Efficacy of Silodosin for Relieving Benign Prostatic Obstruction: Prospective Pressure Flow Study

Yoshihisa Matsukawa,* Momokazu Gotoh, Tomonori Komatsu, Yasuhito Funahashi, Naoto Sassa and Ryohei Hattori

From the Department of Urology, Nagoya University Graduate School of Medicine, Nagoya, Japan

Purpose: We investigated the effect of the new sympathetic α1A-adrenoceptor antagonist silodosin for relieving benign prostatic obstruction by pressure flow study.

Materials and Methods: In this open, nonblinded, prospective study we administered 8 mg silodosin daily for 4 weeks in 60 patients with lower urinary tract symptoms associated with benign prostatic enlargement. As a primary outcome measure, we assessed changes in bladder function and benign prostatic obstruction using pressure flow study. As secondary outcome measures, changes in subjective symptoms and quality of life were assessed by the International Prostate Symptom Score. Objective changes in urination status were also assessed by free uroflowmetry in terms of maximum flow rate and post-void residual urine volume.

Results: A total of 57 patients were enrolled for analysis. In the storage phase of the pressure flow study bladder capacity at first desire to void increased significantly with no significant change in maximum cystometric capacity. Of 24 patients 14 (58.3%) with uninhibited detrusor contractions before administration showed apparent improvement in detrusor overactivity after administration, including 6 in whom uninhibited contractions disappeared. In the voiding phase mean detrusor pressure at maximum flow significantly decreased from 72.5 to 51.4 cm H_2O. The mean bladder outlet obstruction index decreased significantly from 60.6 to 33.8. Obstruction grade assessed by the Schaefer nomogram improved in all except 1 patient. Total symptom and quality of life scores, maximum flow rate and post-void residual urine volume on free uroflowmetry significantly improved.

Conclusions: Silodosin improved lower urinary tract symptoms by improving bladder storage function and relieving benign prostatic obstruction.

Key Words: urinary bladder neck obstruction, prostatic hyperplasia, KMD 3213, adrenergic antagonists, urodynamics

Abbreviations and Acronyms

AR = adrenoceptor
BOOI = bladder outlet obstruction index
BPE = benign prostatic enlargement
BPH = benign prostatic hyperplasia
BPO = benign prostatic obstruction
I-PSS = International Prostate Symptom Score
LUTS = lower urinary tract symptoms
pdetQmax = detrusor pressure at Qmax
PFS = pressure flow study
PVR = post-void residual urine
Qmax = maximum flow rate
QOL = quality of life

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* Correspondence: Department of Urology, Nagoya University Graduate School of Medicine, 65-Tsurumai-cho, Showa-ku, Nagoya 466-8550, Japan (telephone: +81-52-744-2985; FAX: +81-52-744-2319; e-mail: yoshi44@med.nagoya-u.ac.jp).

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In BPO cases various LUTS are caused by mechanical bladder outlet obstruction due to BPE or by functional obstruction due to increased tension of prostatic smooth muscle mediated by sympathetic nerves.[1] Changes in bladder function associated with BPO modify LUTS comprising voiding and storage symptoms. Because prostatic smooth muscle contraction is caused by sympathetic α1-AR stimulation, sympathetic α1-AR antagonists are widely used as first line drug therapy for LUTS associated with BPO.[2–4] Sympathetic α1-ARs, in-

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cluding α1A, α1B and α1D-AR subtypes, have been identified with α1A and α1D-AR subtypes localized predominantly in the prostate, urethra and bladder neck, and α1B-AR subtype localized predominantly in blood vessels.[3,5] First-generation α1-AR antagonists such as prazosin and terazosin, which have no selectivity for sympathetic α1-AR subtypes, can cause adverse reactions related to vascular dilatation by inhibiting the α1B-AR subtype. Consequently in recent years second-generation α1-AR antagonists such as tamsulosin and naftopidil, which are selective for the α1A and α1D-AR subtypes, have come into wide use with the aim of decreasing adverse reactions.[6,7]

Sympathetic α1-AR antagonists improve LUTS due to BPO, and provide relief of voiding and storage symptoms.[4,8] These drugs are thought to improve functional obstruction by relaxing prostatic smooth muscles, thereby relieving voiding symptoms. The mechanisms of storage symptom improvement are not clear. The beneficial effects of α1-AR antagonists on subjective symptoms have been investigated in detail based on quantitative symptomatic evaluation using questionnaires such as I-PSS. The objective effects of α1-AR antagonists on lower urinary tract function and particularly the beneficial effects on BPO require evaluation by urodynamic testing. PFS is particularly useful to objectively evaluate bladder contractile function and the degree of BPO. Although there have been few reports of the effects of α1-AR antagonists as measured by PFS, the beneficial effects of doxazosin,[9] tamsulosin[10] and alfuzosin[11] on BPO were reported based on PFS findings.

