Original Research Article

EFFECTS OF TERAZOSIN, SILODOSIN AND ALFUZOSIN ON DEPRESSION AND ANXIETY IN MICE

.

ABSTRACT

Aims: Benign prostatic hyperplasia (BPH) is common urological disease, is characterized by lower urinary tract syndrome, usually associated with sexual dysfunctions. The aim of present study is to investigate the effects of terazosin, silodosin and alfuzosin which are the main treatment options for BPH on depression and anxiety to understand whether these drugs may be effective in BPH caused mood disorders.

Study design: All the drugs were given intraperitoneally (i.p.) in a volume of 0.1 ml per 10 g body weight of mice. Drugs were given 30 min before the experiment. We investigated the effects of terazosin, silodosin and alfuzosin on depression and anxiety, in mice.

Place and Duration of Study: Sample: Department of Pharmacology and Department of Urology, Sakarya University, Animal Research Center, between June 2019 and September 2020.

Methodology: Here, we examined the effects of terazosin (0.5, 1, 2 mg/kg), silodosin silodosin (1, 3, 10 mg/kg) and alfuzosin (3, 6 and 9 mg/kg) on depression and anxiety by using forced swimming test and elevated plus maze test, respectively, in mice (n:96). Additionally, the locomotor activity was evaluated by open field test.

Results: All doses of terazosin, alfuzosin and silodosin significantly increased immobility time, compared to saline group. Silodosin and alfuzosin prolonged the time spent in open arms but terazosin decreased the time spent in open arms compared to saline group. Terazosin, silodosin (1 and 3 mg/kg) and alfuzosin (3 and 6 mg/kg) did not have any effect on the number of entries into the open arms while silodosin (10 mg/kg) and alfuzosin (9 mg/kg) increased the number of entries into open arms.

Conclusion: We found that silodosin and alfuzosin had antidepressant and anxiolytic-like effects, while terazosin had depressant and anxiogenic effects. Patients with BPH who need antidepressant and anxiolytic treatment can be treated with a single drug instead of multiple medications.

Keywords: Terazosin; silodosin; alfuzosin; depression; anxiety; mice

1. INTRODUCTION

Benign prostatic hyperplasia (BPH) is the most common progressive urological disease affecting more than 40% of men over 60 years of age (1). BPH is a disease that causes an increase in prostate volume, a decrease in maximum urine flow rate and the development of acute urinary retention (2). The proportion of men treated for BPH as a result of aging is increasing day by day. In adult men, BPH is characterized by lower urinary tract syndrome (LUTS), usually associated with sexual dysfunctions such as erectile dysfunction and decreased libido (3,4,5). Previous studies have shown that; lower urinary system syndrome and sexual dysfunction include similar pathological mechanisms (6). There is a link between androgens, estrogens, growth factors and neurotransmitters in BPH. The increase in prostate volume in BPH is due to enlargement of both the prostate glandular epithelium and the fibromuscular stroma (7,8). It is a hormone- and age-related disease characterized by histological changes in the prostate gland and enlargement of the prostate, called benign enlargement of the prostate (9). It has negative effects on the quality of life of patients by causing an increase in urinary urgency, nocturia and daytime urinary frequency (10,11,12). One of the main treatment options for patients with BPH is alpha 1 adrenergic receptor antagonists, which act by reducing prostate and bladder smooth muscle tone (13).
BPH is the most important cause of LUTS, which is characterized by nocturnal urination, difficulty urinating, and incomplete evacuation in elderly men (14). In addition, many studies have found that the clinical picture of LUTS/BPH is strongly associated with psychiatric disorders such as depression, anxiety, and susceptibility to stress (15,16-23). Also, in a large cohort study (14) have demonstrated the relationship between LUTS/BPH and depression.

