*British Journal of Urology* (1997), **80**, 606–611

# Clinical comparison of selective and non-selective $\alpha_1$A-adrenoreceptor antagonists in benign prostatic hyperplasia: studies on tamsulosin in a fixed dose and terazosin in increasing doses

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**Objective** To compare the efficacy and safety of a fixed dose (0.2 mg) of tamsulosin, a selective $\alpha_1$A-adrenoreceptor antagonist, with an increasing dose (1–5 mg) of terazosin, a non-selective antagonist, in the treatment of urinary outflow obstruction associated with benign prostatic hyperplasia (BPH) in Korean patients.

**Patients and methods** The study comprised a single-blind and randomized design with tamsulosin or terazosin taken once daily for 8 weeks. A total of 98 patients was enrolled, with 72 patients included in the analyses after 4 and 8 weeks. The primary variables assessed were changes in the maximum urinary flow rate ($Q_{max}$) and the total International Prostate Symptom Score (IPSS), with the post-void residual urine volume, 'obstructive' and 'irritative' questions in the IPSS, and the investigators' global assessment of efficacy also determined. The number of patients with a clinically significant response to treatment with tamsulosin or terazosin was determined and defined as those with $>20\%$ improvement from the baseline $Q_{max}$ or $>20\%$ decrease in total IPSS. Adverse reactions possibly or probably related to study medication were recorded throughout the treatment period.

**Results** Both tamsulosin and terazosin produced similar significant improvements in subjective and objective symptoms of urinary outflow obstruction ($P>0.05$). Systolic and diastolic (standing) blood pressures decreased significantly in patients treated with terazosin ($P<0.05$). The adverse reactions, most frequently dry mouth and dizziness which were usually mild and transient, were significantly higher in patients on terazosin (18 patients, versus one on tamsulosin, $P<0.001$). The changes led to discontinuation of therapy in two patients on terazosin.

**Conclusion** Tamsulosin was as effective as terazosin in treating urinary outflow obstruction associated with BPH, but had a markedly better safety profile.

**Keywords** Benign prostatic hyperplasia, selective and non-selective $\alpha_1$A-adrenoreceptor antagonist, tamsulosin, terazosin, lower urinary tract symptoms

## Introduction

BPH is a major cause of morbidity among elderly men [1]; primarily, it produces bothersome urinary symptoms which decrease the quality of life of these patients and this aspect has become the major focus in the management of this condition. The standard treatment for symptomatic BPH remains TURP. However, drug therapy represents an important alternative to TURP for patients with mild-to-moderate symptoms or for those who are unable or unwilling to undergo surgery because of the risk of both morbidity and mortality, coupled with increased public awareness of non-surgical alternatives.

The use of $\alpha_1$-adrenoreceptor antagonists is a reasonably well established treatment modality for symptomatic BPH [2–7]. $\alpha_1$-adrenoreceptor antagonists relax the smooth muscles of the bladder neck and prostate, decrease bladder outlet resistance and facilitate urinary flow without affecting detrusor smooth muscle contractility. These effects result from the distribution of receptors, which are abundant in the bladder neck, prostatic capsule and stroma, and scarce in the main bladder [8–11]. $\alpha_1$-adrenoreceptor antagonists such as prazosin [2], terazosin [3–5], doxazosin [6], and alfuzosin [7] have been used to treat BPH and increase urinary outflow and improve symptoms. However, their use is associated with adverse reactions such as postural hypotension, dizziness and dry mouth. To reduce these adverse reactions, dose titration is common in clinical practice, but about 10% of patients discontinue medication because of adverse reactions [5].

Recent pharmacological studies of the $\alpha_1$-adrenoreceptor have revealed two subtypes, $\alpha_1$A and $\alpha_1$B [12,13]. The $\alpha_1$A-adrenoreceptor subtype is present in the greatest

Accepted for publication 10 June 1997

concentration in human prostate and is responsible for prostate smooth muscle contraction [14–19]. By contrast, the $\alpha_1$B-adrenoreceptor subtype is involved in smooth muscle contraction of large human arteries [20]. Therefore, a drug with a relatively high affinity particularly for the $\alpha_1$A-adrenoreceptor could be prostate-specific.

