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ORIGINAL ARTICLE

Effects of alfuzosin 10 mg once daily on sexual function in men treated for symptomatic benign prostatic hyperplasia

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We evaluated the effects of extended-release alfuzosin HCl 10 mg once daily (q.d.) on sexual function in men with lower urinary tract symptoms associated with benign prostatic hyperplasia (BPH). In a randomized, double-blind, placebo-controlled study of men aged ≥50 years, after a 28-day placebo run-in period, patients were randomized to receive alfuzosin 10 mg q.d. or matching placebo for 28 days. The mean change from baseline (day 1) in sexual function on day 29 was assessed using the Danish Prostate Symptom Score Sex (DAN-PSSsex) questionnaire. A total of 372 patients were randomized to receive alfuzosin ($n = 186$) or placebo ($n = 186$), with 355 completing the study. At baseline, 64% of the patients reported erectile dysfunction (ED) and 63% reported ejaculatory dysfunction (EjD). For the 320 patients who completed the DAN-PSSsex, alfuzosin treatment was associated with a significant improvement in the mean change from baseline in erectile function on day 29 compared with placebo ($P = 0.02$). No significant difference was observed between the two treatment groups in the mean change from baseline in ejaculatory function on day 29. For patients with ED at baseline, a marginal improvement in erectile function was demonstrated with alfuzosin treatment ($P = 0.09$ vs placebo). For patients with EjD at baseline, the mean change from baseline in ejaculatory function with alfuzosin was comparable to that with placebo. Dizziness was the most common adverse event with alfuzosin treatment (5 vs 0% with placebo), with other adverse events reported with comparable frequency in both treatment groups. After 1 month of treatment, alfuzosin 10 mg q.d. significantly improved erectile function in men with lower urinary tract symptoms/ benign prostatic hypertrophy and had no adverse effect on ejaculatory function.
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Introduction

Recent studies have demonstrated a significant association between lower urinary tract symptoms (LUTS) and sexual dysfunction in aging men.[1–4] In the Multinational Survey of the Aging Male (MSAM-7), which surveyed 12 815 men aged 50–80 years, sexual activity was reported by 83% of the respondents, with 71% reporting at least one episode of sexual activity in the past 4 weeks.[4] Data from the MSAM-7 revealed a high prevalence of both LUTS and sexual dysfunction in older men. Although the frequency of sexual activity decreased with age, sexual function was strongly and independently associated with the severity of LUTS.[4]

It has been proposed that increased α-adrenergic activity may be a common underlying pathophysiological mechanism for benign prostatic hypertrophy (BPH) symptoms (that is, LUTS), erectile dysfunction (ED) and ejaculatory dysfunction (EjD).[5] Thus, blocking α-adrenergic activity in the lower urinary tract may improve both LUTS associated with BPH and sexual dysfunction. In an open-label study of men with LUTS and sexual dysfunction, treatment for 1 year with alfuzosin 10 mg once daily (q.d.) improved both ED and EjD, as assessed with the Danish Prostate Symptom Score sex (DAN-PSSsex) questionnaire.[6]

Alfuzosin, a uroselective α_1-adrenergic receptor antagonist (α-blocker) for the treatment of the symptoms of BPH, is distributed preferentially in the lower urinary tract versus vascular tissues.[7] By selectively blocking α_1-adrenergic receptors, alfuzo-

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sin causes relaxation of smooth muscle in the bladder neck and prostate gland, thereby reducing LUTS and improving urine flow, with minimal effects on blood pressure and a low incidence of sexual side effects.

In 2003, an extended-release formulation of alfuzosin 10 mg q.d. was approved by the US Food and Drug Administration for the treatment of the signs and symptoms of BPH. Alfuzosin 10 mg q.d. was shown to be an effective and well-tolerated treatment for symptomatic BPH in three pivotal, placebo-controlled, clinical trials.[8–11] In these clinical trials, symptom relief during 12 weeks of treatment with alfuzosin 10 mg q.d. or placebo was first assessed at 4 weeks post-treatment using the International Prostate Symptom Score (IPSS) and measurements of peak urinary flow rate (Q_{max}). In a recent placebo-controlled crossover study, men with symptomatic BPH who were known responders to α-blockers demonstrated a significant improvement in Q_{max} as rapidly as 8 h after the initial dose of alfuzosin 10 mg q.d. compared with the initial dose of placebo.[12] The onset of this improvement in Q_{max} correlated with the previously reported peak plasma concentration of alfuzosin.[13]

The present study describes the effects of alfuzosin 10 mg q.d. versus placebo on erectile and ejaculatory function in men with symptomatic BPH. Previously published results of this study indicated that Q_{max} increased significantly from baseline within 24 h after the first dose of alfuzosin 10 mg q.d. compared with placebo, and this improvement was maintained on days 8 and 29.[14] In addition, significant improvements were observed in the total IPSS on day 8 and maintained on day 29 in patients treated with alfuzosin.