Lower urinary tract symptoms (LUTS) secondary to benign prostatic hyperplasia (BPH) are one of the most common disorders in elderly males, and alpha1-blockers are now viewed as first-line agents for the management of LUTS caused by BPH. Alpha1-blockers originally were believed to work by blocking alpha adrenergic receptors found in the prostate and its capsule, and thereby relaxing stromal smooth muscle (24).

Use of medicines in an unapproved indication, age group, dose or administration route is defined as off-label drug use. Although there are negative aspects of off-label drug use, there are various positive aspects. Off label drug use provides new opportunities for existing approved drugs, and reduces the time and cost involved in drug discovery with respect to traditional drug development method. The aim of present study is to investigate the effects of terazosin, silodosin and alfuzosin on depression and anxiety to understand whether these drugs may be effective in BPH caused mood disorders.

2. METHODOLOGY

2.1 Animals

Ninety-six male inbred BALB/c ByJ mice (Animal Research Center, Sakarya-Turkey) aged 7 weeks upon arrival to the laboratory were used in this study. Since female animals mostly don't be used in behavioral tests because they have menstrual cycle which may cause wrong positive or negative results. We used male animals similar to our previous studies (Tanyeri et al. 2013a, 2013b). Animals (4–5 per cage) were kept in the laboratory at 21 ± 1.5 ◦C with 60% relative humidity under a 12 h light/dark cycle (light on at 8.00 p.m.). Tap water and food pellets were available ad libitum. All authors hereby declare that "Principles of laboratory animal care" (NIH publication No. 85-23, revised 1985) were followed, as well as specific national laws where applicable. All experiments have been examined and approved by the appropriate ethics committee. Ethical approval was granted by the Sakarya University Ethics Committee (04.04.2018, Number = 13, Sakarya/Turkey).

2.2. Drugs

Terazosin, Silodosin, Alfuzosin, Imipramine hydrochloride and diazepam were purchased from Sigma Chemicals (St Louis, Mo, USA). Drugs were dissolved in saline. Saline was used as the vehicle controls. All the drugs were given intraperitoneally (i.p.) in a volume of 0.1 ml per 10 g body weight of mice. The doses were chosen based on previous behavioral studies (Sawada et al. 2013, Ulak et al. 2010). Drugs were prepared freshly on the day of experiment.

2.3. Experimental Design

We investigated the effects of terazosin, silodosin and alfuzosin on depression and anxiety by using forced swimming test and elevated plus maze test, respectively, in mice. Additionally, the locomotor activity was evaluated by measuring the total distance traveled in the open field test.

2.1.1 Forced swimming test (FST)

FST was performed which was described by Porsolt et al. (1977, 1978). Briefly, the mice were dropped individually into plexiglas cylinders (height 25 cm, diameter 10 cm) containing 10 cm of water maintained at 23-25°C and left there for 6 min. The duration of immobility (in seconds) was recorded during the last 4 min of the 6-min testing period. The absence of hind leg movement was recorded as immobility by stopwatch cumulation by a single observer who was aware of the treatments during the exposures.

Eighty-eight male inbred BALB/c ByJ mice were used in the Forced Swimming Test. Mice were randomly divided into experimental groups (n=8 mice): saline, imipramine 30 mg/kg (Imip), terazosin 0.5, 1, 2 mg/kg, silodosin 1, 3 and 10 mg/kg and alfuzosin 3, 6 and 9 mg/kg, respectively. All experiments were performed between 10.00 and 12:00 a.m. All drugs or saline were given 30 min before the experiment.

2.3.2 Elevated Plus-Maze (EPM) Test

Anxiety-related behavior was measured by the EPM test. The experiments were conducted in a dimly lit, semi-soundproof room, illuminated with table lamp (80 lux). Maze was made of wood and consisted of two open (29 cm long × 5 cm wide) and closed arms (29 cm × 5 cm with 15 cm high walls) forming a square cross with a 5 cm square center piece. In order to avoid falls the open arms was surrounded by a short (1 cm) plexiglass edge. The maze was elevated 40 cm above the floor. The open arms and central platform were painted white and enclosed arms were painted black.

