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Original Article

Comparison of 7 α_1-adrenoceptor Antagonists in Patients with Lower Urinary Tract Symptoms Associated with Benign Prostatic Hyperplasia: A Short-term Crossover Study

Tohru Araki[a], Koichi Monden[a], and Motoo Araki[b]*

[a]*Araki Urological Clinic, Kurashiki, Okayama 710–0834, Japan, and* [b]*Department of Urology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama 700–8558, Japan*

A crossover study was conducted to identify the best α_1-adrenoceptor (α_1AR) antagonist for individual patients with lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH). One hundred thirteen patients (mean age 70.8 years) were enrolled. All patients met BPH clinical study guidelines. Seven agents were utilized: tamsulosin 0.2 mg, silodosin 8 mg, urapidil 60 mg, naftopidil 50 mg, prazosin 1 mg, terazosin 2 mg, and doxazosin 1 mg. Patients were initially prescribed tamsulosin or silodosin for a week and then urapidil for a week. Two weeks later, they were prescribed the better of the 2 agents for a week and a new agent for the next week. This cycle was repeated until all 7 agents were tested. Efficacy was evaluated with the International Prostate Symptom Score. The agent rankings were doxazosin (25 [22%]), silodosin (22 [19%]), urapidil (19 [17%]), naftopidil (17 [15%]), terazosin (12 [11%]), tamsulosin (11 [10%]), prazosin (7 [6%]). Only 12 patients (11%) changed agents after the crossover study was completed. The major reason was adverse events (83%). We found that each of the 7 α_1AR antagonists has its own supporters. Further, the one-week crossover study was useful in identifying the best agent for the treatment of each individual with LUTS.

Key words: alpha-1 blockers, alpha1-adrenoceptor antagonists, lower urinary tract symptoms, benign prostatic hyperplasia, crossover study

The prevalence of lower urinary tract symptoms (LUTS) secondary to benign prostatic hyperplasia (BPH) increases with age. Moderate to severe symptoms occur in 40 and 80% of men over the ages of 60 and 80 years, respectively [1]. The 2 main medications for management of BPH are α_1-adrenoceptor (α_1AR) antagonists (blockers) and 5α-reductase inhibitors (5-ARI). 5-ARI shrinks the prostate, but this process usually takes 3 to 6 months.

α_1AR antagonists relax prostatic and bladder neck smooth muscle and relieve LUTS by improving bladder outlet obstruction. α_1AR antagonists have a rapid effect, usually within a few days for improving LUTS. Therefore, α_1AR antagonists are considered the most effective monotherapy for the relief of LUTS, irrespective of prostate size [2–4]. However, not all α_1AR antagonists work in all patients [2, 3, 5]. Quite a few dissatisfied patients come to our clinic having tried 1 or 2 α_1AR antagonists at other clinics. They often have better outcomes when they try other

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*Corresponding author. Phone:+81–86–235–7284; Fax:+81–86–231–3986
E-mail:motoosh@md.okayama-u.ac.jp (M. Araki)

α_1AR antagonists. It is well known that there are at least three α_1-adrenoceptor subtypes, α_{1A}, α_{1B} and α_{1D}, in human prostate tissues, but their ratio varies among patients [6–9]. The affinity of α_1AR antagonists is also variable; therefore, the efficacy of α_1AR antagonists differs among patients. Reports have compared 2 or 3 α_1AR antagonists or the effects of combinations of other medications (*e.g.* anticholinergics) [10], but their results are not consistent. To date, no report has compared more than 4 α_1AR antagonists [11–14]. This study is the first report to compare 7 α_1AR antagonists.

Compatibility between patients and agents may be defined by the genetic background [9]. Adverse events are also crucial factors for patients. If one agent is very effective but its associated adverse events are not tolerable, it is not the best agent. As clinicians, we would like to prescribe the best agent as soon as possible. We have utilized a crossover method to identify the best agent among 7 α_1AR antagonists. Here, we report the results and benefits of this method.

