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A comparative study of terazosin and tamsulosin for symptomatic benign prostatic hyperplasia in Japanese patients

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Objective To compare the efficacy and safety of an incremental-dose regimen of terazosin (1–2 mg daily) and a fixed-dose regimen of tamsulosin (0.2 mg daily), on Japanese patients with symptomatic benign prostatic hyperplasia (BPH).

Patients and methods This multicentre, single-blind, randomized trial compared terazosin and tamsulosin over 4 weeks, in 61 patients with symptomatic BPH randomly assigned to terazosin ($n = 31$) or tamsulosin ($n = 30$). Terazosin 0.5 mg twice daily was administered for 2 weeks, followed by 1 mg twice daily for 2 weeks. Tamsulosin (0.2 mg) was administered once daily for 4 weeks. Symptoms were evaluated using the International Prostate Symptom Score (IPSS), and quality of life (QOL) was assessed subjectively before treatment, and again after 2 and 4 weeks of treatment. Objective measurements taken before and after the treatment period were the maximum (Q_{max}) and average (Q_{ave}) urinary flow rates, and the percentage residual urine volume. Improvement was defined as a 25% decrease from baseline in IPSS, >1 point increase in QOL score, and >2.5 mL/s increase in Q_{max}. Adverse reactions potentially related to the study drugs were recorded throughout the treatment period.

Results Both terazosin and tamsulosin produced statistically significant improvements in subjective and objective variables. Neither treatment affected systolic or diastolic blood pressure or pulse rate. Adverse reactions were noted in four patients (three in the terazosin group and one in the tamsulosin group). However, there was no statistically significant difference in the incidence of adverse effects between the groups.

Conclusions Despite the limitations of small sample size and relatively short treatment periods, terazosin and tamsulosin were equally effective in the treatment of symptomatic BPH in Japanese patients, using relatively lower doses than those used in Western countries.

Keywords Benign prostatic hypertrophy, Japanese, terazosin, tamsulosin, randomized trial

Introduction

BPH is so common that it might be considered almost unavoidable in elderly men. In Japan, the prevalence of moderate or severe LUTS caused by BPH increases with age (44% in men aged 50–59 years, 52% in those aged 60–69 years and 63% in those 70–79 years old) [1]. As an age-related disease, the prevalence of BPH is likely to increase substantially during this century. A greater awareness of BPH among both patients and healthcare professionals is likely to increase the number of people presenting for treatment. The long life-expectancy of the Japanese increases the importance of finding an effective treatment for BPH.

TURP has been the recommended treatment for BPH, but carries risks of morbidity and mortality, particularly in elderly men. Moreover, most patients with BPH reportedly choose less aggressive interventions than TURP, although more aggressive than watchful waiting [2]. Recently, several investigations have significantly more α1-adrenergic receptors in hypertrophic prostatic tissue than in normal tissue [3–5] and that blocking urethral α1-adrenoceptors causes the prostatic urethra to relax [6]. First-generation, nonselective α1/α2-antagonists, e.g. phenoxybenzamine, caused a high incidence of adverse reactions (particularly orthostatic hypotension), often leading to discontinuation of treatment [7]. Short-acting α1-selective adrenoceptor antagonists, e.g. prazosin and alfuzosin, were then introduced [8,9]. Recently, the preference has been for longer acting and more uroselective α1-adrenoceptor antagonists [10–13].

Many reports have described the efficacy of each

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α1-adrenoceptor antagonist for BPH, but only one report, by Lee and Lee [14], has compared two such drugs, contrasting the clinical efficacy of tamsulosin with terazosin for symptomatic BPH patients in Korea. In Japan, terazosin, a long-acting α1-selective adrenoceptor antagonist, and tamsulosin, an $\alpha 1_A$-specific adrenoceptor antagonist, are widely administered for symptomatic BPH. The present study reports the results of a comparison of terazosin and tamsulosin for the treatment of symptomatic BPH among Japanese patients.

Patients and methods

This 4-week, randomized, single-blind study by the Hytracin Study Group recruited patients from 21 hospitals (see Acknowledgements); the clinical trial was authorized by the ethical committee of each hospital, and written informed consent was obtained from all patients before commencement.

The pre-trial assessment and establishing a baseline to evaluate the effect of treatment required each patient to undergo a history and symptom assessment, a DRE and TRUS. The severity of symptoms was assessed subjectively using the IPSS (maximum 35 points) [15]; in the IPSS, 'obstructive' symptoms are assessed by questions 1, 3, 5, and 6 (total 20 points) while 'irritative symptoms' are assessed by questions 2, 4, and 7 (total 15 points). Objective symptoms of BPH were evaluated by uroflowmetry and a measurement of the percentage of postvoid residual urine volume (%PVR), defined as the residual urine volume/(voided urine volume + residual urine volume) × 100.

