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Effects of tamsulosin on resting urethral pressure and arterial blood pressure in anaesthetized female dogs

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Abstract

The purposes of the present study were to investigate the effects of the α_1-adrenoceptor antagonists tamsulosin, prazosin and urapidil on resting urethral pressure in anaesthetized female dogs, and to compare the results with their effects on arterial blood pressure. Tamsulosin decreased resting maximal urethral pressure in the urethral pressure profile in a dose-dependent fashion, whereas it had almost no effect on mean arterial blood pressure. Prazosin and urapidil also dose-dependently decreased resting maximal urethral pressure, but these effects were accompanied by decreases in mean arterial blood pressure. Thus, of these three compounds, tamsulosin dose-dependently decreased resting maximal urethral pressure with negligible effect on mean arterial blood pressure in female dogs. These results suggest that tamsulosin will be useful in the treatment of voiding dysfunction associated with bladder outlet obstruction in women, with little hypotensive effect.

Introduction

Benign prostatic hyperplasia is a condition that leads to bladder outlet obstruction and subsequent voiding dysfunction in middle-aged and elderly men. The symptoms of benign prostatic hyperplasia are divided into a storage (irritative) component, such as urinary frequency and urgency, and a voiding (obstructive) component, such as hesitancy and slow urinary flow. However, these storage and voiding symptoms have been observed even in men without benign prostatic hyperplasia, leading to proposals that they be generically termed lower urinary tract symptoms (Abrams 1994). This condition is not gender specific, but is rather considered to represent dynamic bladder outlet obstruction resulting from increases in prostatic (in men) and urethral smooth muscle tone (in men and women) through facilitation of sympathetic activation. Additional aetiologies in women include previous anti-incontinence surgery, severe genital prolapse and urethral narrowing, and the prevalence rate of bladder outlet obstruction has been reported to be 6.5 to 8.3% in detrusor pressure-uroflow studies in women referred for evaluation of lower urinary tract symptoms (Blaivas & Groutz 2000; Groutz et al 2000). Symptom index scores have also been shown to be equivalent in men and women with lower urinary tract symptoms (Chai et al 1993; Okamura et al 2002; Scarpero et al 2003), and a positive correlation was found between the symptom index score and the result of detrusor pressure-uroflow studies in women (Blaivas & Groutz 2000).

α_1-Adrenoceptors are classified into three subtypes: α_{1A}-, α_{1B}- and α_{1D}-adrenoceptors (Hieble et al 1995; Michel et al 1995). α_{1A}-Adrenoceptors are the predominant subtype in the human prostate and male and female urethra (Price et al 1993; Nasu et al 1996, 1998), and mediate the contractile responses in these tissues (Forray et al 1994; Marshall et al 1995). Binding and functional assays using the prostate and urethra of dog or rabbit have confirmed the important role of the α_{1A}-adrenoceptor in mediating the contractile response of these tissues (Leonardi et al 1997).

Tamsulosin is a uroselective α_1-adrenoceptor antagonist with a low incidence of circulatory adverse effects, e.g. dizziness, orthostatic hypotension and tachycardia. It is now in world-wide use for the treatment of the symptoms of benign prostatic hyperplasia (Takenaka et al 1995; Abrams et al 1997; Narayan & Tewari 1998). In male dogs, tamsulosin has been reported to reduce resting urethral pressure at the prostatic site in the urethral pressure profile and to inhibit α_1-adrenoceptor agonist- and nerve stimulation-induced prostatic intraurethral

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pressure elevation (Sudo et al 1996; Leonardi et al 1997; Sato et al 2001; Hancock et al 2002; Ohtake et al 2004). Although some information is available on the effect of tamsulosin on urethral responses to α_1-adrenoceptor agonist and nerve stimulation in female dogs (Shibasaki et al 1992; Ohtake et al 2004), little is known about its effect on resting urethral pressure. Urethral pressure profilometry is an evaluation method used in functional urodynamic studies, and is a valuable tool in the assessment of resting urethral pressure in both nonclinical and clinical studies.

