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## Pharmacological Management of Benign Prostatic Hypertrophy and Prostate Cancer in Older Men

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### ABSTRACT

Benign prostatic hypertrophy (BPH) and prostate cancer are common conditions affecting older men. Treatment options for these conditions depend on the severity of symptoms, comorbidities and patient choice and include observation, medications and surgery.

BPH is an important cause of lower urinary tract symptoms. Alpha-adrenergic antagonists are useful for mild to moderate symptoms of BPH. Trans-urethral resection of the prostate is the most effective treatment for the relief of symptoms and is the only treatment recommended for serious complications of the disease.

After skin cancers, prostate cancer is the commonest malignancy in older males. Hormonal manipulation with luteinising hormone releasing hormone analogues and antiandrogens form the mainstay of treatment of metastatic prostate cancer.

This article will review the use of drugs and their place in the overall management of these disorders.

**Aust J Hosp Pharm 2001; 31: 115-19.**

### INTRODUCTION

Benign prostatic hypertrophy (BPH) and prostate cancer are common problems in older men. BPH is the most common benign tumour to affect men,<sup>1</sup> with evidence at autopsy in 90% of men in their ninth decade. Serious complications are uncommon, but BPH can be associated with considerable morbidity. Prostate cancer is the most common non-skin cancer in males, with 15-30% of men over 50 and 60% of men aged 80 having histological evidence of prostate cancer at autopsy.<sup>2</sup> This review will discuss these two conditions, focusing on the medical treatments available for each disorder.

Treatment modalities depend on the patient and extent or severity of the disease. Pharmacological management of these conditions should be considered in the context of other available treatments, including observation, surgery, radiotherapy or chemotherapy. In frail older men in particular, the patient's cognitive status, level of physical disability, medical co-morbidity, social supports, and likely drug compliance (as well as the

side effects and potential for drug interactions) should always be taken into account before prescribing new medication. It is often these factors, rather than specific age-related pharmacokinetic or pharmacodynamic changes, which determine whether new medication should be started, at what dose it should be given and how closely it should be monitored.

### BENIGN PROSTATIC HYPERTROPHY

#### Prevalence

Histologically, the prevalence of BPH increases with age, with 50% of men in their 50s and 90% of men over 80 having histological evidence of BPH.<sup>3</sup> For the clinical diagnosis of BPH, population-based studies have shown the prevalence of BPH increases from 24% of men in their 50s to over 50% of men in their 70s.<sup>4</sup> A fifty-year-old man has a 20-30% lifetime chance of needing a prostatectomy for bothersome symptoms, or complications of BPH.<sup>5</sup>

#### Pathophysiology

BPH is due to a combination of hormone dependent hyperplasia (mechanical component) and alpha-adrenergic tone (dynamic component).<sup>6-8</sup> The nodular hyperplasia of stromal and epithelial tissues occurs in the peri-urethral transition zone of the prostate and leads to occlusion of the urethral lumen as it expands. This tissue is hormonally sensitive<sup>6</sup> and atrophies when deprived of androgens. Alpha-adrenergic tone contributes to the total urethral resistance via the smooth muscle tone in hyperplastic prostate tissue and the prostate capsule and bladder neck.

#### Clinical

The symptoms due to BPH can be divided into *voiding* symptoms including decreased force of stream, hesitancy, intermittency, straining to void, incomplete emptying and urinary retention and *storage* symptoms including urgency, frequency, nocturia, dysuria and urge incontinence. Collectively, these symptoms are referred to as lower urinary tract symptoms or LUTS. It is now recognised especially in older men, that not all of these lower urinary tract symptoms are due to BPH and may result from detrusor muscle changes not directly related to prostatic obstruction.

#### Treatment

Approximately 50% of men older than 60 years with symp-

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toms of BPH will be bothered enough by prostatic symptoms to seek treatment.<sup>9</sup> The frequency of serious complications from BPH (urinary tract infection, urinary retention, obstructive uropathy and haematuria) is quite low, so for each patient it is important to balance the severity of the symptoms against the risks of treatment.<sup>5,10</sup> Management approaches include observation ('watchful waiting'), medication and surgery.