Each mouse was placed at the center of the maze facing one of the open arms and allowed to explore the maze. During a 5-min test period, the number of entries into both open and enclosed arms of the maze (defined as the entry of all four limbs into the arms) and the time spent in the open arms was recorded. The observer was present always in the same position towards to the open arms and behind the animals. The open arm activity was evaluated as the following: 1) time spent in the open arms relative to the total time spent in the plus-maze (300 s), expressed as a percentage; 2) number of entries into the open arms relative to the total number of entries into both the open and closed arms, expressed as a percentage. These values were used as indices of anxiety in mice. Any animal that fell off the maze was excluded from the experiment.

Elevated plus-maze is one of the tests used to evaluate anxiety in animals. In the normal cases, the animals prefer to stay within the closed arms instead of open arms owing to feel safer. Drugs with anxiolytic properties increase the time spent on the open arm. As the values for both measured parameters changed in the same direction compared to control values (i.e., if both the time spent in the open arms and the number of open arm entries was increased or if both were decreased) and the change in one of the parameters was statistically significant, then an effect on anxiety was considered to have occurred. The time spent in the open arms and the numbers of open arm entries were always observed to change in the same direction.

Eighty-eight male inbred BALB/c ByJ mice were used in the study. Mice were randomly divided into experimental groups in EPM: saline, diazepam 2 mg/kg (Dzm), terazosin 0.5, 1, 2 mg/kg, silodosin 1, 3 and 10 mg/kg and alfuzosin 3, 6 and 9 mg/kg, respectively. Each experimental group consisted of 8 mice. All experiments were performed between 10.00 and 12:00 a.m. All drugs or saline were given 30 min before the experiment.

2.3.3 Open field test

Since compounds altering motor activity may give false positive/negative effects in FST, elevated plus maze test, passive avoidance test and morris water maze test, spontaneous locomotor activity of mice was evaluated by monitoring the activity of the animals in an open field. The animals were placed in the center of the apparatus and behaviors were recorded for a period of 5 min using the Ethovision-XT video tracking system. The locomotor activity was evaluated by measuring the total distance traveled in the apparatus and the speed of the animals.

2.3. Statistics

All data were expressed as mean ± standard error of mean (SEM). Statistical analysis was performed using GraphPad Prism 6.0® software (GraphPad Software, Inc., San Diego, CA). Groups of data were compared with one-way and two-way analysis of variance (ANOVA) and Tukey post-hoc test. Values were considered significantly different at $p < 0.05$.

3. RESULTS

3.1. Forced Swimming Test

One-way ANOVA showed a significant effect of terazosin, silodosin, alfuzosin and imipramine treatment upon immobility time in FST [$F(87,10) = 36,84$, $p<0.0001$]. Post-hoc comparisons revealed that imipramine and all doses of silodosin 1, 3 and 10 mg/kg and alfuzosin 3, 6 and 9 mg/kg significantly reduced immobility time, compared to saline group ($p<0,01$; $p<0,01$; $p<0.001$; $p<0,01$; $p<0.001$; $p<0.001$, respectively, Fig. 1). Additionally, there was a significant difference between imipramine and saline group ($p<0.001$, Fig 1). On the other hand, all doses of terazosin 0.5, 1 and 2 mg/kg significantly increased immobility time, compared to saline group ($p<0,05$; $p<0,01$; $p<0,01$, respectively, Fig. 1).