Here we investigated the effects of the α_1-adrenoceptor antagonists tamsulosin, prazosin and urapidil on resting urethral pressure, and compared the results with their effects on arterial blood pressure in anaesthetized female dogs.

Materials and Methods

Drugs

Tamsulosin hydrochloride ((–)-(*R*)-5-(2-((2-(*o*-ethoxyphenoxy)ethyl)amino) propyl)-2-methoxybenzenesulfonamide hydrochloride) was prepared by Yamanouchi Pharmaceutical Co. Ltd (Tokyo, Japan). Prazosin hydrochloride and urapidil were purchased from Sigma-Aldrich (St Louis, MO, USA). Urapidil was dissolved in physiological saline containing an equimolar amount of HCl. The other compounds were dissolved in physiological saline.

Animals

Female beagle dogs weighing 9.5 to 12.0 kg were housed in a temperature-controlled room with free access to water and were fed once daily. The animal experiments were performed in compliance with the regulations of the institutional Animal Ethical Committee of Yamanouchi Pharmaceutical Co. Ltd.

Measurement of urethral pressure profile

The present experiment was performed by a minor modification of a previously reported method (Sudo et al 1996). Twenty female dogs were divided into four treatment groups of five animals each. Anaesthesia was induced by intravenous (i.v.) administration of pentobarbital sodium (30 mg kg^{-1}) and maintained by continuous i.v. infusion of pentobarbital sodium (4–5 mg kg^{-1} h^{-1}). After endotracheal intubation, the animals were artificially ventilated with room air (respirator SN-480–3, Shinano Seisakusyo, Tokyo, Japan; tidal volume 20 mL kg^{-1}; respiration rate 20 breaths min^{-1}). 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. For i.v. administration of test drugs, a catheter was inserted into the femoral vein. To eliminate the possible influence of residual urine on urethral pressure, a midline abdominal incision was made, and the urinary bladder was emptied during the experiment using a catheter inserted into the bladder through its superior aspect. Following a stabilization period of at least 30 min after the surgical operation, a catheter with two side openings close to the tip (6–8 Fr, Create Medic, Kanagawa, Japan) for measurement of urethral pressure was introduced into the urinary bladder via the external urethral meatus. The catheter was connected to a pressure transducer (TP-400T, Nihon Kohden) and a syringe pump (STC-521, Terumo, Tokyo, Japan) via a three-way tap. The urethral pressure was measured with a pressure amplifier (AP-601G, Nihon Kohden) connected to the pressure transducer. Physiological saline warmed to about 38°C was infused into the urethral catheter at a rate of 1.8 mL min^{-1} using the syringe pump. At the same time, the urethral catheter was withdrawn at a rate of 25 mm min^{-1} using an autonomic withdrawing unit (AU-601G, Nihon Kohden), thereby allowing repeated measurement and recording of the urethral pressure profile.

After at least two reproducible urethral pressure profiles were obtained, maximal urethral pressure on the last urethral pressure profile was defined as the pretreatment value. Tamsulosin (1, 3 and 10 μg kg^{-1}, i.v.), prazosin (3, 10 and 30 μg kg^{-1}, i.v.), urapidil (300, 1000 and 3000 μg kg^{-1}, i.v.) or physiological saline (0.5 mL kg^{-1}, i.v.) were given at increasing doses at about 35-min intervals to all dogs in each respective drug group. The urethral pressure profile was measured 30 min after each dosing. Preliminary data confirmed that the maximal effects of test drugs on urethral pressure were maintained for 15 to 30 min after i.v. administration (data not shown). Evaluation of mean arterial blood pressure was done using data obtained at the time of the maximal effect of a test drug within the 30-min period after each dosing.

Statistical analysis

Data are expressed as the mean ± s.e.m. of five female dogs. Statistical differences among the drug groups in pretreatment values and from the corresponding values in the saline-treated group were analysed using one-way ANOVA and Student's *t*-test respectively, with differences of $P < 0.05$ considered statistically significant. All analyses were performed using the SAS statistical software (SAS Institute, Cary, NC, USA).

