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Effects of tamsulosin on hypogastric nerve stimulation-induced intraurethral pressure elevation in male and female dogs under anesthesia

Akiyoshi Ohtake*, Shuichi Sato, Chikashi Saitoh, Hironori Yuyama, Masao Sasamata, Keiji Miyata

Pharmacology Laboratories, Institute for Drug Discovery Research, Yamanouchi Pharmaceutical Co., Ltd., 21 Miyukigaoka, Tsukuba, Ibaraki 305-8585, Japan

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Abstract

The aim of the present study was to investigate the effects of tamsulosin, an α_1-adrenoceptor antagonist, on hypogastric nerve stimulation-induced intraurethral pressure elevation in anesthetized male and female dogs and to evaluate sex differences in these effects. Additionally, the effects of tamsulosin were also compared with those of other α_1-adrenoceptor antagonists, namely prazosin, naftopidil and urapidil. Tamsulosin dose-dependently inhibited hypogastric nerve stimulation-induced intraurethral pressure elevation, with doses required to induce 50% inhibition of the elevation (ED_{50} values) of 0.72 and 0.74 μg/kg i.v. in anesthetized male and female dogs, respectively. Mean arterial blood pressure slightly decreased after administration of tamsulosin at a dose which inhibited intraurethral pressure elevation almost completely. Prazosin, naftopidil and urapidil also inhibited increases in intraurethral pressure in a dose-dependent fashion, but caused decreases in mean arterial blood pressure at the same doses. The estimated rank order of inhibitory potency for urethral response was tamsulosin>prazosin>naftopidil=urapidil. In conclusion, tamsulosin dose-dependently inhibited increases in intraurethral pressure with little effect on mean arterial blood pressure in both male and female dogs, and these effects were almost equipotent. These results indicate that tamsulosin will be useful in the treatment of dysuria associated with lower urinary tract symptoms in women as well as men.

Keywords: Tamsulosin; Intraurethral pressure; Arterial blood pressure

1. Introduction

Benign prostatic hyperplasia is a condition which leads to bladder outlet obstruction and subsequent voiding dysfunction in middle-aged and elderly men. The enlarged prostate is composed of glandular epithelium and a large stromal component containing mostly smooth muscle (Shapiro and Lepor, 1991). The symptoms of benign prostatic hyperplasia are divided into a storage (irritative) component such as frequency and urgency, and a voiding (obstructive) component such as hesitancy and slow urinary flow. Although the symptoms are the result of increased organ size leading to mechanical obstruction, no correlation between prostate size and symptom severity has been shown (Shapiro and Lepor, 1995). Rather, an important dynamic component results from changes in sympathetic control of prostatic smooth muscle tone. Stimulation of hypogastric nerves, components of the sympathetic nervous system, is known to facilitate the retention of urine by contracting the prostate (Elliot, 1907). Notably, these storage and voiding symptoms have been observed even in men without benign prostatic hyperplasia, leading to proposals that they were termed lower urinary tract symptoms (Abrams, 1994). This condition is not gender-specific, and symptom index scores have been shown to be equivalent in men and women (Chai et al., 1993; Okamura et al., 2002; Scarpero et al., 2003). Together, these observations suggest that lower urinary

* Corresponding author. Tel.: +81 29 863 6635; fax: +81 29 854 1616.
E-mail address: ohtake@yamanouchi.co.jp (A. Ohtake).

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tract symptoms in men and women may share common underlying etiologies, at least in part.

