The Application of Alpha-adrenergic Receptor Blocker in Lower Urinary Tract Dysfunction that is beyond Benign Prostatic Hyperplasia

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The main use of alpha-1 (α-1) adrenergic receptor (AR) antagonists in urology has been to treat lower urinary tract symptoms (LUTS) in men who may have benign prostatic hyperplasia (BPH). Recently, clinical results have demonstrated that α-1 AR blockers have beneficial effects when treating lower urinary tract dysfunctions other than BPH. This paper reviews current knowledge and the applications of α-1 AR blockers in this field.

THE AUTONOMIC NERVOUS SYSTEM AND LOWER URINARY TRACT FUNCTION

The micturition process is innervated by parasympathetic nerves (detrusor contractility), sympathetic nerves (bladder outlet relaxation) and somatic nerves (pudendal nerve, urethral sphincter relaxation). The beneficial effects of α-1 AR blockers are assumed to be associated with the relaxation of prostatic and urethral smooth muscle. Recent investigations have also demonstrated that α-1 AR exists not only in the bladder and urethra, but also in the peripheral ganglia, nerve terminals and central nervous system, which could potentially influence LUTS [1]. The role of sympathetic nerves in bladder filling has recently been emphasized. It has been postulated that α-adrenergic nerves inhibit the reflex activation of detrusor during bladder filling, while β-adrenergic nerves have been demonstrated to relax the derusor. Experimental results support that the hypothesis that released norepinephrine exerts an inhibitory effect on detrusor function via adrenergic innervation [2].

α- AR ANTAGONISTS (BLOCKERS) AND THE TREATMENT OF LOWER URINARY TRACT SYMPTOMS

The human prostate is composed of a glandular component (static) and a smooth muscle component (dynamic). Blockade of the prostate smooth muscle results in relaxation of the prostate and can relieve the prostatic obstruction in patients with BPH. Since α-1A AR is predominantly present (70%-100%) in the human prostate stroma, α-1 AR blockade by an AR antagonist is capable of the modifying dynamic components of BPH [3].

The bladder outlet in men is composed not only of the prostate but also consists of the bladder neck, intraprostatic urethra, and external sphincter. These bladder outlet structures also contain α-1A AR [2]. Therefore, blocking α-1A AR can decrease the resistance of these outlet structures during resting and voiding. In addition, spinal cord α-1 AR expression may also be important in modulating LUTS [1].

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Efficacy of α-Blockers on LUTS

Currently there are five α-1 AR blockers available for the treatment of LUTS. Terazosin, doxazosin, alfuzosin are non-subtype selective α-1 blockers, while tamsulosin blocks α-1A and α-1D ARs, and silodosin blocks α-1A ARs (Table 1). Based on a previous meta-analysis of these α-1 blockers, the efficacies of these α-1 AR blockers are comparable to each other [4]. After treatment with an α-1 AR blocker, improvement in total International Prostate Symptom Score (IPSS) of 30%-45%, and the change in maximum flow rate (Qmax) of 15%-30% were noted. All are superior to placebo [5].

THE EFFECT OF α-1 AR BLOCKERS ON BENIGN PROSTATIC HYPERPLASIA AND BLADDER OUTLET OBSTRUCTION

Bladder outlet resistance is determined by the resistance from the bladder neck, intraprostatic urethra, prostatic proper (glandular and stromal component) and the urethral external sphincter. Bladder outlet obstruction (BOO) can be a result of dysfunction of either one or a combination of the above structures. Distinguishing which one is responsible for the BOO needs careful urological and urodynamic studies. All of the above bladder outlet structures undergo active relaxation during voiding and all of the structures have been found to be innervated with α-1 adrenergic nerves. Therefore, using an α-1 AR blocker can decrease the hyperactivity of α-1 AR and result in relaxation of the bladder outlet.