Results

In anaesthetized female dogs, urethral pressure profilometry was stably performed at least four times in the saline-treated group. The urethral pressure profile assumed a parabolic shape, with the resting maximal urethral pressure observed in the middle part of urethra (Figure 1). There were no significant differences among the groups in pretreatment values for maximal urethral pressure or mean arterial pressure. Tamsulosin at doses of 3 and 10 μg kg^{-1}, i.v., decreased the resting maximal urethral pressure in a dose-dependent fashion (Figures 1 and 3), whereas it had almost no effect on mean arterial blood pressure (Figures 2 and 4). Prazosin at doses of 10 and 30 μg kg^{-1}, i.v., also dose-dependently decreased the resting maximal urethral pressure (Figure 3) and caused decreases in mean arterial blood pressure (Figure 4). Urapidil also dose-dependently decreased the resting maximal urethral pressure at doses of 300–3000 μg kg^{-1}, i.v., (Figures 1 and 3), and

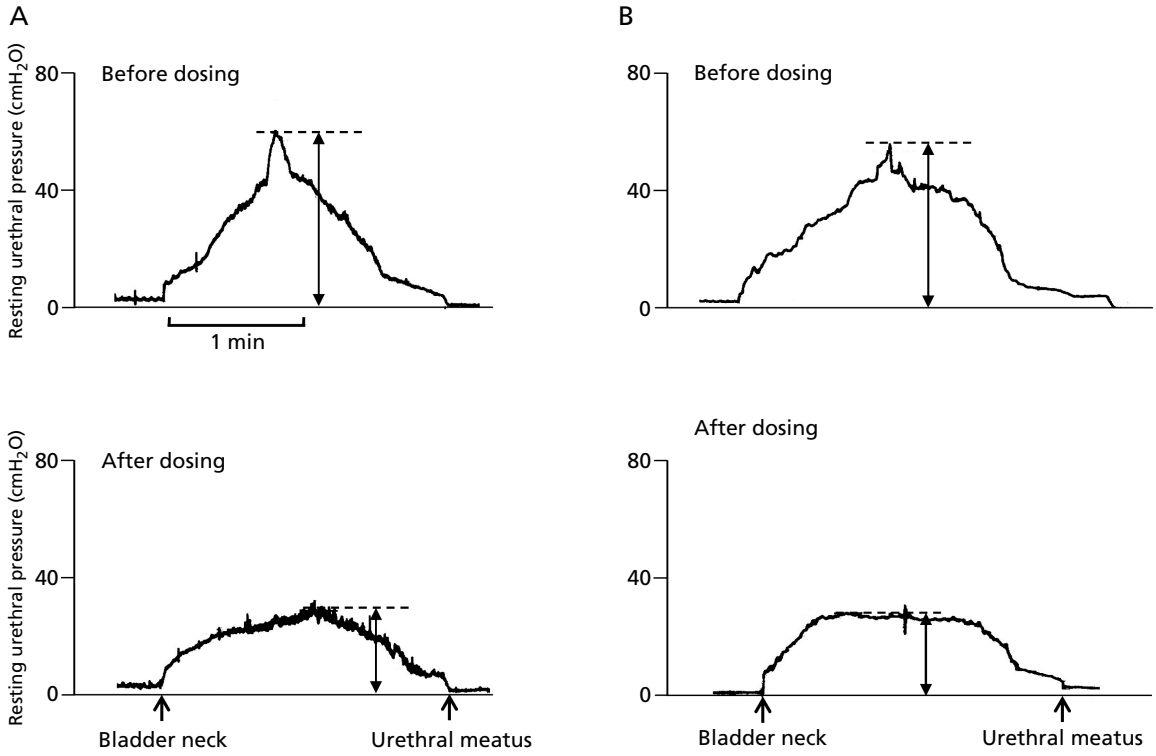

Figure 1 Typical urethral pressure profile traces before and after administration of tamsulosin (A) and urapidil (B) in anesthetized female dogs. Double-headed arrows indicate resting maximal urethral pressure. Tamsulosin at a dose of 10 μg kg^{-1} and urapidil at a dose of 3000 μg kg^{-1} were administered intravenously. To record the urethral pressure profile, physiological saline warmed to about 38°C was continuously infused at a rate of 1.8 mL min^{-1} into the urinary bladder via a catheter while the catheter was simultaneously withdrawn at a rate of 25 mm min^{-1} 30 min after drug administration.

