Management of benign prostatic hyperplasia with silodosin

Tomonori Yamanishi¹
Tomoya Mizuno¹
Takao Kamai¹
Ken-Ichiro Yoshida¹
Ryuji Sakakibara²
Tomoyuki Uchiyama³

¹Department of Urology, Dokkyo Medical University, Tochigi, Japan;
²Department of Neurology, Sakura Hospital, Toho University, Toho, Japan;
³Department of Neurology, Chiba University, Chiba, Japan

Abstract: It has been reported that blockade of $\alpha_{1A}$-adrenoceptor (AR) relieves bladder outlet obstruction, while blockade of $\alpha_{1D}$-AR is believed to alleviate storage symptoms due to detrusor overactivity. Silodosin, $(-)$-1-(3-hydroxypropyl)-5-[(2R)-2-({2-[2-(2,2,2-trifluoroethoxy) phenoxy]ethyl}amino)propyl]-2,3-dihydro-1H-indole-7-carboxamide, is a new $\alpha_{1A}$-AR selective antagonist. Silodosin is highly selective for the $\alpha_{1A}$-AR subtype, showing an affinity for the $\alpha_{1A}$-AR that is 583- and 55.5-fold higher than its affinity for the $\alpha_{1B}$- and $\alpha_{1D}$-ARs, respectively.

In randomized, double-blind, placebo-controlled phase III studies performed in Japan and the United States, silodosin has been shown to be effective for both storage and voiding symptoms associated with benign prostatic hyperplasia. Early effects of silodosin (after 2–6 hours or day 1) on lower urinary tract symptoms have also been reported. In urodynamic studies, detrusor overactivity disappeared in 40% and improved in 35% of patients after administration. In pressure flow studies, the grade of obstruction on the International Continence Society nomogram showed improvement in 56% of patients. The rate of adverse events in the silodosin, tamsulosin and placebo groups was 88.6%, 82.3%, and 71.6%, respectively. The most common adverse event was (mostly mild) abnormal ejaculation (28.1%). However, few patients (2.8%) discontinued silodosin because of abnormal ejaculation. Orthostatic hypotension showed a similar incidence in the silodosin (2.6%) and placebo (1.5%) groups. In conclusion, silodosin improves detrusor overactivity and obstruction and thus may be effective for both storage and voiding symptoms in patients with benign prostatic hyperplasia.

Keywords: alpha-blocker, silodosin, benign prostatic hyperplasia, lower urinary tract symptoms

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 impaired quality of life. BPH is present in 50% of men aged over 50 years, and in about 90% of those over the age of 80 years.¹⁻³ BPH is a progressive condition. Investigation of the natural history of BPH has demonstrated that there is an average annual increase of the International Prostate Symptom Score (IPSS) by 0.18 points, an annual decrease of the maximum flow rate (Qmax) by 2%, and a median increase of prostate volume by 1.9% annually.⁴

The causes of LUTS associated with BPH (LUTS/BPH) include mechanical compression of the urethra due to enlargement of the prostate (mechanical obstruction), and increased urethral resistance induced by an increment of smooth muscle tone due to increased activity of the sympathetic nerves in the lower urinary tract, including prostatic tissue, posterior urethra and bladder neck (functional obstruction).¹
Because baseline tone is present in prostate smooth muscle (due to its rich sympathetic innervation), blockade of prostatic $\alpha_1$-adrenoceptor (AR) results in prostate smooth muscle relaxation, and thus alleviates the dynamic component of BPH.\(^1\)

There are various options for the treatment of BPH, including transurethral resection of the prostate,\(^3,9\) minimally invasive therapies for BPH including microwave thermotherapy,\(^7\) holmium:YAG laser prostatectomy,\(^8,9\) or transurethral resection in saline (TURIS),\(^10,11\) and pharmacotherapy. Among these options, medical therapy with an $\alpha_1$-AR antagonist is widely used as a conservative treatment for LUTS/BPH or neurogenic bladder dysfunction.\(^12-17\) It has been reported that $\alpha_1$-AR antagonists are effective for both storage and voiding symptoms by decreasing bladder outlet obstruction and alleviating detrusor overactivity.\(^14,18-20\)