Methods

Study design

This randomized, double-blind, placebo-controlled study was conducted at 52 sites in the United States from 10 January 2003 to 18 August 2003. An amendment to the original study protocol, made on 22 January 2003, added a secondary end point of assessing the effect of alfuzosin 10 mg q.d. on sexual function after 28 days of double-blind treatment. In the 8-week study, a 4-week placebo run-in period was followed by 4 weeks of double-blind treatment with alfuzosin 10 mg q.d. or matching placebo. Study treatments were to be taken once daily immediately after the evening meal. Study visits took place on day −28 (screening), day 1 (baseline), on day 2 and day 8 of double-blind treatment, and on day 29. The study protocol was approved by the ethics committee of each participating institution, and the study was performed in accordance with good clinical practices. Each patient provided written informed consent before enrollment in the study.

Patients

Patients eligible to enroll in the study were men with the following characteristics at screening (day −28): ≥50 years of age, LUTS associated with BPH for ≥6 months, a total IPSS of ≥13 points, a Q_{max} of ≥5 to 12 ml/s, a voided volume of ≥150 ml, a residual volume of ≤350 ml and an IPSS bother score of ≥3 points. Patients were excluded from the study if they had neurogenic bladder dysfunction, urethral stenosis, isolated bladder-neck disease with no evidence of BPH, acute or chronic bacterial prostatitis in the 3 months before randomization, active urinary tract infection, hematuria, diagnosed or suspected carcinoma of the prostate, urologic endoscopy <1 month before screening, previous prostatic surgery for the treatment of BPH, previous radiation therapy of the pelvic region or urinary retention requiring an indwelling catheter. Exclusion criteria unrelated to BPH included suspected or diagnosed neurological diseases that could affect uroflowmetry studies, poorly controlled insulin-dependent diabetes, stroke or myocardial infarction in the 5 months before screening, unstable angina, severe heart failure, a history of postural hypotension or syncope, active liver disease, renal insufficiency and suspected or diagnosed neoplastic disease. Exclusion criteria related to medication included known hypersensitivity to α-blockers, unresponsiveness to previous treatment with an α-blocker and use of tricyclic antidepressants, anticholinergics, sympathomimetics, first-generation antihistamines, plant extracts for BPH symptoms or investigational drugs within 1 month before screening. Patients expecting to take sildenafil citrate for the treatment of ED at any time during the 8-week study were also excluded. However, erectile function status *per se* was neither an inclusion nor an exclusion criterion for enrollment.

Assessments

A complete physical examination (including digital rectal examination), 12-lead electrocardiography (ECG), laboratory tests and a residual urine measurement by transabdominal ultrasound were performed at screening (day −28) and at the end of double-blind treatment (day 29). Uroflowmetry studies, measurements of standing and supine blood pressure and heart rate, and a review of concomitant medications were performed at all visits. The primary end points for this study were the mean changes from baseline in total IPSS and Q_{max} on day 8. Acute IPSS scores (including the IPSS bother score) were obtained at all visits except day 2 of double-blind treatment. The DAN-PSSsex,[15,16]

which includes one question on erectile function (Question 1A: Can you get an erection?), one question on ejaculatory function (Question 2A: Do you have ejaculations?) and a bother question associated with each of these questions, was completed on day 1 (baseline) and day 29. The responses and corresponding scores for these questions of the DAN-PSSsex range from 0 (normal function or no bother) to 3 (no erection/ejaculation or the greatest degree of bother) (Table 1).

Statistical analysis

The sexual function endpoints were analyzed using an analysis of covariance method in which the baseline value was used as the covariate. Only observed values were used in these data analyses. The intent-to-treat population was used for all analyses of efficacy variables and was defined as all patients who had been randomized, took at least 1 dose of study medication and provided efficacy data that contributed to at least one efficacy analysis. All safety analyses included data from all patients who were randomized and took at least one dose of study medication. The correlations between scores for the DAN-PSSsex erection question and the erection bother question and between scores for the DAN-PSSsex ejaculation question and the ejaculation bother question at baseline were examined using Spearman rank correlation. All statistical tests were two-sided.

