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Review

Medical therapy for clinical benign prostatic hyperplasia: α1 Antagonists, 5α reductase inhibitors and their combination

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Abstract Medical therapy for clinical benign prostatic hyperplasia (BPH) has advanced significantly in the last 2 decades. Many new α1 antagonists and 5α reductase inhibitors (5ARi) are now commercially available. The practicing urologist must decide on the most appropriate medication for his patients, taking into consideration various factors like efficacy, dosing regime, adverse effects, cost, patient's socioeconomic background, expectations, drug availability and his own clinical experience. The use of combination therapy added further to the complexity in clinical judgment when prescribing. We highlight some of the key points in prescribing α1 antagonists, 5ARi and their combination, based on our viewpoints and experience as urologists in an Asian clinical setting.

1. Introduction

Benign prostatic hyperplasia (BPH) is often equated with prostatic enlargement in aging males, but "normal-sized" prostates below 20 mL may also cause bladder outlet obstruction. Such occurrence of prostatic obstruction, with or without significant symptoms, constitutes clinical BPH and its sequelae [1]. Cellular proliferations in the periurethral and transition zones lead to the formation of nodular adenomas, potentially distorting the bladder neck and prostatic urethra. A small adenoma located submucosally along the prostatic urethra may be sufficient to cause obstruction without significant enlargement of the remaining prostate gland [1].

Lower urinary tract symptoms (LUTS) from BPH can be classified into two groups. Voiding symptoms, such as hesitancy and intermittent/weak urinary stream, can be understood as the direct results from prostatic obstruction. Storage symptoms, such as frequency and urgency, may be

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secondary to a combination of factors like detrusor instability, detrusor hypertrophy, decreased bladder compliance and decompensation [2]. Non-urological factors, such as cardiac, neurological and hormonal dysfunctions, may also contribute to LUTS in BPH patients [2].

The choice of medications for BPH was limited in the past, and medications could only provide short-term symptomatic relief at the expense of significant adverse effects. One such example was phenoxybenzamine, a non-selective irreversible α antagonist. Patients risked postural hypotension, light-headedness, fainting spells and recurrent falls for several hours of symptomatic relief. Dose titration was a routine, since controlled release was not an option. BPH progression could not be halted and many patients, despite years of medications, eventually developed complications or required surgical interventions. The concurrent control of BPH-related sexual dysfunctions was almost never discussed.

However things have changed drastically, for the better. Many α1 antagonists are now commercially available, offering advantages of rapid onset, long-lasting efficacy, reduced adverse effects, convenient single daily dosing and many other perks. 5α Reductase inhibitors (5ARi) provide sustained improvements in LUTS and reduce BPH progression, so surgical interventions may be delayed or avoided [3—5]. α1 Antagonists and 5ARi are being used in combination to complement each other's pharmacological action, and the well-known MTOPS and ComBAT studies provided evidence for its success [4,5]. Muscarinic receptor antagonists, phosphodiesterase-5 inhibitors, phytotherapy and their combinations also play increasingly important roles in BPH treatment, though being outside the scope of this chapter.

With more choices in the pharmaceutical market, prescribing the appropriate medical therapy for BPH patients is an increasingly complicated task for the urologists. The fine balance between efficacy, adverse effects and costs is often difficult to achieve, and the different physiological and socioeconomic backgrounds of every BPH patient further complicate matters. In this chapter, we review the use of α1 antagonists, 5ARi and their combination for clinical BPH.

2. α1 Antagonists

2.1. Mechanism of action

BPH causes urinary obstruction by two main mechanisms. Firstly, the increase in prostatic stroma leads to nodular enlargement which, in turn, results in distortion of the prostatic urethra and obstruction to urinary flow [6]. Secondly, there is an increased smooth muscle tone in the prostate and bladder neck, mediated by α1 adrenoceptors [6,7]. These mechanisms account for the static and dynamic components of obstruction. α1 Antagonist, as the name implies, blocks the α1 adrenoceptors in the prostate and bladder neck, thus relieving the dynamic component of obstruction. Certain α1 antagonists, such as tamsulosin and silodosin, exhibit uroselectivity by having a high affinity for α1A adrenoceptors located in the prostate and bladder neck [8,9].

2.2. Efficacy

When dosed correctly, α1 antagonists improve International Prostate Symptom Score (IPSS) by 30%—45% and improve the urinary flow by 15%—30% [10]. They have fast onset of action and patients often experience their therapeutic effects within a week [11]. They improve both voiding and storage symptoms, with maintained efficacy for 4 years [4,5,12]. However, α1 antagonists do not reduce prostatic volume and do not prevent disease progression, so they do not reduce the risk of BPH complications or BPH-related surgery in the long term [4,5,13].

2.3. Adverse effects

α1 Adrenoceptors are found in many organ systems, including the genitourinary tract, the gastrointestinal tract, the vascular system and the iris. Thus the use of α1 antagonists is associated with systemic adverse effects, especially postural hypotension [4,5,14]. α1 Antagonists in the contemporary clinical setting are relatively long-acting, and many do not require dose titration. This reduces fluctuations in serum levels after each dose to reduce systemic adverse effects. Nasal congestion, another adverse effect due to the vasodilatory effect of α1 antagonists, may be bothersome for some patients. The peculiar problem of "floppy iris syndrome" is often overlooked by urologists [15]. While this does not usually cause problems, it may adversely impact on peri-operative outcomes when patients go for cataract surgery. Some α1 antagonists are uroselective, such as tamsulosin and silodosin, with preferential action on α1A adrenoceptors commonly found in the genitourinary tract. Their side effect profiles should, in theory, be safer than those of the other α1 antagonists [8,9]. However, it has been found that ejaculatory dysfunctions are more common among uroselective antagonists due to their concentrated action in the lower urinary tract [16]. α1 Antagonists do not affect libido, and may have a small benefit on erectile function [17]. In clinical practice, it is important to remember that efficacy of any medication is a double-edged sword, and mishaps usually happen when the urologist puts too much focus on the "therapeutic edge" without due consideration for adverse effects.

2.4. Clinical use and points for special mention

Since α1 antagonists have fast onset of action, they are often used as the first line medication in newly diagnosed BPH patients. However, there are several clinical points that deserve special mention:

- Since α1 antagonists do not reduce prostatic volume or prevent BPH progression, their use should be regularly monitored and reviewed [18]. This is especially true among patients who are at high risk of BPH progression, with very large prostates, high grade intravesical prostatic protrusion or clinically proven significant prostatic obstruction [18]. Many of these patients may not have bothersome LUTS, and simply continuing α1 antagonist for prolonged periods without appropriate monitoring