Materials and Methods

One hundred and forty-eight patients were included in this study. Thirty-five patients were excluded from this study: 4 patients dropped out from the study because they found satisfaction with an agent before the crossover study completed, and 31 patients had features that were not compatible with clinical study guidelines. Therefore, 113 patients (mean age, 70.8 years; range, 50–80 years) with LUTS suggestive of BPH were enrolled in the crossover study. All patients met BPH clinical study guidelines: ≥ 50 years of age, International Prostate Symptom Score (IPSS) ≥ 8, quality of life (QOL) index ≥ 2, prostate size ≥ 20 mL, maximum urinary flow rate (Qmax) <15 mL/s, postvoid residual volume (PVR) <100 mL. Qmax was analyzed when the voided volume was ≥ 130 mL (N = 94). Seven agents were utilized in this study: tamsulosin 0.2 mg once daily, silodosin 4 mg twice daily, urapidil 30 mg twice daily, naftopidil 50 mg once daily, prazosin 0.5 mg twice daily, terazosin 1 mg twice daily, and doxazosin 1 mg once daily (Table 1). Each of these doses is the recommended dose in Japanese men. No generic agents were used.

Patients were initially prescribed tamsulosin or silodosin for a week and urapidil for the next week (tamsulosin, silodosin and naftopidil cannot be prescribed at the same time according to the Japanese health care system). Two weeks later, they were prescribed the better of those agents for a week and a new agent for the following week. This cycle was repeated until all 7 agents were tested. There was no withdrawal period (washout) when the patients switched agents. The superiority of agents was based on patient satisfaction. If it was difficult to judge superiority, the agents were judged as "equal."

Table 1 α_1-adrenoceptor antagonists tested in this study

		Dose		Subtype selectivity
1	Prazosin (Pra)	0.5 mg	x2/day	Non-selective
2	Urapidil (Ura)	30 mg	x2/day	Non-selective
3	Terazosin (Tera)	1 mg	x2/day	Non-selective
4	Doxazosin (Dox)	1 mg	x1/day	Non-selective
5	Tamsulosin (Tam)	0.2 mg	x1/day	α1A > D >> B
6	Naftopidil (Naf)	50 mg	x1/day	α1D > A >> B
7	Silodosin (Silo)	4 mg	x2/day	α1A >> D, B

Efficacy was evaluated with the IPSS after the patient had been receiving therapy with the self-chosen best agent for 8 weeks. Prostate volume was measured by transrectal ultrasound (TRUS). Qmax and PVR were also recorded. During the study, other medications were not changed.

Values are reported as the means $\pm$ standard deviations (SDs). The Wilcoxon signed rank test was used to compare the pre and post treatment IPSS, QOL, Qmax, and PVR, and a p-value less than 0.05 was considered significant. Institutional review board approval was obtained for this study (AUC IRB No. 2).

Results

Patient characteristics are summarized in Table 2. The mean IPSS was 18.0 ± 6.4, and the mean QOL index was 4.7 ± 1.1. The mean prostate volume was 44.1 ± 23.7mL. The mean Qmax was 10.7 ± 4.1 mL/s. The mean residual urine volume was 36.0 ± 30.4 mL.

At the end of the crossover study, there were 183 rankings of best agents, because some patients ranked ≥ 2 agents as "equal." The agent rankings were doxazosin (40 [22%]), silodosin (36 [20%]), terazosin (31 [17%]), urapidil (23 [13%]), prazosin (20 [11%]), naftopidil (19 [10%]), and tamsulosin (14 [8%])

(Fig. 1A). On the other hand, the order of the lower-ranked agents (Nos. 4–7) was almost the reverse of the No. 1-ranked agents (data not shown).

