Effects of Acute Treatment With Tamsulosin Versus Alfuzosin on Ejaculatory Function in Normal Volunteers

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Purpose: The frequency of ejaculatory dysfunction in men varies among the α-blockers used in the treatment of lower urinary tract symptoms associated with benign prostatic hyperplasia. We assessed the effect of acute administration of tamsulosin, alfuzosin and placebo on ejaculate volume and sperm concentration in post-ejaculate urine, and addressed the mechanism of action of tamsulosin and alfuzosin on ejaculation.

Materials and Methods: Using a randomized, 3-way crossover design, the effects of 5 days of treatment with 0.8 mg tamsulosin daily, 10 mg alfuzosin daily and placebo on ejaculation in healthy adult men were compared. The primary end points of the study were ejaculate volume and sperm concentration in post-ejaculate urine on each treatment. To aid in clinical interpretation of primary efficacy end points, each primary end point was transformed into a binary outcome, that is subjects with a greater than 20% decrease in ejaculate volume and subjects with a greater than 20% increase in sperm concentration in post-ejaculate urine.

Results: In healthy volunteers who completed the study (48), tamsulosin resulted in significantly decreased ejaculate volume (-2.4 ± 0.17 ml) compared to alfuzosin ($+0.3 \pm 0.18$ ml, $p < 0.0001$ vs tamsulosin) or placebo ($+0.4 \pm 0.18$ ml, $p < 0.0001$ vs tamsulosin, p = nonsignificant vs alfuzosin). Among completers the incidence of more than 20% decreased ejaculate volume was significantly greater with tamsulosin (89.6%) compared to alfuzosin (20.8%, $p < 0.0001$ vs tamsulosin) or placebo (12.5%, $p < 0.0001$ vs tamsulosin, p = nonsignificant vs alfuzosin). While on tamsulosin 35.4% of 48 completers had complete lack of ejaculation (anejaculation) and no subjects experienced anejaculation while on alfuzosin or placebo.

Conclusions: On 0.8 mg tamsulosin daily ejaculatory function in subjects was marked by decreased ejaculate volume in almost 90% of subjects and anejaculation in approximately 35% of participants. These ejaculatory disorders with tamsulosin were not attributed to retrograde ejaculation. In contrast, anejaculation was not observed in any subjects in the alfuzosin or placebo groups.

Key Words: ejaculation, adrenergic alpha-antagonists, prostatic hyperplasia, urinary tract

The efficacy for symptomatic relief of LUTS associated with BPH is comparable for all α-adrenergic receptor antagonists.[1] However, these agents differ in safety and tolerability profiles, particularly with regard to EjD, defined as decreased or absent antegrade ejaculation and reduced sexual satisfaction. In controlled clinical trials the spontaneous patient reported incidence of EjD with TAM was between 4% and 26%, and was dose related.[2–5] In a long-term, open label extension study, more than 30% of patients treated with TAM reported EjD.[6] Incidences of EjD reported in clinical trials with other α-blockers (eg prazosin, doxazosin and alfuzosin) are relatively low (1% or less).[7,8]

Despite the widespread use of α-blockers in the aging population with BPH, little is known about the nature of treatment related EjD. It has been suggested that EjD is due to relaxation of the bladder neck leading to retrograde ejaculation. The relationship between α-blocker treatment and EjD, reduced ejaculate volume, anejaculation, and decreased sexual satisfaction has not previously been described. The primary objective of the current investigation was to assess the effects of TAM, ALF and placebo on ejaculate volume and sperm concentration in post-ejaculate urine, and to address the possible mechanism of action of TAM/ALF in EjD.

METHODS

Subjects

Normal healthy male adults 18 to 36 years old were included in the study. The subjects had normal sexual function as documented by the International Index of Erectile Function[9] with an erectile function domain score of 26 or greater and Danish Prostate Symptom Score–sexual function of 0.[10] Exclusion criteria included abnormalities of sperm or semen based on 2003 World Health Organization semen analysis guidelines,[11] concomitant lower urinary tract disease, previous prostatic surgery or ongoing prostate disease, history or current evidence of postural hypotension or syncope, concomitant use of any medications, clinically relevant biochemical abnormalities, positive urine drug screen, and any chronic or acute disease that could have interfered with study evaluations.

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Study Design

This pilot study used a double-blind, double-dummy, placebo controlled, randomized, Latin square 3-way crossover design. Normal male volunteers underwent 2 separate screenings on days –10 and –5 to evaluate sperm concentrations in semen and post-ejaculate urine. All subjects collected semen following masturbation after abstaining from sexual activity for at least 48 hours but no more than 7 days before collection.

