PHARMACOTHERAPY OF VOIDING DYSFUNCTION IN THE ELDERLY

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INTRODUCTION

Voiding dysfunction in the elderly may have various causes. The process of aging may affect the storage or voiding capacity of the bladder with resultant incontinence or retention of urine. This may be the result of detrusor dysfunction, sphincter weakness (sometimes following surgery), bladder outflow impairment (most commonly due to an enlarged prostate) and neuropathy. In addition, the elderly are more likely to suffer from physical or mental conditions requiring therapy with drugs which could have side effects on the process of micturition.

INNERVATION AND NORMAL FUNCTION OF THE BLADDER AND URETHRA

The bladder and urethra are primarily smooth-muscle structures innervated by the autonomic nervous system.

Both sympathetic and parasympathetic divisions are involved.

The sympathetic outflow

T10 - L2 segments of the cord via ganglia situated along the paravertebral

sympathetic chain (the neuro-transmitter being *acetylcholine*). The post-ganglionic fibres travel though the presacral plexus and to the bladder and urethra (*noradrenaline* acting as the neuro-transmitter). At this level there are two types of receptors:

a) the bladder body (detrusor) contains predominantly β-*receptors*, stimulation of which leads to relaxation allowing the bladder to fill with minimal rise in pressure.

b) the bladder outlet and prostatic capsule are rich in α-*receptors*, stimulation of which leads to closure of the proximal urethra.

Thus, sympathetic stimulation leads to continent filling at low pressure.

The pudendal nerve (somatic)

Innervates the external striated muscle of the distal sphincter mechanism.

DRUGS CAUSING VOIDING DYSFUNCTION IN THE ELDERLY

The physician faced with a patient with voiding dysfunction must inquire diligently into the drugs which the patient is using as well as into his medical history. Very often the patient may be on multi-therapy for a number of conditions which he may not necessarily mention unless specifically asked to by the physician.

The dosage of any drugs which the patient may be taking must be very carefully evaluated as elderly patients are extremely sensitive to many drugs and prone to manifest urological side-effects.

Drugs causing voiding dysfunction in the elderly is shown in Table 1. Some drugs inhibit bladder contraction by decreasing detrusor contractility. As a result the patient may experience difficulty in voiding and may actually go into retention. This may be the result of either an anti-cholinergic effect (as in the case of some anxiolytics, hypnotics, antipsychotics or antiparkinsonian agents) or due to prostaglandin inhibition (as in the case of calcium channel blockers, e.g. verapamil).

Table 1
Commonly used drugs which may cause voiding dysfunction in the elderly

Effect on voiding	Mechanism of action	Drug class
Decreased detrusor contractility-retention	Anticholinergic	Anxiolytics Hypnotics Anti-parkinsonian
	Prostaglandin inhibition	Nsaids
Reduction of bladder tone	Excessive β-stimulation	Antiasthmatics
	Smooth muscle relaxants	Calcium blockers
Bladder neck closure	Unopposed α-stimulation	β-blockers
	Excessive α-stimulation	Anti-allergy drugs Cold medication drugs
Increased frequency of micturition or incontinence	Diuretics	Thiazides Frusemide

On the other hand, unopposed or excessive stimulation of the α-fibres of the bladder neck can result in bladder outflow obstruction. Propranolol, antiallergic and cold medications can have such an effect.

Finally, diuretics commonly used in congestive heart failure and other oedematous conditions can cause considerable discomfort due to increased frequency or even incontinence of urine.

A modern phenomenon is the availability over the counter of many of the above drugs which formerly were only available on prescription.

Cold medications are a case in point and this has prompted Resnik to write: "More than one unfortunate elderly man has "given his cold" to an over-the-counter cold preparation and unnecessary given his prostate to the urologist!"

DRUGS USED TO TREAT URINE INCONTINENCE IN THE ELDERLY

Incontinence in urine is very prevalent in the elderly. Studies in Boston[1] and Michigan[2], U.S.A. have shown that roughly one-third of community-dwelling elderly have difficulty holding urine until they can get to a toilet, and between 15% and 30% are actually incontinent. In institutionalised patients, the prevalence of incontinence is still higher, approaching 50%.

Drugs have only a limited role to play in the therapy of urinary incontinence and have to be combined with other modalities such as timed toileting, reduction in fluid intake, provision of urinals or bedside commodes, avoidance of faecal impaction, use of absorbent pads and in some cases the insertion of an artificial sphincter. Indwelling or condom catheters may provide an easy way out but these are not without their complications in terms of patient morbidity and discomfort and should only be adopted when all other measures have failed. Indeed, Jayachandran et al reported that only 2.5% of the 243 incontinent patients hospitalised in the Institute for Geriatric Care, New York required indwelling catheters while Nordquist et al were able to remove indwelling catheters from 94% incontinent patients admitted to their unit.

