DRUG TREATMENT IN UROLOGY

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Preface

Urology is the most 'medical' of all the surgical specialities. Many of the conditions that present to urologists do not require surgical treatment but are best treated in other ways, including the use of drugs. While antibiotics and analgesics have been with us for many years, it is only in the past 15 years that medical therapy for urological conditions has boomed. Following the advent of effective medical therapy for benign prostatic hyperplasia, effective agents for other benign conditions including urinary incontinence and erectile dysfunction have appeared. At the same time the scientific search for an effective and safe treatment for cancer has accompanied the introduction of multiple agents for the treatment of all the urological cancers, with increasing degrees of efficacy and tolerability. It is inevitable that this progress will continue.

Given the increasing role of drugs within urology, it is perhaps surprising that there has never before been an attempt to produce a comprehensive summary of the urological drugs. This book seeks to address this deficit. The Editors, with a wide range of subspecialty interests covering the breadth of urology, have put together a series of articles that seek to provide for the reader a concise summary of the role of pharmacotherapy in urology. Each chapter deals with either a specific urological condition or with a class of drugs and seeks to outline for each respective agent, the mechanism of action, the evidence for efficacy, safety and tolerability and those practical issues relating to the use of these agents. Clearly the pharmaceutical industry is always seeking new agents either with better efficacy and tolerability than those currently marketed, or with novel mechanisms of action for new indications. Change is often rapid, and for that reason, any book such as this will only provide a snapshot of the drugs available at a particular moment in time.

At the same time as these drugs are being introduced, urology is also changing. With increasing sub-specialization of operative urology most health care systems are training significant numbers of 'office' or 'core' urologists who will inevitably become the main purveyors of medical therapy for urological conditions. It is for this group of urologists that are particularly aiming this book. We hope they will find this book useful as a guide and reference for their everyday practise.

Part 1
Functional Disorders

1: Urinary Incontinence

Stephen J. Griffin & William H. Turner

Introduction

Incontinence of urine occurs when bladder pressure exceeds urethral pressure. If bladder pressure is inappropriately high, this is detrusor overactivity with so-called urge incontinence, whereas if urethral pressure is inappropriately low, this is stress urinary incontinence (SUI). These two conditions, separately or together, cause most of the cases of urinary incontinence seen in clinical practice. A brief outline of each condition is given, together with the rationale for the use of the various types of drug treatments that have been tried for each, before an account of the details of the individual drugs that have been used.

Overactive bladder

Overactive bladder has been defined by the International Continence Society as urgency (with or without incontinence), usually with frequency and nocturia, not explained by metabolic or local pathological factors. The urodynamic manifestation of this is called detrusor overactivity and it denotes involuntary detrusor contractions during the filling phase that may be spontaneous or provoked [1]. A population-based survey in six European countries revealed a prevalence of bladder overactivity between 12% and 22% in 17 000 people over 40 years old [2]. Such symptoms can have a profoundly negative influence on the quality of life, which is similar to diabetes mellitus [3], although paradoxically, many people do not seek medical advice about these symptoms. Although the physiology of the smooth muscle of the bladder is increasingly well understood [4] the pathogenesis of bladder overactivity remains to be fully elucidated, with both myogenic and neurogenic factors probably being involved [5,6].

The symptoms of bladder overactivity have been shown to respond to physical therapies. Randomized controlled trials (RCTs) investigating response rates to bladder training suggest that this is useful in the management of urge incontinence in the short term, but the data are not high quality [7]. Pelvic floor exercises appear to be an effective treatment for SUI and mixed urinary incontinence, although their efficacy with urge incontinence alone is less well documented [8]. These outcomes however,

taken with the lack of side-effects of bladder training and pelvic floor exercises, emphasize their use as first-line treatment for bladder overactivity.

When behavioural techniques fail, the use of medication is appropriate, and many drugs have been used to treat bladder overactivity. Recent data suggest that the combination of bladder training and medication may offer an advantage over medication alone [9].

