Investigation of the Effects of Tamsulosin on Blood Pressure in Normotensive, Controlled Hypertensive, and Uncontrolled Hypertensive Men with Benign Prostatic Hyperplasia

Kenji Yasukawa,* Yasushi Miyazawa, and Yuuki Tajima

International Clinical Development Department, Yamanouchi Pharmaceutical Co., Ltd., 17–1 Hasune 3-chome, Itabashi-ku, Tokyo 174–8612, Japan

(Received January 9, 2001; Accepted January 25, 2001)

Up to the mid-1990s benign prostatic hyperplasia (BPH) was commonly treated surgically. However, surgery is associated with numerous instances of failure, high patient morbidity rates, and substantial annual costs. Tamsulosin, an α_1-adrenergic receptor antagonist, was originally developed as an alternative to surgery for BPH. It significantly improves urinary obstruction by relaxing smooth muscle in the bladder neck and prostate via specific inhibition of the α_{1A}-adrenergic receptor subtype, the predominant subtype in these tissues. However, since α_1-adrenergic receptors also mediate constriction of smooth muscle in the vascular wall, extensive tests were carried out during phase III clinical trials to investigate whether tamsulosin has any effect on mediation of the cardiovascular system. Since BPH is a condition that affects men from middle age and many patients are also hypertensive, a subanalysis was carried out during these phase III clinical trials to investigate whether tamsulosin has any effect on blood pressure control or vasodilation in men who are also being treated for hypertension. During 13-week double-blind administration of once-daily tamsulosin or placebo, no statistically significant differences were observed in blood pressure or heart rate among normotensive, controlled hypertensive, and uncontrolled hypertensive patients. The results of this study demonstrate that tamsulosin can be used in BPH patients who are hypertensive without any restrictions on blood pressure control medication.

Key words —— tamsulosin, benign prostatic hyperplasia, hypertension, hypotensive effect

INTRODUCTION

Benign prostatic hyperplasia (BPH) is a common, nonmalignant clinical condition in older men that results in proliferation of the stromal/epithelial cells of the prostate gland, producing symptoms such as dysuria, urinary retention, urinary obstruction, and urgency that have a significant impact on daily life. BPH is age dependent, with manifestations of tissue hyperplasia in men as early as their 40s. One survey reports that 17% of men aged 50 to 59 years, 27% aged 60 to 69 years, and 37% aged 70 to 79 years have urinary symptoms related to prostatic obstruction,[1] and the histological characteristics of BPH can be found in 88% of autopsies in men ≥ 80 years old.[2] Calculations based on the US Agency for Health Care Policy and Research (AHCPR) BPH diagnostic guidelines[3] in a population-based, cross-sectional study estimated that 5.6 million of the US white male population aged 50 to 79 years are eligible to discuss treatment options for BPH, and that by the year 2020 this number will have doubled due to the aging of the population.[4]

Up to the mid-1990s BPH was commonly treated surgically. Transurethral resection of the prostate (TURP), the most common procedure, was carried out up to 400000 times annually in the U.S.A., at a cost of over US$1 billion, placing a substantial economic burden on the healthcare system.[5] Open prostatectomy has been associated with lower perioperative mortality and retreatment rates than TURP, reducing long-term cost, but it is also more invasive and morbid. More recent minimally invasive surgical techniques such as laser prostatectomy, microwave hyperthermia, and transurethral needle ablation of the prostate have been developed, but the cost of these is difficult to estimate and long-

*To whom correspondence should be addressed: International Clinical Development Department, Yamanouchi Pharmaceutical Co., Ltd., 17–1 Hasune 3-chome, Itabashi-ku, Tokyo 174–8612, Japan. Tel.: +81-3-5916-5312; Fax: +81-3-5916-5606; E-mail: yasukawa.kenji@yamanouchi.co.jp

term outcome is still to be assessed.[6)]

In one study carried out by Kaplan *et al*.[7)] on 174 consecutive patients with previously untreated BPH, most patients when given informed choice between four categories of treatment opted for less aggressive treatments than surgery regardless of symptom severity. One year later, 85% continued to be maintained on their original choice of treatment, indicating a high level of patient satisfaction with their choice. Attempts have therefore been made to develop treatments for BPH that are less invasive, more economical, and associated with fewer side effects, especially for patients with mild to moderate disease, those awaiting or wishing to delay surgery, or those who prefer medical management.[8,9)]

Adrenergic receptors mediate many important responses *in vivo*, one of which is vasoconstriction *via* α_1-receptors in the vascular wall. Arterial and venous vasodilatation occurs when α_1-adrenergic receptors in the vascular wall are blocked. As a result, blood pressure falls because of decreased peripheral vascular resistance and heart rate (HR) rises in response, leading to increased cardiac output. Many α_1-adrenergic receptor antagonists were therefore originally developed and approved for the treatment of hypertension, although since March 2000 physicians in the U.S.A. have been advised against prescribing them for this indication.[10,11)]

It is known that α_1-adrenergic receptor antagonists suppress contraction of smooth muscles other than those in the vascular wall. Researchers noted that they also inhibit contraction of the basal segment of the urinary bladder and prostatic tissue. This provided theoretical evidence for the use of α_1-adrenergic receptor antagonists in the treatment of symptoms such as the sensation of not emptying the bladder and weak stream associated with BPH. Since Caine *et al*. reported that α_1-adrenergic receptor antagonists were effective in the treatment of BPH,[12)] numerous clinical trials demonstrating their efficacy have been carried out. However, some α_1-adrenergic receptor antagonists, such as prazosin, terazosin, and doxazosin,[8, passim)] which were originally developed as antihypertensive agents, have been used off label for treating BPH at the same doses as for treating hypertension. Since BPH patients are mostly elderly and many are also hypertensive, this raised the problem of how to control blood pressure in patients already being treated for hypertension when α_1-receptor antagonists are administered for BPH.