α_1-Adrenoceptor classification comprises three subtypes, termed α_{1A}-, α_{1B}- and α_{1D}-adrenoceptors (Michel et al., 1995; Hieble et al., 1995). α_{1A}-Adrenoceptor is the predominant subtype in the human prostate and male and female urethra (Price et al., 1993; Nasu et al., 1996, 1998) and mediates the contractile response induced by activation of the hypogastric nerve (Elliot, 1907; Forray et al., 1994). Binding and functional assays using the prostate and urethra of dog or rabbit also confirm the important role of α_{1A}-adrenoceptor in mediating the contractile response of these tissues (Leonardi et al., 1997). Tamsulosin is a uroselective α_1-adrenoceptor antagonist with minimal effect on blood pressure and a low incidence of circulatory adverse events, e.g. dizziness, orthostatic hypotension and tachycardia. It is now in use worldwide for the treatment of the signs and symptoms of benign prostatic hyperplasia (Takenaka et al., 1995; Abrams et al., 1997; Narayan and Tewari, 1998). Tamsulosin has 12- to 20-fold and 3-fold higher affinity for α_{1A}-adrenoceptors than α_{1B}- and α_{1D}-adrenoceptors, respectively (Foglar et al., 1995; Leonardi et al., 1997; Taguchi et al., 1997), and about 12-fold higher affinity for α_1-adrenoceptors in the human prostate than in the human aorta (Yamada et al., 1994). In male dogs, tamsulosin inhibits α_1-adrenoceptor agonist- or hypogastric nerve stimulation-induced prostatic intraurethral pressure elevation (Leonardi et al., 1997; Hancock et al., 2002; Sato et al., 2001). However, little information is available concerning the effect of tamsulosin on urethral responses in female dogs (Shibasaki et al., 1992), and sex differences under the same conditions.

The present study was undertaken to evaluate sex differences in the effects of tamsulosin on hypogastric nerve stimulation-induced increases in intraurethral pressure in anesthetized dogs. In addition, the effects of tamsulosin were compared with those of other α_1-adrenoceptor antagonists, namely prazosin, naftopidil and urapidil.

2. Materials and methods

2.1. Drugs

Tamsulosin hydrochloride [(−)-(*R*)-5-[2-[[2-(*o*-ethoxyphenoxy)ethyl]amino] propyl]-2-methoxybenzenesulfonamide hydrochloride] and naftopidil were prepared by Yamanouchi Pharmaceutical Co. Ltd. (Tokyo, Japan). Prazosin hydrochloride and urapidil were purchased from Sigma-Aldrich (St. Louis, MO, USA). Naftopidil and urapidil were dissolved in 0.3N H_3PO_4 containing 10% *N*,*N*-dimethylformamide and physiological saline containing an equimolar amount of HCl, respectively. The others were dissolved in physiological saline.

2.2. Operative procedure

The animal experiments were performed in compliance with the regulations of the Institutional Animal Ethical Committee of Yamanouchi Pharmaceutical Co. Ltd. The operative procedure was performed as previously described (Sato et al., 2001) with minor modification. Male and female beagle dogs weighing 9.0–15.5 and 8.0–13.5 kg, respectively, were fasted overnight. Anesthesia was induced with pentobarbital sodium (30 mg/kg i.v.) and maintained by continuous i.v. infusion of pentobarbital sodium (4–5 mg/kg/h). After endotracheal intubation, the animals were artificially ventilated with room air (respirator: SN-480-3, Shinano Seisakusyo, Tokyo, Japan; tidal volume, 20 ml/kg; respiration rate, 20 breaths/min). Arterial blood pressure was measured with a pressure amplifier (AP-641G, Nihon Kohden, Tokyo, Japan) via a pressure transducer (TP-400T, Nihon Kohden) connected to a catheter inserted into the femoral artery.

A midline abdominal incision was then made and the urinary bladder was emptied using a catheter inserted into the bladder through its superior aspect to eliminate the possible effect of residual urine on intraurethral pressure. A modified thermodilution balloon catheter (5 Fr, Nihon Kohden) was introduced into the urethra via the external urethral meatus. The balloon was then inflated with distilled water and placed in the prostatic and proximal urethra in male and female dogs, respectively. The balloon port of the catheter was connected to a pressure transducer (TP-400T) and the intraurethral pressure was measured with a pressure amplifier (AP-601G). The hypogastric nerves were exposed bilaterally and cut about 2 cm distal to the inferior mesenteric ganglion. The distal end of either the right or left branch of the nerve was placed on a bipolar electrode (IMT-1530, Inter Medical, Nagoya, Japan).

