

High-Dose Terazosin Therapy (5 mg) in Korean Patients with Lower Urinary Tract Symptoms with or without Concomitant Hypertension: A Prospective, Open-Label Study

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Purpose: We determined the efficacy and safety of a relatively high dose of terazosin (5 mg) in Korean patients with lower urinary tract symptoms (LUTS), with or without concomitant hypertension. **Materials and Methods:** From July to December 2006, 200 men who consecutively presented with LUTS were prospectively studied. Eight weeks after treatment, blood pressure (BP), uroflowmetry, and International Prostate Symptom Score (I-PSS) were assessed. For analysis purposes, patients were stratified according to concomitant hypertension. Of the 200 patients, 173 completed the scheduled eight-week treatment period. **Results:** At baseline, no differences were evident in the two groups in terms of I-PSS, Qmax, PVR and BP. After eight weeks of treatment-although I-PSS and uroflowmetry parameters were not significantly different in the two groups-systolic and diastolic BP in the non-hypertensive control group were higher than in the hypertensive group ($p=0.001$ and $p=0.0100$, respectively). Changes in I-PSS, uroflowmetry parameters, and BPs measured at week eight post-treatment commencement did not significantly differ between the two groups. Moreover, the addition of 5 mg of terazosin to antihypertensives did not cause a significant reduction in either systolic or diastolic BP in either group. **Conclusion:** Adding terazosin to existing antihypertensive regimens did not seem to increase the incidence of adverse events. Our findings suggest that 5 mg terazosin is effective and that it has an acceptable safety profile as an add-on therapy for patients with LUTS and concomitant hypertension.

Key Words: Hypertension, prostate, lower urinary tract symptoms, terazosin

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INTRODUCTION

Benign prostatic hyperplasia (BPH) is often encountered in aging men with, usually, one or more co-morbidities. BPH and hypertension occur concomitantly in an estimated 25% of men aged 60 years and older.¹ In addition to their frequent coexistence, BPH and hypertension may have a common etiology in the sympathetic nervous system. Alpha1-adrenoceptor antagonists are the most commonly used first-line drugs for the management of symptomatic BPH. However, alpha1-adrenoceptor antagonists are not first-line therapies for hypertension, and the majority of hypertensive BPH patients will be receiving other antihypertensive agents that may increase the risk of drug interactions and side-effects. In addition, hypertension may reduce the effect of an alpha1-adrenoceptor antagonist on lower urinary tract symptoms (LUTS).² Furthermore, although 5 or 10 mg terazosin daily been routinely used in North America and Europe, terazosin is equally effective for treating symptomatic BPH in Asian patients at lower doses than those used in the West.³⁻⁵ In the present study, we sought to determine the efficacy and safety of a relatively high dose of terazosin (5 mg) in Korean patients with LUTS, with or without concomitant hypertension.

MATERIALS AND METHODS

From July to December 2006, 200 men who presented consecutively with LUTS and who were eligible and willing to participate in this study

were prospectively studied. Before inclusion in this study, all patients provided written informed consent. The Institutional Review Board of our hospital approved the protocol. The study inclusion criteria were as follows: age of at least 45 years, moderate to severe LUTS [International Prostate Symptom Score (I-PSS) ≥ 8], and a reduced maximum flow rate (Q_{max} ; ≤ 15 mL/sec). Exclusion criteria included a recent history of cardiovascular or cerebrovascular disease, hypotension or a history of fainting spells, restricted mobility, bladder cancer, prostate cancer, neurogenic bladder dysfunction, urinary stones, urethral strictures, acute or chronic urethritis, urinary tract history of bladder or prostate surgery or radiotherapy, acute urinary retention, or an indwelling catheter. Patients were also excluded from the analysis if they had a documented history of prostatic intraepithelial neoplasia by biopsy or a serum prostate-specific antigen (PSA) level in excess of 20 ng/mL. Concomitant administration of diuretics, angiotensin-converting enzyme inhibitors, beta-blockers, and/or calcium channel blockers was allowed, but verapamil, alpha-adrenergic antagonists, alpha-agonists, antiandrogen therapy, anticholinergic agents, or androgens were not allowed.

