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ADVANCEMENTS IN PHARMACOLOGIC MANAGEMENT OF THE OVERACTIVE BLADDER

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ABSTRACT

Continued developments in the understanding of lower urinary tract function have led to improvements in the pharmacologic manipulation of bladder dysfunction. Drug delivery changes have produced drugs that provide better efficacy and tolerability, thus improving patient compliance. Improvements in drug delivery systems have altered drug bioavailability and pharmacokinetics. Active current investigation in new agents and delivery systems for intravesical delivery has yielded intriguing early results that may substantially add to the armamentarium for the management of the overactive bladder (urgency, frequency, urge incontinence). New developments in the understanding of the neuropharmacology of the bladder, peripheral pelvic nerves, and sacral cord may provide agents with entirely new drug effects, either as primary agents or agents to be used in combination with currently available drugs. We herein review newer agents and drug delivery systems. UROLOGY **56** (Suppl 6A): 41–49, 2000. © 2000, Elsevier Science Inc.

The pharmacologic management of the overactive bladder has undergone substantial modification in the last several years. Increasing interest in better pharmacologic intervention has been engendered by new estimates of the prevalence of voiding dysfunction ranging from 5% to 25% of women between 15 and 60 years of age, and 12% to 38% over the age of 60.[1] Improved questionnaire instruments such as the Bristol Female Lower Urinary Tract Symptoms questionnaire (BFLUTS)[2] have increased detection rates in recent cohort studies. Recent postal survey data from the United Kingdom using the BFLUTS tool have noted 69% of women over the age of 18 reporting some degree of incontinence over the 30 days before survey completion (61% reported urgency, 46% urge incontinence).[3] Thirty percent of those women stated that the incontinence had significant social or hygienic impact for them, consistent with the International Continence Society definition of incontinence.[4] New oral therapies have now added substantially to the armamentarium for the management of overactive bladder. Herein will be discussed the state of the medical treatment of overactive bladder. In addition, new drug modalities that allow alternative forms of delivery will also be considered.

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PHYSIOLOGY OF DRUG EFFECT

The sites of drug effect for management of bladder overactivity may include the lower urinary tract (both smooth muscle and neural receptors), the peripheral nervous system, and the central nervous system. These drug effects in many cases may be receptor dependent; however, the significance of receptor dependency in humans is not as yet as well established as in some animal models.

The goal of pharmacologic intervention for bladder overactivity is to inhibit detrusor muscular overactivity and thereby increase overall bladder capacity. A concomitant goal is a reduction of sensory afferent activity related to muscular overactivity. Acetylcholine is released from postganglionic parasympathetic nerves, which innervate bladder smooth muscle cells, and is the predominant stimulus for bladder smooth muscle contraction in hu-

0090-4295/00/$20.00
PII S0090-4295(00)01020-7

mans. Cholinergic receptors have been subcategorized into muscarinic and nicotinic types. Muscarinic receptors are primarily responsible for neurologically induced excitations of smooth muscle cells. Muscarinic receptor subtypes have been cloned, and 5 subtypes have been identified. M_1 receptors are primarily located in neural tissue, whereas M_2 receptors are located in cardiac and detrusor smooth muscle. M_3 receptors are located in the detrusor smooth muscle, as well as in salivary and other excretory glands. The M_4 receptor appears to have site selectivity to the cerebral cortex and lung. However, many organs have several different receptor types, and there appears to be no predominant type identified in any particular organ.[5]

Although the M_2 receptor is the predominant receptor subtype in the human body (80%), the M_3 receptor is actually responsible for detrusor contractility. In fact, the mechanism by which the M_2 receptor regulates relaxation of smooth muscle is not yet identified.[6] However, it has been recently shown that there is a change in receptor subtype from M_3 to M_2 after bladder denervation and spinal cord injury states, which produces a detrusor hypercontractile effect. Similar pathophysiologic phenomena may be present in the aging detrusor, as well as the detrusor affected by obstruction. The M_2 and M_3 receptors appear to predominantly mediate detrusor contraction, with M_2 receptors predominating in a 3:1 ratio. The M_3 receptor mediates contraction,[7] and the M_2 receptor opposes sympathetically mediated detrusor contraction.[5,6] The relative synergy between these 2 receptors and the effect of urinary bladder pathology on their relative concentrations is unknown.[5,6] Finally, these receptors may have different subtypes in different organs.[5] The M_3 receptor also mediates salivary secretion and bowel activity. The M_4 and M_5 receptors have been cloned in vitro and have been most thoroughly described.

The mechanism of action of antimuscarinic agents used to treat detrusor overactivity parallels the effect associated with atropine, that of muscarinic receptor blockade. Atropine and atropine-like drugs block muscarinic receptors on bladder smooth muscle cell and depress or prevent bladder contractions due to acetylcholine. This is especially true when given intravenously. In general, atropine and atropine-like drugs depress bladder contractility and involuntary bladder contractions by increasing the total bladder volume at which time first involuntary detrusor contraction occurs and this first contraction is often reduced in amplitude. Due to this antimuscarinic effect, significant depression of detrusor muscular activity occurs; however, significant side effects arise from this mechanism of action. The phenomenon known as atropine resistance results from certain pathologic states that may induce a change in receptor character and/or neurotransmitters, so as to create a state of nonresponsiveness to atropine.