Tamsulosin is a new selective $\alpha_1$A-adrenoreceptor subtype antagonist; it has been reported that the affinity of tamsulosin for $\alpha_1$A-receptors is seven to 38 times greater than that for $\alpha_1$B-receptors [15–20]. In studies in Japan [21,22], Europe [23–25] and the USA [26], tamsulosin, at a dose of 0.2–0.4 mg once daily, produced symptomatic improvement without affecting blood pressure and pulse rate in patients with BPH. Further, patients treated with tamsulosin rarely experienced adverse reactions such as postural hypotension, dizziness and dry mouth. However, no clinical study comparing tamsulosin with non-selective $\alpha_1$-adrenoreceptor antagonists has yet been published.

The aims of the present study were to compare the efficacy and safety of tamsulosin and terazosin in the treatment of urinary outflow obstruction associated with BPH in Korean patients. Tamsulosin was administered in a fixed dose of 0.2 mg and terazosin in escalating doses of 1, 2 and 5 mg to avoid the side-effects of accompanying hypotension.

## Patients and methods

The 9-week, randomized, single-blind study was authorized by the ethics committee of Seoul National University Hospital. The doctors informed their patients of the details of the study and obtained their consent before it commenced. Patients with moderate to severe symptomatic BPH were selected. BPH was diagnosed from the history, symptoms, a DRE and TRUS. The Korean version of the IPSS was used to assess symptoms [27]. The post-void residual urine volume (PVR) was measured by ultrasonography. In total, 98 patients with symptomatic BPH (aged 51–80 years), with a total IPSS of $\geqslant 8$ [28], a maximum urinary flow rate ($Q_{max}$) of 5–15 mL/s and a PVR of $<150$ mL, were enrolled. Patients were excluded if they had prostatic cancer, a serum PSA level $>10$ ng/mL, prostatitis, a neurogenic bladder, bladder cancer, bladder stones, urethral strictures and neurological conditions that might interfere with normal voiding; also excluded were patients with BPH who had undergone transurethral resection or had experienced urinary retention, and patients with marked cardiac, renal or hepatic insufficiency. Patients were not permitted to take concomitant drugs which could influence the outcome of the study, e.g. antiandrogenic hormones and 5α-reductase inhibitors, for at least 4 weeks and α- and β-adrenoreceptor antagonists for at least 1 week before the study.

The patients were randomized into two groups of 49 each, one receiving tamsulosin at a dose of 0.2 mg and the other terazosin at doses of 1 mg on day 1, increasing to 2 mg for the next 6 days and 5 mg thereafter. After a 1 week pretreatment stage, all patients were given the test drug once daily after a meal (tamsulosin) or before bedtime (terazosin) for 8 weeks. During the whole study period of 9 weeks, the medical history of the patient, subjective symptoms as assessed from the IPSS, and objective examinations (e.g. urinary flow rate, PVR, blood pressure and pulse rate in the supine and standing positions, complete blood cell count, serum biochemistry and routine urine analysis) were performed according to the schedule in Table 1. The efficacy and safety was evaluated at the end of 4 and 8 weeks for all analysable patients in both groups.

The primary variables for assessing efficacy were changes in $Q_{max}$ and total IPSS (maximum 35 points) and other variables examined were the PVR, the 'obstructive' (questions 1, 3, 5 and 6 in the IPSS, total 20 points) and 'irritative' symptoms (questions 2, 4 and 7 in the IPSS, total 15 points), and the investigators' global assessment of efficacy. In addition, the number of patients with a clinically significant response to tamsulosin or terazosin treatment was determined, defined as patients with $>20\%$ improvement from the baseline $Q_{max}$ or $>20\%$ decrease in total IPSS [28]. Adverse reactions considered to be possibly or probably related to the study medication were recorded throughout the treatment period.

