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Urodynamic Effects of Silodosin, a New α_{1A}-Adrenoceptor Selective Antagonist, for the Treatment of Benign Prostatic Hyperplasia

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Aims: To investigate urodynamically the effects of silodosin, a new α_{1A}-adrenoceptor-selective antagonist, in the treatment of benign prostatic hyperplasia (BPH). **Methods:** Thirty six male patients with BPH (69.9 ± 7.3 years), who were referred as candidates for surgery, were treated with silodosin (4 mg twice daily). The total International Prostate Symptom Score (IPSS) was 20.7 ± 7.4, maximum flow rate (Q_{max}) was 6.7 ± 3.0 ml/sec, and prostate volume was 45.6 ± 24.5 ml. **Results:** Total IPSS, storage and voiding symptom subscores and QOL score decreased significantly, and Q_{max} increased significantly after 1–12 months of therapy (all $P < 0.05$). In urodynamic study ($n = 29$), maximum cystometric capacity increased significantly ($P = 0.0027$), and detrusor overactivity disappeared in 8 of 20 patients (40%) and improved (bladder capacity increased more than 50%) in 7 (35%) after the therapy. In pressure/flow studies ($n = 27$), the obstruction grade was improved in 15 patients (56%). Detrusor opening pressure, detrusor pressure at Q_{max}, bladder outlet obstruction index, and Schäfer's obstruction class decreased significantly after therapy (all $P < 0.01$). After 12 months, 16 patients (44%) are still on silodosin for 23.3 ± 7.0 (range 12–36) months, and the improvements in IPSS and Q_{max} were stable. Twenty patients withdrew because of insufficient effectiveness in 13 patients (12 patients underwent surgery), side effects in 3, and unknown reasons in 4. **Conclusion:** Silodosin appears to improve detrusor overactivity and obstruction grade in patients with BPH. With silodosin treatment, LUTS could be managed effectively for more than a year in at least 44% of the patients. *Neurourol. Urodynam. 29:558–562, 2010.* © 2010 Wiley-Liss, Inc.

Key words: alpha blockers; BOO; BPH; LUTS; prospective; silodosin; urodynamics

INTRODUCTION

Benign prostatic hyperplasia (BPH) is a common enlargement of the prostate gland that may lead to bladder outlet obstruction, lower urinary tract symptoms (LUTS) and reduced quality of life. BPH is present in 50% of men older than 50 years of age.[1]

Medical therapy with α_1-adrenoceptor (AR) antagonists is widely used as a conservative treatment to relieve benign prostatic obstruction. The urodynamic effects of α_1-AR antagonists on LUTS suggestive of BPH (LUTS/BPH) are relief of bladder outlet obstruction (BOO) and detrusor overactivity (DO), thus they are effective for both voiding and storage symptoms.[2–4] It has been reported that α_{1A}-AR subtypes are predominantly found in the prostate.[5] However, recent study suggested an expression of both α_{1A}- and α_{1D}-ARs in human prostate tissue.[6] Previous meta-analysis has reported that the effects of non-selective α_1-AR antagonists (terazosin or doxazosin) are similar to the effects of an α_{1A}- and α_{1D}-(α_{1A}/α_{1D})-AR antagonist (tamsulosin), although a difference in cardio-vascular side effects was noted.[1,2] Thus selective antagonists for the α_{1A}/α_{1D}-ARs or α_{1A}-AR may be necessary for the treatment of LUTS/BPH.[7] Recently silodosin, a new α_{1A}-AR selective antagonist, has been reported to be effective for both storage and voiding symptoms in BPH patients.[8,9] In a randomized control study comparing silodosin, tamsulosin and placebo, significantly greater improvement of the total International Prostate Symptom Score (IPSS) was obtained with silodosin than with either placebo or tamsulosin.[8] This drug is highly selective for the α_{1A}-AR subtype, with an affinity for the α_{1A}-AR that is 583- and 55.5-fold higher than that for the α_{1B}- and α_{1D}-ARs, respectively.[10] The aim of the present study is to investigate the effects of silodosin in the treatment of LUTS/BPH by means of the IPSS and urodynamic parameters including pressure/flow study. The long-term effects of treatment with silodosin for more than 12 months were also evaluated by how many surgeries were avoided by taking this drug.

