Role of Alpha Blockers in Hypertension with Benign Prostatic Hyperplasia

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Abstract
Hypertension and benign prostatic hyperplasia (BPH) are common disorders of aging men. As the world population is aging these two diseases are becoming a significant public health problem worldwide. Approximately 30% of men treated for BPH have coexisting hypertension.
The α-Adrenergic Blockers: Prazosin, Terazosin and Doxazosin are established agents in the therapy of hypertension, and are also effective drugs in the treatment of BPH.
It is reasonable to use α-Adrenergic Blockers as the treatment of choice for men with hypertension and BPH.

Introduction
Hypertension and benign prostatic hyperplasia are common, age related disorders in men leading to a substantial burden on health care resources worldwide.
Although hypertension and BPH are two diverse disease entities, still they have some features in common in the form of aetiological involvement of sympathetic nervous system. These two diseases occur concomitantly in about 25% of men over 60 years of age, hence the use of alpha receptor blockers (ABs) to treat both diseases simultaneously is preferable and convenient for patient compliance, cost and safety.¹

Epidemiology of Hypertension
Nearly one billion adults i.e. more than a quarter of the world’s population had hypertension in the year 2000 and is predicted to rise to 1.56 billion by 2025. Hypertension is the fourth contributor to premature death in developed countries and seventh in developing countries.²
The direct and indirect costs of hypertension are enormous. In 2008, the total estimated direct and indirect cost of hypertension was estimated at $69.9 billion.³
In India, prevalence of hypertension has been reported by various studies ranging between 2-15% in urban India and 2-8% in rural India.⁴,⁵
Hypertension is an established and modifiable risk factor for cardiovascular disease and the prevalence of hypertension increases with age.⁶ The probability that a middle-aged or elderly individual will develop hypertension in his or her lifetime is 90%.
The population of India with persons aged 65 and above has been projected to increase from 51 million in 2005 to 65 million in 2015 and 76 million in 2020.⁷

Epidemiology of BPH
BPH is a common and progressive disease of aging men and the prevalence of BPH increases with age.⁸ Around 50% of men above 65 years of age (more than 80% among men 70-79 years of age) suffer some symptoms of BPH.⁹ Over the coming years, however, an increasing number of patients may report prostatic problems as the world’s population is aging. With increasing public awareness about prostate gland, more men are likely to present to their physician. Also, the men in their 50s and 60s no longer consider themselves old and are not prepared to accept the negative impact of BPH on their quality of life.¹ By the year 2020 around 200% increase in the number of persons over 60 years of age is expected.¹⁰
The cost of managing BPH has a considerable impact on healthcare budgets worldwide.
Six of the main industrialised nations spent almost 3 billion USD in 1990 on prostate surgery alone.11 Indirect costs are difficult to quantify, however, data from Sweden and UK suggest that it ranges between 4-20% of the total cost of prostatic surgery.12,13

BPH is a histological diagnosis involving proliferation of smooth muscle and epithelial cells of the prostate gland. The enlarged gland causes clinical manifestations due to static component i.e. direct bladder outlet obstruction from enlarged prostatic tissue or due to dynamic component from increased smooth muscle tone and resistance within the enlarged gland. The common symptoms due to enlarged prostate are described as lower urinary tract symptoms (LUTS) including voiding symptoms (hesitancy, poor stream, intermittent urinary stream, terminal dribbling and sense of incomplete evacuation of bladder) and storage symptoms (frequency, urgency, nocturia). The therapy for BPH targets one or both of the disease components (static or dynamic) for relief of LUTS.14

**Concomitant Hypertension and BPH**

Prevalence of hypertension and BPH increases with age, hence both are common diseases in elderly males. Around 25% of the men above 60 years of age have concomitant hypertension and BPH.1 Although hypertension and BPH are two different disease processes, it has been postulated that age related increase in sympathetic tone may be a common factor in their pathophysiology.1,15 The sympathetic nervous system plays an important role in both hypertension and BPH via alpha adrenergic fibres and receptors.

In a study by Bourke and Griffin, it was found that men admitted for elective prostatectomy had higher blood pressure (BP) than age matched patients admitted for non genitourinary surgery. Relative risk of hypertension was around 10 in BPH patients with age 45-64 years and 5 in patients 65 years and above. They postulated that hypertension was a risk factor for BPH.16

In view of larger number of persons with concomitant Hypertension and BPH, it would be worthwhile to monitor BP by Urologists in all cases of BPH and to assess urinary functions in all elderly males with hypertension by the physicians. In this context, use of a single pharmacological agent (ABs) to treat both the diseases have the potential cost effectivity, compliance and convenience.1

**Role of Autonomic Nervous System in maintenance of arterial pressure**

The autonomic nervous system maintains cardiovascular homoeostasis via pressure, volume, and chemoreceptor signals. Adrenergic reflexes maintain blood pressure over the short term, and adrenergic function, along with hormonal and volume-related factors, modulate the long-term regulation of arterial pressure through the endogenous catecholamines: norepinephrine, epinephrine, and dopamine.17