The patients' demographic differences and any differences in subjective and objective changes between the

**Table 1** The observation and assessment schedule

| | *Before treatment* | *Treatment* | | |
|---|---|---|---|---|
| *Week* | *−1 to 0* | *2* | *4* | *8* |
| *Selection of patient* | | | | |
| Diagnosis | * | | | |
| DRE | * | | | |
| TRUS | * | | | |
| PSA test | * | | | |
| *Efficacy evaluation* | | | | |
| IPSS | ** | | * | * |
| Urinary flowmetry | * | | * | * |
| PVR by ultrasonography | * | | * | * |
| *Adverse reaction evaluation* | | | | |
| Blood pressure | ** | * | * | * |
| Pulse rate | * | * | * | * |
| Adverse reaction | * | * | * | * |
| Laboratory test | * | * | * | * |

baseline and treatment periods were assessed using Student's *t*-test. An ANOVA with Duncan's multiple-range test was used to assess inter- and intra-group differences. The appearance rate of adverse reactions between the groups was analysed using Fisher's exact test. Statistical differences were tested at a significance level of 0.05.

## Results

Of the 98 patients, 26 patients (10 in the tamsulosin and 16 in the terazosin group) were excluded from analysis or were withdrawn, allowing a final evaluation in 72 patients (39 in the tamsulosin and 33 in the terazosin group). The main reasons for exclusion and withdrawal were failure to return to follow-up (16 patients), protocol violation (five patients) and adverse reaction in the terazosin group (two patients). The patients' baseline characteristics, prostate volume and PSA level are shown in Table 2. There were no differences in patient background between the groups for any comparison ($P > 0.05$).

### *Efficacy*

The mean (SD) IPSS in the tamsulosin and terazosin groups during the pre-treatment period is shown in Table 3. The mean (SD) scores at 4 and 8 weeks after treatment were 12.7 (7.2) and 11.4 (7.2), and 14.7 (8.0) and 13.4 (7.2) in the tamsulosin and terazosin groups, respectively. The total IPSS was significantly better than baseline at 4 and 8 weeks after treatment in both groups ($P < 0.01$, ANOVA with Duncan's multiple-range test). There was a significant reduction in the total IPSS from baseline to endpoint with tamsulosin and terazosin (Table 3), these values being similar ($P > 0.05$). Like the total IPSS, the 'obstructive' and 'irritative' symptom scores improved significantly in both groups ($P < 0.05$), with no difference between them ($P > 0.05$, Table 3).

The mean (SD) $Q_{max}$ measured before treatment was similar in both groups (Table 2) and the respective values at 4 and 8 weeks after treatment were 11.0 (3.7) and 11.6 (3.6), and 11.7 (5.0) and 10.9 (4.1) mL/s in the tamsulosin and terazosin groups, respectively. The $Q_{max}$ was significantly better than baseline at 4 and 8 weeks after treatment in both groups ($P < 0.05$, ANOVA with Duncan's multiple-range test). The mean increase in $Q_{max}$ from baseline to endpoint was about 20% in both groups (Table 3), the differences before and after treatment being significant in both ($P < 0.05$). There were no significant differences in $Q_{max}$ between the groups at 4 and 8 weeks after treatment ($P > 0.05$).

**Table 2** Baseline characteristics of the patients included in the study

| *Mean (SD)* | *Tamsulosin* | *Terazosin* |
|---|---|---|
| Age (years) | 68.1 (7.6) | 66.1 (9.4) |
| Weight (kg) | 61.6 (7.7) | 61.7 (8.7) |
| Height (cm) | 165.1 (3.7) | 167.2 (4.6) |
| Prostate volume (mL)* | 30.8 (12.0) | 27.1 (7.2) |
| PSA level (ng/mL) | 3.0 (2.2) | 2.8 (2.6) |
| $Q_{max}$ (mL/s) | 9.5 (2.9) | 9.2 (2.7) |

Differences not significant for any comparison (Student's *t*-test).
*Estimated by TRUS.

Five patients in the tamsulosin group and eight in the terazosin group showed abnormal PVRs (>50 mL) at baseline; the mean (range) reduction in PVR after treatment was 44% (27–54) with tamsulosin and 62% (9–95) with terazosin, again with no difference in the improvement between the groups ($P > 0.05$).

