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Terazosin in benign prostatic hyperplasia: effects on blood pressure in normotensive and hypertensive men

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Objective To determine the effects of terazosin on blood pressure and on antihypertensive therapy when used in managing benign prostatic hyperplasia (BPH).

Patients and methods Safety data from a large, multinational study were analysed retrospectively. Normotensive and hypertensive patients received escalating dosages of terazosin for 10 weeks and were maintained on 5 or 10 mg daily doses for 16 weeks (single-blind period). After the initial treatment period, only men having sufficient improvements in International Prostate Symptom Score ($\geqslant 30\%$) and in peak flow rate ($\geqslant 10\%$) were randomly assigned to continue terazosin or to receive placebo for 24 weeks (double-blind period).

Results In hypertensive patients, terazosin reduced systolic blood pressure (SBP) and diastolic blood pressure (DBP) during the single-blind period; these clinically significant reductions were maintained in patients receiving terazosin during the double-blind period. However, in normotensive and controlled hypertensive patients terazosin produced no clinically significant mean changes in SBP or DBP during either study period. Terazosin did not adversely affect patients receiving concomitant antihypertensive medication.

Conclusion Terazosin is a safe treatment for BPH in normotensive and hypertensive men, including men who are already taking additional antihypertensive drugs.

Keywords Terazosin, benign prostatic hyperplasia (BPH), selective α-1-blocker, hypertensive patients, long-term safety, randomized withdrawal

Introduction

More than half of men beyond middle age have histological evidence of BPH and $\approx 25\%$ of men will require treatment by the age of 80 years [1–4]. The irritative and obstructive urinary symptoms associated with BPH limit daily activities and reduce the quality of life for many millions of men worldwide [4–8]. Although prostatectomy has been a widely accepted treatment for symptomatic BPH, this surgical procedure may fail in up to 20% of men, will need to be repeated within 8 years in 15% of men, and is associated with such complications as impotence (10% of men), urinary tract infection (8%), epididymitis (5%), and incontinence (3%) [9].

The drawbacks of prostatectomy have generated interest in pharmacological agents for medically managing symptomatic BPH, including α-blockers. Several studies have shown that the selective, long-acting α-1 adrenoceptor antagonist terazosin is effective in relieving bothersome urinary symptoms, improving peak urinary flow rates (PFRs), reducing residual urine volume, and improving overall patient status and quality of life [4,9–16].

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Terazosin was originally developed as an antihypertensive agent and is now well-established as safe and effective in this context [17–19]. In view of terazosin's potential to lower blood pressure or to interact with concomitant antihypertensive agents when used in the medical management of BPH, safety data from a large, multinational, placebo-controlled, randomized withdrawal study were analysed retrospectively. This study included normotensive, controlled hypertensive, untreated hypertensive, and uncontrolled hypertensive patients, all of whom also had symptomatic BPH.

Patients and methods

Normotensive, i.e. diastolic blood pressure (DBP) < 90 mmHg, and hypertensive men (DBP $\geqslant 90$ mmHg) aged 45 years with a diagnosis of BPH, and IPSS $\geqslant 12$, FR of 5–15 mL/s, a voided volume $\geqslant 100$ mL, and post-void residual volume < 300 mL were eligible for the study. Antihypertensive treatment with agents other than verapamil was permitted, and the dosage could be adjusted at the investigator's discretion. The maximum allowable DBP was 115 mmHg for patients not receiving antihypertensive treatment. Patients who received medications that might have interfered with the study or

pharmacological treatment for BPH, either currently or within the previous 3 months (e.g. α-adrenergic antagonists, antiandrogens, herbal extracts, or GnRH analogues), were ineligible for the study. Also ineligible were patients who had experienced either a myocardial infarction or transient ischaemic episode within the previous 6 months, or had a history of fainting spells, orthostatic hypotension, or blackouts. Other reasons for exclusion from the study included known or suspected prostate cancer, urethral stricture, bladder neck obstruction, gross haematuria, insulin-dependent diabetes mellitus, renal or hepatic impairment, genitourinary disorders, a history of cerebrovascular accidents, or a history of hypersensitivity or unresponsiveness to α-adrenergic antagonists.

