RESEARCH ARTICLE / *Araştırma Makalesi*

The Effects of Oxybutynin on Learning and Memory Functions in Passive Avoidance and Morris Water Maze Tests in Mice

Oksibutininin Farelerde Pasif Sakınma ve Morris Su Tankı Testlerinde Öğrenme ve Bellek İşlevleri Üzerine Etkileri

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Abstract

Objective	Overactive bladder (OAB) constitutes the majority of childhood incontinence causes. Oxybutynin is an antimuscarinic agent frequently used for children in the treatment of OAB. This study aimed to investigate the effects of an antimuscarinic drug oxybutynin on learning and memory.
Materials and Methods	We assessed the effects of oxybutynin on learning and memory functions using the Passive Avoidance (PA) and the Morris Water Maze (MWM) Test in mice. Forty nine male inbred BALB/c ByJ mice were randomly divided into experimental groups; saline; scopolamine 0,6 mg/kg, oxybutynine 1 mg/kg, oxybutynine 2 mg/kg, oxybutynine 4 mg/kg and scopolamine 0,6 mg/kg+ oxybutynine 4 mg/kg. Each experimental group consisted of 8-9 mice in tests.
Results	Oxybutynin treatment (1 mg/kg, 2 mg/kg, and 4 mg/kg) did not show a significant difference in the retention time on the second day compared to the control and oxybutynin (4 mg/kg) significantly prolonged the retention time in scopolamine-treated mice. In the MWM Test, oxybutynin (1 mg/kg, 2 mg/kg, and 4 mg/kg) has no effect on the time spent in the target quadrant. Scopolamine (0.6 mg/kg) alone significantly reduced time spent in the target quadrant, but oxybutynin (4 mg/kg) significantly prolonged time spent in the target quadrant in scopolamine-treated mice. Also, scopolamine significantly increased the mean distance to the escape platform, while oxybutynin (4 mg/kg) significantly decreased the mean distance to the escape platform in scopolamine-treated mice.
Conclusion	In our study, oxybutynin did not affect learning and memory, but it plays a role ameliorating the learning and memory deficits. The results of this study show that the use of oxybutynin in patients with OAB does not affect learning and memory.

Keywords oxybutynin; scopolamine; learning; memory; mice

Öz

Amaç	*Aşırı aktif mesane (AAM) çocukluk çağı inkontinans nedenlerinin çoğunluğunu oluşturmaktadır. Oksibutinin, AAM tedavisinde çocuklarda sıklıkla kullanılan antimuskarinik bir maddedir. Çalışmamızın amacı antimuskarinik ilaçlardan biri olan oksibutininin öğrenme ve bellek üzerine etkilerinin araştırılmasıdır.*
Gereç ve Yöntemle	*Farelerde Pasif Sakınma (PA) Testi ve Morris Su Tankı (MWM) Testini kullanarak oksibutinin'in öğrenme ve hafıza üzerindeki etkilerini değerlendirdik. 49 erkek BALB/c ByJ fareler rastgele deney gruplarına ayrıldı; salin; skopolamin 0,6 mg/kg, oksibutinin 1 mg/kg, oksibutinin 2 mg/kg, oksibutinin 4 mg/kg and skopolamin 0,6 mg/kg+ oksibutinin 4 mg/kg. Deney grupları 8-9 fareden oluşuyordu.*
Bulgular	*Oksibutinin tedavisinin (1 mg/kg, 2 mg/kg ve 4 mg/kg) kontrole göre ikinci gün tutma süresinde önemli bir farklılık göstermezken, skopolamin uygulanmış farelerde oksibutinin (4 mg/kg) retansiyon süresini önemli ölçüde uzatmıştır. MWM Testinde, oksibutinin (1 mg/kg, 2 mg/kg ve 4 mg/kg) hedef kadranda geçirilen süre üzerinde hiçbir etkisi yoktur. Skopolamin (0,6 mg/kg) tek başına hedef kadranda harcanan süreyi önemli ölçüde azalttı, ancak oksibutinin (4 mg/kg), skopolamin ile tedavi edilen farelerde hedef kadranda geçirilen süreyi önemli ölçüde uzattı. Ayrıca, skopolamin, kaçış platformuna olan ortalama mesafeyi önemli ölçüde artırırken, oksibutinin (4 mg/kg), skopolamin ile tedavi edilen farelerde kaçış platformuna olan ortalama mesafeyi önemli ölçüde azalttı.*
Sonuç	*Çalışmamızda oksibutinin öğrenme ve belleği etkilemezken, bozulmuş öğrenme ve bellek üzerine olumlu etkileri olduğu görülmüştür. Bu çalışmanın sonuçları AAM'li hastalarda oksibutinin kullanımının öğrenme ve hafızayı etkilemediğini göstermektedir.*