Patients were evaluated with respect to the following: detailed medical history, physical examination, blood pressure (BP), urinalysis, serum PSA, transrectal ultrasonography, uroflowmetry, post-voiding residual (PVR) urine volume by bladder scanning (BVI-3000, Diagnostic Ultrasound Co., Redmond, WA, USA), and I-PSS evaluation. Histories regarding concomitant diseases and all current medications were obtained from each patient. Terazosin was initiated at a dose of 1 mg once daily for the first seven days, 2 mg once daily for the next seven days, and 5 mg once daily for the following six weeks. After treatment, BP, uroflowmetry, PVR, and I-PSS were assessed.

The primary outcome of efficacy (symptom severity) was determined based on changes in LUTS. Baseline symptom severity and treatment efficacy were determined using I-PSS. Changes in Q_{max} , PVR, and BP were used as secondary outcomes of efficacy. Potentially important changes in BP were analyzed by counting the number of subjects (outliers) with a supine systolic BP of <

85 mm Hg and a diastolic BP of < 45 mm Hg, and subjects with a decrease in supine systolic BP of > 30 mm Hg or in diastolic BP of > 20 mm Hg. These changes in BP were considered clinically important because they represent changes expected to produce hypotensive symptoms including dizziness, flushing, or syncope in some patients.⁶ Adverse events were captured at eight weeks (at the end of the study) via interview. Safety was analyzed on an intent-to-treat (ITT) basis on subjects who took the study drug at least once and who were assessed for relevant variables at least once.

For analysis purposes, patients were stratified according to concomitant hypertension. Survey responses were coded and analyzed using descriptive statistics. All values are expressed as medians (5 - 95th percentiles) or numbers (%). The two groups were compared with respect to medians of each domain using the Mann-Whitney U-test or the Kruskal-Wallis test. Categorical variables were compared using the Fisher's exact test. The Wilcoxon signed-rank test was used to compare values before and after treatment in each group. A 5% level of significance was used for all statistical testing, and statistical analyses were performed using a commercially available analysis program, SPSS (SPSS Inc., Chicago, IL, USA).

RESULTS

Of the 200 patients, 190 patients received treatment, including 111 in the non-hypertensive control group and 79 in the hypertensive group. Of the 190 treated patients, 173 completed the eight weeks of treatment. Patient clinical characteristics were comparable in the two groups (Table 1). Baseline and post-treatment clinical parameters are shown in Table 2. At baseline, no differences were evident in the two groups with respect to I-PSS, Q_{max} , PVR, and BP. After eight weeks of treatment, I-PSS and uroflowmetry parameters and BP were not significantly different in the two groups. Terazosin treatment was associated with a significant improvement in subjective symptoms and most objective parameters in both groups. However, values of PVR and BVE did not change with treatment in either group, and

Table 1. Patients' Clinical Characteristics

	Control group	Hypertensive group	<i>p</i> *
No.	102	71	
Age (yrs)	61.5 (56.3 - 75.2)	62.2 (55.7 - 75.2)	0.845
Symptom duration (months)	13.0 (2.0 - 74.6)	12.0 (1.0 - 105.6)	0.599
Serum prostate-specific antigen (ng/mL)	1.04 (0.37 - 4.33)	1.01 (0.25 - 3.53)	0.795
Total prostate volume (mL)	21.6 (14.1 - 38.9)	23.7 (13.3 - 43.1)	0.216
Transition zone volume (mL)	7.4 (4.2 - 17.1)	7.9 (3.6 - 25.5)	0.163
Transition zone index	0.34 (0.21 - 0.53)	0.36 (0.20 - 0.60)	0.549

*Mann Whitney U-test.