The study consisted of three experimental periods; the first was a 2-week lead-in period with placebo. The second a single-blind phase comprising a 10-week terazosin dose-escalation period (1 mg initial dose, 2 mg daily for 13 days, 5 mg daily for 4 weeks, 10 mg daily for 4 weeks) followed by a 16-week maintenance period (5- or 10-mg daily doses, as tolerated). The third was a 24-week, randomized, placebo-controlled, double-blind period during which only responders from the single-blind period either continued their maintenance dosage or received placebo (randomized withdrawal phase). Responders were those patients whose IPSS decreased $\geqslant 30\%$ from baseline to the end of the single-blind period and PFR increased $\geqslant 10\%$ during the same period. Nonresponders were considered to have completed the study at the end of the single-blind period.

Patients were evaluated every other week during the first month of the study, then every fourth week during the next 2 months, and then every 8 weeks during the remainder of the study. SBP, DBP and pulse rate were determined at each evaluation visit after the patient had been sitting for 5 min. These vital signs were determined at approximately the same time of day at each evaluation visit and before receiving the scheduled nightly dose of study drug for that evaluation day.

All adverse experiences were mapped to a COSTART-3 (Coding Symbols for Thesaurus of Adverse Reaction Terms) Dictionary. For the double-blind period, when the combined number of events was $\geqslant 6$, the adverse experiences were compared between treatment groups using Fisher's exact test. For the single- and double-blind periods, mean changes from baseline to final visit for vital-sign data were analysed using a paired *t*-test. The double-blind mean changes from baseline to final visit for vital-sign data were also compared between treatments with a one-way ANOVA with treatment group as the factor of interest. Baseline vital signs for the single-blind period were obtained at visit-2 (end of lead-in period). Baseline vital signs for the double-blind period were obtained at the final single-blind visit.

For the statistical analysis, patients were divided into four blood pressure groups based on baseline DBP and the use of concurrent antihypertensive medication at visit-2; normotensive, controlled hypertensive, untreated hypertensive, and uncontrolled hypertensive. Normotensives were patients with a DBP < 90 mmHg receiving no antihypertensive medication. Controlled hypertensives were patients with a DBP < 90 mmHg being treated with concurrent antihypertensive medication. Untreated hypertensives were patients with a DBP $\geqslant 90$ mmHg receiving no antihypertensive medication. Uncontrolled hypertensives were patients with DBP $\geqslant 90$ mmHg despite treatment with antihypertensive medication. All clinical trial procedures were approved by an Institutional Review Board/Ethics Committee and were in accordance with the Declaration of Helsinki.

Results

A total of 427 patients were enrolled in the study. Post-baseline blood pressures were available for 404 patients. A total of 207 patients qualified for and were randomized into the double-blind phase of the study. Post-baseline blood pressures were available for 197 of the 207 randomized patients. Failure of patients to advance to the double-blind period was largely because adverse events resulted in premature discontinuation (87 patients) or because of insufficient improvement in IPSS and/or PFR (85 patients).

The mean (range) age of the patients entering the single-blind period was 63.6 (44–92) years, and of those entering the double-blind period was 63.7 (45–82) years in the placebo group and 63.3 (48–92) years in the terazosin group. Caucasians composed 96% of patients entering the single-blind period and, in the double-blind period, 98% of the placebo group and 95% of the terazosin group. For patients entering the single-blind period, the mean (range) height was 171.7 (154–193) cm and weight 76.7 (51–113) kg. As reported recently [13], 58% (219/378) of patients in this randomized withdrawal study completing the single-blind period experienced $\geqslant 30\%$ improvement in the IPSS by the end of the single-blind period.

