Terazosin in the Treatment of Hypertension and Symptomatic Benign Prostatic Hyperplasia: A Primary Care Trial

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Background. Terazosin, an alpha$_1$ blocker initially used as an antihypertensive, was approved in 1993 for use in the treatment of benign prostatic hyperplasia (BPH) symptoms. This study was designed to determine the safety and efficacy of terazosin in treating patients with concomitant BPH and hypertension.

Methods. Middle-aged men with essential hypertension were enrolled by their primary care physicians in community practice. Those with symptoms of benign prostatic hyperplasia were identified by a Boyarsky scale score. The study was a 12-week, dose-escalation, open-label protocol for men aged 45 years and older.

Results. Enrollment in the study totaled 5365 patients. Of these, 1483 had Boyarsky scores of ≥7, indicating symptomatic BPH. All patients with elevated blood pressure at the beginning of the study, including those with symptomatic BPH, showed significant reduction in blood pressure at the end of the 12-week trial. The patients with symptomatic BPH had statistically significant improvement in their BPH voiding symptoms. In the 1483 patients with BPH symptoms, terazosin produced a mean reduction of 55% in overall Boyarsky scores, 57% in obstructive symptom scores, and 54% in irritative symptom scores. In patients with baseline blood pressure ≤150/90 mm Hg, blood pressure reductions were statistically significant but clinically irrelevant. Adverse events were mild.

Conclusions. Terazosin is safe and effective in treating concomitant hypertension and BPH.

Key words. Prostatic hypertrophy; hypertension; terazosin; adrenergic alpha receptor blockaders. (*J Fam Pract 1994; 39:129-133*)

Benign prostatic hyperplasia (BPH), both symptomatic and asymptomatic, is a problem commonly seen in middle-aged and older men. Anatomically, BPH is present in nearly 50% of men of age 60 years, and increases to 85% by age 85.[1] The chance of a 50-year-old man requiring transurethral resection of the prostate (TURP) during his lifetime is estimated to be 29%.[2] In spite of the widespread acceptance of TURP (nearly 400,000 procedures are performed annually in the United States), there has been increasing interest in pharmacologic treatments to relieve the symptoms of BPH.[3] TURP remains the standard treatment for symptomatic BPH, but it is apparent that there is a need for an effective alternative treatment. Although the surgical mortality rate for TURP is only 0.2%, postoperative morbidity is approximately 18%, and at least 16% of patients do not show significant postsurgical improvement in their symptoms.[3,4]

Patients have also expressed a preference for pharmacologic treatment over prostate surgery. In one study of 37 men undergoing TURP, 67% said that, given the choice, they would have chosen drug therapy as an alternative to surgery.[5]

Pharmacological research on BPH has focused on alpha$_1$ blockers. Originally, the nonselective alpha blocker phenoxybenzamine hydrochloride was the treatment of interest, but recently, more attention has been focused on the selective alpha$_1$ blockers terazosin, doxazosin mesylate, prazosin hydrochloride, indoramin, and alfuzosin.[6-16]

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Terazosin (Hytrin, Abbott Laboratories, North Chicago, Ill), a once-a-day selective alpha$_1$ blocker that was originally developed and marketed as an antihypertensive agent, is the first of these agents to be approved by the US Food and Drug Administration for the treatment of symptomatic BPH.[11-16] Research to date has involved relatively small trials (15 to 285 patients) conducted in controlled, double-blind studies in academic urological environments. In a double-blind, placebo-controlled trial of 57 patients, Fabricus and associates[15] reported a 54% improvement in peak urine flow, a 68% improvement in the obstructive symptom score, and a 34% improvement in the irritative symptom score.

The current study was developed to evaluate the effect of terazosin on blood pressure, metabolic variables, and BPH symptoms in primary care patients with hypertension. We are reporting the results from a subset of patients who, in addition to hypertension, had symptomatic BPH at enrollment in the trial.

