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The Effect of Tamsulosin on the Response of the Rabbit Bladder to Partial Outlet Obstruction

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Aim: To determine if tamsulosin treatment prevents or decreases the incidence and severity of outlet obstruction-induced bladder dysfunction in rabbits. **Materials and Methods:** Male New Zealand White rabbits were treated with tamsulosin or vehicle for 4 weeks with treatments initiated 1 week prior to sham or obstruction surgery. Cystometry was done on anesthetized rabbits 21 days after surgery. The bladders were then removed, weighed, and prepared for in vitro whole bladder studies. Responses to 32 Hz field stimulation (FS), carbachol, phenylephrine, and KCl were measured. **Results:** Obstruction resulted in a significant increase in bladder weight, which was unchanged by tamsulosin treatment and a significant increase in micturition pressure in the vehicle-treated group but not in the tamsulosin-treated group. Compliance was significantly decreased in both obstructed groups. The vehicle-treated obstructed rabbits had a very sharp increase in intravesical pressure as the bladder reached capacity; this was not seen in the tamsulosin-treated obstructed rabbits. Tamsulosin did not change the pattern of modifications in contractile responses induced by bladder outlet obstruction. **Conclusions:** In vitro responses of vehicle and tamsulosin-treated obstructed rabbit groups in this study were similar. A greater micturition pressure was found for the vehicle-treated obstructed group than for the tamsulosin-treated obstructed group, which was probably due to decreased urethral resistance in the latter. On a functional basis, the higher compliance at capacity and decreased micturition pressure in the tamsulosin-treated obstructed group would be considered beneficial for bladder function. *Neurourol. Urodynam. 25:89–94, 2006.* © 2005 Wiley-Liss, Inc.

Key words: bladder; bladder outlet obstruction; BPH; LUTS; rabbit; tamsulosin

INTRODUCTION

Urinary bladder dysfunction secondary to benign prostatic hyperplasia (BPH) in man is a major health problem [Zderic et al., 1996]. Nearly 80% of the male population will seek medical relief for the symptoms which include urgency, frequency, and nocturia [Girman and Guess, 2000]. It is apparent that these distressing symptoms are the result of significant changes in the physiology and pharmacology of the obstructed bladder [Zderic et al., 1996]. It is also well established that relief of the obstruction through surgery at the level of the prostate per se does not always reverse the underlying abnormalities of the detrusor [Fawzy, 2001]. Understanding the nature of the changes and the links between obstruction and alterations in the detrusor could have profound implications for the treatment of the disorder.

Alpha-1 adrenergic receptor blockers, such as tamsulosin, have proven to be very effective in the treatment of the symptoms of BPH [Andersson et al., 2002]. It has been suggested that obstruction stimulates an upregulation of alpha-1 adrenergic receptors in the bladder [Perlberg and Caine, 1982; Hampel et al., 2002]. Thus, by binding to alpha-1 receptors, alpha-blockers can relieve the symptoms of BPH [Andersson et al., 2002]. The specific aims of this project were to first establish if partial outlet obstruction in rabbits results in increased alpha-1 adrenergic responsiveness in the bladder body, and then determine if tamsulosin treatment prevented or decreased the incidence and severity of the bladder dysfunctions induced by outlet obstruction. In addition, it was assessed whether tamsulosin treatment had any effect on the functional deterioration of the bladder noticed by altered responsiveness to the muscarinic agonist carbachol, and stimulation of neuronal autonomic responses by electrical field stimulation (FS), or KCl.

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MATERIALS AND METHODS

Drug Treatment

Adult male New Zealand White rabbits (3–5 kg) (Millbrook Breeding Labs, Amherst, Massachusetts) were separated into four groups of 8–14 rabbits each. Four ALZET 4ML2 osmotic pumps (ALZA Corporation, Mountain View, CA) were implanted in each rabbit. Rabbits in groups 1 and 2 received pumps containing tamsulosin (8.1 mg/ml distilled water); those in groups 3 and 4 received pumps containing vehicle. The pumps were placed in the subscapular neck region and delivered 27 μg tamsulosin/kg/day (0.25 μl/hr) for 4 weeks continuously.

