REVIEW

The pharmacological treatment of urinary incontinence

K.-E. ANDERSSON, R. APPELL[1], L.D. CARDOZO[2], C. CHAPPLE[3], H.P. DRUTZ[4], A.E. FINKBEINER[5], F. HAAB[6] and R. VELA NAVARRETE[7]

The Department of Clinical Pharmacology, Lund University Hospital, Lund, Sweden, [1]Department of Urology, The Cleveland Clinic Foundation, Cleveland, Ohio, USA, [2]King's College Hospital, London, UK, [3]Department of Urology, Royal Hallamshire Hospital, Sheffield, UK, [4]Service Urologie, Hopital Tenon University of Toronto, Mount Sinai Hospital, Ontario, Canada, [5]Department of Urology, University of Arkansas for Medical Sciences, Little Rock, USA, [6]Urogynecology Unit, Paris, and [7]Department of Urology, Universidad Autonoma, Madrid, Spain

Introduction

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 [1,2]. Malfunction at various levels may result in micturition disorders, which roughly can be classified as disturbances of storage or of emptying. Failure to store urine may lead to various forms of incontinence (mainly urge and stress incontinence), and failure to empty can lead to urinary retention, which may result in overflow incontinence. Theoretically, a disturbed storage function can be improved by agents that decrease detrusor activity, increase bladder capacity and/or increase outlet resistance. Many drugs have been tried, but the results are often disappointing, partly through poor treatment efficacy and side-effects [3]. The development of pharmacological treatment has been slow, and the use of some of the currently prescribed agents is founded more on tradition than on evidence based on results from controlled clinical trials [4–8].

In the present review of drugs in current use for the treatment of urinary incontinence, agents specifically used to treat urinary tract infections and interstitial cystitis have not been included. The currently used terminology conforms with the recommendations of the ICS. Drugs have been evaluated using different types of evidence (Table 1). Evidence of pharmacological and/or physiological efficacy means that a drug has been shown to have desired effects in relevant preclinical experiments or in healthy volunteers (or in experimental situations in patients); the present clinical drug recommendations are based on evaluations made using a modification of the grading of evidence found in the Agency for Health Care Policy and Research (AHCPR) guidelines (Table 2).

Accepted for publication 31 August 1999

Table 1 Types of evidence

Type	*Condition*
Pharmacodynamic	*In vitro*
	In vivo
Pharmacokinetic	Absorption
	Distribution
	Metabolism
	Excretion
Physiological	Animal models
	Clinical phase I
Clinical	Trials
	'practice'

Bladder contraction

Normal bladder contraction in humans is mediated mainly through stimulation of 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 shown in most animal species, but seems to be of little importance in normal human bladder muscle [1]. However, atropine-resistant (nonadrenergic, noncholinergic, NANC) contractions have been reported in normal human detrusor and may be caused by ATP [9–11]. A significant degree of atropine resistance may exist in morphologically and/or functionally changed bladders, and has been reported to occur in hypertrophic bladders [12,13], interstitial cystitis [14], and in neurogenic bladders [15]. The importance of the NANC component to detrusor contraction *in vivo*, normally, and in different micturition disorders, remains to be established.

Drugs used to treat bladder hyperactivity

Studies have documented a 33–61% prevalence of an overactive bladder in the elderly over the age of 65 years

Table 2 Drugs used in the treatment of bladder hyperactivity, stress and overflow incontinence

Drug	Evidence*		
	Pharmacological/ physiological	*Clinical*	*Assessment*
Bladder hyperactivity			
Antimuscarinic drugs			
Atropine, hyoscyamine	E	C	–
Propantheline	E	A	R
Emepronium	E	A/B	R
Trospium	E	A	R
Tolterodine	E	A	R
(Darifenacin)	Under investigation		
Drugs acting on membrane channels			
Calcium antagonists	Under investigation		
Potassium-channel openers	Under investigation		
Drugs with mixed actions			
Oxybutynin	E	A	R
Dicyclomine	E	B	–
Propiverine	E	A	R
Flavoxate	U	B/C	–
(Terodiline)	E	A	–
α-adrenoceptor antagonists			
Alfuzosin	U	B/C	–
Doxazosin	U	B/C	–
Prazosin	U	B/C	–
Terazosin	U	B/C	–
Tamsulosin	U	B/C	–
β-Adrenoceptor agonists			
Terbutaline	U	B/C	–
Clenbuterol	U	B/C	–
Salbutamol	U	C	–
Antidepressants: Imipramine	E	A	R
Prostaglandin synthesis inhibitors			
Indomethacin	U	B	–
Flurbiprofen	U	B	–
Vasopressin analogue: Desmopressin	E	A	R
Other drugs			
Baclofen	E	C	–
Capsaicin	E	B	–
Resiniferatoxin	Under investigation		
Stress incontinence			
α-Adrenoceptor agonists			
Ephedrine	E	B/C	–
Norephedrine (phenylpropanolamine)	E	B	–
Other drugs			
Imipramine	U	C	–
Clenbuterol	U	B	–
(Duloxetine)	Under investigation		
Hormones: Oestrogens	E	–	–
Overflow incontinence			
α-adrenoceptor antagonists			
Alfuzosin	E	B	–
Doxazosin	E	B	–
Prazosin	E	B	–
Terazosin	E	B	–
Tamsulosin	E	B	–
(Phenoxybenzamine)	E	A/B	–
Muscarinic receptor agonists			
Bethanechol	E	B/C	–