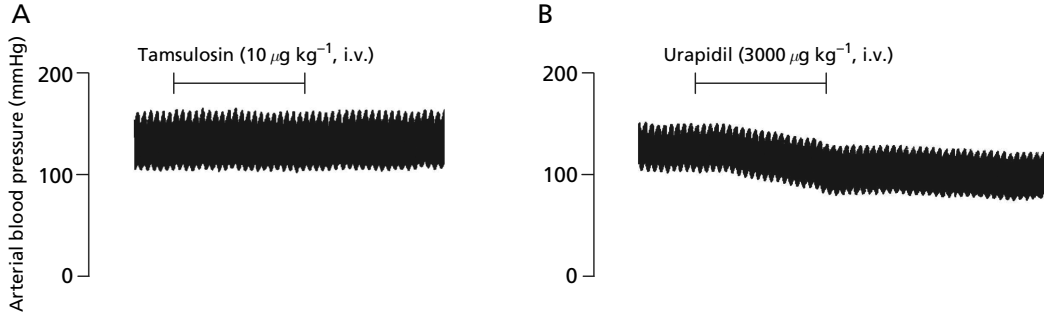

Figure 2 Typical arterial blood pressure traces before and after administration of tamsulosin (A) and urapidil (B) in anaesthetized female dogs. Tamsulosin at a dose of 10 μg kg^{-1} and urapidil at a dose of 3000 μg kg^{-1} were intravenously administered over a 1-min period.

decreased mean arterial blood pressure at doses of 1000 and 3000 μg kg^{-1}, i.v. (Figures 2 and 4).

Discussion

Pharmacotherapy has become the first choice of treatment for benign prostatic hyperplasia (Narayan & Tewari 1998). Although improvement of symptoms has been obtained with α_1-adrenoceptor antagonists, 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 that has shown uroselectivity in non-clinical (Yamada et al 1994; Hatanaka et al 2001; Sato et al 2001) and clinical (Takenaka et al 1995; Abrams et al 1997; Narayan & Tewari 1998; Reits et al 2004) studies, and is now in worldwide use for the treatment of symptoms associated with 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; Blaivas & Groutz 2000; Groutz et al 2000; Okamura et al 2002; Scarpero et al 2003). Given that the α_{1A}-adrenoceptor subtype is predominant in urethra as

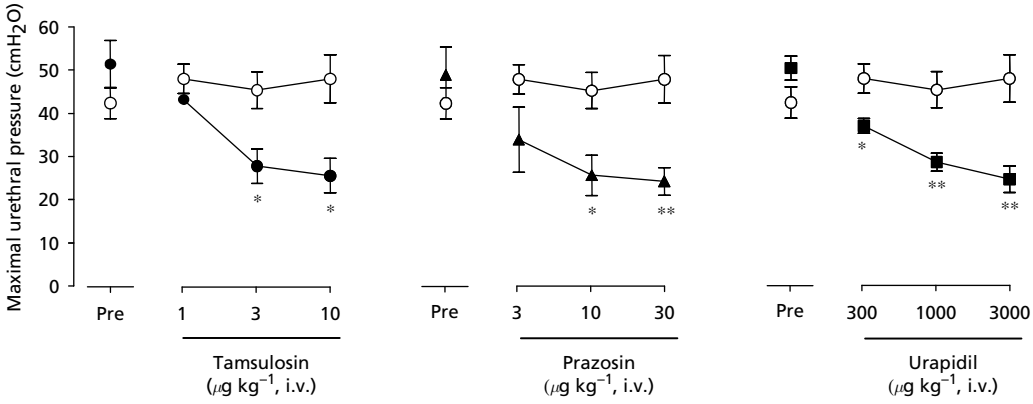

Figure 3 Effects of tamsulosin, prazosin and urapidil on resting maximal urethral pressure in anaesthetized female dogs. Each point represents the mean ± s.e.m. of five dogs. The open circles show the saline-treated group. $*P < 0.05$, $**P < 0.01$, significant difference from the saline-treated group (Student's *t*-test).