Other neural regulatory mechanisms involved in bladder muscular contraction may include the purinergic system, an adenosine triphosphate (ATP)–mediated system, which in animal systems may function in close parallel to the cholinergic receptor system. Five receptor subtypes have been identified, P_2X_1 through P_2X_5. The phenomenon of atropine resistance may arise from the purinergic (ATP) system, which may facilitate bladder contractility, especially in spinal cord injury and other neuropathic states.

Another neurotransmitter present in the central nervous system is substance P. Substance P has been demonstrated to be involved in central nervous system recognition of inflammatory conditions as well as bladder function and hyperalgesia. The receptor for substance P in the central nervous system is termed the natural killer (NK)-1 type. Antagonists of substance P produce inhibition of micturition in animal models.

Certain local nerve subtypes also play a role in neural recognition of bladder events. Small unmyelinated C-afferent fibers and larger myelinated A delta fibers are involved in central recognition of bladder events, with C-fibers remaining quiescent except in the presence of inflammatory of noxious stimuli.[8] C-fiber activity is prominent in many neuropathic disorders including multiple sclerosis and spinal cord injury. Vanilloid receptors (VR_1)[9] when activated by nociceptive stimuli, activate the small C-fiber afferents and instigate sensory threshold recognition of pain or other noxious stimuli. Selective blockade of the VR_1 by vanilloid-like substances (capsaicin and resiniferatoxin) will desensitize the vanilloid receptors in a reversible but long-lasting manner.

For years, the goal of pharmacologic management of detrusor muscular and sensory overactivity has been downregulation of cholinergic neurotransmission. However, this has been hampered by substantial side effects associated with many of the currently available agents. In addition, low bioavailability resulting in substantial fluctuations in plasma concentration affects the overall efficacy and limits the overall ultimate effect of these agents in targeted patients.

Current pharmacologic choices for the management of detrusor sensory and muscular overactivity include: anticholinergic agents, musculotropic relaxants, tricyclic agents, calcium channel blockers and α-blockers. Other options include various intravesical agents that are currently under development at this time (Table I).

TABLE I. ***Currently or previously prescribed pharmacologic agents for overactive bladder***

Agent	Type/Class	Dose	Comment
Oxybutynin chloride (Ditropan*)	Tertiary amine/ antimuscarinic	2.5–5 mg tid/qid	—M_2 M_3 receptor agonist —Smooth muscle relaxant —Local anesthetic
Propantheline bromide (Pro-Banthine†)	Quartenary amine	15–30 mg tid	—50% reduction in urge incontinence —Pure anticholinergic, significant gut side effects
Hyoscyamine sulfate (Levsin‡, Cystospaz§)	Muscle relaxant	0.125 mg qid	—Weak anticholinergic effects, similar to belladonna alkaloids
Dicyclomine hydrochloride (Bentyl*)	Muscle relaxant	20 mg tid	—Direct smooth muscle relaxant, with antimuscarinic activity —Reported improvement rates up to 73%
Flavoxate hydrochloride (Urispas‖)	Muscle relaxant	100–200 mg tid/qid	—Tertiary amine with very weak anticholinergic properties
Imipramine hydrochloride (Tofranil¶)	Tricyclic antidepressant	10–50 mg tid	—Central and peripheral effect —Also sedative and antihistaminic —31% cure rate and 2%–77% urge reduction rate
Doxepin (Sinequan#)	Tricyclic antidepressant	50 mg	Same as above
Terodiline	Calcium channel blocker	25 mg bid	—Direct smooth muscle contractility reduction —Torsade de pointes arrhythmias —Withdrawn from market
Pinacidil, ZD6169	Potassium channel openers	Variable	—Smooth muscle relaxant —Side-effect profile complicated by dizziness and edema
Flurbiprofen, indomethacin	Prostaglandin inhibitors	Variable	—Anti-inflammatory —Muscle relaxant

* *Watson Laboratories, Corona, California.*
† *Roxane Laboratories, Columbus, Ohio.*
‡ *Schwarz Pharmaceuticals, Milwaukee, Wisconsin.*
§ *Polymedica, Woburn, Massachusetts.*
‖ *Alza Pharmaceuticals, Mountain View, California.*
¶ *Novartis, East Hanover, New Jersey.*
# *Pfizer, New York, New York.*

RECENTLY APPROVED AGENTS

Tolterodine (Detrol)

Tolterodine (Detrol; Pharmacia & Upjohn, Kalamazoo, Michigan) represented the first new introduction into the antimuscarinic market in 2 decades. Tolterodine is a muscarinic receptor antagonist with more specificity for the M_2 receptor. This drug also has less M_3 receptor activity with a direct correlate of less dry mouth. Bioavailability after oral administration is variable, which may reflect differences in inter-individual differences in hepatic metabolism.[10] The half-life of tolterodine is approximately 4 hours. Time to peak therapeutic effect is 2 hours, and >90% of the drug is protein bound. The primary metabolic pathway is cytochrome P_3A_4 and cytochrome P_2D_6. The role of any degradation products in the overall safety and efficacy profile of tolterodine is unknown; however, the metabolite PNU 20057 has been shown to have direct detrusor effects.[11] This drug may demonstrate some organ selectivity in that it produces

less xerostomia than immediate-release oxybutynin; however, this may be more reflective of M_3 receptor affinity differences between organs than global receptor effects.[12]

The standard dose of tolterodine is 1–2 mg twice daily, although clinical trials have investigated doses as high as 4 mg twice daily. Higher doses (4 mg) have been reported to be associated with increased rates of urinary retention and dry mouth rates approaching 56%.[13] Rates of side effects were not noted to be higher in poor or extensive metabolizers of tolterodine, in grouped analysis, suggesting the overall tolerability of the formulation at lower doses.[14] In a pooled analysis,[15] evaluating 4 trials over a 12-week study time frame with 1,120 patients included, and in comparison with immediate-release oxybutynin and placebo, there was reduced dry mouth severity associated with tolterodine and essentially equal reductions in frequency and incontinence episodes between tolterodine and immediate-release oxybutynin. Clearly, as tolterodine levels were increased, better efficacy was obtained, albeit with a greater side-effect profile.

