

The Effects of Some Alpha-1 Adrenergic Antagonists on Trigone Smooth Muscle of Rat Bladder

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Abstract: This study was performed for investigating of the effects of tamsulosine and doxazosine *in vitro* on trigone smooth muscle of rat bladder. Fifty rats which were 250-300 gr were used for this study. One strip shape trigone preparat was prepared for each of the isolated bladder. At first, 1 gram of stretch was applied to tissues and after waiting for training to media. Next, determination of the level of electrical stimulation which created submaximal contraction after training time and this stimulation was performed with adding different concentrations of phenylephrine. At the end of this process, effective dosage was found, for trigone was determined by applying different concentrations of phenylephrine (10-8 M, 10-7 M, 10-6 M, 10-5 M) respectively. Firstly 10-9 M dosage of doxazosine was added as a adrenergic receptor antagonists which tamsulosine (10-8M, 10-7M, 10-6M, 10-5M) and doxazosine (10-9M, 10-8M, 10-7M, 10-6M) and waited for 20 minute. Then, effective dosage of phenylephrine (10-5 M) was added to the solution and waited for 7 minute, again. After this process, electrical stimulation was applied for contraction of the tissue. After stimulation, tissue was washing once for every two minute twice and by resting, tissue was waited until it got its starting stretching value. Same processes were performed for tamsulosine and doxazosine other dosages. As a result, when we compared the amplitudes of the responses of all concentrations of doxazosine at trigone smooth muscle with amplitude of a response of effective concentration of phenylephrine. Alone, a decrease in the amplitudes were found in the ration of 10 % (10-9M), 14 % (10-8M) 21 % (10-7M), 28 % (10-6M) respectively related to increase of concentration. Similarly, when we compared the amplitudes of the responses of all concentrations of tamsulosine with amplitude of a response of effective concentration of phenylephrine. Alone, a decrease in amplitudes were found in the ration of 32 % (10-8M), 37 % (10-7M) 41 % (10-6M), 46 % (10-5M) respectively related to increase of concentration. Prevention of contractions which was done with tamsulosine hydrochloride more effectively than doxazosine mesylate was determined. With these results, we showed that doxazosine and tamsulosine inhibited noradrenaline based contractions at the rat trigone smooth muscle and this results can be used both for *in vitro* and *in vivo* for future studies.

Key words: Alpha adrenergic antagonist, rat, trigone, *in vitro*

INTRODUCTION

Alpha-1 adrenergic receptor antagonists are most commonly used in benign prostate hyperplasia and illnesses of lower urinary tract and obstruction in the area of bladder outflow. By the usage of these drugs, the decrease in the obstruction symptoms due to urination (weak urination, urinating for a long time, urinating drop by drop etc.) and the symptoms of irritate storing (frequently urinating, nocturia, dysuria, strain urination) can be seen on ill people. Although this usage of alpha-1 adrenergic antagonists on the goal receptors of lower

urinary tracts, it is not absolutely recognized^[1].

At the end of pharmacological and functional studies, it is found that there are three down types of (α_{1a} , α_{1b} , α_{1c}) alpha adrenergic antagonists^[2]. On the other hand Testa *et al.*^[3] state that there are all three types of all adrenergic receptors in rat bladder^[4-7], α_{1a} adrenergic in rabbit prostate and α_{1a} and α_{1b} adrenergic receptors in uretra more densely.

Tamsulosine hydrochloride can be used in the treatment of some symptoms such as prostate in lower urinary tract system, prostatic uretra, obstruction due to bladder or dysuria and painful urinating. At the end of

placebo controlled studies, the connection of tamsulosine hydrochloride with α_1 adrenergic receptor subtypes is found as $\alpha_{1a} \geq \alpha_{1d} \approx \alpha_{1b}$ ^[8,9]. By blocking α_{1a} and α_{1d} adrenergic receptors with the effect of inhibition of a adrenergic receptors in medulla spinalis and sympathetic nervous system, the contraction of detrusor smooth muscle is prevented, so the problems related to instability of detrusor smooth muscle of bladder and storing urinate are decreased^[9]. Doxazosin mesylate is a kinasoline derivate that is in structural connection with prazosin and terazosin. Doxazosin is equally effective for each three types of alpha-1 adrenergic receptors and also this connection is 400 times higher than alpha-2 adrenergic receptors. Doxazosin is commonly used for the treatment of hypertension and moreover; the studies on its effects on prostate tissue on BPH are stil going on^[10-12]. In this study, the effects of tamsulosin hydrochloride and doxazosin mesylate from alpha-1 adrenergic receptor antagonists on rat bladder trigone smooth muscle will be examined.