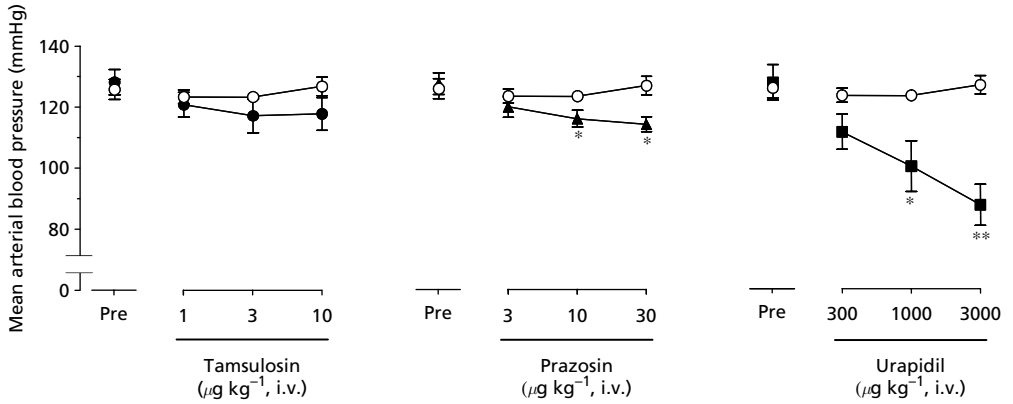

Figure 4 Effects of tamsulosin, prazosin and urapidil on mean arterial blood pressure in anaesthetized female dogs. Each point represents the mean ± s.e.m. of five dogs. The open circles show the saline-treated group. $*P < 0.05$, $**P < 0.01$, significant difference from the saline-treated group (Student's *t*-test).

well as prostate (Price et al 1993; Nasu et al 1996, 1998) and mediates the contractile response of these tissues (Forray et al 1994; Marshall et al 1995), pharmacotherapy using α_1-adrenoceptor antagonists like tamsulosin may also be effective in female patients with lower urinary tract symptoms.

The urethral closure mechanism-generated resting urethral pressure in women is mainly produced by urethral sphincter activity of smooth and striated muscle components (Thind 1995). Additional factors include the urethral sealing function of the rich vascular plexus and fibroelastic tissue in the urethral submucosa (Woodburne 1968; Raz et al 1972). Urethral pressure profilometry was originally introduced by Brown and Whickham (Brown & Whickham 1969), and has been used to assess the function of the urinary continence system in both non-clinical and clinical studies. In the present study, repeated measurement of the urethral pressure profile was successfully performed in anaesthetized female dogs. This urethral pressure profile assumed a parabolic shape, and the resting maximal urethral pressure was observed in the middle part of the urethra. These results are in agreement with previous data (Rosin et al 1980). Tamsulosin, prazosin and urapidil decreased the resting maximal urethral pressure by about 50% at the highest dose. These results suggest that urinary continence in female dogs may be partly regulated in the middle part of the urethra, and that α_{1A}-adrenoceptors are involved in the regulation of resting urethral tone. α_1-Adrenoceptor antagonists are hence considered to reduce urethral resistance by blocking α_{1A}-adrenoceptors in urethral smooth muscle. Phentolamine, a non-selective α-adrenoceptor antagonist, is also reported to induce an approximately 65% reduction in resting maximal urethral pressure in the same manner (Donker et al 1972). The present study was conducted under pentobarbital anaesthesia in accordance with the methods of a previous study (Sudo et al 1996), but the influence of the anaesthesia on urethral pressure could not be ruled out. However, given that there is no large difference in the inhibitory effect of prazosin on urethral pressure between anaesthetized and non-sedated conditions (Sudo et al 1996; Fischer et al 2003), anaesthesia is considered to have not affected the reliability of the study.