Drugs with a purely or largely muscarinic (M) antagonist (anticholinergic) action have been extensively used, probably on the basis that voiding contractions are mediated by release of acetylcholine (ACh) from the excitatory innervation of the detrusor, and subsequent activation of M receptors (mainly the M3 subtype) on detrusor smooth muscle cells [4]. There seem to be more M2 than M3 receptors in the detrusor, many located prejunctionally: their role is unclear at present, but stimulation may also be important in disease states [10]. It remains uncertain whether the use of anticholinergics to treat bladder overactivity actually has a rational basis, given that it is still not clear if activation of the detrusor M receptors is a critical part of the aetiology of overactive bladder contractions [11]. This might account for the generally disappointing efficacy of the anticholinergics in clinical practice [12]. Drugs that might reduce the effect of overactive bladder contractions in other ways have been used, including those that block L-type calcium channels (thereby reducing the rise in intracellular calcium necessary for detrusor cell contraction), drug with actions loosely described as smooth muscle relaxants, drugs that activate potassium channels (thereby reducing detrusor smooth muscle cell excitability), and drugs that may act on the afferent limb of the micturition reflex. The lack of high clinical efficacy of all of these drugs probably also reflects our lack of a clear understanding of the pathophysiological basis of overactive bladder contractions. Relatively few of the whole group of drugs that have been used have a level 1 evidence base [13], and although there is clear guidance on good practice for clinical trials that investigate drug therapy [14], its use in the study of drug treatment of urinary incontinence remains disappointing [15]. Only those agents in common clinical use at present (oxybutynin, propiverine, tolterodine and trospium) and those in development are discussed: other agents, now little used (e.g. dicyclomine, propantheline, flavoxate), are not considered.

Anticholinergics

Anticholinergics increase the volume to the first spontaneous detrusor contraction during filling and the bladder capacity, but decrease the amplitude of the first contraction. Currently available agents are not bladder-selective and often cause typical atropine-like side-effects (due to blockage of M

receptors), including dry mouth and/or eyes, upper and lower gastrointestinal symptoms, tachycardia and accommodation paralysis. Indeed, these agents are contraindicated in narrow angle glaucoma. Given the uncertainty about the pathophysiological basis of bladder overactivity, the wide distribution of M receptors and the lack of bladder-specific M receptors, it is not surprising that atropine-like side-effects are common. Trials report dropout rates between 12% and 63% and placebo response in up to 45% of participants [8]. The side-effect profile of presently used medication underlines the use of drug treatment as second-line therapy for bladder overactivity.

TOLTERODINE

Tolterodine is a tertiary amine that is a competitive non-selective antimuscarinic agent [16]. *In vitro*, the affinity of tolterodine for bladder muscarinic receptors is similar to that of oxybutynin, whereas its affinity for guinea-pig parotid muscarinic receptors is less than that of oxybutynin. This tissue selectivity is claimed to be preserved *in vivo* in animal models [17]. It is metabolized via cytochrome P450, yielding a 5-hydroxymethyl active metabolite [18]: both these compounds have a half-life of 2–3 h. The low lipophilicity of tolterodine and its metabolites means that they do not cross the blood–brain barrier, and this presumably accounts for a low incidence of cognitive side-effects. It is available in two preparations: immediate-release (IR) (1–2 mg twice daily) or extended-release (ER) (4 mg once daily).

Several randomized, placebo-controlled trials, over 4–12 weeks, have demonstrated benefit of IR tolterodine compared with placebo, with respect to micturition diary variables and urodynamic end points in patients with neurogenic detrusor overactivity and bladder overactivity [18,19]. Studies typically show significant improvement in the number of voids per day, urine volume per void, number of incontinent episodes and pad usage, and the volume at first detrusor contraction, volume at normal desire to void and maximum cystometric capacity are all increased. These effects are maintained with longer treatment over a 9-month period [20]. However, dry mouth is three times more likely with tolterodine than placebo [8], occurring in up to 40% of patients taking tolterodine IR [21].