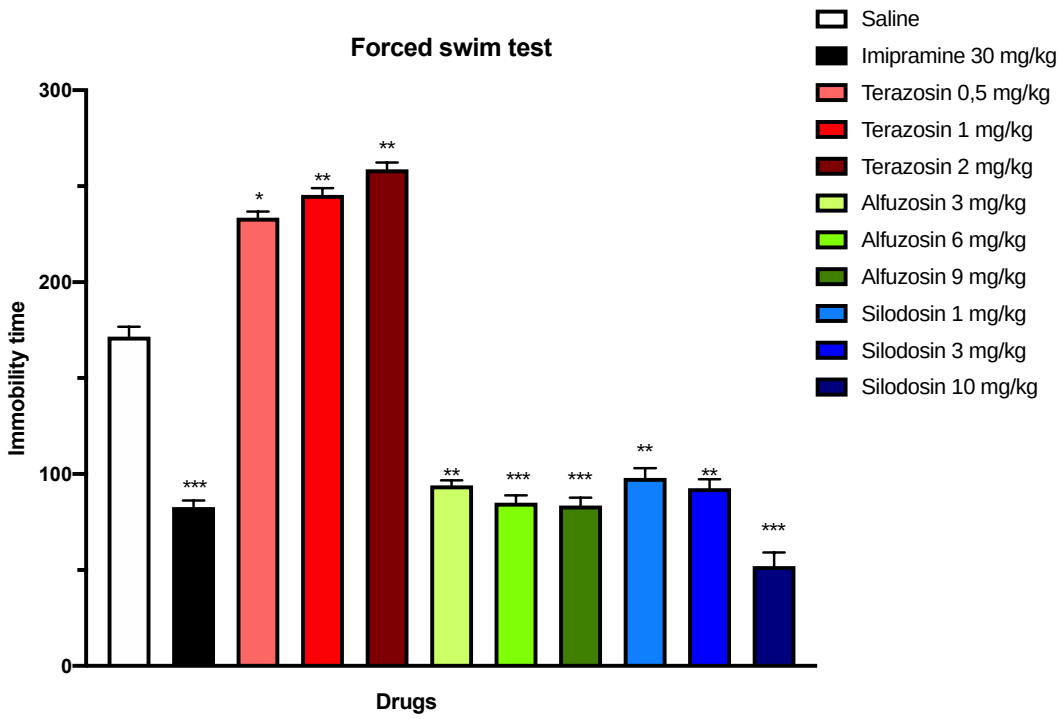

Fig. 1. Immobility time (in seconds) in the forced swim test (n=8)

****: p<0.001 compared to Saline group, by ANOVA (Tukey test), **: p<0.01 compared to Saline group, by ANOVA (Tukey test), *: p<0.05 compared to Saline group, by ANOVA (Tukey test)*
Mean ± S.E.M = Mean values ± Standard error of means

3.1 Elevated Plus Maze Test

One-way ANOVA showed a significant effect of drug treatment upon the time spent staying in open arms in EPM test [F (87,10) =37,57, p<0.0001; Fig. 2a]. Post-hoc comparisons revealed that diazepam (2 mg/kg) significantly increased the time spent in open arms compared to saline group (p<0.001) and silodosin (1, 3 and 10 mg/kg) and alfuzosin (3, 6 and 9 mg/kg) prolonged the time spent in open arms (p< 0.001) (Fig 2a). But on the other hand, terazosin decreased the time spent in open arms compared to saline group (p<0.05).