Previous data showed that tamsulosin reduced the resting urethral pressure at the prostatic site in male dogs at the same dose range as that used in this study (Sudo et al 1996). In addition, tamsulosin was reported to inhibit hypogastric nerve stimulation-induced intraurethral pressure

elevation in both male and female dogs, with almost equal effects (Ohtake et al 2004). These data indicate that there is no sex difference in the effect of tamsulosin because it inhibited urethral responses by blocking α_{1A}-adrenoceptors in both prostate and urethra equipotently (Leonardi et al 1997). Given this background, findings that tamsulosin significantly improves lower urinary tract symptoms in men (Lee & Lee 1997; Djavan 2003; Narayan et al 2003) suggest its possible usefulness in women with lower urinary tract symptoms. In fact, tamsulosin is reported to reduce resting urethral pressure in healthy women (Reits et al 2004). Furthermore, tamsulosin has also been reported to relieve lower urinary tract symptoms and increase maximum urinary flow rate in women at the same dose at which it improves voiding dysfunction in men with benign prostatic hyperplasia (Kakizaki & Koyanagi 2000). This study was not placebo-controlled and the number of patients was low, however, indicating the need for confirmation in a larger controlled study.

In contrast to prazosin and urapidil, which significantly decreased arterial blood pressure, tamsulosin had only a negligible effect on arterial blood pressure in female dogs in this study. Although the decrease by prazosin was significant, actual values were not largely different from those of tamsulosin. Tamsulosin has 12- to 20-fold and 2- to 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). Prazosin and urapidil are non-selective antagonists for α_1-adrenoceptor subtypes (Testa et al 1993; Takei et al 1999). These data suggest that α_{1B}-adrenoceptors partly regulate blood pressure in dogs. In addition, since urapidil has activity as a 5-HT_{1A} receptor agonist that induces hypotension by acting on central sites (Ramage 1991), it is considered to show more potent hypotension than other α_1-adrenoceptor antagonists.

In human arteries, systemic investigation of α_1-adrenoceptor subtype based on mRNA and protein expression data has found an overall dominance of α_{1A}-adrenoceptors, but that α_1-adrenoceptor density doubles with ageing and this is mostly due to an increase in α_{1B}-adrenoceptor (Rudner et al 1999). A lack of α_{1B}-adrenoceptor antagonism may therefore partly abolish the vascular effects of α_1-adrenoceptor antagonists in the elderly. However, it has recently been suggested that the uroselective profile of tamsulosin cannot be explained by its subtype selectivity for α_1-adrenoceptors only. Rather, tamsulosin shows highly sustained occupancy of α_1-adrenoceptors in the rat prostate after a marked reduction in plasma concentration (Ohkura et al 1998), and pharmacological concentrations in dogs are highly retained for longer times in target organs such as prostate and urethra than in plasma and arteries (Hatanaka et al 2001; Sato et al 2001). The high distribution to urethra may therefore also have contributed to the uroselectivity of tamsulosin in the present study and in humans. Moreover, tamsulosin can be made available in a sustained-release formulation with a decreased absorption rate, allowing single-daily oral administration. Transient orthostatic hypotension is often seen after the initial administration of an α_1-adrenoceptor antagonist, and is considered to reflect the absorption rate of the drug (Takenaka et al 1995). Indeed, prazosin and urapidil must be orally administered twice daily with dose titration to avoid these effects.

Conclusions

Tamsulosin, which has been used for the treatment of dysuria associated with benign prostatic hyperplasia, dose-dependently decreased the resting maximal urethral pressure with negligible effect on mean arterial blood pressure in female dogs. These findings suggest that tamsulosin will be useful in the treatment of voiding dysfunction associated with bladder outlet obstruction in women as well as men, with little hypotensive effect.

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