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SIDE EFFECTS IN PHARMACOTHERAPY OF BENIGN PROSTATIC HYPERPLASIA

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ABSTRACT: Pharmacotherapy of benign prostatic hyperplasia includes various options with differing side effects profile ,including alpha blockers, 5-alpha reductase inhibitors, phosphodiesterase inhibitors, anticholinergics, and beta 3 agonists, each with unique efficacy and safety considerations.

INTRODUCTION

Benign Prostatic Hyperplasia (BPH) is an age-related condition affecting the prostate gland, with a histologic prevalence that increases significantly with age, reaching 80-90% in men in their 70s and 80s[1]. In BPH there is an abnormal non cancerous growth of smooth muscle and stromal cells in the transitional zone of prostate leading to urethral compression and causing a range of lower urinary tract symptoms[2]. BPH-related lower urinary tract symptoms (LUTS) can be divided into two categories. Voiding symptoms, like hesitancy and intermittent/weak urinary stream. Storage symptoms, such as frequency and urgency, may arise due to a mix of factors including detrusor instability, detrusor hypertrophy, reduced bladder compliance, and decompensation[3]. The initial approaches for men experiencing lower urinary tract symptoms (LUTS) due to benign prostatic hyperplasia (BPH) typically involve conservative lifestyle modifications and the use of medication as primary options[4]. In surgical treatment of BPH, there are some possible surgical complications hence pharmacological management remains the physicians first choice for pateints with BPH .Pharmacotherapy of BPH includes alpha blockers,5-alpha reductase inhibitor, phosphodiesterase inhibitor, anticholinergics and beta 3 -agonists . It's crucial for clinicians and patients to thoroughly discuss medication side effects when deciding on healthcare options for treating BPH.

ALPHA BLOCKERS

Different adrenergic receptor subtypes (alpha1A, alpha1B, alpha1D) show specific locations in the human prostate. In benign prostatic hyperplasia (BPH), alterations in the expression levels of these subtypes, particularly alpha1B-AR, are not solely attributed to hyperplasia-induced tissue changes, indicating potential relevance to BPH development. Blocking of alpha-1A receptors reduces the smooth muscle contraction, decreasing tension in the prostate and bladder neck muscles. Consequently, this lowers obstruction at the bladder neck and improve the symptoms[5]. Alpha-1 adrenergic receptor antagonists, commonly referred to as alpha-1 blockers, are the initial medical treatment recommended for alleviating male lower urinary tract symptoms associated with benign

prostatic hyperplasia.The effectiveness and side effects of alpha-1 adrenergic blockers depend on their selectivity for receptor subtypes, aiming to minimize undesirable effects on blood pressure.

Nonselective alpha-1 adrenoceptor antagonists also called "alpha-blockers such as prazosin, terazosin, doxazosin, and alfuzosin were available for use in the medical management of BPH.The primary side effects linked to a1-blockers include cardiovascular events such as postural hypotension, dizziness,and asthenia. These effects may be attributed to the decrease in blood pressure resulting from the vasodilatory impact of alpha1-blockers on smooth muscle and endothelial cells[6].Dizziness and fatigue were significantly more common with doxazosin than placebo (11% vs 7%, and 6%vs3%, respectively)[7]. Alfuzosin commonly causes dizziness (6.1%) compared to placebo (2.9%), and there were no notable alterations in blood pressure, even in elderly or hypertensive individuals. Sexual side effects, such as abnormal ejaculation, were infrequent (0.6%) with alfuzosin[8]. Non selective alpha blockers have a far little impact on ejaculatory functions[9].

Alpha-blockers with selectivity for the 1A subtype are designed to enhance prostate symptom relief while minimizing systemic side effects. Side effects that occurred more frequently in tamsulosin-treated patients included rhinitis, abnormal ejaculation,infection, and dizziness. Asthenia was minimized with tamsulosin, presumably because of subtype selectivity. The incidence and severity of abnormal ejaculation were shown to be dose dependent[10]. IFIS(Intraoperative Floppy Iris Syndrome) the iris becoming floppy during surgery, accompanied by narrowing of the pupil and iris protrusion through incisions. This condition is closely linked to tamsulosin used for benign prostatic hyperplasia (BPH)[11].

Silodosin has a high selectivity for the α1A-AR subtype and for the lower urinary tract[12].Silodosin treatment led to swift and lasting relief of urinary symptoms over a 12-week period. The medication was well received, exhibiting a minimal occurrence of orthostatic hypotension.The main treatment-related side effect of silodosin was mild retrograde ejaculation, observed in 28.1% of patients versus 0.9% on placebo. However, only 2.8% of those taking silodosin discontinued treatment due to this side effect.[13]

PHOSPHODIESTERASE INHIBITOR

PDE5 inhibitors enhance lower urinary tract oxygenation, induce smooth muscle relaxation, suppress LUT stroma proliferation and transdifferentiation, decrease bladder afferent nerve activity, and mitigate prostate inflammation[14].Side effects associated with the use of PDE5 inhibitors include back pain, heartburn, headache, flushing, and nasal congestion[15]. Additionally, the concurrent use of alpha-1 blockers and PDE5 inhibitors may elevate the occurrence of symptomatic hypotension and other related symptoms like headache and dizziness .Caution must be exercised in prescribing this medication due to the significant concern of serious cardiovascular events.[16]

