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The Dose-Dependent Effects of Duloxetine on the Mechanical Muscle Activities of Rat Diaphragms

Duloksetinin Sıçan Diyafram Kası Mekanik Aktiviteleri Üzerine Doz Bağımlı Etkileri

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ÖZET

Amaç: Duloksetin çok geniş bir hastalık yelpazesinde hastalara reçete edilen bir etken maddedir. Duloksetin içeren ilaçların prospektüsünde farklı kas dokuları üzerindeki birçok yan etkisinden bahsediliyor olsa da diyafram kası üzerindeki muhtemel etkileri hakkında kısıtlı bilgi bulunmaktadır. Diyafram ise solunum fonksiyonları için önemli role sahip bir iskelet kasıdır. Bu çalışmada farklı dozlardaki duloksetinin in vitro diyafram kası mekanik aktiviteleri üzerindeki olası etkileri incelendi. Ayrıca diyafram kasına ait bu aktivitelerdeki etkilenimler duloksetin reçete edilen hastaların solunum fonksiyonları açısından tartışıldı.

Gereçler ve Yöntem: 16 adet 24 haftalık erişkin Wistar-Albino sıçanlar rastgele seçimle duloksetin (DLXT) ve çözücü (VHC) olarak iki gruba ayrıldı. Her iki gruba ait sıçanlardan anestezi altında diyafram kasları izole edildi ve 5mL hacimli izole organ banyosuna aktarılan kas şeritleri 2g'lik ön gerime ayarlandı. DLXT grubuna ait sıçanlardan izole edilen diyafram kaslarına kümülatif olarak 1, 10, 20, 30, ve 40 µg/mL olacak şekilde duloksetin, VHC grubuna ise aynı hacimde çözücü uygulandı. Kas preparatlarının kasılması 0.5 Hz frekansta, 1 ms süreli kare uyaranlar kullanılarak oluşturulan elektrik alan stimülasyonu ile sağlandı.

Bulgular: Kasılma eğrilerinden kasılma kuvveti ($g.mg^{-1}$), kasılma süresi (s), gevşeme süresi (s), eğri altında kalan alan ($g.mg^{-1}.s$), $+dF/dt_{max}$ ($g.mg^{-1}.s^{-1}$) ve $-dF/dt_{max}$ ($g.mg^{-1}.s^{-1}$) verileri elde edildi. DLXT grubunda gevşeme süresi, eğri altında kalan alan, $+dF/dt_{max}$ ve $-dF/dt_{max}$ parametreleri 10 µg/mL duloksetin uygulaması ile VHC grubuna kıyasla anlamlı fark oluşturdu. 30 µg/mL duloksetin uygulamasında ise benzer bir farklılık kasılma kuvveti ve kasılma süresinde gözlendi.

Sonuç: Sonuç olarak, duloksetinin bu çalışmada ortaya çıkan diyafram kası kasılma parametreleri üzerindeki etkileri, solunum fonksiyonlarını olumsuz yönde etkileyebileceğini düşündürmektedir. Bu yüzden duloksetin reçete edilen hastalarda solunum fonksiyonlarının takip edilmesi önemli olacaktır.

Anahtar Kelimeler: Antidepresanlar, diyafram, duloksetin, izometrik kasılma, solunum

ABSTRACT

Aim: Duloxetine is an active ingredient prescribed to patients for a wide range of conditions. Although the information with purchased drugs containing duloxetine mention various side effects on different muscle tissues, there is limited research available on the potential effects on the skeletal muscle of the diaphragm, which plays an important role in respiratory functions. In this study, the potential effects of different doses of duloxetine on in vitro mechanical activities of the diaphragm muscle were examined. Additionally, the impact of these activities on the diaphragm muscle was discussed in terms of the respiratory functions of patients prescribed duloxetine.