At the endpoint, 20 (51%) and 29 patients (74%) in the tamsulosin group and 15 (45%) and 26 patients (79%) in the terazosin group were considered to have a clinically significant improvement in $Q_{max}$ (>20% increase) and IPSS (>20% decrease), respectively. In the investigators' global assessment of efficacy, 72% of patients in tamsulosin and 67% in terazosin group were considered to be moderately or much improved. The distribution of those responding in $Q_{max}$ and IPSS and moderately to much-improved patients in global assessment was not different between the groups ($P > 0.05$).

### *Safety*

Tamsulosin was very well tolerated, with one patient experiencing headache (Table 4). In contrast, 18 patients in the terazosin group experienced 27 adverse reactions (Table 4), although these adverse reactions were generally mild. Two patients in the terazosin group withdrew from the study due to dry mouth and dizziness (one patient each). The difference in adverse reaction profile between the groups was significant ($P < 0.001$, Table 4). Six patients had abnormal laboratory test values but these changes were not considered to be related to the treatment.

Standing and supine systolic and diastolic blood pressures tended to decrease in both treatment groups and the difference was statistically significant in the terazosin-treated patients for systolic and diastolic blood pressure when standing, and for diastolic blood pressure when supine. The pulse rate did not change significantly in either position in both groups (Table 3).

## Discussion

Compared with baseline values, tamsulosin and terazosin improved the subjective and objective symptoms of

**Table 3** The mean (SD) change in total, 'irritative' and 'obstructive' symptom scores, $Q_{max}$, blood pressures and pulse rates, from baseline to endpoint

| | *Baseline* | *Endpoint* | *Change (%)* | P *paired* t-*test* |
|---|---|---|---|---|
| *Tamsulosin* (n = *39)* | | | | |
| Total IPSS | 17.8 (6.8) | 11.4 (7.2) | −6.4 (−36) | <0.01 |
| Irritative | 7.4 (3.9) | 4.8 (3.5) | −2.6 (−35) | <0.05 |
| Obstructive | 10.4 (4.6) | 6.6 (4.7) | −3.8 (−37) | <0.01 |
| *Terazosin* (n = *33)* | | | | |
| Total IPSS | 21.4 (7.2) | 13.4 (7.2) | −8.0 (−37) | <0.01 |
| Irritative | 9.1 (3.9) | 5.9 (3.1) | −3.2 (−35) | <0.01 |
| Obstructive | 12.3 (4.5) | 7.5 (4.7) | −4.8 (−39) | <0.01 |
| $Q_{max}$ *(mL/s)* | | | | |
| Tamsulosin | 9.5 (2.9) | 11.6 (3.6) | +2.1 (22) | <0.05 |
| Terazosin | 9.2 (2.7) | 10.9 (4.1) | +1.7 (19) | <0.05 |
| *Blood pressure (mmHg) (systolic/diastolic)* | | | | |
| Tamsulosin | | | | |
| Supine | 146.8 (26.2) | 142.6 (26.7) | −4.2 (−3) | NS |
| | 89.4 (15.4) | 82.8 (13.7) | −6.6 (−7) | NS |
| Standing | 140.7 (26.3) | 131.3 (19.6) | −9.4 (−7) | NS |
| | 87.7 (17.8) | 82.3 (14.8) | −5.4 (−6) | NS |
| Terazosin | | | | |
| Supine | 142.4 (26.7) | 132.4 (19.8) | −10.0 (−7) | NS |
| | 90.3 (15.7) | 78.2 (9.5) | −12.1 (−13) | <0.01 |
| Standing | 138.7 (24.8) | 122.6 (24.1) | −16.1 (−12) | <0.01 |
| | 88.3 (16.9) | 76.9 (11.9) | −11.4 (−13) | <0.05 |
| *Pulse rate (bpm) (supine/standing)* | | | | |
| Tamsulosin | 78.2/80.5 | 75.3/83.7 | −2.9/3.2 | NS |
| Terazosin | 77.4/85.9 | 72.4/83.9 | −5.0/−2.0 | NS |

