1110-5704
African Journal of Urology

Vol. 7, No. 3, 2001
94-102

AN OPEN STUDY OF THE EFFICACY, SAFETY AND TOLERABILITY OF DOXAZOSIN IN THE SYMPTOMATIC TREATMENT OF BENIGN PROSTATIC HYPERPLASIA

EGYPTIAN MULTICENTER STUDY GROUP*

KEY WORDS: Doxazosin, α1-adrenoceptor antagonist, BPH

ABSTRACT

A total of 333 patients, 50 years or older, were included in this 12-week, multicenter (30 investigational sites), baseline placebo-controlled study to determine the efficacy and safety of doxazosin, a selective α_1-adrenoceptor antagonist, in the treatment of benign prostatic hyperplasia (BPH). The diagnosis was based on clinical manifestations, digital rectal examination and uroflowmetry. The treatment duration included a 2-week placebo washout phase and a 12-week active treatment phase (6 visits). Twenty-one patients were lost to follow-up during the placebo run-in phase and 312 patients completed the study. During the active treatment phase, the starting dose was 1 mg/day for 2 weeks that was titrated to 2 mg/day for 5 weeks. Titration was further increased to 4 mg/day if there was no increase in the peak flow rate (Q_{max}) ≥ 3ml/sec and / or no reduction in the mean International Prostate Symptoms Score (I-PSS) ≥30%. The blood pressure was assessed at baseline and at each subsequent visit. At the end of the treatment phase, doxazosin showed a remarkable effect on the efficacy parameters with I-PSS improving from 19.55±5.27 to 9.25±3.77 ($p < 0.0001$). The peak flow rate (Q_{max}) increased from 8.92±3.51 to 13.27±7.41 ($p< 0.0001$) and the average mean flow (Q_{mean}) rate increased from 4.56±2.53 to 6.65±5.85 ($p< 0.0001$). Doxazosin caused a mean reduction in blood pressure in hypertensive patients, (n=131) of 13.5 / 7.5-mmHg ($p< 0.0001$), while clinically insignificant changes were observed in the blood pressure of normotensive patients (n=181). In those patients the mean reduction in blood pressure was 4.2 / 2.5-mmHg ($p< 0.0001$). Adverse events were experienced by 24 patients (7.69%), in form of headache, dizziness, fatigue and somnolence, which were generally mild to moderate in intensity. Only 4 patients (1.28%) were withdrawn due to side effects (dizziness, somnolence or fatigue). We conclude that doxazosin, a third generation α_1-adrenoceptor antagonist, is an effective agent for the treatment of BPH and is well tolerated by the majority of patients.

* A. Abdel Aziz, M.D.; I. Abdel-Hafeez, M.D.; A. Abdel-Hakim, M.D., M. Abdel-Malek, M.D.; A. Abdel-Meguid, M.D.; M. Abo-Elhassan, M.D.; U. Abo-Farha, M.D.; M. Abo-Guindy, M.D.; A. Arafa, M.D.; A. Ashamallah, M.D.; A. Bahgat, M.D.; M. Elakkad, M.D.; H. El-Bialy, M.D.; H. El-Damanhoury, M.D.; M. Eldomairy, M.D.; A. Elkasaby, M.D.; A. Gaafar, M.D., M. Gaballah, M.D. ; B. Hathut, M.D.; A. Ibrahim, M.D.; I. Khalaf, M.D.; M. Moaatamed, M.D.; Sh. Morad, M.D.; R. Moustafa, M.D.; M. Rafik, M.D.; M. Abdel-Azeem M.D.; H. Rashwan, M.D.; S. Mohamed, M.D.; A. Salama, M.D.; M. Shalaby, M.D.; I. Shoukry, M.D.; H. Torky, M.D.