The second-, or, as it is also called, third-generation α_1-adrenergic receptor antagonist tamsulosin was specifically developed for the treatment of BPH. It exhibits selectivity for the α_{1A}-adrenergic receptor, the predominant α-receptor subtype in the prostate, prostatic capsule, prostatic urethra, and bladder neck,[8,13–15)] resulting in smooth muscle relaxation in the prostate and bladder neck, which causes an improvement in symptoms and urinary flow rate. Unlike other α_1-adrenergic receptor antagonists, however, it was intended to have minimal effect on other α-adrenergic receptor subtypes and thus low potential for side effects due to α-adrenergic blockade in other systems, *e.g*., vasodilatation. Since many BPH patients are hypertensive, it was necessary to study the effect of tamsulosin on blood pressure control in patients already being treated for hypertension.

MATERIALS AND METHODS

Two multicenter, placebo-controlled, double-blind, phase III clinical trials, US92-03A and US93-01, were carried out in the U.S.A. between 1992 and 1993 to investigate the safety and efficacy of tamsulosin 0.4 mg once daily or tamsulosin 0.8 mg once daily.[16,17)] Both studies included subgroup analyses comparing the effect of tamsulosin on the sitting vital signs of controlled hypertensives, uncontrolled hypertensives, and normotensive patients to determine whether tamsulosin had clinically useful antihypertensive activity and whether its concomitant use in treated hypertensives had an additive effect. Written informed consent was obtained from all patients prior to commencement of the study.

Both US92-03A and US93-01 enrolled men aged ≥ 45 years with signs and symptoms of BPH. Patients in both studies entered a 4-week, single-blind screening phase. During this period, patient eligibility for the study and protocol compliance were assessed at two or three clinic visits. Patients were required at each visit to show symptoms of urinary obstruction by a total score on the American Urological Association (AUA) Symptom Score questionnaire for BPH ≥ 13 and bladder outlet obstruction as defined by a peak urinary flow rate (Q_{max}) ≥ 4 and ≤ 15 ml/sec (measured by Urodyn® 1000, Dantec Measurement Technology A/S, Skovlunde, Denmark). During this testing procedure, each patient was required to void a total urine volume of ≥ 125 ml. Each patient was also required to demonstrate a postvoid residual urine volume of < 300 ml as measured by abdominal ultrasound. On comple-

tion of the screening phase, patients were randomized to receive either tamsulosin 0.4 mg/day, tamsulosin 0.4 mg/day for one week followed by tamsulosin 0.8 mg/day, or daily placebo for 13 weeks. The dose increase in the tamsulosin 0.8 mg/day group was made for all patients assigned to this group regardless of initial patient response.

Eligible patients were permitted concomitant medications provided that they would not interfere with the action of tamsulosin, potentiate adverse events, or influence the symptoms of BPH. Use of other α-adrenergic receptor antagonists, α-adrenergic receptor agonists, drugs with anticholinergic activity (including antihistamines other than terfenadine), antispasmodics, parasympathomimetics, and cholinomimetics was not permitted. Patients were permitted to take acetylsalicylic acid and paracetamol, but nonprescription cold and allergy remedies containing any of the above classes were not allowed.

In US92-03A, patients remained at the study center after receiving the first randomized test agent (visit 4) for an 8-hr observation period, during which clinical status, response to therapy, vital signs, orthostatic response, and electrocardiograms were monitored. In addition, if changes in a patient's status occurred in terms of a decrease in diastolic blood pressure (DBP), elevation in HR, and/or symptoms related to the cardiovascular system, an emergent schedule of measurements was implemented. Subsequent visits to the study center for safety and efficacy tests were scheduled at 1 week and 2, 4, 7, 10, and 13 weeks (visits 5–10 inclusive). All visits were scheduled 4–8 hr after dosing with tamsulosin to coincide with peak plasma drug levels.

In US93-01, the first dose of double-blind medication was taken the day following visit 3. Subsequent visits (4–8) took place at 1, 2, 5, 9, and 13 weeks. Patients did not remain for observation during any visit in the double-blind administration period. They were contacted by telephone to determine their tolerance of the first dose of study medication (the day after visit 3) and again when an increase in the dose of study medication was possible (the day after visit 4). Visits 4 and 5 were scheduled 4–8 hr after dosing to coincide with peak plasma drug levels, and visits 6, 7, and 8 were scheduled 24–27 hr after dosing to coincide with trough plasma drug levels.

For the subgroup analyses of hypertensive and normotensive patients in both studies, patients were defined as:

1) controlled hypertensive if they had a history of hypertension or were currently being treated for hypertension with a US Food and Drug Administration (FDA)-approved antihypertensive medication and had an average of the last two DBP measurements in the sitting position of < 90 mmHg during the single-blind placebo evaluation period;
2) uncontrolled hypertensive if their average sitting DBP was ≥ 90 mmHg in the same period regardless of any antihypertensive medication they were taking; or
3) normotensive if their average sitting DBP was < 90 mmHg in the same period, they did not have a history of and were not receiving medication for hypertension, and were not hypertensive at baseline.

Patients who took a medication indicated for the treatment of hypertension and other indications, but which was taken for an indication other than hypertension and those who started, stopped, changed dosage, or switched antihypertensive medication during the double-blind treatment period were excluded from the subgroup analysis.

For normotensives, controlled hypertensives, uncontrolled hypertensives, and all hypertensives combined, actual values of sitting vital signs and change from baseline scores were summarized on a visit-by-visit basis, as well as at the study endpoint (defined as the final visit preceding which the patient had not discontinued taking the test agent for more than two days, including the day of the visit). Tests for interactions between treatment and subgroup were based on analysis of variance with effects for treatment, investigator site, subgroup (controlled hypertensive, uncontrolled hypertensive, or normotensive), and treatment-by-subgroup interaction.