The kidneys receive extensive sympathetic nerve supply, which upon activation reduces sodium excretion by increasing tubular reabsorption or decreasing the filtered load of sodium via alpha adrenergic receptor activation. Increased renal sympathetic nerve activity also activates renin angiotensin system leading to enhanced tubular sodium reabsorption.18 The most convincing evidence to establish the role of renal nerves in human hypertension is the recent observation that renal sympathetic nerve ablation by a radio frequency emitting catheter leads to significant reduction in blood pressure in cases of resistant hypertension.19

**Role of Autonomic Nervous System in Benign Prostatic Hyperplasia**

Autonomic nervous system overactivity has a positive correlation with symptom score and other BPH measures and may contribute to LUTS in men with BPH.20

Prostatic smooth muscle cells contribute to a significant volume of the prostate gland and their contractile properties are similar to that seen in other smooth muscles in the body. Active smooth muscle tone in the gland is regulated by the adrenergic nervous system.21
Medical Treatment of BPH with α-Adrenergic Blockers

Rationale

The rationale for α-adrenergic blockers in the treatment of clinical BPH is based on the hypothesis that BPH is in part caused by bladder outlet obstruction (BOO) mediated by α1-adrenergic receptors associated with prostatic smooth muscle. The smooth muscle is one of the major cellular constituents of BPH. The human prostate contracts in the presence of α1-adrenergic agonist norepinephrine. The observation of high levels of smooth muscle α1-receptors and norepinephrine in the human prostate suggests an important role of adrenergic innervations in prostatic function (Figure 1).

Activation of α1-adrenergic receptors leading to increase in prostatic smooth muscle tone with urethral constriction and impaired flow of urine is a major factor in the pathophysiology of symptomatic BPH. Also, the α1-adrenergic receptors mediate the symptoms of BPH via their activation within CNS and urinary bladder.

Classification of α-Adrenergic Blockers

The two basic subtypes of α-receptors: α1 and α2 are distributed ubiquitously throughout the human body. α1-receptors are typically located presynaptically and down-regulate norepinephrine release via a negative feedback mechanism leading to smooth muscle relaxation on stimulation.

α1-receptors are post synaptic receptors that affect the response to neurotransmitter release. Several subtypes of α1-receptors have been identified and classified into three groups: α1A, α1B and α1D.

The α1A receptors are predominantly expressed by prostatic stromal smooth muscle cells. The α1B receptors are mainly located in the smooth muscles of arteries and veins including the microvasculature within the prostate gland.

The α1D receptors are mainly located in the bladder body and dome, and also in the spinal cord where they play a role in the sympathetic modulation of para-sympathetic activity. The α1D receptors mediate the irritative components of LUTS.

The knowledge of α1 receptor subtype location and function is the key to effective therapy for BPH. The blockade of α1A adrenoceptor receptors reduces prostatic tone and improve the dynamic aspects of LUTS. The blockade of α1B receptors leads to arterial and venous dilatation due to relaxation of smooth muscles in the vessel walls. In some patients, this may lead to giddiness and hypotension due to reduced total peripheral vascular resistance.

As the stimulation of α1D receptors leads to detrusor overactivity, the blockade of this receptor can reduce irritative voiding symptoms. Thus, combined blockade of α1A and α1D receptors is a good option in the management of BPH as it combines the benefit of reduction in prostatic smooth muscle tone and decreased detrusor instability without the cardiovascular side effects of α1B receptor blockade.

Clinical Experience with α-Adrenergic Blockade

First Generation Alpha Blockers

Phenoxybenzamine was the first generation of α- blocking agents found to be useful for relief of BPH symptoms. It is a nonselective α1 and α2 receptor blocker. Its use has been discontinued due to significant side effects of syncope, orthostatic hypotension, reflex tachycardia, cardiac arrhythmia and retrograde ejaculation, mostly due to α2-receptor blockade.

Second Generation Alpha Blockers

Postsynaptic, selective α-adrenoceptor antagonists lower blood pressure by decreasing peripheral vascular resistance. They are effective antihypertensive agents used either as monotherapy or in combination with other agents.

The second generation α-blocking agents: Prazosin, terazosin, doxazosin and alfuzosin were developed in an effort to reduce the side effects. These are specific to α1 receptor and have reduced α2 receptor activity hence, they improve LUTS symptoms with lesser vasodilatation related side effects.

Prazosin was the first AB developed as second generation drug in this series. It exerts its antihypertensive effect by relaxation of peripheral arterioles due to post-synaptic α receptor blockade. It does not block presynaptic α receptors which modulate the release of neurotransmitter, thereby avoiding adverse effects due to reflex activation of sympathetic nervous system. The antihypertensive properties of Prazosin make it an obvious choice for the treatment of hypertension, at the same time it can be used for the treatment of LUTS associated with BPH, thus it is the drug of choice for the patients who suffer from both the problems concomitantly.