### Observation

Unless there is a clear contraindication, observation alone is often recommended for those with mild symptoms or older patients in whom the risks of surgery are high.<sup>11</sup> Studies have shown that after 5 years of observation, 40% of patients with moderate prostatism have an improvement in symptoms, 45% are the same, and only 15% have deteriorated.<sup>6</sup> Simple observation is not appropriate if there is a clear indication for treatment, including urinary retention, recurrent urinary tract infections, gross haematuria, bladder calculi or renal impairment due to BPH.<sup>10</sup>

### Medical Management

Medical management is indicated in men with mild to moderate symptoms, in younger men concerned about the potentially permanent impact on sexual function of bladder neck surgery, in men waiting for surgery or those in whom surgery is contraindicated. Alpha-adrenergic blocking agents are the mainstay of medical management with the 5-alpha reductase inhibitor finasteride less commonly prescribed.

#### Alpha<sub>1</sub>-Adrenergic Antagonists

Alpha-adrenergic antagonist drugs were initially unpopular because of significant side effects (especially postural hypotension), but newer agents have now been introduced with fewer peripheral side effects.

#### *Prazosin*

Prazosin was one of the earliest drugs to be used in the treatment of BPH and is still the only alpha<sub>1</sub>-adrenergic antagonist listed as an unrestricted benefit on the Australian Pharmaceutical Benefits Scheme (PBS). It needs to be taken twice daily and should be started at low doses because of the risk of postural hypotension, e.g. 0.5 mg twice daily, increasing to 2 mg twice daily as tolerated. In frail older men at risk of falling, postural hypotension is of particular concern and limits the usefulness of the drug in this patient group.

#### *Terazosin*

Terazosin is a newer alpha<sub>1</sub>-receptor blocker, which only needs to be taken once daily. It is available through the Repatriation Pharmaceutical Benefits Scheme (RPBS) in Australia for treatment of BPH where surgery is inappropriate, or where other drug treatment has failed or is contraindicated. It has been shown to improve voiding flow rates and symptom scores at doses of 5 to 10 mg daily in men with moderately severe symptoms.<sup>12</sup> Relief of irritative symptoms such as frequency or dysuria is usually apparent at 5 mg (possibly even at 2 mg) while 10 mg is often needed to relieve obstructive symptoms of hesitancy, dribbling and urinary retention.<sup>12</sup>

Terazosin should be given at night and, to minimise postural hypotension, the dose should be titrated grad-

ually from a 1 mg dose either until symptoms develop or the 10 mg maximum dose is reached. It has few side effects in comparison to prazosin (aesthenia, minimal postural hypotension and dizziness in 5-10% of cases). Initial studies suggest that hypotension only occurred in those with previous hypertension,<sup>12</sup> and there was no effect on sexual function or prostate specific antigen (PSA) levels.<sup>6</sup> Terazosin should be used cautiously in those with known hypertension and is contraindicated in men with postural hypotension. No dosage modification is needed in older men.

#### *Other non uro-selective alpha blockers*

Doxazosin and alfuzosin (neither of which is available in Australia on the PBS or RPBS) have similar efficacy and side effect profiles to terazosin.

#### *Tamsulosin*

Tamsulosin is the newest, most uro-selective alpha<sub>1</sub>-blocker and was listed on the RPBS in May 2000. It has a selective higher affinity for the alpha<sub>1a</sub>-receptors found in the prostate and seems to have minimal effect on peripheral vascular alpha<sub>1</sub>-receptors, causing little dizziness or hypotension.<sup>13-15</sup> Tamsulosin can therefore be started at the effective dose of 0.4 mg daily, ensuring more rapid onset of action, with increases to 0.8 mg if required. Studies so far have shown that tamsulosin is as effective as terazosin or doxazosin in improving symptom scores or voiding flow rates. The average increase in maximal flow rates is of the order of 2 to 3 mL/sec; 30% of subjects have an increase of  $\geq 3$  mL/sec, and 70% have a clinically significant improvement in symptom score. The major side effects are dizziness occurring in 6% and abnormal ejaculation occurring in up to 5-16% of men.<sup>8,16,17</sup> The beneficial effects of tamsulosin have been shown to persist for up to 3 years.<sup>17</sup>