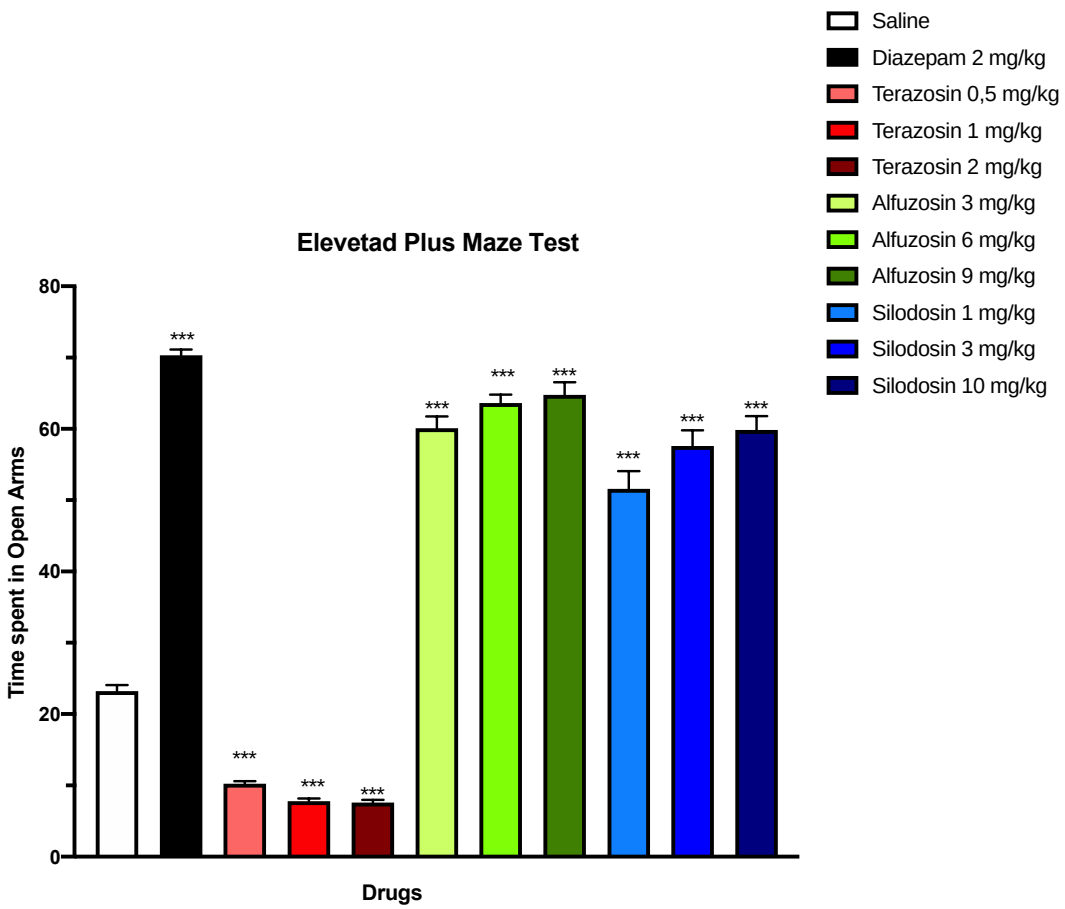

Fig. 2a. Percentage of time spent in the open arms (2a) in elevated plus-maze test. (n=8)

****: p<0.001 compared to Saline group, by ANOVA (Tukey test), **: p<0.01 compared to Saline group, by ANOVA (Tukey test), *: p<0.05 compared to Saline group, by ANOVA (Tukey test)*
Mean ± S.E.M = Mean values ± Standard error of means

One-way ANOVA displayed an important effect of drug treatment upon the number of entries to the open arms in EPM test [F(87,10)=10,759, p<0.0001; Fig. 2b]. Post-hoc comparisons revealed that diazepam (2 mg/kg) significantly increased the number of entries to the open arms compared to saline group (p<0.001). Terazosin (0,5, 1 and 2 mg/kg), silodosin (1 and 3 mg/kg) and alfuzosin (3 and 6 mg/kg) did not have any effect on the number of entries into the open arms while silodosin (10 mg/kg) and alfuzosin (9 mg/kg) increased the number of entries into the open arms (p< 0.01 and p< 0.05, respectively) (Fig 2b).

