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Management of Bladder, Prostatic and Pelvic Floor Disorders

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Since its introduction in the late 1970s for the treatment of strabismus and blepharospasm, botulinum toxin (BoNT) has been increasingly used in the interventional treatment of several other disorders characterized by excessive or inappropriate muscle contractions. Over the years, the number of primary clinical publications has grown exponentially, and still continues to increase. It has been shown that BoNT blocks cholinergic nerve endings in the autonomic nervous system but does not block non-adrenergic non-cholinergic responses mediated by nitric oxide (NO).

The present paper reviews a number of recent clinical indications for urological and pelvic floor dysfunctions, such as overactive and neurogenic bladder, non-bacterial prostatitis, benign prostatic hyperplasia, chronic anal fissure, or conditions associated to hyperactivity of the puborectalis muscle during straining. These indications provide a new promising palette of indications for future usage of BoNT in clinical practice.

Keywords: Anus; Autonomic nervous system diseases; Benign prostatic hyperplasia; Botulinum toxin; Constipation; Detrusor-sphincter dyssynergia; Fissure-in-ano; Gastrointestinal motility; Overactive bladder; Pelvic floor; Prostate; Urinary retention

Abbreviations

BPH, benign prostatic hyperplasia; **BoNT**, botulinum neurotoxin; **DSD**, detrusor-sphincter dyssnergia; **EAS**, external anal sphincter; **IAS**, internal anal sphincter; **LIS**, lateral internal sphincterotomy; **LUT**, lower urinary tract; **NO**, nitric oxide; **RCT**, randomized controlled trial

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INTRODUCTION

The action of botulinum neurotoxins (BoNTs) on the autonomic nervous system has been greatly elucidated during the course of recent years. It has been shown that BoNTs block cholinergic nerve endings in the autonomic nervous system, but do not block non-adrenergic non-cholinergic responses mediated by nitric oxide (NO) (Morris *et al.*, 2001). This specificity of action has further promoted the interest on the possible clinical applications of BoNTs to treat overactive smooth muscles and sphincters.

Clinical reports have documented the beneficial

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effects of BoNT to treat various neurogenic lower urinary tract disorders associated with muscle overactivity (*e.g.*, detrusor hyperreflexia, detrusor sphincter dyssynergia) and has also extended applications to non-neurogenic conditions, such as idiopathic detrusor overactivity, non-bacterial prostatitis or benign prostatic hyperplasia (BPH).

The clinical experience over the last years with BoNT in urological impaired patients will be illustrated in this paper. Moreover, this paper presents current data on the use of BoNT to treat pelvic floor, anal and rectal disorders.

THE CONTROL OF MICTURITION

The lower urinary tract (LUT) encompasses the urinary bladder and the urethra and has two main functions: storage and voluntary voiding of urine. LUT is innervated by 3 groups of peripheral nerves: sacral parasympathetic, lumbar sympathetic, and sacral somatic nerves. The bladder is surrounded by the detrusor muscle bundles, whereas the urethra contains a dual sphincter mechanism: the internal sphincter is a smooth muscle that surrounds the vesical neck and the posterior urethra and receives adrenergic and cholinergic innervation; the external sphincter is composed by two parts: a smooth component that is intrinsic to the urethra and mainly under autonomic control; a striated component that encircles the membranous urethra and is innervated by the pudendal nerve (Mathias and Bannister, 1999). During bladder filling the internal sphincter remains contracted due to tonic background adrenergic tone. The detrusor muscle produces coordinated bladder contractions leading to bladder voiding. It is innervated by the pudendal nerve; cholinergic fibers predominate in the body of the bladder, but adrenergic fibers are present in the body and the neck of the bladder. LUT is innervated by 3 groups of peripheral nerves: sacral parasympathetic, lumbar sympathetic, and sacral somatic nerves.

