BMJ Learning

Benign prostatic hyperplasia: treatment in primary care

Anand K Patel, Christopher R Chapple

This article provides information on how to treat patients with lower urinary tract symptoms that are suggestive of bladder outflow obstruction, secondary to benign prostatic hyperplasia

How do I treat it?

The treatment of lower urinary tract symptoms that are suggestive of bladder outflow obstruction, secondary to benign prostatic hyperplasia, should aim to relieve symptoms and improve quality of life, as well as attempt to prevent progression of clinical disease and the development of complications. These benefits need to be balanced against potential side effects of treatment.

Watchful waiting

Patients with mild symptoms that have little impact on quality of life and who have no evidence of complications can be managed conservatively. They should be advised to reduce fluid intake and avoid caffeinated drinks and alcohol if appropriate. This requires the use of frequency and voiding charts.

It may be helpful to review the drugs they are taking, such as diuretics, and any impairment of mental state, dexterity, or mobility should be optimised to limit the impact on quality of life.[1] Patients selected for watchful waiting should be encouraged to seek medical advice if their symptoms deteriorate, so appropriate treatment can be initiated promptly.

Medical treatment

Options if medical treatment is needed are:

- α Antagonists
- 5α Reductase inhibitors
- Combination therapy.

α Antagonists

Contraction of the prostatic smooth muscle occurs after activation of the α_1 adrenoceptors. Inhibition of these receptors relaxes the muscle in the bladder outflow tract; this decreases urinary outflow resistance and helps improve the symptoms. α Antagonists are the first line treatment for benign prostatic hyperplasia.

Summary points

- Benign prostatic hyperplasia leads to progressive clinical disease in a proportion of patients
- α Antagonists rapidly improve lower urinary tract symptoms, and alfuzosin and tamsulosin (as once daily preparations) are the safest options
- 5α Reductase inhibitors reduce prostatic volume by 20-30% but take up to six months to improve symptoms
- 5α Reductase inhibitors are more effective in patients with larger prostates who are at high risk of progression of disease
- Long term combination therapy (α antagonist plus 5α reductase inhibitor) decreases progression of disease in patients at high risk

Benefits

α Antagonists act rapidly (usually within 48 hours), and improvement of symptoms is immediately noticeable to the patient. About 70% of men will respond to this treatment, and non-responders can be identified rapidly and other treatments instigated.

Evidence

Many randomised controlled trials have been performed, and recent systematic reviews have confirmed that all α antagonists have a similar efficacy and that newer longer acting drugs are no more effective than older ones.[2] These drugs tend to improve symptom scores by 30-40% and improve the maximum flow rate by 15-30%.[3] Unlike 5α reductase inhibitors, they do not affect prostate volume and therefore do not alter disease progression.

Side effects

Although all α antagonists have similar efficacies, their side effects differ because they have different actions on α receptors in other organ systems, particularly the

This article is based on a module that is available on BMJ Learning (www.bmjlearning.com)

Urology Research, J Floor, Royal Hallamshire Hospital, Sheffield S10 2JF

Anand K Patel
research registrar

Christopher R Chapple
professor of urology and consultant urological surgeon

Correspondence to:
CR Chapple
c.r.chapple@sheffield.ac.uk

BMJ 2006;333:535–9

Side effects of α antagonists

Cardiovascular system
Postural hypotension
Headaches
Dizziness

Central nervous system
Dizziness
Asthenia
Somnolence

Genitourinary system
Abnormal ejaculation

cardiovascular, central nervous, and genitourinary systems (box).

Abnormal ejaculation is a recognised side effect of treatment with an α antagonist.[4] No α antagonist has been shown definitely to have a better profile for this side effect, although a higher incidence of abnormal ejaculation has been reported for tamsulosin.

Elderly patients are less likely to discontinue treatment because of ejaculatory dysfunction than cardiovascular side effects. The cardiovascular side effects should determine the choice of α antagonist in older patients but not in younger men.