The adrenergic receptors were originally divided into $\alpha$-AR and $\beta$-AR categories, but application of molecular biological methods has since confirmed nine total AR subtypes: $\alpha_{1A}$, $\alpha_{1B}$, $\alpha_{2A}$, $\alpha_{2B}$, $\alpha_{2C}$, $\beta_1$, $\beta_2$, and $\beta_3$.\(^21,22\)

It was reported that the $\alpha_{1A}$-AR subtype is predominant in the prostate,\(^23\) but recent studies have detected the expression of both $\alpha_{1A}$ and $\alpha_{1D}$-ARs in human prostate tissue.\(^24-26\) It has been reported that $\alpha_{1A}$-AR blockade relieves bladder outlet obstruction, while the blocking the $\alpha_{1D}$-AR is believed to alleviate storage symptoms due to detrusor overactivity.\(^1\) However, silodosin (KMD-3213 or (±)-1-(3-hydroxypropyl)-5-[(2R)-2-(2-[2-(2,2,2trifluoroethoxy)phenoxy]ethyl)amino)propyl]-2,3-dihydro-1H-indole-7-carboxamide], a new $\alpha_{1A}$-AR selective antagonist, has been reported to be effective for both storage and voiding symptoms in BPH patients.\(^27,28\)

This suggests that the $\alpha_{1A}$-AR alone is responsible for both storage and voiding symptoms in LUTS/BPH.

This review discusses the efficacy of silodosin for the treatment of LUTS/BPH, as well as the role of the $\alpha_{1A}$-AR for storage and voiding dysfunction in BPH.

**Pharmacology, mode of action, and pharmacokinetics of silodosin**

Silodosin is highly selective for the $\alpha_{1A}$-AR subtype, showing an affinity for the $\alpha_{1A}$-AR that is 583- and 55.5-fold higher than its affinity for the $\alpha_{1B}$- and $\alpha_{1D}$-ARs, respectively (Table 1).\(^29,30\) The selectivity of silodosin for the $\alpha_{1A}$-AR versus the $\alpha_{1B}$-AR was reported to be 38-fold greater than that of tamsulosin hydrochloride in studies using Chinese hamster ovary cells expressing three human $\alpha_1$-AR subtypes.\(^27,29\) Evaluation of the uroselectivity of silodosin and comparison with that of tamsulosin and prazosin in vivo has shown that silodosin demonstrates good uroselectivity (determined from the ratio of the dose reducing intraurethral pressure to that decreasing blood pressure), in rats and dogs.\(^31,32\)

Murata and colleagues\(^33\) performed binding experiments with [\(^3\)H]-KMD (silodosin) and [\(^3\)H]-prazosin using human prostatic or aortic membranes and found that [\(^3\)H]-KMD bound to prostatic membranes with a higher affinity than [\(^3\)H]-prazosin, but did not bind strongly to aortic membranes. Investigation of competition with [\(^3\)H]-prazosin revealed that silodosin had over 200-fold higher affinity for human prostatic membranes than for aortic membranes. In functional experiments, silodosin exhibited more than 100-fold higher affinity for human prostate tissue than for the mesenteric artery. By measuring the specific binding of [\(^3\)H]prazosin to the rat prostate after oral administration of silodosin, Yamada and colleagues\(^34\) estimated that $\alpha_{1A}$-AR occupancy in the human prostate would be around 60%–70% at 1–6 hours after the oral administration of silodosin at doses of 3.0, 8.1, and 16.1 $\mu$mol. Thereafter, receptor occupancy decreased to 24% (8.1 $\mu$mol) and 54% (16.1 $\mu$mol) by 24 hours. Despite there being almost two orders of difference in the free plasma concentration achieved by clinically effective oral dosages of silodosin, tamsulosin, and terazosin, there is comparable prostatic $\alpha_1$-AR occupancy by these drugs.