Table 1: Patient Assessment

Assessment at Baseline Visit	Assessment at Follow-Up Visits
PSA & digital rectal examination (DRE)	
Blood pressure	Blood pressure at each follow-up visit
Uroflowmetry parameters:	Uroflowmetry parameters at weeks 2, 7 and 12:
* Maximum flow rate (Qmax)	* Maximum flow rate (Qmax)
* Mean flow rate (Qmean)	* Mean flow rate (Qmean)
I-PSS symptom score	I-PSS sympom score at weeks 2, 7 and 12

INTRODUCTION

Benign prostatic hyperplasia (BPH) occurs in 40% to 70% of men aged between 60 and 70 years. Nearly 80% of men will have BPH within their lifetime and nearly 30% will undergo surgery from the condition[1]. Increasingly, patients decide against surgery to manage their BPH. Medical therapy offers relief of BPH symptoms with a minimal risk to the patients.

It is histologically known that the enlarged prostate gland is not only composed of glandular epithelial tissue but also has a large stromal component, the latter containing a preponderance of smooth muscle. The prostatic capsule contains striated muscle that is continuous with that of the bladder external sphincter. Although the volume of the glandular tissue may lead to the static component of obstruction, much influence on the autonomic and somatic innervation of the smooth muscle in the prostate may lead to so-called dynamic constriction. It is well known that the size of the prostate does not correlate with the degree of the obstruction. Transurethral resection of the prostate (TURP) is particularly effective as it removes obstructing tissue contributing to both the static and dynamic component[2].

Controlled clinical trials have shown phenoxybenzamine, a nonselective α_1-antagonist, to be effective in increasing the flow rate and decreasing the frequency of micturition in patients with BPH[3-4]. Its use, however, is limited by adverse reactions. These adverse events are primarily the result of a non-selective blockade of α_1-receptors and include postural hypotension, which is often accompanied by tachycardia. In addition, a non-selective blockade may induce inhibition of ejaculation and aspermia of the ejaculate due to impaired smooth muscle contraction in the vas deferens and ejaculatory duct[5-6].

Clear clinical advantages have been achieved through the development of long acting, third-generation, selective α_1-adrenoceptor antagonists such as doxazosin[7]. It offers the advantage of a rapid onset of action in the treatment of BPH. Significant urodynamics and symptomatic improvement take place as early as 1-2 weeks after initiation of treatment[8].

While adverse events may occur with any selective α_1-adrenoceptor inhibitor, doxazosin seems generally well tolerated. The prolonged time to achieve peak plasma concentration and the longer half-life may confer advantages in terms of tolerability over the more rapidly absorbed and eliminated selective α_1-inhibitors[9].

This multi-center study has been performed to assess the efficacy and safety of doxazosin. We report the results on patients with symptoms of outflow obstruction due to BPH who were followed up for a period of 12 weeks.

PATIENTS AND METHODS

A total of 333 male patients aged >50 years were enrolled in an open non-comparative study to evaluate the efficacy and safety of doxazosin in the treatment of symptoms of BPH. The study was conducted at 30 investigational sites in Egypt. Inclusion criteria in this study required male patients aged between 50

Table 1: Maximum Flow Rate Before and After Treatment

	Maximum Flow Rate Mean±SD	P-Value
Week – 2 (Visit 1) Placebo run-in phase	8.81±3.0	
Week 0 (Visit 2)	8.92±3.51	0.563
Week 2 (Visit 3)	10.37±3.95	<0.001*
Week 7 (Visit 5)	11.53±4.26	<0.0001*
Week 12 (Visit 7)	13.27±7.41	<0.0001*

* = significant

Table 2: Mean Flow Rate Before and After Treatment

	Mean Flow Rate Mean±SD	P-Value
Week – 2 (Visit 1) Placebo run-in phase	4.43±2.56	
Week 0 (Visit 2)	4.56±2.53	0.233
Week 2 (Visit 3)	5.27±2.98	<0.001*
Week 7 (Visit 5)	5.76±3.14	<0.0001*
Week 12 (Visit 7)	6.65±5.85	<0.0001*

*= significant

Table 3: I-PSS Before and After Treatment

	I-PSS Mean±SD	P-Value
Week – 2 (Visit 1) Placebo run-in phase	19.99±5.37	
Week 0 (Visit 2)	19.55±5.27	<0.001*
Week 2 (Visit 3)	14.76±4.84	<0.0001*
Week 7 (Visit 5)	12.12.±4.57	<0.0001*
Week 12 (Visit 7)	9.25±3.77	<0.0001*