Materials and Methods: Sixteen adult Wistar-Albino rats, each 24 weeks old, were randomly divided into two groups: duloxetine(DLXT) and vehicle(VHC). Diaphragm muscles were isolated from rats in both groups under anesthesia and transferred to a 5mL volume isolated organ bath, in which muscle strips were adjusted to a 2g preload. For DLXT group, the diaphragm muscles were cumulatively treated with duloxetine at concentrations of 1, 10, 20, 30, and 40 µg/mL, while VHC group received the same volume of the vehicle. Contractions were induced using square pulses of 0.5 Hz frequency and 1 ms duration.

Results: From the contraction curves, data was obtained on contraction force($g.mg^{-1}$), contraction time(s), relaxation time(s), under area curve($g.mg^{-1}.s$), $+dF/dt_{max}$($g.mg^{-1}.s^{-1}$), and $-dF/dt_{max}$($g.mg^{-1}.s^{-1}$). In DLXT group, relaxation time, area under the curve, $+dF/dt_{max}$, and $-dF/dt_{max}$ parameters showed significant differences compared to the VHC group with the application of 10 µg/mL duloxetine. Similar difference was observed in contraction force and contraction time with the application of 30 µg/mL duloxetine.

Conclusions: The effects of duloxetine on diaphragm muscle contraction parameters observed in this study suggest that duloxetine may adversely affect respiratory functions. It is therefore important that the respiratory functions in patients prescribed duloxetine be closely monitored.

Keywords: Antidepressants, diaphragm, duloxetine, isometric contraction, respiratory

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INTRODUCTION

Duloxetine is a selective serotonin-norepinephrine reuptake inhibitor (SNRI) used to treat urinary incontinence, diabetic neuropathic pain, depression, and anxiety (1). The side effects on muscles listed in the information commercially supplied with duloxetine include muscle pain, cramps, stiffness, and trismus (2). The diaphragm, a skeletal muscle, has been the main instrument of many studies because it plays an important role in respiration. When the diaphragm contracts, the thoracic volume increases and pleural pressure decreases, thus facilitating the flow of air into the lungs while breathing (3).

Respiratory dysfunctions are often caused by respiratory conditions such as asthma and chronic obstructive pulmonary disease. However, they can also occur in patients without any known respiratory system disorders (4). Although limited information is available about the relationship between psychological conditions and respiratory symptoms, some studies have suggested that psychological symptoms may be associated with a higher risk of developing asthma (5). Additionally, psychological stress that accompanies respiratory disorders can exacerbate respiratory problems, making treatment for depression essential for healthy breathing in these individuals (6). Respiratory disorders, a metabolic disease that affects the entire body and is reported in diabetes, are considered an important comorbidity that can affect the course of Type 2 diabetes (7).

Consequently, duloxetine is currently prescribed to patients who may experience secondary respiratory problems. The aim of this study is to investigate whether duloxetine has a detrimental effect on the mechanical activities of the diaphragm muscle in rats, thus impacting respiratory functions. The study was conducted in vitro by applying different concentrations of duloxetine to an isolated diaphragm muscle in an organ bath.

MATERIALS AND METHODS

Animals and Groups

Experiments were performed upon 16 adult (24 weeks old) Wistar-Albino rats with body weights ranging from 250 to 320 grams. The rats, who had unrestricted access to food and water, were housed in conditions which were exposed to 12 hours of light and then 12 hours of darkness. The subjects were randomly divided into two groups, one being labeled as the vehicle (VHC; n=8), and the other as the duloxetine (DLXT; n=8) group. Diaphragm muscles from both groups were isolated, transferred to an organ bath, and the effects of duloxetine on contraction parameters were examined. Duloxetine was dissolved in a vehicle consisting of 10% ethanol (32221, Honeywell International Inc., Germany) and 90% saline (23414134, OSEL Drug A.Ş., Türkiye). The procedures employed in this study were approved on February 08, 2024 (Approval number 2024-07) by the Local Ethics Committee for Animal Experiments at Necmettin Erbakan University, Experimental Medical Application and Research Center.