Anahtar Kelimeler *oksibutinin; skopolamin; öğrenme; bellek; fare*

INTRODUCTION

The International Continence Society defines overactive bladder as the presence of "urinary urgency, usually accompanied by frequency and nocturia, with or without urgency urinary incontinence, in the absence of urinary tract infections or other obvious pathology." The overactive bladder symptoms are urgency, frequency, nocturia, and urgency incontinence.[1] The ICS defines urinary frequency as the patient complaint of urinating too often during the daytime. Nocturia is one or more voids per night, preceded and followed by sleep. Urgency is sudden, compelling desire to pass urine that is difficult to defer. Urgency incontinence is the involuntary leakage of urine accompanied or immediately preceded by urgency.[2]

OAB occurs due to abnormal contractions of the bladder detrusor muscle caused by the stimulation of specific muscarinic receptors. Therefore, antimuscarinic agents such as oxybutynin, tolterodine, trospium, solifenacin, and darifenacin have long been used in the pharmacological treatment of OAB that they cause a decrease in urinary frequency and an increase in bladder capacity.[3]

Since contraction of the detrusor muscle and bladder emptying are primarily mediated by stimulation of muscarinic receptors by acetylcholine that anticholinergic agents such as oxybutynin and tolterodine are recommended as first-line therapy for overactive bladder.[4]

Oxybutynin is a relatively nonselective antimuscarinic agent which has been used for the management of OAB for over 30 years.[5,6] Oxybutynin is highly metabolized by CYP3A4, which is predominantly found in the intestinal wall and liver. N-desethyl oxybutynin (DEO), one of the metabolites of oxybutynin, is thought to be related to the anticholinergic side effects of oxybutynin. Anticholinergic side effects of orally administered OXY, primarily dry mouth, may limit its efficacy.[7] Oxybutynin has been commonly associated with adverse effects such as dry mouth, constipation, headache, dyspepsia, and dry eyes.[8,9]

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 methods. The passive avoidance and morris water maze tests are useful for the evaluation of cognitive performance (learning and memory).[10]

Therefore, the goal of this study was to evaluate the effect of nonselective antimuscarinic agent oxybutinine administration on learning and memory in the passive avoidance and moris water maze tests.

MATERIALS and METHODS

Animals

Forty nine male inbred BALB/c ByJ mice (Animal Research Center, Sakarya-Turkey) aged 7 weeks upon arrival to the laboratory were used in this study. Animals (4–5 per cage) were kept in the laboratory at 21 ± 1.5 ^{0}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 procedures involving animals were in compliance with the European Community Council Directive of 24 November 1986, and ethical approval was granted by the Sakarya University Ethics Committee (04.04.2018, Number = 12, Sakarya/Turkey).

