ARTICLE

Drugs for benign prostatic hypertrophy

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SUMMARY

Benign prostatic hyperplasia is a common condition. It can cause problems with urine storage and voiding, and the severity of symptoms may be unrelated to the size of the prostate.

When drug treatment is required, benign prostatic hyperplasia can be managed with monotherapy or combination therapy. Most patients are managed with selective alpha blockers.

Patients with larger prostate volumes may benefit from a 5-alpha-reductase inhibitor, usually in combination with an alpha blocker.

Introduction

Lower urinary tract symptoms are common and can be classified into either storage (e.g. urinary frequency, nocturia and urgency) or voiding symptoms (weak stream, intermittency of flow, hesitancy).[1] Voiding symptoms in men are usually due to bladder outflow obstruction, of which benign prostatic hyperplasia is the most common cause. It is managed by Australian GPs on over 200 000 occasions each year.[2] While benign prostatic hyperplasia is the histological definition, the term benign prostatic hypertrophy is commonly used when describing the clinical syndrome.[3,4] Although medical or structural complications from benign prostatic hyperplasia are relatively uncommon, bothersome symptoms can affect the patient's quality of life.

The treatment depends on the severity of symptoms. These can be assessed by the International Prostate Symptoms Score (I-PSS).[5] This score quantifies incomplete emptying, frequency, intermittency, urgency, weak stream, straining and nocturia, as well as overall bother, using a 5-point Likert scale.[6]

Management approaches range from observation only, to medical therapy, to minimally invasive, endoscopic or open surgery.[5,7] Men with bothersome lower urinary tract symptoms without complications from benign prostatic hyperplasia, such as urinary retention, hydronephrosis or impaired kidney function, are often good candidates for medical therapy.[8]

Medical therapy

Lower urinary tract symptoms due to benign prostatic hyperplasia are caused by three main factors:[3,4,7]

- dynamic – tone of the prostatic smooth muscle and bladder neck
- static – enlarging prostatic adenoma causing mechanical obstruction
- compensatory – hypertrophy and irritability of the bladder muscle (detrusor).

Medical therapy for benign prostatic hypertrophy largely works by reducing dynamic and static components. In the last decade, clinical trials have shown that drug therapy is beneficial, however the currently available drugs vary in their efficacy depending on the patient's profile.

Alpha blockers

Alpha$_{1a}$ adrenergic receptor inhibition with selective (tamsulosin, silodosin, terazosin, alfuzosin) or non-selective (prazosin) drugs treat the dynamic component of benign prostatic hyperplasia by relaxing smooth muscle in the prostate and bladder neck. This causes the urethral lumen to widen so improving urinary flow.[3] Alpha blockers can improve symptoms and increase the maximal urinary flow rate.[3,5,9-12]

Prazosin was previously the most commonly used alpha blocker, but it requires multiple daily dosing. There are limited efficacy data therefore international guidelines no longer recommend prazosin for lower urinary tract symptoms.[4] Studies have also shown that prazosin has an average discontinuation rate of 17%, due to systemic adverse effects such as dizziness and headaches, presumably caused by postural hypotension.[3]

Tamsulosin is a selective blocker for the alpha$_{1a}$ receptor subtype. It is available in a slow-release formulation, which reduces the systemic adverse effects such as postural hypotension and the need for dose titration.[12] Tamsulosin is a commonly prescribed drug in Australia but reimbursement is only covered by the Repatriation Pharmaceutical Benefits Scheme.

Silodosin is a newer drug that is highly selective for alpha$_{1a}$ receptors. It has demonstrated a similar efficacy to tamsulosin.[13,14]

Adverse effects

Although systemic adverse effects are less frequent with the more selective alpha blockers, they increase the risk of ejaculatory dysfunction.[3] Other adverse effects of alpha blockers include retrograde

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ejaculation, erectile dysfunction, nasal congestion, hypotension, dizziness and tachycardia.[3-5,7,14]

Alpha blockers, particularly tamsulosin, have been associated with intra-operative floppy iris syndrome. This increases the technical difficulty of cataract surgery and increases the incidence of complications such as posterior capsule rupture, iris trauma and vitreous loss.[15] The incidence in patients taking tamsulosin can be 40–90%.[15] If an alpha blocker is being considered for a patient awaiting cataract surgery, it is essential that the ophthalmologist is informed, ideally before the drug is prescribed.