METHODS

Thirty six male patients with BPH (mean age 69.9 ± 7.3 years), who were referred to our institution as candidates for surgery, were included in the study. The patients were considered as candidates for surgery for the following reasons: medical treatment with other α-AR antagonists was not adequately effective, there was a history of urinary retention, and/or the patient had severe BPH according to the criteria reported by Homma et al.[11] According to these criteria, patients with more than 2 of the following are defined as having severe BPH: total IPSS of 20 or more; maximum flow rate (Q_{max}) of less than 5 ml/sec or postvoid

Conflicts of interest: none.
Chris Winters led the review process.
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residual urine volume (PVR) of 100 ml or more; prostate volume of 50 ml or more; IPSS-QOL index of 5 or more.[11] All of the patients desired to undergo surgery and were on the waiting list. Patients were asked to take silodosin for 3 months during the waiting period for surgery, and those who agreed to do so were included in the study. Patients were excluded if they had prostatic cancer, urethral stricture, a severe cardiac or cerebrovascular disorder, hepatic disorder, or renal dysfunction. Patients who were being treated with an anti-cholinergic, another α-AR antagonist, or a β-AR agonist or antagonist discontinued that treatment at least 2 weeks prior to the study. No patients were taking anti-androgen medication. Urinalysis was performed for all patients, and patients with cystitis or bacterial prostatitis were treated with antibiotics accordingly.

The study was conducted in accordance with the Helsinki Declaration. The approval of the Institutional Review Board at our institution and informed consent from each subject were obtained before entry into the study.

After 1-week observation period, LUTS were assessed by the IPSS and quality of life (QOL) score. The IPSS sub-scores were assessed as individual scores as well as storage symptom scores (frequency, urgency, and nocturia), voiding symptoms (intermittency, decreased urinary stream, and straining) and a post-micturition symptom score (feeling of incomplete emptying).[12] Free urinary flow rate and PVR were evaluated at the end of the observation period and after the therapy. PVR and the percent of residual urine [%PVR: PVR/(PVR + voided volume) × 100%] were measured by ultrasonography.

Video-urodynamic studies including pressure/flow studies were performed. A 6-F double lumen catheter was inserted transurethrally, and a water cystometrogram was recorded at an infusion rate of 50 ml/min with the patient in a supine position. Simultaneously, abdominal pressure was measured with a balloon catheter inserted transrectally. Detrusor pressure was measured by electrically subtracting the abdominal pressure from the intravesical pressure. DO is defined as involuntary detrusor contractions during the filling phase which may be spontaneous or provoked.[12] The amplitude of the DO was calculated as the amplitude of the largest overactive detrusor contraction during the filling phase, and was calculated as 0 cm H_2O when the DO was disappeared after the therapy. Bladder volume at the first involuntary contraction (FIC) was calculated as the maximum bladder capacity when the DO was disappeared after the therapy.

At maximum cystometric capacity, patients assumed a standing position, and the pressure/flow study was performed. Methods, definitions and units conform to the standards recommended by the International Continence Society, except where specifically noted.[12] The bladder outlet obstruction index (BOOI), formerly known as the Abrams-Griffith number, is defined as detrusor pressure at $Q_{max} - 2Q_{max}$.

Silodosin in a daily dose of 8 mg (given as 4 mg twice daily) was administered. The effects of the drug were assessed by changes in the IPSS and uroflowmetric parameters before and after therapy, and video-urodynamic studies were performed before and 3 months after therapy.