Patients with a total IPSS of > 13 and a maximum urinary flow rate (Q_{max}) of < 12 mL/s were invited to participate in the trial. Patients with histories of TURP or urinary retention were excluded. Patients with any of the following were also excluded: neurogenic bladder, organic urethral stricture, prostatic carcinoma, bladder calculus, bladder diverticulum, overt UTI, marked disorders of other organ systems (including renal or hepatic insufficiency), senile dementia, known history of drug hypersensitivity or cardiovascular disorders.

Patients were randomized to receive either terazosin ($n = 31$) or tamsulosin ($n = 30$). Terazosin-treated patients received terazosin 1 mg daily (0.5 mg after breakfast and supper) for the first 2 weeks and 2 mg daily (1 mg after breakfast and supper) for the following 2 weeks. Tamsulosin-treated patients received a fixed dose of 0.2 mg daily throughout the treatment period. Subjective assessments of symptoms, uroflowmetry, laboratory examinations, BP and pulse rate monitoring were carried out according to the schedule outlined in Table 1.

After completing therapy, all patients were reviewed at a case conference and symptom scores evaluated by the committee members, who were unaware of the treatment of individual patients. Efficacy was assessed by the criteria reported by Homma *et al.* [16], with slight modification (Table 2). When the patient was better than 'fair' in the efficacy grading of the IPSS, quality-of-life (QOL) score, and Q_{max}, the patient was assessed as 'improved'.

Table 1 The monitoring schedule for each patient after obtaining informed consent

	Trial period (4 weeks)		
Step	*0*	*2*	*4*
Efficacy evaluation			
IPSS	+	+	+
Free uroflowmetry (Q_{max}, Q_{ave}, %PVR)	+		+
Adverse reaction evaluation			
BP and pulse rate	+	+	+
Blood chemistry	+		+
Adverse reactions			+

The background characteristics of both groups were compared using a chi-square test or Fisher's exact test. Subjective symptoms after 2 and 4 weeks of treatment and uroflowmetry data after 4 weeks of treatment were compared with those before treatment (i.e. at baseline) using Wilcoxon's signed-rank test (Table 1). Differences between groups were analysed using the Mann–Whitney *U*-test. The rate of adverse reactions between groups was analysed using Fisher's exact test. Statistical differences were tested at a significance level of 0.05.

Results

Of the 61 patients enrolled, four (three in the terazosin and one in the tamsulosin group) were excluded from analysis or withdrawn. Two terazosin-treated patients were excluded because of protocol violation and one was withdrawn because of an adverse reaction. One patient in the tamsulosin group failed to return for follow-up. Thus, 57 patients were evaluated for treatment efficacy (28 in the terazosin and 29 in the tamsulosin group), while all 61 patients enrolled were assessed for adverse reactions.

There were no statistically significant differences between treatment groups in age, prostatic size or concomitant diseases at baseline (Table 3). The total IPSS was significantly better than baseline at 4 weeks in both groups ($P < 0.001$), but the values at baseline, 2 weeks and 4 weeks after treatment were not significantly different between groups ($P = 0.559$, 0.360, 0.854, respectively). While the irritative symptom scores for both groups improved from baseline, there was no statistically significant difference between the

Table 2 The criteria for evaluating treatment efficacy

Efficacy	*IPSS after treatment/baseline*	*QOL score baseline to after treatment*	Q_{max} *(mL/s) after treatment to baseline*
Excellent	$\leqslant 0.25$	$\geqslant 4$	$\geqslant 10$
Good	$\leqslant 0.5$	3	$\geqslant 5$
Fair	$\leqslant 0.75$	1 or 2	$\geqslant 2.5$
Poor/worse	>0.75	$\geqslant 0$	<2.5

When the patient was assessed as better than fair in IPSS, QOL score and Q_{max}, the patient was considered as 'improved'.

groups; similarly, the obstructive symptom scores improved significantly after treatment in both groups ($P<0.05$ compared to baseline), but there was no significant difference between groups. The QoL score was significantly better after treatment ($P=0.0023$ and $P=0.0012$ for terazosin and tamsulosin, respectively), but there was no statistically significant difference between groups ($P=0.759$; Table 3).

Although the Q_{max} before treatment was similar in both groups, values after 4 weeks were significantly better than at baseline ($P=0.0102$) in the terazosin group, but the improvement in the tamsulosin group was not significant ($P=0.0532$). The Q_{ave} values were significantly greater at 4 weeks ($P=0.008$ and 0.0043 for terazosin and tamsulosin, respectively, compared with baseline) but there was no significant difference between the groups at either time. There were no significant differences in %PVR either within or between groups at the various times (Table 3). There were no significant differences within or between groups at different times in either systolic or diastolic BP, or pulse rate, throughout the trial (Table 3).