Surgical Induction of Partial Outlet Obstruction

One week following pump implantation, mild partial outlet obstructions were created in the rabbits in groups 1 and 3, and those in groups 2 and 4 were given sham operations. Rabbits were anesthetized with 30 mg/kg ketamine and 5 mg/kg xylazine. Anesthesia was maintained with isoflurane. Bladders were catheterized through the urethra with an 8 Fr. Foley catheter (Mentor Urology, Santa Barbara, CA) and the bladder exposed through a midline incision. The bladder neck and urethra were cleared of fat and connective tissue. A mild obstruction was created by placing a 2-zero silk ligature loosely around the catheterized urethra so that the tip of a curved hemostat could fit comfortably between the ligature and the urethra. The catheter was then removed and the wound was closed with catgut. Each rabbit was placed in the recovery room and observed for several hours postoperatively until it recovered from anesthesia. Food and water intake and urine excretion were monitored daily, and each rabbit was observed for signs of pain and discomfort. For analgesia, Nubain (0.1 mg/kg, im) was given following surgery. Sham surgery consisted of anesthesia and exposing the bladder and urethra, but no ligature was placed.

Cystometry

After 21 days of obstruction each rabbit was anesthetized with ketamine and xylazine, the obstructive ligature was removed, and the bladder catheterized. The volume of urine in the bladder was recorded. Intravesical pressure was monitored on a model D (Grass Instruments, Quincy, MA) polygraph using a P23XL Statham pressure transducer (Grass Instruments). Cystometry was done at 1.4 ml/min until either a micturition contraction or overflow incontinence occurred. Functional bladder capacity is defined as the volume at which a micturition contraction occurs. In obstructed rabbits, the micturition contraction is often not strong enough to fully empty the bladder, and the remaining volume can often exceed the functional capacity. This volume is defined as the residual volume.

Whole Bladder

The bladder was excised as an intact organ as low on the urethra as possible and mounted on an electrode-tipped "J" tube as an isolated whole bladder and placed within a 300 ml bath filled with oxygenated Tyrodes solution maintained at 37°C. The bladder was filled to 20 ml and the contractile responses to FS (32 Hz), carbachol (20 μM), phenylephrine (100 μM), and KCl (120 mM) were measured.

The selected conditions for this experiment were shown to elicit maximal responses for carbachol and KCl in bladder body strips of non-obstructed animals while showing a decreased responsiveness in bladder-obstructed conditions. The conditions for FS at 32 Hz were shown to be most sensitive to decreased responsiveness by mild, as well as severe bladder obstruction in rabbits.

Statistical Analyses

Data are expressed as means ± SEM. Analysis was done using 1- or 2-way ANOVA followed by Bonferroni's multiple range test. A P-value <0.05 was considered significant.

RESULTS

The level of obstructive dysfunction is based on the bladder weight (level of hypertrophy) [Kato et al., 1990]. In general, bladder weights under 10 g are considered mild obstructions.

Two obstructed rabbits receiving vehicle had bladders weighing less than 5 g, indicating that they were not obstructed. These rabbits are not included in the results. Nine vehicle-treated sham-operated, eight tamsulosin-treated sham-operated, nine vehicle-treated obstructed, and eight tamsulosin-treated obstructed rabbits completed the study.

Partial outlet obstruction resulted in significant increases in bladder weight compared to sham-operated controls. There were no significant differences in bladder weight between vehicle- and tamsulosin-treated rabbits receiving the same surgical procedure (Table I). Partial outlet obstruction resulted in significant increases in the volume of urine present in the bladder at the time of cytometry (residual).

The time to micturition, and bladder capcity were lower for the obstructed tamsulosin group than for the obstructed vehicle group (Table II). Partial outlet obstruction resulted in an increase in micturition pressure in the vehicle-treated rabbits, but not in the tamsulosin-treated group (Table II). This suggests that either the tamsulosin-treated group generated lower micturition pressures than the vehicle-treated group or the urethral resistance of the tamsulosin-treated group was lower than the vehicle-treated group.