RESULTS

US92-03A

In study US92-03A, a total of 3574 patients were enrolled in the screening phase, of whom 756 were randomized to the three treatment groups (248 to tamsulosin 0.8 mg/day, 254 to tamsulosin 0.4 mg/day, and 254 to placebo) and received at least one dose of study agent. Safety information was collected and recorded from these patients and all were eligible for the safety analyses. Their demographic and background characteristics are shown in Table 1.

The overall test for treatment group differences in mean age was statistically significant, with a dis-

Table 1. Demographic and Background Characteristics of the Safety Population of US92-03A

Characteristic	Placebo	Tamsulosin 0.4 mg/day	Tamsulosin 0.8 mg/day	p value*
No. patients	254	254	248	
Mean age ± S.E. (years)	59.5 ± 0.5	57.3 ± 0.5	59.0 ± 0.5	0.005**
Age distribution (%)				
45–54	74 (29)	104 (41)	71 (29)	
55–64	108 (43)	96 (38)	112 (45)	
65–74	62 (24)	45 (18)	64 (26)	
≥ 75	10 (4)	9 (4)	1 (< 1)	
Race (%)				
Caucasian	228 (90)	230 (91)	229 (92)	
Black	26 (10)	20 (8)	15 (6)	0.232***
Asian/other	0 (0)	4 (2)	4 (2)	
Mean weight ± S.E.**** (kg)	86.7 ± 0.9	87.1 ± 0.9	87.8 ± 0.9	0.694
Blood pressure status (%)				
Normotensive	172 (68)	182 (72)	170 (69)	
Controlled hypertensive	27 (9)	21 (8)	21 (8)	0.814
Uncontrolled hypertensive	41 (16)	37 (15)	40 (16)	
Not calculated	14 (6)	14 (6)	17 (7)	
Severity of baseline disease (AUA symptom score) (%)				
Severe (≥ 20)	114 (45)	118 (46)	121 (49)	0.675
Moderate (8–19)	140 (55)	136 (54)	127 (51)	

*For overall treatment group comparison. **Statistically significant based on analysis of variance with treatment and investigator-site effects (for age and weight) and extended Mantel-Haenszel test with investigator sites as strata for all other characteristics. ***Based on a test of Caucasian vs. Black. ****Calculated at baseline.

proportionate number of younger patients in the two treatment groups. In addition, only one patient in the tamsulosin 0.8 mg/day group was aged ≥ 75 years, whereas the tamsulosin 0.4 mg/day and placebo groups had nine and 10 such patients, respectively. There were no other overall treatment group differences for demographic characteristics among the three patient groups.

The majority of patients were Caucasian (≥ 90% in each treatment group), nondiabetic (≥ 93% in each treatment group), and normotensive (69–72% in each group). For severity of baseline disease (signs and symptoms of BPH) based on total AUA Symptom Score, 45–49% of patients in each treatment group had severe baseline disease (score ≥ 20). Forty-five patients could not be assigned a blood pressure status and were excluded from the analysis of sitting vital signs based on the criteria described above. Of the 231 patients analyzed in the tamsulosin 0.8 mg/day group, 21 (9%) were categorized as controlled hypertensive, 40 (17%) uncontrolled hypertensive, and 170 (74%) as normotensive; of the 240 patients in the tamsulosin 0.4 mg/day group, the numbers were 21 (9%), 37 (15%), and 182 (76%), respectively; and of the 240 placebo patients, the numbers were 27 (11%), 41 (17%), and 172 (72%), respectively.

The largest decrease in mean systolic blood pressure (SBP) from baseline to endpoint was –10.2 mmHg observed in uncontrolled hypertensive patients in the tamsulosin 0.8 mg/day group (Table 2, Fig. 1a). The decrease in SBP observed in uncontrolled hypertensive patients receiving placebo was –8.4 mmHg in the same period. Among controlled hypertensive and normotensive patients, the hypotensive effects were less than those observed in uncontrolled hypertensive patients.

The largest decrease in mean DBP from baseline to endpoint was –8.6 mmHg observed in uncontrolled hypertensive patients receiving placebo (Fig. 1b). The decreases observed in uncontrolled hypertensive patients receiving tamsulosin 0.4 and 0.8 mg/day were –7.2 and –8.5 mmHg, respectively. Among controlled hypertensive and normotensive patients, the hypotensive effects were less than those observed in uncontrolled hypertensive patients.

Table 2. Mean Sitting Blood Pressure and HR at Baseline: Subgroup Analysis of Normotensives, Controlled Hypertensives, and Uncontrolled Hypertensives in US92-03A

	Placebo	Tamsulosin 0.4 mg/day	Tamsulosin 0.8 mg/day
SBP ± S.E. (mmHg)			
Normotensives	127.4 ± 1.2	126.9 ± 1.0	127.0 ± 1.0
Controlled hypertensives	135.6 ± 2.9	130.4 ± 2.4	131.9 ± 3.5
Uncontrolled hypertensives	147.2 ± 2.5	144.7 ± 2.7	145.6 ± 2.9
DBP ± S.E. (mmHg)			
Normotensives	80.2 ± 0.6	80.1 ± 0.6	79.9 ± 0.6
Controlled hypertensives	81.9 ± 1.4	81.0 ± 1.4	84.3 ± 1.6
Uncontrolled hypertensives	97.9 ± 1.1	95.5 ± 1.4	95.8 ± 1.6
HR ± S.E. (bpm)			
Normotensives	70.7 ± 0.7	71.1 ± 0.6	70.0 ± 0.6
Controlled hypertensives	70.4 ± 1.8	73.1 ± 2.0	72.6 ± 2.1
Uncontrolled hypertensives	72.7 ± 1.5	74.5 ± 1.5	73.2 ± 1.6

No clinically important change in HR was observed in any subgroup (Fig. 1c). The largest change in HR was a decrease of 4.4 bpm observed in uncontrolled hypertensive patients treated with tamsulosin 0.8 mg/day.