Concurrent antihypertensive medications

At the baseline of the single-blind treatment period, 21.5% (92/427) of patients were receiving concurrent antihypertensive medications. Antihypertensive drug classes in which $\geqslant 3\%$ of patients received one or more concurrent medications are as follows: β-adrenergic blocking agents (atenolol, betaxolol, bisoprolol, labetalol, metoprolol, oxprenolol hydrochloride, propranolol,

sotalol hydrochloride, and timolol); calcium-channel blocking agents (amlodipine, diltiazem, felodipine, flunarizine dihydrochloride, isradipine, nicardipine, nifedipine, nitrendipine, and verapamil [although verapamil was not allowed by the protocol, two patients were receiving the drug]); and angiotension-converting enzyme (ACE) inhibitors (captopril, enalapril, lisinopril, and perindopril erbumine).

During the double-blind randomized withdrawal period, 22.3% (23/105) of patients in the terazosin group were receiving concurrent antihypertensive agents. Antihypertensive drug classes in which $\geqslant 3\%$ of patients received one or more concurrent medications are as follows: beta-adrenergic blocking agents (atenolol, labetalol, metoprolol, sotalol hydrochloride, and timolol); calcium-channel blocking agents (amlodipine, felodipine, flunarizine dihydrochloride, isradipine, and nifedipine); ACE inhibitors (enalapril, lisinopril, and perindopril erbumine); and diuretics (amiloride, bendroflumethiazide, chlorthalidone, hydrochlorothiazide, and spironolactone).

Vital signs: single-blind treatment period

Terazosin produced clinically and statistically significant mean decreases from baseline in SBP and DBP in untreated and uncontrolled hypertensive patients (Fig. 1**a**). As early as week 2, there were clinically significant DBP decreases of 8.5 mmHg and 7.4 mmHg in the untreated and uncontrolled hypertensive groups, respectively. By contrast, there were no clinically significant mean blood pressure changes in the normotensive and controlled hypertensive groups, although there were statistically significant decreases in SBP and DBP in the normotensive group. There were no clinically or statistically significant changes in pulse rate in any blood pressure group.

In the untreated hypertensive group, mean decreases during the single-blind period in SBP and DBP were 12.6 mmHg and 11.5 mmHg, respectively. In the uncontrolled hypertensive group, mean decreases were 13.6 mmHg and 10.7 mmHg. By contrast, mean decreases in the normotensive group were 3.1 mmHg and 1.7 mmHg, and in the controlled hypertensive group, 2.8 mmHg and 0.2 mmHg. Mean baseline and final-visit SBP and DBP values are shown in Fig. 1 for all four groups.

Vital signs: double-blind randomized withdrawal period

In patients receiving terazosin, there were no statistically or clinically significant mean changes in SBP, DBP or pulse rate during the double-blind period in any of the blood pressure groups (Fig. 1**b**). However, for patients receiving placebo, there was a trend toward increased SBP and DBP in all blood pressure groups, statistically significant in DBP for normotensive patients (Fig. 1**c**). There were no statistically significant differences between groups for mean changes in SBP or DBP for any blood pressure subgroup.

Adverse experiences: single-blind treatment period

The incidence of adverse experiences was comparable among the four blood pressure groups (Table 1). The most common adverse experience during the single-blind period was dizziness, experienced by 21% (41/200) of normotensive patients, 16% (7/44) of controlled hypertensive patients, 25% (34/135) of untreated hypertensive patients, and 13% (six of 48) of uncontrolled hypertensive patients. Other common adverse experiences included headache, asthenia, and somnolence (Table 1). Eighty-seven patients (20%) discontinued the study during the single-blind period due to adverse experiences. The incidence of these experiences was similar among the blood pressure groups; dizziness was the most common cause of discontinuation (29 patients, 7%).

Adverse experiences: double-blind randomized withdrawal period

There were no clinically significant differences in adverse experiences between patients receiving placebo and those receiving terazosin in any of the blood pressure groups (Table 2). The overall incidence of several adverse experiences tended to be lower in patients administered placebo than in those administered terazosin, including dizziness (0% placebo, 3% terazosin), headache (1% placebo, 2% terazosin), and somnolence (0% placebo, 2% terazosin); there were too few patients with adverse experiences in each blood pressure group to warrant statistical analyses. During the double-blind period, nine of 102 patients (9%) in the placebo group and seven of 105 patients (7%) in the terazosin group discontinued the study due to adverse experiences.