Data were expressed as mean plus or minus standard deviation. Pre- and post-treatment data were analyzed with the Wilcoxon matched-pairs signed-ranks test. P values of <0.05 were regarded as statistically significant. The efficacy of the treatment was evaluated according to the standard criteria proposed by Homma et al.[13] and graded as "excellent," "good," "fair," and "poor." Efficacy for IPSS was calculated as pre- to post-treatment scores and efficacy for Q_{max} as the difference.

RESULTS

Four patients had a history of urinary retention. Twenty-two patients had been treated with other α-blockers (mostly tamsulosin or naftopidil), but those were ineffective. The remaining 10 patients had severe grade BPH according to Homma's criteria[11] and all patients desired to undergo surgery.

Prostate volume and serum PSA level were 45.6 ± 24.5 (range 28.5–111.7) ml and 4.1 ± 4.8 (range 0.783–20.3) ng/ml, respectively. Three patients whose serum PSA level was over 4.0 ng/ml and who were suspected of having prostate cancer underwent a needle biopsy of the prostate and were determined to be cancer-free.

In the video-urodynamic study, DO was noted in 24 patients (66.7%). In pressure/flow studies, 30 patients (83%) were ranked as obstructed and 5 (14%) as equivocal. One patient (3%) had an underactive bladder and thus was excluded from the urodynamic evaluation.

At 12 months of therapy, 20 patients withdrew because of insufficient effectiveness in 13 patients (36%), including 12 patients who underwent surgery; side effects in 3 patients (8%); and unknown reasons in 4 patients (11%). Adverse events (abnormal ejaculation and nasal congestion) were noted in other 3 patients, but they continued the medication for 15–36 (average 25.3) months. In total, adverse events were noted in 6 patients (17%): abnormal ejaculation in 2 patients (6%), dizziness in 2, thirst in 2, decrease in platelets in 1, diarrhea or loose stool in 1, skin itching in 1, and stuffy nose in 1. Finally, 16 patients (44%) are continuing treatment with silodosin for 23.3 ± 7.0 (range 12–36) months.

The changes in the total IPSS, and the IPSS subscores for total voiding and total storage, the post-micturition symptom score (feeling of incomplete voiding), and the uroflowmetry parameters before and after the therapy are summarized in Table I. Significant decrease of the nocturia score was observed after 1, 3, and 6 months of therapy ($P < 0.05$ for both; from 2.8 ± 1.4 at the baseline to 2.3 ± 1.5, 2.3 ± 1.2, and 2.1 ± 1.2 after 1, 3, and 6 months of treatment, respectively). According to the standard criteria proposed by Homma et al.[13] the efficacy of silodosin as measured by improvement in the IPSS score was judged as excellent or good (post/pre ratio ≤ 0.50) in 9 of 25 patients (36%), and the efficacy of silodosin with regard to Q_{max} was judged as excellent or good (post-pre difference $\geq$5 ml/sec) in 10 patients (33.3%) after 3 months of therapy.

Urodynamic data could be assessed both before and at 3 months of therapy in 29 patients, excluding 1 patient with underactive detrusor and 6 patients who dropped out at 3 months. The changes in urodynamic parameters before and after the therapy are summarized in Table II. In 20 patients who had DO before the therapy, DO disappeared in 8 patients (40%), improved (bladder capacity increased more than 50% or 100 ml) in 7 (35%), and remained unchanged in 5 (25%).

Pressure/flow study could be assessed both before and after the treatment in 27 patients. After the therapy, detrusor opening pressure, detrusor pressure at Q_{max}, BOOI, and Schäfer's linear passive urethral resistance relation obstruction class decreased significantly ($P = 0.0010$, $P < 0.0001$, $P < 0.0001$, and $P < 0.0001$, respectively) (Table II). In the ICS nomogram, obstruction grade was improved in 15 patients (56%) (obstructed to unobstructed in 5, obstructed to equivocal in 8, and equivocal to unobstructed in 2) and unchanged in

TABLE I. Changes in IPSS and Uroflowmetric Parameters (Mean ± SD)