*= significant

Table 5: Adverse Events Reported During the Study* (24 Patients or 7.69%)

Adverse Events	Percent
Headache	4.5%
Dizziness	1.3%
Fatigue	3.2%
Somnolence	1.3%

*= more than one adverse event in one patient

and 80 years of whom informed consent was obtained before participating in the study, a daytime frequency $\geq$ 8 times, nocturia $\geq$ 2 times/night, I-PSS $\geq$ 12 and a peak flow rate $\geq$ 5 ml/sec and $\leq$ 12 ml/ sec in a total voided volume $\geq$ 150 ml/sec. Patients were excluded from the study if they had been subjected to prostate surgery or any urological surgical intervention within the previous 6 months, if their urinary symptoms and / or the reduction in the urinary flow rate were caused by other diseases than BPH, if they were suffering from acute urinary retention, gross haematuria, bladder stones, recurrent urinary tract infection and / or a large bladder diverticulum, or if the serum prostate specific antigen (PSA) was $\geq$ 10 ng/ml and prostate cancer was not ruled out by biopsy. Exclusion criteria also included clinically significant hepatic or renal dysfunction, cardiovascular disorder, hypotension (BP < 95/60 mmHg), a cardiovascular stroke within the past 6 months or hypersensitivity to alpha-adrenergic blocking agents.

The study protocol called for a phase I during which a placebo was administered for two weeks. Any alpha-blockers, cholinergic or anticholinergic drugs were discontinued. The dose of any concomitant diuretic and / or beta-blocker was kept unchanged during the study. A baseline assessment of BPH variables was made at screening and throughout the study.

Phase II included a 12-week active medication period. Patients received the medication at 8.00 a.m. each day. They began therapy with 1 mg doxazosin once daily for two weeks (weeks 1 & 2). The dose was then increased to 2 mg/ day for another 5 weeks (weeks 3 - 7).

If by the end of week 7 the reduction in symptoms score was less than 30% and / or the increase in urinary flow rate was less than 3 ml/sec, the dose was titrated up to 4 mg/day for the remaining five weeks. Otherwise, the dose was continued as 2 mg daily for the rest of the treatment period.

Assessment of the patients was made according to the schedule given in Table 1.

RESULTS

A total of 333 patients with mild to moderate symptoms of outflow obstruction due to BPH were enrolled in the study. Twenty-one patients were lost to follow-up during the placebo run-in phase. 312 patients completed the study. Their age ranged from 50 to 80 years with a mean of 62.61$\pm$6.73 years. Their serum PSA levels ranged from 0.2 to 5 ng/ml with a mean of 2.17$\pm$1.2.

The peak flow rate, mean flow rate and I-PSS showed progressive improvement during weeks 2, 7 and 12 compared to the pre-treatment values (Tables 2-4) (Fig 1& 2). At the end of week 7, 54 patients (17.3%) showed a reduction in symptom score of more than 30% and / or an increase in urinary flow rate of more than 3 ml/sec and, therefore, the dose was maintained at 2 mg/day until the end of the study period. In the remaining 258 patients (82.7%), the dose had to be increased up to 4 mg/day for the rest of the treatment period.

There was a clinically insignificant decrease in mean systolic and diastolic blood pressure of normotensive patients (n=181) from 131.52$\pm$ 9.6 to 127.34$\pm$10.63 mmHg and from 83.21$\pm$ 6.8 to 80.7$\pm$6.93 mmHg, respectively. (Fig 3).

Doxazosin caused, however, a significant reduction in mean systolic and diastolic blood pressure in hypertensive patients, (n=131) from 154.69$\pm$10.9 mmHg to 141.22$\pm$10.6 and from 93.69$\pm$6.69 to 86.16$\pm$5.2 mmHg, respectively. (Fig 4).