No statistically significant differences were observed in mean change from baseline in sitting SBP, DBP, or HR in the subgroups of controlled and uncontrolled hypertensives and normotensives at the study endpoint. The magnitude and direction of the changes were similar to those observed at visit 6, the first visit after the dose was increased in the tamsulosin 0.8 mg/day group (Fig. 2). Thus the changes observed in patients treated with tamsulosin were not significantly different from those observed in patients receiving placebo, regardless of blood pressure status.

US93-01

In US93-01, 735 of 1417 patients enrolled were randomized to the three treatment groups, of whom 731 received at least one dose of study medication and qualified as the safety population. Demographic and background characteristics were similar among the treatment groups (Table 3). The majority of patients were Caucasian, but balanced with respect to race in each treatment group. Groups were also similar with respect to distribution of age, weight distribution, NYHA classification, severity of baseline disease, diabetes, baseline cholesterol level, baseline triglyceride level, chest X-ray, urine cytology, and urine culture. Seventy-three patients were excluded from the analysis of sitting vital signs based on the criteria described above. Of the 227 patients analyzed in the tamsulosin 0.8 mg/day group, 17 (7%) were categorized as controlled hypertensive, 65 (27%) uncontrolled hypertensive, and 145 (59%) normotensive; of the 220 patients in the tamsulosin 0.4 mg/day group, the numbers were 25 (10%), 65 (26%), and 130 (52%), respectively; and of the 211 placebo patients, the numbers were 15 (6%), 62 (26%), and 134 (56%), respectively.

The largest decrease in mean SBP from baseline to visit 5, the first visit after the dose was increased in the tamsulosin 0.8 mg/day group, was –7.8 mmHg observed in controlled hypertensive patients treated with tamsulosin 0.8 mg/day (Table 4, Fig. 3a). In the same period, the mean decreases in SBP in controlled hypertensive patients in the placebo and tamsulosin 0.4 mg/day groups were –1.2 and –3.6 mmHg, respectively. Among uncontrolled hypertensive and normotensive patients, the decreases in SBP were not dose dependent and the changes were smaller than those observed in controlled hypertensive patients.

The largest decrease in mean DBP from baseline to visit 5 was –6.4 mmHg observed in uncontrolled hypertensive patients treated with tamsulosin 0.4 mg/day (Fig. 3b). The decreases observed in uncontrolled hypertensive patients receiving placebo and tamsulosin 0.8 mg/day were –4.2 and –4.7 mmHg, respectively.

No significant change in HR was observed from baseline to visit 5 in any subgroup (Fig. 3c). The largest change in HR was an increase of 3.1 bpm observed in uncontrolled hypertensive patients treated with tamsulosin 0.8 mg/day.

At visits 4 and 5, vital signs were measured

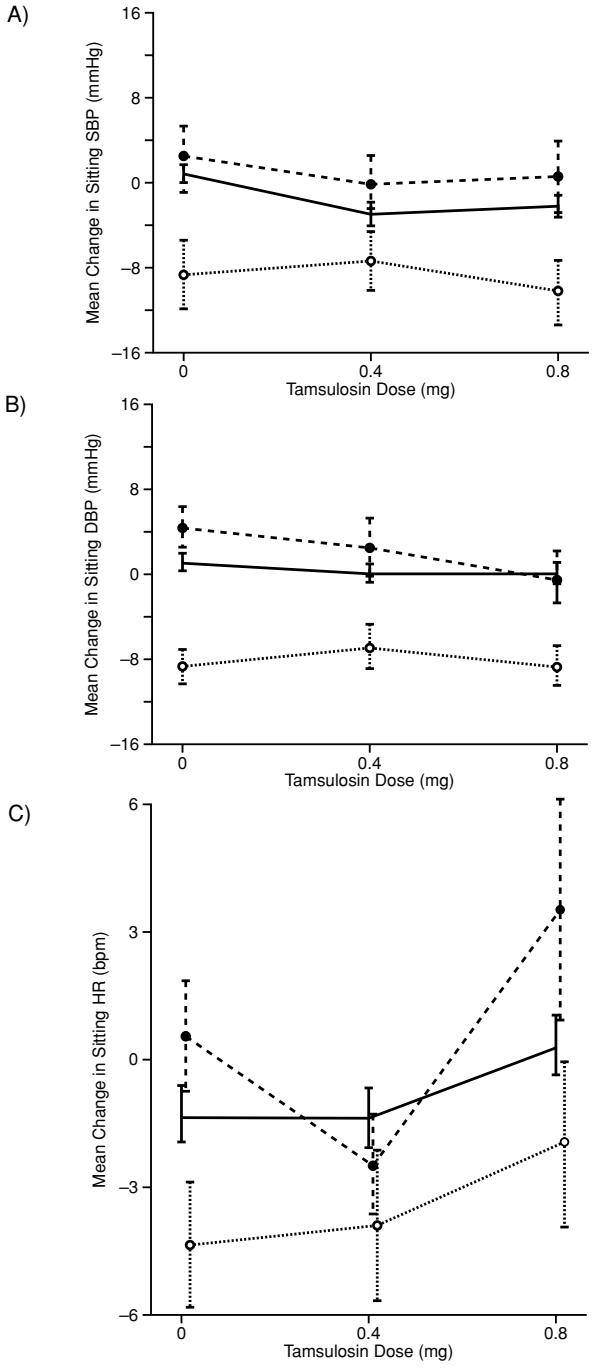

Fig. 1. US92-03A: Mean Change from Baseline in Sitting SBP ($p = 0.700$) (a), DBP ($p = 0.593$) (b), and HR ($p = 0.745$) (c) at Study Endpoint

—, normotensives; – –, controlled hypertensives; ---, uncontrolled hypertensives.

