Urinary Tract Infections & Treatment

Chapter 5

Alpha Adrenergic Blockers in Urinary Obstructions due to Benign Prostatic Hyperplasia

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1. Introduction

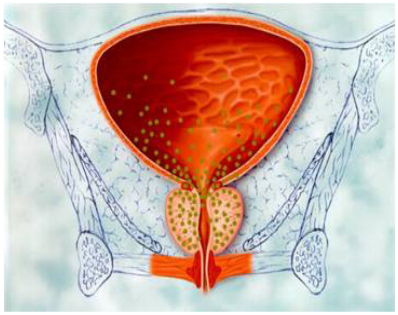
Benign prostatic hyperplasia (BPH) is the nonmalignant enlargement of prostate gland due to increase in number of stromal and epithelial cells [1]. Prevalence has been found to increase with advancing age affecting over 80% men above 70 years. As men age, the caliber of the urinary stream diminishes [2]. The diminution of the urinary stream was assumed to be attributable to Bladder Outlet Obstruction (BOO) arising directly from the BPH. It was also assumed that BOO resulted in lower Urinary Tract Symptoms (LUTS), that range from mild to severe obstructive and irritative symptoms of weak stream, abdominal straining, hesitancy, incomplete bladder emptying, terminal dribbling, nocturia and dysuria [3]. Other conditions associated with BPH are acute or chronic urinary tract infection, hematuria, acute urinary retention and chronic renal failure. The bladder Outlet Obstruction (BOO) is produced in men with BPH via two mechanisms involving a dynamic component and a static component [4]. The dynamic component is related to the tone of smooth muscle fibres in the bladder neck, surgical capsule and fibromuscular stroma while the anatomical or static component is due to the mechanical compression exerted by the increased prostate bulk.

The indications for treating BPH include reversing of signs and symptoms of the disease or preventing the progression of the disease. The symptoms of BPH could be alleviated by both minimal invasive or interventional surgical procedure or medical treatments. Surgical therapy is recommended for men with severe symptoms, and is associated with morbidity, mortality, high cost and complications [5]. Pharmacological treatment with drugs like 5-alpha reductase inhibitors or alpha blockers has proven to be a safe and effective option for managing patients with mild to moderate symptoms of LUTS associated with BPH [6]. Increased prostatic

mass can be reduced effectively by lowering the level of dihydrotestosterone with usage of a 5-alpha reductase inhibitors thus reduced prostatic size or by relaxing prostatic smooth muscle by blockade of sympathetic adrenergic functions responsible for high urethral pressure . Antagonism of effect of noradrenaline at alpha adrenoreceptor reduces the smooth muscle cell tone thereby leading to a reduction in the dynamic component of BOO. Alpha blockers have been shown to produce a 30% increase in urinary flow rate and 29% reduction in residual urine volume with a corresponding improvement in Lower Urinary Tract Symptoms (LUTS) [7].

2. Pharmacology of Adrenergic Receptors

The alpha adrenergic receptors are transmembrane glycoproteins and have been classified as alpha-1 and alpha-2 each with further three subtypes. According to International Union of Pharmacology (IUPHAR), 3 native alpha-1 adrenoceptors (alpha-1A, alpha-1B and alpha-1C) have been identified. Their cloned counterparts have been designated alpha-1a, alpha-1b and alpha-1d with their respective genomes located on human chromosomes 8, 5 and 20. All the three subtypes of alpha-1 adrenoceptors have been identified in prostatic stromal tissue, however, alpha-1a subtype predominates in the prostate, bladder neck and urethra whereas alpha-1b and alpha-1d in the vascular smooth muscle [8]. Recently, an additional alpha-1 receptor subtype alpha-1L has been identified which has low affinity for prazosin and is present only in the prostate.