**Table 4** The incidence of adverse reactions related to study medication

| | *Tamsulosin* | *Terazosin* |
|---|---|---|
| Total number of patients enrolled | 49 | 49 |
| Adverse reactions* | | |
| Dry mouth | 0 | 8 (16.3)† |
| Dizziness | 0 | 6 (12.2) |
| Headache | 1 | 4 (8.2) |
| Dyspepsia | 0 | 4 (8.2) |
| Constipation | 0 | 4 (8.2) |
| Skin rash | 0 | 1 (2.0) |
| Discontinuations due to adverse reactions | 0 | 2 (4.1) |
| Total number of adverse reactions | 1‡ | 27 |
| Total number of patients showing adverse reactions | 1‡ | 18 |

*As reported by patient. †Incidence of adverse reactions (%): number of patients showing adverse reactions/ total number of patients analysed. ‡$P < 0.001$, significantly different from the values in terazosin group (Fisher's exact test).

urinary outflow obstruction associated with BPH in 4 and 8 weeks after treatment. The improvements with tamsulosin were similar to those with terazosin. Only one patient in the tamsulosin group had an adverse event, whereas 18 patients in the terazosin group experienced a total of 27 adverse reactions considered to be possibly or probably related to study medication and generally attributable to an $\alpha_1$-adrenoreceptor antagonist. While there were no significant differences in the cardiovascular variables before and after treatment in the tamsulosin group, there was a significant decrease in blood pressure in the terazosin group. The incidence of adverse events such as dizziness associated with blood pressure reduction was 12.2% with terazosin, whereas there were no such changes in the tamsulosin group. Two patients in the terazosin group who experienced dry mouth and dizziness were withdrawn from treatment. The efficacy profile of tamsulosin in this study is in agreement with that reported by others [21–26]. The safety profile as determined from the incidence of adverse reactions and effect on blood pressure and pulse rate was similar to that in a Japanese study reported by Kawabe *et al.* [21,22], but lower than that in European studies reported by Abrams *et al.* [23] and Schulman *et al.* [24]. This different incidence of adverse reactions may be related to the different dosage of tamsulosin in this and Japanese studies (0.2 mg) and European studies (0.4 mg). Patients with BPH in Oriental countries seem to require lower doses than those in Western countries. Thus the present study used tamsulosin and terazosin in doses of 0.2 mg

and 1–5 mg, respectively, as is normal clinical practice in patients in Oriental countries; patients in Western countries are given doses of 0.4 and 1–10 mg, respectively. The efficacy and safety profiles of terazosin were similar to those in previous studies [3–5], even though terazosin in escalating doses of 1, 2 and 5 mg (the usual dose in Korea) were administered to avoid the adverse reactions accompanying hypotension.

In the present study, there was no significant difference in efficacy between tamsulosin (0.2 mg/day) and terazosin at an increasing dose (1–5 mg/day), suggesting that both selective and non-selective $\alpha_1$A-adrenoreceptor antagonists have qualitatively similar efficacy in subjective and objective symptoms of urinary outflow obstruction associated with BPH. However, tamsulosin had a better adverse reaction profile than terazosin, even when the latter was given in an escalating dose. The superior safety of tamsulosin to terazosin may arise from the selective and strong affinity of tamsulosin for the $\alpha_1$A-adrenoreceptor subtype, which is present in the greatest density in human prostate and is responsible for prostate smooth muscle contraction; it thus plays an important role in the dynamic component of bladder outlet obstruction in symptomatic BPH.

Although a comparative major clinical study between selective and non-selective $\alpha_1$A-adrenoreceptor subtype antagonists in symptomatic patients with BPH has not been published, the results of the present study suggest better safety with tamsulosin over the non-selective-subtype antagonist terazosin in patients with symptomatic BPH, even when an increasing dose of terazosin was administered. If more extensive comparisons of tamsulosin against other non-selective $\alpha_1$-adrenoreceptor antagonists confirm the better tolerance and efficacy profile for the selective $\alpha_1$-adrenoreceptor antagonist, these agents will be ideally placed to provide an important alternative in the treatment of patients with mild to moderate symptomatic BPH and in those awaiting or unable to undergo surgery.

## Acknowledgement

We thank Dr Keun-Young Yoo, Department of Preventive Medicine, Seoul National University College of Medicine, for his statistical consultation, and all those who willingly participated in this study.

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