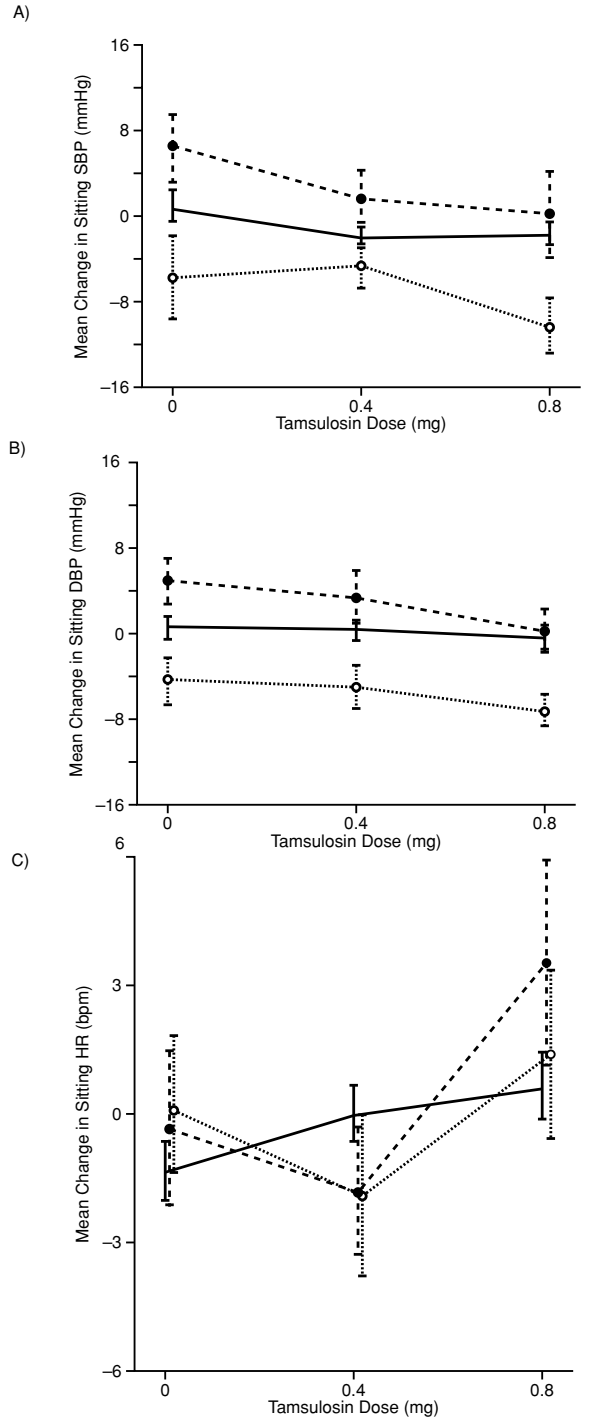

Fig. 2. US92-03A: Mean Change from Baseline in Sitting SBP ($p = 0.537$) (a), DBP ($p = 0.706$) (b), and HR ($p = 0.390$) (c) at Visit 6

—, normotensives; – –, controlled hypertensives; ---, uncontrolled hypertensives.

4–8 hr after dosing and at visits 6–8, 24–27 hr after dosing. Therefore, approximately 70–80% of the data analyzed at the study endpoint were obtained at trough plasma concentrations. No statistically significant difference was observed in mean change from baseline in sitting SBP, DBP, and HR among the patient subgroups either at visit 5 or the study endpoint (Fig. 4). The magnitude and direction of the changes were almost the same at visit 5 and the study endpoint.

Table 3. Demographic and Background Characteristics of the Safety Population in US93-01

Characteristic	Placebo	Tamsulosin 0.4 mg/day	Tamsulosin 0.8 mg/day	p value
No. patients	239	248	244	
Mean age ± S.E. (years)	58.1 ± 0.5	58.6 ± 0.5	58.3 ± 0.5	0.766
Age distribution (%)				
≤ 44	0 (0)	0 (0)	1 (<1)	0.947
45–54	85 (36)	89 (36)	84 (34)	
55–64	100 (42)	100 (40)	105 (43)	
65–74	47 (20)	53 (21)	47 (19)	
≥ 75	7 (3)	6 (2)	7 (3)	
Race (%)				
Caucasian	225 (94)	233 (94)	231 (95)	0.220
Black	10 (4)	15 (6)	9 (4)	
Asian	4 (2)	0 (0)	4 (2)	
Other	0 (0)	0 (0)	0 (0)	
Mean weight ± S.E. (kg)*	87.5 ± 0.9	89.2 ± 1.0	86.9 ± 0.9	0.177
Blood pressure status (%)				
Normotensive	134 (56)	130 (52)	145 (59)	
Controlled hypertensive	15 (6)	25 (10)	17 (7)	0.481
Uncontrolled hypertensive	62 (26)	65 (26)	65 (27)	
Not classified	28 (12)	28 (11)	17 (7)	
Severity of baseline disease (AUA symptom score) (%)				
Severe (≥ 20)	104 (44)	90 (36)	104 (43)	0.473
Moderate (≤ 7–19)	135 (56)	158 (63)	140 (58)	

*Weight was not reported for one patient in the tamsulosin 0.4 mg group and one patient in the placebo group.