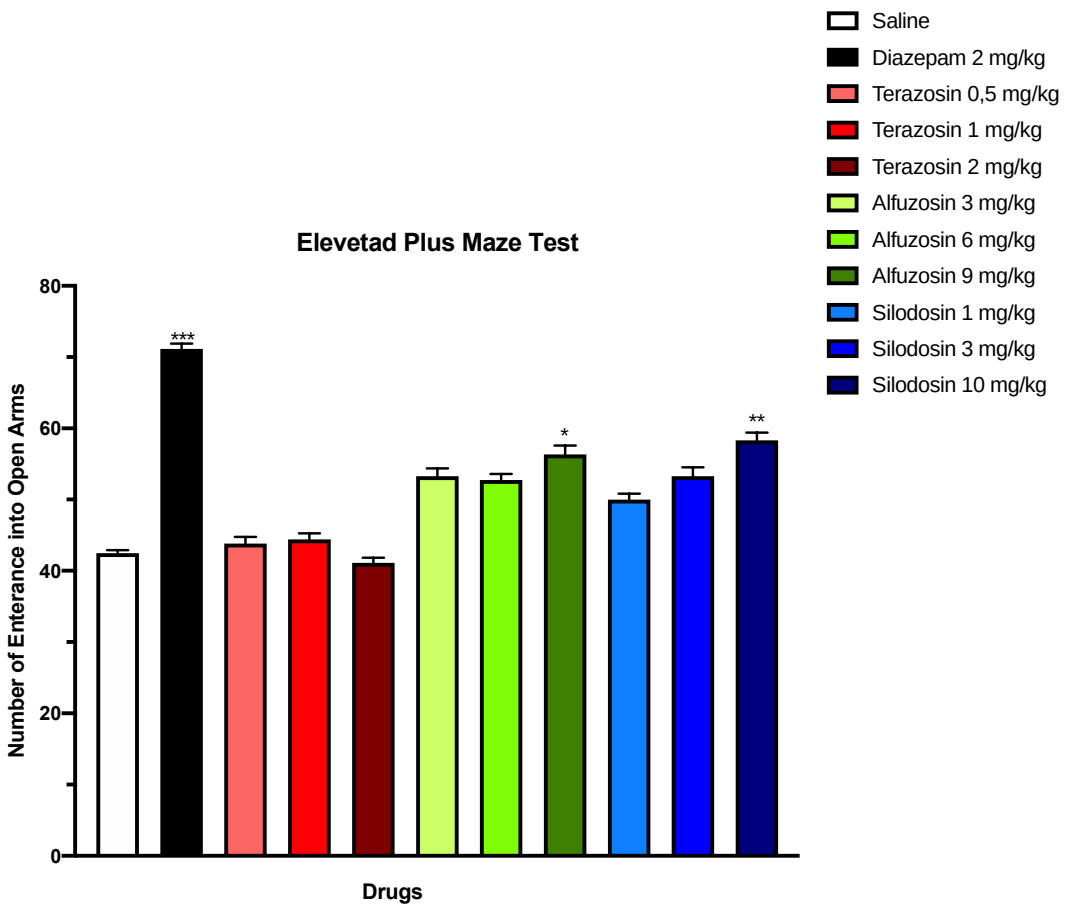

Fig. 2b. Percentage of number of entries into open arms (2b) in elevated plus-maze test. (n=8)

****: p<0.001 compared to Saline group, by ANOVA (Tukey test), **: p<0.01 compared to Saline group, by ANOVA (Tukey test), *: p<0.05 compared to Saline group, by ANOVA (Tukey test)*
Mean ± S.E.M = Mean values ± Standard error of means

3.3. Effects of drugs on locomotor activity in the open field test

It is well known that the effects of drugs on depression and anxiety can be also evoked by drugs which induce hyperactivity or hypoactivity (Maj et al. 1992). Thus, the influence of all the above treatments on the locomotor activity was concurrently evaluated. None of drugs modified the total distance traveled [F(95,11)=0,55; Fig. 3] in the open field test.