Treatment of LUTS/BPH

Among the bladder outlet structures, the urethral smooth muscle and prostatic gland possesses the most important role in BOO. An increase in size of the prostatic gland results in mechanical obstruction of the intraprostatic urethra (static component), while increased smooth muscle tone can cause less relaxation of the bladder outlet (dynamic component). Men with an enlarged prostate (e.g. a total prostate volume of 40 mL or more) might not have BOO if their prostatic urethral muscle tone remains normal. On the other hand, men with a small prostate volume (e.g. a total prostate volume of 30 mL or less) may have BOO due to increased urethral smooth muscle tone. Treatment of male LUTS suggestive of BPH should theoretically be based on the etiology of the LUTS in order to avoid any unnecessary medication or surgical intervention.

When treating LUTS/BPH, α-1 AR blockers are recommended as the first line medication for LUTS in men with a small BPH [6]. Adding a 5-alpha-reductase inhibitor (5-ARI) to the α-1 AR blocker is benefi-

Table 1. Clinical Pharmacology of α-1 AR Blocker and Lower Urinary Tract Symptoms

	Alfuzosin	Doxazosin	Silodosin	Tamsulosin	Terazosin
α1-AR Subtype Selectivity	Non-Subtype Selective	Non-Subtype Selective	$\alpha_{1A}>\alpha_{1D}>\alpha_{1B}$	$\alpha_{1A}=\alpha_{1D}>\alpha_{1B}$	Non-Subtype Selective
Phamacological selectivity	-	-	+	+	-
Clinical selectivity	-	-	+	+	-
Registered for use in hypertension	-	+	-	-	+
Reduces elevated blood pressure	+	+	-	-	+
Usual daily dose (mg)	7.5-10	1-8	8	0.4	1-10
Regimen (doses/day)	1	1	1	1	1

AR, adrenergic receptor

cial for men with an enlarged BPH (total prostate volume >40 mL) with LUTS [7]. Long-term combined treatment with an α-1 AR blocker and 5-alpha-reductase inhibitor reduces the risk of BPH progression, such as acute urinary retention or BPH-related surgery, compared with α-blocker only treatment [8]. In men with prominent overactive bladder (OAB) symptoms and BPH, antimuscarinics have been proved to relieve storage symptoms without affecting the voiding efficiency in men with LUTS/BPH regardless of the prostatic volume [9].

Doxazosin and terazosin suppress prostate growth by inducing apoptosis

Doxazosin and terazosin can relax prostate smooth muscle by blocking α-1 ARs in the prostate. Experimental and clinical evidence has indicated that both of these drugs are able to induce apoptosis in prostate cancer cells *in vivo* and *in vitro*. High concentrations of these α-1 AR antagonists were found to induce apoptosis in about 80% of treated smooth muscle cells [10]. The apoptotic effect is mediated via a mechanism other than α-1 AR blockade, potentially through the quinazoline nucleus. The correlation of prostate smooth muscle cell apoptosis with LUTS improvement may have a therapeutic impact on LUTS/BPH [11].

Urodynamic effects of α-1 AR blockers on LUTS/BPH

A total of 36 men with LUTS/BPH received pressure flow study at baseline and after 3 months of silodosin treatment; there was a decrease in Pdet.Qmax from 80.6 to 48.6 cmH_2O and the BOO index was decreased from 70.2 to 32.6 [12]. In another study, 57 patients were treated with silodosin for 4 weeks and a decrease in Pdet.Qmax from 72.5 to 51.4 cmH_2O and in bladder outlet obstruction index (BOOI) from 60.6 to 33.8 were noted. Selective α-1A blockade of the bladder neck and urethral smooth muscle may be responsible for the reduction of voiding pressure [13]. This poses the question as to whether α-1 AR antagonists improve LUTS by reducing bladder outlet resistance. In another study, patients were stratified into lower and upper halves by baseline IPSS, Qmax and BOO index. Patients with below and above median treatment associated improvement of one parameter exhibited only a small change in the other two parameters. It was concluded IPSS, free Qmax, and BOOI are only loosely related at baseline in terms of treatment related improvement. These results question the hypothesis that α-1 AR blockers improve LUTS by reducing bladder outlet resistance [14].