Urine is stored when the external urethral sphincter muscle (somatic) and the internal urethral sphincter muscle (sympathetic) are contracted and the detrusor muscle and sacral parasympathetic activity are inhibited through sympathetic mediation. Sympathetic integrity is not essential for the performance of micturition. Experimental evidence suggests that sympathetic input causes tonic inhibitory input to the bladder and excitatory input to the urethra. During the act of micturition, descending pathways originating from the pontine micturition center inhibit the external urethral sphincter and sympathetic outflow (inhibition of the vesicosympathetic reflex), activate parasympathetic outflow to the bladder, and activate parasympathetic outflow to the urethra (Mathias and Bannister, 1999). Neural pathways controlling LUT function are organized as simple on-off switching circuits that control urinary bladder filling and emptying. Alpha and C afferent pathways initiate micturition. Alpha fibers exhibit graded response to passive distension, whereas C fibers have a much higher threshold, being activated by inflammation and noxious stimuli. Fullness of the bladder is detected by receptors in the bladder wall, which activate the sacral parasympathetic nerves; the impulses reach the cerebral cortex through the spinothalamic tracts. The act of micturition is both reflex and voluntary.

When a person is asked to void voluntarily, first there is a relaxation of the perineum, then increased tension of the abdominal wall, a slow contraction of the detrusor muscle and the opening of the internal sphincter. The external sphincter must also relax. During bladder filling, impulses from sensory receptors in the peripheral nerves ascend to the brainstem nuclei, which in turn prevent micturition by inhibiting the detrusor muscle and stimulating the pudendum nerve (holding reflex). Sympathetic nerves cause relaxation of the bladder body (beta adrenergic) and tightening of the bladder neck (alpha adrenergic). When the bladder volume reaches a threshold, impulses start to reach the cerebral cortex causing the desire to urinate. At the same time, the sympathetic tone is decreased, and the parasympathetic tone is increased, causing detrusor contraction and relaxation of the smooth urethral sphincter. Striated muscle relaxation is produced voluntarily via the pudendum nerve. Voiding is associated with increased parasympathetic discharges that cause detrusor contraction, and with decreased sympathetic discharges that relax outlet sphincters. By contrast, when sympathetic tone is increased, the detrusor muscle relaxes and outlet sphincters contract.

USE OF BoNT IN LOWER URINARY TRACT DISORDERS

Detrusor-sphincter Dyssynergia

Detrusor-sphincter dyssynergia (DSD) is defined as inappropriate contractions of the urethral sphincter coincident with detrusor contractions (Leippold *et al.*, 2003). This is a major cause of morbidity in spinal cord injury patients. The resulting high intravesical pressures and poor bladder emptying may lead to autonomic dysreflexia, severe urinary tract infections, renal damage and premature death. DSD is typically managed with medication, or surgery to destroy sphincter function. All of these treatments have associated complications. The possibility to induce a reversible sphincterotomy

TABLE I Studies utilizing botulinum toxin injections into the urethra.

Design	Outcome	Reference
Open. 11 patients (BoNT-A)	PVR decreased Bladder pressure unchanged	Dykstra *et al.*, 1988
Double-blind, placebo-controlled, crossover study. 7 patients [5/2 (BoNT-A/placebo)]	PVR decreased Bladder pressure decreased	Dykstra and Sidi, 1990
Open. 24 patients (BoNT-A)	PVR no change Bladder pressure unchanged	Schurch, 1998
Open. 5 patients (BoNT-A)	PVR unchanged Bladder pressure decreased	Gallien *et al.*, 1998
Open. 17 patients (BoNT-A)	PVR decreased Bladder pressure decreased	Petit *et al.*, 1998
Open. 1 patient (BoNT-A)	PVR decreased	Mall *et al.*, 2001
Open. 21 patients (BoNT-A)	PVR decreased Bladder pressure decreased	Phelan *et al.*, 2001
Double-blind, non-controlled. 13 patients [5/8 (BoNT-A /lidocaine)]	PVR decreased Bladder pressure unchanged	de Seze *et al.*, 2002
Open. 29 patients (BoNT-A)	PVR unchanged Bladder pressure decreased	Kuo, 2003

with BoNT injections in spinal cord injured patients have been described in the past (Dykstra *et al.*, 1988). A literature review showed that nine citations, ranging from single case reports to prospective trials, document treatment of DSD with BoNT (Table I). Studies utilizing BoNT injections into the bladder and prostate have been reported in Table II.

BoNT has been either injected transurethrally, via cystoscope, or transperineally under electromyographic control. However, the dose, dilution volume and intervals between consecutive injections are extremely variable (Beleggia *et al.*, 1997; Schurch *et al.*, 1997; 2000b; Gallien *et al.*, 1998; Petit *et al.*, 1998; de Seze *et al.*, 2002; Parratte *et al.*, 2003). The outcome measures to assess efficacy of BoNT treatment were: urethral pressure and post-void residual volume.