Out of 183 agents chosen as best, the 113 agents the patients continued to take were slightly different. They were silodosin (26 [23%]), doxazosin (24 [21%]), urapidil (18 [16%]), terazosin (15 [13%]), naftopidil (12 [11%]), tamsulosin (11 [10%]), and prazosin (7 [6%]) (Fig. 1B). The major reasons they selected an "equal" No. 1 agent were the following: 1. Adverse events (orthostatic hypotension) on terazosin, prazosin and doxazosin, 2. Preference for once-daily agents over twice-daily agents.

A few months after they selected their No. 1 agent at the end of the crossover study, 12 patients (11%) changed agents for various reasons. As a result, silodosin decreased by 4%, terazosin decreased by 2%, and naftopidil increased by 4% (Fig. 1C). Each agent had its own supporters. The reasons patients changed agents were the following:

1. Adverse events (8) (A. orthostatic hypotension on doxazosin (1), terazosin (1), prazosin (1), and silodosin (1); B. nocturia (1) and rough finger (1) on terazosin; C. nasal stuffiness (1) and retrograde ejaculation (1) on silodosin).
2. Insufficient effect with naftopidil (1) and silodosin (1).
3. I and II (orthostatic hypotension and insufficient effect with doxazosin (1), retrograde ejaculation and insufficient effect on silodosin (1)).

The IPSS was analyzed in 97 patients who completed it at baseline and 8 weeks after receiving the self-chosen best agent (Table 3). The mean IPSS decreased by 3.8, and the mean QOL index decreased by 1.6. Each symptom domain analysis demonstrated that voiding symptoms (intermittency, weak stream, straining) decreased by 1.4, storage symptoms (frequency, urgency, nocturia) decreased by 1.5, and incomplete emptying decreased by 0.9. Nocturia alone decreased by 0.6. There were 24 to 61% of unimproved patients on IPSS, QOL or each IPSS domain. Qmax was analyzed in 64 patients who met the criteria (voided volume $\geq$ 130 mL). Qmax significantly increased by 1.5 mL/s. PVR (78 patients) decreased by 1.1 mL, but it was not significant ($p = 0.93$).

Table 4 shows the IPSS change stratified by

Table 2 Patient characteristics

	N	Mean ± SD (range)
Age (years)	113	70.8 ± 8.6 (50–80)
IPSS	113	18.0 ± 6.4 (8–35)
QOL score	113	4.7 ± 1.1 (2–6)
Prostate volume (mL, TRUS)	113	44.1 ± 23.7 (20–153)
Qmax (mL/s)*	94	10.7 ± 4.1 (3.2–14.5)
Residual volume (mL)	113	36.0 ± 30.4 (0–95)

IPSS, International Prostate Symptom Score; QOL, quality of life; SD, standard deviation; TRUS, transrectal ultrasound.
*Qmax was analyzed when urine volume was ≥130 mL.