IPSS	0 M (n = 36)	1 M (n = 30)	3 M (n = 25)	6 M (n = 17)	12 M (n = 16)
Total IPSS	20.7 ± 7.4	14.7 ± 8.6***	12.8 ± 8.0***	12.2 ± 9.3**	13.7 ± 7.7*
Total storage subscores	7.6 ± 4.0	6.0 ± 4.1*	5.0 ± 3.0**	4.5 ± 3.2**	5.3 ± 3.6
Total voiding subscores	10.3 ± 4.4	7.2 ± 4.5***	6.5 ± 5.1***	6.5 ± 5.7*	7.0 ± 4.1
Post-micturition score	2.8 ± 1.9	1.4 ± 1.7**	1.3 ± 1.5**	1.3 ± 1.7**	1.5 ± 1.6*
QOL score	4.8 ± 1.2	3.7 ± 1.6**	3.7 ± 1.4*	3.2 ± 1.4**	3.5 ± 1.2*
Free uroflowmetry	0 M (n = 36)	1 M (n = 29)	3 M (n = 28)	6 M (n = 23)	12 M (n = 16)
Average flow rate (ml/sec)	3.0 ± 1.5	4.3 ± 2.8**	3.5 ± 1.4*	5.1 ± 2.8***	7.6 ± 11.6***
Maximum flow rate (ml/sec)	6.7 ± 3.0	9.5 ± 5.0**	8.4 ± 3.5*	10.4 ± 4.5***	10.5 ± 5.4***
Postvoid residual urine (PVR: ml)	169.9 ± 119.5	117.3 ± 73.9***	94.0 ± 90.1**	73.0 ± 55.8*	64.0 ± 47.8**
%PVR	52.3 ± 26.7	41.2 ± 22.2*	39.4 ± 22.9*	27.8 ± 13.5*	27.9 ± 16.8**

Wilcoxon matched-pairs signed-ranks test compared to the baseline (0 M).
*$P < 0.05$.
**$P < 0.01$.
***$P < 0.001$.

12 (44%) (obstructed to obstructed in 9, and equivocal to equivocal in 3).

The characteristics of the 13 patients who did not respond to silodosin therapy were as follows: mean age, 71.2 ± 6.6 years; history of other α-blocker therapy, 8 patients; mean prostatic volume, 58.3 ± 24.7 ml; mean total IPSS, mean IPSS subscores for voiding and storage, mean QOL score and Q_{max}, 19.6 ± 4.6, 12.3 ± 4.6, 7.3 ± 2.6, 4.9 ± 0.8, and 7.1 ± 3.5 ml/sec, respectively, at baseline; DO was noted at baseline in 9 patients (69.2%), which resolved completely or improved in 5 patients (55.6%) after 3 months of therapy; the mean BOOI and Schäfer's linear passive urethral resistance relation obstruction class were 78.2 ± 44.2 and 4.45 ± 1.6, respectively, at baseline, and 32.2 ± 34.9 and 2.62 ± 1.6 respectively, after 3 months of therapy ($P = 0.0010$ and $P = 0.0078$, respectively); the obstruction grade in the ICS nomogram was "obstructed" in 12 patients and "equivocal" in 1 patient, and 6 of the 11 patients tested (63.6%) showed improvement. No significant differences in these characteristics were found between the patients who showed treatment response and those who did not.

DISCUSSION

BPH is a common enlargement of the prostate gland that may lead to bladder outlet obstruction, LUTS and reduced quality of life.[1] Published reports have shown the efficacy of α_1-AR antagonists in improving urodynamics and producing symptomatic improvement in the treatment of BPH. It has been reported that α_1-AR antagonists are effective for both storage and voiding symptoms because they decrease BOO and alleviate DO.[1–4,7] On the contrary, it has also been reported that α_1-AR antagonists improve LUTS but fail to relieve BOO.[14,15] Therefore, it may be important to verify the effects of this new α_{1A}-AR antagonist by objective measures such as a urodynamic study including a pressure/flow study.