Table 2 (*Cont'd*)

Drug	*Evidence**		
	Pharmacological/ physiological	*Clinical*	*Assessment*
Carbachol	E	B/C	–
Anticholinesterase inhibitor: Distigmine	E	B/C	–
Other drugs			
Baclofen	E	B	–
Benzodiazepines	E	C	–
Dantrolene	E	C	–

*E, effective; U, unproven; A, good quality RCT; B, clinical studies; C, 'expert' opinion; R, recommended.

[15–17]. It appears that detrusor hyperactivity may be the result of several different mechanisms, both myogenic [18] and neurological [19]. Most probably, both factors contribute to the genesis of the hyperactive bladder.

An abundance of drugs has been used for the treatment of the hyperactive detrusor (Table 2). However, for many of them, clinical use is based on the results of preliminary, open studies rather than randomized, controlled clinical trials (RCTs). It should be stressed that in many trials on both detrusor instability and detrusor hyper-reflexia, there has been such a high placebo response that meaningful differences between placebo and active drug cannot be detected. However, drug effects in individual patients may be both useful and important.

Antimuscarinic (anticholinergic) drugs

Muscarinic receptors mediate not only normal bladder contraction, but also the principal contractions of overactive bladders, and antimuscarinic drugs are able to produce an almost complete paralysis of the normal bladder when injected parenterally. Several studies suggest that detrusor contractions can also be blocked in patients with bladder hyperactivity [20–23]. On the other hand, there are several reports of insufficient efficacy for antimuscarinic drugs given orally to patients with unstable detrusor contractions [24–27]. It is unclear to what extent this can be attributed to low bioavailability, side-effects limiting the dose that can be given, or to atropine resistance.

Atropine and related antimuscarinic drugs are tertiary amines. They are well absorbed from the gastrointestinal tract and pass easily into the CNS; side-effects on the CNS may therefore limit their use. Quaternary ammonium compounds are not well absorbed, pass into the CNS to a limited extent, and have a lower incidence of CNS side-effects [28]. They still produce well-known peripheral antimuscarinic side-effects, e.g. accommodation paralysis, constipation, tachycardia and dryness of mouth. All antimuscarinic drugs are contraindicated in patients with narrow-angle glaucoma.

Antimuscarinic agents are still the most widely used treatment for urge and urge incontinence [8]. However, currently used drugs lack selectivity for the bladder [29] and effects on other organ systems (Fig. 1) may result in side-effects which limit their usefulness. Theoretically, drugs with selectivity for the bladder may be obtained, if the receptor subtype(s) mediating bladder contraction, and those producing the main side-effects of antimuscarinic drugs, were different. One way of avoiding many of the antimuscarinic side-effects is to administer the drugs intravesically. However, this is practical only in a limited number of patients.

Several subpopulations of muscarinic receptors have been identified, and five different subtypes (m_1-m_5) have been cloned. Pharmacologically, five different subtypes (M_1-M_5) have been defined [29–31], all with a wide distribution in the body. The subtypes that can be detected in the human bladder and those responsible for bladder contraction have been studied using various approaches. Cultured human detrusor cells expressed M_3 receptors linked to phosphoinositide hydrolysis [32], and an important role for M_3 receptors is widely accepted (Fig. 2). M_1, M_2, and M_3 receptor subtypes were detected in human detrusor muscle by receptor binding; there was a distinct predominance of M_3 receptors [33]. However, Yamaguchi *et al.* [34] were able to show the presence of mRNA encoding the m_2 and m_3 subtypes, but not the m_1, m_4 and m_5 subtypes in the human bladder. Using subtype-specific immunoprecipitation, Wang *et al.* [35] detected only m_2 and m_3 subtypes in human and rabbit detrusor membranes, the ratio of $m_2 : m_3$ being 3 : 1. Despite a predominance of m_2 receptors in the detrusor of several species, it has been found that the pharmacologically defined M_3 receptor mediates bladder contraction [35,36]. However, recently, at least in the rat, M_2 receptors were also shown to be