Figure 1 displays the mean cystometric patterns for the four groups of rabbits. There were no differences between the vehicle- or tamsulosin-treated sham groups (Fig. 1A). Comparisons of the full cystometry curves by 2-way ANOVA indicated that partial outlet obstruction resulted in significant decreases in

TABLE I. Effects of Treatments on Bladder Weight, Residual Volume, and Bladder Capacity

		Mean ± SEM (range)		
Treatment	No. of subjects	Bladder wt (g)	Residual (ml)	Capacity (ml)
Sham vehicle	9	2.80 ± 0.42 (1.62–5.60)	18.6 ± 5.9 (0–54)	39.7 ± 11.8 (6–124)
Sham tamsulosin	8	2.68 ± 0.17 (2.17–3.52)	32.0 ± 6.2 (6–56)	39.3 ± 8.0 (12–70)
Obstructed vehicle	9	8.39 ± 1.08[a,b] (5.00–13.52)	93.0 ± 23.4[a] (27–268)	56.3 ± 13.3 (7–106)
Obstructed tamsulosin	8	10.86 ± 1.19[a,b] (6.06–14.98)	116.3 ± 22.6[a,b] (50–225)	22.5 ± 1.6 (21–25)

[a]Significantly different from vehicle-treated sham-operated group at $P < 0.05$.
[b]Significantly different from tamsulosin-treated sham-operated group at $P < 0.05$.

compliance in both the vehicle- and tamsulosin-treated obstructed groups compared to the sham-operated rabbits (Fig. 1B,C). The vehicle-treated obstructed rabbits had a very steep increase in intravesical pressure as the bladder reached capacity (Fig. 1B). At capacity, the intravesical pressure developed by the vehicle-treated obstructed rabbits was significantly greater than that developed by either vehicle- or tamsulosin-treated sham-operated rabbits (Fig. 1B). After treatment with tamsulosin, the increase in intravesical pressure at capacity was not observed (Fig. 1C,D). These findings indicate that the obstructed group receiving tamsulosin were more compliant at capacity than the obstructed group receiving vehicle. Compliance (change in intravesical pressure) between 80% and 100% capacity for the sham groups were similar (2.5 ± 2 cm H_2O for tamsulosin shams and 2.3 ± 1.5 cm H_2O for vehicle shams). Obstructed-vehicles showed a compliance of 10 ± 4 cm H_2O, whereas the obstructed-tamsulosin group had a compliance similar to that of the shams (2.5 ± 3 cm H_2O).

The functional responses to 32 Hz FS is presented in Figure 2. Partial outlet obstruction resulted in significant decreases in the responses in both groups. No statistically differences were noted between vehicle and tamsulosin. Similarly, partial outlet obstruction significantly reduced the responses to carbachol in both groups (Fig. 3). In addition, the tamsulosin sham was significantly lower than the vehicle sham (Fig. 3). There were no statistical differences in the responses to KCl (Fig. 4). Phenylephrine did not have any effects on intravesical pressure (data not shown).

DISCUSSION

Tamsulosin is a commonly used and effective treatment for the symptoms of BPH (urgency, frequency, and nocturia) [Dunn et al., 2002; Nickel, 2003]. The filling (irritative) symptoms in patients with BPH and outflow obstruction have been associated with bladder dysfunction produced by the obstruction. Due to the beneficial effects of tamsulosin and other alpha-1-adrenoceptor blockers on these symptoms, interest has focussed on the possible interference of tamsulosin with alpha-1-adrenoceptor-mediated processes taking place in the bladder. A recent clinical study indicated that treatment with tamsulosin resulted in a reduction of bladder mass (evaluated using ultrasound analysis) and that the reduction of

TABLE II. Cystometric Characteristics

		Mean ± SEM (range)	
Treatment	No. of subjects	Time to micturition (min)	Micturition pressure (cm H_2O)
Sham vehicle	9	26.4 ± 8.4 (4–88)	21.2 ± 2.3 (15–35)
Sham tamsulosin	7	30.6 ± 5.7 (15–50)	28.1 ± 6.7 (13–66)
Obstructed vehicle	5	33.3 ± 15.1 (5–88)	55.3 ± 6.0[a,b] (40–72)
Obstructed tamsulosin	5	15.8 ± 0.6 (15–17)	37.2 ± 9.2 (13–70)

[a]Significantly different from vehicle-treated sham-operated group at $P < 0.05$.
[b]Significantly different from tamsulosin-treated sham-operated group at $P < 0.05$.