MATERIALS AND METHODS

In this research, 50 male rats which were 250–300 gr weigh used. These animals were anesthezied with 2.5% sodium penthotal and they were killed by cervical dislocation that is appropriate to the rules of ethic. Each isolated bladder were put in to “tyrode” solution (NaCl; 148.9, KCl;2.7, CaCl; 1.8, NaPO₄H₂;0.2, NaCO₃;11.9, MgCl₂;1.2, glucose;5.5 mM). Then by taking the trigone out, a piece of stripe tissue in the dimension of 5–6 mm x 2 mm was got. The down part of these preperats was bound to force transducer and isometric smooth muscle movements were saved by the via of “force transducer” and acquisiton system (Biopac MP30 system).

At first, 1 gram of stretch was applied to tissues. They were waited in tyrode solution for at least 1 hour in the condition of changing every 15 min for adaption to medium. By following the adaption duration, voltage frequency and stimulus depth in which submaximal contraction provided were determined for two tissues (32 Hz, 1 msc and 20 V). Then all tissues were stimulated at the same frequency value, stimulation duration and electric current during the trial (Diagram1).

Diagram 1. Original record by electrical field stimulation applied for rat bladder trigon smooth muscle at various frequency: After determining the level of stimulus creating the maximal contraction belonging to tissues, by having dosage response curve belonging to phenylephrine, the effective dosage providing the maximal contraction at trigone was determined. For this, by

applying six different dosages of pheynlephrine (10⁻⁹ M, 10⁻⁸ M, 10⁻⁷ M, 10⁻⁶ M, 10⁻⁵ M, 10⁻⁴ M) respectively at submaximal voltage and by giving stimulus to the media after 8-10 min than adding first 10⁻⁹M dosage of phenylephrine contraction of tissue was provided. After the aplication of phenylephrine, by washing the tissue twice for every two minute, it was provided to reach its starting strecting value. The other dosage of phenylephrine were put in to the media not cumulatively respectively 10⁻⁸M, 10⁻⁷M, 10⁻⁶M, 10⁻⁵M and 10⁻⁴M and the same process was followed. By measuring the saved responses gram, maximum contraction which occurred in presence of phenylephrine was determined as the effective dosage.

By considering the C_{max} value stated for tamsulosin and doxazosin the effective dosages for each drug were calculated. These dosages were calculated as 10⁻⁹M, 10⁻⁸ M, 10⁻⁷M and 10⁻⁶M for doxazosin, 10⁻⁸M, 10⁻⁷M, 10⁻⁶M, 10⁻⁵M for tamsulosin. Firstly, doxazosin 10⁻⁹M dosage of antagonist drugs was added in to both goblets and waited for 7 min. At the end of this period, by giving stimulus contraction of tissue was provided. After the stimulus, by washing the tissue twice for the other dosages of doxazosine (10⁻⁸ M, 10⁻⁷ M, 10⁻⁶ M).

The tissue was rested for 45 min before passing to the responses of contraction with tamsulosin 10⁻⁸ M was put in to media respectively and waited for 20 min, then the effective dosages of phenylephrine (10⁻⁵ M) was put and waited for more 7 min. At the end of this period, by giving stimulus the contraction occurred. By adding the other dosages of tamsulosin (10⁻⁷ M, 10⁻⁶ M, 10⁻⁵ M) into media respectively, the same process that was followed. The washing process that was done between the applications was followed respectively as the same as it was stated above.

The contraction value that occurred as a result of electrical stimulation in the presence of the effective dosage of phenylephrine was accepted as 100%. By following the same process in the presence of tamsulosin and doxazosin, the contractions were measured and they were compared with the contractions that were got in the previous application, the prevention ration of drugs' contraction was calculated as percentage.

As the statistical method, “Variance Analyse” and Duncan tests was applied in the comparison of amplitute values for each trigone and p<0.05 difference level was accepted as important in the study.

