
Combination Drug Therapy for Benign Prostatic Hyperplasia (BPH)

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Summary

Background

The incidence of benign prostatic hyperplasia peaks 80% in old age. Bothering symptoms and progression to acute urinary retention and need for surgery are important concerns. Alpha blockers and 5 alpha reductase inhibitors address these to variable extents. This article reviews the current place of medical therapy in the treatment of BPH, with a focus on combination therapy.

Data Source

A medline literature search was performed to identify original studies

including global multi-center trials and reviews on the subject.

Conclusion

BPH symptom reduction and shrinkage of prostate size by the use of a combination of alpha adrenergic uroselective blocker (Tamsulosin) and 5 alpha iso-enzyme inhibitor (Dutasteride) is a first option of therapy in the management of BPH especially in those cases that are surgical risks with the category of mild to moderate prostate symptom scores.

Introduction

Benign prostatic hyperplasia (BPH) is the most common cause of urinary bladder outflow obstruction (BOO) in men aged 50 years and above(1). Patient age, androgenic stimulus, genetic and some environmental factors are etiological determinants. The incidence of the disease is about 14% in men 40 years to 49 years of age but prevalence rises to about 80% in men older than 70 years of age (2-4). The active form of testosterone, the dihydrotestosterone (DHT) stimulates prostatic cellular proliferation with attendant reduction in programmed cell death (apoptosis) (5-6). This results in increased prostatic size. The cellular proliferation, concentrated in the peri - urethral and transitional zones, is accompanied by increase in the stromal content (smooth muscles) and this combination results in symptoms of bladder outlet obstruction (Fig 1) manifesting with voiding/obstructive and storage/irritative symptoms in various combinations (1,6) Other associated symptoms are abdominal pain, haematuria, haemospermia, and erectile dysfunction.

The progression of BPH and worsening of symptoms results in acute retention of urine (AUR) and demand for BPH related surgery (7). The risk of AUR is 23% in a 60 year old by the time he becomes 80 years old (2,3). This also increases morbidity and mortality of BPH. The need to halt the progression has given impetus to the

development of effective medical therapies. But to know for which group of patients the therapies would be most efficacious, it is necessary to stratify them. Two factors reported to predict the progression to AUR include prostatic volume >30cc and serum prostatic specific antigen >1.5ng/ml and <10.0ng/m. Patients outside this range may not benefit from the medical therapies (8).

Drug Treatment Of BPH

The discussion on medical therapy focuses on the merits of monotherapy versus combination drug therapy. Two main lines of medical therapies involve the use of alpha-adrenergic blockers and 5- α reductase inhibitors (5). Medical therapy is a first option of treating patients with mild to moderate lower urinary symptoms (LUTs). Apart from symptom resolution, these therapies can further stop the disease progression to acute retention of urine (AUR) or BPH-related surgeries with the attendant complications (9).

Alfuzocin and tamsulosin are uro-selective (acts only on α 1a and α 1d adrenergic subtypes found in prostatic capsule, prostatic smooth muscle, bladder neck smooth muscle (10-13). The drugs act by reducing muscle tone. At the level of the bladder neck, reduction of muscle tone will improve the outlet obstruction in patients with BPH (Fig. 2). Towards this end, the proportion of the stromal tissue to the epithelial glandular tissue is a key

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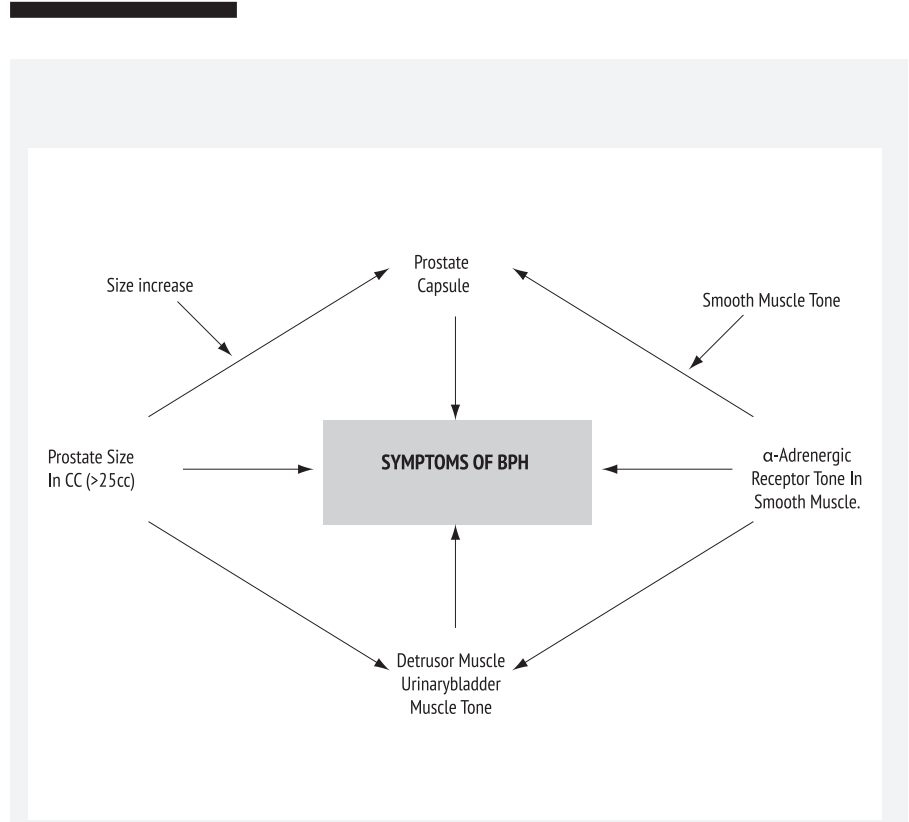