Alpha Receptors in The Neck And Sphincter

The rationale for this treatment is based on that noradrenaline acts at α_1-adrenergic receptors in the neck and sphincter of the urinary bladder to promote contraction and urinary retention. Noradrenaline also acts at α_1-adrenergic receptors to control the smooth muscles in the prostate capsule and prostate urethra[9]. Thus selective α_1- adrenergic receptor (α_1-AR) antagonists relieve the obstruction due to dynamic component by relaxing the smooth muscle in and around the prostate and bladder neck without affecting the detrusor muscle of the bladder wall. Other mechanism contributing to the beneficial effect of α1-adrenoreceptors antagonist in the benign prostatic hyperplasia is that some of these agents also induce apoptosis in both epithelial and stromal cells of prostate with little effect on cell proliferation [10]. The alpha adrenergic blockers that have been used in the treatment of BPH can be grouped according to receptor subtype selectivity and duration of serum elimination half lives [11].

2.1. Non Selective Alpha Blockers

Phenoxybenzamine is a non selective alpha adrenoceptor blocker which irreversibly blocks both alpha-1 and alpha-2 receptors. The beneficial effects of oral phenoxybenzamine in BPH were first reported by Caine et al in 1976 [12]. Phenoxybenzamine at a dose of 10 mg twice daily for 14 days produced an improvement in peak urinary flowrate (Qmax) by 82% as against placebo (30%).

Phenoxybenzamine

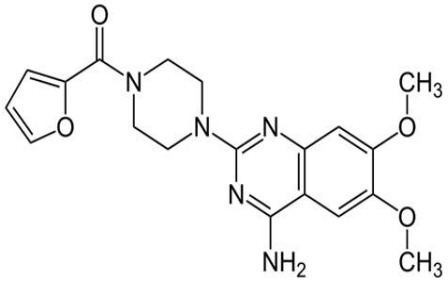
However, it produced side effects which are generally associated with alpha-2 receptor blockade like dizziness, hypotension, nasal stuffiness and impaired ejaculation in 30% of the patients . As it is chemically related to nitrogen mustard, evidences of its mutagenic and carcinogenic potential have also been documented [13]. Besides phenoxybenzamine, other non selective alpha blockers which have undergone clinical evaluation for the treatment of BPH are nicergoline and thymoxamine.

Further extensive knowledge and good understanding about the identification, distribution and concenteration of three subtypes of the α1-adrenoreceptors (α_{1A}, α_{1B} and α_{1D}) in the prostate, bladder, neck, brain and vascular smooth muscle has led to the development of uroselective α1-adrenergic antagonists with reduced side-effects. The α_{1B} subtype is predominant in blood vessels whereas α_{1A} is predominant in prostate

(a) Short acting

Prazosin:

Prazosin was the first selective α_1-adrenergic receptor antagonist investigated for BPH in 1970 [14]. Prazosin contains a piperazinyl quinazoline nucleus and is selective α_1-adrenergic antagonist, with affinity 1000-fold greater than that for α_2-receptor. Several double blind, randomised, placebo controlled trials have been conducted to assess its effectiveness in improving the symptoms of BPH. In a study conducted by Kirby and associates 80 men with BPH between 50–80 years of age were given 2 mg of prazosin or placebo twice daily for 1 month.

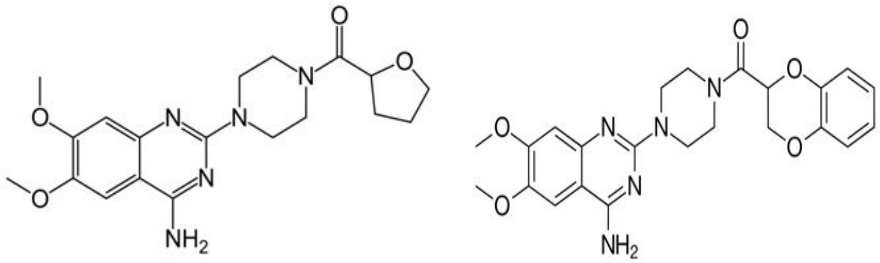


Prazosin

Prazosin produced 59% improvement in Qmax against 6% in placebo group [15]. It also produced a significant reduction in postvoid residual volume (PVRV) and voiding frequency. The most important adverse effect related to Prazosin was postural hypotension but stuffy nose, headache and retrograde ejaculation had also been reported on continuous use for a long period. Later on it was withdrawn from market and no further larger, randomized clinical trials were conducted [14]. Short half life of 2–3 hours and significant first dose effects like postural hypotension and syncope limit its usefulness as a current therapy for BPH.