Isolation of Diaphragm Muscle and Transfer to the Organ Bath

Since isolated fresh diaphragm muscle was required in the study, rats were dissected by cervical dislocation under anesthesia (80 mg/kg ketamine and 10 mg/kg xylazine). The diaphragm muscle was accessed through thoracotomy and the preparation was isolated. The excised diaphragm tissue was placed in a modified Krebs solution (in mM: 15 $NaHCO_3$, 5 KCl, 1 $MgCl_2$, 135 NaCl, 2 $CaCl_2$, 1 Na_2HPO_4, 11 glucose at pH 7.4, gassed with a mixture of 95% O_2 and 5% CO_2), and muscle strips of dimensions 20x5 mm were obtained (8). The muscle strips were tied together with 4-0 silk thread and placed in a 5 ml isolated organ bath. The costal side of the strips was attached to a force transducer (MAY FDT 05, Commat Ltd., Ankara, Türkiye) and the other side was connected to a micromanipulator. The muscle preparations, adjusted to a pre-load of 2g, were subjected to a 30-minute rest period, during which the Krebs solution was refreshed every 10 minutes. During this time, the muscle was stimulated using a (BSLSTM100, BIOPAC Systems Inc., USA) custom-designed electric field electrode stimulator, which delivered 1 ms duration square pulses at a frequency of 0.5 Hz. The stimulation voltage started at 5 Volts and was gradually increased to determine the supramaximal stimulus voltage (9).

In Vitro Drug Application

The stock solution was prepared by adding the vehicle to 120 mg of duloxetine to attain a total volume of 10 mL. In the DLXT group, cumulative doses of duloxetine were applied in the isolated organ bath at concentrations of 1, 10, 20, 30, and 40 µg/mL in order to determine the potential effects of the vehicle on the results in the DLXT group. The procedures applied are schematically summarized in Figure 1.

Data Obtained from Isometric Contraction Recordings

The following parameters were determined from the contraction traces: Contraction force ($g.mg^{-1}$), contraction time (s), relaxation time (s), area under the curve ($g.mg^{-1}.s$), maximum rate of force development ($+dF/dt_{max}$; $g.mg^{-1}.s^{-1}$), and maximum rate of force decline ($-dF/dt_{max}$; $g.mg^{-1}.s^{-1}$). Contraction force, area under the curve, $+dF/dt_{max}$, and $-dF/dt_{max}$ data were normalized by dividing the weight of the muscle in mg. The data for each application in all subjects was

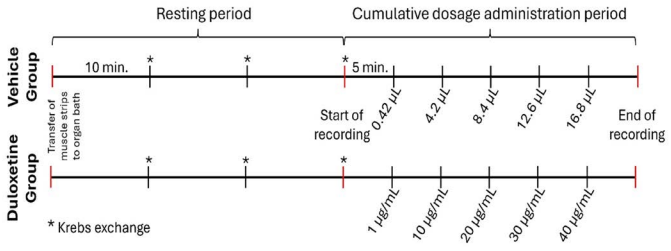

Figure 1. Procedures applied to the experimental groups.

determined by calculating the average of 10 different values (10).

Statistical Analyses

All data was presented as mean ± standard deviation (SD) and normal data distribution was tested with Kolmogorov-Smirnov. In order to analyze the effects of different doses applied to the same group, one-way ANOVA, followed by the Tukey post-hoc test was used, and a nonparametric t-test was used to determine the significance between the VHC and DLXT groups. $p<0.05$ was considered statistically significant.

RESULTS

In this study, which investigated the potential adverse effects of duloxetine prescribed to patient groups at risk of secondary respiratory problems on the mechanical activities of the diaphragm muscle, concentration-dependent results were obtained. The initial preloads set to 2g were reassessed after a rest period and were found to be 1.66±0.29g in the VHC group and 1.62±0.26g in the DLXT group. No statistically significant difference was found between the preloads of the groups ($p=0.9613$, non-parametric t-test). While no difference was found in contraction forces between the groups before the administration of duloxetine and vehicle, cumulatively applied duloxetine showed a dose-dependent inhibition effect (Figure 2).