Fig. 1: Factors That Lead To Symptoms Of Benign Prostate Hyperplasia(BPH)

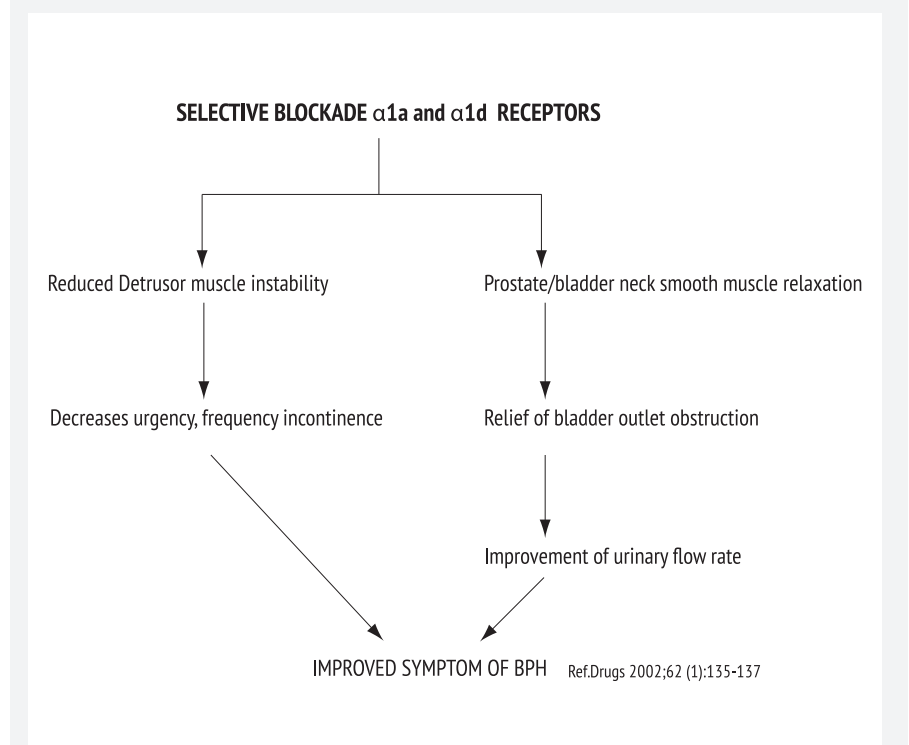


Fig. 2: Mechanism Of Action Of Uroselective α1-Blockers

factor in the development of symptoms of BPH (11) and the α -adrenergic blockade is dependent on the percentage area density of the prostate smooth muscle (12). The number of these receptors increase with the prostatic size. Consequently, benign prostatic enlargement has more receptors compared to normal sized prostate (13,14). The clinical application of this uroselectivity has resulted in the use of alfuzocin and tamsulocin in the initial treatment of BPH before progression to acute retention and need for surgery.

Both drugs are effective in treatment of symptoms (LUTS) and improving peak urinary flow rate (Q max) by causing relaxation of the smooth muscles of the prostate gland and bladder neck (15). They do not however affect the prostatic volume (7).

Tamsulocin has a rapid onset of action of one week while alfuzocin works within 2-3 weeks. Alfuzosin additionally improves the sex drive in elderly men with erectile dysfunction (7)

The maximum improvement is felt at 6 months (24 weeks) but may continue to 18 months (64 weeks) (9). The effects of these α -blockers are greater in younger patients (<60yrs) and smaller prostate volumes (<30cc). Treatment failure is associated with the baseline prostate volumes (larger than 40cc), prostate specific antigen (PSA) levels and drugs compliance (9).

Five α -reductase inhibitors (ARIs) form the other group of drugs in the initial treatment of BPH. The two iso-enzymes, 5 α -reductase1 and 2, convert testosterone to its active form, dihydrotestosterone (DHT).

