306

Lee H N[1], Lee Y[2], Han J[3], Jo W J[1], Ju S H[1], Lee K S[1], Lee K[1]

1. *Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea,* ***2.*** *Masan Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, Korea,* ***3.*** *Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea*

THE EFFECTS OF CHRONIC USE OF DOXAZOSIN ON ALPHA 1-ADRENERGIC RECEPTORS IN MEN WITH BENIGN PROSTATIC HYPERPLASIA

Hypothesis / aims of study

Alpha 1-adrenoceptor (α1-AR) antagonist has been used as the predominant medical therapy for the patients with lower urinary tract symptoms (LUTS) secondary to benign prostatic hyperplasia (BPH) because α1-AR can improve voiding and storage symptoms. Chronic administration of α1-AR antagonists may result in an alteration, possible up-regulation, in prostatic α1-AR properties, such that the effectiveness of these agents may be altered [1]. We aimed to examine whether the change of α1-AR subtype expression levels in the prostate occurred by long term administration of Doxazosin in mRNA and protein level. We evaluated the correlation between the change of α1-AR subtype expression level and the long-term efficacy of α1-AR antagonist.

Study design, materials and methods

The primary objective of this study was to evaluate the changes of mRNA and protein expression level in α1-AR from baseline to 12 month treatment of Doxazosin. Secondary objective was to evaluate the clinical efficacy of Doxazosin on improving of LUTS based on the parameters of bladder diaries, International Prostate Symptom Score (IPSS), patient's perception of bladder condition (PPBC) questionnaire, and uroflowmetry. The correlation between the change of α1-AR mRNA and protein expression level and the clinical efficacy of 12 month Doxazosin treatment was analyzed.

The patients who met the following criteria were included in this study ; 1) male aged 50 years and above (with no upper limit of age), 2) severe symptom of LUTS ; IPSS ≥ 8, 3) voided volume ≥ 120 ml and maximum flow rate (MFR) < 15 ml/s, 4) baseline prostate specific antigen (PSA) 4-10 ng/ml, 5) pathologically confirmed BPH by transrectal ultrasound guided biopsy, 6) no medical therapy for BPH at screening.

All patients were performed transrectal ultrasound guided biopsy for prostate because their PSA level were above 4 ng/ml and the results were confirmed as BPH pathologically. After biopsy, one 4mg tablet of doxazosin (Cardura XL^{TM}, Pfizer Inc, New York, NY) was given once a day before bedtime for 12 months. After 1 year of medication, transrectal prostate biopsy was repeated for obtaining prostate tissue. The expression level of mRNA for total α1-AR and α1a, α1b, and α1d subtypes were analyzed by real-time RT-PCR. Total and each subtype expression level of protein for α1-AR were evaluated by western blot analysis before and after the medication.

The clinical efficacy of doxazosin were evaluated by change of prostate volume, serum PSA level, IPSS, quality of life (QoL) index, MFR, and post-void residual urine volume (PVR), The parameters of bladder diary, and score of PPBC questionnaire at baseline and at the end of 12 months treatment. We evaluated the correlation between the change of α1-AR expression levels after the 12 month administration period and the change of clinical parameters, especially according to the dominant type of α1-AR subtypes and up-regulation or down-regulation of α1-AR expression. We defined "up-regulation" as the expression of mRNA or protein was increased more than five percent of baseline values; "down-regulation" as the expression of mRNA or protein was decreased more than five percent of baseline values.

Results

Twenty-five patients were enrolled and 20 patients who aged 49-72 (median age 66, interquartile range 60-68) with LUTS secondary to BPH were completed this 12-month study. Doxazosin administration for 12 months did not significantly alter the expression level of total α1-AR mRNA in the prostate. The median expression levels (interquartile range) of mRNAs for total α1-AR before and after doxazosin administration were 3.41 (1.51-5.45) and 2.67 (0.78-7.72) relative expression/beta-actin, respectively. Whereas, the expression level of protein were changed significantly after the doxazosin medication. Total and subtype α1a, α1b, and α1d AR expression level of protein were increased significantly ($p<0.05$) (Table).