Following a stabilization period of at least 30 min after operation, the urethral response was confirmed by epinephrine (3 μg/kg i.v.) via a catheter inserted into the femoral vein. Nerve stimulation was then performed with a train of rectangular pulses at 4–10 V, 10 Hz, 2 ms width and 5 s duration. After stabilization of the responses to stimulation at about 5-min intervals, tamsulosin [0.22, 0.67, 22 and 67 nmol/kg (0.1, 0.3, 1 and 3 μg/kg)], prazosin [2.4, 7.1, 24 and 71 nmol/kg (1, 3, 10 and 30 μg/kg)], naftopidil [25, 76, 250 and 760 nmol/kg (10, 30, 100 and 300 μg/kg)] or urapidil [26, 77, 260, 770 and 2600 nmol/kg (10, 30, 100, 300 and 1000 μg/kg)] were given by i.v. administration at increasing doses at about 30-min intervals in each dog, with hypogastric nerve stimulation performed at 5, 10, 15 and 30 min after each dosing. The maximal effects of test drugs on urethral response and mean arterial blood pressure within 30 min after each dosing were used for evaluation.

2.3. Statistical analysis

Data are expressed as the mean±S.E.M of five male or female dogs. ED_{50} values, the dose required to induce 50% inhibition of intraurethral pressure elevation, were determined by linear regression analysis. Statistical differences were analyzed using Student's *t*-test, with differences of $P<0.05$ considered statistically significant. All data analyses were performed using the SAS statistical software (SAS Institute, Cary, NC, USA).

3. Results

3.1. Male dogs

In anesthetized male dogs, hypogastric nerve stimulation increased intraurethral pressure by 25–27 cmH_2O, and baseline values of mean arterial blood pressure were 120–133 mmHg in each group. Tamsulosin (22 and 67 nmol/kg i.v.) significantly inhibited the increase in intraurethral pressure (Fig. 1), with an ED_{50} value of 1.6 nmol/kg i.v. (Table 1). Mean arterial blood pressure was not affected by tamsulosin at doses up to 22 nmol/kg i.v., but was decreased by about 10 mmHg at the highest dose of 67 nmol/kg i.v., which almost completely inhibited intraurethral pressure elevation (Fig. 2). Prazosin (24 and 71 nmol/kg i.v.), naftopidil (760 nmol/kg i.v.) and urapidil (260–2600 nmol/kg i.v.) also significantly inhibited the increase in intraurethral pressure. Unlike tamsulosin, however, these α_1-adrenoceptor antagonists decreased mean arterial blood pressure at doses which inhibited urethral responses. By ED_{50} values for urethral response, the inhibitory effect of tamsulosin was 6.1-, 110- and 88-fold more potent than those of prazosin, naftopidil and urapidil, respectively.