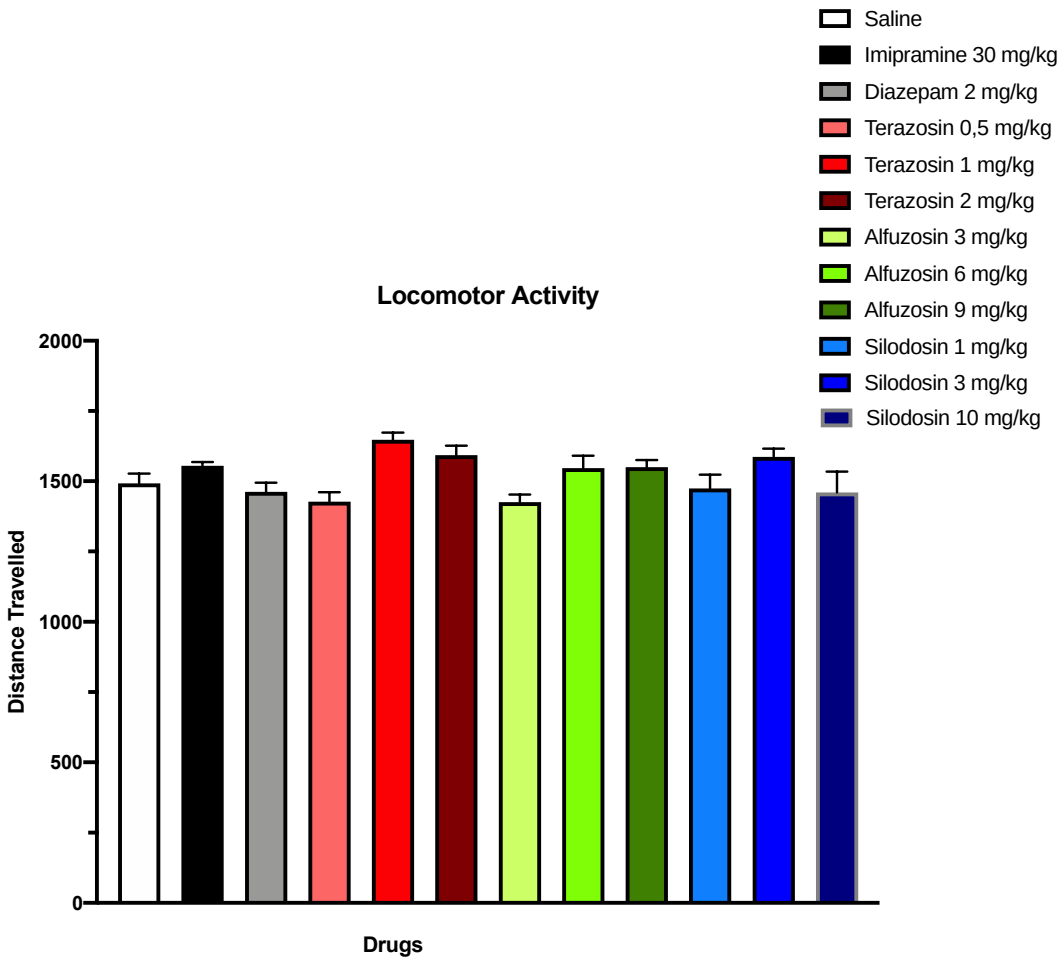

Fig. 3. Effect of drugs on total distance traveled in locomotor activity test. (n=8)

3. DISCUSSION

BPH is a common problem in the aging man. In patients with BPH, lower urinary system symptoms (LUTS) such as frequent urination, sudden urination, inability to empty urine, and urinary incontinence are observed. Apart from the stress caused by the whole daily life, patients with BPH live with the fear of frequent toilet calls, inability to urinate and sometimes even incontinence due to LUTS. In addition to all this stress, they wake up at night with the feeling of urine and their sleep is interrupted.

There are many studies of depression in patients with BPH. In these patients, besides the problems related to the cause of BPH, it is possible that the number of nocturia is a confounding factor in depression. As the number of nocturia increases, the night's sleep will be frequently interrupted, which can affect depression. In a study, men and women with LUTS were evaluated with the urinary-specific quality of life form related to LUTS, and they reported the lowest quality of life and high anxiety and depression. In the anxiety assessment, 35.9% of the men and 53.3% of the women were found to be compatible with anxiety, and in the depression assessment, it was found to be compatible with depression in

29.8% of the men and 37.6% of the women. When men and women are evaluated separately; In both groups, storage symptoms and bladder fullness were significantly associated with anxiety and depression, but not with voiding symptoms (32).