Adverse events occurred during the treatment in 24 of our patients (7.69%), as shown in Table 5. These were generally mild to moderate in severity and included headache, dizziness, fatigue and somnolence, which occurred in 4.5%, 1.3%, 3.2% and 1.3%, respectively. Only 4 patients (1.2%) discontinued treatment because of these side effects.

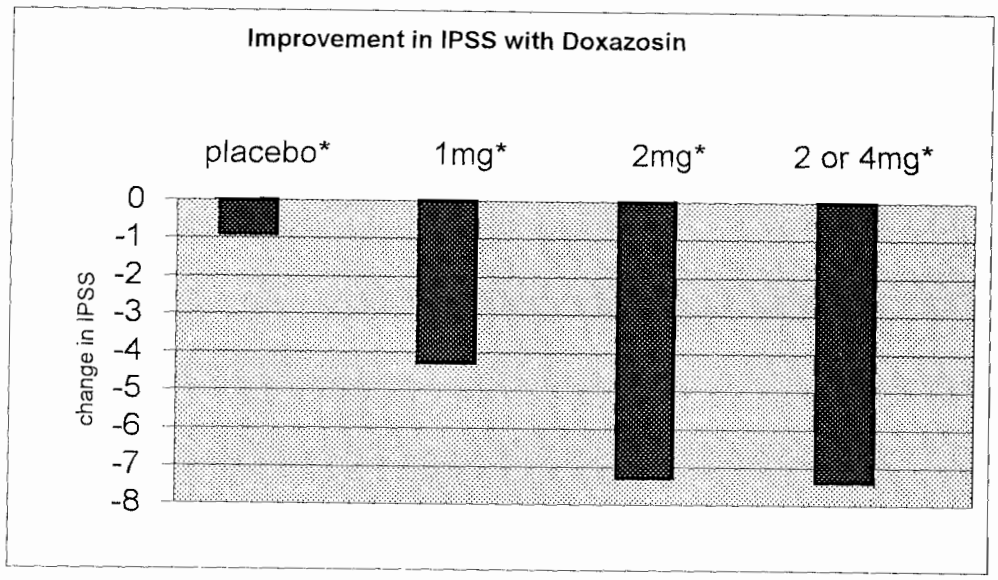

Fig. 1: Diagram illustrating the improvement in I-PSS with Doxazosin ($p<0.001$)

DISCUSSION

Benign prostatic hyperplasia (BPH) is one of the most common disease processes affecting the aging male. It is now clear that significant portions of the symptoms are due to obstruction and age-induced detrusor dysfunction. Moreover, obstruction may induce a variety of neural alterations in the bladder and prostate that contribute to the symptoms[1].

Surgery was the standard approach to BPH treatment for many years. However, there remains a moderate potential for complications, and some patients judge the outcome of their surgery unsatisfactory. Increasingly, patients decide against surgery to manage their BPH. Medical therapy including alpha-adrenergic blockers offers relief of BPH symptoms with minimal risk to the patients[10].

The rationale for alpha-blockers in the treatment of BPH is based on the hypothesis that clinical BPH is, in part, due to prostate smooth muscle mediated bladder outlet obstruction[3]. Shapiro and associates reported that the smooth muscle is one of the dominant cellular constituents of BPH, accounting for 40% of the area density of the hyperplastic prostate[2]. Caine and co-workers reported that the human prostate contracts in the presence of the alpha-adrenergic agonist norepinephrine[11]. The most definitive evidence that blockade of α_1 – adrenoceptors relieves bladder outlet obstruction is the direct relationship between the area density of the prostate smooth muscle and change in peak flow rate observed in 26 subjects undergoing prostate biopsy before initiating terazosin therapy in a study carried out by Shapiro et al.[4].

Alpha adrenoceptor antagonists may also reduce irritative symptoms not only by relieving obstruction, but also by blocking α_1-adrenoceptors in the bladder[5]. Effects of the drugs on the central nervous system may contribute to the action on irritative symptoms[2]. Moreover, α_1-adrenoceptor blockers have been shown to depress sphincter activity and reduce firing in the pudendal afferent pathway[6].