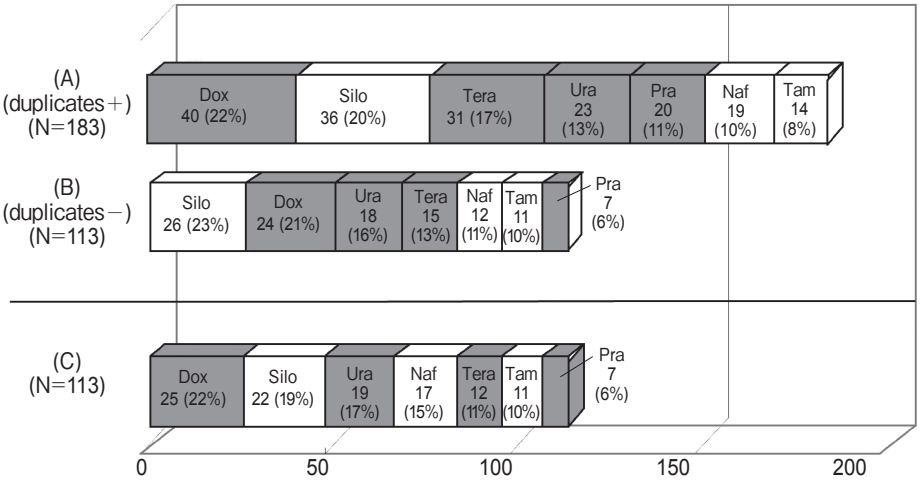

Fig. 1 Best α_1-adrenoceptor antagonists. **A**, 183 agents including duplicates; **B**, Best agent patients selected to continue at the end of the crossover study; **C**, α_1AR antagonists a few months after patients took (B) agents. Non-selective agents are in gray and selective are in white. Prazosin (Pra), urapidil (Ura), terazosin (Tera), doxazosin (Dox), tamsulosin (Tam), naftopidil (Naf), silodosin (Silo).

Table 3 IPSS and objective parameters at baseline and after 8 weeks of administration of the agent each patient selected

(1) IPSS

IPSS domain					1	2	3	4	5	6	7
	IPSS	QOL score	Voiding symptoms*	Storage symptoms**	Incomplete emptying	Frequency	Intermittency	Urgency	Weak stream	Straining	Nocturia
a. Baseline											
mean±SD	18±6.3	4.8±1.1	8.6±3.5	7.0±3.5	2.4±1.8	2.8±1.8	2.3±1.8	1.7±1.6	4.2±1.1	2.1±1.8	2.5±1.3
range	8－35	2－6	0－15	1－15	0－5	0－5	0－5	0－5	0－5	0－5	0－5
b. After treatment											
mean±SD	14.2±5.8	3.1±1.4	7.2±3.2	5.5±2.8	1.5±1.3	2.1±1.3	1.9±1.5	1.5±1.1	3.7±1.3	1.6±1.3	1.9±1.1
range	3－28	0－6	1－15	1－12	0－5	0－5	0－5	0－4	0－5	0－5	0－5
c. Improvement	3.8±6.3	1.6±1.5	1.4±3.3	1.5±3.4	0.9±1.8	0.7±1.7	0.4±1.8	0.2±1.6	0.5±1.4	0.5±1.6	0.6±1.1
(%)	21	35	16	21	38	25	17	12	12	24	24
d. Unimproved patients (%)***	30	24	37	39	42	43	57	61	59	59	52
P value (a v.s. b)	<0.0001	<0.0001	<0.0001	<0.001	<0.0001	<0.001	<0.05	0.23	<0.001	<0.01	<0.0001

*Voiding symptoms, IPSS domain (3, 5, 6); **Storage symptoms, IPSS domain (2, 4, 7); ***Unimproved patients, patients with unchanged or increased IPSS score.
N＝97

(2) Maximum flow rate (Qmax (mL/sec))

a. Baseline	
mean±SD	9.3±3.1
range	2.7－14
b. After treatment	
mean±SD	10.8±2.9
range	3.7－14
c. Improvement	1.5±3.5
(%)	16
P value (a v.s. b)	<0.0001

N＝64, who voided ≥130 mL both at baseline and after treatment

(3) Residual Urine Volume (mL)

a. Baseline	
mean±SD	36.6±32.4
range	0－95
b. After treatment	
mean±SD	35.5±27.3
range	0－95
c. Improvement	1.1±33.8
(%)	3
P value (a v.s. b)	0.93

N＝78

agent. Total IPSS improvements were considerable (＞4.5) with doxazosin, terazosin and tamsulosin. QOL index improvement was considerable (＞1.8) with prazosin, doxazosin and urapidil. Voiding symptom improvements were considerable with naftopidil and silodosin. Storage symptom improvements were considerable with tamsulosin, terazosin and doxazosin.

Adverse events were identified on 86 occasions in 49 patients (Table 5). All adverse events were resolved by discontinuing the agents. The incidence of adverse events was highest with silodosin (24%), and retrograde ejaculation accounted for 44% of them. Orthostatic hypotension was seen frequently with terazosin, prazosin, urapidil and doxazosin. Only 4 of 16 patients with retrograde ejaculation discontinued their agents. However, all patients with other adverse events discontinued their agents.