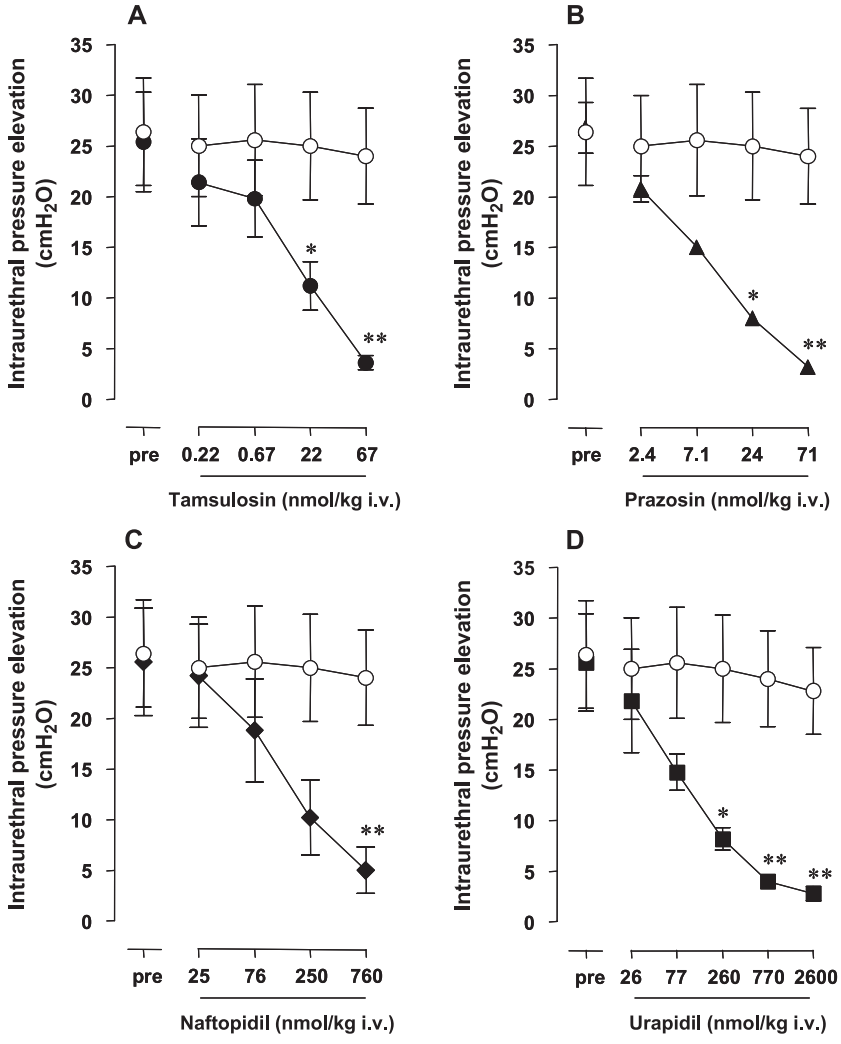

Fig. 1. Effects of tamsulosin (A), prazosin (B), naftopidil (C) and urapidil (D) on hypogastric nerve stimulation-induced intraurethral pressure elevation in anesthetized male dogs. (○) saline-treated group; (●) tamsulosin-treated group; (▲) prazosin-treated group; (◆) naftopidil-treated group; (■) urapidil-treated group. Each point represents the mean±S.E.M. of five dogs. *$P<0.05$, **$P<0.01$, significant difference from the saline-treated group (Student's *t*-test).

Table 1
ED_{50} values of tamsulosin, prazosin, naftopidil and urapidil for the inhibition of hypogastric nerve stimulation-induced intraurethral pressure elevation in anesthetized male and female dogs

	ED_{50} values (95% confidence limits) [potency ratio]	
	Male	Female
Tamsulosin	1.6 (1.3–2.0) [1]	1.7 (1.3–2.1) [1]
Prazosin	9.7 (5.9–16) [1/6.1]	9.5 (6.9–13) [1/5.6]
Naftopidil	170 (100–290) [1/110]	130 (63–280) [1/76]
Urapidil	140 (110–190) [1/88]	320 (150–690) [1/190]

ED_{50} values (nmol/kg i.v.) are the doses required to induce 50% inhibition of intraurethral pressure elevation and were determined by linear regression analysis (n=5). The potency ratio represents the value obtained based on a tamsulosin value of 1.