b) Long acting

The next advancement in drug therapy was the advent of selective α_1-drugs, Terazosin and Doxazosin. Both are structural close analog of Prazosin, originally developed as antihypertensive agents [16]. Terazosin and Doxazosin have longer half lives thus can be given once a day. It is recommended that these drugs should be titrated slowly over 1-2 weeks due to first dose syncope to a maximum of 10mg for Terazosin and 8 mg for doxazosin [17,18].



Terazosin **Doxazosin**

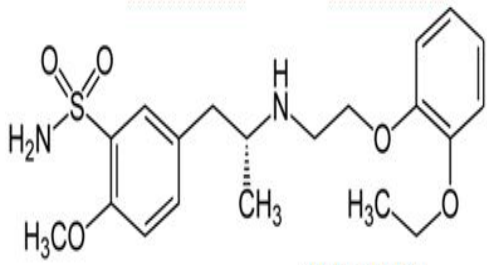
Lepor and colleagues reported that significant increase in average flow rates has been observed without affecting voided or residual volume. The clinical efficacy and safety of Terazosin and Doxazosin documented in several studies has shown Terazosin therapy doesn't affect blood pressure control in patients receiving concurrent antihypertensive medication, whereas mild to moderate adverse events like fatigue dizziness has been observed with doxazosin [19]. Although Terazosin and Doxazosin have never been compared, but there is only slight difference in their efficacy and side effects and they are believed to be equally clinically effective[18].

Selective α1-adrenergic antagonists such as parazosin, doxazosin, terazosin, though

effective in improving the symptoms of BPH, were found to be suboptimal because of dose limiting side effects. These included hypotension, dizziness, muscle fatigue and were believed to be mediated by the blockade of α1-adrenoreceptors in vascular and central nervous system. Currently Tamsulosin and Alfuzosin are the most widely prescribed medications as selective α_1-AR antagonists for the LUTS associated with BPH.

Tamsulosin

Tamsulosin hydrochloride is a competitive antagonist of α_1-AR with the chemical name (-)-(R)-5-[2-[[2-(o-Ethoxyphenoxy) ethyl] amino] propyl] -2-methoxybenzenesulfonamide[20]. Tamsulosin was the third uroselective α_1-AR antagonist approved for use in the treatment of symptomatic BPH. It was brought into market as the first subtype selective α_1-AR antagonist with ten fold more selectivity for α_{1A}-receptor subtype compared to α_{1B} -receptor subtype[21]. It is well absorbed with half-life of 5 to 10 h. It is extensively metabolised by the cytochrome P450 system [22].

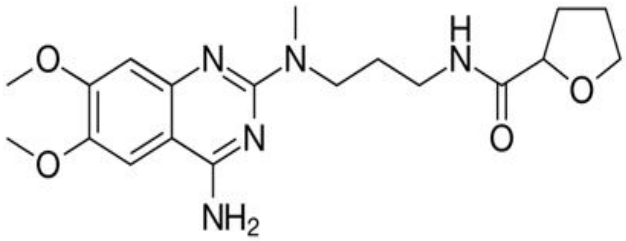


Tamsulosin

A significant reduction in maximum urinary flow rate compared with placebo has been observed after one dose (0.4 mg or 0.8mg) of Tamsulosin in patients with symptomatic BPH [21]. Tamsulosin have minimal cardiovascular effects. The risk of dizziness is lower with Tamsulosin than with Doxazosin and Prazosin. The drug also demonstrated a lower probability of orthostatic hypotension, but a higher rate of ejaculatory dysfunction (10%) and does not appear to cause erectile dysfunction or reduced sexual drive [22].