All of our patients were candidates for surgery and thus seemed to have somewhat severe LUTS (total IPSS of 20.6 ± 7.4) and low Q_{max} (6.7 ± 3.0 ml/sec). All patients had abnormal findings in the urodynamic study: DO was noted in 24 patients (66.7%), 30 patients (83%) had an obstruction grade, 5 (14%) were equivocal, and 1 (3%) patient had an underactive bladder. One patient with an underactive detrusor was excluded from the urodynamic evaluation. He was satisfied with the drug and stayed on the medication for 36 months but had an underactive detrusor after 3 months of therapy.

In our study with silodosin, significant improvement of LUTS, as determined by the IPSS including voiding, storage and post-micturition symptom subscores, was observed up to 12 months of therapy. Significant increase of the urinary flow rates and decrease of the PVR was also observed up to

TABLE II. Changes in Urodynamic Parameters Before and at 3 Months After Silodosin Treatment

	Before (n = 35)	After (n = 29)	*P* values[a]
First desire to void (ml)	193.1 ± 105.5	230.3 ± 99.9	0.0974
Maximum cystometric capacity (ml)	356.1 ± 139.6	409.1 ± 122.2	0.0027
Bladder compliance (ml/cm H_2O)	40.5 ± 51.9	45.0 ± 34.2	0.3806
Detrusor overactivity (DO)	Before (n = 23)	After (n = 20)	*P* values[a]
Amplitude of the largest DO contraction (cm H_2O)[b]	85.3 ± 35.3	37.4 ± 42.9	0.0003
Bladder volume at FIC (ml)[c]	285.34 ± 112.8	380.6 ± 136.87	0.0003
Pressure flow study	Before (n = 35)	After (n = 27)	*P* values[a]
Detrusor opening pressure (cm H_2O)	77.8 ± 42.9	52.2 ± 20.7	0.0010
Detrusor pressure at Q_{max}	80.6 ± 37.8	48.6 ± 25.3	<0.0001
Bladder outlet obstruction index	70.2 ± 38.1	32.6 ± 29.2	<0.0001
Schäfer's linear passive urethral resistance relation obstruction class	4.5 ± 1.5	2.6 ± 1.5	<0.0001
Watts factor at Q_{max} (μW/mm^2)	9.9 ± 6.6	8.8 ± 6.0	0.7784

[a]Wilcoxon matched-pairs signed-ranks test compared to the baseline (0 M).
[b]The amplitude of the DO was calculated as the amplitude of the largest overactive detrusor contraction during the filling phase, and was calculated as 0 cm H_2O when the DO was disappeared after the therapy.
[c]Bladder volume at the first involuntary contraction (FIC) was calculated as the maximum bladder capacity when the DO was disappeared after the therapy.

12 months of therapy. These results appeared to be similar to those reported by Kawabe et al.[8] Of note, significant decrease of the nocturia score was observed after 1, 3, and 6 months of therapy (by 0.56, 0.55, and 0.71 points, on average, respectively). It has been reported that nocturia respond to the blockade of α_{1D}-ARs, but crossover comparison studies of tamsulosin and naftopidil showed different effects, depending on the reports.[1,16,17] All these commercially available α_1-AR antagonists contain α_{1A}-AR antagonist activity to a greater or lesser extent, so the effect of these drugs on nocturia may not be solely due to the blockade of α_{1D}-AR.

Blockade of the of α_{1A}-AR was reported to relieve bladder outlet obstruction, while the blockade of the α_{1D}-AR was believed to alleviate storage symptoms due to DO.[1] The predominant distribution of α_{1D}-ARs over α_{1A}-ARs has been reported in the human detrusor, suggesting a possible role of α_{1D}-adrenoceptors in controlling DO.[18] However, the expression of α_1-ARs has been reported to be too low to produce any contraction in human normal and obstructed bladders.[19] Another possible mechanism of α_1-AR antagonists in relieving DO may be that they inhibit the micturition reflex by acting on ARs in the lumbosacral spinal cord.[20–22] Although the expression of α_{1D}-ARs seems to predominate in the human spinal cord,[20] intrathecal injection of both α_{1D}- and α_{1A}-AR-selective antagonists decreased micturition reflex in the rat.[21,22]