ER tolterodine has become available and a large multicentre, double-blind, randomized, placebo-controlled study compared tolterodine ER 4 mg once daily with tolterodine IR 2 mg twice daily, in patients with urinary frequency, urge incontinence, and symptoms of bladder overactivity for more than 6 months [22]. More than 500 patients were enrolled into each of the three arms for the 12-week study period. Efficacy was evaluated using micturition diaries that documented the number of incontinence

episodes per week, number of micturitions per 24 h, voided volume and the number of pads used per 24 h. There was a significant improvement in all micturition diary variables in both the ER and IR regimens, compared with placebo. The median reduction (from baseline) in urge incontinence episodes was 71% for tolterodine ER, 60% for tolterodine IR and 33% for placebo, and this reached statistical significance for the ER versus IR regimens ($p < 0.05$). Furthermore, dry mouth was reported significantly less often by those taking the ER preparation compared with those on tolterodine IR 2 mg twice daily. A recent secondary analysis of a placebo-controlled study showed a clinically important reduction in urgency with tolterodine ER [23]. In a follow-up study, tolterodine ER was shown to have a good side-effect profile at 12 months [24].

A number of RCTs have compared tolterodine IR 2 mg twice daily with oxybutynin IR 5 mg twice or three times daily [25–27]. There was comparable improvement in urinary frequency in all three studies and similar improvement in the number of incontinence episodes for both drugs in two studies [25,27]. Although Leung *et al.* did not show improvement with either agent with respect to incontinence episodes, improvement in urinary leakage using the urinary pad test was demonstrated with both agents [26]. However, this was statistically significantly better in the tolterodine group. Tolterodine also had a statistically significant better adverse effect profile in two out of three of these studies [25,27]. Leung *et al.* did not demonstrate significantly different adverse effect profiles between the two drugs [26].

The OBJECT study [28] prospectively compared tolterodine IR 2 mg twice daily with oxybutynin ER 10 mg once daily in patients with bladder overactivity. In this multicentre, double-blinded, parallel-group study, 378 patients were randomized and treated, and 87% completed the 12-week study. Oxybutynin ER was significantly more effective than tolterodine in each of the main outcome measures: weekly urge incontinence episodes, total incontinence episodes and urinary frequency compared with baseline values. Furthermore, there was no significant difference in dry mouth rates between the two groups. However, the study compared the ER form of oxybutynin with the standard preparation of tolterodine, and so an advantage in terms of side-effects might have been expected.

The Antimuscarinic Clinical Effectiveness Trial (ACET) addressed this issue [29]. This trial compared tolterodine ER 2 mg or 4 mg with oxybutynin ER 5 mg or 10 mg in 1289 patients with bladder overactivity. It was an open-label, multicentre trial with site selection and an 8-week treatment period. Investigators in one arm were blinded to the existence of the other arm in an attempt to limit bias. Primary efficacy variables were changes in patient perception of bladder condition and patient assessment of treatment

benefit using a validated questionnaire. Severity of dry mouth was assessed using a visual analogue scale. An improved bladder condition was perceived by 70% of patients in the tolterodine ER 4 mg group, compared with 60% in the tolterodine ER 2 mg group, 59% in the oxybutynin ER 5 mg group and 60% in the oxybutynin ER 10 mg group (all $p < 0.01$ vs tolterodine ER 4 mg). In addition, patients treated with tolterodine ER 4 mg reported a significantly lower severity of dry mouth than those treated with oxybutynin ER 10 mg. However, this study lacked a placebo arm, and although open-label studies may better reflect clinical practice, the authors acknowledged that they were open to bias from both physicians and patients. The two agents in ER form were also compared in the OPERA study, and whilst oxybutynin ER had a greater impact on urinary frequency, it had a higher risk of dry mouth [30]. This study was also limited by lack of a placebo arm.