The efficacy of terazosin and tamsulosin in BPH was evaluated by the criteria listed in the Table 2. Judging by these criteria, 67%, 54% and 44% of patients in the terazosin group had improvements in IPSS ($\geqslant 25\%$ decrease), QOL score ($\geqslant 1$ point decrease), and Q_{max} ($\geqslant 2.5$ mL/s increase), respectively, compared with 68%, 52% and 30% of patients in the tamsulosin group. Overall, 52% of the patients in the terazosin group and 62% in the tamsulosin group were considered improved, but there was no statistically significant difference in efficacy between the two groups ($P=0.984$).

Three patients in the terazosin group had adverse reactions; two were able to complete the trial despite one experiencing dizziness and another dyspepsia, while the third patient withdrew from the trial complaining of palpitation. In the tamsulosin group, one patient developed a skin rash (a rare adverse reaction to this drug), but was able to complete the trial, the symptom resolving after the treatment period. The incidence of adverse reactions between groups was not significantly different.

Discussion

Since Caine *et al.* reported the therapeutic efficacy of phenoxybenzamine in BPH [6], α-adrenoceptor antagonists of three different types have been used to treat this condition. These are the first-generation, nonselective α1/α2-antagonists (e.g. phenoxybenzamine), the selective α-antagonists (e.g. the short-acting agents prazosin and alfuzosin and the long-acting drugs, terazosin and doxazosin) and the prostate-specific α_{1A}-adrenoceptor antagonists, e.g. tamsulosin [13]. As a high incidence of adverse reactions was reported for the first-generation, nonselective adrenoceptor antagonists, selective α-antagonists have been preferred [17]. In Japan, terazosin and tamsulosin are widely used for the treatment of BPH. Although an incremental dose regimen of terazosin (2–10 mg once daily at bedtime) [10] is recommended in Western countries, 1–2 mg daily is advised in Japan. The dose of terazosin required to maintain effective blood levels in Japanese people is about one-third of that required in Caucasians and the dose suitable for treating BPH seems to be lower in Japan than that in Western countries [18]. A dose-determining study of terazosin in Japanese patients with hypertension showed that 1 mg daily was a suitable therapeutic dose [18]. Subsequently, terazosin has been widely used in Japan at doses of 1–2 mg daily (the recommended dose established for BPH). Tamsulosin is also used in high doses in Western countries (as high as 0.4 mg daily), but a dose of 0.2 mg daily is recommended in Oriental countries [12,14].

Several placebo-controlled studies of the efficacy of terazosin and tamsulosin have been published [10,12,19–22], but only one comparative study is available [14]. The present study compared the efficacy of these two adrenoceptor antagonists at a low dose. Compared with baseline values, both terazosin and tamsulosin improved the total subjective symptoms after 4 weeks of treatment. After 2 weeks, irritative symptoms except urinary urgency were improved and after 4 weeks, all irritative symptoms improved significantly in both groups. All obstructive symptoms improved at 2 weeks in both groups. Lepor *et al.* [10] reported that terazosin 2 mg daily did not improve

Table 3 The patients' baseline values and the results after 2 and 4 weeks of treatment

	Terazosin			*Tamsulosin*		
Mean (SD) variable	*0*	*2*	*4*	*0*	*2*	*4*
Age (years)	66.2 (7.8)*			65.1 (8.5)		
Prostate volume (mL)	28.1 (3.2)			28.1 (9.7)		
Concomitant disease (%)	64.5			63.3		
IPSS						
Total	18.8 (6.0)	13.5 (6.2)	10.1 (6.5)	20.6 (7.0)	13.6 (8.2)	12.5 (7.5)
Irritative	7.4 (2.6)	5.5 (2.5)	4.6 (2.3)	7.5 (4.1)	5.7 (3.6)	5.0 (3.5)
Obstructive	10.7 (4.8)	7.7 (4.5)	5.4 (5.3)	12.8 (5.1)	7.9 (5.4)	8.1 (5.3)
QOL score	4.4 (1.1)	–	3.5 (1.4)	4.7 (1.0)	–	3.8 (1.5)
Q_{max} (mL/s)	8.5 (2.0)	–	10.9 (4.8)	8.1 (2.5)	–	9.7 (4.2)
Q_{ave} (mL/s)	4.6 (1.4)	–	6.0 (2.4)	3.9 (1.7)	–	4.8 (2.6)
% PVR	19.9 (18.8)	–	15.2 (13.0)	15.2 (13.0)	–	12.7 (18.3)
Blood pressure (mmHg)						
Systolic	143.5 (4.8)	135.0 (3.7)	135.0 (3.6)	141.4 (4.2)	132.9 (4.8)	135.9 (4.4)
Diastolic	80.7 (3.1)	78.1 (2.1)	78.7 (2.4)	81.6 (3.0)]	78.9 (3.5)	82.1(3.5)
Pulse (b.p.m.)	72.8 (2.8)	72.2 (2.1)	72.6 (1.8)	80.1 (2.7)	79.9 (2.4)	77.6 (3.5)