In our study, significant increase of the maximum bladder capacity was noted, and the DO resolved completely or improved in 75% of the patients. The urodynamically beneficial effects of silodosin on the DO appeared to be greater than those of naftopidil, an α_{1A}/α_{1D}-AR selective antagonist, in that the DO resolved completely or improved in 57% of the patients.[4] An inhibition of DO after intravenous administration of silodosin has also been reported in a rat model of hormone-induced BPH.[23] Most of the effect of silodosin in the clinical dose appeared to be due to the blockade of the α_{1A}-AR, suggesting that the α_{1A}-AR is predominantly involved in DO in BPH. One of the explanations for the effectiveness of silodosin in treating both storage and voiding dysfunction may be that the drug improved BOO and thus alleviated DO that had been caused by BOO. Improvement in DO may reflect secondary effects due to a relief of prostatic urethral tension.[23] Another mechanism of the improvement in DO is that BOO causes ischemic changes that lead to DO.[24] The α_{1A}-AR may predominate in small arteries, including bladder arteries, in some elderly patients, and an α_{1A}-AR antagonist may increase blood flow to the bladder, which may eventually alleviate DO.[25]

In pressure flow studies, silodosin significantly reduced the detrusor opening pressure, detrusor pressure at Q_{max}, BOOI and Schäfer's linear passive urethral resistance relation obstruction class. Obstruction grade in the ICS nomogram was improved in 56% of patients who initially had an obstruction or equivocal grade. In our previous study with naftopidil, detrusor pressure at Q_{max} tended to decrease (by 8.9 cm H_2O, $P = 0.09$), BOOI decreased significantly (by 14.6, $P = 0.04$), and 29%of patients showed improvements in terms of the obstruction grade in the ICS nomogram.[4] Tanaka et al.[26] reported that detrusor pressure at Q_{max} decreased significantly (by 11.3 cm H_2O, $P = 0.0015$) as a result of terazosin treatment in patients with BPH. Although the effects of silodosin on these pressure/flow parameters appeared to be greater than those of naftopidil and terazosin, the comparisons were not from a head-to-head study. Watts factor at Q_{max} did not change significantly in the treatment with silodosin, suggesting that detrusor contractility was not affected by the silodosin treatment. A similar result was reported in terms of the Watts factor in treatment with terazosin.[26]

At the end of the follow-up, 16 patients (44%) are continuing on medication with silodosin for 23.7 ± 7.2 (range 12–36) months. There were no significant differences in the baseline characteristics or changes in the urodynamic parameters between the 13 patients who showed treatment response and the remaining who did not. Adverse events were noted in six patients (17%) including three patients who withdrew because of adverse events. The most frequent adverse event was abnormal ejaculation in two patients (6%), including one patient (3%) who discontinued treatment. It has been reported that tamsulosin can also cause abnormal ejaculation due to the decrease in α_{1A}-AR mediated seminal vesicle contraction and emission, rather than true retrograde ejaculation.[1]

There were no patients with urinary retention during the whole study period. Consequently, silodosin helped at least 44% of the patients avoid invasive surgery, and LUTS could be managed safely in those patients by taking silodosin for more than 1 year.

CONCLUSION

The total IPSS, QOL score, and Q_{max} improved significantly after treatment with silodosin for 12 months. DO disappeared in 8 patients (40%) and improved in 7 (35%) patients. In pressure flow studies, the obstruction grade in the ICS nomogram improved in 15 patients (56%), and detrusor opening pressure, detrusor pressure at Q_{max}, BOOI, and Schäfer's linear passive urethral resistance relation obstruction class decreased significantly. Silodosin appears to improve DO and obstruction grade and to be effective in treating both storage and voiding dysfunction in patients with BPH. LUTS could be managed effectively for more than 1 year in at least 44% of the patients with silodosin treatment.

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