Discussion

Both BPH and benign essential hypertension are highly prevalent conditions [19]. The pathogenesis of both these disorders is associated with an increased tone of sympathetically innervated smooth muscle. Recently it has been reported that there is a concomitance of the two conditions [20], perhaps as a result of increased overactivity of the sympathetic nervous system as a whole [21].

Overall, $\approx 43\%$ of men over the age of 60 suffer from LUTS and about half of these men have significant impairment in quality of life as a result [8]. In the case

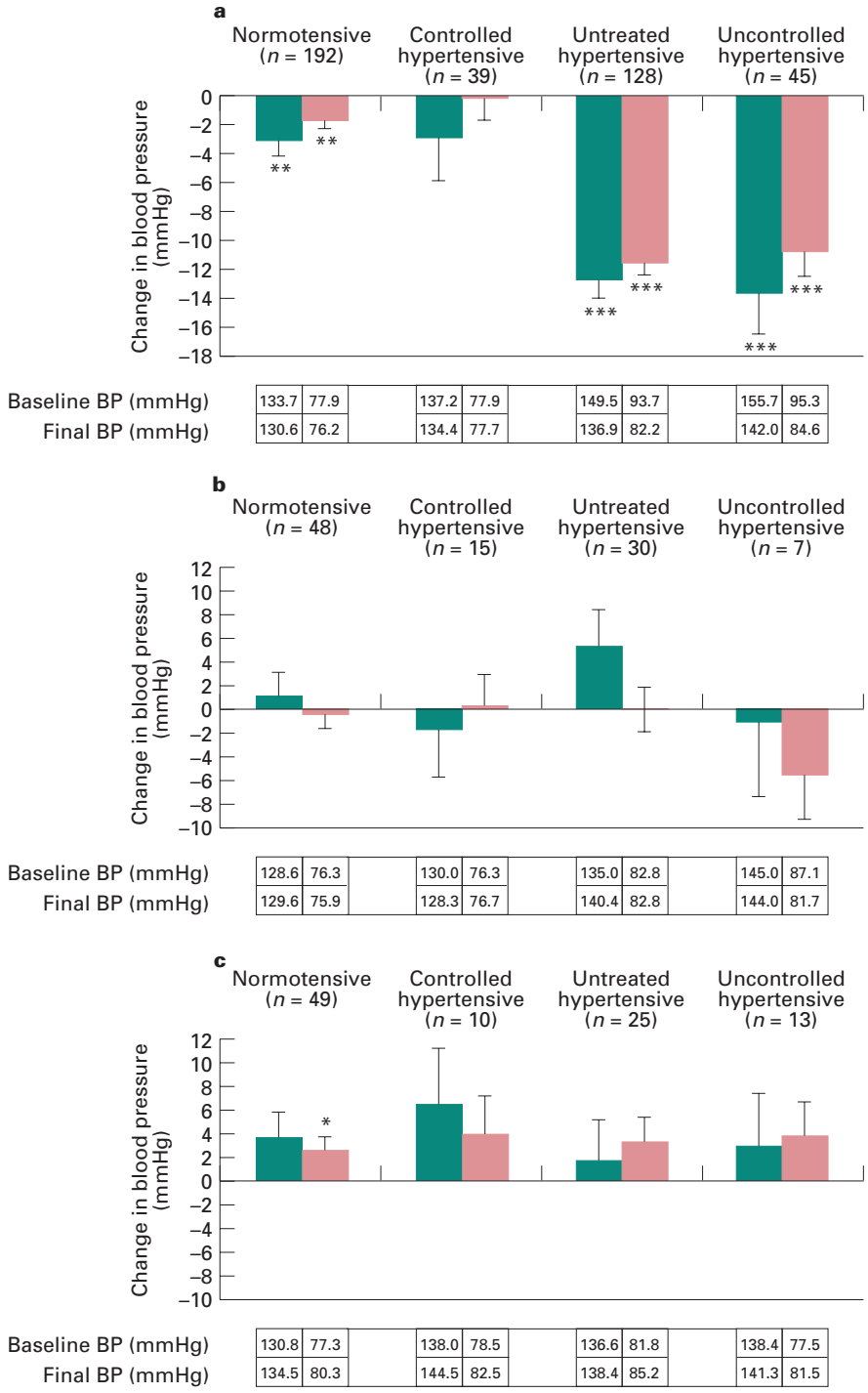

Fig. 1. **a**, Single-blind treatment period; mean changes from baseline to final visit in systolic blood pressure (SBP green) and diastolic blood pressure (DBP red). Asterisks represent statistically significant intragroup mean changes from baseline at $^{**}P < 0.01$ and $^{***}P < 0.001$. **b**, Double-blind randomized withdrawal period; terazosin group, mean changes from baseline to final visit in SBP and DBP. **c**, Double-blind randomized withdrawal period; placebo group, mean changes from baseline to final visit in SBP and DBP. Asterisk (*) represents statistically significant intragroup mean change from baseline at $P < 0.05$.

of benign essential hypertension, ≈28% of men aged 60–69 years are affected [22]. Thus, a considerable number of men are affected by one or the other condition, and many by both. The concomitance of LUTS and essential hypertension is reflected in this study; a quarter of men with BPH entering the trial were being treated with concurrent antihypertensive medications.