#### Finasteride

Finasteride inhibits 5-alpha reductase, the enzyme which converts testosterone to the biologically active dihydrotestosterone. In Australia, it is available on the Repatriation Pharmaceutical Benefits Scheme (RPBS). Inhibition of this enzyme causes androgen deprivation and reduces prostate size.<sup>6</sup> Studies have shown that finasteride in a daily dose of 5 mg reduced prostate volume and led to minor improvements in symptom scores and urinary flow rates,<sup>18,19</sup> especially if the prostate is more than moderately enlarged. The usual dose is 5 mg, with no dose reduction required for older men or those with renal impairment. The main side effects include reduced libido, impotence and sexual dysfunction.<sup>6</sup>

While finasteride has been shown to reduce the need for surgery and risk of acute urinary retention,<sup>20</sup> it takes 6 to 12 months to be effective<sup>10</sup> so has no role in the acute treatment of symptoms. Finasteride does lead to statistically significant improvements in symptom scores and flow rates, but these are of questionable clinical significance and the magnitude of this effect is small in comparison to surgical treatment. For example, the average improvement in flow rate is between 1 to 2 mL/sec, compared to 9.8 mL/sec post trans-urethral prostatectomy. Some studies have shown limited efficacy with up to 40% of patients gaining no benefit.<sup>21</sup>

A study examining the combined use of finasteride and terazosin showed no improvements in symptom

scores or flow rates in those taking the combination therapy in comparison to those on terazosin alone. Combination therapy is therefore not recommended.<sup>21,22</sup>

Alpha<sub>1</sub>-antagonists have a more rapid onset of action and higher success rate and in men without a significantly enlarged prostate should be regarded as the drug of first choice, especially if the new uro-selective agents become more widely available. Finasteride has fewer side effects, but a much slower onset of action. Even in men with larger glands (>40 to 50 mL), alpha<sub>1</sub>-antagonists are equally effective and finasteride is not now widely used.

### **Surgical Management**

Trans-urethral resection of the prostate (TURP) remains the most effective treatment for the relief of symptoms of prostatic hypertrophy<sup>9,16,23</sup> and is the only recommended treatment for serious complications of the disease. It results in symptomatic improvement in 80-90% of patients,<sup>5</sup> although the benefit is reduced (40%) if the patient has irritative symptoms (which are more common in elderly men) or a small gland (40-70%). The overall complication rate for TURP is 18% which increases to 23% if the patient is over 80.<sup>5</sup> Alternatives to prostatic resection include prostatic stents and other surgical modalities (laser TUR, microwave) which have had variable success and are still not widely available.

### **Conclusion**

BPH is a common problem in older men. Drugs do have a place in the treatment of men with mild to moderate symptoms, or in those who cannot have surgery, although TURP is a more effective way of relieving symptoms. The limited availability of newer alpha<sub>1</sub>-blockers such as terazosin (and of finasteride) in Australia is also likely to have influenced prescribing patterns and perhaps contained more widespread use of these drugs.

## **PROSTATE CANCER**

### **Incidence**

Prostate cancer is the most common non-skin cancer in males and caused 2449 deaths in Australia in 1997.<sup>24</sup> The incidence rate for prostate cancer in Australia is 120 cases/100 000 men,<sup>25</sup> with a mortality rate of 25/100 000.<sup>26</sup> The median age at diagnosis is 72 years,<sup>27,28</sup> and there is an average loss of life expectancy of 8 years.<sup>29,30</sup> Prostate cancer is usually asymptomatic, particularly in the early stages, but with increased screening for prostate cancer 60-80% of men are now diagnosed with localised disease.<sup>31</sup>

### **Investigations**

There are two screening investigations available for prostate cancer: the prostate specific antigen (PSA) blood test and digital rectal examination. PSA is elevated in 70-80% men with prostate cancer for up to 13 years before diagnosis,<sup>32</sup> although there is little evidence that screening with PSA for prostate cancer saves lives.<sup>33</sup> Digital rectal examination is used for diagnosis and monitoring. It detects 20-35% of cancers that would have been missed by PSA alone, but is subject to operator error and will miss 44% of organ-confined cancer.<sup>31</sup>

### **Treatment**

Untreated five-year survival is 91-100% for localised dis-

ease (similar to age-matched population), 85-95% for regional disease and only 26-31% for those with distant metastases.<sup>32</sup> Treatment options for prostate cancer depend on the stage and histological grade of the cancer, the age of the patient and co-morbidities. Alternatives include observation, surgery, radiotherapy, hormonal therapy and manipulation, and chemotherapy.