Discussion

There are currently 8 α_1AR antagonists available worldwide. Alfuzosin is not available in Japan. Urapidil and naftopidil are not available in western countries. Djavan *et al.* carried out a meta-analysis of 4 α_1AR antagonists (tamsulosin, doxazosin, terazosin, and alfuzosin). They concluded that the efficacy of these 4 α_1AR antagonists was similar [15]. American Urological Association (AUA) and European Urological Association (EUA) guidelines support these data [3, 5]. However, their efficacy differs among individuals. Therefore, in daily clinical practice, we switch agents when one is not effective. However, existing crossover studies are based on up to 3 agents. Shouldn't we test all available agents? This question led us to conduct the current study.

Table 4 IPSS change by different α_1-adrenoceptor antagonists at baseline and after 8 weeks of administration of the patient-selected agent

IPSS domain					1	2	3	4	5	6	7
	IPSS	QOL score	Voiding symptoms	Storage symptoms	Incomplete emptying	Frequency	Intermittency	Urgency	Weak stream	Straining	Nocturia
All (N=97)	−3.8±6.3	−1.6±1.5	−1.4±3.3	−1.5±3.4	−0.9±1.8	−0.7±1.7	−0.4±1.8	−0.2±1.6	−0.5±1.4	−0.5±1.6	−0.6±1.1
Silodosin (N=24)	−2.5±5.8	−1.1±1.4	−1.9±2.9	0.0±3.1	−0.7±1.6	+0.1±1.5	−0.3±1.8	+0.2±1.6	−0.8±1.0	−0.8±1.0	−0.3±1.0
Doxazosin (N=22)	−5.1±6.6	−2.1±1.2	−1.5±3.3	−2.4±3.7	−1.2±1.6	−1.1±1.7	−0.7±1.6	−0.5±1.9	0.0±1.7	−0.8±1.8	−0.8±1.1
Urapidil (N=14)	−3.0±5.7	−1.9±1.6	−0.9±3.6	−1.3±2.9	−0.9±1.7	−0.9±1.5	−0.4±2.1	−0.1±1.4	−0.7±1.1	+0.2±1.3	−0.2±1.3
Terazosin (N=14)	−4.8±7.5	−1.4±1.5	−0.9±3.1	−2.6±4.2	−1.4±2.0	−0.8±2.0	−0.5±1.9	−0.8±1.6	0.0±1.0	−0.4±1.5	−1.0±1.0
Tamsulosin (N=9)	−4.7±7.2	−1.7±1.5	−1.2±4.2	−2.9±3.1	−0.6±2.0	−1.3±1.2	−0.1±2.4	−0.4±1.5	−1.1±1.6	0.0±1.7	−1.1±1.3
Naftopidil (N=8)	−2.8±6.0	−1.6±1.9	−2.6±3.9	+0.1±2.5	−0.3±1.0	+0.3±1.4	−0.5±1.8	+0.5±1.3	−1.1±1.5	−1.0±1.6	−0.6±1.1
Prazosin (N=6)	−3.2±6.6	−2.2±1.6	−1.0±2.9	−1.7±2.7	−0.5±3.1	−1.2±1.3	+0.2±1.6	−0.5±1.6	−0.7±0.6	−0.5±1.6	0.0±0.6

Table 5 Adverse events

	N (%)	Cardiovascular	Gastrointestinal	Retrograde ejaculation	Overactive bladder	Others
Silodosin	27 (24%)	2	6	12	1	6
Terazosin	14 (12%)	8	1	2	1	2
Prazosin	12 (11%)	7	2	1	1	1
Urapidil	10 (9%)	5	2	2	1	0
Doxazosin	9 (8%)	6	1	1	1	0
Tamsulosin	8 (7%)	3	1	2	1	0
Naftopidil	7 (6%)	4	1	2	0	0
Total	86/791*(11%)	35	14	22	6	9