Phenoxybenzamine, a non-selective alpha-blocker was shown to be highly effective in the management of BPH but was associated with a high incidence of adverse clinical events[10-12]. Prazosin was one of the first α_1-adrenoceptor blockers to be investigated for the treatment of BPH. The efficacy of phenoxybenzamine and

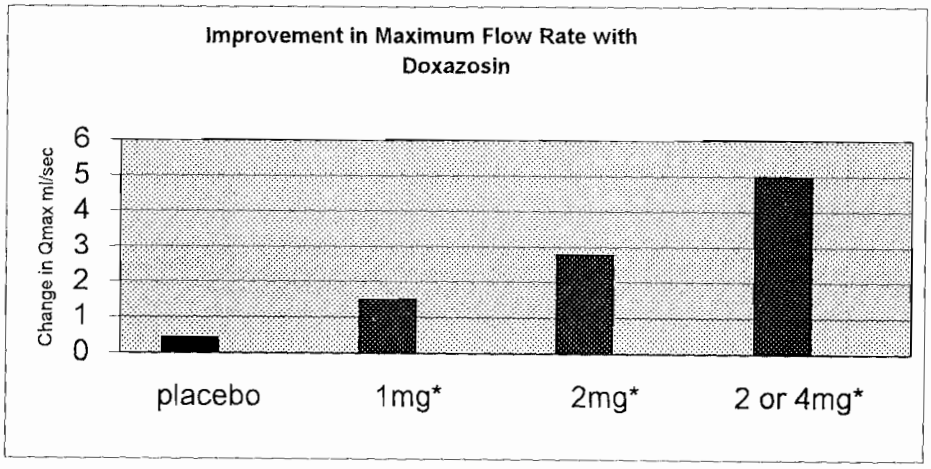

Fig. 2: *Diagram illustrating the improvement in maximum flow rate with Doxazosin (* p<0.001)*

prazosin are comparable; however prazosin is better tolerated, implying that efficacy and toxicity are mediated primarily by the α_1- and - α_2 adrenoceptors respectively[13]. Prazosin and other α_1-blockers including alfuzasin require at least three-times-daily dosage owing to their relatively short serum elimination half lives[14].

Doxazosin is a highly selective α_1-antagonist and it is almost 100 times more effective that α_2-adrenoceptors[15]. It has a mean half-life of 22 hours and a relatively slow onset of action with peak serum concentrations being achieved 2 - 6 hours after dosage. As a result of these features, doxazosin has a smooth onset of action when given once daily[16].

In an open non-comparative study on 38 male patients with mild to moderate prostatism treated with doxazosin for three months, Abdel-Azim et al, 1996,[17] reported that the maximum flow rate increased by a mean of 2.4 ml/sec and that 54.1% of the patients showed an improvement of more than 50% in the maximum flow rate. Similarly, the mean flow rate increased by a mean of 2.6 ml/sec. At the end of their study the mean prostate symptom score had decreased by 10.6 points (63.3%).

In another open non-comparative study carried out on 27 patients with outflow obstruction due to BPH treated with doxazosin for 12 weeks, Khalaf and El-Gallad, 2000,[18] reported a progressive significant improvement of I-PSS, maximum and mean flow rate within the first two weeks of treatment and throughout the study period compared with baseline data [I-PSS from 16.3 to 8.63 ml/sec ($p<0.001$), Qmax from 8.84 to 13.18 ml/sec ($p<0.001$) Qmean from 3.99 to 5.74 ml/sec ($p<0.001$)] .

A similar efficacy was demonstrated in two multi-center randomized double-blind placebo-controlled studies. These trials involved 456 patients, 287 of whom were treated with doxazosin. The maximum urine flow rate increased by 2.6 ml/sec in patients treated with doxazosin, compared to 1.1 ml/sec in patients treated with the placebo. In total, 36% of the patients in the doxazosin group showed an improvement of more than 50% in the maximum flow rate, compared to 17% of the patients in the placebo group. There was also a significantly greater increase in mean flow rate in doxazosin-treated patients compared to placebo-treated patients (1.1 ml/sec versus 0.2 ml/sec respectively). Overall, doxazosin improved the urinary symptoms of BPH by 66.5% compared to 35.2% using the placebo[19,20].