Table 4. Mean Sitting Blood Pressure and HR at Baseline: Subgroup Analysis of Normotensives, Controlled Hypertensives, and Uncontrolled Hypertensives in US93-01

	Placebo	Tamsulosin 0.4 mg/day	Tamsulosin 0.8 mg/day
SBP ± S.E. (mmHg)			
Normotensives	126.1 ± 1.1	123.5 ± 1.1	126.1 ± 1.0
Controlled hypertensives	137.5 ± 3.3	132.9 ± 3.0	135.6 ± 3.2
Uncontrolled hypertensives	137.9 ± 1.8	142.9 ± 1.8	137.1 ± 1.5
DBP ± S.E. (mmHg)			
Normotensives	82.0 ± 0.5	81.0 ± 0.6	80.8 ± 0.5
Controlled hypertensives	86.5 ± 1.6	83.6 ± 1.4	84.4 ± 1.7
Uncontrolled hypertensives	94.7 ± 0.8	95.1 ± 1.0	94.5 ± 0.9
HR ± S.E. (bpm)			
Normotensives	67.5 ± 0.8	68.9 ± 0.8	67.6 ± 0.7
Controlled hypertensives	67.9 ± 1.6	67.9 ± 2.0	69.9 ± 1.5
Uncontrolled hypertensives	69.4 ± 1.0	70.5 ± 1.0	71.8 ± 1.3

Concomitant Administration of Antihypertensive Agents

Although the primary receptor subtype responsible for blood pressure regulation, or the side effects associated with α_1-adrenergic receptor antagonists, has yet to be conclusively identified, it has been suggested that the α_{1B}-adrenergic receptor may regulate smooth muscle contraction in human large arteries. In developing tamsulosin, a drug that specifically targets the α_1-adrenergic receptor, it was predicted that its use might avoid blood pressure-related side effects, and that it could therefore be safely

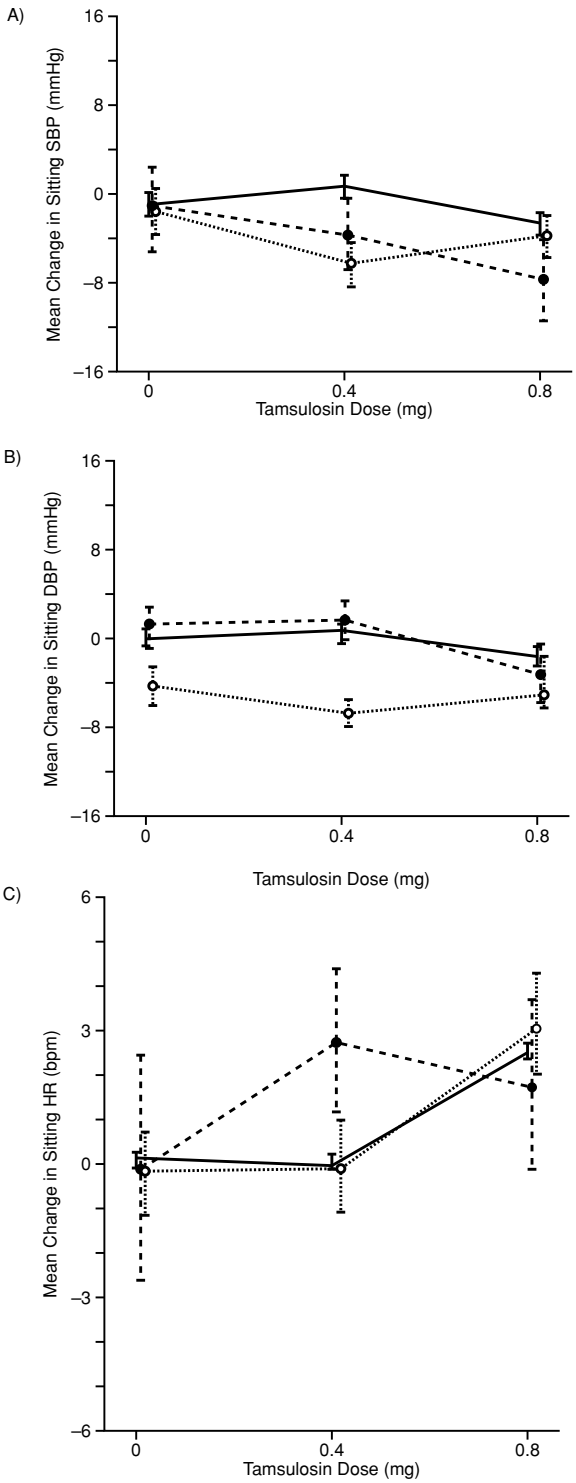

Fig. 3. US93-01: Mean Change from Baseline in Sitting SBP ($p = 0.177$) (a), DBP ($p = 0.183$) (b), and HR ($p = 0.752$) (c) at Visit 5

—, normotensives; – –, controlled hypertensives; ---, uncontrolled hypertensives.