Doxazosin is α1 receptor blocker with high bioavailability and a long plasma half life resulting in prolong pharmacologic activity following a single oral dose. Doxazosin is effective in relieving BOO via reduction in prostatic tone.

Doxazosin and other α-adrenergic blockers may influence smooth muscle growth in the prostate. In patients with BPH, treated with α1 receptor blocker there is a decreased expression of myosin heavy chain messenger RNA, which is a functional marker for the smooth muscle phenotype.
hypertensive and normotensive subjects. Tamsulosin does not lower the BP in hypertensive men but can be safely given with other antihypertensive medications.23

Silodosin is a newer agent with high selectivity for α1A receptors (which predominate in male bladder outflow tract) relative to α1D receptors. Clinical studies suggest that Silodosin has rapid onset of action and sustained relief of LUTS with a positive cardiovascular safety profile and no significant BP lowering effect.24

Naftopidil is a selective α1D adrenergic receptor antagonist. It has been shown to improve storage symptoms in the patients with BPH with better preserved sexual function as compared to selective α1A receptor blockers.35 Its long term clinical efficacy remains to be established (Table 1).

### Adverse Side Effects of α-blocking Agents

All α-blocking agents may be associated with adverse reactions depending upon dosage and selectivity. Dizziness is the most common side effect which is thought to result from the effect on CNS or other unconventional mechanism unrelated to the effects on blood vessels as dizziness may even be associated with highly selective α1 receptor blocker like Tamsulosin. Hypotension is less common with longer acting drugs and occurs least with α1A selective agents. Dizziness and hypotension are more common in patients over 65 years of age. Ejaculatory dysfunction is also a side effect of this group of drugs.

Intraoperative floppy iris syndrome (IFIS) occurs in around 2% cases of cataract surgery leading to poor preoperative pupil dilatation, iris billowing, prolapse and progressive intraoperative miosis. The association of IFIS is well established with Tamsulosin, but has also been reported less commonly with other α1 receptor blockers like Terazosin, Doxazosin and Alfuzosin. The α1D is the predominant receptor subtype in the iris dilator muscle as well. The persistence of IFIS long after the discontinuation of Tamsulosin suggests a semipermanent muscular atrophy and loss of tone of iris muscles.36

### α-Adrenergic Blocker Therapy and Coexisting Hypertension

The α-Adrenergic Blockers: Prazosin, Terazosin and Doxazosin are established agents for the treatment of hypertension. Approximately 30% of men treated for BPH also have hypertension and it is convenient to use α-adrenergic blockers as the treatment of choice for men with hypertension and BPH.36

The ALLHAT study (anti hypertensive and lipid lowering treatment to prevent heart attack trial)37 questioned the use of doxazosin in men at risk of developing congestive heart failure. This study did not

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Significant changes in systolic BP were observed in various clinical trials using doxazosin and lowering of BP was a desirable outcome in these patients.28

Terazosin is selective α1 receptor antagonist with a relatively long plasma half life so that once a day dosing is possible. Kirby29 has examined the mean changes in BP in subjects who were normotensive or hypertensive at baseline. In normotensive patients, small, clinically insignificant decrease in BP was recorded. Untreated hypertensive men had larger and clinically significant decrease in BP. In men with medically controlled hypertension, terazosin had no clinically significant effect on BP, on the other hand, in men with poorly controlled medically treated hypertension, terazosin significantly lowered BP. The ability to treat two common coexisting conditions (BPH and hypertension) is a potentially desirable feature of this drug.

Alfuzosin is another second generation α1 receptor antagonist, which has a short plasma half life and has been found to be a safe and effective agent in the treatment of BPH. The efficacy of Alfuzosin is similar to other second generation α1 receptor antagonists whereas, the cardiovascular side effects and BP changes are reported to be lower as compared to other agents of this group, hence it has been labelled as a uroselective drug.30

Alfuzosin needs to be given in 2-3 daily doses, while the extended/ sustained release formulations require only once a day dosing.

### Third Generation Alpha Blockers

The third generation α-blocking agents: Tamsulosin and Silodosin are more specific α1 blocking agents acting on prostatic α1 receptors, selectively targeting the smooth muscle cells in the prostate gland with lesser side effects related to other α receptors.

Tamsulosin is the most widely used α-blocking agents in the management of BPH and exhibits some degree of specificity for α1A adrenergic receptors.31 Clinical trials have suggested that it provides relatively rapid improvement in symptoms as well as peak urinary flow rate and the beneficial effects are sustained over time.32 A large multicentre trial has demonstrated that the mean changes in systolic and diastolic blood pressure in the placebo and tamsulosin groups were not significantly different for both
assess the relative risks and benefits of doxazosin in men with BPH and hypertension nor did it have any bearing on the use of doxazosin in combination with other antihypertensive drugs. Hence doxazosin and other α-adrenergic blockers remain acceptable agents to treat BPH with coexisting hypertension.36

References