Drugs

Oxybutynine and scopolamine were purchased from Sigma Chemicals (St Louis, Mo, USA). Drugs were dissolved in saline. Saline was used as the vehicle controls. Drugs were given intraperitoneally (i.p.) in a volume of 0.1 ml per 10 g body weight of mice. The doses are; saline; scopolamine 0,6 mg/kg, oxybutynine 1 mg/kg, oxybutynine 2 mg/kg, oxybutynine 4 mg/kg and scopolamine 0,6 mg/kg+ oxybutynine 4 mg/kg. The doses were chosen based on previous behavioural studies.[11,12] Drugs were prepared freshly

on the day of experiment. All drugs or saline were given 30 min before the experiment. Scopolamine has frequently been used in cognition models to induce impairment and identify the potential of test compounds to reverse these impairments. Because of this, we used scopolamine.

Experimental Design

In our randomised controlled experimental study; we investigated the effects of oxybutynine on learning and memory by using passive avoidance and morris water maze in mice. Additionally, the locomotor activity was evaluated by measuring the total distance moved in the open field test.

1. Passive Avoidance (PA) test

Animals were trained in a one-trial, step-through PA apparatus to evaluate memory based on contextual fear conditioning and instrumental learning. A decrease in retention latency indicates an impairment in memory in the PA task. The apparatus consisted of a box with an illuminated part (L 7 × 12.5 × h 14 cm) and a dark part (L 24 × 12.5 × h 14 cm), both equipped with a grid floor composed of steel bars (0.3 cm diameter) spaced 0.9 cm apart. The inhibitory avoidance task consisted of two trials. On the first day of training, the mice were individually placed into the light compartment and allowed to explore the boxes. The intercompartment door was opened after a 10 second acclimation period. In the acquisition trial, each mouse was placed in the illuminated compartment, which was lit by a bright bulb (2000 lux). If the mouse stepped into the dark compartment (2/3 of the tail in the dark compartment), the door was closed by the experimenter, and an inescapable foot shock (0.3 mA/1 second) was delivered through the grid floor of the dark compartment. A cut-off time of five minutes was selected. The time taken to enter the dark compartment (training latency) was recorded. Immediately after the shock, the mouse was returned to the home cage. The retention trial started 24 hours after the end of the acquisition trial. The animals received drugs prior to retention training. Each mouse was placed in the illuminated compartment as in the training trial. The door was opened after a 10 second acclimation period. The step-through latency in the retention trial (with a maximum 300 seconds cut-off time) was used as the index of retention of the learned experience. A shock was not applied during the retention trial.

Forty nine male inbred BALB/c ByJ mice were used in the study. Mice were randomly divided into experimental groups in PA test: saline; scopolamine 0,6 mg/kg, oxybutynine 1 mg/kg, oxybutynine 2 mg/kg, oxybutynine 4 mg/kg and scopolamine 0,6 mg/kg+ oxybutynine 4 mg/kg. Each experimental group consisted of 8-9 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. Morris Water Maze (MWM) test

The MWM comprised a circular pool (90 cm diameter) filled with water (22°C) and rendered opaque by addition of small black balls. The pool was located in a dimly lit, soundproof test room with various visual cues, including a white/ black colored poster on the wall, a halogen lamp, a camera, and the experimenter. The maze was divided into four quadrants, and three equally spaced points served as starting positions around the edge of the pool. The order of the release positions was varied systematically throughout the experiment. A circular escape platform (6 cm diameter and 12 cm high) was located in one quadrant 1 cm above the water surface during the familiarization session and 1 cm below the water surface during the other sessions. Video tracking was conducted with a video camera focused on the full diameter of the pool. Navigation parameters were analyzed using the Ethovision 8.5 video analysis system (Noldus Ethovision XT). Mice were trained in MWM five times per day (familiarization session, S1, S2, S3, and S4). One familiarization and four acquisition sessions were carried out using the MWM. During the familiarization session and acquisition phase of experiment, each mouse underwent three trials. The delay between trials was 60 seconds, and a 1-day interval was used between each sessi-

on. For each trial, the mouse was removed from the home cage and placed in the water maze at one of three randomly determined locations with its head facing the center of the water maze. After the mouse had found and climbed onto the platform, the trial was terminated and the escape latency was recorded. If the mouse did not climb onto the platform in 60 seconds, the trial was terminated, and experimenter guided the mouse to the platform; an escape latency of 60 seconds was recorded. Twenty-four hours after the final acquisition session, a "probe trial" was used to assess the spatial memory retention of the location of the hidden platform. During this trial, the platform was removed from the maze and the mouse was allowed to search the pool for 60 seconds. The percent of time spent in each quadrant was recorded.

