were given as following: Group 1, saline for 7 days (control); Group 2, tadalafil 1 mg/kg single dose; Group 3, tadalafil 10 mg/kg single dose; Group 4, tadalafil 1 mg/kg for 7 days; Group 5, tadalafil 10 mg/kg for 7 days. After treatments, electrical contractions were re-performed to analyze the differences in ECG parameters. For the isometric contractions, hearts were isolated and

connected to the isometric power transducer to determine the functionality of myocardium in terms of contractile forces, durations and frequencies. Serum samples were then collected to assay cardiac toxicity markers: cardiac creatine kinase (CK-MB) and cardiac Troponin I (cTn-I) via Enzyme-Linked Immunosorbent Assay (ELISA).

Electrocardiogram (ECG)

ECG was performed using BIOPAC MP36 (Biopac Systems, Inc., Camino Goleta, CA, USA)[12]. Rats were placed onto the recording platform for sufficient time to acclimate and their legs were restrained with adhesive tape. ECG electrodes (Skintact, FS-RG1/10, Innsbruck, Austria) were inserted for the limb lead at derivation I and II; V+, V- and ground were connected to the limbs. The V- electrode was inserted into the right arm, the V+ electrode was inserted into the left leg and the ground electrode was inserted into the right leg. ECG was recorded for 2 min as a minimum (0.05-100 Hz, AHA). Speed of electrocardiography was 50 mm/s and amplitude was 1 mV=10 mm[13]. Data were saved and processed using AcqKnowledge software (Biopac Systems, Inc., Camino Goleta, CA, USA). The parameters determined from ECG traces were: PR, QRS, QT, Tp, Te intervals, pathological Q and heart beats/min. ECG evaluation was interpreted by the same expert cardiologist in our study.

Cardiac mechanogram

Isometric mechanogram is a noninvasive method to determine the contractile characteristics of the muscle. Practically, the isometric mechanogram allows us to measure the contractile forces, durations and frequencies. In experimental studies measuring the isometric contractions, it is suggested using minimal pre-tension force before initiation of the contractility, as this is likely to impact both time-specified force and rate of force development. In vivo isometric mechanogram was conducted as previously described[14]. An incision was made at the midline of the sternum. Heart was isolated from the pericardial sac. A silk ligature was attached to the ventricular apex and connected to an isometric force transducer (MAY-FDT-10, COMMAT Co. Ankara, Turkey). Heart was allowed to equilibrate under 5 g resting tension and washed every 2 min with fresh Krebs solution containing (in mmol/L): 119 NaCl, 4.6 KCl, 1.2 $MgSO_4$, 7 H_2O, 1.5 $CaCl_2$, 2 H_2O, 1.2 KH_2PO_4, 15 $NaHCO_3$ and 11 glucose. A pre-tension force of 5 g was applied to standardize the contractions. Force transducer output was connected to BIOPAC MP36 (Biopac Systems, Inc., Camino Goleta, CA, USA). Data were saved and processed using AcqKnowledge software (Biopac Systems, Inc., Camino Goleta, CA, USA). Parameters determined from the isometric mechanogram were myocardial contractile forces, durations and frequencies.

Enzyme-linked immunosorbent assay (ELISA)

Serum samples were collected and centrifuged (4000 rpm, rt.) for 10 min. Concentrations of serum CK-MB and cTn-I were measured by ELISA in strict accordance with the manufacturer's instructions (Rat Tn-I ELISA kit, E-EL-R0055, Elabscience Biotechnology Co.,USA; Rat CK-MB ELISA kit, E-EL-R1327, Elabscience Biotechnology Co.,USA).

Statistical analysis

Data was defined as arithmetic mean and standard deviation. In order to apply parametric tests, Kolmogorov Smirnov test was used to determine whether the samples had normal distribution and whether the variances were homogeneous. For multiple groups, analysis of variance test with *post-hoc* Tukey's test for significance difference was used for normally distributed data. Kruskal Wallis test with Mann Whitney U test under Bonferroni correction was used for the analysis of none normally distributed data. The p values less than 0.05 were considered significant. The data was evaluated at the 95% confidence interval. SPSS 17.0 program was used for statistical analysis.

RESULTS

Tadalafil 1 mg/kg and 10 mg/kg on ECG

Parameters determined from ECG traces were; RR, QRS, PR, QT, Tp, Te intervals, dysrhythmia and heart beats/min. We compared these parameters in the pre-drug ECG with post-drug ECG. There were no significant differences regarding RR, QRS, PR, QT, Tp and Te intervals between the groups (Table 1). Although insignificant, we found that QT and heart rate per minute in treatment groups were shorter than Group 1, and RR in treatment groups were longer than Group 1. We observed ST depression in Group 3 and Group 4.