Table 1 Danish prostate symptom score sex questionnaire (DAN-PSSsex)

Question	*Responses (score)*
1A: Can you get an erection?	Yes, with a normal stiffness (0) Yes, with a slight reduction in stiffness (1) Yes, with a big reduction in stiffness (2) No, I cannot get an erection (3)
1B: If you have difficulty getting an erection, how bothersome is this for you?	Not at all (0) A little bit (1) Moderately (2) Very much (3)
2A: Do you have ejaculations?	Yes, with a normal amount of semen (0) Yes, with a slightly reduced amount of semen (1) Yes, with a very reduced amount of semen (2) No
2B: If you ejaculate with a reduced amount of semen or if you do not ejaculate at all, how bothersome is this for you?	Not at all (0) A little bit (1) Moderately (2) Very much (3)
3A: If you have ejaculations, do you experience any pain/discomfort when ejaculating?	No (0) Yes, slight pain/discomfort (1) Yes, moderate pain/discomfort (2) Yes, strong pain/discomfort (3)
3B: If you have pain/discomfort when ejaculating, how bothersome is this for you?	Not at all (0) A little bit (1) Moderately (2) Very much (3)

Results

A total of 372 patients were randomized to treatment with alfuzosin 10 mg q.d. ($n=186$) or placebo ($n=186$), with 355 (alfuzosin, 176 (95%); placebo, 179 (96%)) completing the study. The two treatment groups were comparable with respect to age, total IPSS, Q_{max} values and other characteristics at baseline (Table 2).

On Days 1 and 29, 320 patients completed the DAN-PSSsex (alfuzosin, $n=159$; placebo, $n=161$). At baseline, 64% of the patients reported ED and 63% of the patients reported EjD. At baseline, erection and ejaculation scores of the DAN-PSSsex correlated significantly with the related bother question, indicating that patients were bothered by their ED and their EjD (erection: $n=158$, $r=0.70$, $P<0.0001$; ejaculation: $n=144$, $r=0.60$, $P<0.0001$).

On day 29, erectile function was improved from that at baseline for patients receiving alfuzosin 10 mg q.d., whereas erectile function decreased from that at baseline for those receiving placebo ($P=0.02$ vs placebo; Figure 1). For patients with ED at baseline, the mean (s.d.) change from baseline in erectile function indicated greater improvement in erectile function on day 29 for those receiving alfuzosin 10 mg q.d. (−0.19 (0.60)) than those receiving placebo (−0.08 (0.59)), but the between-group comparison was not significant ($P=0.09$).

The mean change from baseline in ejaculatory function on day 29 was not significantly different between the two treatment groups ($P=0.31$; Figure 2). For patients with EjD at baseline, the mean (s.d.) change from baseline in ejaculatory function on day 29 indicated that the improvement was comparable for patients receiving alfuzosin (−0.16 (0.68)) and those receiving placebo (−0.15 (0.62)).

The percentage of patients who experienced treatment-emergent adverse events was similar for the alfuzosin 10 mg q.d. (25%) and the placebo (23%) groups. The most frequently reported treatment-emergent adverse event in the alfuzosin 10 mg q.d. group was dizziness (5%). Other adverse events were reported with comparable frequency in both groups (Table 3). No deaths were reported in this study. Only one serious adverse event was reported in the alfuzosin 10 mg q.d. group (non-insulin-dependent diabetes mellitus); no serious adverse

Table 2 Baseline demographics and clinical characteristics of men with LUTS/BPH

	Alfuzosin 10 mg q.d. (n = *185*)	*Placebo* (n = *185*)
Age (years)	63.5 (8.4)	64.4 (8.0)
Ethnicity		
Black/African American	161 (87.0)	166 (89.7)
White/Caucasian	10 (5.4)	6 (3.2)
Other	14 (7.6)	13 (7.0)
Weight (kg)	87.8 (14.1)	88.0 (16.2)
Prostate volume estimated by DRE (cm^3)[a]	41.2 (20.1)	38.8 (20.2)
IPSS (score range 0–35)[b]	17.0 (7.0)	17.8 (6.4)
IPSS bother score (score range 0–6)[b]	3.6 (1.2)	3.8 (1.1)
Q_{max} (ml/s)	10.9 (4.6)	11.1 (4.5)

Abbreviations: BPH, benign prostatic hypertrophy; DRE, digital rectal examination; IPSS, International Prostate Symptom Score; LUTS, lower urinary tract symptoms; Q_{max}, peak urinary flow rate.
All values represent mean (s.d.).
[a]Calculated as $(4/3 \times 3.14 \times \text{width}/2 \times \text{height}/2 \times \text{length}/2)/1000$;
[b]A higher score indicates a worse outcome.