Forty nine male inbred BALB/c ByJ mice were used in the study. Mice were randomly divided into experimental groups in MWM test: saline; scopolamine 0,6 mg/kg, oxybutynine 1 mg/kg, oxybutynine 2 mg/kg, oxybutynine 4 mg/kg and scopolamine 0,6 mg/kg+ oxybutynine 4 mg/kg. Experimental group consisted of 8 mice except saline group (n=9). All experiments were performed between 10.00 and 12:00 a.m. All drugs or saline were given 30 min before the MWM test.

3. Open field test

Since compounds altering motor activity may give false positive/negative effects in 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 moved in the apparatus and the speed of the animals.

Statistical Analysis

Data were expressed as mean± S.E.M. (Standart Hata Ortalaması) The statistical analysis was performed using one-way or two-way analysis of The statistical analysis (InStat Statistical Software Program) was performed using one-way or two-way analysis of variance (ANOVA) followed by Tukey's post hoc test. $P<0.05$ was considered as statistically significant.

RESULTS

1. Passive Avoidance Test

There was no significant difference in first day latency among the groups. The second day latency (retention latency) significantly differed between the groups [$F(47,5)=19,938$ $p<0.0001$ (Figure. 1). Scopolamine significantly shortened the second day latency compared to the saline group ($p<0.001$). While oxybutynin (1 mg/kg, 2 mg/kg, and 4 mg/kg) did not show a significant difference in the retention time on the second day compared to the control, oxybutynin (4 mg/kg) significantly prolonged the retention time in scopolamine-treated mice ($p<0.001$).

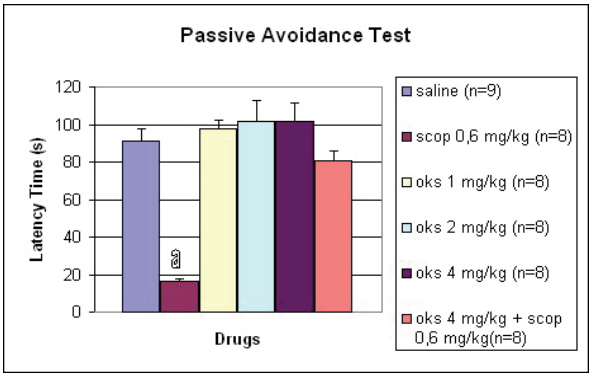

Figure 1: The latency of mice during the passive avoidance test (PAT). Data are presented as mean ± standard error of the mean (SEM). a: $p < 0.001$, compared to the saline group by ANOVA (Tukey test).

Oks; oxybutynin, scop; scopolamine. (n=8).

Table 1: The latency of mice during the passive avoidance test (PAT). Data are presented as mean ± standard error of the mean (SEM). a: p < 0.001, compared to the saline group by ANOVA (Tukey test).

Drugs	Latency (s) Mean ± S.E.M	No of mice	p
Saline	91.15±6.47	9	
Scop 0.6 mg/kg	16.45±1.39	8	p<0.001 (saline & scop)
Oks 1 mg/kg	97.47±5.1	8	p>0.05 (saline & oks 1)
Oks 2 mg/kg	101.83±11.10	8	p>0.05 (saline & oks 2)
Oks 4 mg/kg	101.58±10.01	8	p>0.05 (saline & oks 4)
Scop 0.6 +oks 4 mg/kg	80.53±5.59	8	p>0.05 (saline & scop+oks 4)
(Oks; oxybutynin, Scop; scopolamine, Mean ± S.E.M; Mean values ± Standard Error of Means, No; number)			