3.2. Female dogs

In anesthetized female dogs, hypogastric nerve stimulation increased intraurethral pressure by 16–18 cmH_2O, and baseline values of mean arterial blood pressure were 121–131 mmHg in each group. Tamsulosin (22 and 67 nmol/kg i.v.) significantly inhibited the increase in intraurethral pressure (Fig. 3), with an ED_{50} value of 1.7 nmol/kg i.v. (Table 1). Mean arterial blood pressure was not affected by tamsulosin at doses up to 22 nmol/kg i.v., but was decreased by about 10 mmHg at the highest dose of 67 nmol/kg i.v., which almost completely inhibited intraurethral pressure elevation (Fig. 4). Prazosin (7.1–71 nmol/kg i.v.), naftopidil (250 and 760 nmol/kg i.v.) and urapidil (770 and 2600 nmol/kg i.v.) also significantly inhibited the increase in intraurethral pressure. Unlike tamsulosin, however, naftopidil and urapidil decreased mean arterial blood pressure at doses which inhibited urethral responses. By ED_{50} values for urethral response, the inhibitory effect of tamsulosin was 5.6-, 76- and 190-fold more potent than those of prazosin, naftopidil and urapidil, respectively.

4. Discussion

Pharmacotherapy has become the first choice of treatment for benign prostatic hyperplasia (Narayan and Tewari, 1998). Successful improvement of the symptoms has been observed with α_1-adrenoceptor antagonists; nevertheless, the use of first-generation α_1-adrenoceptor antagonists is often limited by adverse effects such as dizziness, hypotension and the first-dose phenomenon. Tamsulosin is a second-generation α_1-adrenoceptor antagonist which has shown uroselectivity in preclinical (Yamada et al., 1994; Hatanaka et al., 2001; Sato et al., 2001) and clinical (Takenaka et al., 1995; Abrams et al., 1997; Narayan and Tewari, 1998) studies, and is now in use worldwide for the treatment of the signs and symptoms of benign prostatic hyperplasia.

Lower urinary tract symptoms suggestive of bladder outlet obstruction have been reported in women as well as men (Chai et al., 1993; Okamura et al., 2002; Scarpero et al., 2003). Given that the α_{1A}-adrenoceptor subtype is predominant in urethra as well as prostate (Price et al., 1993; Nasu et al., 1996, 1998) and mediates the contractile response of these organs (Forray et al., 1994; Marshall et al., 1995), pharmacotherapy using α_1-adrenoceptor antagonists may also be effective in women with lower urinary tract symptoms. In the present study, sex differences in the effects of tamsulosin on intraurethral pressure and mean

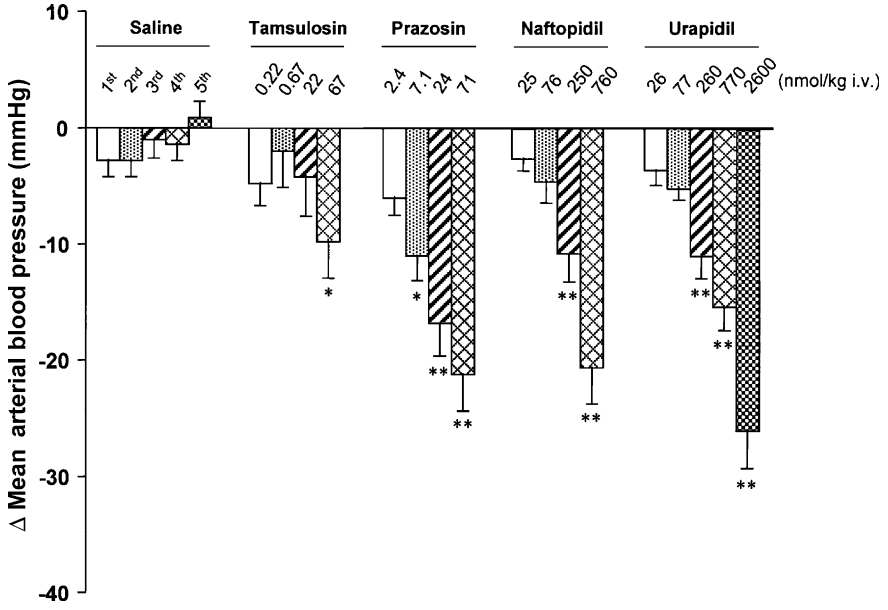

Fig. 2. Effects of tamsulosin, prazosin, naftopidil and urapidil on mean arterial blood pressure in anesthetized male dogs. Each column represents the mean±S.E.M. of five dogs. *P<0.05, **P<0.01, significant difference from the saline-treated group (Student's t-test).