Abrams' demonstrated a 71% reduction in urgency incontinence with immediate-release oxybutynin versus tolterodine (47%) versus placebo (19%).[16] It was also shown to reduce urinary frequency by an additional 20% over placebo rates of 39%. (Significant placebo reductions in urinary frequency in these studies as well as other anticholinergic studies can be attributed to the active participation of patients in their care with modification of volume intake and the resultant effect on urgency and frequency.) Similar frequency reductions were obtained with oxybutynin and tolterodine in that study. However, substantial benefits with dry mouth were noted with tolterodine, and approximately twice the number of patients required withdrawal from that study because of side effects related to oxybutynin ingestion. The remainder of the side-effect profile was similar in type to the other tertiary amines. Central nervous system side effects such as headache and asthenia have been reported in clinical trials with this agent.[17–19] Sixty-two percent of patients remain on therapy at 12 months or more.[20]

A recent large-scale clinical trial demonstrated again the efficacy and tolerability of tolterodine in 1,022 patients' urgency, frequency, and urge incontinence. Treated patients showed a 46% reduction in urge incontinence episodes compared with placebo ($P = 0.0005$), with significant improvements noted in frequency (reduced by 15%) and pad usage (36% reduction), with substantial improvement in volume voided per micturition (21%). No significant difference between treated or placebo groups was noted for patients withdrawing due to tolerability concerns, although 40% of patients perceived substantial benefit from treatment (compared with 22% for placebo) The only tolerability concern that significantly segregated tolterodine from placebo was that 30% of actively treated patients experienced dry mouth (18% mild severity) compared with only 8% of placebo-treated patients.[21,22]

A new once a day delivery system for tolterodine has recently been evaluated and will be released in the first quarter of 2001.

DITROPAN XL

The newest oral addition to the anticholinergic market is long-acting oxybutynin (Ditropan XL; Alza Corporation, Mountain View, California). This drug uses a slow-release technology known as the oral osmotic (OROS) technology. The OROS delivery technology osmotically delivers steady-state serum levels over a 24-hour time frame, which avoids the peaks and troughs associated with the intermittent dosing schedules of the immediate-release formulation (zero-order kinetics).[23] Plasma levels rise over a 4- to 6-hour period and then remain steady-state for a 24-hour period after oral ingestion. Stable plasma concentrations are achieved by day 3 of continuous ingestion. Drug metabolism is not affected by dietary intake.

The primary metabolic pathway of oxybutynin chloride is the cytochrome P_3A_4 system, and the half-life of oxybutynin chloride is approximately 3 hours.[24] The half-life of the XL formulation is 12 to 13 hours. The primary metabolite of oxybutynin is N-desethyl oxybutynin.[23] Both parent and metabolite have antimuscarinic activity; however, the metabolite is thought to be the primary cause of adverse effects associated with oxybutynin ingestion. After oral ingestion of immediate-release oxybutynin, levels of metabolite increase to a level 6-fold higher than the parent compound. Newer delivery methods have attempted to decrease these high serum levels of metabolite.

Oxybutynin chloride (immediate release) undergoes extensive first-pass metabolism in the proximal gut wall owing to resident cytochrome P3A4 in that location which degrades a percentage of the ingested oral dose. This metabolic step limits drug bioavailability and produces high levels of desethyloxybutynin.[25] Bioavailability with the XL formulation is higher, suggesting a reduced first-pass effect. This reduced first-pass effect occurs due to decreased absorption in the proximal small gut and increased absorption in the distal gut and large bowel.

Pooled clinical studies submitted to the US Food and Drug Association (FDA) revealed an 83%–90% reduction in urgency incontinence episodes associated with ingestion of this drug.[26] In the phase 3

studies that have been completed, 429 patients were enrolled with a dropout rate of only 1% due to dry mouth and a 7% total anticholinergic adverse event dropout rate. Substantial differences between rates of dry mouth between patients on immediate release (46%) and sustained release (25%) were reported by Anderson *et al.*[27] The safety and efficacy of anticholinergic agents in specific populations have been recently questioned. Utilization of anticholinergics in the elderly is substantiated by the FDA trials of Ditropan XL, which suggests comparable efficacy rates across all age ranges. In an open-label study evaluating urge incontinence patients, equal numbers of patients >65 years old, as compared with those aged <65, obtained complete continence (41% versus 46%). In addition, dry mouth rates were similar (28% in the >65 age population and 21% in the <65 age population). Similar reductions in first reports of dry mouth and severity of dry mouth were cited by Versi *et al.* in a comparison study of 226 patients on either immediate-release oxybutinin chloride or Ditropan XL.[28] Reports of cognitive dysfunction with oxybutynin ingestion (reductions in mini-mental scores and changes in electroencephalogram activity)[29–31] have not been substantiated within comparison groups of patients aged <64, between 65 and 74, and >75 years of age as rates of non-xerostomia–related anticholinergic adverse events were 5.1%, 7%, and 7.5%, respectively (not statistically significant).[32]