In the VHC group, no statistically significant difference was determined in contraction force, contraction time, relaxation time, and the area under the curve data, compared to the previous measurements at different doses. In the DLXT group, a 30 µg/ml duloxetine concentration produced a statistically significant inhibitory effect on contraction force and contraction time data compared to the VHC group. This inhibitory effect was observed at a 10 µg/ml duloxetine concentration for relaxation time and the area under the curve data (Figure 3).

In the DLXT group, compared to previous measurements, the maximum value of force changes during contraction and relaxation decreased at a 10 µg/ml dose of duloxetine. When

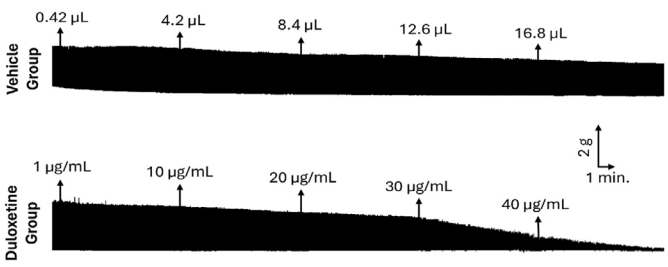

Figure 2. An example of contraction records obtained from cumulative dose administration.

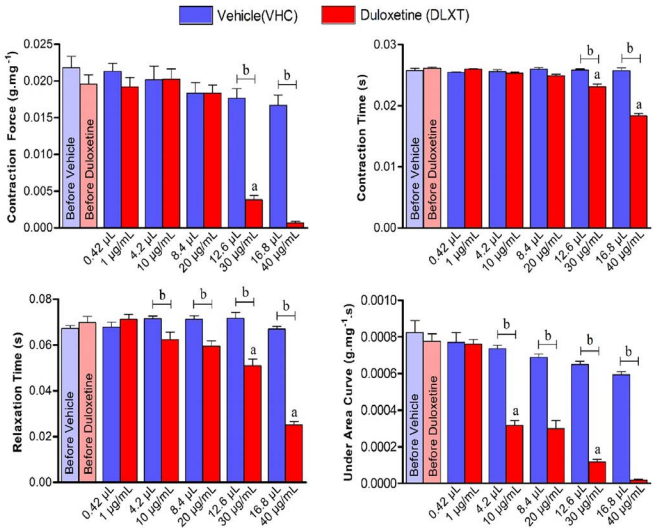

Figure 3. Data obtained from contraction curves at five different doses and control contractions before dose administration, including contraction force, contraction time, relaxation time, and area under the curve. The data is presented as mean ± standard deviation (SD). The letter 'a' indicates the significance of an ANOVA test with $p<0.05$ between consecutive measurements within the same group, while 'b', indicates the significance of a nonparametric t-test with $p<0.05$ between the two groups for measurements at the same dose.

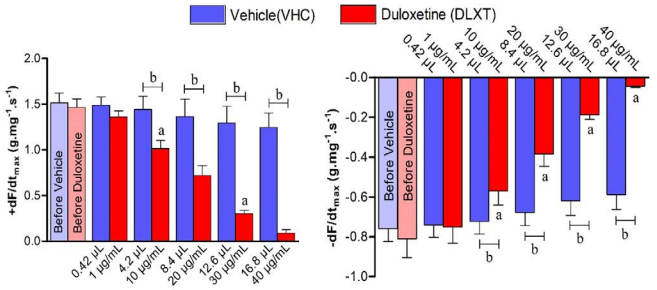

Figure 4. Data obtained from contraction curves at five different doses and control contractions before dose administration, including $+dF/dt_{max}$, $-dF/dt_{max}$. The data is presented as mean ± standard deviation (SD). The letter 'a' indicates the significance of an ANOVA test with $p<0.05$ between consecutive measurements within the same group, while 'b' indicates the significance of a nonparametric t-test with $p<0.05$ between the two groups for measurements at the same dose.

comparing the DLXT and VHC groups, the $+dF/dt_{max}$ and $-dF/dt_{max}$ values decreased at the same dose (Figure 4).