### **Surgery**

Radical prostatectomy is undertaken in men with clinically localised prostate disease and a greater than 10-year life expectancy. It is performed via a retropubic or perineal approach and has been shown to improve survival for men with more poorly differentiated disease.<sup>31</sup> The main complications are urinary incontinence and impotence. Long-term incontinence at 1 year post-operatively has been reported in up to 3% of men, and impotence in between 50-80% of men over 70.<sup>34</sup>

### **Radiotherapy**

Radiotherapy is administered as external beam or interstitial therapy and is used for localised disease and extracapsular local invasion. Radiotherapy provides good local disease control, with survival similar to surgery,<sup>35</sup> and relief from symptoms such as obstruction, pain and bleeding. Interstitial radiotherapy (brachytherapy) has improved with newer techniques and there is now minimal procedure-related morbidity, with fewer bladder or bowel complications.<sup>31,36</sup>

### **Observation**

Patients for whom observation ('watchful waiting') is indicated are those with clinically localised, low grade cancer who have a life expectancy of less than 10 years.<sup>31,35,37</sup>

### **Hormonal Therapy and Manipulation**

Hormonal therapy or manipulation is used for locally advanced or metastatic disease or for relapse after local therapy.<sup>31,37</sup> In general, it is a palliative measure for localised disease and should only be used if a patient refuses or is unable to have more aggressive treatment. Toxicity related to androgen ablation, including impotence, hot flushes, fatigue and potential for osteoporosis, has led to a tendency to not begin hormonal treatment in patients with asymptomatic advanced cancer. However, recent studies have shown that development of symptoms is delayed and possibly survival is improved when treatment is commenced earlier.<sup>38</sup> Treatment should always be started in those with symptoms, or those with large metastatic load and a high risk of complications<sup>35</sup> such as spinal cord compression. Neo-adjuvant hormone therapy should be considered for locally advanced disease if this is to be treated with radiotherapy.<sup>35</sup>

Overall, approximately 80% of men with metastatic disease have symptomatic improvement with hormonal manipulation. The median duration of response is between 1-2 years but varies with disease burden and patient performance status.<sup>39</sup> Median overall survival after beginning hormonal therapy is in the range of 2 to 3 years.<sup>40</sup>

### **Orchidectomy and Diethylstilboestrol**

Bilateral orchidectomy is the most well established mode of hormonal manipulation and is simple and cost-

effective. It is still useful if urgent control of disease is required (for example, for impending spinal cord compression) and for those men without access to hormonal treatment.<sup>41</sup> Diethylstilboestrol is an effective older agent which acts by inhibiting luteinising hormone release hormone (LHRH) release from the hypothalamus but is no longer commonly used due to thromboembolic complications.<sup>31,41</sup>

### LHRH Analogues

LHRH analogues act by binding to pituitary receptors. This causes a surge in luteinising hormone (LH) leading to elevated testosterone levels in turn causing an inhibitory feedback loop that reduces testosterone production. The anterior pituitary is depleted of LH and there is also down regulation of the testicular LH receptors. Available agents include leuprorelin and goserelin. They are given every one to three months in depot injectable form; leuprorelin by a deep intramuscular injection and goserelin by the subcutaneous injection of a pellet using a large gauge needle. The initial elevation in androgen levels may be associated with a 'flare' reaction of bone pain, and a risk of increasing tumour size, within 5 to 7 days of treatment. This effect can be minimised by the use of an antiandrogen (e.g. cyproterone acetate or flutamide) for 7 days prior and 3 weeks after commencing treatment.<sup>35</sup>

These agents are suitable in older men in whom drug compliance may be a problem. Apart from the flare reaction, major side effects are the problems associated with longer-term androgen ablation therapy such as hot flushes, decreased muscle mass, decreased libido, gynaecomastia, and psychological or cognitive changes.