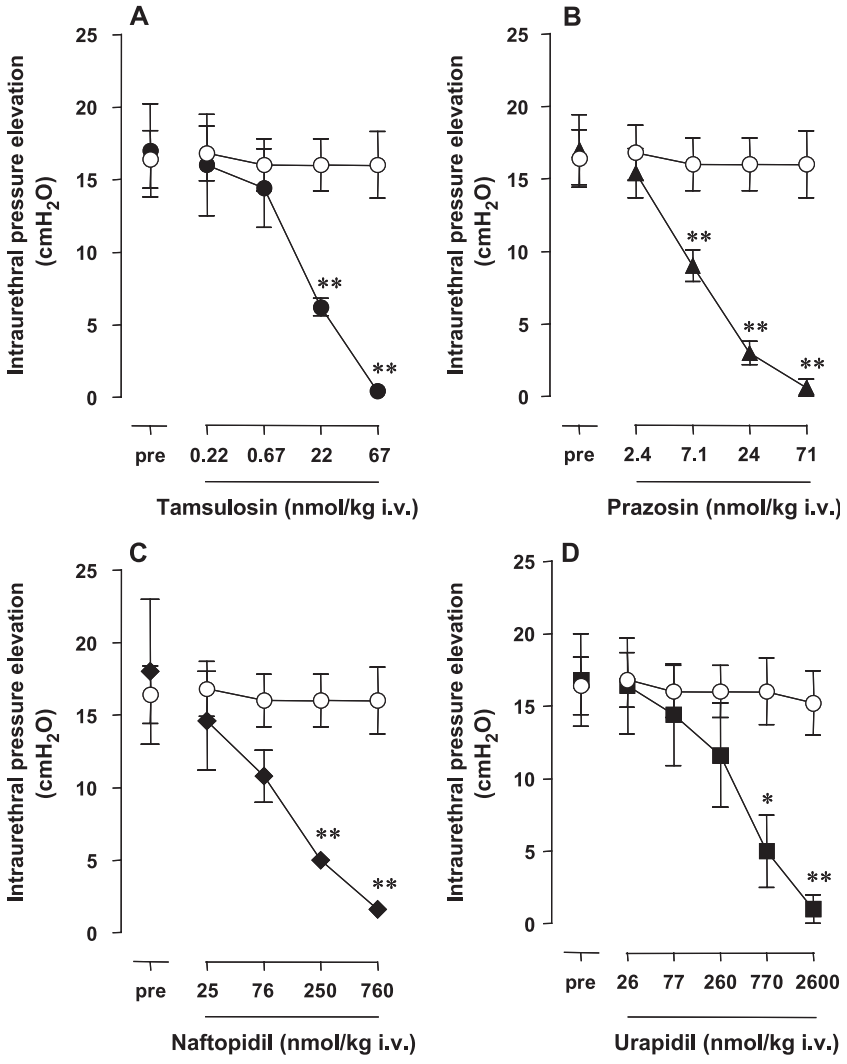

Fig. 3. Effects of tamsulosin (A), prazosin (B), naftopidil (C) and urapidil (D) on hypogastric nerve stimulation-induced intraurethral pressure elevation in anesthetized female dogs. (○) saline-treated group; (●) tamsulosin-treated group; (▲) prazosin-treated group; (◆) naftopidil-treated group; (■) urapidil-treated group. Each point represents the mean±S.E.M. of five dogs. *P<0.05, **P<0.01, significant difference from the saline-treated group (Student's t-test).

arterial blood pressure were examined in male and female dogs, and the effects were compared with those of prazosin, naftopidil and urapidil.