TROSPIUM CHLORIDE

Trospium chloride is a quaternary ammonium compound that blocks M1–M3 receptors non-selectively: its pharmacology has been summarized recently [31]. *In vitro*, it has higher affinity for M receptors than do flavoxate, oxybutynin or tolterodine [32]. It has a half-life of 5–15 h with low biological availability (5%), and does not cross the blood–brain barrier [16]. The standard dose is 20 mg orally, twice daily.

The efficacy of the oral regimen has been proven in a number of double-blind placebo-controlled trials in patients with neurogenic detrusor overactivity [33], detrusor overactivity and bladder overactivity [34,35]. The urodynamic effect of treatment is an increased volume at first unstable contraction, and increased maximum cystometric capacity during filling. No significant decrease in maximum detrusor pressure at first unstable contraction is observed [34,35]. Frohlich *et al.* report that 47.9% of patients treated with trospium recorded a 'cure' or 'marked improvement', compared with 19.7% receiving placebo ($p < 0.0001$) [35]. Gastrointestinal side-effects and dry mouth were experienced by 21.7% and 14%, respectively, of patients in the treatment arm, compared with 18.7% and 8.4% in the placebo arm. However, post-marketing surveillance studies in over 10 000 patients show that this drug is well tolerated [31], with dry mouth reported by 4.1% of patients and gastrointestinal upset by less than 1%, and an overall occurrence of adverse events of approximately 5%.

Twenty milligrams twice daily trospium has been compared with 5 mg oxybutynin three times daily in patients with spinal cord injury having neurogenic detrusor overactivity [36]. This randomized, double-blind, multicentre study compared the two treatment arms at 2 weeks with respect to urodynamic parameters and subjective symptoms. There were similar

increases in maximum cystometric capacity, compliance and residual volume. Both regimens produced a significant decrease in maximum voiding pressure, with no statistically significant difference between the groups. However, severe dry mouth was only experienced by 4% of patients taking trospium compared with 23% in the oxybutynin arm. Furthermore, the oxybutynin group had a 16% dropout rate compared with 6% in the trospium group.

The same trospium regimen is compared with 2 mg tolterodine twice daily in patients with bladder overactivity [37]. In this placebo-controlled multicentre trial of 234 patients with bladder overactivity both treatments reduced voiding frequency, but only the decrease in the trospium-treated group reached statistical significance compared with placebo. Dry mouth was similar in both groups.

Mixed action anticholinergics

OXYBUTYNIN

Oxybutynin is a tertiary amine with antimuscarinic, muscle relaxant and local anaesthetic effects and high affinity for M1 and M3 receptors [16]. It undergoes extensive first-pass metabolism, yielding the active metabolite *N*-desethyl oxybutynin: the plasma half-life is around 2 h, but there is wide individual variation [38]. It is available as an IR form, (2.5–5 mg orally twice to four times daily) or ER form (5–10 mg orally once daily to a maximum of 30 mg) preparation. When taken orally, much of the pharmacodynamic effect of the drug is thought to be due to the active metabolite, *N*-desethyl oxybutynin, which has a higher plasma concentration than the parent compound [39]: the active metabolite may also be largely responsible for the drug's adverse effects. Oxybutynin ER yields lower plasma levels of the active metabolite compared with oxybutynin IR, suggesting decreased first-pass metabolism [40]. In addition, salivary output is higher with less dry mouth when comparing oxybutynin ER with oxybutynin IR [40–42]. Transdermal oxybutynin bypasses first-pass metabolism and is associated with less dry mouth than the IR preparation [43].

Several controlled studies have demonstrated the efficacy of oxybutynin in the treatment of bladder overactivity and detrusor hyperreflexia. Thüroff *et al.* [44] reviewed 15 RCTs that included nearly 500 patients treated with oxybutynin. The mean decreases in incontinence and frequency were 52% and 33%, respectively. The mean overall subjective improvement rate was 74%, with adverse effects reported by 70% of patients. Side-effects are typically systemic antimuscarinic effects – dry mouth, constipation, blurred vision – and are generally dose-related. However, oxybutynin can also cross the blood–brain barrier, causing cognitive impairment that can be particu-

larly problematic with the elderly and with children treated with intravesical oxybutynin.