Phase 3 trials of Ditropan XL indicate better patient compliance, reduced side effects, and equivalent efficacy to the immediate-release formulation of oxybutynin. Complete continence rates of the XL formulation range between 41% and 50%. In parallel trials with immediate-release oxybutynin, continence rates ranged between 28% and 40%. Seventy-five percent of patients on XL formulation will find either the 5- or 10-mg dosing level effective.[26,27]

Historically, only 18% of patients remained on long-term (>6 months) therapy with immediate-release oxybutynin chloride. However, recent data suggest much better compliance with Ditropan XL. A recent open-label study of 1,069 patients in a community setting evaluated compliance and tolerability over a prolonged period in patients ingesting Ditropan XL. Sixty percent of patients remained on drug at 12 months, at doses of 15 mg or lower. Sleep disturbance improved from 74% of patients to 46% after 3 months of therapy. Significant reductions were also noted in the incontinence impact questionnaire scores (41%, with 5 of 9 daily activities impacted at baseline decreasing to 15% at 3 months of treatment). Eighty percent of patients at 6 months reported that medication worked well or very well, and 88% were pleased or extremely pleased with therapy. Efficacy was maintained throughout the 12-month study period in the responding patients. The majority of patients discontinuing therapy did so by 3 months, with 14% ceasing ingestion due to adverse events (5.2% dry mouth, 5.2% other anticholinergic side effects). Sixteen percent of patients discontinued therapy due to adverse events over the 12-month time frame, with an additional 3.8% stopping therapy due to lack of efficacy. Central nervous system side effects totaled only 4.5%. The study concluded that long-term Ditropan XL treatment was well tolerated, efficacious, and substantially improved the quality of life of most patients in the study.[33]

The OROS delivery system also demonstrated superior tolerability to conventional oxybutynin in measured objective effects on salivary output. In a randomized, blinded cross-over study that compared oxybutynin (immediate release, 5 mg), placebo, tolterodine (2.0 mg twice daily), and Ditropan XL (10 mg), all active drugs demonstrated significant reduction in salivary output as compared with placebo. Among the active agents, Ditropan XL demonstrated the least reduction in salivary output, and overall the changes in salivary output were similar between Ditropan XL and tolterodine.[34]

The OROS delivery system has substantially altered the bioavailability of oxybutynin chloride. Improved bioavailability has produced superior efficacy compared with the immediate formulation, while markedly improving patient tolerability.

ALTERNATIVE ORAL AGENTS IN TRIALS

Trospium Chloride

The quartenary amines in general demonstrate no central nervous system side effects. Molecular size and hydrophilicity prevents the distribution of these compounds to the central nervous system. However, gastrointestinal side effects substantially alter the tolerability profile of this class of medications. Other tolerability issues such as xerostomia, constipation, and anhydrosis are similar to the tertiary amines. Trospium chloride is a member of this class and has parallel tolerability issues as well as demonstrating atropinelike antispasmodic effects.[35] No changes in central nervous system electroencephalographic activity has been noted after acute ingestion in volunteers.[36] It demonstrates a high affinity for M_1 and M_3 receptors, with relatively less affinity for the M_2 site. Drug binding to these receptors appears to be prolonged binding as compared with other anticholinergics.[35] Extensive experience has been accrued in Germany with this drug, and clinical trials within the United States will begin soon.

Trospium is administered 3 times a day, with doses including 5, 15, and 30 mg. The half-life is variable, 5 to 21 hours, with the majority of the drug undergoing renal excretion without molecular degradation. Only 6% of ingested drug is bioavailable, which parallels levels seen with other tertiary amines and may be reflective of intestinal absorption differences with this drug.[37–39] In a study of 2,647 evaluable patients treated for 30 days with trospium, frequency was reduced by 40% and urge symptomatology by 87%. Only 28 adverse events were reported in this population.[40]

Additionally, trospium is well tolerated with intravesical administration and appears to be only minimally absorbed sytstemically.[41] This finding may indicate a substantial direct musculotropic effect. This parallels the musculotropic activity seen with intravesical oxybutynin.[41]

Darifenicin

Another selective antimuscarinic agent in development is darifenicin. This drug is an M_3-selective antagonist, with an 11-fold higher affinity for this receptor compared with the M_2 receptor.[42,43] In vitro, it appears to be selective for detrusor receptors, and specifically in canine and rodent models has clear affinity for bladder over salivary gland.[43] However, this selectivity is not as profound in other mammalian species.[43] Currently ongoing clinical phase 2 trials may better reveal the human tolerability/efficacy profiles. In a small study of 18 patients treated with 10 mg of darifenicin, improvement in urodynamic parameters was seen.[44] Other data indicate an improvement in quality-of-life parameters after acute treatment with darifenicin.[44]

Clinical trials are either ongoing or contemplated for NK-receptor antagonists, specific muscarinic subtype agonists/antagonists, and racemic oxybutynin.