Alfuzosin

Open label studies with alfuzosin have shown that patients with pre-existing cardiovascular disease or those taking other drugs are at increased risk of developing cardiovascular side effects with this drug. This is also the case for patients over 74 years.[5]

However, prolonged release formulations have fewer age related side effects and are associated with only a slightly increased risk of cardiovascular side effects in patients with pre-existing hypertension.[6] The side effects therefore depend on the formulation, and this should be considered carefully when choosing a preparation.

Doxazosin

Four studies have shown an increase in cardiovascular side effects when this drug is used in patients with known or treated hypertension. Data were consistent across all four studies but were not statistically significant, probably because of the low number of patients in the hypertensive subgroups.[5]

Terazosin

Blood pressure was lowered more frequently with this drug than with placebo, but cardiovascular side effects were not significantly different in the hypertensive and non-hypertensive subgroups.[7]

Tamsulosin

Trials have confirmed that tamsulosin is well tolerated and that side effects are not significantly different from placebo in elderly patients and patients with hypertension.[8]

Three randomised controlled trials have studied the effect of concurrent treatment with tamsulosin and antihypertensive drugs (nifedipine, enalapril, and atenolol). They found no alteration in the pharmacodynamic response and no need to adjust the dose of the antihypertensive drugs.[9] Blood pressure is lowered further when a phosphodiesterase type 5 inhibitor (sildenafil, tadalafil, and vardenafil) is added to most α antagonists, although this effect is minimal with tamsulosin.[10]

Recently a new controlled release delivery system for tamsulosin—the oral controlled absorption system (Flomaxtra XL) has been developed to achieve continuous and consistent absorption of tamsulosin throughout the gastrointestinal system. This new preparation maintains consistent 24 hour plasma concentrations of the drug.[11] However, the efficacy is similar to existing preparations.

Doses

- Alfuzosin: 2.5 mg three times a day or 10 mg once a day (once daily preparation)
- Doxazosin: 1-8 mg once a day (usual maintenance dose 2-4 mg once a day)
- Tamsulosin: 0.4 mg once a day (same dose for modified release formulations)
- Terazosin: 1-10 mg once a day (usual maintenance dose 5-10 mg once a day). This drug needs to be titrated to its therapeutic dose to avoid first dose hypotension. It therefore has a slower onset of action than drugs that are started at their therapeutic dose.

Recommendations

α Antagonists are suitable for patients with moderate to severe lower urinary tract symptoms and a low or intermediate risk of progression of disease. Based on systematic reviews, tamsulosin and once daily preparations of extended release alfuzosin have the lowest risk of cardiovascular adverse events and are suitable as first line agents, especially in high risk and elderly patients.[12] The other α antagonists are appropriate for younger patients or those unlikely to have cardiovascular side effects.

Floppy iris syndrome, which may cause technical problems during cataract surgery, has recently been reported as a side effect of α antagonists. This syndrome is seen most often with tamsulosin, and ophthalmologists undertaking cataract surgery need to identify patients who are taking an α antagonist.[13]

5α Reductase inhibitors

Testosterone is converted to dihydrotestosterone by the enzyme 5α reductase within prostate cells. Dihydrotestosterone acts on prostatic tissue to induce

GP tips

Refer all patients with complications of benign prostatic hyperplasia (haematuria, retention, renal dysfunction, and recurrent urinary tract infections)

Although all α antagonists have a similar efficacy, the tolerability and side effects are determined by the formulation given

Make patients aware that 5α reductase inhibitors take about six months before improvements in symptoms are seen

5α Reductase inhibitors decrease serum prostate specific antigen concentrations by about 50%

benign prostatic hyperplasia. 5α Reductase inhibitors decrease the production of dihydrotestosterone, thereby arresting prostatic hyperplasia.

Two 5α reductase inhibitors are licensed in the United Kingdom, finasteride and dutasteride (table 1).

Benefits

5α Reductase inhibitors are thought to decrease the progression of disease and the development of acute urinary retention. They are especially beneficial for patients with risk factors for progression of disease (table 2).[15]

The reduction in risk is a consequence of the decrease in prostate volume with the use of 5α reductase inhibitors. However, shrinkage is slow and symptoms often do not improve in the first six months of treatment.