Methods

Primary care physicians, including family, generalist, and internal medicine physicians who were in active community practice throughout the United States, were recruited as investigators. The study was an open-label, dose-escalation design. Physicians were asked to recruit up to five patients, each of whom met the following criteria: male, aged 45 years or older, and having a new diagnosis of or currently being treated for hypertension. Criteria for exclusion were any of the following: prostatic cancer; clinically significant preexisting diseases, such as congestive heart failure, angina, or renal impairment (serum creatinine >2.0 mg/dL [>176.8 μmol/L]); and a history of syncope.

Seven hundred twelve protocol kits were distributed, each of which contained materials for enrolling five patients. Since a few physicians enrolled more than five patients and received an additional kit, the actual number of participating physicians was somewhat less than 712.

At the first visit, a brief medical history was taken, focusing on the duration and treatment of hypertension. If the patient's history suggested prostate problems, a baseline Boyarsky symptom score was obtained. The Boyarsky scale measures severity of BPH symptoms, both irritative and obstructive, by means of a questionnaire comprising 9 categories for patient symptom self-assessment on a Likert-type scale of 0 to 3. A patient was considered to have clinically significant BPH symptoms if he scored ≥7 on the Boyarsky scale.

Terazosin therapy was begun at the first visit, as monotherapy, or as an addition to ongoing antihypertensive therapy, or as a replacement for another form of antihypertensive therapy. As a precaution, patients who were currently taking beta blockers for any reason continued to take them. Terazosin therapy was begun with an initial 1-mg bedtime dose followed by 2 days of 1-mg doses. The dosage was increased to 2 mg daily on day 4.

An optional second visit was available at 2 weeks to allow for dose titration up to 5 mg, if needed for blood pressure control. A third interim visit was scheduled 6 weeks into the study to monitor blood pressure and record any adverse events. Dose titration, if necessary for blood pressure control, was performed at this visit. The fourth and final evaluation occurred after the 12th week of the study. At each visit, a blood pressure measurement and pulse rate were obtained after the patient had been sitting quietly for 5 minutes. Boyarsky scores were obtained at the initial and final visits. Adverse events (type, date of onset, duration, severity and relation to terazosin, and outcome) were obtained at each visit.

Results

Blood pressure data were available for 5365 patients, whose mean age was 62.3 (range, 45 to 99) years. Of these men, 1483 (27.6% of enrolled patients) had Boyarsky scores ≥7, which is diagnostic for symptomatic BPH. Both groups of patients were similar, except that the mean age of patients with symptomatic BPH was somewhat greater than that of the total group screened. The patients' racial and ethnic distribution was Asian (2%), black (13%), white (79%), Hispanic (5%), other (1%), and unknown (1%).

Table 1 shows the reductions in both the systolic and diastolic blood pressure measurements that occurred by the end of the 12-week treatment period for all patients and for the patient population with clinically significant BPH symptoms at baseline. The mean reductions in systolic and diastolic blood pressures were similar for patients with and without BPH symptoms. All reductions in blood pressure were statistically significant at the .001 level.

In the patient population as a whole, decreases in blood pressure were proportional to the baseline elevation of the systolic and diastolic pressures. The mean reduction among patients with systolic pressures of <150 mm Hg was 4.3 mm Hg, and the mean diastolic reduction among patients with baseline diastolic readings of <90 mm Hg was 3.2 mm Hg. Although these reductions were statistically significant, they are clinically irrelevant. This observation supports the safety of using terazosin for BPH symptoms in patients with normal blood pressures.