Oxybutynin ER uses an osmotic drug delivery system to release the drug in a controlled fashion over 24 h [45]. This reduces the variations in plasma levels that occur with the IR preparation. Studies comparing the ER with the IR preparation have failed to show any improvement in efficacy with respect to symptom control of the ER compared with the IR preparation [40–42]. However, the side-effect profile is better with the ER preparation.

Transdermal oxybutynin has demonstrable efficacy for the treatment of bladder overactivity compared with placebo [46]. The incidence of dry mouth was comparable with the placebo arm. However, the most common adverse event was site pruritis (noted in up to 16.8% of patients). Davila *et al.* [43] further demonstrated that transdermal oxybutynin had similar efficacy in the treatment of urge urinary incontinence, with less dry mouth. Transdermal oxybutynin was shown to have efficacy similar to tolterodine ER, but a lower anticholinergic side-effect profile, at the expense of more skin irritation [47].

Intravesical oxybutynin has been used successfully for the treatment of neurogenic detrusor overactivity and detrusor overactivity in both children and adults [16]. The efficacy of oxybutynin is well documented and the International Consultation on Incontinence recommended it and tolterodine as the drugs of choice for bladder overactivity [16].

PROPIVERINE

Propiverine is a benzilic acid derivative with anticholinergic and calcium antagonistic actions [48]. It has a bioavailability of 40% and undergoes extensive first-pass metabolism. There are three metabolites that seem to be active; however, the pharmacological characteristics of this drug remain to be elucidated [16]. It is administered orally 15 mg three times daily, increased to four times daily if necessary.

Nine randomized studies using propiverine for the treatment of bladder overactivity were collated by Thüroff *et al.* [44]. Subjective improvement was reported by 77%, and objective improvement in bladder capacity and urinary frequency was noted. Bladder capacity increased by 64 ml and there was a reduction in urinary frequency by 30%. Madersbacher *et al.* [48] report similar efficacy between propiverine 15 mg three times daily and oxybutynin IR 5 mg twice daily in a multicentre, randomized, double-blind placebo-controlled trial using urodynamic parameters to assess efficacy. However, the incidence and severity of dry mouth was less in the patients treated with propiverine.

Propiverine is also effective in the treatment of neurogenic detrusor overactivity in patients with spinal cord injury [33]. In a prospective, double-blind, randomized, multicentre trial, bladder capacity at first contraction increased by 72 ml, maximal cystometric capacity increased by 104 ml and maximum detrusor pressure decreased by 27+/− 32 cm H_2O [33]. Dry mouth was reported by 37% of patients on propiverine and 28% on placebo, with accommodation disturbance in 8% and 2%, respectively [33].

NEWER AGENTS

Darifenacin is a selective M3 receptor antagonist that is currently being evaluated in phase III studies. Initial work in patients with detrusor overactivity suggests urodynamic effects comparable with oxybutynin, with less effect on salivary flow.

Solifenacin is a long-acting antimuscarinic agent. Enhanced bladder selectivity has been claimed [49], and the preliminary results of a study comparing solifenacin with tolterodine and placebo show a significant improvement in symptoms of bladder overactivity [50], but more detail on the efficacy compared with existing anticholinergics is required.

Activation of detrusor muscle through M receptors requires influx of calcium to the detrusor muscle cell and mobilization of calcium from the sarcoplasmic reticulum [4]. The calcium channel blocker, verapamil, used intravesically can increase bladder capacity and decrease leakage in patients with detrusor overactivity [51].