Side effects

Side effects are:

- Erectile dysfunction
- Reduced libido
- Ejaculatory disorders
- Gynaecomastia
- Breast tenderness.

Evidence

Finasteride

A systematic review of 19 randomised placebo controlled trials showed that symptom scores and flow rates consistently improved and prostate volume decreased by 25% in patients on finasteride.[16] However, about a third of men stopped taking finasteride over two years. Only 6% of these men stopped because of lack of benefit and 12% stopped because of side effects, and the number of men who stopped taking finasteride was not significantly different from those who stopped taking placebo.

Dutasteride

Two multicentre randomised placebo controlled trials lasting two years with open label extension for a further two years have been pooled.[17] These showed improved symptom scores, a 26% decrease in prostatic volume, and improved urinary flow rates with dutasteride. They also showed a 57% reduction in relative risk of acute urinary retention and a 48% reduction in relative risk of the need for prostatic surgery.

However, a large head to head randomised multicentre comparison trial between finasteride and dutasteride found no significant difference between these drugs with respect to their safety profiles or changes in prostate volume, symptom score, or peak flow rate.[14 18] Thus little difference exists between the two drugs, and a dual action 5α reductase inhibitor does not seem to be of additional benefit in the management of benign prostatic hyperplasia.

Table 1 Reduction in dihydrotestosterone by 5α reductase inhibitors[14]

Drug	Type of enzyme inhibited	Reduction of serum dihydrotestosterone
Finasteride	5α reductase type 2	70-75%
Dutasteride	5α reductase types 1 and 2 (dual action)	90-95%

Table 2 Risk factors for progression of disease

Measure	Risk factor
Age	>70 years
International prostate symptom score	>7 (moderate or severe lower urinary tract symptoms)
Prostate volume	>30 ml
Concentration of prostate specific antigen (proxy for prostate volume)	>1.4 ng/ml
Peak urinary flow rate	<12 ml/s
Post void residual urine volume	>100 ml

Doses

- Finasteride: 5 mg once daily
- Dutasteride: 0.5 mg once daily.

Cautions

Both dutasteride and finasteride decrease serum concentrations of prostate specific antigen by about a half, and reference values need to be adjusted if a patient is suspected of having or is being followed up for prostate cancer.

Recommendations

5α Reductase inhibitors are a suitable option in patients with moderate or severe lower urinary tract symptoms with an obviously enlarged prostate or prostate specific antigen concentration greater than 1.4 μg/litre.[19] Both currently available agents have similar efficacies and profiles of adverse events. It should be stressed to the patient that there may be no apparent improvement in symptoms for six months and that treatment will need to continue long term.

Combination therapy

The well publicised medical therapy of prostatic symptoms (MTOPS) multicentre randomised controlled trial looked at the long term progress (mean 4.5 years) of patients randomised to either placebo, finasteride, doxazosin, or both (combination therapy).[20]

The trial showed that finasteride and doxazosin had a similar ability to prevent progression of disease (34-39% compared with placebo), but the combination of both drugs was more effective (66% compared with placebo). However, the end points used to measure progression of disease were controversial.

The risks of progression to acute urinary retention or the necessity for surgery were also significantly reduced by both finasteride and combination therapy, but not by doxazosin alone. However cumulatively more side effects were reported with combination therapy, and it must be borne in mind that the risk of retention in this population is low (0.6/100 person years) and the decision about whether to operate is a subjective end point.

Recommendations

The medical therapy of prostatic symptoms trial presents the first evidence that combination therapy for more than a year is better than monotherapy at preventing progression of disease. It suggests that this approach should be adopted in patients at high risk of progression (high prostate volume, high concentration of prostate specific antigen (where prostate cancer has been excluded), or high post void residual urine volume) who also have symptoms. Unfortunately, these

are the only data from a randomised controlled trial that are available to support this strategy.

It is important to realise that patients will need to be on combination therapy indefinitely, with only a small improvement in symptom score compared with monotherapy. A population cost-benefit analysis of improving progression of disease has yet to endorse this approach to treatment, and any therapeutic advantage of combination therapy needs to be balanced against the increased side effects and costs.

