Effect of Vardenafil on Blood Pressure Profile of Patients With Erectile Dysfunction Concomitantly Treated With Doxazosin Gastrointestinal Therapeutic System for Benign Prostatic Hyperplasia

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Purpose: We investigated the effect of the combination of the doxazosin gastrointestinal therapeutic system and 10 mg vardenafil on the hemodynamic status of patients with benign prostatic hyperplasia and erectile dysfunction.

Materials and Methods: This was a double-blinded, randomized, placebo controlled crossover trial. Patients with benign prostatic hyperplasia and erectile dysfunction treated with the doxazosin gastrointestinal therapeutic system on a regular basis, with no other antihypertensive events, were recruited. Subjects took 10 mg vardenafil or placebo in a randomized crossover fashion with a washout period of at least 7 days between each treatment. The supine and standing blood pressure of the subjects was recorded from 1 hour before to 6 hours after the administration of vardenafil or placebo. The primary outcome of the study was the maximal change in standing systolic blood pressure of the subjects from 1 half hour before to 6 hours after the administration of drugs.

Results: A total of 37 patients, 25 (67.6%) and 12 (32.4%) on the doxazosin gastrointestinal therapeutic system at 4 mg and 8 mg, respectively, completed the trial. The combination drug therapy resulted in a maximal decrease in standing systolic blood pressure of 6.18 mm Hg (95% CI −12.02, −0.33; p = 0.039). Only 1 patient had an asymptomatic standing systolic blood pressure of less than 85 mm Hg. Otherwise no symptomatic hypotension or clinically significant adverse cardiovascular event was observed during the study.

Conclusions: In patients on the doxazosin gastrointestinal therapeutic system for benign prostatic hyperplasia a single 10 mg dose of vardenafil had no symptomatic hemodynamic effects.

Key Words: adrenergic alpha-antagonists, phosphodiesterase inhibitors, prostatic hyperplasia, erectile dysfunction

With the aging of the population the incidence of benign prostatic hyperplasia and erectile dysfunction has been increasing in recent years. Evidence suggests that these 2 conditions are closely linked.[1,2] Increasingly elderly patients have both conditions, and require combination therapy with an α_1-adrenergic receptor blocker (α_1-AR blocker) and a PDE5 inhibitor. However, the potential risk of profound hypotension due to the vasodilatory effect of both drugs is of concern. Several studies have been performed to address the issue and their results are summarized in table 1.[3–8] In general no clinically significant hemodynamic effect has been observed in patients treated concomitantly with a uroselective α_1-AR blocker (tamsulosin) and a PDE5 inhibitor. However, the combination of a PDE5 inhibitor with other nonuroselective α_1-AR blockers may result in a significant decrease in blood pressure or an adverse event, and so caution must be taken. For example, it is recommended to start from 5 mg vardenafil in patients taking an α_1-adrenergic receptor blocker instead of the usual recommended starting dose of 10 mg.

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Doxazosin GITS is a prolonged release preparation characterized by a push-pull osmotically activated controlled release formulation.[9] This new formulation has been found to be well tolerated with an overall incidence of adverse events much less than that of the initial nonGITS formulation, comparable to that of placebo. Because of the minimal hemodynamic side effects of doxazosin GITS, we investigated the hemodynamic interaction between this drug and 10 mg vardenafil in patients with BPH and ED.

MATERIALS AND METHODS

A double-blinded randomized placebo controlled crossover trial was conducted with 2 days of treatment. The study protocol was approved by a local ethics committee. Patients with ED and BPH were recruited from a specialty clinic. The inclusion criteria were patients 50 to 80 years old, clinically diagnosed with LUTS secondary to BPH, on stable use of doxazosin GITS (more than 4 weeks) without having clinically significant side effects and erectile dysfunction with an IIEF-5 score of 21 or less.[10] Exclusion criteria were known congestive heart failure, unstable angina, arrhythmia or myocardial infarction. Patients with known hypertension and on any additional antihypertensive agent were also excluded from study. Moreover, patients with known contraindications for vardenafil including concurrent use of nitrate medication were excluded from study.

