

## BENIGN PROSTATIC HYPERPLASIA

### SUMMARY



**BPH affects the quality not quantity of life.**



**Surgery is regarded as the "gold standard" in BPH treatment.**



**Alpha blockers are the drugs of first choice for medical management.**



**Finasteride may be of benefit in patient's with large prostate glands.**

### INTRODUCTION

Benign prostatic hyperplasia (BPH) is a non-malignant enlargement of the prostate due to excessive cellular growth of both the glandular and stromal elements of the gland.<sup>1</sup> It is the most common benign tumour in men.<sup>2-4</sup> BPH is identifiable in 50% of men over 60 years and the prevalence increases with age.<sup>5,6</sup> It can affect a patient's quality of life significantly as well as representing a significant burden to the health service.<sup>4</sup> While surgery remains the "gold standard" for treatment of BPH the introduction of several new drugs has increased the therapeutic options available.

### PATHOPHYSIOLOGY

The aetiology of this condition is thought to involve alterations in hormonal balance associated with ageing.<sup>7</sup> Patients commonly present with obstructive voiding symptoms. These occur due to coalescence and compression of peri-urethral nodules which impede the flow of urine. Further obstruction is caused by an increase in the tone of the prostatic smooth muscle.<sup>2,3,6,8</sup> The bladder wall thickens in response to this obstruction and secondary detrusor instability occurs. This results in the irritative symptoms associated with BPH.<sup>9-12</sup> The clinical course of patients with BPH is variable.

### DIAGNOSIS

A shared care approach to BPH although still in its infancy is favoured. Screening programmes are being encouraged in general practice.<sup>10</sup> Initial evaluation should assess not only the extent of the patient's symptoms (*Table 1*) but also his suitability for the various treatment options available. Objective findings of BPH on physical examination include palpation of an enlarged prostate or a distended bladder, urine dipstick analysis and serum creatinine. Prostate specific antigen (PSA) a serum marker for prostate cancer can be measured where a high index of suspicion exists. Other investigations that may be carried out, though usually in a hospital setting, include uroflowmetry and pressure flow studies.<sup>3,6,10,13</sup>

**Table 1 Symptoms Associated with BPH**

| <u>Obstructive Symptoms</u> | <u>Irritative Symptoms</u> |
|-----------------------------|----------------------------|
| Hesitancy                   | Frequency                  |
| Straining                   | Urgency                    |
| Weak stream                 | Nocturia                   |
| Terminal dribbling          | Urge incontinence          |
| Prolonged voiding           | Small voided volume        |
| Retention                   |                            |
| Overflow incontinence       |                            |

## **TREATMENT**

Treatment options for BPH are categorised as either surgical or non-surgical intervention. The choice of therapy must be based on the individual patient, the nature, severity and duration of symptoms and the efficacy and side effects of treatment.<sup>3</sup>

## **SURGERY**

In terms of outcome, surgery is still regarded as the "gold standard" in BPH treatment. The main surgical intervention employed is the Transurethral Resection of Prostate (TURP). This has been the mainstay of treatment for BPH for the last 60 years.<sup>14</sup> It is particularly useful for obstructive symptoms although irritative symptoms may also improve where bladder preoperative changes are not prolonged or excessive.<sup>10</sup> Surgical management is recommended for patients with the most advanced disease.<sup>15</sup> Beneficial though TURP is, it is not without adverse effects. Approximately 10% of men do not have a satisfactory outcome, with 75% reporting adverse effects such as retrograde ejaculation (75%) and impotence (5-10%).<sup>5</sup>

Several minimally invasive procedures have been investigated as alternatives to surgery in recent times. These procedures have a lower morbidity than conventional surgery and include balloon dilation, laser ablation treatments and thermotherapy. The long term effectiveness of these procedures however still needs to be fully evaluated.<sup>5,9,10,13,14,16</sup>

## **WATCHFUL WAITING**

Watchful waiting involves continued re-evaluation of the patient with BPH using no medical or surgical therapy. This is an appropriate treatment strategy for patients with mild disease. Patients should be monitored periodically by reassessment of symptom level, physical findings and routine laboratory testing.<sup>12,13,16-18</sup>

## **DRUG TREATMENT**

Drug therapy for BPH is indicated in patients with moderate symptoms of bladder obstruction for whom a strong indication for surgery does not exist. The two main pharmacological approaches to the management of BPH are alpha blockers and 5-alpha reductase inhibitors.

### **Alpha Blockers**

These agents are most beneficial in patients with mild to moderate symptoms of BPH.<sup>19</sup> They act by decreasing the smooth muscle tone of the prostate and bladder neck thereby ameliorating symptoms of bladder outflow obstruction. As such they have a role in the treatment of patients with obstructive symptoms of BPH and remain the drugs of first choice for medical management of BPH.<sup>2,5,11,13,18</sup>

The advantages of using alpha blockers are threefold. Firstly, the onset of action is rapid (within four weeks) compared to finasteride. This is particularly useful for patients seeking prompt relief. Secondly, additional benefits in patients with concomitant hypertension may be gained and finally they are less likely to interfere with male sexual function or the usefulness of PSA in the detection of prostate cancer.<sup>1,11,13</sup> Alpha blockers are not thought to reduce complication rates or the eventual need for surgery and do not alter the underlying disease in BPH.<sup>5,11</sup>

Blockade with successful alleviation of symptoms was first reported with the non-selective alpha blocker, phenoxybenzamine.<sup>10</sup> Its use for this indication has diminished due to the high incidence of adverse effects and the introduction of more selective agents.