Drugs which are used in the treatment of incontinence act either by inhibiting detrusor contraction or by increasing outlet resistance.

Of the drugs listed in Table 2 we have little use for *ephedrine, pseudoephedrine* and *flavoxate* whilst *propantheline* has been largely superceeded by *oxybutynin.* This drug, together with *imipramine,* form the mainstay of our present pharmacological management of incontinence of urine.

Table 2
Drugs used to treat urine incontinence in the elderly

Drug	Mode of action
Detrusor Inhibition	
Propantheline bromide (Pro-bantine)	Anticholinergic
Oxybutynin (Ditropan)	Anticholinergic Direct smooth muscle relaxant
Flavoxate (Urispas)	Smooth muscle relexant
Imipramine (Tofranil)	Anticholinergic
Increase Outlet Resistance	
Imipramine (Tofranil)	Anticholinergic
Ephedrine sulphate	α–adrenergic agonist
Pseudoephedrine HCI (Sudafed)	α-adrenergic agonist

Imipramine acts both at bladder neck level increasing outlet resistance as well as by inhibiting detrusor contractions. We have found it very useful in the treatment of mild stress incontinence in elderly females as well as to treat the transient incontinence, due to sphincter weakness, in the post-prostatectomy male. It is our practice to start with a small dose, usually 25mg nocte gradually increasing to 25-50mg tds (although this is hardly every necessary).

Oxybutynine has proved an excellent drug in the management of urge incontinence and the treatment of bladder instability. It is primarily an anticholinergic drug but also exerts a direct muscle relaxing effect on the detrusor. Urodynamic studies have shown that many elderly patients with incontinence of urine have detrusor hyperreflexia resulting in bladder instability. Their symptoms are often identical to those seen in

prostatism and accounts for the fact that some patients remain symptomatic after prostatectomy. In this group of patients, and in those with clinical urge incontinence, oxybutynine gives excellent results, in the region of 70% good response rate with a dose of 2.5mg to 5mg tds. Patients should be screened for glaucoma and cardiac abnormalities before administration. One should also be alert to the possibility that oxybutynine administration may mask an underlying intra-vesicular pathology, e.g. carcinoma in situ, which may be the cause of the detrusor instability and which requires treatment on its own merit.

One problem with oxybutynine is that while it has been used very successfully for over ten years and has long been approved by the Food and Drug Administration of the U.S.A. it is still not yet licenced in the U.K. and is only available on a named-patient basis in the U.K. and in Malta. This may possibly create medico-legal problems should there be any serious side-effectrs from the drug. In practice this has not been a problem, for side-effects have been minor (usually those associated with an anti-cholinergic drug) and easily reversible.

DRUG THERAPY OF BLADDER OUTFLOW OBSTRUCTION IN THE ELDERLY

Prostatism is a symptom complex that indicates obstruction to urinary flow of prostatic origin.

Apart from the commonly noted obstructive symptoms (slow stream, hesitancy, postmicturition dribble, frequency and nocturia) there is often associated bladder instability manifested by urgency and urge incontinence. It is important to recognise the latter symptoms which may not always respond to prostatectomy and may be more amenable to drug therapy as described previously under urge incontinence.

The commonest cause of bladder outflow obstruction in the elderly is an enlarged prostate (benign or malignant). Table 3 gives the pharmacological treatment of benign prostatic hyperplasia in the elderly.

Table 3
Pharmacological treatment of benign prostatic hyperplasia in the elderly

Drugs which reduce outlet resistance	
Phenoxybenzamine HCI (Dibenyelene)	(non-selective) α-adrenergic antagonist
Prazosin HCI (Hypovase, Minipress)	α_1-adrenergic antagonist
Drugs which reduce prostatic volume	
Androgen deprivation:	
Diethyl stilboestrol	
Anti-androgens	Cyproterone acetate Flutamide
LHRH-agonists	
5-alpha-reductase inhibitors	

Benign prostatic hyperplasia

Benign prostatic hyperplasia (BPH) is the most common organic obstruction met with clinically. 80% of men above the age of 70 years will have histological evidence of it and it has been estimated that 20%-25% of men who live up to the age of 80 years will require prostatectomy for BPH.