The scores of IPSS, QoL index, PPBC were improved significantly after 12 months. Doxazosin treatment ($p<0.01$). MFR, PVR, prostate volume and parameters of bladder diary such as micturitions per 24 hours, nocturnal micturitions, daytime micturitions, and functional bladder capacity were not changed significantly after 12 months. There is no significant difference of clinical parameters such as prostate volume, MFR, PVR, IPSS, PPBC, and bladder diary variables between α1a-dominant group and α1d-dominant group. Up-regulation of total mRNA expression was showed in 12 patients and down-regulation in 5 patients. Symptom improvement with Doxazosin was not different according to the change of mRNA and protein expression.

Interpretation of results

Doxazosin medication significantly improved LUTS in men with symptomatic BPH. Even Doxazosin medication did not alter the expression level of α1-AR mRNA, there were significant increased expression of α1-AR protein. The results that the changes in mRNA expression do not guarantee parallel changes in protein expression may be explained by the lack of highly selective α1-adrenoceptor subtype antagonists and of highly specific antibodies for α1-adrenoceptor subtypes [2] or the limitation of using too small prostate tissues. Symptom change were not correlated with the change of the expression of mRNA or protein of . α1-AR.

Concluding message

Doxazosin administration can lead to the change of α1-AR subtype expression levels in protein level. However, the expression level of α1-AR mRNA level was not changed significantly. Considering that the correlation of clinical parameters with the

expression of mRNA and protein was not clear, the change of mRNA or protein by chronic administration of α1-AR antagonist may not be definitely related to the change of long-term treatment effectiveness.

Table. Change from baseline to 12 months of treatment in expression level of mRNA and protein for alpha 1-adrenoceptor obtained from 20 patients analyzed by real-time RT-PCR and western blot (median, interquartile range ; mean ± S.E.M)

	Baseline		After 12 months medication		*p*-value
	Median (interquartile range)	Mean ± S.E.M	Median (interquartile range)	Mean ± S.E.M	
mRNA expression					
Total α1 AR	3.41 (1.51-5.45)	4.43 ± 0.87	2.67 (0.78-7.62)	4.22± 0.89	0.8497
α1a-AR	1.42 (0.69-1.98)	1.66 ± 0.30	1.27 (0.46-2.42)	2.17 ± 0.57	0.8124
α1b-AR	0.51 (0.09-0.97)	0.70 ± 0.19	0.30 (0.03-0.75)	0.59 ± 0.17	0.6286
α1d-AR	1.42 (0.59-2.93)	2.08 ± 0.47	0.79 (0.11-1.62)	1.46 ± 0.45	0.3191
Protein expression					
Total α1 AR	1.59 (1.35-1.98)	1.62 ± 0.12	2.08 (1.44-2.43)	1.96 ± 0.13	0.0046*
α1a-AR	0.49 (0.47-0.68)	0.56 ± 0.05	0.61 (0.49-0.85)	0.68 ± 0.06	0.0129*
α1b-AR	0.51 (0.43-0.55)	0.51 ± 0.04	0.57 (0.49-0.78)	0.61 ± 0.05	0.0196*
α1d-AR	0.58 (0.40-0.65)	0.55 ± 0.04	0.76 (0.59-0.85)	0.67 ± 0.06	0.0078*

*p<0.05, Paired T test or Wilcoxon signed rank test, S.E.M ; standard error of the mean, α1 AR; alpha 1 adrenoceptor, α1a-AR; alpha 1a adrenoceptor, α1b-AR; alpha 1b adrenoceptor, α1d-AR; alpha 1d adrenoceptor

References

1. British Journal of Pharmacology (2002) 135;1757-64.
2. European Journal of Pharmacology (1999) 375;261-76

Specify source of funding or grant	**This study was supported by the Samsung Medical Center Samsung Biomedical Reserch Institute.**
Is this a clinical trial?	**Yes**
Is this study registered in a public clinical trials registry?	**Yes**
Specify Name of Public Registry, Registration Number	**ClinicalTrials.gov NCT00730418**
Is this a Randomised Controlled Trial (RCT)?	**No**
What were the subjects in the study?	**HUMAN**
Was this study approved by an ethics committee?	**Yes**
Specify Name of Ethics Committee	**Samsung Medical Center Institutional Review Board**
Was the Declaration of Helsinki followed?	**Yes**
Was informed consent obtained from the patients?	**Yes**