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Current Concepts in the Treatment of Disorders of Micturition

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Summary

Disorders of micturition may be divided into disturbances of the storage function of the bladder, and disturbances of the emptying function. The main symptoms of disturbances of storage function are frequency, urgency and incontinence. Hyperactivity of the bladder may lead to urge incontinence, and incompetence of the urethral closure mechanism to stress incontinence.

There are many drugs available for treating bladder hyperactivity, but their efficacy as judged from controlled clinical trials (when available) is often limited. Bladder contraction in man is mediated by stimulation of muscarinic receptors, and when given parenterally anticholinergic drugs have been shown to depress bladder hyperactivity irrespective of the underlying cause. Clinically, however, treatment of urge incontinence with anticholinergic drugs is often unsatisfactory. Lack of effect of oral treatment and systemic side effects limit the use of available agents. Drugs with 'mixed' actions (anticholinergic

and 'direct' muscle effects), for example oxybutynin and terodiline, have well-documented efficacy in bladder hyperactivity. Side effects are common with oxybutynin; terodiline seems to be well tolerated.

The aim of drug treatment of stress incontinence is to increase outflow resistance. Although there is only limited possibility of improving the condition with drugs, beneficial effects can be obtained in some patients by use of orally active α-adrenoceptor agonists (e.g. phenylpropanolamine) and/or oestrogens.

The main symptom of disturbed bladder emptying is urinary retention. Drug therapy is aimed at improving the contractile activity of the detrusor or reducing urethral outflow resistance. Drugs used for improving bladder contractility include parasympathomimetic agents, e.g. bethanechol or carbachol, and intravesical instillation of prostaglandins. Although the efficacy of both types of treatment is open to question, bethanechol seems to be widely used.

Increased outflow resistance may be seen in patients with parasympathetic decentralisation of the lower urinary tract or in patients with benign prostatic hypertrophy. These patients may respond favourably to α-adrenoceptor blockers such as phenoxybenzamine or prazosin.

The bladder and urethra constitute a functional unit which is controlled by a complex interplay between the central and peripheral nervous systems and local regulatory factors (Andersson & Sjögren 1982; Wein et al. 1987). Disturbances at various levels may result in disorders of the 2 main functions of this unit, storage and emptying. Failure to store urine may lead to various forms of incontinence, and failure to empty results in urinary retention. Pharmacological interventions have been used in attempts to treat these disorders, although often with limited success. To improve a disturbed storage function the treatment should aim at decreasing detrusor activity, increasing bladder capacity and/or increasing outlet resistance. To facilitate bladder emptying the agents given should increase the intravesical pressure, and/or decrease the urethral resistance.

1. Failure to Store

1.1 Urge Incontinence

Urge incontinence is defined as involuntary loss of urine associated with a strong desire to void (Bates et al. 1976). It may be subdivided into motor urge incontinence and sensory urge incontinence. Motor, but not sensory, urge incontinence is associated with an increased contractile activity in the detrusor muscle during the filling phase of the bladder, either in the form of uninhibited (involuntary) bladder contractions and/or decreased compliance. Uncontrolled bladder contractions may occur in connection with neurological diseases or lesions, but can also be associated with outflow obstruction, inflammation and irritative processes in the bladder muscle, or they may be idiopathic.

In man, normal bladder contraction is mediated mainly through muscarinic receptors in the detrusor muscle. Atropine resistance, i.e. contraction of isolated bladder muscle in response to electrical nerve stimulation after pretreatment with atropine, has been demonstrated in most animal species (see Andersson & Sjögren 1982), but does not seem to occur in normal human bladder muscle (Kinder & Mundy 1985; Sibley 1984; Sjögren et al. 1982). It appears that bladder hyperactivity may be the result of several different mechanisms and it is unlikely that the hyperactivity which occurs in primary instability without morphological changes is mediated by the same mechanism as hyperactivity in a morphologically changed bladder, such as may occur secondary to prostatic hypertrophy (Andersson 1986).

There is an abundance of drugs available for treatment of the overactive detrusor (table I). However, for many of them, estimations of efficacy are based on the results of preliminary, open studies rather than controlled clinical trials. It

Table I. Drugs used in the therapy of bladder hyperactivity

Anticholinergic drugs
Propantheline bromide
Emepronium bromide
Drugs with 'direct' effects
Flavoxate
Calcium antagonists
Drugs with mixed actions
Oxybutynin
Dicyclomine
Terodiline
Imipramine
β-Adrenoceptor agonists
Terbutaline
Clenbuterol
α-Adrenoceptor antagonists
Phenoxybenzamine
Prazosin
Prostaglandin synthetase inhibitors
Indomethacin
Flurbiprofen
Other drugs
Baclofen
Desmopressin
Bromocriptine

should be stressed that in many trials on detrusor instability there has been such a high placebo response that meaningful differences between placebo and active drug cannot be demonstrated. However, drug effects in individual patients may be useful and important.