It was assumed in the past that the obstructive symptoms of BPH were due entirely and solely to the mechanical effect of the prostatic tissue. However, this concept did not explain two clinical observations well known to practicing urologists: firstly, the frequent changes in the patient's prostatic symptoms, and secondly, the fact that the symptoms of prostatism do not appear to correlate clinically with the prostate size. Marco Caine proposed the concept of two components in organic obstruction of this type, namely the *'mechanical '* and *'dynamic '*. The mechanical component is the basic physical obstruction produced by

the presence of the tissue itself, whereas the dynamic component is a super-added obstruction due to the tone of the prostatic muscle which, as has been described above, is rich in α-adrenoreceptors[3]. Although the mechanical obstruction may increase over a period of time it is not subject to fluctuations whereas the dynamic component can vary according to the degree of sympathetic stimulation and hence the state of the muscle tone. As a corollary, one would expect that pharmacological blockade of the α-adrenoceptors would result in the reduction of the dynamic component to a minimum with possible amelioration in the patient's symptoms.

In 1976 Caine[4] published the first encouraging results using the α-adrenergic drug, phenoxybenzamine, and since then there have been many favourable reports regarding the use of α-antagonists to reduce bladder outlet resistance in patients with benign prostatic hyperplasia. We have been using phenoxybenzamine since 1978 and in our experience we can achieve symptomatic amelioration in the patient's voiding in up to 70% of patients with objective improvement on uroflowmetry in half of these. In addition to the expected improvement in the objective parameters we have noted a surprising and welcome improvement in the irritative symptoms of frequency, urgency and nocturia although the explanation for this is not quite clear. With the usual dose of 10mg bd or tds, the commonest side effects have been tachycardia, dizziness and hypotension. We tend to use a lower dose of 10mg nocte (just before bed-time) with no reduction in the beneficial clinical effect and with minimal side-effects.

There are two types of α-adrenergic receptors: the α_1 are post-synaptic receptors on the effector cell, mediating the response of the cell to the liberated noradrenaline, whereas the α_2 are presynaptic on the terminations of the adrenergic neurones and are concerned with the feedback regulation of noradrenaline production in the nerve. It has been shown[3] that the vast majority of the receptors present in the bladder neck and human prostate are α_1 in type.

The drug *prazocin* is a pure α_1-blocker and might therefore hold the theoretical advantage that it does not interfere with the α_2 receptors moderating the feedback mechanisms controlling noradrenaline production. It has less tendency than phenoxybenzamine, a pure α-blocker, to produce tachycardia. In our hands both phenoxybenzamine and

prazocin have been equally effective with comparable side-effects.

Our indications for α-adrenergic blockers in the treatment of benign prostatic hyperplasia can be summarised as follows:

a) as the sole line of therapy in patients with early prostatism or with minimal flow impairment on urodynamic studies. In many patients the symptoms of prostatism, having reached a certain point, remain static.

b) in patients who require prostatectomy but who are too frail or unwilling to undergo operation or during the waiting period for operation to minimise the danger of acute retention.

Apart from reducing outlet resistance, prostatic obstructive symptoms might be expected to improve if prostatic volume could be reduced.

Castrated individuals do not develop BPH and castration has been shown to promote regression of BPH in both man and dog[5]. One would therefore expect that *drugs which induce androgen deprivation* would also induce shrinkage of the hyperplastic human prostate. Although this has been shown to be the case, the limited clinical efficiency and the universal development of erectile dysfunction limit the clinical value of androgen deprivation for the treatment of BPH. Anti-androgen hormone therapy is virtually limited to the treatment of the malignant prostate and will be more fully discussed under that heading.

Promising results have been recently registered using *5-Alpha-Reductase inhibitors.* Testosterone is metabolised in the prostate of dihydrotestosterone by the enzyme 5α-reductase. Inhibition of 5α-reductase activity by pharmacological methods have been shown to cause suppression of dihydrotestosterone levels, while circulating levels of testosterone are maintained. The expected clinical advantage would be the preservation of muscular strength and libido which are dependant on and mediated by testosterone. In clinical trials to date prostate volume has been shown to decrease by a mean of 18% at 12 weeks and 28% after six months therapy with a mean change in the maximum urinary flow of 3ml/sec. Toxicity to date has been negligible and there have been no drug-related side effects. Both the circulating and intra-prostatic levels of dihydrotestosterone are markedly reduced. These preparations hold promise for the immediate future.

HORMONAL THERAPY OF ADVANCED PROSTATE CANCER IN THE ELDERLY

Carcinoma of the prostate is the second most common site of cancer affecting males in the USA and Western Europe, and an increased mortality rate has been observed in most countries.

There is no standard way of treating carcinoma of the prostate. Therapeutic strategies vary from continent to continent and sometimes even within the same institution. Modalities of treatment range from withholding treatment in focal carncinoma of the prostate particularly in the elderly to more aggressive therapy in the form of radical prostatectomy or/and radiotherapy in the younger patient where the disease is still localised to the prostate. Unfortunately, at the time of diagnosis, over 70% of all carcinomas already extend beyond the boundary of the prostate and are, therefore, no longer suitable for curative surgery. Because of this, palliative therapy is of paramount importance in the management of the tumour.