Figure 1 Mean (s.e.) change from baseline in erectile function on day 29, as assessed with question 1A of the DAN-PSSsex (score range 0–3). Lower scores indicate better function. Patients receiving alfuzosin 10 mg q.d. displayed a significant improvement in erectile function compared with those receiving placebo (*$P = 0.02$).

events were reported in the placebo group. Nonserious treatment-emergent adverse events that led to withdrawal from the study were reported in three (2%) patients receiving alfuzosin 10 mg q.d. and one (1%) patient receiving placebo. No clinically meaningful abnormalities were observed in physical examination findings or laboratory test, vital sign, ECG and residual urine measurements.

Discussion

In the present study, after 1 month of treatment with alfuzosin 10 mg q.d., erectile function was significantly improved and ejaculatory function was not adversely affected in men with symptomatic BPH when compared with placebo. Data from another recent study suggested that treatment with alfuzosin 10 mg q.d. for 1 year leads to significant improvements in both ED and EjD in men with LUTS.[6]

The finding in the present study that alfuzosin 10 mg q.d. treatment did not worsen EjD suggests that alfuzosin may provide an advantage over some other commonly prescribed α-blockers for the treatment of LUTS/BPH. Some α-blockers have been shown to be associated with sexual side effects, most notably EjD, in men with LUTS/BPH. For example, the incidence of EjD in two pivotal placebo-controlled studies conducted in the United States was 8% for patients receiving tamsulosin 0.4 mg q.d. and 18% for those receiving tamsulosin 0.8 mg q.d. versus 0.2% for those receiving placebo.[17] Large-scale, direct comparator studies of the different α-blockers are needed to evaluate further the effects of these treatments on male sexual function.

In the present study, the DAN-PSSsex was used to assess sexual function. The questions of the DAN-PSSsex have not been formally validated, but the questionnaire has been used to assess sexual func-

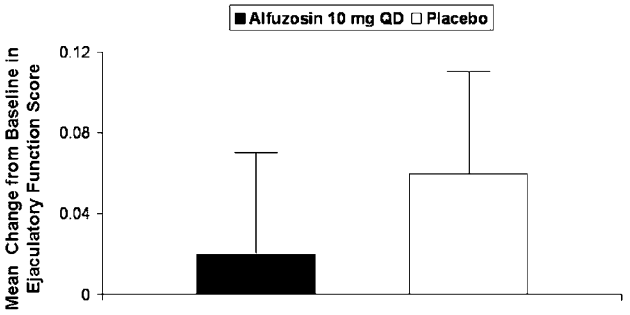

Figure 2 Mean (s.e.) change from baseline in ejaculatory function on day 29, as assessed with question 2A of the DAN-PSSsex (score range 0–3). Lower scores indicate better function. No significant difference was observed in ejaculatory function between patients receiving alfuzosin 10 mg q.d. and those receiving placebo.

Table 3 Most common adverse events

Adverse event	*Alfuzosin 10 mg q.d.* (n = *185*), n *(%)*	*Placebo* (n = *185*), n *(%)*
Dizziness	11 (5)	0
Headache	5 (3)	2 (1)
Upper respiratory tract infection	4 (2)	2 (1)
Orthostatic hypotension	3 (2)	4 (2)
Ejaculatory disorder	1 (1)	1 (1)
Erectile dysfunction	1 (1)	2 (1)

tion in various clinical trials. The question on ejaculatory function in the DAN-PSSsex (that is, 'Do you have ejaculations?') assesses only the presence or absence of ejaculation and the amount of semen and does not provide any information on other ejaculation problems, such as a reduced strength or force of the ejaculation, delayed ejaculation and retrograde ejaculation. Therefore, patients experiencing ejaculatory problems other than the absence of ejaculation or reduced ejaculate volume are not adequately assessed using the DAN-PSSsex. Future studies using the recently validated Male Sexual Health Questionnaire,[18] which includes a seven-item ejaculatory function domain, should provide further insights on the effects of α-blockers on the different aspects of ejaculatory function in men with BPH.

Approximately two-thirds of the men with LUTS/BPH in the present study had ED and/or EjD at baseline. These rates are comparable to those observed in a study of men aged 48–90 years of age conducted in the United Kingdom, which found the prevalence of ED and EjD to be 70% at baseline (before any treatment of LUTS/BPH).[19] The rates seen in the present study were somewhat higher than the prevalence rates of approximately 40–60% for ED and EjD observed in other studies.[3,20–23] It should be noted that these studies had important differences in sample sizes, patient age ranges and the types of questionnaires and survey methods used. Taken together, however, the results of these studies clearly indicate that ED and EjD are common conditions in men with LUTS/BPH.

In conclusion, after 1 month of treatment with alfuzosin 10 mg q.d., improvements in sexual function were demonstrated in men with LUTS/BPH. Additional studies are warranted to further elucidate the extent to which alfuzosin 10 mg q.d. treatment may improve sexual function in men with symptomatic BPH.

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