ALTERNATIVE DRUG DELIVERY

New avenues for drug delivery include intravesical, transdermal, intravaginal, and electromotive (an enhancement technique for transepithelial absorption). The advantage of these alternative delivery pathways is avoidance of gut absorption and possible intermediate metabolism in the intestinal wall before hepatic metabolism. This concern is greatest for drugs that are predominantly metabolized by the cytochrome oxidase system (eg, oxybutynin chloride). Data obtained from metabolism of intravesical administration of oxybutynin chloride suggest that improved bioavailability of active parent compound and lower concentrations of metabolite are associated with this method of drug delivery, which, in theory, would also be seen with transdermal and other alternative delivery modes.[45,46]

Transdermal delivery is currently being evaluated in FDA trials in the United States (Watson Pharmaceuticals, Salt Lake City, Utah). Optimal dosing and type of delivery patch is as yet to be determined. Intravaginal and electromotive methods are also being actively investigated. Current clinical trials are in progress to investigate oxybutynin chloride–impregnated pessary systems for overall efficacy and tolerability.

Organ-specific gene therapy may provide the most specific and elaborate delivery vehicle for future applications in the management of the overactive bladder. Recent positive results obtained with the human simplex virus vector, which mediates expression of the B-nerve growth factor in a rat model of diabetic cystopathy, may be a harbinger of the delivery models of the future.[47]

Intravesical Agents

Intravesical drug delivery has theoretic and real advantages in patients who cannot tolerate oral anticholinergic agents or in patients who require higher levels of local drug delivery to achieve effect. Advantageous effects of intravesical instillation of atropine, phentolamine, verapamil, lidocaine, and bupivaciane have been reported in detrusor dysfunction. Although most studies indicate a substantial improvement in tolerability with intravesical oxybutynin administration, some studies have shown similar side-effect profiles as compared with oral administration this route.[48–56] On the basis of what is known about gut metabolism, reduced first pass metabolism through the gut wall, may explain the lower incidences of side effects associated with this administration level of the drug. Standard intravesical formulations of oxybutynin also demonstrate substantial differences in effective drug concentration. Recent intravesical delivery systems use a physiologic solution containing oxybutynin and have shown consistent drug serum levels, probably reflecting improved bioavailability. Current technologic development of a chronic intravesical pump delivery system is underway (Situs Corporation, San Diego, California) (Figure 1). The reservoir is currently being used for a 30-day dwell time within the bladder and requires cystoscopic insertion and removal. Other types of sustained-release delivery systems use fibrinogen-based adhesion with active agents commingled with the fibrinogen adhesive in order to enhance drug delivery to target areas. This technology has to date only been used for intravesical drug delivery of chemotherapeutic agents but has applicability to other urothelial indications.[57]

Intravesical delivery of 2 new agents provides a promising future treatment alternative. Capsaicin

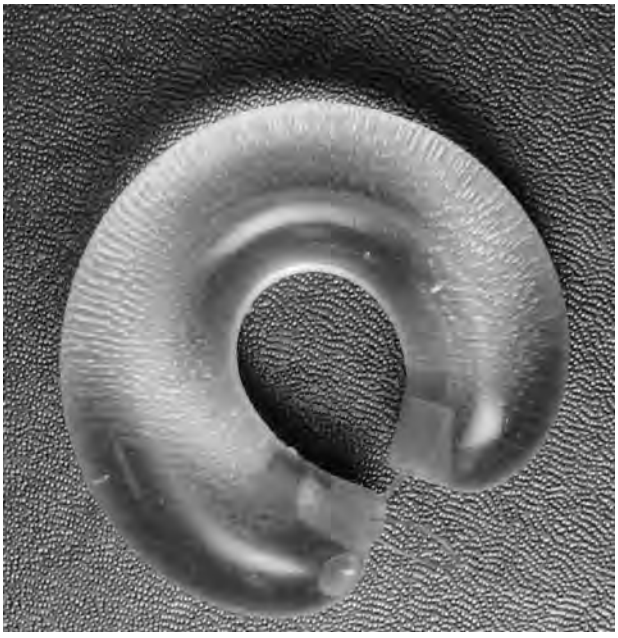

FIGURE 1. *The intravesical delivery of oxybutynin chloride can be regulated by the use of a reservoir that delivers drug uniformly over a 30-day time frame. The current version (Situs Corporation, San Diego, California) is inserted by a transurethral approach, filled intravesically, and left indwelling for 1 month. It is then removed (when empty) and replaced using the same technique.*

is derived from the capsicum peppers. It is a vanillyl amide and interacts with vanilloid receptors within the urinary bladder. Capsaicin has been shown to interact with sensory neurons and, although associated with local irritation with initial exposure, repeated exposure causes desensitization.[11,58,59] Resiniferatoxin (RTX), derived from the cactus relative *Euphorabia resinifera*, shares a vanilloid configuration with capsaicin and is an analog with much higher potency. Both agents have been used for topical allergic indications.