Terazosin is a quinazoline with the ability to selectively block α-1-adrenoceptors. Terazosin's safety and efficacy in the treatment of hypertension is well established [23–26], but only in patients with BPH has it been possible to extensively study the agent's effect on the blood pressure of normotensive men. The present data confirm that terazosin produces only minor, clinically

Table 1 The incidence of the most common adverse experiences during the single-blind treatment period. 'Most common' is an incidence ⩾4% for combined patients. Normotensive = DBP < 90 mmHg without antihypertensive medication. Controlled hypertensive = DBP < 90 mmHg with antihypertensive medication. Untreated hypertensive = hypertensive (DBP ⩾ 90 mmHg) not receiving antihypertensive medication. Uncontrolled hypertensive = hypertensive (DBP ⩾ 90 mmHg) despite receiving antihypertensive medication

		Hypertensive				
	Normotensive	*Controlled*	*Untreated*	*Uncontrolled*	P*	*Combined*
Number	200	44	135	48		427
Number (%) with:						
Dizziness	41 (21)	8 (18)	35 (26)	6 (13)	0.246	90 (21)
Headache	21 (11)	2 (5)	25 (19)	6 (13)	0.058	54 (13)
Asthenia	15 (8)	5 (11)	6 (4)	2 (4)	0.340	28 (7)
Pharyngitis	7 (4)	4 (9)	8 (6)	3 (6)	0.347	22 (5)
Somnolence	6 (3)	3 (7)	8 (6)	4 (8)	0.233	21 (5)
Back pain	7 (4)	2 (5)	6 (4)	3 (6)	0.750	18 (4)
Flu syndrome	8 (4)	1 (2)	7 (5)	0 (0)	0.478	16 (4)

*Determined by Fisher's exact test, comparison of four blood pressure groups for each adverse event.

Table 2 The incidence of most common adverse experiences during the double-blind randomized withdrawal period for patients with BPH who were normotensive, controlled hypertensive, untreated hypertensive and uncontrolled hypertensives. Definitions as Table 1