Important triggers of anxiety in women are nocturia, urgency, stress urinary incontinence, urinary incontinence during sexual intercourse; In men, nocturia, urgency, incomplete urination and bladder pain were detected. Depression triggers in women as low urinary pressure, urgency, stress incontinence; frequency and incomplete urination were found in men. For depression, weak discharge, urgency, and stress urinary incontinence were significant for women, and perceived frequency and incomplete ejaculation were significant for men (32).

Alpha 1 receptors are G protein-coupled receptors commonly found in the central nervous system and peripheral nervous system. They show different effects depending on their location (behavioral, autonomic, and endocrine). The role of α1 blockers in depression is controversial. In a previous study, they stated that amitriptyline, desimipramine and fluoxetine are down-regulated the α1A receptor subtype and this effect contributed to its antidepressant effect (33). There have been articles stating that α1 antagonists, prazosin and benoxathian, may have antidepressant-like effects in FST and TST (tail suspension test) (34, 35, 36). In addition, there is an article stating that prazosin alone is depressing, but when used with imipramine, it increases the antidepressant effect of imipramine (37). Also, contrary to these, there are also articles stating that it can increase depression in those taking electroconvulsive therapy or antidepressant therapy. (38,39,40,41).

Various models of depression are used to evaluate the effects of drugs on depression. The FST is a rapid, low-cost, and simple behavioral test that is widely used to determine whether drugs have an antidepressant effect. The FST is based on the measurement of inactivity time. The duration of immobility is measured after administration of drugs. Duration of immobility is significantly shorter in antidepressant drug given group compared to the control. In our study, imipramine, and all doses silodosin 1, 3 and 10 mg/kg and alfuzosin 3, 6 and 9 mg/kg significantly reduced immobility time, compared to saline group. But at all used doses of terazosin increased immobility time, compared to saline group.

In the elevated plus maze test, which is one of the tests used to assess anxiety in animals, animals normally prefer to stay in closed arms instead of open arms to feel more secure. However, drugs with anxiolytic properties increase the time spent in the open arm. Results of our study revealed that diazepam (2 mg/kg) and silodosin (1, 3 and 10 mg/kg) and alfuzosin (3, 6 and 9 mg/kg) prolonged the time spent in open arms, but on the other hand terazosin decreased the time spent in open arms compared to saline group.

Diazepam (2 mg/kg) significantly increased the number of entries into open arms compared to saline group. Terazosin (0,5, 1 and 2 mg/kg), silodosin (1 and 3 mg/kg) and alfuzosin (3 and 6 mg/kg) did not have any effect on the number of entries into the open arms while silodosin (10 mg/kg) and alfuzosin (9 mg/kg) increased the number of entries into open arms.

It is a known fact, some compounds altering motor activity may lead to false positive or negative effects in behavioral tests. For this reason, in the present study, we used the locomotor activity test to determine the impact of the investigated compound on locomotion. None of drugs affected locomotor activity of mice in the open field test.

We found that silodosin and alfuzosin have antidepressant and anxiolytic-like effects, while terazosin has depressant and anxiety-like effects. In this regard, studies reporting that

receptor subtypes may have different effects even in the same receptor types and that prazosin potentiates the antidepressant effect support our study.

4. CONCLUSION

In conclusion, in our study, we found that silodosin and alfuzosin had antidepressant and anxiolytic-like effects, while terazosin had depressant and anxiogenic effects. We think that this effect is probably related to alpha 1 receptor subtypes. Further studies on the effects of receptor subtypes are needed to find out why three alpha 1 blockers do not show the same effect. Also, patients with BPH who need antidepressant and anxiolytic treatment can be treated with a single drug instead of multiple medications. All these findings will open new horizons to develop drugs for BPH with depression and anxiety in the future.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

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