Our results are consistent with the data obtained from the previous studies. The maximum flow rate increased from 8.92±3.51 ml/sec to 13.27±7.41 ml/sec, and the mean flow rate increased from 4.56±2.53 to 6.65±

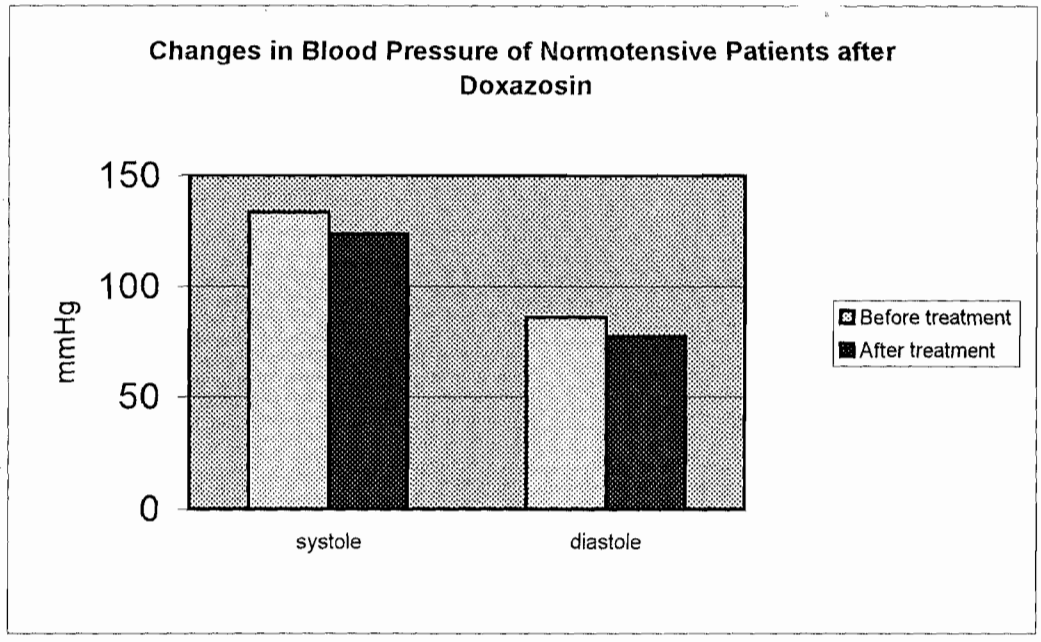

Fig. 3: Diagram illustrating the changes in blood pressure of normotensive patients after Doxazosin ($p<0.001$ – clinically insignificant)