5-alpha-reductase inhibitors

The enzyme 5-alpha-reductase converts testosterone to dihydrotestosterone in the prostate.[16] Inhibition of this enzyme reduces androgenic dihydrotestosterone and subsequently reduces prostatic tissue volume and the static contribution to symptoms.[3,17-19] Dutasteride inhibits both the type 1 and type 2 isoenzymes of 5-alpha-reductase, while finasteride only inhibits the type 2 isoenzyme.[20]

The 5-alpha-reductase inhibitors reduce the progression of benign prostatic hypertrophy, manifested as acute urinary retention or the need for surgery.[21] Compared to alpha blockers, dutasteride and finasteride are more effective in men with larger prostate volumes (>40 mL) or prostate specific antigen (PSA) concentrations above 1.4 ng/mL.[19-21] Finasteride or dutasteride monotherapy is likely to have minimal to no difference for the I-PSS and urinary flow rates compared to placebo among men with prostate volumes less than 40 mL.[8,21-23] Overall the changes in I-PSS and flow rate are less than those with alpha blockers.[3]

The symptomatic benefit can take 3–6 months to emerge.[3,5] The drugs can reduce PSA concentrations by 57–66%.[24,25]

Adverse effects

The most common adverse effects of 5-alpha-reductase inhibitors are erectile dysfunction, decreased libido, decreased ejaculate and decreased semen count.[26] These adverse effects can be irreversible and debilitating, therefore counselling is strongly recommended before prescribing.[26,27]

Combination therapies

The MTOPS trial[28] studied a combination of doxazosin and finasteride (vs monotherapy with placebo, doxazosin or finasteride) and the CombAT trial studied a dutasteride and tamsulosin combination (vs monotherapy with dutasteride or tamsulosin).[7,29] Both of these trials consisted of large cohorts (over 3000 patients each). They found that combination therapy with an alpha blocker and 5-alpha-reductase inhibitor provided a greater improvement in lower urinary tract symptoms compared to monotherapy.[7] Both studies confirmed a reduced relative risk of urinary retention or benign prostatic hyperplasia-related surgery with combination therapy.[28,29] A fixed-dose combination of tamsulosin and dutasteride is now available on the Pharmaceutical Benefits Scheme (PBS) with an authority streamlined listing. However, combination therapy also has an increased risk of adverse effects such as sexual dysfunction, and this needs to be balanced against potential benefits for urinary symptoms.[30]

For select men with bladder outlet obstruction secondary to benign prostatic hyperplasia and concomitant storage symptoms such as urgency and frequency, the combination of an alpha blocker with anticholinergic drug can be helpful.[31] Anticholinergic drugs inhibit acetylcholine-mediated bladder contraction and thus can reduce detrusor overactivity, a compensatory factor contributing to lower urinary tract symptoms. However, anticholinergic therapy in patients with elevated residual urine volume or a history of spontaneous urinary retention should only be considered with a urological opinion.[3]

Phosphodiesterase-5 inhibitors

Phosphodiesterase-5 inhibitors are more commonly used to treat erectile dysfunction. They can be effective in the treatment of lower urinary tract symptoms due to benign prostatic hyperplasia, however they are less effective than alpha blockade therapy according to measures such as I-PSS and maximum urinary flow rate.[32] Phosphodiesterase-5 inhibitors reduce smooth muscle tone in the detrusor, prostate and urethra by increasing intracellular cyclic guanosine monophosphate.[3] As erectile dysfunction is a common adverse effect of 5-alpha-reductase inhibitors, they are sometimes used in combination to counteract it and also to reduce lower urinary tract symptoms.[33]

The combination of phosphodiesterase-5 inhibitors with an alpha blocker results in greater reductions in I-PSS, post-void residual volumes and quality-of-life scores, and greater increases in maximum urinary flow rate than both drugs used as monotherapy.[32] Tadalafil has an indication for benign prostatic hypertrophy and erectile dysfunction. Headache is a common adverse effect of phosphodiesterase-5 inhibitors. They should be avoided in patients receiving nitrates for ischaemic heart disease or those with poor cardiac function.

Referral

Urological referral is indicated for patients who have ongoing symptoms despite medical therapy. It is also indicated for complications including hydronephrosis, deteriorating kidney function, recurrent urinary tract infections, progressive deterioration of residual volume or macroscopic haematuria.

Surgery has a role in the management of benign prostatic hyperplasia. The options range from minimally invasive therapies (e.g. prostatic urethral lift, transurethral needle ablation) to the more invasive transurethral resection of the prostate, and enucleation prostatectomy in select cases.

Conclusion

In the last decade, selective alpha blockers have become the mainstay of drug therapy for uncomplicated benign prostatic hypertrophy. In the absence of contraindications, the first-line therapy for all men is an alpha blocker. In men with larger prostate volumes, combination therapy with an alpha blocker and 5-alpha-reductase inhibitor has been shown to have increased efficacy.

Patients must be informed about the adverse effect profile of these drugs to make a collaborative and holistic decision about which drug to use. Combinations of drugs are likely to have more adverse effects than monotherapy. ◀

Conflict of interest: none declared

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SELF-TEST QUESTIONS

True or false?

1. Phosphodiesterase-5 inhibitors should not be used to treat erectile dysfunction in men with benign prostatic hypertrophy.
2. Flopsy iris syndrome is an adverse effect of alpha blockers.

Answers on page 173

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