Potassium channel openers (KCOs) reduce smooth muscle cell excitability, and may therefore be useful in bladder overactivity by addressing the myogenic component of its aetiology [11]. Recent *in vivo* data support this use [52]. There are KCOs currently in phase II/III studies in patients with bladder overactivity symptoms.

Stress urinary incontinence

The anatomical factors that relate to SUI have been reviewed recently [53]: they cannot be treated pharmacologically. However, it is postulated that women with SUI have reduced maximum urethral closure pressures (MUCP), as they have lower resting urethral pressures than age-matched continent women. Various agents have been used, without much success, in an attempt to improve urethral pressure. Urethral pressure is substantially mediated by activation of α-adrenoceptors in urethral smooth muscle [4,54], and so drugs that might augment the activation of these receptors have been used over some years to attempt to treat SUI. The role of the

vascular plexus of the lamina propria of the female urethra remains to be agreed upon [55,56], but it seems likely that it may contribute significantly. Both the vasculature and smooth muscle within the lamina propria and the smooth muscle of the urethra may be sensitive to oestrogen, and this has been used to try to treat SUI [16].

Several α-adrenoceptor agonists have been used to treat SUI: they share the anticipated side-effects that include anxiety, tremor, headache, palpitations and hypertension, and so should be used with caution in those with cardiovascular disease. Indeed, the Food and Drug Administration (FDA) in the USA has asked for norephedrine (phenylpropanolamine) to be withdrawn from the market because of concerns about hypertension. In a placebo-controlled study, 27 of 38 patients with SUI responded to ephedrine, but those with severe symptoms did less well [57]. By contrast, in a placebo-controlled study of norephedrine, only a moderate response was seen in 25 women with SUI [58]. In a placebo-controlled study of methoxamine in women with SUI, there was no significant rise in MUCP, but systolic hypertension and symptomatic side-effects did occur [59]. The β_2-adrenoceptor agonist clenbuterol has been used to treat SUI, although the rationale is hard to see. A randomized study compared clenbuterol with pelvic floor exercises, and found that either drug or drug and pelvic floor exercises were better than pelvic floor exercises alone [60]. Currently good evidence is lacking for the use of adrenoceptor agonists or antagonists of any sub-type for the treatment of SUI.

Duloxetine inhibits re-uptake of noradrenaline and 5-HT. It has been used in a placebo-controlled study in 683 women with SUI and with mixed incontinence and produced around 50% reductions in incontinence episodes compared with around 25% reductions by placebo, in all women, and in those with more severe symptoms [61]. A recently published placebo-controlled trial compared duloxetine 40 mg bd with placebo in 494 women with SUI [62]. There were demonstrable and statistically significant reductions in the frequency of incontinent episodes (median decrease 50% vs 29%), and there was an improvement in disease-specific quality of life. Discontinuations with duloxetine were significantly higher (22% vs 5% for placebo), with nausea being the most common reason for discontinuation. There is a suggestion in the clinical trials that the nausea diminishes with time.

Vaginally administered oestrogens have been used in the treatment of SUI. Meta-analyses [63,64] of controlled trials using oestrogens to treat SUI found improvement in MUCPs and subjective symptomatic improvement. However, there was no objective improvement in the amount of urinary leakage. Oestrogens, therefore, may be helpful with the associated symptoms of frequency and urgency, but are not an effective treatment alone for SUI.

Nocturnal enuresis

Bedwetting results in low self-esteem and may affect personal relationships and career development, but self-esteem in enuretic children returns to normal after adequate treatment [65]. It has, therefore, been suggested that active treatment should be started early when a patient presents with nocturnal enuresis. Some studies have shown that one of the factors contributing to nocturnal enuresis in children is absence of a normal nocturnal increase in ADH [66].

DESMOPRESSIN

Desmopressin (1-desamino-8-D-arginine vasopressin; DDAVP) is a synthetic analogue of arginine vasopressin. It has pronounced antidiuretic effect and is practically devoid of vasopressor actions [16]. It was available initially as an intranasal spray and is now also available in oral tablet form. It has been used for the treatment of nocturnal enuresis for some years, generally at a dose of 0.02 mg intranasal spray at bedtime. Night-time administration of desmopressin increases water reabsorption in the collecting ducts of the kidneys, causing a reduction in nocturnal urine volume [67].