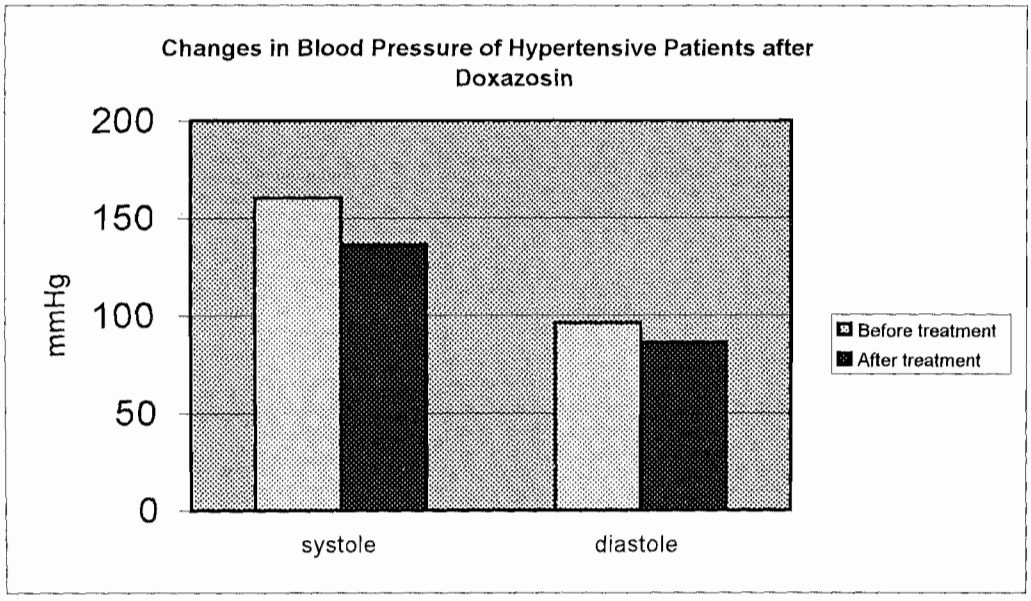

Fig. 4: Diagram illustrating the changes in blood pressure of hypertensive patients after Doxazosin ($p<0.0001$)

5.85 ml/sec. Also the I-PSS decreased from 19.55±5.27 to 9.25±3.77. The beneficial effects of doxazosin were seen within the first 2 weeks of treatment. This confirms the results of other studies proving that doxazosin is different from the 5-alpha reductase inhibitor, finasteride, which needs to be given for at least 6 months to exert its maximum effect[16].

In our study, at baseline, 181 of our patients (58%) were normotensive and clinically insignificant changes were observed in their blood pressure at the end of the study. The mean systolic and diastolic blood pressure decreased from 131.52±9.6 to 127.34±10.63 mmHg and from 83.21±6.8 to 80.7±6.93 mmHg respectively. This is because doxazosin lowers blood pressure when the sympathetic derive is high. Doxazosin caused a significant reduction in the mean systolic and diastolic blood pressure in hypertensive patients, (n=131) from 154.69±10.9 mmHg to 141.22±10.6 and from 93.69±6.69 to 86.16±5.2 mmHg, respectively. In contrast, the drug has less effect on the resistance vessel tone in normotensive patients.

Adverse effects occurred in 24 of our patients (7.69%). These were generally mild to moderate and in the form of headache, dizziness, fatigue and somnolence. This is similar to the incidence of treatment-related adverse events reported in other studies[20,21].

The once-daily dosage schedule makes doxazosin administration convenient, especially in the elderly with frequently prescribed multiple medication for a wide variety of ailments[22]. In addition, the low rate of discontinuation due to adverse events (1.28%) enhances patients compliance.

Similar short-term studies conducted by Ozbey et al., 1999, and Abrams, 1997, concluded that doxazosin is an important treatment option for patients with BPH[23,24]. On the other hand, long-term studies demonstrated that doxazosin was significantly effective and well tolerated in the treatment of BPH in normotensive and hypertensive patients[25,26].

In conclusion, doxazosin has proved to be effective in the cure of impaired flow and has a significant and positive impact on symptoms of BPH. It is safe and well tolerated by patients. Moreover, its additional effect on blood pressure is a great advantage for patients with hypertension as a concomitant disease.