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TABLE 1. *Summary of the literature on the combined use of an α_1-adrenergic receptor blocker and a phosphodiesterase inhibitor*

	Terazosin (mg)	Doxazosin (mg)	Alfuzosin (mg)	Tamsulosin (mg)	No. Subjects	Outcome (No.)	References
Sidenafil (mg):							
25	—	—	10 Once daily formulation	—	21	No clinically significant hemodynamic interaction	Kaplan et al[3]
100	—	4	—	—	28	No clinically significant hemodynamic interaction	De Rose et al[4]
Tadalafil (mg):							
20	—	8	—	—	18	Significant decrease in BP (16)	Kloner et al[5]
20	—	—	10 Once daily formulation	—	18	No clinically significant hemodynamic interaction	Giuliano et al[6]
20	—	—	—	0.4	18	No clinically significant hemodynamic interaction	Kloner et al[5]
Vardenafil (mg):							
5 or 10	5 or 10	—	—	—	20	Standing SBP less than 85 mm Hg (1)	Kloner[7]
10	10	—	—	—	8	Standing SBP less than 85 mm Hg (6)	Kloner[7]
20	10	—	—	—	37	Standing SBP less than 85 mm Hg (9)	Kloner[7]
10 or 20	—	—	—	0.4	22	No clinically significant hemodynamic interaction	Auerbach et al[8]

Informed consent was obtained from each subject. Background information including age, duration of BPH and ED symptoms, weight, concurrent medication and medical history of other chronic illness of the subjects was obtained. Subjects were told to continue taking doxazosin GITS during the study. For patients already using other PDE5 inhibitors, they were advised to stop the drug for 2 weeks before the study. Randomization took place before the drug treatment by using preset envelopes using a permuted block design with a random block size of 2, 4 and 8. The subjects then entered the treatment phase which consisted of 2 treatment stages. They took 10 mg vardenafil, the recommended starting dose for normal adult patients, or placebo in a randomized crossover fashion with a washout period of at least 7 days between each treatment.

For each treatment the subjects were hospitalized on the morning of the day of the investigation. Supine and standing BP were monitored from 1 hour before drug administration. Then a single oral 10 mg dose of vardenafil or a placebo was given. BP (supine and standing) was monitored for at least 6 hours afterward. This period was chosen because the plasma concentration of the drug reaches a peak 1 hour after administration and the drug elimination half-life is 3 to 5 hours.[11] For each blood pressure measurement 2 readings were taken and the average was used for subsequent statistical analysis. During the study period the subject lay in a supine position for 5 minutes before each supine BP measurement. The subject was then instructed to sit on the side of the bed with the legs dependent for at least 5 seconds before moving to a standing position. Standing BP was taken after the subject had been standing for at least 1 minute. The subjects were monitored continuously for 6 hours after the administration of drug.

The calculation of the sample size was based on the statistics of a previous trial on the effect of vardenafil and tamsulosin on the BP of normotensive men,[8] and assumed an effect size of 0.5. With this assumption it was calculated that a sample size of more than 34 patients should provide 80% power to detect a difference in 3.5 mm Hg in standing SBP using a 2-tailed test with a significance level of 5%. With an assumed dropout rate of approximately 15% the estimated sample size was 40.

The primary efficacy variable of the study was the mean maximal change of standing SBP from 1 half hour before (baseline) to 6 hours after the administration of vardenafil or placebo.[5] Other secondary end points of the study were the mean maximal post-baseline change in supine SBP, the mean maximal post-baseline changes in standing and supine DBP, and the pattern of change, measured every half hour, in SBP and DBP from 1 half hour before to 6 hours after the administration of vardenafil or placebo.[5] The mean post-baseline maximal change in SBP and DBP, and the difference in SBP and DBP after the administration of vardenafil or placebo were assessed by paired t testing.

The safety of all of the subjects was analyzed by calculating the percentages of patients experiencing minimal SBP less than 85 mm Hg, minimum DBP less than 45 mm Hg, maximum decrease of SBP 30 mm Hg or greater and maximum decrease of DBP 20 mm Hg or greater from those of the baseline, as well as the proportion of adverse events for the whole population. All tests were performed using SPSS® 13.0 with a significance level of 0.05.

RESULTS

Between April 2006 and July 2007, 40 patients were recruited for this study with a mean age of 65.5 years (range 47 to 79). Three patients withdrew after the first visit because of difficulty in finding time for the second visit (2) or for unspecified personal reasons (1). Two of the patients had taken the placebo and 1 had taken vardenafil during the first visit, and none of the 3 had an adverse event during treatment. The demographic characteristics of the remaining study subjects are summarized in table 2. The number of subjects taking 4 mg and 8 mg doxazosin GITS was 25 (67.6%) and 12 (32.4%), respectively. There were 7 patients with a history of PDE5 inhibitor consumption, of whom 6 were on 50 mg sildenafil and 1 was on 100 mg sildenafil. The I-PSS and IIEF-5 scores of the subjects are listed in table 3. The majority of subjects had moderate to severe LUTS and ED.

The mean maximal change in BP after the administration of vardenafil or placebo is shown in table 4. There was a statistically significant higher mean maximal change