Table-1. Results of the electrocardiogram, isometric cardiac mechanogram and cardiac injury markers of serum samples (n=6 per group)

Variables	Group 1 (Control- salin 7 days)	Group 2 (Tadalafil 1 mg/kg 1 day)	Group 3 (Tadalafil 10 mg/kg 1 day)	Group 4 (Tadalafil 1 mg/kg 7 days)	Group 5 (Tadalafil 10 mg/kg 7 days)
RR interval (ms)	0.144±0,063	0.186±0.025	0.196±0.039	0.175±0.026	0.174±0.019
QRS interval (ms)	0.021±0.004	0.021±0.002	0.020±0.003	0.020±0.003	0.021±0.003
Heart rate (per/min)	350±45	336±33	317±51	350±59	360±38
PR interval (ms)	0.052±0.006	0.054±0.003	0.051±0.004	0.046±0.005	0.054±0.004
QT interval (ms)	0.106±0.002	0.104±0.007	0.100±0.007	0.099±0.010	0.105±0.011
TP interval (ms)	0.028±0.010	0.026±0.006	0.026±0.004	0.028±0.010	0.025±0.005
TE interval (ms)	0.048±0.010	0.050±0.015	0.055±0.010	0.050±0.011	0.057±0.009
Contraction durations (ms)	0.399±0.127	0.474±0.250	0.418±0.116	0.285±0.092	0.332±0.035
Contractile forces (g)	2.807±1.153	2.272±0.845	2.573±1.443	2.885±0.496	2.357±0.691
Contraction frequencies (Hz)	1.211±0.336	1.259±0.175	1.088±0.398	1.439±0.273	1.809±0.622
CKMB (pg/ml)	575.32±83.54	395.56±124.38*	377.81±79.61*	523.76±146.11	449.99±117.32
Troponin I (pg/ml)	293.56±210.14	260.94±123.84	246.24±64.18	557.37±262.40	316.60±161.76

* a significant decrease in serum CK-MB levels in Group 2 and 3, compared to Group 1 (p=0.019 and 0.002, respectively). CK-MB: cardiac creatine kinase

Tadalafil 1 mg/kg and 10 mg/kg on cardiac mechanogram

Myocardial contractile forces, durations and frequencies were measured on the isometric cardiac mechanogram after tadalafil treatments. Insignificant decreases were observed in myocardial ventricular contractile forces in treatment groups (Figure 1). As shown in Figure 2 and 3, the differences in contraction durations (Figure 2) or frequencies (Figure 3) were not statistically significant compared to the control (p>0.05).

Tadalafil 1 mg/kg and 10 mg/kg on serum cTn-I and CK-MB

We found a significant decrease in CK-MB in Group 2 and 3, compared to Group 1 (p=0.019 and 0.002, respectively). We found no significant difference in cTn-I levels in treatment groups, compared to Group 1 (Table 1).

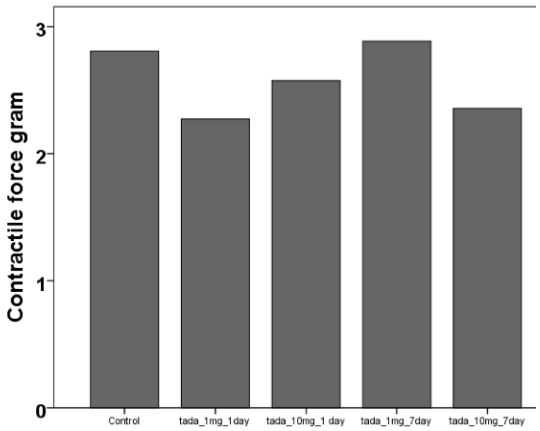

Figure 1. the differences in myocardial ventricular contractile forces among treatment groups were not statistically significant (n=6 per group, p>0.05).

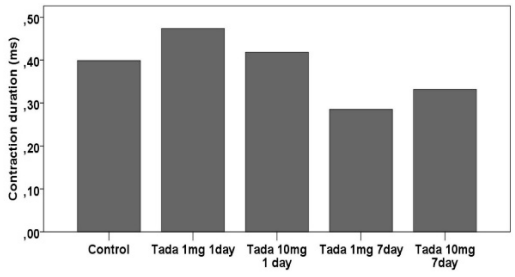

Figure 2. The differences in the contraction durations among treatment groups were not statistically significant (n=6 per group, p>0.05).

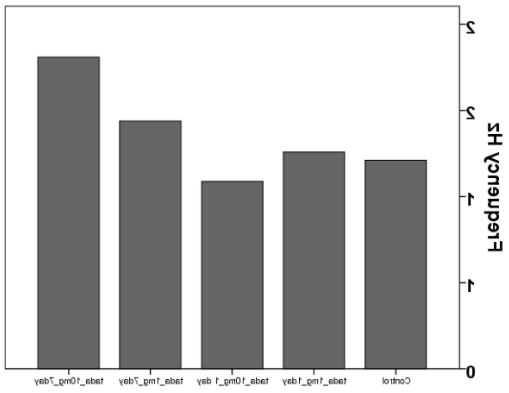

Figure 3. The differences in the contraction frequencies among treatment groups were not statistically significant (n=6 per group, p>0.05).

DISCUSSION

In this study, we hypothesized that treatment with tadalafil may benefit cardiac parameters. Our data demonstrated that PDE-5 inhibition by tadalafil 1 and 10 mg/kg revealed a significant decrease in CK-MB.