2. Morris Water Maze Test

There was a significant difference between drug groups or their combination [Two-way ANOVA post-hoc Tukey test; (F (48,5) =14,574; p<0.0001; Figure 2] in the time spent in the target quadrant during the probe trial of the MWM test when oxybutynine groups were evaluated. Oxybutynin (1 mg/kg, 2 mg/kg, and 4 mg/kg) has no effect on the time spent in the target quadrant. Scopolamine (0.6 mg/kg) alone significantly reduced time spent in the target quadrant, but oxybutynin (4 mg/kg) significantly prolonged time spent in the target quadrant in scopolamine-treated mice, compared to scopolamine group(p<0.0001).

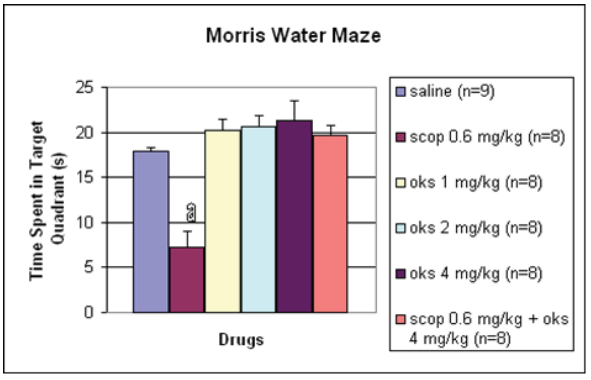

Figure 2: The time spent in target quadrant during the probe trial in Morris Water Maze test. Data are presented as mean ± standard error of the mean (SEM). a: p < 0.001, compared to the saline group by ANOVA (Tukey test).
Oks; oxybutynin, scop; scopolamine. (n=8).

Table 1: The time spent in target quadrant during the probe trial in Morris Water Maze test. Data are presented as mean ± standard error of the mean (SEM). a: p < 0.001, compared to the saline group by ANOVA (Tukey test).

Drugs	Time spent in target quadrant (s) Mean ± S.E.M	No of mice	p
Saline	17.88±0.45	9	
Scop 0.6 mg/kg	20.25±1.19	8	p<0.001 (saline & scop)
Oks 1 mg/kg	7.25±1.72	8	p>0.05 (saline & oks 1)
Oks 2 mg/kg	20.62±1.28	8	p>0.05 (saline & oks 2)
Oks 4 mg/kg	21.37±2.10	8	p>0.05 (saline & oks 4)
Scop 0.6 +oks 4 mg/kg	19.62±1.08	8	p>0.05 (saline & scop+oks 4)
(Oks; oxybutynin, Scop; scopolamine, Mean ± S.E.M; Mean values ± Standard Error of Means, No; number)			

There was a significant difference between drug groups or their combination [Two-way ANOVA post-hoc Tukey's test; F(48,5)=3,994; p=0,0046; Figure 3] in the mean distance to the escape platform in the probe trial of the MWM test when oxybutynine groups were evaluated. There was no significant effect of oxybutynin (1 mg/kg, 2 mg/kg, and 4 mg/kg) on the mean distance to the escape platform in naïve mice. Scopolamine significantly increased the mean distance to the escape platform, while oxybutynin (4 mg/kg) significantly decreased the mean distance to the escape platform in scopolamine-treated mice, compared to scopolamine group (p<0.05).