**Efficacy of silodosin in the treatment of BPH**

In Japan, 8 mg/day (4 mg twice daily) was considered to be the recommended clinical dose of silodosin, based on the results of phase II and phase III trials of 4 mg/day versus 8 mg/day in patients with LUTS/BPH.\(^27\) In the United States, a dosage of 8 mg once daily was used in phase III studies.\(^28\)

Kawabe and colleagues\(^37\) conducted a randomized, double-blind, placebo-controlled study of silodosin for BPH at 88 centers in Japan. Inclusion criteria were men aged $\geq$ 50 years with an IPSS of $\geq$ 8, a quality-of-life (QoL)
Thus blockade of $\alpha_{1A}$-ARs can lead to smooth muscle relaxation in these areas, resulting in improved symptoms and urinary flow rates. On the other hand, $\alpha_{1A}$-ARs are largely located on vascular smooth muscle, so antagonizing these receptors can cause relaxation of this tissue, and thus impair the cardiovascular mechanisms involved in the regulation of blood pressure. $\alpha_{1A}$-AR expression increases by two-fold in representative (mammary) arteries with aging, with
the ratio of $\alpha_2/\alpha_1$ increasing, whereas no alteration occurs in veins. A previous meta-analysis showed that the effects of nonselective $\alpha_1$-AR antagonists (terazosin or doxazosin), and those of the $\alpha_1/\alpha_1$-AR antagonist (tamsulosin) were similar, although there was a difference with respect to cardiovascular side effects.\textsuperscript{1,18} Therefore, agents with a high selectivity for the $\alpha_1/\alpha_1$-AR or $\alpha_1$-AR may have beneficial effects on LUTS/BPH with minimal effects on blood pressure, as occurs with nonselective $\alpha_1$-AR antagonists.

It has been reported that blockade of $\alpha_1$-AR relieves bladder outlet obstruction, while blockade of $\alpha_1$-AR alleviates storage symptoms due to detrusor overactivity.\textsuperscript{1} The role of $\alpha_{1D}$-AR in detrusor overactivity can be explained as follows. Predominance of $\alpha_{1D}$-AR over $\alpha_1$-ARs at the mRNA and protein levels has been reported in human detrusor.\textsuperscript{45} An increase in $\alpha_{1D}$-AR mRNA and protein expression was reported in obstructed and hypertrophied rat bladder, suggesting a possible role of $\alpha_{1D}$-AR in controlling detrusor overactivity.\textsuperscript{46} However, the expression of $\alpha_1$-ARs has been reported to be too low to produce contraction in normal and obstructed human bladders.\textsuperscript{47} Another possible mechanism by which $\alpha_1$-AR antagonists could alleviate detrusor overactivity may be inhibition of the micturition reflex by acting on $\alpha_{1A}$-ARs in the lumbosacral spinal cord.\textsuperscript{48,49} Although the expression of $\alpha_{1D}$-AR seems to be predominant in the human spinal cord,\textsuperscript{44} intrathecal injection of $\alpha_{1D}$- or $\alpha_{1L}$-AR selective antagonists inhibits the micturition reflex in the rat.\textsuperscript{49,50} Moreover, it has not been confirmed whether the commercially available $\alpha_1$-AR antagonists are distributed to the spinal cord. Consequently, it is unclear whether the $\alpha_{1A}$-AR is the only AR subtype responsible for detrusor overactivity.

It has been reported that nocturia responds to $\alpha_{1D}$-AR blockade. In a cross-over study comparing tamsulosin ($\alpha_{1A}$-AR $>$ $\alpha_{1D}$-AR) with naftopidil ($\alpha_{1D}$-AR $>$ $\alpha_{1A}$-AR), relief of storage symptoms was significantly better in subjects given naftopidil.\textsuperscript{1,51–54} However, this issue is still controversial and different results have been reported by other authors.\textsuperscript{1,55,56} Recently, Kira and colleagues\textsuperscript{57} studied the efficacy of silodosin in 85 patients with LUTS/BPH who were resistant to tamsulosin (n = 39) or naftopidil (n = 46), and reported a rapid and significant decrease in scores of decreased urinary stream and nocturia (both $p < 0.01$), which were the most bothersome symptoms among IPSS. All of the clinically available $\alpha_1$-AR antagonists have $\alpha_{1A}$-AR antagonist activity to a greater or lesser extent, so the effect of these drugs on storage symptoms and nocturia may not be solely related to blockade of the $\alpha_{1D}$-AR.