Studies report that treatment with desmopressin for nocturnal enuresis over a period of 6 months or more results in a halving in the number of wet nights in 50–85% whilst 40–70% report being completely dry [65]. Furthermore, patients do not develop tolerance to the drug over time. Cure rates upon cessation of therapy are difficult to interpret, as there is an annual spontaneous recovery rate of approximately 15% [65]. However, data suggest that treatment with desmopressin further improves the cure rate. In addition, tapered dose cessation is associated with better cure rates than immediate cessation of the drug.

Long-term treatment with desmopressin for nocturnal enuresis has no significant side-effects. Van Kerrebroeck [65] reviewed 1083 patients treated with desmopressin spray or tablets and found only 53 (5%) patients experienced adverse effects that could be related to treatment. The most frequent adverse effects were headache (2% of all patients) and abdominal pain (1% of all patients). Furthermore, desmopressin does not influence endogenous ADH secretion.

Neurogenic incontinence

Neurogenic lower urinary tract dysfunction can be broadly divided into two categories: bladders that fail to empty successfully and those that fail to store urine adequately. Failure to empty results from either detrusor hypocontractility or increased outlet resistance caused by detrusor sphincter dyssynergia

(DSD), whilst failure to store is neurogenic detrusor overactivity. The underlying aetiology of neurogenic lower urinary tract dysfunction can be complex and problems with storage and bladder emptying can coexist.

Failure to empty

Clean intermittent catheterization (CIC) is the main therapeutic measure used to provide adequate bladder emptying in patients with neurogenic bladder where manual dexterity is adequately preserved. Patients for whom this is not a viable option may be considered for therapy to decrease outlet resistance.

Botulinum toxin blocks the release of ACh from nerve terminals reversibly over a prolonged period of time. Insertion of toxin to selected muscular tissues has been used to treat various conditions including achalasia, anal fissure, strabismus and torticollis. Dykstra *et al.* first evaluated injection of botulinum A toxin into the rhabdosphincter of men with spinal cord injury for the treatment of DSD [68]. In this small study ($n = 11$), patients had cystoscopic injection of toxin into the rhabdosphincter via a needle electrode attached to an electromyography machine to confirm correct needle position. There was a decrease in urethral pressure profile and post-void residual urine after treatment. A similar study in patients with spinal cord injury with DSD found 21 of 24 patients were significantly improved with a significant decrease in post-void residual urine [69]. The response lasted 3–9 months, making re-injection necessary. The authors claim this is safe, although expensive, alternative management in patients with DSD who cannot perform CIC and do not want permanent surgical sphincterotomy.

Failure to store

Neurogenic detrusor overactivity is often treated with anticholinergic therapy initially, along standard lines, although this is not always effective. Recent work has turned attention to modulation of the afferent side of the innervation of the lower urinary tract, because of experimental data suggesting that unmyelinated C fibres may mediate the afferent limb of the micturition reflex in certain circumstances, such as spinal lesions [6]. This C fibre activity may also be involved in the genesis of detrusor overactivity in patients with neuropathic lower urinary tract dysfunction [6].