RESULTS AND DISCUSSION

In this study, effects of tamsulosin hydrochloride and doxazosin mesylate of alpha adrenergic antagonist

drugs on rat bladder trigone smooth muscle were researched. The reason for preferring rat animal material was that alpha adrenergic receptors scattered in all anatomic sections of bladder homogenously which was different from other species^[9]. At the end of studies going on many years, tamsulosin of alpha adrenergic receptor antagonists which had selective pharmacological features and which was effective for alpha-1a adrenergic receptors being densely in prostate tissue was developed^[13]. Lyseng-Williamson *et al.*^[9] stated that the average selectiveness featured stated for tamsulosin's alpha-1a adrenergic receptor was 3,9-38 times more when compared with alpha-1b and 3-20 times more when compared with alpha-1b. As a result of tamsulosin's high interest for receptors, it caused having less side effect when compared with the other alpha adrenergic antagonists such as doxazosin, terazosin, prazosin and alfuzosin. Doxazosin mesylate didn't show the selective features for down types of adrenergic receptors and it influenced every three receptors in the same ration^[11,12]. In the study, tamsulosin hydrochloride was preferred as its strong selective interest for alpha-1a adrenergic receptors and being the newest drug, on the other hand doxazosin mesylate was preferred as it didn't show the selectiveness for down types of adrenergic receptors and being among the first used drugs.

In the study, it was determined that the contractions occurred by Electric Field Stimulation (EFS) in the presence of various concentrations of phenylephrine (10^{-9} M, 10^{-8} M, 10^{-7} M, 10^{-6} M, 10^{-5} M) increased due to the increase of concentration. This fact provided that the concentrations created by phenylephrine occurred through adrenergic receptors at rat bladder trigone smooth muscle (alpha 1 and alpha 2). Longhurst and Uvelius^[6] provided that while phenylephrine caused loosening at body part of detrusor smooth muscle by letting releasing acetylcholine at presynaptic ganglions and noradrenaline at postynaptic ganglions, it was at the same place with trigone field. Any information belonging to effective concentration of phenylephrine for rat trigone smooth muscle wasn't come across in done literature archive, however it was stated that concentration in which maximal contraction provided was 10^{-2} M^[14] for aort and 10^{-2} M^[15] for human prostate tissue in the studies done on various tissues with phenylephrine. Therefore, the 10^{-5} M dosage of phenylephrine which provided maximal contraction was chosen as effective concentration used in the experiment (Table 1 and Diagram 2). The reason for the difference between effective concentration of phenylephrine can be thought as the density and distribution of adrenergic receptor at tissues can change according to organs and types.

Table 1: The amplitude values (g) in the presence of electrical stimulation and the various dosages of phenylephrine on rat bladder trigone smooth muscle (n = 10)

Concentration(M)	Amplitude (g) X±Sx
EFS	2.16±0.35 ^a
PE10 ⁻⁹ M + EFS	2.19±0.37 ^a
PE10 ⁻⁸ M + EFS	2.33±0.38 ^b
PE10 ⁻⁷ M + EFS	2.45±0.39 ^c
PE10 ⁻⁶ M + EFS	2.52±0.40 ^d
PE10 ⁻⁵ M + EFS	2.63±0.41 ^e
PE10 ⁻⁴ M + EFS	2.42±0.37 ^{bcd}

a,b,c,d,e,f: Differences between the values involving different letters on the same column are significant (p<0,05)

Table 2: The amplitude values (g) with the application of electrical stimulus of rat bladder trigone smooth muscle in the presence of only effective phenylephrine and doxazosin mesylate and various concentration of tamsulosine hydrochloride (n = 20)

EFS (V _{rmsc} , Hz) + Concentration (M)	Amplitude (g) X±Sx
PE 10 ⁻⁵ M +EFS	2.66±0.30 ^a
DOK 10 ⁻⁹ M +PE 10 ⁻⁵ M + EFS	2.42±0.27 ^b
DOK 10 ⁻⁸ M +PE 10 ⁻⁵ M + EFS	2.30±0.27 ^c
DOK 10 ⁻⁷ M +PE 10 ⁻⁵ M + EFS	2.11±0.25 ^d
DOK 10 ⁻⁶ M +PE 10 ⁻⁵ M + EFS	1.93±0.24 ^e
TAM 10 ⁻⁸ M +PE 10 ⁻⁵ M + EFS	1.82±0.23 ^f
TAM 10 ⁻⁷ M +PE 10 ⁻⁵ M + EFS	1.69±0.22 ^g
TAM 10 ⁻⁶ M +PE 10 ⁻⁵ M + EFS	1.57±0.20 ^h
TAM 10 ⁻⁵ M +PE 10 ⁻⁵ M + EFS	1.46±0.19 ⁱ

a,b,c,d,e,f,g,h,i: Differences between the values involving different letters on the same column are significant (p<0,05)

