Diseases of the urinary system

Drugs acting on the bladder and urethra

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The bladder has a dual function: it acts as a reservoir for urine and also expels its contents when full by active contraction at a socially convenient time. These twin functions are reflected in the complex innervation and in the variety of drugs which affect both the bladder and the urethra.

The nerve supply to the bladder is a triple system including intercommunicating sympathetic, parasympathetic, and somatic nerves. Acetylcholine is the chemical transmitter at parasympathetic postganglionic and somatic nerve endings, while noradrenaline is the main transmitter at postganglionic sympathetic nerve endings. The bladder and urethra are rich in adrenergic receptors: α -receptors predominate in the base, bladder neck, and proximal urethra, and β -receptors are found principally in the vault of the bladder. Embryologically the urethra originates from the urogenital sinus, and consequently in women this organ is sensitive to changes in oestrogen and progesterone levels.

Functional abnormalities

Four main functional abnormalities may affect the bladder and urethra.

Increased bladder activity (uninhibited detrusor contractions) may be either primary (unknown aetiology) or secondary to an upper motor neurone lesion or—in men—outflow obstruction. The symptoms are urgency, urge incontinence, frequency, and incontinence at rest or at night (enuresis) or associated with exertion or change in position.

Decreased bladder activity (atonicity) is secondary to a lower motor neurone lesion, to bladder overdistension, or to a combination of the two. Temporary lesions may follow epidural or spinal anaesthesia.

Urethral sphincter dysfunction (genuine stress incontinence) is a result of one or more of the following factors: descent of the urethrovesical junction; weakness of muscles, ligaments, and fascia around the bladder neck; or periurethral fibrosis leading to a rigid urethra.

Atrophic change (in women) may affect the distal urethra.

Treatment

Before treating increased bladder activity or atonicity the doctor must make a neurological assessment and exclude outflow obstruction.

INCREASED BLADDER ACTIVITY

Drugs can be used to control the uninhibited contractions and the incontinence that may result. Those available include:

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Postganglionic anticholinergic agents such as atropine, propantheline—dosage 15-200 mg three times a day—and emepromium bromide—200 mg four times a day. These act by competing for the same drug receptors as acetylcholine. The main side effects (which are least with emepromium) include dry mouth, blurred vision, and retention of urine. Emepromium bromide should be taken with water.

Tricyclic antidepressants such as imipramine may be effective. These drugs have anticholinergic properties, slow the turnover rate of 5-hydroxytryptamine, and block the active reuptake into cellular stores of circulating noradrenaline, thereby encouraging stimulation of α -adrenergic receptors. They have no effect on dopamine receptors. The dosage is 25-50 mg two or three times a day, or 25-50 mg at night for enuresis. Side effects may include dry mouth, postural hypotension, cardiac arrhythmias, and urinary retention.

Sympathomimetic beta-adrenergic stimulants have been used with some success, though caution is necessary because of the side effects of cardiac stimulation. Orciprenaline has been used in a dose of 20 mg four times a day; salbutamol, 4 mg four times a day, and terbutaline, 5 mg three times a day, are more selective and less prone to cause cardiac side effects.

Musculotropic drugs—flavoxate hydrochloride is a tertiary amine chromone that has a selective action (rather like papaverine) on smooth muscle fibres. It exerts its effect by increasing the local concentration of cyclic adenosine monophosphate. The dose is 200 mg four times a day and side effects are uncommon.

Bromocriptine decreases the frequency, nocturia, and urgency and increases the functional bladder capacity as assessed by cystometry.¹ It is thought to act as a dopamine agonist; by reducing prolactin secretion it inhibits prostaglandin secretion. Bromocriptine should be given in incremental doses (because of side effects of nausea and vomiting), starting at 1.25 mg for two days and then increasing to 2.5 mg daily for two days and finally 2.5 mg twice a day.

A suggested drug regimen for symptoms of bladder overactivity such as urgency, incontinence, and frequency is to start treatment with flavoxate or emepromium at a dose of 200 mg four times a day. The dose of Flavoxate may be increased to 300 mg four times a day without harmful effects. If there is no response, a β -adrenergic stimulant may be used alone or in combination with one of the anticholinergic drugs.

Enuresis is often caused by an involuntary detrusor contraction occurring during sound sleep. To be effective, drugs should either block motor impulses from the central nervous system or increase cerebral awareness of a full bladder during sleep. Ephedrine (30 mg at night) and imipramine (25-30 mg at night) have been successful. The former releases noradrenaline, which is an α -adrenergic stimulant and produces constriction of the bladder neck and which at the same time increases cerebral awareness. Its main side effect in children therefore is sleeplessness.

DECREASED BLADDER ACTIVITY

Atonicity of the bladder may lead to difficulty in voiding or to retention of urine with overflow. The aim of drug treatment is to encourage complete emptying of the bladder either by stimulating it or by relaxing the urethral sphincter mechanism. Drugs may be used in conjunction with catheter drainage.

Cholinergic drugs—Choline esters, such as carbachol and bethanechol chloride, act by stimulating parasympathetic nerves to release acetylcholine at nerve endings. They are long acting and are not destroyed by cholinesterase. Bethanechol chloride has fewer nicotinic effects and is therefore preferable to carbachol. The oral dose is 5–30 mg up to four times a day. For carbachol the dose is 1–4 mg up to four times a day; its side effects include stimulation of smooth muscle elsewhere, principally in the gastrointestinal tract.

Anticholinesterases. Acetylcholine may be potentiated in the body by anticholinesterase drugs, which inactivate cholinesterase enzymes. Distigmine bromide is given either as an intramuscular injection (0.5 mg) or as a 5 mg tablet daily, and its action lasts for 24 hours. There are no important side effects, though gastrointestinal symptoms may appear if the drug is continued for more than five days.