1.1.1 Anticholinergic Drugs

There are reasons to believe that muscarinic receptors mediate not only normal bladder contractions but also the main part of contractions in hyperactive bladders. Atropine and other anticholinergic drugs are known to produce an almost complete paralysis of the normal bladder when injected intravenously. Several studies suggest that blockade of detrusor contractions can also be achieved in patients with bladder hyperactivity (Cardozo & Stanton 1979; Low 1977; Naglo et al. 1981). On the other hand, there are several reports of insufficient efficacy of anticholinergic drugs given orally to patients with unstable detrusor contractions (see, for example, Bonnesen et al. 1984; Ritch et al. 1977; Walter et al. 1982; Zorzitto et al. 1986). It is unclear to what extent this can be attributed to low bioavailability (making it difficult to achieve sufficient drug concentrations in the effector organ), or to side effects (limiting the dose that can be given), or if atropine resistance really occurs in some cases of unstable bladder.

In the treatment of the unstable bladder, propantheline bromide and emepronium bromide are probably the most widely used drugs. These drugs have pronounced effects on bladder function when given parenterally (Blaivas et al. 1980; Boman & von Garrelts 1973; Cardozo & Stanton 1979; Low 1977; Syversen et al. 1976; Ulmsten & Andersson 1977). However, intramuscular emepronium bromide (0.15 mg/kg) was not found to have any effect in 6 elderly subjects suffering from urinary incontinence due to small capacity, hyper-reflexic bladders (Perera et al. 1982). This raises the question of whether or not atropine-resistant activation may occur in some cases.

Both propantheline bromide (Vose et al. 1979) and emepronium bromide (Sundwall et al. 1973) possess low biological availabilities (5 to 10%) which vary markedly between individuals. Propantheline bromide is usually given in a dose of 15 to 30mg 4 times daily, while the emepronium bromide dosage must be kept in the range 200mg 3 to 4 times daily or higher. To obtain an optimal effect individual titration of the drugs is necessary: the dose is increased until incontinence is eliminated or until untoward side effects preclude further increase. Using this approach in 26 patients with uninhibited detrusor contraction Blaivas et al. (1980) obtained a complete clinical response in all but 1, who did not tolerate more than propantheline 15mg 4 times daily. The range of dosages varied from 7.5 to 60mg 4 times daily. In 72 women with detrusor instability, Massey & Abrams (1986) studied emepronium carrageenate in a double-blind, placebo-controlled, randomised crossover trial. Dosages were individually titrated. Out of 72 patients entering the study, 5 were withdrawn during the titration phase, 24 were treated with a low

dose (1200mg daily), and 43 with a medium/high (1600/2000mg daily) dose. A dose-dependent improvement, both of symptoms and of micturition parameters, was found.

Emepronium bromide has often been attributed a ganglionic blocking action, and it has been suggested that such an effect would contribute to a favourable and selective effect on the bladder muscle. However, this has never been documented clinically and there is no experimental evidence that anticholinergic drugs have a selective effect on bladder muscle. Muscarinic receptors in detrusor muscle do not exhibit characteristics which distinctly separate them from muscarinic receptors in other organs (Nilvebrant et al. 1985). The available anticholinergic drugs will, therefore, cause systemic side effects independent of which drug is used.

As atropine and related anticholinergics are tertiary amines, they are well absorbed from the gastrointestinal tract, and penetrate the central nervous system (CNS) well. CNS side effects will, therefore, often limit their use. Quarternary ammonium compounds have a lower incidence of CNS side effects, but produce well-known peripheral anticholinergic side effects such as accommodation paralysis, tachycardia and dryness of mouth. Emepronium bromide has been reported to cause oesophageal damage (Johnsen et al. 1982; Kavin 1977; Kobler et al. 1978) and this prompted the development of emepronium carrageenate (Bagger et al. 1985; Massey & Abrams 1986), from which active substance is released only in the presence of excess hydrogen or sodium ions. No oesophageal damage has so far been reported with this preparation.

1.1.2 Drugs with 'Direct' Actions

Flavoxate

The mechanism of flavoxate's effect on smooth muscle has not been established (Cazzulani et al. 1984; Fredericks et al. 1978). Cazzulani et al. (1984) found the drug to have moderate calcium antagonistic activity and an ability to inhibit phosphodiesterase; no anticholinergic effect was found (Cazzulani et al. 1985). Local analgesic properties have also been reported (Bradley & Cazort 1970; Kohler & Morales 1968). *In vivo* an active metabolite may contribute to its effects (Pietra et al. 1986).