Alfuzosin

Alfuzosin is a quinozoline based α_1-AR antagonist **(7)** that has been approved in France since 1988 for the symptomatic treatment of BPH [7]. It has got similar affinity for all of the α_1 receptor subtypes, but when administered orally is found to be concentrated in the prostate . It is the fourth α_1-selective blocker approved by the FDA for the treatment of symptomatic BPH. It has a half life of 5 hrs and is administered in 3 divided doses



Alfuzosin

The drug is available in an immediate (2.5 mg t.i.d.), sustained (5 mg b.i.d.) and extended release formulation (10mg/day) to improve treatment compliance[23]. According to AUA guidelines, Alfuzosin has comparable clinical efficacy with Tamsulosin and the other approved alpha blockers and doesn't cause ejaculatory dysfunction.

4. Others

Niguldepine, Nifidepil, Naftopidal and Silodocin are similar agents under investigation. Number of α_{1A} subtype selective antagonists belonging to different structural classes of compounds such as SNAP 5089 and 5540 (dihydropyridine), GG818 (oxazole), SNAP 6021 (dihydropyrimidinone), SNAP 7915 (oxazolidinone) and phenylpiperazine analogues have been disclosed recently [24, 25, 26].

5. Combination Therapy

The distinct mechanism of actions of 5α-reductase inhibitors and α_1-AR antagonists on the respective static and dynamic components of BPH lend themselves to use as combination therapy. Combination therapy is reserved for patients with an enlarged prostate gland and who have symptoms of bladder outlet obstruction. The rationale for this recommendation is that, a rapid relief of symptoms will be provided by the α_1-AR antagonists without targeting the underlying disease process and a mid or more sustained relief of symptoms will be provided by the 5α-reductase inhibitors [27]. The efficacy and safety of the treatment with different combinations versus treatment with either agent alone has been investigated by different groups in large mulitcentral trials .

Initially combination of Finasteride and Terazosin and then of Finasteride and Doxazosin were evaluated over a period of one year and data revealed that treatment with α_1-AR antagonists alone or in combination therapy has significantly improved the symptom score and flow rate compared with placebo or Finasteride alone, but there is no significant difference between patient treated with combination therapy and patient treated with α_1-AR antagonists alone [28]. These trails were subsequently followed by MTOPS wherein combination of Finasteride and Doxazosin was studied over a period of 4.5 years. It was found that risk of acute urinary retention (AUR) and need for BPH related surgery was significantly lower in Finasteride and combination therapy versus placebo, whereas neither of these outcomes was reduced

significantly with Doxazosin alone [29].

The CombAT study is underway to further examine the role of combination (Dutasteride and Tamsulosin) over the α_1-AR antagonists (Tamsulosin). It would represent the next major step in assessing the overall value of combination therapy in men with symptomatic BPH and it findings will assist primary care while making treatment decision [30].

All the three studies demonstrated a higher incidence of impotence in the combination therapy compared with that of 5α-reductase inhibitors; in addition to the expected higher incidence of α_1-AR antagonists mediated dizziness and hypotension. Also the increased cost of combination therapy demands consideration. Cost effectiveness studies by Nickel suggest that combination therapy is best suited for men at high risk for BPH progression (i.e. with high symptom score, large prostate volume and low q_{max} value) who are able to tolerate the increased side effects [31].

6. Conlcusion

The alpha-1 adrenoreceptor and its subtypes mediating contraction of smooth muscles including that of prostate are of potential clinical relevance to alpha adrenoceptor blockade in BPH . α-Blockers are more likely to reduce symptoms of BPH and are medical therapy of choice for symptomatic patients with a low risk of clinical progression (prostate volume < 30-40 ml)[135]. However, it is important to monitor patient carefully since these drugs are short acting, as symptoms return very quickly if a man stops taking medication, in addition these drugs have no effect on the size of the prostate.

7. References

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