CAPSAICIN

Vanilloids are agents that activate vanilloid receptors, and these are expressed almost exclusively by primary sensory neurons involved in nociception and neurogenic inflammation [70,71]. Vanilloid receptors are

activated by drugs like capsaicin, the active ingredient in hot peppers of the genus Capsicum. This causes initial excitation, then desensitization of the neuron. Capsaicin has been shown to prevent rhythmic bladder contractions induced by bladder distension in the spinal cat [72], and was therefore used clinically in patients with neurogenic detrusor overactivity unresponsive to conservative treatment. Capsaicin is lipid-soluble and has to be dissolved in 30% ethanol in saline in order to be suitable for intravesical instillation. It also produces profound excitation of the vanilloid receptors before desensitization, causing intense pain on instillation, sometimes requiring anaesthesia [73]. De Ridder *et al.* have reported on 79 patients with refractory neurogenic detrusor overactivity treated with intravesical capsaicin [74]. Most patients in this study had multiple sclerosis and suffered from detrusor overactivity refractory to anticholinergic medications and CIC. They report that 80% showed some degree of clinical or urodynamic response. Patients without spinal cord disease did not do well, suggesting unmyelinated C fibre afferents are important in spinal man. Greater disability was also associated with poorer outcome. However, investigations and populations in different centres were not standardized. In one centre, the policy for pretreatment instillation of lignocaine changed midstudy. In addition, there was no standardized follow-up protocol. There was no placebo arm to this study, as the authors claimed that this would be difficult due to pungency of capsaicin.

RESINIFERATOXIN

Resinferatoxin is a natural vanilloid derived from a cactus-like plant, *Euphorbia resinifera*, commonly found in Morocco. It is 1000 times more potent than capsaicin and is therefore pharmacologically active at much lower concentrations than capsaicin. This limits excitatory effects whilst still producing rapid desensitization. Cruz *et al.* initially performed a pilot study in seven neurologically impaired patients with detrusor overactivity [75]. There was no early deterioration in symptoms as with capsaicin, and itching or mild discomfort only lasted a few minutes. Improvement in urinary frequency and increased bladder capacity was noted in approximately half the patients and was sustained for approximately 3 months. Lazzeri *et al.* found no burning sensation on instillation, and immediate significant increase in bladder capacity with intravesical resiniferatoxin (which was not sustained at 4 weeks), without significant change in bladder pressure in patients with an unstable detrusor [76]. However, the limitations of this study include the solubility of resiniferatoxin in saline without alcohol. Lazzeri *et al.* have also shown a significant increase in bladder capacity with high-dose resiniferatoxin in spinal man in whom capsaicin

has failed [77]. High-dose resiniferatoxin can also induce detrusor areflexia in these patients.

BOTULINUM TOXIN

A new approach to neurogenic detrusor overactivity has been pioneered by Schurch *et al.*, who have used cystoscopic injection of botulinum A toxin [78]. The drug is injected at 20–30 sites within the bladder, excluding the trigone. At 6 weeks, 89% of patients with traumatic spinal cord injury having severe neurogenic detrusor overactivity and incontinence had restoration of continence [78]. Furthermore, significant increases in mean reflex volume, cystometric capacity, post-void residual volume and decrease in detrusor voiding pressure were recorded. The requirement for anticholinergic medication was markedly decreased or withdrawn, and improvement was sustained at 9 months after treatment, without side-effects. Recently, a retrospective European multicentre study in 200 patients with spinal cord injury/disease, neurogenic detrusor overactivity or neurogenic incontinence confirmed these findings [79]. Furthermore, there have been preliminary reports of successful use of this agent for treatment of bladder overactivity [80].

Conclusions

Urinary incontinence is a debilitating condition. Therapeutics has an important role in the treatment of incontinence. Some success has also been achieved with the treatment of SUI pharmacologically. Desmopressin has a well-accepted role in the treatment of nocturnal enuresis in children. Anticholinergic medications result in statistically significant improvement in patients with detrusor overactivity and neurogenic detrusor overactivity, with response rates of 50–70% reported. However, randomized, placebo-controlled trials have shown placebo responses up to 45% and atropine-like side-effects are common. In patients with neurogenic detrusor overactivity, intravesical botulinum A toxin can help patients who have failed to respond to anticholinergics, and it may have a role for other patient groups. Newer anticholinergic agents acting through novel pathways and drugs targeting bladder afferents may help further in the therapeutic battle against detrusor overactivity, but this remains to be seen.

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