Dykstra and Sidi (1990) treated spinal cord injury patients with an initial dose of 140 U BoNT, injected transurethrally via cystoscope, and subsequent weekly doses of 240 U (on average, 3 times), until maximum decrease in post-void residual volume was attained. Eight patients out of 11 improved. Urethral pressure decreased on average by 27 cm H_2O, residual urine volume decreased by an average of 146 ml. The duration of effect was approximately 50 days, and side effects were not observed. A prospective study on 24 patients with spinal cord injury, compared the effect of a single injection (100 Botox U) to that of 3 injections repeated at monthly intervals (Schurch, 1998; Leippold *et al.*, 2003). Improvement was observed in 87.5% of the patients on maximum urethral pressure during DSD (by 48%), DSD duration (by 47%) and basal urethral pressure (by 20%). Repeated injections provided a longer duration of effect on voiding dysfunction (9-13 months) compared to that of a single injection (2-3 months).

Due the high risk of autonomic dysreflexia, general anaesthesia may be necessary in patients with lesions above T6, in order to perform transurethral BoNT injections into the urethral sphincter. Satisfactory results were also obtained using the transperineal approach (Gallien *et al.*, 1998), that does not require general anesthesia. In keeping with this observation, comparable results were obtained with the transurethral and transperineal approaches when the same BoNT doses were injected (Leippold *et al.*, 2003).

A recent double-blind study on 13 spinal cord injury patients with DSD, compared BoNT (100 Botox U) with lidocaine (4 ml of 0.5% solution), when applied into the external urethral sphincter with a single transperineal injection (de Seze *et al.*, 2002). All outcome measures improved in the BoNT group, but not in the lidocaine group. This observation brings BoNT injections into the external urethral sphincter into the first line of treatment for DSD in spinal cord injured patients, although RCT comparing the effects of BoNT treatment to placebo are still lacking. Clinical effects occurred within 7 days and lasted for up to 6 months; the patients had to be subsequently re-injected to maintain the improvement. The short duration of efficacy using

TABLE II Studies utilizing botulinum toxin injections into the bladder and prostate.

Design	Outcome	Reference
Neurogenic bladder: Open. 21 patients (BoNT-A)	Bladder capacity increased Bladder pressure decreased	Schurch *et al.*, 2005
Neurogenic bladder: Open. 20 patients (BoNT-A)	Bladder capacity increased Bladder pressure unchanged	Schulte-Baukloh *et al.*, 2005
Neurogenic bladder: Open. 15 patients (BoNT-A)	Bladder capacity increased Bladder pressure decreased	Riccabona *et al.*, 2004
Neurogenic bladder: Open. 200 patients (BoNT-A)	Bladder capacity increased Bladder pressure decreased	Reitz *et al.*, 2003
Neurogenic bladder: Randomized, 25 patients [12/13 (BoNT-A/RTX)]	Greater reduction in incontinence episodes and greater increase in bladder capacity	Giannantoni *et al.*, 2004
Neurogenic bladder: Open. 1 patient (BoNT-B)	Bladder capacity decreased Bladder pressure decreased	Pistolesi *et al.*, 2004
Neurogenic bladder: Open. 2 patients (BoNT-B)	Improvement in urodynamic and clinical parameters	Reitz *et al.*, 2003
Non-neurogenic bladder: Open. 15 patients (BoNT-B)	Urinary frequency decreased	Dykstra *et al.*, 2003
Non-neurogenic bladder: Open. 35 patients (BoNT-A)	IIQ and UDI symptom scores decreased	Rapp *et al.*, 2004
Interstitial cystitis: Open. 13 patients (BoNT-A)	Improvement in symptom scores and urodynamic parameters	Smith *et al.*, 2004
Benign prostatic hyperplasia: Randomized, placebo-controlled. 30 patients [15/15 (BoNT-A/placebo)]	Maximum flow rates increased AUA scores decreased	Maria *et al.*, 2003

this approach may raise controversies when it is compared to surgical sphincterotomy, particularly in patients with complete tetraplegia, who require a durable effect. By contrast, BoNT treatment into the external urethral sphincter appears to be a worthwhile option in patients with DSD and high residual volume due to acute incomplete spinal cord injury or multiple sclerosis (Leippold *et al.*, 2003).