			Hypertensive					
	Normotensive		*Controlled*		*Untreated*		*Uncontrolled*	
	Placebo	*Terazosin*	*Placebo*	*Terazosin*	*Placebo*	*Terazosin*	*Placebo*	*Terazosin*
Number	50	49	10	15	27	31	13	8
Number (%) with:								
Dizziness	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)	1 (3)	0 (0)	0 (0)
Headache	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	2 (7)	0 (0)	0 (0)
Asthenia	0 (0)	0 (0)	1 (10)	0 (0)	1 (4)	0 (0)	0 (0)	0 (0)
Pharyngitis	2 (4)	1 (2)	0 (0)	1 (7)	1 (4)	2 (7)	0 (0)	0 (0)
Somnolence	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Back pain	2 (4)	0 (0)	0 (0)	0 (0)	0 (0)	1 (3)	0 (0)	0 (0)
Flu syndrome	0 (0)	2 (4)	0 (0)	0 (0)	1 (4)	0 (0)	0 (0)	0 (0)

insignificant blood pressure reductions in normotensive men with BPH; furthermore, similarly minor decreases in blood pressure were seen in those previously hypertensive men whose blood pressure had already been controlled by other agents (Fig. 1). This is reassuring for urologists, who may feel uncertain about the wisdom of prescribing an α-blocker to a patient with BPH who is already on existing antihypertensive therapy. The present data suggest that it is safe to do so, and then perhaps to slowly withdraw the ACE inhibitor, β-blocker, or calcium-channel blocker, as terazosin may adequately control both BPH-associated symptoms and hypertension as monotherapy. A notable exception to this rule is the calcium-channel blocker verapamil, which more commonly is used as an anti-arrhythmic agent. Verapamil has been reported to interact with terazosin [27], and the combination of these agents should probably be avoided.

A notable finding of this study is that the incidence of adverse events was higher during the single-blind than during the double-blind period. Although a possible explanation is that patients experiencing adverse events were 'selected out' during the single-blind phase, previous terazosin studies show that most adverse events occur during the initial months of therapy (during dose escalation) and decrease thereafter [28,29].

Terazosin's lowering of the blood pressure of hypertensive men and its minimal effect in normotensive men makes the current quest for more 'uroselective' α-blockers a questionable enterprise. Recently, it has been discovered that the α-1 adrenoceptor exists in subtypes α-1A, α-1B and α-1D [30]; α-1A adrenoceptors

predominate in the prostate [31] and in contrast, α-1B and α-1D adrenoceptors are present in vascular smooth muscle, as well as in the liver and spleen [32]. Theoretically, α-blockers that exhibit selectivity for the α-1A subtype should be more uroselective than agents like terazosin, which blocks all three adrenoceptor subtypes.

The only currently available agent with modest (5- to 35-fold) selectivity for the α-1A subtype is tamsulosin. However, the degree of tamsulosin's α-1A selectivity is contentious [33], evidence of α-1A selectivity is conflicting [34] and the overall efficacy–tolerability profile of tamsulosin (0.4 mg) [35–37] does not seem appreciably different from that of terazosin (1–10 mg) [10,16,38,39]. Compared with terazosin, tamsulosin appears to produce a slightly lower magnitude of improvement in symptom score (terazosin 32–45%, tamsulosin 29–36%) and PFR (terazosin 18–34%, tamsulosin 13–22%), and is associated with a higher incidence of abnormal ejaculation (terazosin 0–1%, tamsulosin 4–6%). Side-effects such as dizziness (terazosin 3–26%, tamsulosin 3–7%) and asthenia (terazosin 6–14%, tamsulosin 0–3%) appear to be less common with tamsulosin, although data from the USA suggest an increased incidence with tamsulosin (dizziness 15%, asthenia 8%) [40]. Only a well-designed, double-blind, direct comparison will reveal whether tamsulosin carries significant advantages.

Other α-1A adrenoceptor blockers with higher pharmacological selectivity (1000-fold) are on the horizon, and it will be interesting to see whether these highly selective agents can be used at higher doses to produce greater efficacy without cardiovascular or other side-effects. Until such agents become available, urologists should continue to use α-blocking agents that have been extensively investigated. Terazosin's beneficial effect on LUTS due to BPH is well established, and to this may be added the new knowledge that terazosin carries the advantages of normalizing blood pressure in hypertension with only minimal blood pressure effects in normotensive men, and not adversely affecting patients receiving concomitant antihypertensive medication.

Acknowledgements

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