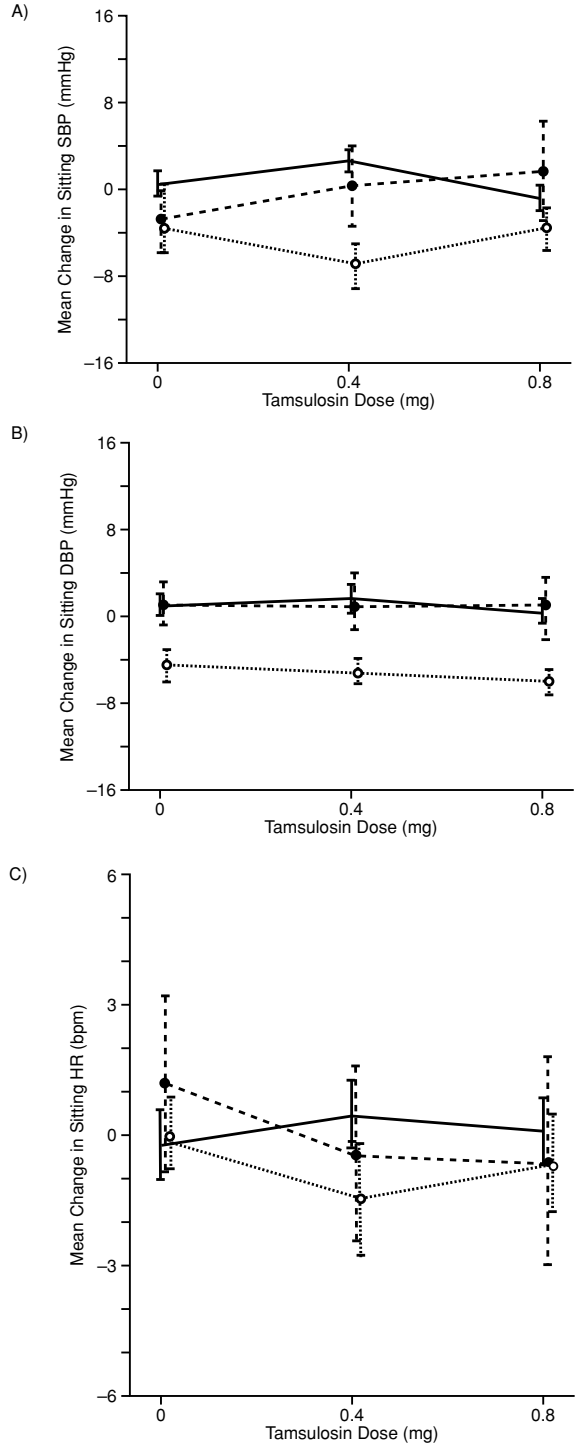

Fig. 4. US93-01: Mean Change from Baseline in Sitting SBP ($p = 0.126$) (a), DBP ($p = 0.975$) (b), and HR ($p = 0.819$) (c) at Study Endpoint

—, normotensives; – –, controlled hypertensives; ---, uncontrolled hypertensives.

coadministered with drugs specifically prescribed for hypertension, such as α-blockers, angiotensin-converting enzyme (ACE) inhibitors, and calcium channel blockers. Hypertension is common in men with BPH, and these medications are likely to be prescribed for such patients rather than using α_1-adrenergic receptor antagonists, which are indicated for both BPH and hypertension, since they are no longer recommended for the latter indication.[10,11] Three

Table 5. Mean Changes in Blood Pressure in Patients Treated with Antihypertensive Medication in Conjunction with Tamsulosin or Placebo. Reproduced, with permission, from Lowe[20]

	Baseline	Change	
	Day 4 (placebo)	Day 11 (0.4 mg/day)	Day 19 (0.8 mg/day)*
Nifedipine			
SBP (mmHg)			
Tamsulosin	129.5/152.3**	−9.0/−2.0	−11.4/−1.1
Placebo	122.0/149.0	−1.5/−3.5	−7.0/−3.5
DBP (mmHg)			
Tamsulosin	83.7/99.7	−4.5/−2.0	−3.1/−2.0
Placebo	77.0/95.0	−0.5/1.0	−5.0/0.5
Enalapril			
SBP (mmHg)			
Tamsulosin	115.7/146.3**	0.0/+2.7	+1.3/+3.3
Placebo	111.5/140.0	+8.0/+9.0	+3.0/−0.5
DBP (mmHg)			
Tamsulosin	74.7/99.0	−0.3/−5.0	+2.0/−4.7
Placebo	73.0/93.5	−0.5/−0.5	−4.0/0.0
Atenolol			
SBP (mmHg)			
Tamsulosin	117.0/150.5**	−2.7/−8.5	−8.0/−5.7
Placebo	124.5/161.0	−3.0/−6.0	−11.5/−4.7
DBP (mmHg)			
Tamsulosin	77.5/96.7	−4.0/−4.7	−4.7/−5.5
Placebo	77.5/96.0	−2.0/−2.0	−6.0/−1.5

*Changes in SBP and DBP from baseline to days 11 and 19 were not clinically significant. **Values indicate minimal/maximal SBP.

studies of concomitant administration of tamsulosin 0.4 mg/day and 0.8 mg/day with 3 different antihypertensive medications reported no clinically significant differences in blood pressure or HR.[18–21] Each study enrolled 12 men aged ≥ 45 years with mild-to-moderate, uncomplicated idiopathic or essential hypertension that was being adequately controlled by maintenance doses of nifedipine (US93-02), atenolol (US93-03), or enalapril (US93-05). After a 5-day placebo baseline assessment period, patients were randomized to receive either placebo or tamsulosin 0.4 mg/day for seven days followed by 0.8 mg/day for seven days if the patient's sitting DBP was ≥ 65 mmHg or if no signs of hypotension were observed, in addition to continuing their maintenance antihypertensive medications. No effect of tamsulosin was seen on the pharmacodynamic profiles of the antihypertensive drugs and no dose adjustment of the antihypertensive medication was required. There was no clinically significant difference among the tamsulosin and placebo groups in mean change in SBP, DBP, or HR over 24 hr on selected study days or throughout the study period, including no change when tamsulosin therapy was initiated or the dosage increased (Table 5).[20]

DISCUSSION

The results of the US92-03A and US93-01 subanalyses indicate that there is no untoward clinical effect of tamsulosin on the blood pressure or HR in hypertensive or normotensive BPH patients.

The decreases in blood pressure observed in controlled hypertensive patients treated with tamsulosin were neither dose dependent nor clinically meaningful, suggesting that tamsulosin has no drug interactions with other antihypertensive agents. These results agree with those obtained in smaller controlled studies of commonly used antihypertensive agents in hypertensive BPH patients, in which no hypotension was recorded with coadministration of tamsulosin.

In one study carried out by Kirby[22] on the effect on blood pressure in 207 normotensive and hypertensive men with BPH following treatment with terazosin, an α-adrenergic receptor antagonist that is not selective for the α_{1A}-subtype, clinically and

statistically significant mean decreases in SBP and DBP were observed in hypertensive patients who were not receiving or responding to concurrent antihypertensive medication as well as statistically significant decreases in normotensive patients and patients whose hypertension was being controlled by medication. Furthermore, when these patients either continued treatment with terazosin or received placebo, those who continued with terazosin showed no changes in SBP, DBP, or HR, while those who received placebo showed a trend toward SBP and DBP returning to pretreatment levels in all blood pressure groups. Thus the nonselective α-adrenergic receptor antagonist terazosin has marked antihypertensive effects in normotensive and hypertensive patients regardless of whether they receive concurrent antihypertensive medication.