Cardiac CK-MB is one of the most important biomarkers postulating any cardiac tissue damage[15]. Osman et al. revealed elevation in the levels of serum CK-MB isoform and troponin-I in isoproterenol-induced arrhythmia group[16]. Cardiac troponins are also the reference diagnostic biomarkers for acute coronary syndromes due to their high accuracy and strong foresight in the prognosis of acute cardiac injury. Since serum levels of cTn-I increase in proportion to the area of injury and rise even before detecting cardiac histopathological changes, it has been considered highly sensitive biomarker in detecting earlier myocardial damage[17]. This was the reason we used both markers of cardiac toxicity in this study. We found that tadalafil reduced the release of CK-MB in serum compared to the control group. CK-MB levels were measured significantly lower due to its reduction in myocardial damage. In our study, we found its cardioprotective effectiveness in this aspect. This data reveals similar results to previous studies showing a decrease in lactate dehydrogenase and CK with acute administration of the PDE inhibitor sildenafil in a model of cardiac failure[18].

PDE-5 inhibition causes muscle relaxation by preventing the degradation of cGMP formed upon activation of sGS. It is known that NO has numerous modulatory actions in myocardium and vascular tissue. Experimental studies with NO synthase (NOS) inhibitors or NOS genetic deletion claimed that cardiovascular diseases were attributed to NO deficiency. The knockdown of cGMP in particular is important at regulation of cardiomyocytes. In animal studies, an increase in miyocardial PDE-5 levels was attributed to cardiac insufficiency[19]. In an experimental coronary artery ligation model, tadalafil treatment 1 mg/day for 4 weeks contributed to a 70% reduction in the area of ischemic injury. It provided benefit in cardiac hypertrophy and restoration of ejection fraction[20].

We have previously mentioned that PDE-5 inhibitors have protective roles against cardiac remodeling, cardiac damage and ventricular failure. On the other hand, there are multiple studies in which these cardioprotective effects cannot be clearly determined[21,22]. Consistently, our findings also provided that ameliorating effect of tadalafil in cardiac contraction durations or frequencies were not significant. We may consider the following assumptions: PDE-5 inhibitors act on the cardiovascular pathway via NO/cGMP/ PKG pathway most frequently. However, the cardiac beneficial actions of PDE-5 inhibitors are also evident through several other signaling pathways, including the oxidation, apoptosis, PI3K/Akt and ERK [23–25]. Hence, PDE-5 and related cGMP pathway may be associated with both endothelial and cardiomyocyte function. These assumptions may support the results of tadalafil not being observed to have a significant effect on cardiac contractile response in this study. Therefore, PDE5 inhibition probably did not alter myocardial contractile

function. Further studies are needed to confirm this hypothesis and determine whether tadalafil directly affects cardiomyocytes.

The traces in ECG initiating cardiotoxicity are known as the presence of pathological Q wave, the loose of R progression in precordial derivations, new left bundle branch block development, QRS widening and QT interval prolongation[26]. In our study, tadalafil treatment in all groups provided insignificant shortening of QT. We found that it does not show proarrhythmic activity on ECG because it acts via cGMP and NO and has no effect on ion channels responsible for cell conduction. Nagy et al. reported that oral administration of sildenafil to dogs reduces arrhythmia severity[27]. The differences in heart rates were not significant, although tadalafil promoted a slow heart rate and a prolongation in RR. Cardiac beneficial actions of tadalafil may depend on the dose and duration of the agent. Previous studies have reported that sildenafil, vardenafil and tadalafil provided significant cardioprotective effects in epinephrine-induced arrhythmia in rats, and that tadalafil was more beneficial than others in cardiac recovery. The underlying mechanism was PDE-5 inhibitors promoted a suppression in cardiac sympathetic action, reactive oxygen species inhibition, adiponectin expression, a decrease in LDH and CK, and suppression of apoptosis[28]. With our data, we cannot emphasize the positive therapeutic effects of tadalafil on electrical myocardial contraction. However, it is clear that it did not exert an obvious distruption on myocardial electrical contraction.

We have some limitations in this study. Since this is an experimental animal study, the number of animals in each group is smaller than the groups created in clinical studies. On the other hand, it is a positive situation that no animals died during the study. Herein, we could not evidence CK-MB downregulation by our histolopathological study that depicted amelioration of heart tissue damage and necrotic changes in the cardiac myocytes of tadalafil group. Another limitation is that treatment duration was relatively short. In future studies, we may plan to extend the period to three weeks with chronic applications.

In conclusion, multiple investigations have been performed to analyze the mechanism of PDE-5 inhibitors. It is noteworthy that tadalafil 1 and 10 mg/kg reduced serum CK-MB. Shortening in QT and decrease in heart rate may have important implications on myocardial functions. These findings give the impression that tadalafil does not worsen cardiac functions, instead it reduces myocardial damage and provides electrical stabilization, which may reduce major adverse cardiovascular events caused by malignant ventricular arrhythmia. In this respect, these results may guide new studies.

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