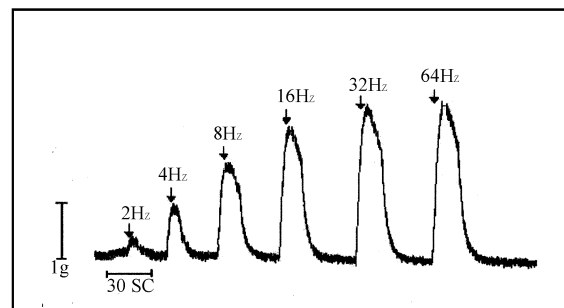


Diagram 1: Original record by electrical field stimulation applied to rat bladder trigone smooth muscle at various frequency

Diagram 2. The effective dosage-response curve of phenylephrine (n = 20): Alabaster and Davey^[16] with Davey^[17] stated in the studies done on isolated aort ring of rabbit, brain membranes and venas of dogs that interest of doxazosine for alpha-1 adrenergic receptors was more than its interest for alpha-2 adrenergic receptors. Also, in vivo studies, it was concluded that blood pressure and contractions of rat bladder decreased as a result of giving doxazosine to rats intraspinally^[18,19], giving it in vessel to cats^[20] and dogs. These were the proof of that doxazosine showed antagonist effect to alpha-1 adrenergic receptors.

The contractions gotten by applied electrical stimulation in the presence of effective concentration of

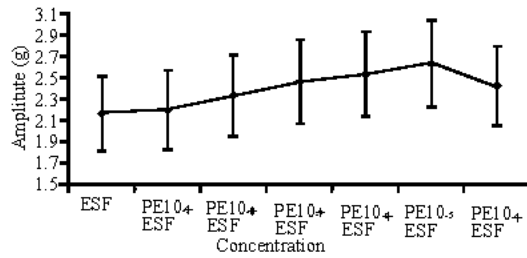


Diagram 2: The effective dosage-response curve of phenylephrine (n = 20)

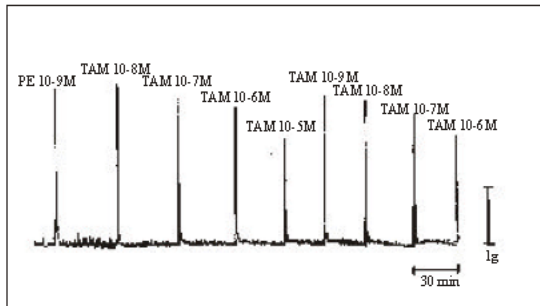


Diagram 3: The original records belonging to amplitudes by electrical stimulations of rat bladder trigone smooth muscle in the presence of various concentration of phenylephrine and doxazosin mesylate and tamsulosine hydrochloride (n = 20)

phenylephrine with various dosage of doxazosine (10^{-9} M, 10^{-8} M, 10^{-7} M, 10^{-6} M) were less ($p < 0,05$) than the amplitudes of contractions occurred by only effective concentrations phenylephrine Table 2. This fact showed that all concentrations of doxazosine inhibited the contractions originated from noradrenaline on rat trigone smooth muscle due to the concentration of the drug. In the study, when compared with the only usage of effective dosage of phenylephrine, the responses taken to phenylephrine in the presence of all concentration of doxazosin decreased respectively in the ration of 10 % in 10^{-9} M concentration, 14 % in 10^{-8} M concentration, % 21 10^{-7} M concentration and 28 % in 10^{-6} M concentration. This result showed that contractions occurred as a result of phenylephrine's at rat trigone smooth muscle setting into action alpha-1 adrenergic receptors could be prevented due to the increase in the density of doxazosin. Any studies including the effects of doxazosin on rat trigone bladder smooth muscle weren't come across, but Seo *et al.*^[21], stated that doxazosin inhibited the contractions occurred by noradrenalin at rabbit trigone and cavernose tissues in the ration of 10 %. At the same time Koç^[22] informed that doxazosin had a pressing effect on the contractions occurred by noradrenaline at rat vas deferens, seminal vesicle and epididymis smooth

muscles. This ideas proved that doxazosin had alpha-1a adrenergic receptor antagonist effect. This result reminded that alpha-1a adrenergic receptors at rat bladder trigone smooth muscle could be prevented by doxazosin, therefore the follow of urine could be easen by loosening the neck part of bladder.