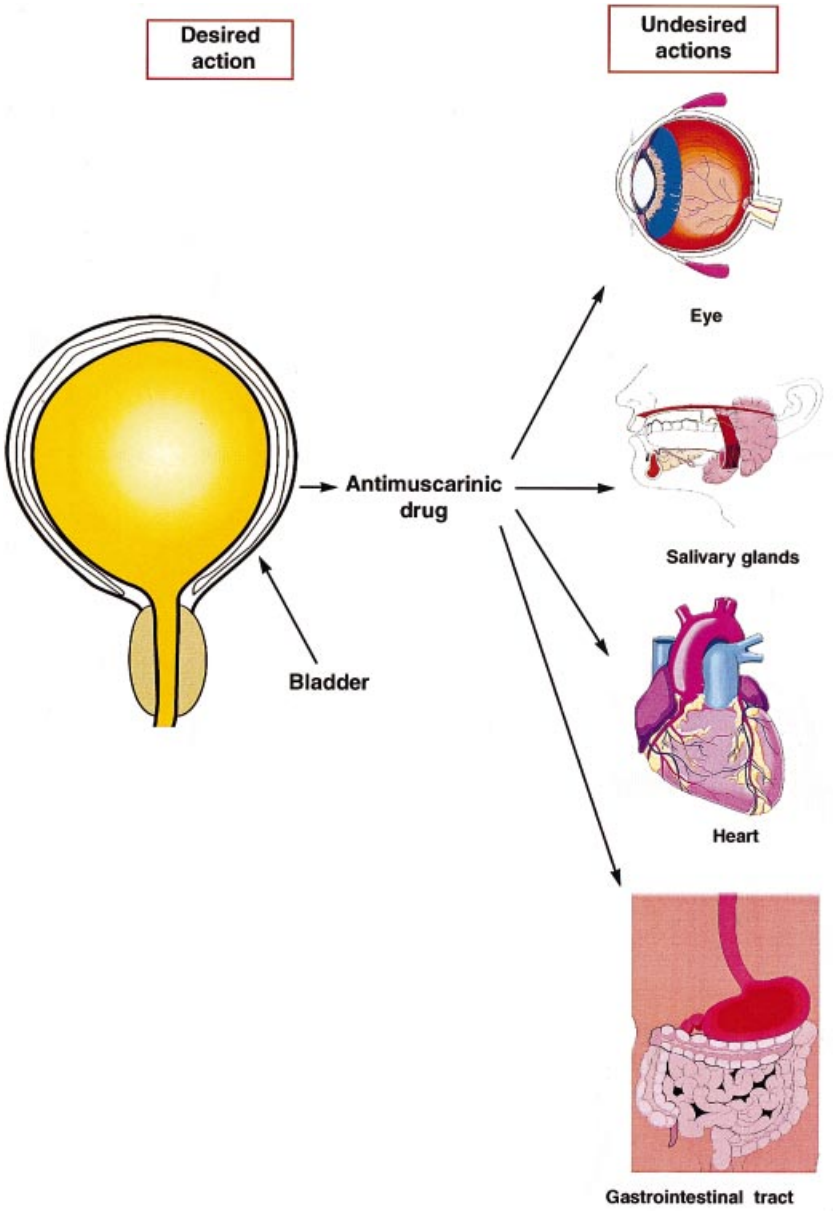

Fig. 1. The effects of antimuscarinic drugs in different target organs.

able to mediate bladder contraction *in vitro* as well as *in vivo* by reversing β-adrenoceptor-mediated relaxation [37]. What this means for the human bladder is unclear.

Future studies with muscarinic receptor antagonists with a selectivity for M_3 receptors, such as darifenacin [38,39], vamicamide [40] and zamifenacin [41], will reveal whether or not the principle of selective M_3 receptor antagonism offers therapeutic advantages. As M_3 receptors are located not only in the bladder but also in the salivary glands and the intestine, this could mean that two of the most common side-effects, dry mouth and constipation, will not be avoided.

Atropine (dL-hyoscyamine) is rarely used to treat detrusor hyperactivity because of its systemic side-effects, which preclude its use. However, in patients with detrusor hyper-reflexia, intravesical atropine may be effective for increasing bladder capacity without causing any systemic adverse effects, as shown in open pilot trials [42,43].

The pharmacologically active antimuscarinic half of atropine is L-hyoscyamine. Although widely used, few clinical studies are available to evaluate the antimuscarinic activity of L-hyoscyamine sulphate.