Alpha-adrenergic blockers include phenoxybenzamine, phenolamine, and thymoxamine. These block the α -adrenergic receptors at the bladder neck and decrease bladder neck and urethral resistance. Phenoxybenzamine may be given in an intravenous dose of 1.0 mg/kg; it must be well diluted and given slowly over a period of one hour. Given by mouth, the starting dose is 10 mg daily, which may be increased incrementally to 30 mg daily, provided that side effects such as tachycardia and postural hypotension do not appear. Bethanechol chloride (50–100 mg daily) and phenoxybenzamine (20–30 mg daily) have been used in conjunction to overcome urinary retention, the former having cholinergic effects on the bladder and the latter an α -adrenergic blocking action on the bladder neck.²

The prostaglandins are effective stimulators of smooth muscle. In vitro both PGE₂ and F₂ α have been shown effectively to stimulate strips of bladder muscle.³ When, however, I have used PGE₂ intravesically in vivo (0.5 mg twice a day) I have not found it successful in initiating bladder contractions, possibly because of poor absorption across the transitional epithelium of the bladder.

Finally, in this context retention of urine may result from spasm of the external urethral sphincter. Relaxants such as baclofen, 5–15 mg three times a day, or orphenadrine, 50–100 mg twice or thrice a day, may be used, with incremental increases in dose. Unfortunately muscle weakness and sedation are frequent side effects of higher doses.

HORMONE TREATMENT

There is clinical evidence that the bladder and urethra are influenced by the hormonal variations within the normal menstrual cycle, so that symptoms of frequency, urgency, and incontinence may be more obvious in the week before menstruation. At the approach of the menopause the mucosa of the female urethra undergoes atrophic change similar to that in the genital tissues. Oestrogen may then alleviate symptoms of urgency, frequency, and stress incontinence, for oestrogenisation of the epithelial cells and proliferation of the lining mucosa of the urethra improves hermetic closure. It may also act by enhancing the α -adrenergic response of the urethral musculature and vasculature.

By contrast, progesterone facilitates the β -adrenergic response and produces a deterioration in urinary continence,⁴ which is noticeable in the week preceding menstruation.

Side effects of drugs

Not surprisingly, in view of the wide range of drugs affecting the bladder and urethra, the genitourinary tract is unusually susceptible to drugs used elsewhere in the body—especially if there is any bladder or urethral disorder. These side effects are of two main types. Firstly, there may be difficulty in voiding or frank retention of urine. Pre-existent straining to void, incomplete bladder emptying, and a slow urinary stream are all

symptoms suggestive of outflow obstruction, which may be aggravated by the following drugs:

Antihistamines—principally the H₁ blockers, which are anticholinergic and are mainly used for sedation, Parkinsonism, and motion sickness.

Phenothiazine tranquillisers, such as chlorpromazine, which have an anticholinergic effect; they also have an α -adrenergic blocking effect and can cause incontinence.

Tricyclic antidepressant drugs, such as imipramine and amitriptyline have anticholinergic properties.

Levodopa, used in the treatment of Parkinsonism, which is an α -receptor stimulant.

Secondly, incontinence may be aggravated by drugs; any tendency to incontinence associated with urethral sphincter dysfunction will be increased by the following drugs:

Diphenylhydantoin, used in the treatment of epilepsy, which is an α -blocking agent.

Thioridazine, a phenothiazine tranquilliser, is another α -adrenergic blocker.

Reserpine, used as an antihypertensive agent, which depletes tissues and nerve endings of stored noradrenaline and 5-hydroxytryptamine.

Conclusion

Despite the surprising variety of drugs that can affect the bladder and urethra few are potent. Uninhibited detrusor contractions (both primary and secondary to upper motor neurone disease) and atonicity or hypotonicity are difficult to treat adequately. Both conditions have been relatively neglected by clinical pharmacologists and advances in drug treatment are overdue.

References

- ¹ Farrar, D, and Osborne, *British Journal of Urology*, 1976, **48**, 235.
- ² Khanna, O, *Urology*, 1976, **8**, 316.
- ³ Abrams, P, and Feneley, R, *British Journal of Urology*, 1976, **47**, 909.
- ⁴ Caine, M, and Raz, S, *Abstract of 16th Congress*, p 30. Amsterdam, International Society of Urology, 1973.

Is a protective mask necessary for glass engraving when using flexible drive with carborundum or diamond burs? If pulmonary protection is necessary what type of mask is advised?

Glass engraving is usually a small skilled operation emitting only a small quantity of dust. Where ordinary glass is being engraved the dust is of the nuisance type and needs no special precautions. Certain glasses, however, contain lead—for instance, lead crystal. Even so, it is unlikely that airborne levels will reach appreciable proportions if the normal practice of clean working conditions, the avoidance of large accumulations of dust and of eating or smoking at the workplace, and the adoption of reasonable methods of work, such as keeping the material wet, are followed. Respiratory protection is not usually adopted in the industry for these reasons.

A young, overworked, overweight executive with moderate hypertension wishes to take up sailing. Is this wise?

What worries me is that the cabin cruiser would be an ideal venue for a lazy weekend with plenty of eating, drinking, and smoking, while the boat's engine is allowed to do the work. If he is really serious about sailing then it would be an ideal form of relaxation and exercise away from his business, and moreover he cannot be contacted. He should still eschew the evening in the bar reminiscing and, at any rate at first, should avoid competitive racing. It would probably help if he were broken in gently by a good teacher, or if he acted as crew for an experienced sailor.