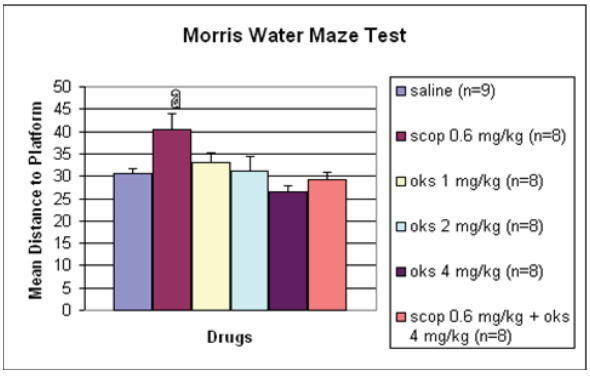

Figure 3: The mean distance of platform in Morris Water Maze test. Data are presented as mean ± standard error of the mean (SEM). a: p < 0.001, compared to the saline group by ANOVA (Tukey test).
Oks; oxybutynin, scop; scopolamine. (n=8).

Table 3: The mean distance of platform in Morris Water Maze test. Data are presented as mean ± standard error of the mean (SEM). a: p < 0.001, compared to the saline group by ANOVA (Tukey test).

Drugs	Mean distance to platform (cm) Mean ± S.E.M	No of mice	p
Saline	30.58±1.16	9	
Scop 0.6 mg/kg	40.57±3.42	8	p<0.001 (saline & scop)
Oks 1 mg/kg	32.96±2.32	8	p>0.05 (saline & oks 1)
Oks 2 mg/kg	31.1±3.37	8	p>0.05 (saline & oks 2)
Oks 4 mg/kg	26.53±1.44	8	p>0.05 (saline & oks 4)
Scop 0.6 +oks 4 mg/kg	29.1±1.77	8	p>0.05 (saline & scop+oks 4)
(Oks; oxybutynin, Scop; scopolamine, Mean ± S.E.M; Mean values ± Standard Error of Means, No; number)			

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

It is well known that the effects of drugs on learning and memory can be also evoked by drugs which induce hyperactivity or hypoactivity.13 Thus, the influence of all the above treatments on the locomotor activity was concurrently evaluated. Neither oxybutynine (1, 2 and 4 mg/kg) nor scopolamine modified the total distance moved [F(47,5)=2,117; Figure 4] in the open field test.

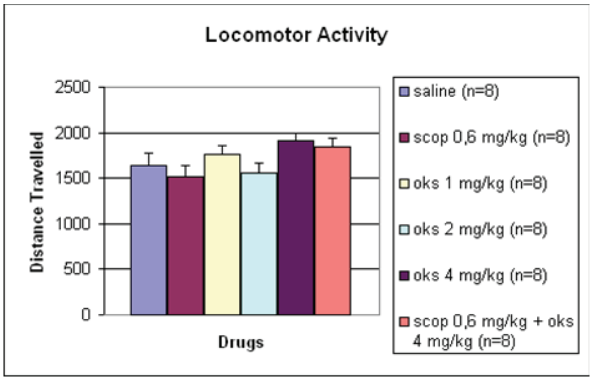

Figure 4: Effect of drugs on total distance traveled in locomotor activity test. Data are presented as mean ± standard error of the mean (SEM).
Oks; oxybutynin, scop; scopolamine. (n=8).

DISCUSSION

The motor nerve supply to the bladder is via the parasympathetic nervous system, which affects detrusor muscle contraction. This is mediated by acetylcholine acting on muscarinic receptors (M1, M2 and M3) subtypes at the level of the bladder activity. OAB occurs due to abnormal contractions of the bladder detrusor muscle caused by the stimulation of specific muscarinic receptors by acetylcholine. The rationale for using anticholinergic drugs in the treatment of overactive bladder syndrome is to block the parasympathetic acetylcholine pathway and thus abolish or reduce the intensity of detrusor muscle contraction.14,15,16,17

The passive avoidance test is useful for the evaluation of cognitive performance (learning and memory) and is based on the natural tendency of rodents. Rodents inherently tend to be in the dark environment. The animals avoid moving from the illuminated to the dark compartment of apparatus as they learn that they will be exposed to electric shocks in the dark section. There is a positive correlation between cognitive performance and the latency to moving from the illuminated compartment, the better the memory

Table 3: Effect of drugs on total distance traveled in locomotor activity test. Data are presented as mean ± standard error of the mean (SEM).