EFFECT OF α-1 AR BLOCKERS ON BLADDER NECK DYSFUNCTION

Bladder neck is α-1A predominant and normal micturition is associated with adequate opening of the bladder neck. α-adrenergic nerves might inhibit detrusor contractility at spinal cord level, while increased α-adrenergic activity might inhibit detrusor contractility; these would result in a low flow rate and a large postvoid residual (PVR). Treatment with an α-adrenergic blocker is able to relax the bladder neck and improve Qmax as well as LUTS in patients with primary bladder neck dysfunction. Long-term alpha-blocker therapy in children has been shown to treat primary bladder neck dysfunction (BND) in children. A total of 51 neurologically normal children with primary BND underwent alpha-blocker therapy for at least 1 year. All were symptomatic, with abnormal flow parameters and an electromyography (EMG) lag time >6 sec. After treatment, the Qmax improved, EMG lag time decreased and 85% of patients reported subjective symptomatic relief. Among them, 29% of patients were able to stop α-blocker therapy. However, among the fifteen patients who stopped medication, eight had to resume α-blocker therapy due to symptom relapse and only three remained asymptomatic [15].

ALPHA-BLOCKER THERAPY FOR FEMALE LOWER URINARY TRACT SYMPTOMS

Female LUTS is not correlated with BOO. Women with OAB or pelvic floor dysfunction may also have LUTS. α-1 ARs are present in the female urethra. In a previous study of terazosin therapy for female LUTS, 100 women with LUTS and an IPSS ≥8 were treated with terazosin or a placebo. The response rate was found to be 80% among the terazosin treated patients vs. 55% in placebo group ($p<0.02$). Only the frequency and straining items in IPSS showed a significant reduction with terazosin together with the KHQ quality of life (QoL) domains [16]. Another prospective longitudinal open-label study also showed that tamsulosin had a significant effect on functional BOO in 63 women. After therapy, voiding symptoms improved in 71.4% of the patients, and in 66.7% of the patients with BOO associated with storage symptoms. Recurrent urinary tract infection were reduced by 50% in 81% of the patients. Qmax improved in 57.1% of the patients and PVR improvement was observed in 66% [17].

EFFECT OF α-1 AR BLOCKERS ON NOCTURIA

In a MTOP study of 3,047 men with LUTS/BPH treated with doxazosin, finasteride, a combination of these two drugs, or placebo, doxazosin alone was to effectively reduce nocturia. At 4 years, a reduction in nocturia was significantly noted with doxazosin (0.46), finasteride (0.29) and the combined drugs (0.42) compared to the placebo (0.11, $p<0.05$). Findings for men >70 years old were similar to those below this age[18].

α-ADRENERGIC RECEPTORS IN THE BLADDER

α-AR blockers were introduced for the treatment of male LUTS in the early 1990s. In isolated human detrusor muscle, the drugs stimulating α-1 AR produce a small and variable contractile effect [19]. After much research, it has been found that the distribution of α-1 AR in the mammalian body is as follows. α-1A AR shows highest expression in the liver, heart, cerebellum and cerebral cortex. α-1B AR shows the highest expression in the spleen, kidney and fetal brain. α-1C AR is expressed in cerebral cortex and aorta. There are three subtypes of α-1 ARs in the bladder with α-1A AR being largely found in human bladder trigone and base, but not in the bladder dome [20]. Only α-1A (34%) and α-1D (66%) AR mRNAs were found to be expressed in the bladder [21], but it has been found that the presence of α-1 AR subtypes may change in patients suffering from BOO [22] and neurogenic voiding dysfunction (NVD) [23].