Alternative treatments

Several plant extracts have been reported to improve lower urinary tract symptoms due to benign prostatic hyperplasia.[21] These include:

- Extract of *Serenoa repens* (saw palmetto) berry
- Extract of *Curcurbita pepo* (pumpkin) seed
- Extract of *Urtica dioica* (stinging nettle) root
- Extract of *Opuntia* (cactus) flower
- Extract of *Hypoxis rooperi* (South African star grass)
- Extract of *Pygeum africanum* (African plum tree).

Some studies suggest that these extracts are as effective as α antagonists. However, the studies are often poorly designed, and the extracts have not undergone the same scrutiny as conventional drugs for efficacy, purity, and safety. The World Health Organization international consultation on urological disease consensus group does not recommend treatment with these extracts until more robust evidence exists.[2]

Surgical management

Surgery is performed less often now that effective pharmacotherapy is available, but it is an excellent option for improving symptoms and decreasing progression of disease in patients who develop complications or who have inadequately controlled symptoms on medical treatment.

Sample questions

1. A 74 year old man attends your surgery with lower urinary tract problems, mainly storage symptoms. What should you do?
   a. Start him on a 5α reductase inhibitor (such as finasteride)
   b. Start him on an α antagonist (such as doxazosin)
   c. Perform urinalysis and tell the patient to keep a voiding diary
2. A 68 year old man presents with a four day history of worsening lower urinary tract symptoms. He now also has suprapubic pain and difficulty voiding. What should you do?
   a. Contact the local urology department and arrange admission
   b. Check his creatinine concentration and then decide whether to refer him or request an ultrasound scan
   c. Start alfuzosin 10 mg once daily to reduce symptoms quickly
3. A 75 year old man who is taking nifedipine and atenolol for hypertension presents with mild obstructive lower urinary tract symptoms. What should you do?
   a. Start an α blocker
   b. Manage initially with watchful waiting
   c. Start a 5α reductase inhibitor

When should I refer my patient?

The National Institute for Health and Clinical Excellence produced guidelines to help doctors decide who to refer to secondary care.[22] It recommends referring patients with:

- Suspected complications
- Haematuria
- Renal impairment
- Hydronephrosis
- Recurrent urinary tract infections
  Suspected prostate cancer
  Large residual volumes of urine (>200 ml)
  An unclear diagnosis
  No improvement on initial medical treatment.
  You should refer your patient urgently if they have:
- Acute or chronic urinary retention
- Renal failure
- Any suspicion of neurological dysfunction.

Contributors: AKP wrote the article with the help of CRC who recently chaired the World Health Organization committee into the medical treatment of benign prostatic hyperplasia. CRC checked the article for accuracy and relevance, and he ensured that it was up to date and agreed with current guidelines. CRC is guarantor.

Competing interests: CRC has acted as a consultant or received research funding (or both) from Pfizer, Astellas, Abbott, and Recordati Pharmaceuticals. AKP has no competing interests to declare.