Drugs	Distance travelled (cm) Mean ± S.E.M	No of mice	p
Saline	1634.37±141.12	8	
Scop 0.6 mg/kg	1521.52±111.42	8	p>0.05 (saline & scop)
Oks 1 mg/kg	1760.62±95.49	8	p>0.05 (saline & oks 1)
Oks 2 mg/kg	1550.87±115.43	8	p>0.05 (saline & oks 2)
Oks 4 mg/kg	1908.53±92.44	8	p>0.05 (saline & oks 4)
Scop 0.6 +oks 4 mg/kg	1846.25±92.91	8	p>0.05 (saline & scop+oks 4)
(Oks; oxybutynin, Scop; scopolamine, Mean ± S.E.M; Mean values ± Standard Error of Means, No; number)			

performance the longer the the latency. The Morris water maze is one of the most widely used behavioral test to examine the effects of drugs on spatial memory and learning which is related to hippocampus and long-term potentiation.[18] In this test, animals are expected to solve the maze needed to escape from water.

Some experimental models related to impairing cognitive functions have been developed. These models are widely used to reveal the effects of drugs that have therapeutic potential to treat cognitive disorders. Scopolamine or dizocilpine has frequently been used in cognition models to induce impairment and identify the potential of test compounds to reverse these impairments. In the present study, Scopolamine impaired cognitive functions. As in previous studies, scopolamine has caused a decrease in latency time in passive avoidance test; in other words, it has impaired cognitive functions. However, oxybutynin (1 mg/kg, 2 mg/kg, and 4 mg/kg) did not show a significant difference in the retention time on the second day compared to the control, but Oxybutynin (4 mg/kg) significantly prolonged the retention time in scopolamine-treated mice. As a result, oxybutynin ameliorated cognitive functions impaired by scopolamine, but did not cause improvement in rats with cognitive functions.

It has been shown in previous studies that NMDA receptor antagonists MK-801 and phencyclidine impair acquisition learning and reference memory in the MWM test.[19,20] Also, scopolamine also impaires learning and reference memory in the MWM test.[21] Oxybutynin (1 mg/kg, 2 mg/kg, and 4 mg/kg) has no effect on the time spent in the target quadrant. Scopolamine (0.6 mg/kg) alone significantly reduced time spent in the target quadrant, but oxybutynin (4 mg/kg) significantly prolonged time spent in the target quadrant in scopolamine-treated mice. And also there was no significant effect of oxybutynin (1 mg/kg, 2 mg/kg, and 4 mg/kg) on the mean distance to the escape platform in naïve mice. Scopolamine significantly increased the mean distance to the escape platform, while oxybutynin (4 mg/kg) significantly decreased the mean distance to the escape platform in scopolamine-treated mice.

Overall, the data presented in this article suggest that oxybutynin had no effect on learning and memory, also reversed the learning and memory impaired with scopolamine. Further preclinical and clinical studies with oxybutynin should be done to support all these hypothesis and these findings will open new horizons to develop drugs for OAB in the future.

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Conflicts of Interest

None declared.

Declaration of Contribution:

Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; MHT, MEB

Drafting the work or revising it critically for important intellectual content; MHT, MEB, PT

Final approval of the version to be published; MHT, MEB, PT, AÖ, RKK, ŞNBB

Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved; OM

Ethical approval:

Ethical approval was granted by the Sakarya University Ethics Committee (04.04.2018, Number = 12, Sakarya/Turkey).