ROLE OF α-1 BLOCKERS IN AN OVERACTIVE BLADDER

Urothelial dysfunction, myogenic factors and neurogenic factors may cause OAB. β-adrenergic AR is responsible for relaxation of the detrusor whereas α-adrenergic AR may play a minor role in detrusor contraction. The normal human detrusor predominantly expresses α-1D AR (66%) and α-1A AR (34%). In control animals, the distribution of α-1 AR is 70% α-1A, 5% α-1B and 25% α-1D mRNA. However, in BOO rats, the distribution of α-1 AR changed to 23% α-1A, 2% α-1B and 75% α-1D mRNA [24]. The changes in α1-AR mRNA expression are similar in the bladder dome, mid-body, and bladder base. α-1D ARs have a 10 to 100- fold higher affinity for endogenous norepinephrine than other subtypes. Taking this into consideration, an α-1 AR blocker targeting α-1D AR might help to relax the detrusor through blocking α-1D AR. Therefore, the use of a non-selective α-1 AR blocker might have an advantage when treating OAB associated with BOO rather than a selective α-1A blocker.

A stable bladder depends not only on the balance between adrenergic nerves and parasympathetic nerves, but also on the balance between α-ARs and β-ARs. The balance between α-ARs and β-ARs may change in BOO [25]. In dog bladder muscles, a decrease in β-AR function rather than an increased α-AR function was noted. In mildly BOO rats, there is an increased detrusor response to phenylephrine, suggesting the presence of enhanced α-AR function [26]. Among patients with benign prostatic obstruction (BPO) who are treated with α-AR antagonists, detrusor overactivity (DO) may disappear. In the parasympathetic decentralization cat bladder, a change from β-AR dominated relaxation in the normal bladder to α-AR dominated response has been noted [23]. An α-1 AR blocker might have a therapeutic effect on detrusor hypertonicity in patients with BOO with parasympathetic decentralization.

In control bladders, the mRNAs of α-1A, α-1B, α-1D, β-1, β-2 are expressed at very low levels, while β-3 AR is highly expressed. In BOO bladders the expression of α-1A, α-1D, β-2 and β-3 AR increases, but expression of α-1B and β-1 decreases. Nomiya concluded that it was not likely that the detrusor α-1 ARs are responsible for OAB in BOO [27].

Many contributing factors including BOO and ischemic effect have been postulated to induce OAB. Whether α-blocker can improve blood flow to the bladder and improve bladder function has been investigated in rats with BOO. Partial BOO was produced in rats for 2 weeks and tamsulosin was subcutaneously administered for 2 weeks. The expression of α-1 AR mRNA in the vesical artery was measured by RT-PCR. Bladder blood flow (BBF) was significantly reduced in the BOO rats and tamsulosin significantly increased BBF in the BOO rats. Tamsulosin ameliorated the decrease in mean voided volume among the BOO rats. The expression of α-1 AR mRNA in the urinary bladder was α-1A > α-1D and no α-1B was found. This study thus suggests that tamsulosin improves bladder overactivity by improving the BBF [28].

Another study investigated whether α-blockers improved chronic ischemia of the lower urinary tract in patients with LUTS. The BBF and prostatic blood flow were measured by transrectal color doppler ultrasound (TRCDUS) and color pixel density (CPD). The bladder was filled slowly with 0.2 M KCl and patients with LUTS were treated with tamsulosin for 5 weeks. TRCDUS and CPD were measured at baseline and after α-blocker treatment. The results showed that the mean CPD increased 58% in LUTS compared with 157% in the normal controls during filling to maximal capacity (322 vs. 481 mL). After α-blocker treatment, the maximum capacity increased to 382 mL and the CPD increased to 132.8% [29].

OAB has been found to be elicited by activation of capsaicin sensitive primary afferents (CSPA). The CSPA can be desensitized by capsaicin or resiniferatoxin (RTX) in new born rats. Whether α-1 AR blockers can improve bladder storage function via CSPA remains unknown. RTX desensitized rats and controls were subjected to cerebral infarction (middle cerebral artery). Rhythmic bladder contractions were recorded at baseline and after cerebral infarction (CI). Silodosin intravenously was found to dose-dependently increase the bladder capacity of the CI rats without decreasing contraction pressure, but had no effect on RTX-CI rats. PGE2 intraurethral administration reduced the bladder contraction interval (BCI) in the non-RTX-CI rats. Silodosin significantly prolonged BCI in the non-RTX-CI rats receiving PGE2 treatment. This study shows that α-1A AR activates C-fiber afferents and that an α-1A AR blocker can improve bladder storage function in CI-rats [30].