DISCUSSION

Serotonin and norepinephrine are two of the brain's primary neurotransmitters. As duloxetine, through its function as an SNRI, is an inhibitor of the reuptake of these neurotransmitters, thus increasing their availability in the brain, duloxetine is widely used in the treatment of many conditions, including anxiety, obsessive-compulsive disorder, depression, urinary incontinence, and diabetic neuropathic pain, due to its ability to regulate synaptic transmission between brain cells (11,12). While the side effects of duloxetine on muscles are frequently mentioned in the research; the effects of the drug on the diaphragm muscle are not widely elucidated. Although the use of the drug is generally considered safe with tolerable side effects, reports have indicated toxic effects and rarely reported cases of death due to overdose (13,14).

There is the potential for patients who have been prescribed duloxetine to experience respiratory difficulties as a secondary condition due to their existing illnesses. The diaphragm is a skeletal muscle that plays a crucial role in respiration by contracting to reduce pleural pressure and thus facilitate breathing (10). Therefore, duloxetine has the potential to both impair diaphragm muscle function through an exacerbation of existing respiratory problems, or to actually be a direct cause of respiratory issues.

There are a number of studies which suggest that significant side effects can occur in patients treated with different doses of duloxetine in clinical applications. While Müller et al. reported that approximately 70% of patients who were treated for depression with duloxetine experienced a reduction of symptoms, they also experienced low cardiovascular levels and sexual dysfunction (15). Polychroniou et al. stated that about 50% of patients discontinued the medication due to side effects (16). Thase et al. found a significant decrease in PR and QRS intervals in the electrocardiogram data of patients receiving 120 mg/day duloxetine (17). In a case report by Eyal and Yaeger, attention was drawn to a newborn mother who had been taking 90 mg/day of duloxetine, and who exhibited weak crying, low muscle tone, respiratory distress, and a low Apgar score at birth (18). Finsterer and Habitzl describe a patient who used duloxetine and aripiprazole and experienced progressive generalized weakness, myalgia, and muscle stiffness, which lead to difficulties in walking and moving (2). Sahan and Parlakkaya Yıldız published a case report indicating that duloxetine (30 mg/day) prescribed to a 45-year-old patient who complained of headaches, anxiety, and fear resulted in hyponatremia after one week of use (19). In a study conducted by Wang et al., (20) it was found that duloxetine blocks voltage-dependent Na^+ channels, and this blocking property was associated with the drug's analgesic effect.

In a rat's diaphragm muscle, an increase in Na+ permeability depolarizes the membrane, resulting in the release of Ca^{++} from the sarcoplasmic reticulum and a subsequent trigger of a series of biochemical events that lead to muscle contraction (21). Possible disturbances in Na^+ homeostasis affect action potential kinetics, which in turn impact contraction performance (22). It is believed that the mechanical activity disorders observed in our findings may be due to the adverse effects of duloxetine on ionic activities.

Since this study was conducted only on adult female rats, possible age and sex-dependent differences could not be elucidated. Additionally, as a fundamental research study, the effects of duloxetine on respiratory functions were investigated solely through the mechanical activity of the diaphragm muscle. The finding of this study should therefore be supported by future studies that examine underlying molecular and ionic mechanisms.

CONCLUSION

In conclusion, the adverse effects of duloxetine on diaphragm muscle contraction parameters revealed in this study suggest that the drug may negatively impact respiratory functions. It is therefore recommended that care should be taken to monitor the respiratory functions of patients who are prescribed duloxetine.

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