Eligible volunteers received each of 3 treatments in 1 of 6 randomly assigned sequences. Study drugs were administered as 1 10 mg ALF tablet every day and 2 TAM matching placebo capsules, two 0.4 mg TAM over-encapsulated capsules every day and 1 ALF matching placebo tablet, and 1 ALF matching placebo tablet and 2 TAM matching placebo capsules every day. Subjects were housed in the clinical study unit from days 0 to 5 in 3 separate treatment periods, each separated by a 10-day washout period. The study drug was administered on days 1 to 5 following a meal.

All subjects underwent clinical and laboratory evaluations including semen collection and evaluation on days 0 and 5 of each treatment period following the same abstinence requirements as screening visits. During treatment (days 1, 2, 3 and 4) sitting and standing blood pressure and heart rate were measured, and all adverse events were recorded. Investigators determined adverse event severity and potential relationship to the study drugs.

Statistical Methods

A minimum of 8 subjects in each treatment group was calculated to be sufficient to detect a clinically significant 25% difference in ejaculate volume compared with a null hypothesis mean of 3.86 with 80% power. The 0.8 mg dose of TAM was chosen to ensure observation of an evaluable incidence of EjD in this mechanistic study and was based on observations in pivotal clinical trials that 18% of patients receiving this dose experienced EjD.[4]

The ITT population was defined as all subjects randomized to a treatment sequence, who received study drug in at least 2 treatment periods, and had at least 1 baseline and 1 posttreatment semen and post-ejaculate urine value for at least 2 of the 3 periods. Completers were defined as subjects who received study medication for 5 days per period with baseline and a day 5 assessment of semen volume and post-ejaculate urine semen concentration for all 3 treatment periods. The per protocol population was the subset of completers who did not violate the protocol in any fundamental manner. Safety analysis was based on randomized subjects who took at least 1 dose of study medication.

Baseline values for all semen related variables were calculated as the mean of the measurements obtained on days –10, –5 and 0 of treatment period 1. Baseline values for each laboratory and clinical safety variable were the last values recorded before taking the study medication on or before day 1 of period 1.

Primary study end points were the change from baseline in ejaculate volume and the change from baseline in post-ejaculate urine sperm concentration on day 5 following each treatment period. To aid in clinical interpretation of primary efficacy end points, each primary end point was transformed into a binary outcome measure (dichotomized), with subjects with a greater than 20% decrease in ejaculate volume on day 5 compared to baseline and subjects with a greater than 20% increase in sperm concentration observed in the post-ejaculate urine on day 5 compared with baseline. Anejaculation was defined as 100% decrease in ejaculate volume compared with baseline volume.

For the primary assessments an ANCOVA appropriate for a 3-way crossover design was used with ejaculate volume and post-ejaculate urine sperm concentration as the dependent variables of primary interest. The ANCOVA model included terms for treatment, sequence, period, subject within sequence, and 2 covariates for carryover effects of ALF and TAM, ie there was a possibility that the responses obtained after particular periods might be affected by the active treatments (ALF or TAM) administered in the previous period. In this study the ANCOVA design allowed the carryover effects to be estimated and effectively separated from estimates of treatment means. These covariates have values 0 or ± 1 depending on the treatment in the preceding visit. All statistical tests were 2-sided and conducted at the 5% level of significance. No adjustments for multiple comparisons were made and values were not imputed for missing data points.

RESULTS

Subjects

A total of 166 subjects were screened for entry into the study. A total of 57 patients were randomized to receive study medication. Four patients discontinued early, that is 1 subject discontinued while taking placebo because of an adverse event and 3 subjects (2 while taking ALF and 1 while on placebo) withdrew consent. Thus, the ITT population constituted 53 men. Individuals were randomly assigned to 1 of the 6 possible treatment sequence groups. All groups were similar with respect to age, race, weight and ejaculatory function parameters. Baseline demographic characteristics for the ITT patient sample as a whole are shown in table 1.

There were no substantial differences among the treatment sequences with respect to the number of subjects who completed the study per the protocol. More than 90% of subjects completed treatment with study drugs and placebo. Results reported here focus on the completer population, which was the same as the per protocol population (48) in this study.

Ejaculate Volume

The mean change from baseline in ejaculate volume was significantly higher with TAM (–2.4 $\pm$ 0.17 ml) compared with placebo (+0.4 $\pm$ 0.18, $p < 0.0001$) or ALF (+0.3 $\pm$ 0.18,

TABLE 1. *Baseline demographic characteristics and semen parameters among subjects who took study medication*

Mean age (SD)	25 (4.36)
No. race (%):	
White	8 (14.0)
Black	44 (77.2)
Asian	1 (1.8)
Hispanic	3 (5.3)
Other	1 (1.8)
Kg wt (mean, SD)	76.4 (10, 62)
Ejaculate vol range (ml)	1.5–6.2
Post-ejaculate urine sperm concentration range (10^6/ml)	0.0–5.2