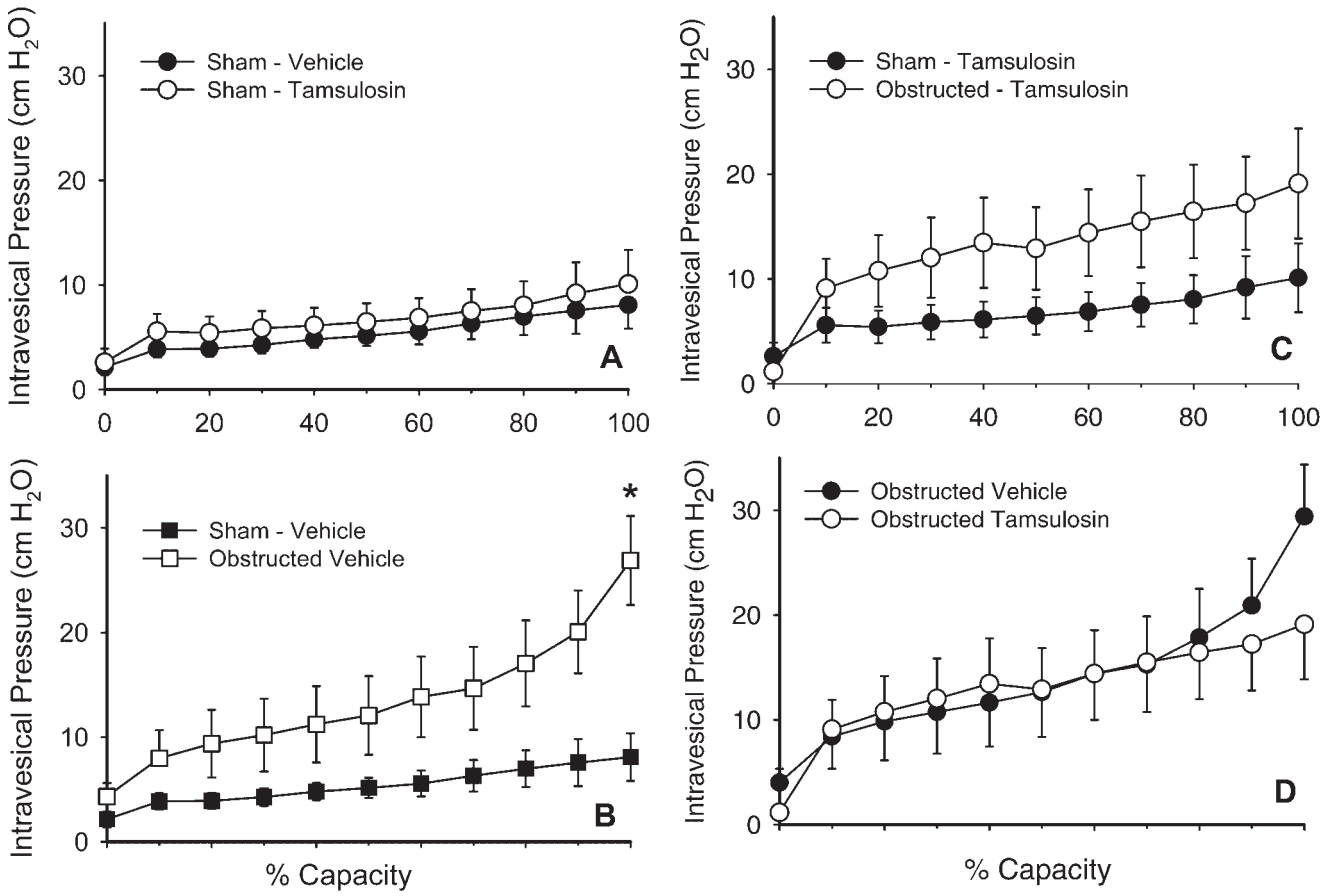

Fig. 1. In vivo cystometric curves. **A**: comparison of curves for vehicle- and tamsulosin-treated sham-operated rabbits; (**B**) comparison of curves for vehicle-treated sham-operated and obstructed rabbits; (**C**) comparison of curves for tamsulosin-treated sham-operated and obstructed rabbits; and (**D**) comparison of curves for vehicle- and tamsulosin-treated obstructed rabbits. Bladders were filled at 1.4 ml/min until a micturition contraction or leakage occurred. Each point indicates the mean ± SEM. Numbers of subjects are indicated in Table I.