Palliative therapy is based on androgen deprivation for it is known that carcinoma of the prostate is androgen-dependent for varying lengths of time during the course of its development. This fact was suspected even in the last century because carcinoma prostate had never been observed in eunuchs. However, it was the pioneer work of Charles Huggins and his co-workers in the 1940's[5] that firmly established the rationale of androgen withdrawal and established orchidectomy as the mainstay of therapy in advanced carcinoma prostate. Removal of the testes (orchidectomy) eliminates the source of about 90% of the total androgen concentration. The other 10% are produced by the adrenal glands and are not affected by orchidectomy. The operation is simple, effective in controlling spread of the cancer and cost-effective. The drawbacks are the adverse psychological impact at least in some patients, the risk due to any surgical procedure and the occurrence of hot flushes similar to those in menopausal women. This has stimulated the search for pharmacological means of androgen-deprivation as a substitute of or adjunct to orchidectomy (Table 4).

Table 4
Carcinoma prostate

		Endocrine therapy
1.	Orchidectomy	
2.	Oestrogens:	Diethyl stilboestrol (DES) Ethinyl oestradiol Phosphorylated stilboestrol (HONVAN)
3.	Anti-androgens:	Cyproterone acetate (Androcur) Flutamide Ketoconazole Medroxyprogesterone acetate (MPA)
4.	LHRH-analogues:	Buserelin } block the release of Zoladex } gonadotrophic hormone depot (chemical castration)
5.	Adrenalectomy:	Surgical Medical - aminogluthemide

Oestrogens act by influencing the pituitary-gonadal regulatory system. They interfere with central receptors and cause inhibition of LHRH secretion. Consequently LH secretion is decreased and the testosterone concentration falls to castration levels (adrenal androgen secretion is not affected). Although oestrogens (in the form of diethyl stilboestrol, ethinyl oestradiol or phosphorylated stilboestrol) have been the classic drug therapy for prostatic cancer for many years, they may cause unpleasant and severe side effects: nausea, vomiting, painful gynaescomastia and, more seriously, a high morbidity and mortality (particularly in the elderly) from cardiovascular complications. Nowadays, oestrogen therapy is being replaced by other drugs, mainly the anti-androgens and LHRH analogues, which are just as efficient and with fewer side effects.

Anti-androgens inhibit the effect of androgens at the target organs by competing with them for the receptor cells. The best known in this category of drugs are *cyproterone* acetate and *flutamide.* While the therapeutic efficacy of these drugs is identical to conventional oestrogen therapy they have minimal cardiovascular side effects and are relatively safe.

LHRH agonists (Buserilin, Zoladex depot) act by exerting a continuous stimulation on the pituitary gland which adapts to this unphysiological situation by loosing its LHRH receptors. This adaptation process (usually referred to as down-regulation) takes time, usually 2 to 3 weeks. In the initial stages of treatment testosterone levels increase (with a possible flare-up of bone pains and other symptoms) but after down-regulation has taken place testosterone levels fall to castration levels. One advantage of these drugs is that they can be administered as a compliance. They can be combined with anti-androgens particularly in the early stages to minimise the initial tumour flare.

With the new endocrine regimes, antiandrogens, LHRH agonists and combination of these drugs, quality of life can be maintained much better than before and the psychological impact of orchidectomy can be prevented.

CONCLUSION

The urologist with an understanding of the neuromuscular function of the bladder can solve the voiding dysfunction problems of many elderly patients with judicious alteration or administration of drugs. However, when prescribing, the extraordinary sensitivity of the elderly to these drugs must be taken into account to avoid significant side effects.

REFERENCES

1. Resnick NM, Yalla SA (1987). Aging and its effect on the bladder. Seminars in Urol., 5: 82-86.
2. Diokono AC, Brock BM, Herzog AR, et al (1985). Prevalence of urologic symptoms in the non-institutionalised elderly. J. Urol., 133: 179A (abstract).
3. Caine M (1986). Role of sympathetic blocking agents in outflow obstruction. Clinical Science, 70 (Suppl. 14): 635-683.
4. Caine M, Pfau A, Perlberg S (1976). The use of alpha-adrenergic blockers in benign prostatic obstruction. Br. J. Urol., 48: 255-263.
5. Huggins C, Stevens RE, Hodges CV (1941). Effects of castration on advanced carcinoma of the prostate gland. Arch. Surg., 43: 209.0