It is well known that tamsulosin is an effective agent in the management of BPH, which unlike other α-adrenergic receptor antagonists does not require dose titration and has a rapid onset of action. Tamsulosin has lower side effects on the cardiovascular system than other α-adrenergic receptor antagonists such as terazosin, and the results of US92-03A and US93-01 also demonstrate that tamsulosin can be used in BPH patients who are hypertensive without any restrictions on blood pressure control medication.

REFERENCES

1) Bruskewitz, R. (1999) Management of symptomatic BPH in the US: Who is treated and how? *Eur. Urol.*, **36** (Suppl. 3), 7–13.
2) Barry, M. J. (1990) Epidemiology and natural history of benign prostatic hyperplasia. *Urol. Clin. North Am.*, **17**, 495–507.
3) McConnell, J. D., Barry, M. J., Bruskewitz, R. C., Bueschen, A. J., Denton, S. E., Holtgrewe, H. L., Lange, J. L., McClennan, B. L., Mebust, W. K., Reilly, N. J., Roberts, R. G., Sacks, S. A. and Wasson, J. H. (1994) *Benign Prostatic Hyperplasia: Diagnosis and Treatment, Clinical Practice Guideline, No. 8*, Agency for Health Care Policy and Research, Public Health Service, US Department of Health and Human Services. AHCPR Publication No. 94-0582, Rockville, Maryland.
4) Jacobsen, S. J., Girman, C. J., Guess, H. A., Oesterling, J. E. and Lieber, M. M. (1995) New diagnostic and treatment guidelines for benign prostatic hyperplasia. Potential impact in the United States. *Arch. Intern. Med.*, **155**, 477–481.
5) Kortt, M. A. and Bootman, J. L. (1996) The economics of benign prostatic hyperplasia treatment: A literature review. *Clin. Ther.*, **18**, 1227–1241.
6) Jepsen, J. V. and Bruskewitz, R. C. (1998) Recent developments in the surgical management of benign prostatic hyperplasia. *Urology*, **51** (Suppl. 4A), 23–31.
7) Kaplan, S. A., Goluboff, E. T., Olsson, C. A., Deverka, P. A. and Chmiel, J. J. (1995) Effect of demographic factors, urinary peak flow rates, and Boyarsky symptom scores on patient treatment choice in benign prostatic hyperplasia. *Urology*, **45**, 398–405.
8) Chapple, C. R. (1996) Selective α_1-adrenoceptor antagonists in benign prostatic hyperplasia: Rationale and clinical experience. *Eur. Urol.*, **29**, 129–144.
9) Moul, J. W. (1993) Benign prostatic hyperplasia: New concepts in the 1990s. *Postgrad. Med.*, **94**, 141–152.
10) National Heart, Lung, and Blood Institute, National Institutes of Health. News Release, March 8, 2000. *NHLBI stops part of study-High blood pressure drug performs no better than standard treatment*. Available at: http://www.nhlbi.nih.gov/new/press/mar08-00.htm. Accessed August 12, 2000.
11) ALLHAT Collaborative Research Group (2000) Major cardiovascular events in hypertensive patients randomized to doxazosin vs chlorthalidone: The Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial (ALLHAT). *JAMA*, **283**, 1967–1975.
12) Caine, M., Pfau, A. and Perlberg, S. (1976) The use of alpha-adrenergic blockers in benign prostatic obstruction. *Br. J. Urol.*, **48**, 255–263.
13) Lepor, H., Tang, R. and Shapiro, E. (1993) The alpha-adrenoceptor subtype mediating the tension of human prostatic smooth muscle. *Prostate*, **22**, 301–307.
14) Chapple, C. R., Burt, R. P., Andersson, P. O., Greengrass, P., Wyllie, M. and Marshall, I. (1994) Alpha-1-adrenoceptor subtypes in the human prostate. *Br. J. Urol.*, **74**, 585–589.
15) Miranda, H. F., Ramirez, H., Castillo, O., Minneman, K. P. and Pinardi, G. (1994) α_{1A}-Adrenergic receptors in the isolated human prostate. *Pharmacol. Commun.*, **4**, 181–188.
16) Lepor, H., for the Tamsulosin Investigator Group (1998) Phase III multicenter placebo-controlled study of tamsulosin in benign prostatic hyperplasia. *Urology*, **51**, 892–900.
17) Narayan, P., Tewari, A. and members of United States 93-01 Study Group (1998) A second phase III multicenter placebo controlled study of 2 dosages of modified release tamsulosin in patients with

symptoms of benign prostatic hyperplasia. United States 93-01 Study Group. *J. Urol.*, **160**, 1701–1706.
18) Starkey, L. P., Trenga, C., Miyazawa, Y. and Ito, Y. (1995) Lack of clinical interaction effects between tamsulosin and enalapril. *Clin. Pharmacol. Ther.*, **57**, 166, Abstract PII-11.
19) Starkey, L. P., Yasukawa, K., Trenga, C., Miyazawa, Y. and Ito, Y. (1994) Study of possible pharmacodynamic interactions between tamsulosin and nifedipine in subjects with essential hypertension. *J. Clin. Pharmacol.*, **34**, 1019, Abstract 45.
20) Lowe, F. C. (1997) Coadministration of tamsulosin and three antihypertensive agents in patients with benign prostatic hyperplasia: Pharmacodynamic effect. *Clin. Ther.*, **19**, 730–742.
21) Beduschi, M. C., Beduschi, R. and Oesterling, J. E. (1998) Alpha-blockade therapy for benign prostatic hyperplasia: From a nonselective to a more selective alpha$_{1A}$-adrenergic antagonist. *Urology*, **51**, 861–872.
22) Kirby, R. S. (1998) Terazosin in benign prostatic hyperplasia: Effects on blood pressure in normotensive and hypertensive men. *Br. J. Urol.*, **82**, 373–379.