Silodosin, which was recently developed as a new α1-AR antagonist, is purely selective for α1A-AR subtypes. This agent demonstrated affinity for the α1A-AR subtype that was 583-fold higher than for the α1B-AR subtype and 55.6-fold higher than for the α1D-AR subtype.[12] A phase III study of silodosin revealed its prominent beneficial effects on subjective symptoms and on the urinary flow rate on uroflowmetry.[13] This drug was launched in 2007 in Japan and in 2009 in the United States. To our knowledge there is no report of the objective effects of this drug on bladder function and BPO based on urodynamic testing. We investigated the effects of silodosin on bladder function and BPO using PFS in patients with LUTS due to BPE.

PATIENTS AND METHODS

The current investigation was an open, nonrandomized, single center prospective study. The protocol was approved by the ethics committee of Nagoya University Graduate School of Medicine, Nagoya, Japan.

Study participants were patients with untreated BPE who visited our hospital from January 2007 to October 2008 complaining of LUTS. Study inclusion criteria were 1) I-PSS total score 8 points or greater, 2) I-PSS-QOL score 3 points or greater, 3) prostate volume 20 ml or greater on transperitoneal or transrectal ultrasonography, 4) urination Qmax greater than 100 ml but less than 15 ml per second on uroflowmetry, 5) PVR less than 100 ml and 6) patient age greater than 50 years. We excluded patients 1) on oral treatment with α-antagonists, anticholinergic agents, antidepressants, anti-anxiety agents or antiandrogens, 2) suspected of having prostate cancer, 3) with neurogenic bladder dysfunction, bladder calculus or active urinary tract infection, 4) with serious cardiac complications, 5) with renal complications (serum creatinine 2 mg/dl or greater) and 6) with hepatic dysfunction (aspartate aminotransferase/alanine aminotransferase at least 2-fold higher than reference values).

Silodosin as 4 mg capsules was administered orally twice daily for a total of 8 mg daily in 60 patients for 4 weeks. I-PSS and I-PSS-QOL scores, Qmax on free uroflowmetry and PVR were evaluated at baseline and 4 weeks after administration. PFS was performed before and after administration. For PFS bladder capacity at first desire to void, maximum cystometric capacity and the presence (pressure increase magnitude) or absence of uninhibited detrusor contractions in the storage phase were investigated along with Qmax, pdetQmax and PVR in the voiding phase. Apparent improvement in overactive bladder was defined as the disappearance of uninhibited detrusor contractions or a decrease in amplitude of uninhibited contractions of greater than 15 cm H_2O. On PFS the degree of obstruction was assessed in terms of BOOI[14] according to International Continence Society recommendations before and after silodosin administration. Also, the obstruction grade of 0 to 6 based on the Schaefer nomogram was evaluated and baseline findings were compared with those after silodosin administration. Patients unable to continue oral administration due to adverse reactions and those who could not be evaluated after administration were excluded from analysis. Primary outcome measures were changes in bladder function and BPO on PFS. Secondary outcome measures were changes in subjective symptoms and QOL on I-PSS, and urination status on free uroflowmetry in terms of Qmax and PVR.

PFS was performed by one of us (YM) based on standard International Continence Society methods.[15] A 6Fr single pigtail catheter was placed in the bladder transurethrally to measure intravesical pressure and an additional 8Fr catheter was inserted in the bladder to inject physiological (0.9%) saline solution. A balloon catheter was inserted from the anus to measure abdominal pressure. The test was done with the patient standing. Physiological saline solution was injected into the bladder at 50 ml per minute after evacuating the bladder. Intravesical pressure, abdominal pressure and detrusor pressure in the storage phase were simultaneously measured and recorded. After the patient expressed the maximum desire to urinate the catheter for injection was removed, leaving the 6Fr catheter to measure intravesical pressure, abdominal pressure, detrusor pressure and urinary flow in the voiding phase, which were recorded simultaneously. Statistical analysis was done with the paired or nonpaired