bladder mass may be related to improved symptoms [Sironi et al., 2002]. In experimental BOO models in animals differential results are found: In mildly obstructed rabbits, there was no consistent decrease in bladder weight in tamsulosin-treated animals at a similar exposure level of the drug [Korstanje et al., 2002]. In rats alpha-1 adrenoceptors were found to be upregulated in obstructed bladders [Hampel et al., 2002]; consistently, the effects of alpha-1 adrenoceptor

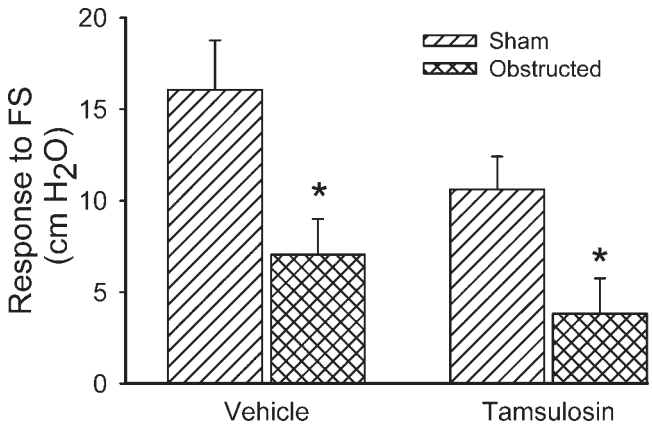

Fig. 2. Responses of in vitro whole bladders to 32 Hz electrical field stimulation (FS). Each bar indicates the mean ± SEM. Numbers of subjects are indicated in Table I. *, significantly different from sham at $P < 0.05$.

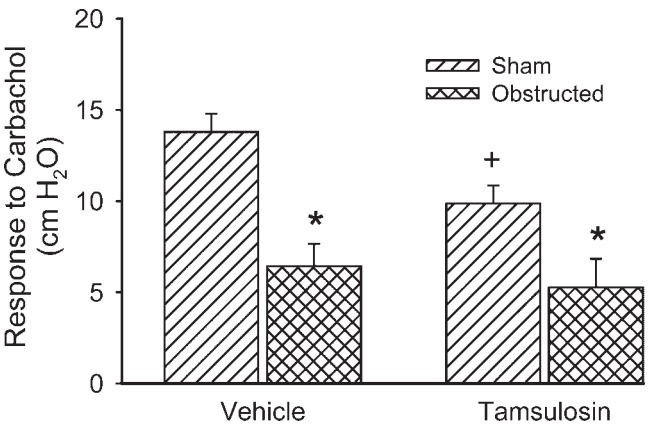

Fig. 3. Responses of in vitro whole bladders to carbachol (20 μM). Each bar indicates the mean ± SEM. Numbers of subjects are indicated in Table I. *, significantly different from obstructed; +, significantly different from vehicle groups at $P < 0.05$.

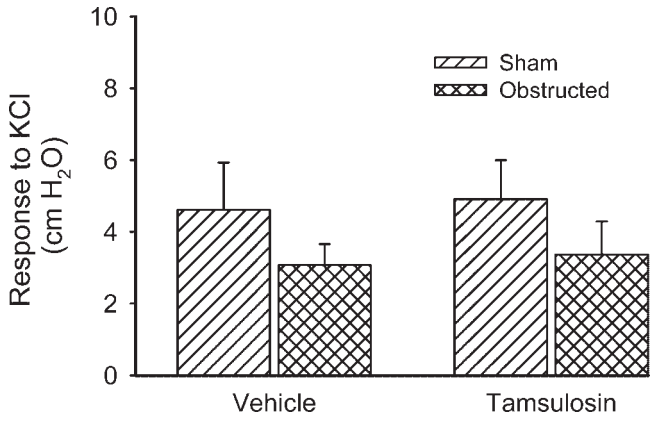

Fig. 4. Response of in vitro whole bladders to KCl (120 mM). Each bar indicates the mean ± SEM. Numbers of subjects are indicated in Table I.

blocking drugs on bladder function were shown [Andersson, 1999].