We previously performed urodynamic studies of naftopidil, an $\alpha_{1A}/\alpha_{1D}$-adrenoceptor selective antagonist, and found that detrusor overactivity disappeared in three (21%) and improved in five (36%) of 14 patients with detrusor overactivity.\textsuperscript{20} Consequently, the effects of silodosin on detrusor overactivity appeared similar to those of naftopidil.\textsuperscript{20,38} Since the affinity of silodosin for the $\alpha_{1A}$-AR is 583- and 55.5-fold higher than its affinity for the $\alpha_{1B}$- and 1ARs, respectively,\textsuperscript{29} most of the effect of this drug at the clinical doses should be due to $\alpha_{1A}$-AR blockade, suggesting that $\alpha_{1A}$-AR is the predominant subtype involved in detrusor overactivity in BPH. One of the reasons that $\alpha_{1A}$-AR antagonists improve both storage and voiding dysfunction may be that bladder outlet obstruction is reduced and this alleviates detrusor overactivity that was caused by obstruction. Improvement in detrusor overactivity may reflect secondary effects due to a relief of prostatic urethral tension.\textsuperscript{40} Another possible mechanism for the improvement of detrusor overactivity is that obstruction causes ischemia (and reperfusion) that leads to detrusor overactivity and bladder dysfunction.\textsuperscript{58–60} The $\alpha_{1A}$-AR may predominate in the small arteries, including the bladder arteries of elderly patients and $\alpha_{1A}$-AR antagonist may therefore increase blood flow to the bladder and thus alleviate detrusor overactivity.\textsuperscript{43,44}

Previously, the efficacy of selective $\alpha_{1A}$-AR antagonist has been questioned because RS-17053, N-[2-(2-cyclopropylmethoxy)ethyl]-5-chloro-alpha, alpha-dimethyl11H-indole-3-ethanamine hydrochloride, a selective $\alpha_{1A}$-AR antagonist, effectively relaxed prostate smooth muscle and increased urine flow in men, but did not relieve LUTS.\textsuperscript{1} The difference of efficacy between silodosin and RS-17053 may be due to the difference in their affinity for the $\alpha_{1A}$-AR. Drugs such as prazosin, RS-17053 and 5-methylurapidil show low affinity for the $\alpha_{1L}$-AR, but silodosin and tamsulosin show high affinity. The $\alpha_{1L}$-AR has pharmacological properties that distinguish it from the three classical $\alpha_1$-ARs ($\alpha_{1A}$, $\alpha_{1B}$, and $\alpha_{1D}$-AR). Muramatsu and colleagues\textsuperscript{61} studied radioligand binding and functional bioassay experiments on the cerebral cortex, vas deferens and prostate of wild-type (WT) mice and $\alpha_{1A}$-AR, $\alpha_{1D}$-AR and $\alpha_{1L}$-AR gene knockout (AKO, BKO and DKO) mice. They found that $[^{3}H]$-silodosin bound to intact segments of the cerebral cortex, vas deferens, and prostate from WT, BKO, and DKO mice, but not AKO mice. The binding sites were composed of two components with high and low affinities for prazosin or RS-17053, indicating the pharmacological profiles of $\alpha_{1A}$-AR and $\alpha_{1L}$-AR. In membrane preparations of WT mouse cortex, $[^{3}H]$-silodosin bound to a single population of prazosin high-affinity sites.
suggested the presence of $\alpha_{1\text{A}}$-ARs alone. In contrast, $[^{3}H]$-prazosin bound to two components having $\alpha_{1\text{A}}$-AR and $\alpha_{1\text{B}}$-AR profiles in intact segments of WT and DKO mouse cortices, but AKO mice lacked $\alpha_{1\text{A}}$-AR profiles and BKO mice lacked $\alpha_{1\text{B}}$-AR profiles. Noradrenaline produces contraction through $\alpha_{1\text{L}}$-ARs in the vas deferens and prostate of WT, BKO, and DKO mice. However, such contraction is abolished or markedly attenuated in AKO mice. The $\alpha_{1\text{L}}$-AR has been identified as binding and functional entities in WT, BKO, and DKO mice, but not in AKO mice, suggesting that $\alpha_{1\text{L}}$-AR is one phenotype derived from the $\alpha_{1\text{A}}$-AR gene. Morishima and colleagues performed in binding assays with tissue segments and membrane preparations of human prostates using $[^{3}H]$-silodosin, and reported that the $[^{3}H]$-silodosin binding sites in intact segments were divided into two distinct types with different affinities for prazosin and RS-17053, while the binding sites in membrane preparations showed single high affinity for these drugs. They concluded that the $\alpha_{1\text{L}}$-AR and $\alpha_{1\text{A}}$-AR coexist as pharmacologically distinct entities in intact tissues, but not in crude membrane preparations. In functional experiments, silodosin and tamsulosin potently inhibited the contractile response to noradrenaline, while prazosin, RS-17053 and BMY 7378 showed weak antagonism, suggesting that the $\alpha_{1\text{A}}$-AR involved in the contractile response to noradrenaline is the $\alpha_{1\text{L}}$-AR subtype.