* Represents standard deviation.

obstructive and irritative symptoms compared with placebo. However, a placebo-controlled double-blind study in Japan showed that a 4-week treatment with terazosin 2 mg daily improved subjective symptoms [23]. Although tamsulosin at 0.2 mg daily failed to improve irritative symptoms in the initial study by Kawabe *et al.* [12], two of three irritative symptoms were improved in the present trial. These differences may be attributable to variation in the questionnaires used in the two studies for evaluating the severity of symptoms. Q_{max} and Q_{ave} were better in the terazosin group but only Q_{ave} improved in the tamsulosin group, confirming the findings of previous reports [14,21].

The improvements in subjective symptom scores and objective uroflowmetry data with terazosin were similar to those with tamsulosin. Although in the present study there were no significant changes from baseline in BP or pulse rate with either treatment, decreased BP has been reported in Korean patients treated with terazosin [14]. This difference may be attributable to the different incremental doses of terazosin used in the Korean study (1 mg daily increasing to 5 mg daily).

Adverse reactions such as dizziness, palpitations and dyspepsia, which are generally attributed to α1-adrenoceptor antagonists [13], were reported by only three of 31 patients in the terazosin group and none in the tamsulosin group. The relatively low incidence of adverse reactions related to BP reduction in both treatment groups may be attributable to the lower doses used in this trial, and that BP was not lowered significantly in this series. One patient treated with tamsulosin complained of a skin rash (a very rare adverse reaction to this agent; unpublished data, Yamanouchi Pharmaceutical Co.).

In the present study, terazosin and tamsulosin had similar overall efficacy (52% and 62%, respectively), suggesting that long-acting α_1-selective and α_{1A}-specific adrenoceptor antagonists have qualitatively similar efficacy on subjective and objective variables of BPH. Compared with the present study, the Korean study [14] used the same dose of tamsulosin but used a higher incremental dosage of terazosin (1–5 mg once daily). These investigators concluded that tamsulosin was better than terazosin because there was no difference in efficacy between them but there was a favourable adverse reaction profile for tamsulosin. However, in the present study, with the dose of terazosin reduced to 1–2 mg daily and administered twice daily, the incidence of adverse reactions was minimal and terazosin appeared to be tolerated as well as tamsulosin.

It is apparent that medication is becoming the preferred option for managing BPH and several new drugs, e.g. α1-adrenoceptor antagonists and 5α-reductase blockers, are now available to treat this condition. 5α-Reductase inhibitors reportedly reduce the static component of benign prostatic obstruction by decreasing the size of the prostate. Alternatively, α1-adrenoceptor antagonists can relieve LUTS from BPH by reducing the dynamic component of obstruction, making these agents preferable for treating patients with smaller prostates [24]. Suitable doses of these drugs vary according to race, constitution and the socio-economic condition of the country. Careful comparative studies of these drugs are necessary to establish the ideal therapeutic strategy for symptomatic

BPH in each country, and to establish differences between therapeutic agents for BPH. Excluding meta-analyses, the present comparative study is only the second to be reported. There is a need for a large, multicentre, prospective, comparative study to establish the ideal therapeutic agent and optimal dosage regimen for safe and effective management of BPH.

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Editorial comment

I congratulate these authors on conducting a comparative study of two contemporary α-adrenergic antagonists. The authors acknowledge the deficiencies within the study, i.e. the small sample size and relatively short treatment periods used; nevertheless, comparative work such as this is essential to allow the objective comparison of contemporary pharmacotherapeutic agents. This study is one of only a handful of comparative studies to be published in the field of α-adrenergic blockade. The doses used here reflect the recommended therapeutic doses for these agents in Japan.

Meta-analyses of existing data rely upon comparing data derived from studies often carried out using subtly different inclusion and exclusion criteria, and based on patient groups derived from different populations. Whilst structured reviews of the existing literature, such as those carried out by the Cochrane Collaboration, attempt to compensate for these methodological differences, it is clear that the most accurate way of investigating the potential differences between therapeutic agents used in routine clinical practice for the management of symptomatic BOO is to design comparative trials of agents, using pragmatic study designs (which has not been the norm in the past) and to carry out direct comparisons in many patients who are followed for an adequate period.

A further gap in knowledge relates to the contemporary use of α1-adrenergic antagonists in routine clinical practice, as all of the existing observational studies tend to focus on the use of one particular agent and are no doubt (because of their design) interventional, thereby potentially influencing the results that are obtained. There is a desperate need for a large-scale observational study examining the contemporary use of all existing agents for the management of symptomatic BOO in the primary care setting.

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