Propantheline bromide is a quaternary ammonium compound, not selective for muscarinic receptor subtypes, which has a low (5–10%) and individually varying biological availability [4]. It is usually given in a dose of 15–30 mg four times daily, but to obtain an optimal effect, individual titration of the dose is necessary, and often a higher dosage. Using this approach in 26 patients

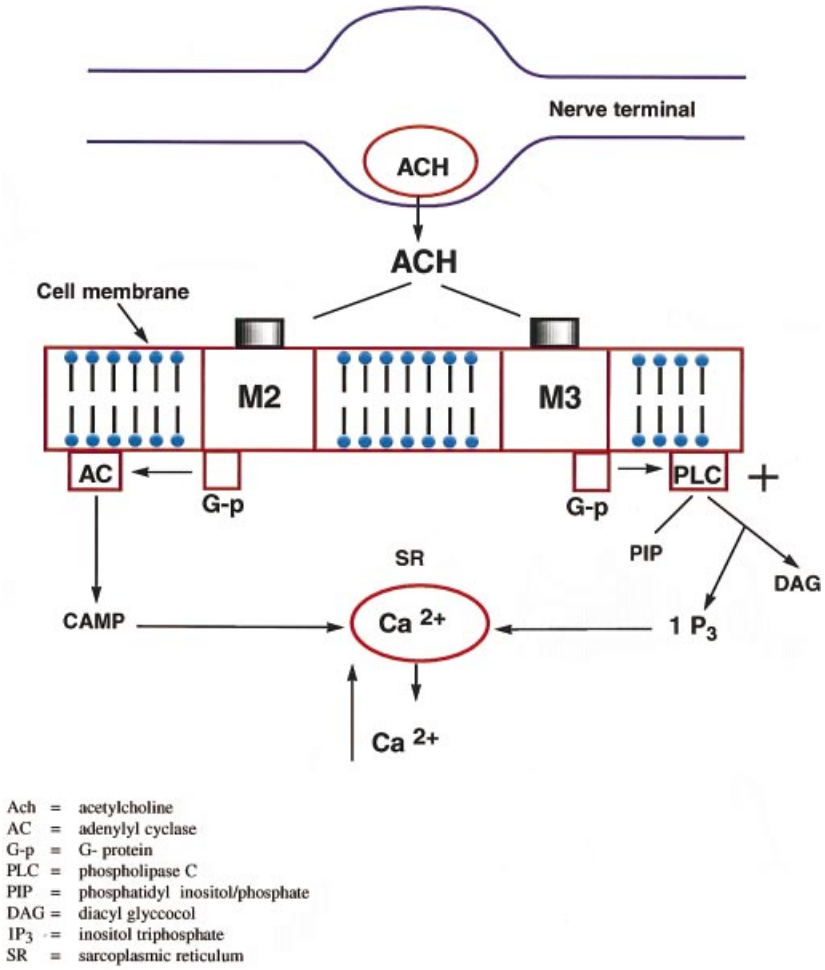

Fig. 2. Bladder contraction is mediated by the stimulation of muscarinic M_2 and M_3 receptors.

with uninhibited detrusor contractions, Blaivas *et al.* [22], in an open study, obtained a complete clinical response in all patients but one, who did not tolerate more than propantheline 15 mg four times daily. The range of dosages varied from 7.5 to 60 mg four times daily. In contrast, Thüroff *et al.* [44] comparing the effects oxybutynin 5 mg × 3, propantheline 15 mg × 3 and placebo in a randomized, double-blind, multicentre trial on the treatment of frequency, urgency and incontinence related to detrusor hyperactivity (154 patients with idiopathic detrusor instability or detrusor hyperreflexia), found no differences between the placebo and propantheline groups. In another randomized comparative trial with crossover design (23 women with idiopathic detrusor instability), and with dose titration, Holmes *et al.* [45] found no differences in efficacy between oxybutynin and propantheline. Leys [46] found no significant differences in the effect on enuretic children comparing propantheline 15–45 mg × 4 to placebo. Propantheline has a documented effect on detrusor hyperactivity and may, in individually titrated doses, be clinically useful.

Emepronium bromide or carrageenate is a quaternary ammonium compound lacking selectivity for muscarinic receptor subtypes. It has a low biological availability (5–10%) which varies markedly between individuals [47]. The dosage must be kept in the range 200 mg 3–4 times daily or higher. To obtain an optimal effect, individual titration of the drug is necessary; the dose is increased until incontinence is eliminated or until untoward side-effects preclude further increase. Positive effects in patients with urge incontinence have been shown in controlled clinical trials, e.g. [48,49]. Massey and Abrams [49] studied the effects of emepronium carrageenate in women with detrusor instability in a double-blind, placebo-controlled, randomized crossover trial. Dosages were individually titrated; of 72 patients entering the study, five were withdrawn during the titration phase, 24 were treated with 1200 mg daily and 43 with 1600/2000 mg daily. There was a dose-dependent improvement of both symptoms and micturition values. However, some investigators have shown emepronium to exert no significant effects on the bladder when administered orally [50].

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.