Safety and tolerability of silodosin

In a randomized, double-blind, placebo-controlled study reported by Kawabe and colleagues, the rates of adverse events and drug-related adverse events in the silodosin, tamsulosin, and placebo groups were 88.6%, 82.3%, and 71.6%, respectively, and 69.7%, 47.4%, and 36.4%, respectively. The most common adverse event in the silodosin group was abnormal ejaculation, which occurred more often in this group than in the tamsulosin group (22.3% vs 1.6%).

In two randomized, placebo controlled, phase III studies of silodosin performed in the United States, the most common treatment-emergent adverse event was (mostly mild) retrograde (abnormal) ejaculation (28.1% for silodosin versus 0.9% for placebo), followed by dizziness (3.2%), diarrhea (2.6%), orthostatic hypotension (2.6%) headache (2.4%), nasopharyngitis (2.4%), and nasal congestion (2.1%). However, few patients receiving silodosin (2.8%) discontinued because of retrograde ejaculation. Proportions of patients with treatment-emergent orthostatic hypotension were similar for silodosin (2.6%) and placebo (1.5%). It has been reported that tamsulosin can also cause abnormal ejaculation. The cause of abnormal ejaculation has been reported to be due to decrease of emission caused by decreasing $\alpha_{1\text{A}}$-mediated seminal vesicle contraction, or an impaired function of the vas deferens, rather than producing true retrograde ejaculation.

Intraoperative floppy iris syndrome (IFIS) is characterized by small pupils and iris billowing during cataract surgery in patients taking $\alpha_{1}$-AR antagonists. The overall prevalence of IFIS is 1%–2% among patients undergoing cataract surgery, but it occurs in 43%–63% of patients taking tamsulosin. However, all $\alpha_{1}$-AR antagonists are capable of producing these effects by blockade of $\alpha_{1}$-ARs in the iris dilator muscle, and IFIS may occur at a high incidence during silodosin administration. All of the effects of $\alpha_{1}$-AR antagonists on pupil size resolved within eight hours of administration in the white albino rabbit model. Iris hooks are required to dilate the pupil when IFIS occurs, so patients planning cataract surgery should inform their ophthalmologist that they are taking $\alpha_{1}$-AR antagonists.

Conclusions

Silodosin improves detrusor overactivity and reduces the grade of obstruction, and thus may be effective for both storage and voiding dysfunction for the treatment of LUTS/BPH. Incidence of orthostatic hypotension was low, and the most common adverse event was mild abnormal ejaculation and thus could be a first-line treatment of LUTS/BPH.

Disclosures

The authors report no conflicts of interest in this work.

References