Data presented are medians (5th-95th percentiles).

Table 2. Data at Baseline and Post-Treatment

	Baseline	After treatment	<i>p</i> *
International Prostate Symptom Score (item no.)			
Total sum (1 - 7)	23.0 (18.0 - 27.0)	14.0 (9.0 - 19.5)	< 0.001
Voiding symptoms (1,3,5,6)	13.0 (10.0 - 16.0)	9.0 (5.0 - 12.5)	< 0.001
Storage symptoms (2,4,7)	9.0 (6.5 - 11.0)	5.0 (3.0 - 7.0)	< 0.001
Quality of life index	5.0 (4.0 - 6.0)	3.0 (2.5 - 4.0)	< 0.001
Uroflowmetry			
Maximum flow rate (mL/s)	11.0 (9.0 - 13.0)	16.0 (14.0 - 19.0)	< 0.001
Post-void residual (mL)	10.0 (0.0 - 30.0)	10.0 (0.0 - 30.0)	0.538
Bladder voiding efficiency (%)	94.5 (88.6 - 100.0)	95.6 (90.1 - 100.0)	0.152
Blood pressure			
Systolic (mmHg)	133.0 (125.0 - 143.0)	129.0 (119.5 - 138.0)	< 0.001
Diastolic (mmHg)	79.0 (70.5 - 83.0)	72.0 (65.5 - 77.0)	< 0.001

*Wilcoxon signed rank test.

Data presented are medians (5th-95th percentiles).

changes in I-PSS, uroflowmetry parameters, and BP due to treatment were not significantly different between the groups (Table 3). Changes in BP according to the class of concomitant antihypertensives received are shown in Table 4. The addition of 5 mg terazosin to antihypertensives did not cause a significant reduction in either systolic or diastolic BP in either group, and adding terazosin to existing antihypertensive regimens did not increase the incidence of adverse events. The incidences of withdrawal because of adverse

events were 0% in the hypertensive group and 2.7% in the control group (Table 5).

DISCUSSION

To the best of our knowledge, this is the first study to evaluate the safety and effectiveness of 5 mg terazosin in Korean men with LUTS, with or without concomitant hypertension. Two of the results obtained are of note. First, in the present

Table 3. Differences Attributed to Treatment

No.	Control group	Hypertensive group	<i>p</i> *
No.	102	71	
International Prostate Symptom Score (item no.)			
Total sum (1-7)	-8.0 (-16.9, 0.0)	-7.0 (-19.0, 1.0)	0.313
Voiding symptoms (1,3,5,6)	-5.0 (-10.9, 2.0)	-4.0 (-12.0, 2.0)	0.339
Storage symptoms (2,4,7)	-4.0 (-7.9, 1.0)	-3.0 (-8.0, 1.4)	0.432
Quality of life index	-2.0 (-3.0, 0.0)	-2.0 (-3.0, 0.0)	0.980
Uroflowmetry			
Maximum flow rate (mL/s)	6.0 (0.0, 11.9)	5.0 (0.0, 16.0)	0.730
Post-void residual (mL)	0.0 (-64.3, 49.0)	0.0 (-91.6, 73.2)	0.444
Bladder voiding efficiency (%)	0.0 (-18.1, 18.3)	0.0 (-18.6, 22.1)	0.135
Blood pressure			
Systolic (mmHg)	-6.0 (-3.0, 14.9)	-4.0 (-20.6, 24.0)	0.109
Diastolic (mmHg)	-6.0 (-20.0, 4.9)	-4.0 (-19.4, 14.4)	0.124
Potentially clinically important changes	3 (2.9%)	2 (2.8%)	1.000 [†]

*Mann Whitney U-test.

[†]Fisher's exact test.

Data presented are medians (5th-95th percentiles).

study, 5 mg terazosin was found to be safe in Korean men with LUTS with or without hypertension, and second, subjective and objective parameters improved in both the hypertensive and the non-hypertensive control groups.