1 Madersbacher S, Alivizatos G, Nordling J, Sanz CR, Emberton M, de la Rosette JJ. EAU 2004 guidelines on assessment, therapy and follow-up of men with lower urinary tract symptoms suggestive of benign prostatic obstruction (BPH guidelines). *Eur Urol* 2004;46:547-54.
2 Chapple C, Artibani W, Berges R, Kaplan S, Michel M, Perrin P, et al. New medical developments in the management of LUTS in adult men (World Health Organization report, committee 6). In: McConnel J, Abrams P, Denis L, Khoury S, Roehrborn C, eds. *Male lower urinary tract dysfunction*. Jersey: Health Publications, 2006:143-94.
3 Milani S, Djavan B. Lower urinary tract symptoms suggestive of benign prostatic hyperplasia: latest update on alpha-adrenoceptor antagonists. *BJU Int* 2005;95(suppl 4):29-36.
4 Lowe FC. Treatment of lower urinary tract symptoms suggestive of benign prostatic hyperplasia: sexual function. *BJU Int* 2005;95(suppl 4):12-8.
5 Barendrecht MM, Koopmans RP, de la Rosette JJ, Michel MC. Treatment of lower urinary tract symptoms suggestive of benign prostatic hyperplasia: the cardiovascular system. *BJU Int* 2005;95(suppl 4):19-28.
6 Van Kerrebroeck P, Jardin A, van Cangh P, Laval KU. Long-term safety and efficacy of a once-daily formulation of alfuzosin 10 mg in patients with symptomatic benign prostatic hyperplasia: open-label extension study. *Eur Urol* 2002;41:54-60; discussion:1.
7 Lowe FC, Olson PJ, Padley RJ. Effects of terazosin therapy on blood pressure in men with benign prostatic hyperplasia concurrently treated with other antihypertensive medications. *Urology* 1999;54:81-5.
8 Chapple CR, Baert L, Thind P, Hofner K, Khoe GS, Spangberg A. Tamsulosin 0.4 mg once daily: tolerability in older and younger patients with lower urinary tract symptoms suggestive of benign prostatic obstruction (symptomatic BPH). The European Tamsulosin Study Group. *Eur Urol* 1997;32:462-70.
9 Lowe FC. Coadministration of tamsulosin and three antihypertensive agents in patients with benign prostatic hyperplasia: pharmacodynamic effect. *Clin Ther* 1997;19:730-42.
10 Kloner RA, Jackson G, Emmick JT, Mitchell MI, Bedding A, Warner MR, et al. Interaction between the phosphodiesterase 5 inhibitor, tadalafil and 2 alpha-blockers, doxazosin and tamsulosin in healthy normotensive men. *J Urol* 2004;172:1935-40.
11 Chapple CR. The oral controlled absorption system (OCAS(R)): the evolution of tamsulosin for the treatment of lower urinary tract symptoms suggestive of benign prostatic hyperplasia (LUTS/BPH). *Eur Urol Suppl* 2005;4:20-2.
12 Crawford ED. Management of lower urinary tract symptoms suggestive of benign prostatic hyperplasia: the central role of the patient risk profile. *BJU Int* 2005;95(suppl 4):1-5.
13 Chang DF, Campbell JR. Intraoperative floppy iris syndrome associated with tamsulosin. *J Cataract Refract Surg* 2005;31:664-73.

14 Andriole GL, Kirby R. Safety and tolerability of the dual 5α-reductase inhibitor dutasteride in the treatment of benign prostatic hyperplasia. *Eur Urol* 2003;44:82-8.
15 Speakman MJ, Kirby RS, Joyce A, Abrams P, Pocock R. Guideline for the primary care management of male lower urinary tract symptoms. *BJU Int* 2004;93:985-90.
16 Edwards JE, Moore RA. Finasteride in the treatment of clinical benign prostatic hyperplasia: a systematic review of randomised trials. *BMC Urol* 2002;2:14.
17 Roehrborn CG, Marks LS, Fenter T, Freedman S, Tuttle J, Gittleman M, et al. Efficacy and safety of dutasteride in the four-year treatment of men with benign prostatic hyperplasia. *Urology* 2004;63:709-15.
18 GlaxoSmithKline trial registration website. Study No: ARI40001, year 1. Last updated 22 December 2004. http://ctr.gsk.co.uk/Summary/dutasteride/studylist.asp (last accessed 18 Jul 2006).
19 Kaplan S, Garvin D, Gilhooly P, Koppel M, Labasky R, Milsten R, et al. Impact of baseline symptom severity on future risk of benign prostatic hyperplasia-related outcomes and long-term response to finasteride. The Pless Study Group. *Urology* 2000;56:610-6.
20 McConnell JD, Roehrborn CG, Bautista OM, Andriole GL Jr, Dixon CM, Kusek JW, et al. The long-term effect of doxazosin, finasteride, and combination therapy on the clinical progression of benign prostatic hyperplasia. *N Engl J Med* 2003;349:2387-98.
21 Chapple CR. Pharmacological therapy of benign prostatic hyperplasia/lower urinary tract symptoms: an overview for the practising clinician. *BJU Int* 2004;94:738-44.
22 National Institute for Clinical Excellence. *Clinical guidelines and referral protocols—referral practice: a guide to appropriate referral from general to specialist services.* London: NICE, May 2000.