The clinical effects of flavoxate in patients with detrusor instability and frequency, urge and incontinence have been studied in both open and controlled investigations but with varying rates of success (Delaere et al. 1977; Grüneberger 1984; Jonas et al. 1979; Stanton 1973). Stanton (1973) compared emepronium bromide and flavoxate in a double-blind crossover study of patients with detrusor instability and reported improvement rates of 83% and 66% after flavoxate or emepronium bromide, respectively, both administered as 200mg 3 times daily. In another double-blind randomised crossover study, Robinson and Brocklehurst (1983) investigated the combined effects of 4 times daily administration of flavoxate 100mg and emepronium bromide 200mg in elderly women with detrusor instability. Despite evidence of a pharmacological effect on the bladder, the therapeutic efficacy of the combination was disappointing.

Other investigators have not been able to show any beneficial effect of flavoxate at the usually recommended dosage of 100 to 200mg 3 to 4 times daily (Briggs et al. 1980). No effect was observed in women with detrusor instability administered flavoxate 200mg intravenously (Cardozo & Stanton 1979).

In general, few side effects have been reported during treatment with flavoxate. On the other hand its efficacy, compared to other therapeutic alternatives, is not well documented.

Calcium Antagonists

Influx of extracellular calcium is important for detrusor muscle contractions (Andersson & Forman 1986) and this can be blocked by calcium antagonists. Forman et al. (1978) showed that in isolated human bladder muscle nifedipine pretreatment effectively suppressed contractions induced by several agonists and also caused relaxation when administered after the agonist. Nifedipine and other calcium antagonists also inhibit contractions induced by electrical stimulation in bladder muscle

from animals and from man (Andersson & Forman 1986).

There have been few clinical studies of the effects of calcium antagonists in patients with unstable bladders (Andersson & Forman 1986). Rud et al. (1979) found that nifedipine reduced the frequency and amplitude of unstable detrusor contractions, increased bladder capacity and also gave symptomatic relief. These results could not be confirmed by Laval and Lutzeyer (1980) who found that nifedipine had no significant effect on unstable detrusor contractions.

In a double-blind placebo-controlled study, Palmer et al. (1981) found that flunarizine caused both symptomatic and urodynamic improvement in women with urge incontinence. Unfortunately, their results could not be confirmed by several other investigators (Anderson & Murray 1984; Fanciullacci et al. 1985; Ferrari et al. 1985).

Intravesical administration of verapamil was reported to depress detrusor activity in rabbits (Gotoh et al. 1986). Preliminary data in man suggest that intravesical instillation of verapamil increases bladder capacity and decreases the degree of leakage during cystometry in patients with detrusor hyper-reflexia. The effect was less pronounced in patients with non-neurogenic hyperactivity (Mattiasson et al. 1987).

The available information does not suggest that systemic therapy with calcium antagonists is an effective way to treat bladder hyperactivity. However, the possibility that intravesical therapy with these drugs will be useful cannot be excluded, nor the fact that calcium antagonists may enhance the effects of anticholinergic agents (Andersson et al. 1987a).

1.1.3 Drugs With Mixed Actions

Some drugs used to block bladder hyperactivity have been shown to have more than 1 mechanism of action. They all have a more or less pronounced anticholinergic effect and, in addition, an often poorly defined 'direct' action on bladder muscle.

Oxybutynin

Oxybutynin has been attributed with a pronounced direct muscle relaxant effect, whereas its anticholinergic action was considered moderate (Anderson & Fredericks 1977; Lish et al. 1965). However, investigations *in vitro* on human bladder tissue revealed that oxybutynin was a potent anticholinergic drug with high affinity for muscarinic receptors in human bladder tissue and that it effectively blocked carbachol-induced contractions (Nilvebrant et al. 1985).

Several studies have shown that oxybutynin is effective in controlling bladder hyperactivity (Brooks & Braf 1980; Diokno & Lapides 1972; Gajewski & Awad 1986; Homsy et al. 1985; Moisey et al. 1980; Paulson 1978; Riva & Casolati 1984). In a randomised, double-blind, crossover trial of 30 patients with detrusor instability, Moisey et al. (1980) compared oxybutynin 5mg 3 times daily with placebo. The study was completed by 23 patients; 5 withdrew because of severe side effects. Of the patients who completed the trial, 17 (69%) had symptomatic improvement and nine had improvement on urodynamic assessment. The effect of oxybutynin in the management of idiopathic detrusor instability in women was studied by Cardozo et al. (1987) in a double-blind, fixed-dose, placebo-controlled trial. Oxybutynin was significantly better than placebo in improving lower urinary tract symptoms and urodynamic parameters. However, 8 of 20 women receiving oxybutynin stopped medication because of side effects and of those completing active therapy 80% suffered significant side effects, of dry mouth or dry skin.

Oxybutynin has a well-documented therapeutic effect in bladder hyperactivity, although it is also associated with a high incidence of side effects. These are typically anticholinergic in nature and are often dose-limiting. It might, therefore, be questioned whether oxybutynin in the dosage usually used clinically (5mg 3 times daily) has other than anticholinergic actions.

Dicyclomine

In addition to a direct relaxant effect on smooth muscle dicyclomine also has an anticholinergic action (Downie et al. 1977; Johns et al. 1976; Khanna

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