### Androgen Receptor Antagonists

#### *Steroidal Agents*

Cyproterone acetate is a steroidal antiandrogen taken in a dose of from 100 to 300 mg daily. When given after orchidectomy or with LHRH analogues, it reduces the frequency of hot flushes due to androgen deprivation,<sup>35</sup> although there is a suggestion it may be associated with reduced survival when compared to non-steroidal antiandrogens in this situation.<sup>40</sup> The most important adverse effects are cardiotoxicity (occurring in 8-10% of cases) and severe hepatotoxicity in 2-5%.<sup>42</sup> Cyproterone is therefore not recommended for long-term use.<sup>35</sup>

#### *Non-Steroidal Antiandrogens*

The non-steroidal androgen receptor antagonists flutamide, bicalutamide or nilutamide can be used in addition to orchidectomy or LHRH analogues. Usual daily doses are 750 mg for flutamide and 50 mg for bicalutamide. Flutamide has the disadvantage in older men of requiring three times a day dosing, whereas bicalutamide is taken only once daily. The most important side effect of flutamide is hepatotoxicity, with elevations in aminotransferase levels usually occurring within the first few months of treatment. Liver function tests therefore need to be monitored regularly after starting therapy. Both agents may cause diarrhoea, and lead to the hormonal side effects of longer-term androgen ablation therapy. Nilutamide is not usually recommended as it has a greater range of side effects.

In Australia, flutamide and bicalutamide are only approved for use on the PBS in combination with LHRH analogues, where they are useful in controlling the symp-

oms of the flare reaction associated with commencement of these agents in the shorter term, or for combined androgen blockade in the longer term. When used as monotherapy in metastatic prostate cancer, there is some evidence that non-steroidal antiandrogens are less effective than orchidectomy or LHRH analogues.<sup>43</sup>

### Combined Androgen Blockade

Combined androgen blockade (CAB) is the use of androgen suppression therapy (orchidectomy or LHRH analogue) in conjunction with an antiandrogen to block adrenal as well as testicular androgens. Most studies, including a recent meta-analysis, have shown little or no survival benefit from combined androgen blockade<sup>40</sup> and this is not currently recommended as routine management.<sup>35</sup>

### Neo-Adjuvant Hormonal Therapy

Hormonal therapy has been shown in a series of prospective trials to be effective when used prior to radiotherapy or surgery as *neo-adjuvant therapy*. LHRH analogues and antiandrogens have been shown to reduce positive margin rate,<sup>44</sup> tumour size, PSA, pathologic stage and time to disease progression<sup>45</sup> in men undergoing radical prostatectomy for clinically localised prostate cancer. Neo-adjuvant therapy does not improve recurrence or survival rate,<sup>37</sup> and it may make surgery and subsequent histology more difficult.<sup>37,46</sup> In locally advanced disease, androgen suppression combined with radiotherapy gives better short-term local control and longer disease free survival with a suggestion of increased overall survival if an LHRH analogue is continued post radiotherapy.<sup>47</sup>

### Chemotherapy

Chemotherapeutic regimens have been developed which have been shown to be effective in hormone-refractory prostate cancer.<sup>37,48</sup> In this setting, chemotherapy can lead to a clinical and biochemical response, but has not yet been shown to increase survival. Successful combinations include mitozantrone and prednisolone, estramustine (combination mustard and oestradiol) and paclitaxel or etoposide, and oral estramustine and etoposide. Chemotherapy is not widely used for prostatic cancer in Australia.

### Other Palliative Therapy

Analgesia for locally extensive or bony disease is also important, especially when the disease becomes refractory to hormone treatment. Bone pain may be effectively treated with steroids or non-steroidal analgesics, bisphosphonates<sup>49</sup> or with local radiotherapy, the latter often in single doses. In men with more extensive disease and with adequate marrow reserves, strontium 89 or hemibody X-ray therapy are effective for the relief of bone pain.<sup>35</sup> Narcotic analgesia however may eventually be necessary and at this stage involvement of a local palliative care service, in conjunction with those providing medical care, can be very worthwhile in optimising pain relief, treating other symptoms and addressing the psycho-social needs of the patient and his family.

### Conclusion

Prostate cancer is a common problem affecting a significant number of older men. With increased awareness

and screening, the disease is now usually localised at the time of diagnosis. Treatment options for localised disease include observation, surgery and local radiotherapy, with the choice being influenced by patient preference and life expectancy. Metastatic disease is usually treated by hormonal manipulation; the main hormones used are LHRH agonists and antiandrogens. Research into different types of chemotherapy continues, but although there are symptomatic improvements, survival benefit has yet to be achieved. It is important to establish the severity of symptoms for the older patient and to tailor a treatment regimen which takes account of the patient's expectations, co-morbidities, and social circumstances.

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Submitted: February 2001

Accepted after external review: May 2001