(49 patients, 86 incidents)
*7 (agents) × 113 (patients) = 791

A patient evaluates a medication based on what bothers him the most. For example, when nocturia is the main problem, the patient will not be happy if his urinary stream improved but his nocturia did not change. Objective evaluations, such as Qmax and PVR change, depend on patient health status and storage volume. Therefore, we utilized patient satisfaction as the primary evaluation. To determine the best agents in a short period of time, the test period per agent was set at 1 week, and there was no wash-out period.

We learned 2 things from this study:

1. There were no agents without any supporters.

Kojima *et al.* quantified α_1AR subtype expression in the prostate of men with LUTS by reverse transcriptase-polymerase chain reaction (RT-PCR) [8, 9]. They demonstrated that the mRNA expression levels of α_1AR-subtypes in BPH tissue differed among patients and that genetic differences were responsible for the diverse responses to subtype-selective α_1AR antagonists. That report gives our study a scientific background. However, our results demonstrated that there was no difference in patient choice of non-selective and selective agents (Table 1, Fig. 1). In fact, there are more non-selective agents in the higher ranks. For example, Nos. 1, 3, 4, and 5 in Fig. 1A

are non-selective agents. This suggests that the mixed ratio of α_{1A}, α_{1B} and α_{1D} may be more important than the selectivity of subtypes. More studies are needed to elucidate the reason for this result.

2. A one-week crossover study is useful for patients to select the best agent, although it has some limitations with regard to the determination of adverse events.

Usually 4 to 12 weeks are used to evaluate α_1AR antagonists [2, 3, 5, 11–20]. A one-week test may give an advantage to fast-working agents. α_1AR antagonists become effective within 1 to 7 days [2, 15, 17–22]. The $t_{1/2}$ of α_1AR antagonists is as short as < 20 h. Therefore, a 1-week crossover study does not necessarily affect patient evaluation. However, one week is too short to evaluate adverse events. There were 12 patients (11%) who changed agents a few months after the end of the crossover study. Ten (83%) changed because of adverse events. This fact supports the conclusion that our study design is sufficient or even better at identifying the most effective agent without being affected by adverse events. In other words, patients can select the best agent based on a 1-week crossover study. If adverse events appear thereafter, they can switch to the second best agent, and the frequency of this switch may be as low as 11%.

Another reason we used a 1-week crossover study is that the safety of α_1AR antagonists is well known, and their associated adverse events other than orthostatic hypotension are trivial [2, 3, 11–13]. Even the rate of orthostatic hypotension in a large cohort study (N = 53,824) was between 3 and 4 per 10, 000 person-days [23]. The adverse events were also trivial in our study, as expected (Table 5).

Recently, combination therapies with α_1AR antagonists and 5α-reductase inhibitors have been reported [24, 25]. The MTOPS study demonstrated that doxazosin and finasteride reduced the long-term risk of acute urinary retention and the need for invasive therapy [24]. The CombAT study demonstrated that dutasteride and tamsulosin provided significantly greater symptom benefit than either monotherapy at 4 years [26]. The effects of 5α-reductase inhibitors also vary among individuals. When combination therapy is utilized, a crossover test of α1AR antagonists may benefit patients.

Our study focused on patient satisfaction. Patient satisfaction is one of the ultimate goals in clinical practice. We often see dissatisfied patients who have been on ineffective α_1AR antagonists for years. If patients are not satisfied with one agent, we should try others. Our crossover study is useful for identifying the best agents in a typical practice. In conclusion, the optimal α_1AR antagonist varies among patients. Each of the 7 α_1AR antagonists had its own supporters. A one-week crossover study was useful and efficient in identifying the best agent for each individual in the treatment of LUTS suggestive of BPH.

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