Table 2 shows the overall reductions in Boyarsky scores in the 1483 patients with baseline scores ≥7. There

Table 1. Blood Pressure Changes after 12-Week Treatment of All Patients and of Patients with Benign Prostatic Hyperplasia (BPH) Symptoms

Variable	N	Mean Baseline (mm Hg)	Mean Change* (mm Hg)
Systolic blood pressure			
All patients	5365	159.0	−16.4
Patients with baseline (mm Hg):			
≤150	2065	139.0	−4.3
151–180	2689	165.8	−20.7
≥181	611	196.4	−38.4
Diastolic blood pressure			
All patients	5365	94.3	−10.3
Patients with baseline (mm Hg):			
<90	1942	83.0	−3.2
91–100	2365	97.2	−12.0
>101	1058	108.5	−19.4
Systolic blood pressure of patients with BPH	1459	156.8	−16.5
Diastolic blood pressure of patients with BPH	1459	92.2	−10.1

**All reductions in mean blood pressure were statistically significant at P=.001.*

was a mean reduction in the total score of 6.5 points from a baseline of 11.9, representing a 55% change. There was a mean reduction in obstructive symptoms of 3.8 points from a baseline of 6.7, representing a 57% change, and a reduction in irritative symptoms of 2.8 points from a baseline of 5.2, representing a 54% change. The number

Table 2. Changes in Boyarsky Scores at Pretreatment and Posttreatment Symptom Evaluations for All Patients Aged ≥45 Years with a Total Baseline Score of ≥7

Variable	Mean Baseline Score	Mean Change (%)*
All patients (N=1483)		
Total score	11.9	−6.5 (55)
Obstructive score	6.7	−3.8 (57)
Irritative score	5.2	−2.8 (54)
Patients with baseline total score of 7 to 11 (mild) (n=820)		
Total score	8.9	−4.6 (52)
Obstructive score	4.8	−2.8 (54)
Irritative score	4.1	−2.0 (49)
Patients with baseline total score of 12 to 16 (moderate) (n=437)		
Total score	13.6	−7.7 (57)
Obstructive score	7.9	−4.5 (57)
Irritative score	5.8	−3.2 (55)
Patients with baseline total score of 17 to 21 (severe) (n=182)		
Total score	18.5	−10.8 (58)
Obstructive score	10.6	−6.1 (58)
Irritative score	7.9	−4.6 (58)

**All reductions in Boyarsky scores were statistically significant at P=.001.*

Table 3. Posttreatment Changes in Benign Symptoms Among 1483 Patients with Baseline Total Boyarsky Score ≥7

Voiding Symptom	Symptomatic Patients with Improvement at Final Visit No. (%)	Symptomatic Patients Who Were Symptom-Free at Final Visit No. (%)
Obstructive		
Hesitancy (n=1246)	931 (74.7)	491 (39.4)
Intermittency (n=1184)	839 (70.9)	539 (45.5)
Terminal dribbling (n=1211)	872 (72.0)	509 (42.0)
Urinary stream (n=1349)	970 (71.9)	513 (38.0)
Incomplete emptying (n=1260)	916 (72.7)	587 (46.6)
Irritative		
Nocturia (n=1430)	1037 (72.5)	283 (19.8)
Daytime frequency (n=1314)	865 (65.8)	482 (36.7)
Urgency (n=1287)	922 (71.6)	588 (45.7)
Dysuria (n=636)	492 (77.4)	424 (66.7)

of symptomatic patients who were symptom-free at the final visit ranged from 19.8% of patients with nocturia to 66.7% of patients with dysuria (Table 3).

The degree of BPH symptom improvement corresponded with the initial severity of the symptoms. The patients with mild to moderate symptoms achieved Boyarsky scores of <7 (asymptomatic), whereas those with more severe disease achieved scores of 7 to 10 points (mildly symptomatic).

Adverse events were reported in 629 (11.09%) of the 5672 patients screened. This figure is somewhat lower than that reported for placebo controlled trials of terazosin. Because of the open-label design and the small number of patients assigned to each physician, there may have been underreporting of side effects. Adverse events reported in more than 1% of patients included asthenia (1.87%), headache (1.39%), and dizziness (2.45%). Thirty-five patients dropped out of the study, 13 of whom did so because of adverse drug reactions.