5-ALPHA REDUCTASE INHIBITOR

5-alpha reductase inhibitors (5-ARIs) used in the treatment of prostatic hyperplasia (BPH), as they target the enzyme 5-alpha reductase responsible for converting testosterone into dihydrotestosterone (DHT).Two 5 -ARIs are currently available for the treatment of BPH -finasteride and dutasteride work by impeding the conversion of testosterone, leading to decreased DHT levels. Consequently, this process aids in shrinking an enlarged prostate and preventing the advancement of BPH[17] .5-ARI treatments are associated with a range of side effects in BPH patients, including decreased libido, erectile dysfunction, and gynacomastia[18].Certain research indicates sexual dysfunction even after discontinuation of finasteride treatment[19].The Prostate Cancer Prevention Trial (PCPT) revealed that finasteride, like dutasteride, effectively lowered the occurrence of prostate cancer. However, it's important to note that finasteride may also elevate the likelihood of high-grade Gleason prostate tumors[20].In 2011, a postmarketing submission was forwarded to the US Food and Drug Administration indicating an association between finasteride and symptoms of depression, self-harm, and suicide[21].An analysis of VigiBase, the World Health Organization's worldwide repository of safety reports, revealed heightened indications of suicidal tendencies, depression, and anxiety among individuals under 45 years old who were using finasteride at low doses[22] .

ANTI CHOLINERGICS

Anticholinergic agents reduces the involuntary contractions of the bladder detrusor muscle by blocking the binding of acetylcholine to the M2 and M3 muscarinic receptor subtypes[23]. The FDA has approved various MRAs(muscarinic receptor antagonists), including tolterodine, oxybutynin fesoterodine, , solifenacin, darifenacin and trospium. These medications are mainly utilized to address storage symptoms related to lower urinary tract symptoms (LUTS) and overactive bladder (OAB)[24] .MRAs may lead to various side effects, such as dry mouth, itching, constipation, challenges with urination, nasopharyngitis, and dizziness. Most frequently reported side effect is xerostamia with a prevalence ranging from 3.7% to 15.9%[23].A Meta analysis found that there was increased risk of acute urinary retention in patient treated with antimuscarinic agents compared alpha blockers.[25]

BETA -3 AGONISTS

Beta-adrenoceptors are found largely in the urethra, bladder and prostate. Notably, the b3-adrenoceptor subtype is significantly more abundant in these tissues compared to the b1 and b2 subtypes[26].A new therapeutic approach for treating benign prostatic hyperplasia (BPH) in men involves Beta-3 adrenoceptor (B3AR) agonists, which facilitate detrusor muscle relaxation in urinary bladder[27] . Mirabegron treatment commonly leads to side effects such as constipation, headaches, nasopharyngitis, urinary tract infections and hypertension. Among these, hypertension and urinary tract infections are the most frequently reported[28].The safety and effectiveness of mirabegron were assessed by combining data from three randomized controlled trials and two additional phase III studies. The primary side effect, arterial hypertension, was commonly reported in both the combined studies and one of the phase III trials. Nevertheless, the incidence of hypertension in mirabegron-treated groups (10.9% and 12.4%) was similar to that in placebo- or antimuscarinic-treated groups (9.3% and 11.8%).[29]

PHYTOTHERAPY

Phytotherapy, which involves using plant-based herbal preparations, is believed to offer advantages for men with Lower Urinary Tract Symptoms (LUTS). However, the available evidence supporting these benefits is limited.Phytotherapy for bph is not recommended by the AUA or EUA .Such treatment mainly include extracts from Saw palmetto, Cucurbita pepo L., Prunus africana, Urtica dioica L, and Secale cereale L[30].A meta analysis suggests that commonly reported side effects of saw palmetto are abdominal pain ,diarrhea,nausea,fatigue,headache reduced libido and rhinitis. Although isolated case reports and data from spontaneous reporting systems mention more severe events like death and cerebral hemorrhage, the causality is uncertain[31].

CONCLUSION

Pharmacotherapy plays a pivotal role in managing benign prostatic hyperplasia (BPH), aiming to alleviate lower urinary tract symptoms. Alpha blockers, targeting adrenergic receptors, often cause cardiovascular side effects, such as postural hypotension and dizziness. Selective alpha-1A blockers like tamsulosin and silodosin show improved efficacy with fewer systemic effects, though both are is associated with ejaculation disorders in elderly patients. Phosphodiesterase inhibitors (PDE5) exhibit potential benefits in BPH by enhancing lower urinary tract function but may lead to side effects like back pain and headache, especially when used concurrently with alpha blockers. 5-alpha reductase inhibitors (5-ARIs) such as finasteride and dutasteride can cause sexual dysfunction, gynecomastia, and potential psychological effects, emphasizing the need for careful consideration. Anticholinergics, used for storage symptoms, carry side effects like dry mouth and constipation, and may increase the risk of acute urinary retention. Beta-3 agonists like mirabegron, targeting the bladder, have reported side effects such as headaches and hypertension. While phytotherapy is not recommended by major guidelines, saw palmetto may cause abdominal pain, diarrhea, and reduced libido, with uncertain causality for more severe events. Overall, a thorough discussion of medication side effects is crucial for informed decision-making in BPH management.

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