Capsaicin has shown efficacy in the treatment of detrusor hyperreflexia related to spinal cord injury and multiple sclerosis, with improved cystometric bladder capacity and decreased bladder motor activity for up to 9 months after instillation.[60,61] Further chronic therapy was noted to diminish hyperreflexia for up to 5 years after instillation.[62] In this study, 44% of patients obtained complete continence due to abolition of phasic detrusor activity, and 36% were substantially improved. Das *et al.* also demonstrated substantial improvement in 60% of treated patients.[63] In a randomized trial, mean bladder capacity substantially increased (172 mL to 312 mL), with significant reduction in urinary leakage after capsaicin administration. Side effects (suprapubic pain and hematuria) were self-limited and resolved within 1 week after instillation. Due to a selective activation of sensory C-fibers, capsaicin has also been used as an agent to treat bladder pain syndromes and has been reported to be successful for ameliorating pain in 4 of 5 patients with interstitial cystitis for up to 10 weeks after administration.[64]

RTX is a more potent neural antagonist than capsaicin and can be used in much lower concentrations. RTX used at concentrations of 50–100 nM produced sustained improvement in incontinence and bladder capacity in 5 of 7 neurologic patients for up to 3 months.[65] Cystometric bladder capacity increased by 50% to 900% in the improved patients. Similar effects were seen in 7 patients with idiopathic detrusor overactivity, with mean improvement in bladder capacity increasing from 175 mL to 281 mL for a short period. This effect was not sustained at 4-week follow-up.[66] No side effects were noted with administration at this concentration. In a dose escalation study of 26 patients with neurologic voiding dysfunction, improvements were noted in incontinence and cystometric capacity with 8 of 15 incontinent patients noting dramatic improvement in urinary loss.[67] Cystometric capacity was noted to increase by 500% in some patients. Optimal dosing and method of administration for RTX is yet to be determined.

Intravesical delivery allows site-specific drug delivery with a reduced side-effect profile as compared with oral delivery systems. The cumbersome nature of intravesical delivery, however, will limit the applicability of this approach to patients who have failed standard therapies.[68,69]

CONCLUSION

Continued advancements in the elucidation of physiologic and pathophysiologic lower urinary tract responses will provide more directed targeting of pharmacologic interventions to improve bladder storage capabilities. Improved delivery methods will augment therapeutic interventions, and in some cases the delivery methods may be the most important component of therapy.

Further understanding of neuroreceptor behavior and interactions will also guide more specific pharmacologic interventions for bladder overactivity. Results with new, more specific agents are anxiously anticipated.

REFERENCES

1. Thomas TM, Plymat KR, Blannin J, *et al:* Prevalence of urinary incontinence. **281:** 1243–1245, 1980.

2. Jackson S, Donovan J, Brookes S, *et al*: Bristol female lower urinary tract symptoms questionnaire: development and psychometric testing. Br J Urol **77:** 805–812, 1996.

3. Swithinbank L, Donovan J, Du Heaume JC, *et al*: Urinary symptoms and incontinence in women: relationships be-

tween occurrence, age, and perceived impact. Br J Gen Pract **49:** 897–900, 1999.

4. Bates P, Bradley WE, Glen E, *et al*: The standardization of terminology of lower urinary tract function. J Urol **121:** 551–554, 1979.

5. Eglen RM, Hedge SS, and Watson N: Muscarinic receptor subtypes and smooth muscle function. Pharmacol Rev **48:** 531–565, 1996.

6. Wang P, Luthin GR, and Ruggieri MR: Muscarinic receptor subtypes mediating urinary bladder contractility and coupling to GTP binding proteins. J Pharmacol Exp Ther **273:** 959–966, 1995.

7. Schwantes U, and Topfmeier P: Importance of pharmacological and physicochemical properties for tolerance of antimuscarinic drugs in the treatment of detrusor instability and detrusor hyperreflexia—chances for improvement of therapy. Int J Clin Pharmacol Ther **37:** 209–218, 1999.

8. Chancellor MB, and De Groat WC: Intravesical capsaicin and resiniferatoxin therapy: spicing up the ways that we treat the overactive bladder. J Urol **162:** 3–11, 1999.

9. Hegde SS, Choppin A, Bonhaus D, *et al*: Functional role of M_2 and M_3 muscarinic receptors in the urinary bladder in vitro and in vivo. Br J Pharmacol **120**(8): 1409–1418, 1997.

10. Nilvebrant L, Anderssin KE, Gillberg PG, *et al*: Tolterodine—a novel bladder selective antimuscarinic agent. Eur J Pharmacol **327:** 195–207, 1997.

11. Nilvebrant L, Gillberg PG, and Sparf B: Antimuscarinic potency and bladder selectivity of PNU 200577, a major metabolite of tolterodine. Pharmacol Toxicol **81:** 169–172, 1997.

12. Wallis RM, and Napier CM: Muscarinic antagonists in development for disorders of smooth muscle function. Life Sci **64:** 395–401, 1999.

13. Rentzhog L, Stanton SL, Cardozo L, *et al*: Efficacy and safety of tolterodine in patients with detrusor instability: a dose ranging study. Br J Urol **81:** 42–48, 1998.

14. Larsson G, Hallen B, and Nilvebrandt L: Tolterodine in the treatment of overactive bladder: an analysis of the pooled phase II efficacy and safety data. Urology **53:** 990–998, 1999.

15. Appell R: Clinical efficacy and safety of tolterodine in the treatment of overactive bladder: a pooled analysis. Urology **50:** 90–96, 1997.

16. Abrams P, Freeman R, Anderstrom C, *et al*: Tolterodine, a new antimuscarinic agent: as effective but better tolerated than oxybutynin in patients with an overactive bladder. Br J Urol **81:** 801–810, 1998.

17. Messelink EJ: Treatment of the overactive bladder with tolterodine, a new muscarinic receptor antagonist. Br J Urol **83:** 48–52, 1999.

18. Kelleher CJ, Cardozo LD, Khullar V, *et al*: A medium term analysis of the subjective efficacy of treatment for women with detrusor instability and low bladder compliance. Br J Obstet Gynecol **104:** 988–993, 1997.