One recent study assessed the effects of α-AR antagonists on urethral perfusion pressure (UPP) in the female rats and the therapeutic potential of these drugs when treating female BOO. After tamsulosin administration, the bladder contraction frequency decreased and the duration of urethral relaxation (high frequency oscillations) were prolonged significantly. The changes in the UPP and Pves curves were similar for male and female rats. It was concluded that α-1A AR blockers may not only improve obstruction symptoms, but also irritative symptoms [31].

EFFECT OF α-1 AR BLOCKERS ON DISTAL URETERAL STONES

Distal ureteral stones cause LUTS and OAB. The distal ureter is innervated by α-drenergic ARs and therefore agents that primarily activate α-ARs tend to stimulate ureteral and pelvic activity. Several recent studies have demonstrated that α-a blockers are effective for the management of distal ureteral stones [32]. A total 73 patients with a distal ureteral stone were divided in 4 groups: (A) <5 mm, (B) 5-10 mm without doxazosin, (C) <5 mm with doxazosin, (D) 5-10 mm with doxazosin for 4 weeks. Spontaneous stone passage was documented in 60% of group A (8.8 days), 85% of group C (7.6 days), 43.75% of group B (12.1 days), 72.7% of group D (7.1 days). The number of pain episodes was significantly lower in group D compared to group B. This study revealed that doxazosin treatment proved to be a safe and effective approach to distal ureteral stone expulsion [33].

Another study investigated 39 children with lower ureteral stones (<10 mm) who were treated with ibuprofen (n=20, group 1) and doxazosin (n=19, group 2). Stone expulsion was observed in 14 (70%) of group 1 and 16 (84%) of group 2 (p>0.05) with durations of 6.1 and 5.9 days, respectively. Administration of doxazosin daily in children to treat distal ureteral stones is therefore not superior to analgesics alone [34].

EFFECT OF α-1 AR BLOCKERS ON CHRONIC PROSTATITIS/ CHRONIC PELVIC PAIN SYNDROME

Category III chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) is characterized by LUTS, pain and dysfunctional voiding. There is no standard treatment for CP/CPPS. The origin of LUTS and pelvic pain is thought to be prolonged smooth muscle contractions in the bladder and prostate caused by α-1 AR activation. Clinical experience with α-1 blockers suggests they might be of benefit because they promote smooth muscle relaxation. Alfuzosin, tamsulosin and terazosin have been shown to be effective when treating CP/CPPS [35].

The etiology of CP/CPPS remains unknown to urologists. Bacterial infection and chronic neurogenic inflammation have been suggested as causes. In a 4-yr, phase 3, placebo-controlled study (REDUCE trial) to determine if daily dutasteride 0.5 mg reduces the risk of biopsy detectable prostate cancer, the pathological analysis provided evidence of a relationship between the degree of LUTS and the degree of chronic inflammation of the prostate. More severe chronic inflammation of the prostate was found to be associated with a higher IPSS score [36].

LUTS, pain, and QoL were assessed in patients with chronic non-bacterial prostatitis treated with an α-blocker. A total of 60 men were randomized to 4 mg doxazosin or placebo groups for 3 months and then were assessed by IPSS, pain scale, and QoL index. A significant difference between the overall IPSS, pain, and QoL scores of the two groups, in favor of doxazosin group (p=0.001), was found [37].

A meta-analysis of nine studies that included a total of 734 patients with CP/CPPS was carried out involving terazosin or placebo treatment for 4 weeks to 6 months. Long-term (>3 months) use of the α-blocker significantly decreased symptoms in patients with CP/CPPS compared with the placebo. However, no improvement in pain across either groups was noted [38].