References

1. *Tomaszewski J. Postmenopausal overactive bladder. Prz Menopauzalny 2014;13(6):313-329.*
2. *Corsos J, Przydacz M, Campeau L, Witten J, Hickling D, Honeine C, et. al. CUA Guideline on adult overactive bladder 2017;11:E142–E173.*
3. *Lam S, Hilas O. Pharmacologic management of overactive bladder. Clinical Interventions in Aging 2007;2:337–345.*
4. *Yoshimura N, Chancellor MB. Current and future pharmacological treatment for overactive bladder. J Urol 2002;168:1897–1913.*
5. *Product Information, 2004a. Ditropan XL®, oxybutynin chloride extendedrelease tablets. Ortho-McNeil Pharmaceutical, Inc., New Jersey, USA.*
6. *Staskin DR, MacDiarmid SA. Pharmacologic management of overactive bladder: practical options for the primary care physician. Am J Med 2006;119:24S–8S.*
7. *Zobrist RH, Schmid B, Feick A. Pharmacokinetics of the Rand S-enantiomers of oxybutynin and N-desethyloxybutynin following oral and transdermal administration of the racemate in healthy volunteers. Pharm Res 2001;18:1029–1034.*
8. *Abramowicz M, et al. Detrol LA and Ditropan XL for overactive bladder. Med Letter 2001;43:28–29.*
9. *Abramowicz M, et al. Oxybutynin transdermal (Oxytrol) for overactive bladder. Med Letter 2003;45:38–39.*
10. *Mutlu O, Akar F, Celikyurt I, Tanyeri P, Ulak G, Erden F. 7-NI and ODQ disturbs memory in the elevated plus maze, morris water maze, and radial arm maze tests in mice. Drug Target Insights 2015;9:1–8.*
11. *Sawada H, Oeda T, Yamamoto K, Umemura A, Tomita S, Hayashi R et al. Trigger medications and patient-related risk factors for Parkinson disease psychosis requiring anti-psychotic drugs: a retrospective cohort study. BMC Neurology 2013;13:145.*
12. *Ulak G, Mutlu O, Tanyeri P, Komsuoglu FI, Akar F, Erden F. Involvement of serotonin receptor subtypes in the antidepressant-like effect of trim in the rat forced swimming test. Pharmacology Biochemistry & Behavior 2010;95:308-314.*
13. *Maj J, Rogóz Z, Skuza G, Sowińska H. The effect of antidepressant drugs on the locomotor hyperactivity induced by MK-801, a non-competitive NMDA receptor antagonist. Neuropharmacology. 1992;31:685-691.*
14. *Madhuvrata P, Cody JD, Ellis G, Herbison GP, Hay-Smith EJ, et al. Which anticholinergic drug for overactive bladder symptoms in adults. Cochrane Database Syst Rev 2012;1:CD005429.*
15. *Robinson D, Cardozo L, Milsom I, Pons ME, Kirby M, Koelbl H, et al. Oestrogens and overactive bladder. Neurourol Urodyn 2014;33:1086-1091.*
16. *Robinson D, Toozs-Hobson P and Cardozo L. The effect of hormones on the lower urinary tract. Menopause Int 2013;19:155-162.*
17. *Oefelein MG. Safety and tolerability profiles of the anticholinergic agents used for the treatment of overactive bladder. Drug Saf 2011;34:733-754.*
18. *Vorhees CV & Williams MT. Morris water maze: procedures for assessing spatial and related forms of learning and memory. Nat Protoc 2006;1:848–858.*
19. *Tanyeri P, Buyukokuroglu ME, Mutlu O, Ulak G, Akar FY, Celikyurt IK, et. al. Effects of ziprasidone, SCH23390 and SB277011 on spatialmemory in the Morris water maze test in naive and MK-801 treated mice. Pharmacol Biochem Behav 2015;138:142–147.*
20. *Zain MA, Rouhollahi E, Pandy V, Mani V, Majeed AA, Wong WF, et. al. Phencyclidine dose optimisation for induction of spatial learning and memory deficits related to schizophrenia in C57BL/6 mice. Exp Anim 2018;67:421–429.*
21. *Nigam A, Kulshreshtha M, Panjwani D. Pharmacological evaluation of Hibiscus abelmoschus against scopolamine-induced amnesia and cognitive impairment in mice. Adv Hum Biol 2019;9:116-123.*