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COMPARISON BETWEEN ALPHA1A DOMINANT ADRENERGIC RECEPTOR ANTAGONIST TAMSULOSIN AND ALPHA1D DOMINANT ADRENERGIC RECEPTOR ANTAGONIST NAFTOPIDIL FOR THE EFFICACY AND SAFETY IN THE TREATMENT OF BENIGN PROSTATIC HYPERPLASIA: A RANDOMIZED CONTROLLED STUDY

Aims of study

Tamsulosin is a third-generation alpha-adrenergic receptor (AR) blocker that is used world-wide for the treatment of benign prostatic hyperplasia (BPH). Tamsulosin exhibits selectivity for the $alpha_{1a}$ AR subtype, with the advantage of a low incidence of adverse events. Naftopidil is an alpha AR blocker with selectivity for the $alpha_{1a}$ and $_{1d}$ subtypes, exhibiting a higher affinity for the $alpha_{1d}$ subtype compared with $alpha_{1a}$. In terms of human lower urinary tract localization of the $alpha_{1a}$ and $_{1d}$ AR subtypes, the $alpha_{1a}$ AR subtype predominates in the prostate and urethra, while the $alpha_{1d}$ AR subtype predominates in the bladder. In rats with bladder outlet obstruction, a remarkable increase in $alpha_{1d}$ gene expression was reported, which might contribute to detrusor overactivity following obstruction (1). In a clinical randomized cross-over study, it was reported that naftopidil was superior to tamsulosin in improving nocturia in patients with BPH (2). It is of clinical value to compare the clinical effects of the $alpha_1$ blockers that have different subtype affinity. This study was designed to compare the efficacy and safety of the $alpha_{1d}$ AR antagonist naftopidil with those of the $alpha_{1a}$ AR antagonist tamsulosin in the treatment of BPH.

Study design

Males aged 50 years or above with signs and symptoms of BPH, were eligible for participation in the study if they met the following requirements: a total International Prostate Symptom Score (IPSS) of 8 or higher, bladder outlet obstruction as defined by a peak urinary flow rate (Qmax) lower than 15 ml/sec with voided volume of 150 ml or more, and prostate volume of 20 ml or more estimated by ultrasonography. The enrolled patients with BPH were randomized to receive either tamsulosin or naftopidil for 12 weeks. Patients randomized to tamsulosin received 0.2 mg/day for 12 weeks. Patients randomized to naftopidil received 25 mg/day for 2 weeks, followed by 50 mg/day for 10 weeks. The primary efficacy parameters were changes in the total IPSS, a peak flow rate (Qmax) on free uroflowmetry, and the residual urine volume, from the baseline to the end point (12 weeks). Secondary efficacy parameters comprised average urinary flow rate (Qave), changes in total IPSS storage score, total IPSS voiding score, and IPSS-QOL Index, from the baseline to the end point. Improvement relative to the baseline in all the efficacy parameters was also assessed on each visit (2, 4, 8, and 12 weeks). Data on all the randomized patients were included in the safety analyses of adverse events and changes in blood pressure. The within-group differences in the efficacy parameters were analyzed using the Wilcoxon test, and between-group differences for the two treatment groups were analyzed using the Mann-Whitney U test. Differences in the incidence of adverse events between the two groups were analyzed using the chi-square test.

Results

Analysis was performed on 144 of the 194 enrolled patients, who were eligible for inclusion in the efficacy analysis, including 75 patients form the tamsulosin group and 69 from the naftopidil group (Table). There was no significant difference in all the evaluated parameters between the two groups at the baseline.

Primary efficacy parameters: Statistically significant improvements were obtained in all three primary efficacy parameters both in tamsulosin- and naftopidil-treated patients. However, there was no significant difference in the improvement of any primary efficacy parameter between the two groups.

Secondary efficacy parameters*:* Although statistically significant improvements were observed in all four secondary efficacy parameters for both treatment groups, there was no significant difference in the improvement of any secondary efficacy parameter between the two groups.

The mean changes for the within-group from the baseline were significant during all visits for both treatment groups and there were no significant between-group differences in all primary and secondary parameters during all visits except after 2 weeks. There was overall trend for the total IPSS score, storage score, and voiding score to progressively improve across the consecutive visits until 12 weeks.
Safety analyses: Adverse events were comparable in the two treatment groups. Following treatment, there was no significant change in systolic and diastolic blood pressure in both groups.

Table:Results of primary and secondary efficacy parameters at the baseline and the end point

		Baseline	12 weeks	Change	Within-group
Total IPSS	Tamsulosin	17.1 (6.2)	8.8 (5.6)	-8.4 (6.9)	p < 0.0001
	Naftopidil	15.5 (5.8)	9.6 (6.6)	-5.9 (6.0)	p < 0.0001
	Between-group	p = 0.0881	p = 0.05736	p = 0.0595	
Qmax	Tamsulosin	8.8 (3.3)	10.9 (5.9)	2.1 (5.7)	p = 0.0017
	Naftopidil	9.2 (3.4)	11.3 (5.5)	2.1 (4.2)	p=0.0008
	Between-group	p = 0.6087	p = 0.5213	p = 0.7087	
Residual urine	Tamsulosin	41.9 (54.6)	32.3 (39.2)	-9.6 (44.1)	p = 0.0617
	aftopidil	43.7 (58.0)	30.1 (57.2)	-13.6 (55.1)	p = 0.0029
	Between-group	p = 0.6087	p = 0.5213	p = 0.2182	
Total voiding score	Tamsulosin	10.1 4.9)	4.8 (3.8)	-5.3 (5.0)	p < 0.0001
	Naftopidil	8.5 (4.7)	4.7 (3.9)	-3.7 (4.7)	p < 0.0001
	Between-group	p = 0.0704	p = 0.8875	p = 0.1264	
Total storage score	Tamsulosin	7.9 (3.0)	4.4 (2.8)	-3.4 (3.5)	p < 0.0001
	Naftopidil	7.0 (3.7)	4.6 (3.3)	-2.4 (3.0)	p < 0.0001
	Between-group	p = 0.1133	p = 0.9623	p = 0.0679	
Qave	Tamsulosin	4.3 (1.9)	5.3 (2.7)	1.0 (2.4)	p = 0.0009
	Naftopidil	4.5 (1.7)	5.7 (3.1)	1.2 (2.6)	p = 0.0012
	Between-group	p = 0.3808	p = 0.6644	p = 0.6364	
QOL index	Tamsulosin	4.4 (0.9)	3.0 (1.3)	-1.4 (1.5)	p < 0.0001
	Naftopidil	4.5 (1.0)	3.1 (1.2)	-1.3 (1.4)	p < 0.0001
	Between-group	p = 0.8998	p = 0.6373	p = 0.8006	

Data presented as mean (SD)

Concluding message

This study revealed that naftopidil was as effective and safe as tamsulosin. Both drugs were effective in improving storage symptoms as well as voiding symptoms. However, there were no differences in clinical efficacy and adverse events between different AR alpha$_1$ antagonists with different affinity to alpha$_1$ AR subtypes, alpha$_{1a}$ and alpha$_{1d}$.

References

1. Increased alpha 1 adrenergic bladder susceptibility in rats with bladder outlet obstruction-a possible cause for irritability. Abstract No 34, 2000 ICS
2. Assessment of two alpha 1 adrenoceptor antagonists, naftopidil and tamsulosin hydrochloride, on voiding disturbance in benign prostatic hyperplasia. A randomized cross-over study. Abstract No. 198, 2002 ICS