MANAGEMENT OF DETRUSOR SPHINCTER DYSSYNERGIA BY α-BLOCKERS

Urethral sphincter muscle contraction is under sympathetic control. Whether α-1 ARs plays a role in detrusor sphincter dyssynergia (DSD) remains unclear. One study found that terazosin was not an effective approach to reducing voiding pressure. However, in a subset of five patients who developed bladder neck obstruction showed a marked improvement in voiding pressure and an increased ease of voiding when treated with terazosin [39]. Another study found that there was a significant decrease in Pdet and a fall in MUCP in DSD patients treated with terazosin 10 mg QD. The role of α-blockers in treating DSD therefore remains debatable [40].

A decrease in bladder compliance can ameliorate renal function in patients with NVD. Antimuscarinics are the first line treatment for low compliance bladders; however, their therapeutic effect remains limited. A combined therapy consisting of antimuscarinics, imipramine and an α-blocker to treat decreased compliance related to neurogenic bladder has been tested in patients. A retrospective chart review of the NVD treated with antimuscarinics alone or with the combined therapy was performed. The mean bladder pressure at capacity decreased 52% and compliance increased five fold when the patients were treated with two therapy. The mean bladder pressure at capacity increased 67% and compliance increased 9.7 fold when the patients were treated with three drugs. This study demonstrated that a combined therapy consisting of two or three drugs is able to improve compliance, decrease bladder pressure and improve clinical outcome [41]. Since α-1 AR subtypes may change during NVD causing hypertonicity of the detrusor [23], the treatment of low compliant bladder with non-subtype selective α-1 AR blockers may be beneficial.

EFFECT OF α-1 AR BLOCKERS ERECTILE DYSFUNCTION

α-1A adrenergic receptors are required for normal contractility of the vas deferens and consequent sperm ejaculation as well as having a function in fertility [42]. Recent large scale epidemiological studies have documented a strong association between LUTS and erectile dysfunction (ED). In a recent randomized trial, sildenafil had a positive effect on LUTS. Phosphodiesterase type 5 inhibitors (PDE-5) such as tadalafil are the first-line treatment for ED, might play a role in the management of LUTS in the future [43]. Although some patients do not respond to such treatment, patients that are comobid with LUTS and ED may be treated with an α-1A blocker and a PDE-5 [44]. Clinical data suggest that the addition of an α-1 AR blocker, such as alfulzosin, may be beneficial. In a study on the effect of α-1 blocker therapy on erectile functions in patients with LUTS due to BPH, doxazosin significantly improved total IPSS, QoL-I and Qmax. There was also an improvement in International Index of Erectile Function for Erectile Function (IIEF-EF) scores after doxazosin treatment for 6 weeks, but this was only significant for patients with LUTS and ED. The efficacy (Qmax improvement) for doxazosin when treating LUTS was better in patients without ED [45].

In vitro, the combination of alfulzosin and tadalafil is more efficient than each compound alone when relaxing adrenergic tone or enhancing nitrergic relaxation of the human corpus cavernosum. This effect might be beneficial in ED patients who do not show sufficient improvement when treated with PDE-5 inhibitors alone [46]. A combination of

sildenafil and doxazosin exerts a greater relaxing effect on the contraction response curve with phenylephrine or norepinephrine compared with each compound alone in both tissue. Doxazosin significantly increased the ability of sildenafil to inhibit NE-induced contractions in cavernosal strips. Sildenafil and doxazosin reduced the adrenergic tone of prostatic and cavernosal smooth muscle and their combination provided a significant benefit when targeting the relaxation of both tissues [47].

CONCLUSION

α-1 AR blockers can be used to treat BPH and LUTS. Recent basic studies and various clinical investigations have demonstrated that α-1 AR blockers can also be used to treat female LUTS, nocturia, DSD with neurogenic bladder, chronic prostatitis, lower ureteral stones, and might have a potential role in reducing detrusor overactivity in patients with BOO and OAB. Combined therapy involving a α-1 AR blocker and a PDE-5 inhibitor seems to provide a beneficial effect among patients who are suffering from ED and have an inadequate response to PDE-5 inhibitor alone.

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