Optimal alpha-blocker doses vary by race, constitution, and socio-economic status. Lepor et al.⁶ reported that 2 mg terazosin daily did not improve obstructive or irritative symptoms as compared with placebo. However, a placebo-controlled double-blind study in Japan showed that a four-week treatment with 2 mg terazosin daily improved subjective symptoms.⁷ Lee and Lee⁵ found that 0.2 mg tamsulosin was better than 1-5 mg terazosin, because although no difference in efficacy was found between them a more favorable adverse reaction profile was found for tamsulosin. Okada et al.⁴ reported that reducing terazosin to 1-2 mg daily caused adverse reactions to fall to minimal levels, and that terazosin appeared to be as well-tolerated as tamsulosin. These findings suggest that careful studies on alpha-blockers are required to establish ideal

therapeutic strategies for symptomatic BPH on a country-by-country basis, and are needed to establish differences between therapeutic agents for the treatment of BPH.

A previous study showed that hypertensive BPH patients have more severe LUTS than normotensive BPH patients, and that hypertension worsens LUTS and may reduce the efficacy of terazosin.² However, in the present study, clinical parameters at baseline were similar in the two study groups. In addition, I-PSS and uroflowmetry parameters improved in both groups after terazosin administration, and the two groups were similar with respect to these parameters. In the present study, patients were given 1 mg terazosin once daily for the first week, 2 mg once daily for the second week, and 5 mg once daily for the following six weeks. Nakamura et al.⁸ investigated the effect of terazosin at 2 mg/day for one week on Q_{max}, and reported a significant improvement after only two days of treatment. Thus, the dose of terazosin appears to be lower, and the duration of treatment necessary to achieve

Table 4. Baseline and Post-Treatment Values, and Difference between the Two for Blood Pressures in Hypertensive Patients

	No.	Baseline	Post-treatment	Difference	<i>p</i> *
Systolic BP (mmHg)					
Diuretics	18	140.0 (112.0 - 164.0)	133.5 (109.0 - 157.0)	- 6.0 (- 24.0, 22.0)	0.127
ACE inhibitors	3	140.0 (137.0 - 180.0)	140.0 (125.0 - 168.0)	- 12.0 (- 15.0, 3.0)	0.285
Beta-blockers	11	133.0 (108.0 - 161.0)	130.0 (110.0 - 170.0)	- 2.0 (- 31.0, 16.0)	0.755
Calcium antagonist	19	132.0 (100.0 - 168.0)	133.0 (112.0 - 176.0)	- 2.0 (- 23.0, 32.0)	0.948
Combination A [†]	13	131.0 (120.0 - 170.0)	130.0 (107.0 - 156.0)	- 6.0 (- 17.0, 24.0)	0.346
Combination B [§]	7	136.0 (108.0 - 149.0)	133.0 (110.0 - 145.0)	- 8.0 (- 16.0, 30.0)	0.600
<i>p</i> value [†]		0.496	0.821	0.739	
Diastolic BP (mmHg)					
Diuretics	18	78.5 (63.0 - 92.0)	75.5 (60.0 - 86.0)	- 3.0 (- 18.0, 13.0)	0.138
ACE inhibitors	3	76.0 (74.0 - 88.0)	71.0 (70.0 - 77.0)	- 4.0 (- 17.0, 1.0)	0.285
Beta-blockers	11	80.0 (64.0 - 94.0)	70.0 (60.0 - 93.0)	- 4.0 (- 22.0, 8.0)	0.061
Calcium antagonist	19	80.0 (58.0 - 95.0)	74.0 (56.0 - 95.0)	- 4.0 (- 26.0, 22.0)	0.227
Combination A [†]	13	74.0 (67.0 - 90.0)	72.0 (60.0 - 89.0)	- 5.0 (- 20.0, 14.0)	0.327
Combination B [§]	7	80.0 (65.0 - 90.0)	75.0 (65.0 - 80.0)	- 1.0 (- 19.0, 15.0)	0.343
<i>p</i> value [†]		0.943	0.932	0.964	

BP, blood pressure; ACE, angiotensin-converting enzyme.