19. Millard R, Tuttle J, Moore K, *et al*: Clinical efficacy and safety of tolterodine compared to placebo in detrusor overactivity. J Urol **161:** 1551–1555, 1999.

20. Wein AJ, Abrams P, and Appell R: Tolterodine is effective and well tolerated during long term use in patients with overactive bladder. J Urol **161:** 35, 1999. Abstract 125A.

21. Chancellor M, Freedman S, and Mitcheson HD: Tolterodine, an effective and well tolerated treatment for urge incontinence and other overactive bladder symptoms. Clin Drug Invest **19:** 83–91, 2000.

22. Brynne N, Stahl MMS, Hallen B, *et al*: Pharmacokinetics and pharmacodynamics of tolterodine in man: a new drug for the treatment of urinary bladder overactivity. Int J Clin Pharmacol Ther **35:** 287–295, 1997.

23. Gupta SK, and Sathyan G: Pharmacokinetics of an oral once a day controlled release oxybutynin formulation compared with immediate release oxybutynin. J Clin Pharmacol **39:** 289–296, 1999.

24. Yarker Y, Goa KL, and Fitton A: Oxybutynin: a review of its pharmacologic and pharmacokinetic properties, and its therapeutic use in detrusor instability. Drugs Aging **6:** 243–262, 1995.

25. Waldek K, Larrson B, and Andersson KE: Comparison of oxybutynin and its active metabolite N-desethyloxybutynin in the human detrusor and parotid gland. J Urol **157:** 1093–1097, 1997.

26. Gleason DG, Susset J, White C, *et al*: Evaluation of a new once daily formulation of oxybutynin for the treatment of urinary urge incontinence. Urology **54:** 420–423, 1999.

27. Anderson RU, Mobley D, Blank B, *et al*: Once daily controlled versus immediate release oxybutynin chloride for urge urinary incontinence. J Urol **161:** 1809–1812, 1999.

28. Versi E, Appell RA, Mobley D, *et al*: Dry mouth with conventional and controlled release oxybutynin in urinary incontinence. Obstet Gynecol **95:** 718–721, 2000.

29. Katz IR, Sands LP, Bilker W, *et al*: Identification of medications that cause cognitive impairment in older people: the case of oxybutynin chloride. J Am Geriatr Soc **46**(1): 8–13, 1998.

30. Donnellan CA, Fook L, McDonald P, *et al*: Oxybutynin and cognitive dysfunction. BJM **315:** 1363–1364, 1997.

31. Dimpfel W, Todorova A, and Vonderheid-Guth B: Electrophysiological evaluation of potential adverse drug effects of tolterodine, oxybutynin and trospium chloride on the central nervous system. J Urol **163:** 226, 2000. Abstract 1005.

32. Tuttle J, Antoci J, Appell RA, *et al*: Controlled release oxybutynin for overactive bladder in an elderly population. Proceedings of the American Geriatric Society; Nashville, Tennessee; September, 2000.

33. Appell R, Diokno A, Antoci J, *et al*: One year prospective, open label trial of controlled release oxybutynin for overactive bladder in a community based population. Neurourol Urodyn **19**: 526, 2000. Abstract 117.

34. Chancellor MB, Appell RA, Sathyan G, *et al*: Effect of controlled release oxybutynin and tolterodine on salivary output. Neurourol Urodyn **19**: 494, 2000. Abstract 9.

35. Breuel HP, Murtz G, Bondy S, *et al*: Safety and tolerance of trospium chloride in the high dose range. Arzneimittelforschung 461–464, 1993.

36. Pietzko A, Dimpfel W, Schwantes U, *et al*: Influence of trospium chloride and oxybutynin on quantitative EEG in healthy volunteers. Eur J Clin Pharmacol **47:** 337–343, 1994.

37. Langguth P, Kubis A, Krumiegel G, *et al*: Intestinal absorption of the quartenary trospium chloride: permeability lowering factors and bioavailability for oral dosage forms. Eur J Pharmacol Biopharmacol **43:** 265–272, 1997.

38. Eckert RE, Wilhelm A, Schwantes U, *et al*: Modulation der zytoplasmatischen Ca-konzentration isolierter Myozyten des detrusor vesicae durch anticholinergika. Akt Urol **26:** 4–6, 1995.

39. Schwantes PA, Zallner M, Schwantes U, *et al*: Effektivitat und akzeptanz einer tospiumchlorid—therapie bei patienten mit drang—inkontinenz. Acta Ther **20:** 133–149, 1994.

40. Massad CA, Kogan BA, and Trigo Roche FE: The pharmacokinetics of intravesical and oral oxybutynin chloride. J Urol **148:** 595–597, 1992.

41. Frolich G, Burmeister S, Wiedemann A, *et al*: Intravesical trospium chloride, oxybutynin, and verapimil for relaxation of detrusor muscle: a placebo controlled, randomized clinical trial in Germany. Arzneimittelforschung **48:** 486–491, 1998.

42. Newgreen DT, Anderson CWP, Carter TJ, *et al*: Darifenicin—a novel bladder selective muscarinic antagonist for the treatment of urge incontinence. J Urol **136**: 600, 1996. Abstract 1156.

43. Wallis RM, Burges RA, Cross PE, *et al*: Darifenicin, a se-

lective muscarinic M_3 antagonist. Pharmacol Res **31:** 54–57, 1995.