(Accepted 3 August 2006)

doi 10.1136/bmj.38946.616551.BE1

Lesson of the week

Acute renal failure induced by contrast medium: steps towards prevention

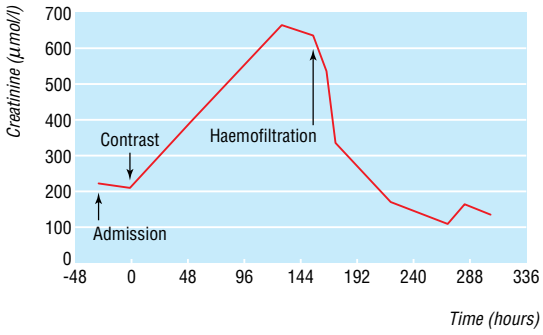
R Mathew, K Haque, W Woothipoom

Acute renal failure is a well known complication of procedures that involve iodinated contrast media.[1] Despite this, contrast medium induced nephropathy accounts for about 12% of all cases of hospital acquired renal failure.[2] Prevention of this type of nephropathy is crucial as it is associated with prolonged hospital stay, risk of permanent renal impairment, and a more than fivefold increase in mortality.[3 4] We report a case of acute renal failure in a woman with chronic renal disease who was investigated for metastatic breast cancer with contrast enhanced computed tomography. This case shows the importance of carrying out a risk assessment for contrast medium induced nephropathy before using procedures that involve iodinated contrast media.

Case report

An 81 year old woman with type II diabetes was admitted after a hypoglycaemic episode. She had a four week history of non-productive cough, which failed to resolve with antibiotics. She had been treated with surgery and radiotherapy for breast cancer 13 years previously. She also had stage 3 kidney disease and hypertension.

Breast examination was normal but there were signs of a left sided pleural effusion. Chest x ray showed a possible left sided coin lesion and pleural effusion. Her white blood cell count was 5.6×10^9/litre, C reactive protein was 15 mg/litre, and the pleural aspirate was an exudate containing 38 g/litre protein and 0.5×10^9/litre white blood cells. Plasma creatinine was 224 µmol/litre, which was not very different from her preadmission value. In view of the history of breast cancer, contrast enhanced computed tomography of the chest and abdomen was performed. No abnormalities were detected in the lungs, but a lesion, suggestive of metastasis, was detected in the left adrenal.



Serum creatinine values during admission in a woman with contrast medium induced acute renal failure

Over the next two days, the patient became increasingly nauseous and anorexic. Creatinine rose to 392 µmol/litre (figure). Despite supportive treatment for acute renal failure she became anuric, her blood pressure began to drop, and creatinine rose to 664 µmol/litre. She was transferred to the intensive care unit, where haemofiltration was started. Her renal function started to recover over the next few days and her condition began to improve.

Discussion

Nephropathy induced by contrast medium is defined as an impairment in renal function that occurs within 72 hours of giving contrast medium.[5] This impairment is characterised by an increase in serum creatinine of at least 44 µmol/litre or 25% above the baseline. Creatinine typically peaks three to five days after contrast administration and returns to baseline values within two weeks. Renal replacement therapy is needed in a minority of patients, and in-hospital mortality may be as high as 62% in these cases.[4] No specific treatment is available for contrast medium induced nephropathy and management is supportive.

Risk assessment for renal failure must be performed before procedures involving the administration of contrast media

University College London, London WC1E 6BT
R Mathew
medical student

North Middlesex University Hospital, London N18 1QX
K Haque
specialist registrar in care of the elderly medicine

Care of the Elderly Medicine, North Middlesex University Hospital
W Woothipoom
consultant physician

Correspondence to:
R Mathew
rgmathew@hotmail.com

BMJ 2006;333:539–40