Discussion

Terazosin, which has been marketed in the United States as an antihypertensive agent for approximately 6 years, was approved in 1993 for the treatment of symptomatic BPH. Because there are only limited data on the long-term use of terazosin or other alpha$_1$ blockers in BPH, it is not yet possible to fully evaluate these agents as an alternative to TURP. It is not known, for example, what percentage of men who are taking terazosin or other alpha$_1$ blockers will eventually require TURP because of disease progression. Long-term open-label studies that may help answer this question are currently under way.

Until the current study, no work has been published

on the use of terazosin in patients with *concomitant* BPH and hypertension. Earlier terazosin BPH research has been conducted in traditional double-blind fashion by urological researchers. The studies have generally been limited in size and have not involved primary care physicians or community practice settings that would replicate routine practice. The present study evaluates the safety and efficacy of terazosin when prescribed by primary care physicians in community practice settings.

The strengths and limitations of the study design are self-evident. On the positive side, the large patient population gives the study the "power of numbers," and the study setting allows for the "real world" experience of practicing physicians. On the negative side, the open-label design of this study, necessitated by the use of a large number of practice-based physicians, did not permit the elimination of placebo effect, which may be important in the evaluation of BPH.[17] In a double-blind study, Lepor and associates[13] detected a placebo effect in the treatment of symptomatic BPH with terazosin at improvement levels (total, irritative, and obstructive symptom scores reduced 2.3, 0.4, 1.9, respectively) that were less than one half of the improvement seen among patients in our study. Isaacs[17] suggested that the expectation of relief may actually decrease the sympathetic nervous stimulation of the prostate and thus reduce symptoms. It should also be noted that patients' subjective reports of symptom severity, which are highly susceptible to placebo effect, play an important role in both the diagnosis of symptomatic BPH and the decision to perform surgery.

Caine[18] described how BPH symptoms result from two physiologic components. The "dynamic component" is mediated by alpha-adrenergic control of smooth muscle tone in the prostate. The "mechanical component" is the fixed anatomical obstruction caused by prostatic enlargement. Furuya and colleagues[19] further determined that 40% of urethral pressure in patients with BPH was caused by the dynamic component (from increased alpha-adrenergic tone), and 53% was related to the mechanical component caused by the hyperplastic gland. Terazosin and other alpha$_1$ blockers act only on the dynamic component of BPH; they have no effect on the fixed, mechanical obstruction or on the hyperplastic process.

Prostate size does not necessarily correlate with symptom severity. For reasons that are not well understood, some BPH patients may have severe symptoms, while others with the same degree of prostatic hyperplasia may have few or no symptoms. Neither an increased level of alpha-adrenergic receptors, nor an upgrading of the alpha-adrenergic receptors, nor an increased functional response has been demonstrated in men with symptomatic BPH as compared with asymptomatic men with prostatic hyperplasia.[20–22] Regardless of the current lack of understanding about the physiologic mechanisms involved in symptomatology, the efficacy of terazosin in reducing BPH symptoms has been well documented.[6–16] When compared with similar prostate symptom scales, the Boyarsky scale, which was the primary measurement of BPH efficacy in this trial, has excellent internal and external validity.[23–25]

This study demonstrated that the use of terazosin in men who are aged ≥45 years and have hypertension and symptomatic BPH not only reduced their elevated blood pressure but also significantly improved their BPH symptoms during the 12-week trial period. These statistically significant improvements were accompanied by limited and mild side effects. In addition, patients with essentially normal blood pressures achieved a reduction in BPH symptoms without clinically relevant or symptomatic reductions in blood pressure.

This study documents that terazosin can be used safely and effectively by primary care physicians to treat hypertension and symptomatic BPH, whether these conditions occur individually or concomitantly. Our results underscore the need for long-term controlled trials of terazosin and other alpha$_1$ blockers to determine whether these agents have the potential for delaying or perhaps even avoiding the trauma and expense of prostate surgery.

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