To date, most in vivo studies investigating the potency and pharmacological selectivity of α_1-adrenoceptor antagonists have used exogenous agonists such as phenylephrine and epinephrine to elevate intraurethral pressure (Shibasaki et al., 1992; Leonardi et al., 1997; Hancock et al., 2002; Witte et al., 2002). In contrast, electrical stimulation of the hypogastric nerve causes the release of endogenous neurotransmitters, which in turn contract the prostate and urethra (Imagawa et al., 1989; Lefevre-Borg et al., 1993). In the present study, we chose to use hypogastric nerve stimulation to elevate intraurethral pressure, considering it to be closer to physiological conditions than administration of exogenous agonist. Results showed that the increase in intraurethral pressure was slightly greater in male than female dogs, although the difference was not significant. From an anatomical standpoint, the prostate, which exists only in males, may reinforce or further increase urethral response. Tamsulosin dose-dependently inhibited the intraurethral pressure elevation in both male and female dogs, and ED_{50} values were almost equal. The effects of prazosin and naftopidil on urethral response in male and female dogs were also almost equipotent. The ED_{50} value of urapidil seemed to be lower in male than in female dogs. As the 95% confidence intervals in the two sexes overlapped, this difference is considered to be within the range of physiological variation. These findings thus indicate that there is no sex difference in the effects of α_1-adrenoceptor antagonists on urethral response, because they inhibited urethral response by blocking α_{1A}-adrenoceptors in both prostate and urethra. As far as we are aware, these results provide the first evidence that α_1-adrenoceptor antagonists demonstrate an equipotent effect on urethral response in males and females of the same species. Tamsulosin was reported to significantly improve lower urinary tract symptoms in men (Lee and Lee, 1997; Djavan, 2003;

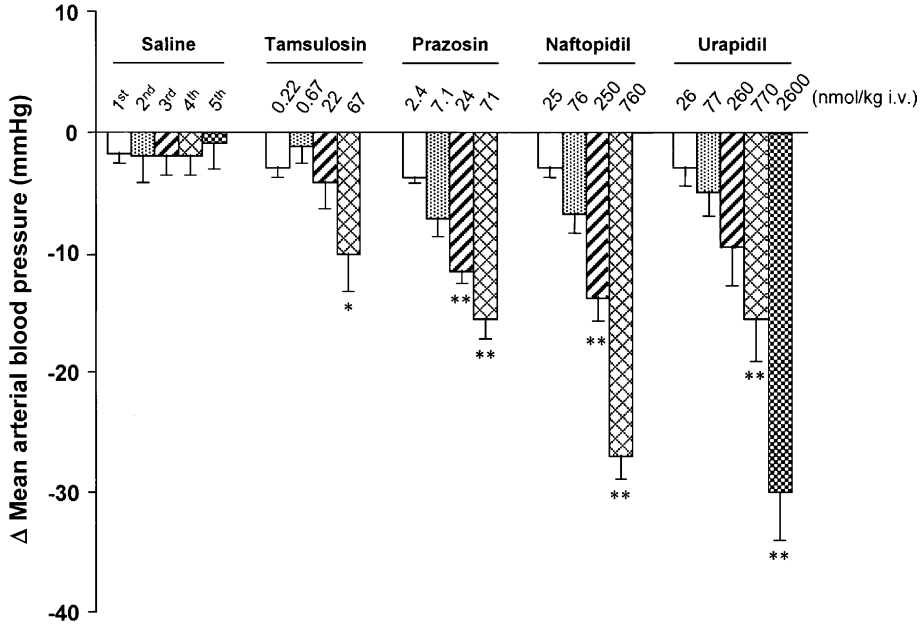

Fig. 4. Effects of tamsulosin, prazosin, naftopidil and urapidil on mean arterial blood pressure in anesthetized female dogs. Each column represents the mean±S.E.M. of five dogs. *P<0.05, **P<0.01, significant difference from the saline-treated group (Student's t-test).