The present study confirmed that obstructed bladders require an increased pressure to empty [Levin et al., 1986] and that this condition is associated with a decreased efficacy of neuronally released neurotransmitter (electrical stimulation) and muscarinergic agonism at functional responses in rabbit bladders [Levin et al., 1997]. The response to KCl-induced depolarization was not significantly impaired, however, and the alpha-1-adrenoceptor agonist phenylephrine failed to show contractile effects. The latter is at variance with results obtained with another selective alpha-1-adrenoceptor agonist, methoxamine in this model [Levin and Wein, 1982], while in the study with mildly obstructed BOO rabbits methoxamine-responsive and -unresponsive bladder dome strips were found [Korstanje et al., 2002].

The study showed that tamsulosin treatment prevented the decrease of compliance at high capacity of the bladder in vivo as seen in the vehicle-treated animals. However, since there were no differences in the in vitro contractile responses to any form of stimulation in the isolated whole-bladder studies, this compliance effect was not likely to be at the level of local alpha-1 adrenoceptors in the bladder. But alpha-1-adrenoceptors are involved in neurotransmission circuits involved in micturition control as well [Ishizuka et al., 1996], and at high capacity there is inevitably a firm distension of the bladder, which triggers bladder afferent firing and subsequent activation of the voiding reflex pathway [De Groat et al., 1999]. This pathway involves a.o. alpha-1-adrenergic receptors at the level of the sacral spinal cord and ganglia. In rats, it was assumed that the reduction of micturition pressure induced by the alpha-1-adrenoceptor blocker doxazosin, was caused by the blockade of spinal cord alpha-1-adrenoceptors [De Groat et al., 1999]. So, our findings could have a similar mechanistic explanation. In addition, blockade of local alpha-1A-adrenoceptors in the urethra by tamsulosin could be expected to lead to relaxation of the urethra, thereby decreasing urethral resistance, thus preventing the build-up of high pressure. An alternative explanation would be that there was less connective tissue (fibrosis) within the bladder of the tamsulosin-treated group than in the vehicle-treated group. This would be explained by a blockade of alpha-1-adrenoceptors (probably of the alpha-1D-type) which couple to protein kinase pathways, mediating fibrosis [Xin et al., 1997]. Further studies will have to be done to examine the bladder wall structure and determine if the improved compliance at capacity was due to there being less connective tissue (fibrosis) in the tamsulosin-treated rabbits.

Since we do not know the metabolism of tamsulosin in rabbits, it is impossible to correlate the dose used in these studies with the effective doses used in man.

Although the mechanistic explanation for our finding is not clear yet, the clinical implications can be contemplated: tamsulosin would be expected to protect against hydronephrosis and kidney damage that can be the consequence of high bladder pressure, for example, after acute urinary retention [Mustonen et al., 2001], while it has been shown that tamsulosin reduces the incidence of acute urinary retention after prostatic surgery [Patel et al., 2003]. So, on a functional basis, the decreased compliance at capacity and lower micturition pressure (which was equal to the micturition pressure of sham-operated rabbits) should be beneficial for bladder function.

CONCLUSIONS

This study shows that in bladder obstructed rabbits tamsulosin treatment does not affect bladder weight, residual volume, and bladder capacity, or the responsiveness of whole bladder in vitro. However, tamsulosin modulates the deteriorated pressure–volume relationship in bladder-obstructed animals by improving the compliance at high capacity of the bladder. It can, therefore, be speculated that tamsulosin would prevent complications of persistent severe bladder outlet obstruction (such as hydronephrosis) and acute urinary retention and would preserve bladder function.

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