Data presented are medians (5th-95th percentiles).

*Wilcoxon signed rank test.

[†] Kruskal-Wallis test.

[‡] A diuretic and another.

[§] Any combination of two or more antihypertensive medications except a diuretic.

Table 5. Adverse Effects

	Control group (%)	Hypertensive group (%)
No.	111	79
Dizziness	13 (11.7%)	7 (8.9%)
Postural hypotension	5 (4.5%)	5 (6.3%)
Asthenia/fatigue	1 (0.9%)	0 (0.0%)
Syncope	1 (0.9%)	0 (0.0%)
Blurred vision	1 (0.9%)	0 (0.0%)
Edema	1 (0.9%)	0 (0.0%)
Gastrointestinal disorders	2 (1.8%)	1 (1.3%)
Discontinued due to adverse events	3 (2.7%)	0 (0.0%)

Data presented are numbers (%).

an improvement appears to be shorter in Asian men than in European men, which may be related to the lower dose required to maintain an effective blood level in Asian men. A dose-determining study on terazosin in Japanese patients with hypertension showed that 1 mg daily was optimal.⁹ However, since it has been reported that terazosin acts on the central nervous system,^{10,11} an increased dosage might additively block alpha-1 receptors in the lumbosacral cord, increase the threshold of bladder sensation, and thus improve collecting disorders. Moreover, an increased dose of terazosin might also block more alpha-1 receptors in the prostate and thus improve voiding.

In the HABIT trial, doxazosin was found to be more effective, with an acceptable safety profile, in concomitant hypertension and BPH, either as a monotherapy or as an add-on therapy.¹² In this study, BP at baseline and BP differences pre-/post-treatment did not significantly differ between the two groups. In addition, incidences of BP outliers were similar in the two groups. Therefore, a terazosin dose of 5 mg daily might not be too high for hypertensive BPH patients. Furthermore, as found by Lowe et al.,¹³ our findings indicate that terazosin can be safely used to treat patients with LUTS regardless of blood pressure status and the antihypertensive regimen used.

In the present study, there was no increase in adverse events in patients with LUTS and concomitant hypertension. In the Hytrin Community Assessment Trial of terazosin, BP related adverse events (i.e., syncope, dizziness, hypotension, postural hypotension, vertigo) were experienced by 13.1% of men who were taking other anti-hypertensives, compared with 15.2% for those who were not.¹⁴ A combined analysis of six placebo-controlled trials involving 996 patients assessed the safety and efficacy of terazosin for the treatment of BPH and concluded that terazosin can be administered safely to both normotensive and hypertensive patients with BPH.¹⁵ Moreover, a recent study stressed that care should be taken when first administering terazosin in a patient receiving the calcium antagonist verapamil, because orthostatic hypotension occurred in six of 24 patients.¹⁶ However, we did not encounter orthostatic hypotension in our patients, although the number of patients was small (n = 19). This

finding suggests that terazosin can be administered safely to hypertensive patients on a calcium antagonist. Furthermore, results of an analysis of adverse event data by a Veterans Affairs cooperative study suggested that dizziness and asthenia associated with alpha-1-adrenoceptor antagonists may not be due to vascular events.¹⁷

Our findings suggest that 5 mg terazosin is effective and has an acceptable safety profile in patients with LUTS with concomitant hypertension, and that terazosin (5 mg) may be safely added to ongoing antihypertensive therapy in this population. However, since this is a short-term follow-up study and may be underpowered statistically, a long-term follow-up and a larger-scale study is needed. In addition, our results demonstrate a need for a study designed to establish the optimal dosage regimen in an Asian population in order to ensure the safe and effective management of LUTS.

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