Narayan et al., 2003), suggesting its possible usefulness in women with lower urinary tract symptoms. Further, it was also reported to relieve lower urinary tract symptoms and increase maximum urinary flow rate in women at a dose which improved dysuria in men with benign prostatic hyperplasia, although this was not a placebo-controlled study and patient number was low (Kakizaki and Koyanagi, 2000).

Tamsulosin had a negligible effect on mean arterial blood pressure in both male and female dogs. In contrast, prazosin, naftopidil and urapidil decreased mean arterial blood pressure at doses at which they inhibited urethral response. Tamsulosin has 12- to 20-fold and 3-fold greater affinity for α_{1A}-adrenoceptors than α_{1B}- and α_{1D}-adrenoceptors, respectively (Foglar et al., 1995; Leonardi et al., 1997; Taguchi et al., 1997). The other drugs differ in their selectivity: prazosin and urapidil are non-selective antagonists for α_1-adrenoceptor subtypes (Takei et al., 1999; Testa et al., 1993), while naftopidil has 3- and 17-fold greater affinity for α_{1D}-adrenoceptors than α_{1A}- and α_{1B}-adrenoceptors, respectively (Takei et al., 1999). The hypotensive effects of these antagonists may be difficult to explain by the differences in their affinity for α_1-adrenoceptor subtypes alone. After all, the α_1-adrenoceptor subtypes primarily responsible for regulating arterial blood pressure have not been accurately established in dogs. Both naftopidil and urapidil are phenylpiperazine derivatives and have activities as 5-HT_{1A} receptor agonists (Borbe et al., 1991; Ramage, 1991), which induce hypotension by acting on central sites. In addition, naftopidil has Ca^{2+}-channel blocking activity (Himmel et al., 1991). In the present study, these α_1-adrenoceptor antagonists thus greatly decreased mean arterial blood pressure. Although α_{1A}-adrenoceptors predominate in many human splanchnic and coronary arteries and α_{1D}-adrenoceptors predominate in aorta (Rudner et al., 1999), no apparent influence on arterial blood pressure has been seen in patients treated with tamsulosin, notwithstanding its high affinity for α_{1A}- and α_{1D}-adrenoceptors (Abrams et al., 1997; Narayan and Tewari, 1998). In addition, given that orthostatic hypotension has been reported in the therapeutic use of tamsulosin for benign prostatic hyperplasia, albeit it with very low incidence (Abrams et al., 1997; Narayan and Tewari, 1998), it will also be made available in a sustained release formulation with a decreased absorption rate. Transient orthostatic hypotension is often seen after the initial administration of an α_1-adrenoceptor antagonist and is an effect which is considered to reflect the absorption rate of the drug rather than the dose used (Takenaka et al., 1995). It has recently been suggested that the uroselectivity profile of tamsulosin cannot be explained by its subtype selectivity for α_1-adrenoceptors only. Tamsulosin shows sustained occupancy of α_1-adrenoceptors in the rat prostate after a marked reduction in plasma concentration (Ohkura et al., 1998). Further, in dogs, pharmacological concentrations of tamsulosin are retained for longer times at target organs such as prostate and urethra than plasma (Hatanaka et al., 2001; Sato et al., 2001). These findings suggest that the uroselectivity of tamsulosin may also relate to its high tissue retention.

In conclusion, tamsulosin dose-dependently inhibited increases in intraurethral pressure with little effect on mean arterial blood pressure in both male and female dogs, and these effects were almost equipotent. These findings suggest that tamsulosin will be useful in the improvement of dysuria associated with lower urinary tract symptoms in women as well as men.

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