There are some researches related to that the contractions occurred by epinephrine and phenylephrine in the studies of *in vivo* done on dog prostate smooth muscle^[23-25] and *in vitro* done on rat prostate^[26] could be prevented by tamsulosin, similarly, contractions of human prostate gland smooth muscle occurred by phenylephrine could be decreased^[1,27] and also the usage of tamsulosin in the treatment of illnesses related to human prostate and lower urinary tracts^[28-31].

The response's taken to phenylephrine's effective concentration in the presence of various concentrations of tamsulosin (10^{-8} M, 10^{-7} M, 10^{-6} M, 10^{-5} M) which showing selective feature for alpha-1a adrenergic receptor being smaller when compared with the amplitudes of concentrations occurred by only effective concentration of phenylephrine showed that tamsulosin inhibited the contractions soursched by noradrenaline on rat bladder trigone smooth muscle due to concentration ($p < 0,05$) (Table 2 and Diagram 3). There are some researchers staving contractions occurred by phenylephrine in dogs' bladder could be prevented with tamsulosin competitively^[3,32-34], furthermore the effects of tamsulosin on amplitude and frequency of contractions in rat bladder was low^[35].

In the study, when compared with the response gotten as a result of the only usage of phenylephrine, contractions occurred by phenylephrine in the presence all concentrations decreased by begining from the lowest concentrations of tamsulosin, respectively in the ration of 32 % of 10^{-8} M concentration, 37 % in 10^{-7} M concentration, 41 % 10^{-6} M concentration and 46 % in 10^{-5} M concentration. This showed that contractions occurred as a result of phenylephrine's setting into action the alpha-1 adrenergic receptors at rat bladder trigone smooth muscle could be prevented due to the increasing density of tamsulosin. Seo *et al.*^[22] found out that tamsulosin decreased contractions occurred by noradrenaline at rabbit trigone smooth muscle in the ration of % 81. This is similar with the finding that contractions could be decreased only % 46 in the study done on rat trigone by using phenylephrine which is a noradrenaline analogue. The reason for proportional diffirence is thought as density of receptors at tissues and diffirence in species.

In the studies done on rat tail^[36,37] and mesenteric artery^[14], it was stated that tamsulosin prevented the contractions occurred by phenylephrine or noradrenaline more strongly than other alpha adrenergic

antagonists such as prazosin, phentolamin, WB-401, 5 methyl-urapidil, spiperone and HV 723. Similarly, it was observed that the contraction occurred in the densest concentration of doxazosin which had no feature of selectiveness was bigger than the contraction occurred in the lowest concentration of tamsulosin. The reason for that was thought as being much of the density of especially alpha-1 adrenergic receptors at neck area were there is trigone smooth muscle and selective and high interest of tamsulosin for alpha-1a adrenergic receptors. Seo *et al.*^[21] informed that tamsulosin prevented the concentrations occurred by phenylephrine at rabbit cavernose smooth muscle could prevented 1000 times than doxazosin and terazosin. In this study, as a result of stimulating of stimulating adrenergic receptors by phenylephrine which is a noradrenaline analogue, the finding; tamsulosin could prevent the contractions occurred in trigone area more strongly than doxazosin as a result of tamsulosin's selective interest for alpha-1a adrenergic receptors attracted the attention.

In the research in which it was found that tamsulosin hydrochloride and doxazosin mesylate of alpha adrenergic antagonists had a inhibitating effect on the contractions sourced by noradrenaline on trigone smooth muscle of *in vitro* rat bladder. Also, in the research it was established that tamsulosin inhibited the contractions strongly whilst doxazosine inhibited them weakly. It was thought that the inhibitating effect of tamsulosin and doxazosin occurred through the prevention of alpha adrenergic receptors at trigone smooth muscle of rat bladder.

CONCLUSION

It was concluded that tamsulosin hydrochloride and doxazosin mesylate could provide easy flow of urine by inhibitating alpha adrenergic receptors in illnesses of neck area of bladder and lower urinary tract resulted in dysuria at cats and dogs; however it was decided that these effects must be supported by clinical studies.

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