DHT activates the androgen receptor complexes that lead to nuclear transcription factors that promote the proliferation and growth of the prostatic cells. 5 α -reductase iso-enzyme type 1 is less concentrated in the prostate cells but abundant in liver

and skin while 5 α -reductase iso-enzyme type 2 is in abundance in the prostate and genital tissues (15).

Finasteride was the first 5 α -reductase (iso-enzyme 2) inhibitor to be studied. Adverse effects associated with its use including reduction of libido and gynaecomastia encouraged the discovery of a second 5 ARI, dutasteride (14). The latter, launched in 2002, is a potent dual inhibitor and inhibits both the iso-enzyme type 1 and type 2.

The suppression of DHT by dutasteride is 95% within the first month of its use. This suppression is reversible when dutasteride is discontinued (16). The intra prostatic DHT suppression has been reported as 89.3% at 2 weeks, 92.4% at 4weeks, and 98.9% at 4months (17).

This reduction of DHT levels has a significant effect on prostatic volume (PV) and reduction reaches 95% clearance in six (6) months in blood. The prostatic volume shrinkage is about 24-25% by the 2nd year of continuous taking of the drug dutasteride (18). This leads to symptoms and flow rate improvement by over 65% with effect maintained over 4 years.

Once an enlarged prostate becomes symptomatic then BPH progression continues to worsen resulting in AUR and BPH related surgery.

The objectives of medical therapy therefore include (i) to treat early disease before symptoms progress to severe forms and avoid AUR/BPH related surgery (ii) to slow down the progression if any (iii) to avoid complications resulting from surgery for the BPH and (iv) to allow patients choices when they demand medical therapy. 5 ARIs fit these objectives.

They control both symptoms of BPH and disease progression to AUR and need for surgery. The men at risk of disease progression benefit the most such as those with prostatic volume > 30cc, PSA of >1.5ng/ml and <10.0 ng/ml, Qmax of less than 12mls/second, ages over 60 years and symptoms severity greater than 7 (19). The low adverse effects (AE's) in long-term use of dutasteride as a dual inhibitor of 5 α reductase iso enzymes (1,2) makes it to be tolerable and acceptable to patients economically and with good compliance, it gives good quality of life according to international prostatic symptom score(IPSS), quality of life(QOL) (20) .

BENEFITS	5 ARIs	ALPHA-BLOCKERS	COMBINATION OF THE TWO
Improvement of symptoms flow rate	✓	✓	✓
Onset of symptom relief in 1-2 weeks	—	✓	✓
Maintenance of symptoms and flow rate improvements	✓	✓	✓
Prevention of symptom progression	✓	✓	✓
Reduction in PV	✓	—	✓
Maintaining reduction in PV	✓	—	✓
Reduce long-term risk of AUR and surgery	✓	—	✓

Table 1: Benefits Profile Of 5 ARI's And Alpha-Blockers And Combination Of The Two

Combination Treatment

Combination drugs medical therapy combines the best of the 5 alpha reductase dual inhibition and alpha-adrenergic blockade for BPH treatment (15). At the onset of treatment, the 5-alpha reductase inhibitors and α -blockers have a combined effect on the symptoms severity reduction, the peak flow rate (Qmax), prostate volume reduction (>30cc). Further benefits of long-term use are reduction of risk for BPH progression to AUR and BPH-related surgery.

The key factors in combination drug therapy are the duration of treatment, (over four years for dutasteride and 6 months for α -blockers).

The maximal effect of alpha blockers is felt at six months. It is therefore possible to withdraw α -blocker drugs after this period without affecting the progressive improvement of symptoms. This allows dutasteride to be continued for longer time(21).

The landmark medical therapy of prostatic symptoms (MTOPs) trial demonstrated over 4 years of the combination of type 2 specific 5 ARI, finasteride and the alpha blocker doxasin was more effective than either agent alone in reducing overall clinical progression (22).

The CombAT (Avodart plus Tamsulosin) trial, 4-year, global, multicenter, randomized, double blind, parallel group study enrolled 4328 men with moderate and severe symptoms of BPH and prostate enlargement: (patients were 50 years and older with prostate volume 30cm + and PSA > 1.5 ng/ml).

The two year analysis showed combination treatment was associated with greater symptoms reduction at 3 months versus dutasteride; greater at 9 months versus

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tamsulosin. The peak flow rate improved versus dutasteride and Tamsulosin from 6 months. The 4-year ComBAT data supported the long term use in men with moderate to severe lower urinary tract symptoms due to BPH and prostate enlargement with greater symptom benefit than either monotherapy (22, 23). (Table 1).

In conclusion, BPH is a universal problem in elderly men with significant impact in their quality of life.

Drug combination medical therapy for BPH is the best first line choice to improve symptoms and prevent progression. Surgery is left for those who do not show improvement or those with severe symptomatology.

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