REFERENCES

1. Garraway WM, Collins GN and Lae RJ (1991): High prevalence of benign prostatic hypertrophy in the community. Lancet, 338:469.
2. Shapiro E and Lepor H (1991): The relationship between histological and chemical response to alpha blockade in men with symptomatic BPH (abstract). J Urol, 145:265.
3. Caine M (1986): The present role of alpha adrenergic blockers in the treatment of benign prostatic hypertrophy. J Urol, 136:1.
4. Shapiro E, Haranto V and Lepor H (1992): Anti-desmin vs. anti-actin for quantifying the area density of prostate smooth muscle. Prostate, 20:259.
5. Caine M, Perlberg S, Shapiro E, Baumann M and Lepor H (1990): Autonomic receptors in asymptomatic and symptomatic BPH. J Urol, 143:179.
6. Hedlund H, Anderson K and Larsson B (1985): Alpha adrenoceptors and muscarinic receptors in isolated human prostate. J Urol, 134:1291.
7 Pool J (1996): Unique aspects of Doxazosin: A third generation alpha-blocker. Eur Urol, 29 (suppl. 1):31.
8. Fawzy A, Braun K, Lewis GP et al. (1995): Doxazosin in the treatment of benign prostatic hyperplasia in normotensive patients: A multicenter study. J Urol, 154:106.
9. Kirby RS (1994): Profile of Doxazosin in hypertensive man with benign prostatic hyperplasia. Br J Clin Pract, Suppl. 74:23.
10. Caine M, Pfau A and Perlberg S (1976): The use of alpha adrenergic blockers in benign prostatic obstruction. Br J Urol, 48:255.
11. Caine M, Raz S and Ziegler M (1975): Adrenergic and cholinergic receptors in the human prostate, prostatic capsule and bladder neck. Br J Urol, 27:193.
12. Caine M, Perlberg S and Meretyk S (1978): A placebo controlled double blind study on the effect of phenoxybenzamine in benign prostatic obstruction. Br J Urol, 50:551.
13. Hedlund H and Andersson KE (1983): Effect of prazosin in patients with benign prostatic obstruction. J Urol, 130:275.
14. Jardin A, Bensadoun H, Delauche-Cavallier MC et al (1990): Alfuzosin for treatment of benign prostatic hypertrophy. Lancet, 337:1457.
15. Yoshimura N, Sasa M, Yoshida O et al. (1990): Alpha 1-adrenergic receptor mediated excitation from the locus coerulus of the sacral parasympathetic preganglionic neuron. Life Sci, 47:789.
16. Janknegt RA (1995): Profile of doxazosin in patients with benign prostatic hyperplasia. Scand J Urol Nephrol, 29:21.

17 Abdel-Azim M, Meshref A, Riyad T and Fathy M (1996): The role of doxazosin in the treatment of BPH. Egyptian J Surg, 15(1):45.

18. Khalaf I and El-Gallad M (2000): An open study of the efficacy, safety and tolerability of doxazosin in the symptomatic treatment of benign prostatic hyperplasia. African Journal of Urology, 6:70.

19. Christenson M, Home J, Rasmussen P et al. (1993): Doxazosin treatment in patients with prostatic obstruction. Scand J Urol Nephrol, 27:39.

20. Chappel C, Carter P, Christmaat et al. (1994): A three months double-blind study of doxazosin as treatment of benign prostatic bladder outlet obstruction. Br J Urol, 74:50.

21. Gillenwater JY, Conn RL, Chrysant SG et al (1995): Doxazosin for the treatment of benign prostatic hyperplasia in patients with mild to moderate essential hypertension. A double-blind, placebo-controlled dose response multicenter study. J Urol, 154:110.

22. Janknegt RA and Chapple CR (1993): Efficacy and safety of alpha-1 blocker Doxazosin in the treatment of benign prostatic hyperplasia. Eur Urol, 24:319.

23. Özbey I, Aksöy Y, Polat , Bicgi O, Demirel A and Okyar G (1999): Effects of doxazosin in men with benign prostatic hyperplasia: urodynamic assessment. Int Urol Nephrol 31(4):471.

24. Abrams P (1997): Urodynamic effects of doxazosin in men with lower urinary tract symptoms and benign prostatic obstruction. Results from three double-blind placebo-controlled studies. Eur Urol;32(1):39.

25. Lepor H, Kaplan SA, Klimberg I, Mobley DF, Fawzy A, Gaffney M, Ice K and Dias N (1997): Doxazosin for benign prostatic hyperplasia: long-term efficacy and safety in hypertensive and normotensive patients. The Multicenter Study Group. J Urol Feb;157(2):525.

26. Fawzy A, Hendry A, Cook E and Gonzalez F (1999): Long-term (4 year) efficacy and tolerability of doxazosin for the treatment of concurrent benign prostatic hyperplasia and hypertension. Int J Urol Jul;6(7):346.

All correspondence to be sent to:

Ismail Khalaf, M.D.
28, Mohamed Tewfiq Diab Street
Nasr City – Cairo 11371
Egypt

Fax: ++20-2-6709709
Email: i.steppert@lycos.com

The French translation of the abstract will follow in the coming issue of the *African Journal of Urology*.