44. Rosario DJ, Cutinha PE, Chapple CR, *et al*: The effects of single dose darifenicin on cystometric parameters and salivary flow in patients with urge incontinence secondary to detrusor instability. Eur Urol **30**: 240, 1996.

45. Brendler CB, Radebaugh LC, and Mohler JL: Topical oxybutynin chloride for relaxation of dysfunctional bladders. J Urol **141:** 1350–1352, 1989.

46. Enzelsberger H, Helmer H, and Kurz C: Intravesical instillation of oxybutynin in women with idiopathic detrusor instability: a randomized trial. Br J Obstet Gynaecol **102:** 929–930, 1995.

47. Phelan MW, Yoshimura N, Goins WF, *et al*: Nerve growth factor (NGF) gene therapy improves rat diabetic cystopathy, but does not increase pain sensation. J Urol **163:** 245–248, 2000.

48. Krishnan KR, Fowler C, Powell J, *et al*: A double blind, randomized placebo controlled, parallel group multicenter study of intravesical oxybutynin in the symptomatic relief of urge incontinence with detrusor instability/hyperreflexia. Neurol Neurourol Urodyn **15:** 674–676, 1996.

49. Palmer LS, Zebold K, Firlit CF, *et al*: Complications of intravesical oxybutynin chloride therapy in the pediatric myelomeningocele population. J Urol **157:** 638–640, 1997.

50. Kaplinsky R, Greenfield S, Wan J, *et al*: Expanded followup of intravesical oxybutynin chloride use in children with neurogenic bladder. J Urol **156:** 753–756, 1996.

51. Madersbacher H, and Knoll M: Intravesical application of oxybutynin: mode of action in controlling detrusor hyperreflexia: preliminary results. Eur Urol **28:** 340–344, 1995.

52. Buyse G, Waldeck K, Verpoorten C, *et al*: Intravesical oxybutynin for neurogenic bladder dysfunction: less systemic side effects due to reduced first pass metabolism. J Urol **160:** 892–896, 1998.

53. Mattiasson A, Ekstrom B, and Anderson KE: Effects of intravesical instillation of verapamil in patients with detrusor hyperactivity. J Urol **141:** 174–177, 1989.

54. Yokoyama O, Ishiura Y, Nakamura Y, *et al*: Urodynamic effects of intravesical instillation of lidocaine in patients with overactive detrusor. J Urol **57:** 1826–1831, 1997.

55. Higson RH, Smith JC, and Hills W: Intravesical lignocaine and detrusor instability. Br J Urol **51:** 500–503, 1979.

56. Weese DL, Roskamp DA, Leach GE, *et al*: Intravesical oxybutynin chloride: experience with 42 patients. Urology **41:** 527–530, 1993.

57. Singh SS, Smith KM, and Brown DM: Drug retention following intravesical delivery of fluorouracil therapeutic adhesive in C3H mouse bladder. Anticancer Drugs **7:** 507–511, 1996.

58. Szallasi A, and Blumberg PM: Vanilloid receptors: new insights enhance potential as therapeutic target. Pain **68:** 195–199, 1996.

59. Dasgupta P, Chandiramani V, Parkinson MC, *et al*: Treating the human bladder with capsaicin: is it safe? Eur Urol **33:** 28–32, 1998.

60. Fowler CJ, Beck RO, Gerard S, *et al*: Intravesical capsaicin for treatment of detrusor hyperreflexia. J Neurol Neurosurg Psychiatry **57:** 169–173, 1994.

61. Geirsson G, Fall M, and Sullivan L: Clinical and urodynamic effects of intravesical capsaicin treatment in patients with chronic traumatic spinal detrusor hyperreflexia. J Urol **154:** 1825–1827, 1995.

62. DeRidder D, Chandramani V, Dasgupta P, *et al*: Intravesical capsaicin as a treatment for refractory detrusor hyperreflexia: a dual center study with long term followup. J Urol **158:** 2087–2090, 1997.

63. Das A, Chancellor MB, Watanabe T, *et al*: Intravesical capsaicin in neurogenic impaired patients with detrusor hyperreflexia. J Spinal Cord Med **19:** 190–193, 1996.

64. Flood H, Byrne DS, Rivas DA, *et al*: Intravesical capsaicin for interstitial cystitis. J Urol **157:** 254, 1997. Abstract 995.

65. Cruz F, Guimares M, Silva C, *et al*: Suppression of bladder hyperreflexia by intravesical resiniferatoxin. Lancet **350:** 640–645, 1997.

66. Lazzeri M, Beneforti P, Turini D, *et al*: Intravesical resiniferatoxin for the treatment of detrusor hyperreflexia refractory to capsaicin. J Urol **159:** 83, 1998. Abstract 316.

67. Rivas DA, Shenot P, Stuligowa K, *et al*: Intravesical resiniferatoxin (RTX) treatment of detrusor hyperreflexia: results of a randomized, double-blind, placebo-controlled, multicenter trial. J Urol **161:** 276, 1999. Abstract 1070.

68. Wiart L, Joseph PA, Petit H, *et al*: The effects of capsaicin on the neurogenic hyperreflexic detrusor : a double blind placebo controlled study in patients with spinal cord disease—preliminary results. Spinal Cord **36:** 95–98, 1998.

69. Lazzeri M, Beneforti P, Benaim G, *et al*: Intravesical capsaicin for treatment of severe bladder pain: a randomized placebo controlled study. J Urol 1996; **156:** 947–950.