Five selective alpha blockers are licensed in Ireland for BPH at present, namely, indoramin, prazosin, terazosin, tamsulosin and alfuzosin. Research has shown that selective alpha blockers are safe and effective in the management of BPH.<sup>1,8,20</sup>

Although few comparative studies of selective alpha blockers exist clinical efficacies are thought to be similar at optimal dose levels.<sup>1,8,20</sup> In the absence of convincing data showing superiority of one agent, the less expensive agents should be considered as first choice. Longer acting agents e.g. terazosin may offer an advantage with regard to patient compliance and possibly side effect profiles.<sup>18</sup> Side effects arise due to predictable pharmacological effects of receptor blockade at sites other than the target site e.g. postural hypotension. This can be minimised by prescribing the dose at night. Other adverse effects reported include tiredness, dizziness, nasal congestion and headache.<sup>1-3,9,11,16-18,21</sup> To minimise adverse effects and improve tolerance to these agents they must be carefully and slowly titrated up to their full therapeutic dosage.<sup>9</sup> Newer prostate selective agents e.g. tamsulosin may minimise vasodilatory side effects however any significant advantage over other selective alpha blockers has yet to be shown.<sup>5</sup>

Clinically significant drug interactions have been reported to occur between alpha blockers and beta blockers, calcium channel blockers and diuretics resulting in an enhanced hypotensive effect.

### **Finasteride**

Finasteride is a 5-alpha reductase inhibitor that blocks the conversion of testosterone to dihydrotestosterone (DHT). DHT is essential for prostatic growth and finasteride ameliorates the symptoms of BPH by causing involution of hyperplastic prostatic tissue.<sup>4,8,11,13,21</sup> It is given in a dose of 5mg once a day. Due to its mode of action, time must be allowed for regression of the enlarged prostate. Improvement of symptoms may take at least six months to occur.<sup>1,2,8,10,11,13,21</sup> Studies have shown finasteride to be most effective in patient's with large prostate glands (> 40g)<sup>12</sup>. A reduction in prostate size of between 20-30% has been reported after 6-12 months of therapy.<sup>5,21</sup> These are characterised by an overgrowth of epithelial elements which would respond best to androgen deprivation therapy by 5 alpha reductase inhibitors.<sup>22</sup> If improvement, occurs the medication must be continued long term otherwise the prostate will regrow to its original size.<sup>8</sup> A recently published study showed that finasteride remains effective when taken for up to four years.<sup>23</sup>

Side effects reported include decreased libido, problems with ejaculation and impotence.<sup>4,5,10,11,17,21</sup> Finasteride is excreted in the semen and is known to be teratogenic to male fetuses giving rise to abnormalities of the external genitalia. The use of condoms is recommended if the sexual partner is pregnant or likely to become pregnant. Women of childbearing potential should avoid handling broken or crushed tablets.<sup>2,5</sup>

Finasteride has been shown to reduce the levels of PSA a tumour marker for screening and monitoring treatment response of prostate cancer. If a patient opts for finasteride treatment a baseline PSA value should be obtained.<sup>4,9</sup>

### **Combination Therapy**

As alpha blockers and finasteride have different modes of action combination therapy may in theory be more effective than either agent alone. However a recent study has shown that although effective this combination of finasteride and terazosin is no more effective than terazosin alone.<sup>24</sup>

### **Other Treatment Options**

GnRH agonists, anti-androgens, progestogens, anticholinergics and phytotherapy are agents investigated as alternative treatments for BPH. GnRH agonists e.g. leuprorelin act by blocking the action of luteinising hormone (LH). This leads to reduced production of testosterone. Studies have shown that prostate volume and severity of urinary symptoms of BPH have been reduced. Anti-androgens e.g. flutamide act by competitive inhibition of androgen receptors in prostatic cells leading to shrinkage of the prostate.<sup>3,4</sup> Progestogens e.g. megestrol possess an androgen suppressing effect by inhibiting LH release and androgen receptor blockade. This results in a decrease in serum testosterone levels leading to a reduction in prostatic volume.<sup>4</sup> Anticholinergics have been used for bladder instability (frequency, urgency) which may mimic or co-exist with BPH. They should only be used after a urodynamic assessment has excluded significant obstruction.<sup>8</sup>

Although these agents have shown beneficial effects in the treatment of BPH, their undesirable side effects and their prohibitive costs have limited their widespread use.<sup>3</sup>

**Cost of 28 Days Therapy (GMS - March 1998)**



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