Overall, the clinical evidence collected on DSD must still be considered preliminary; an effective comparison between the published studies is difficult, due to differences in the injection techniques, toxin brands used and dosages. Larger scale randomized, placebo controlled, studies are warranted in order to develop clear indications for DSD. The choice of appropriate endpoints is also a very important variable: objective and subjective endpoints should probably be combined. An appropriate objective measure would be detrusor leak point pressure that, when elevated, is closely tied to upper tract damage. Subjective measures should include quality of life questionnaires to identify whether the benefits obtained outweigh the downsides (particularly the cost, wearing-off of action and the need to repeat treatment).

Neurogenic Detrusor Overactivity

This condition is associated with high intravesical pressure, reduced capacity, low compliance of the bladder and can lead to upper urinary tract damage. Current treatment options rely mainly on clean intermittent catheterization and on associated anticholinergic medication. However, side effects of the oral treatment are troublesome and reduce patients' compliance. Other treatment options are considered controversial or still under evaluation: stimulation of the pudendal nerve afferents or of the sacral root nerves, sacral root rhizotomy, enterocystoplasty and ileal conduit, intravesical application of vanilloid-antagonists. Recent reports showed improvement of patients with spinal cord injury and severe detrusor overactivity with incontinence resistant to anticholinergic drugs, following injection of 200-400 Botox U into the detrusor muscle (Schurch *et al.*, 2000a,b). Nineteen patients were regularly observed over a 9-month period by clinical and urodynamic checks: six weeks after treatment there was a significant increase in the reflex volume and in the maximum cystometric bladder capacity, associated with a decrease in maximum detrusor voiding pressure; at the 36 weeks follow-up, ongoing improvement

occurred. Anticholinergics were reduced or withdrawn completely. Similar results were obtained by another large study (Reitz *et al.*, 2003). Furthermore, the efficacy of 85-300 Botox U was tested in 17 children with neurogenic detrusor overactivity due to myelomeningocele (Schulte-Baukloh *et al.*, 2002a,b; 2003). Urodynamic checks performed after treatment showed improvement and restoration of continence for the 4 weeks of follow-up. In addition, long-term efficacy of BoNT treatment has been demonstrated in patients with neurogenic detrusor overactivity by the improvement of urodynamic tests (Staehler *et al.*, 2003).

In summary, BoNT injections into the bladder detrusor muscle are indicated in spinal cord injured patients with incontinence due to neurogenic detrusor overactivity (Bagi and Biering-Sorensen, 2004; Schurch *et al.*, 2005). This treatment option is currently indicated in cases where anticholinergic medication fails or is not tolerated and is a valuable alternative to surgery (Schulte-Baukloh *et al.*, 2005).

Idiopathic Detrusor Overactivity or Sensory Urge

Patients with severe detrusor overactivity have been treated with 200 Botox U into the detrusor muscle: 67% of them reported improved continence, lasting for 8 months (Leippold *et al.*, 2003). Unwanted reactions included high residual volume and a case of acute retention; the latter was explained as due to the high toxin doses employed. Partially in keeping with this observation is a marked improvement of bladder overactivity in 12 patients 1 month after treatment with 300 Dysport units, without changes in the residual volume (Radziszewski and Borkowski, 2003). Another prospective study evaluated BoNT in 16 patients suffering from incontinence with motor (9 patients) or sensory urge (7 patients), with or without a neurological impairment. After treatment with 200 Botox U into the detrusor muscle, 13 patients became dry whereas 3 of the patients with sensory incontinence remained incontinent. Nine of the treated patients were free of urge symptoms. Seven patients (1 with motor and 6 with sensory urge) had no clinical improvement.

Urinary Retention

Recent reports demonstrated the efficacy of BoNT in reducing urethral resistance and facilitating voiding efficiency in patients with lesions of the cauda equina, peripheral neuropathies, detrusor failure or poor relaxing urethral sphincter. BoNT injections are placed into the external urethral sphincter: 100 Botox U were injected in a series of patients affected by urinary retention secondary to different conditions (Phelan *et al.*, 2001). After injection, 20 patients were able to void without catheterization. This treatment was repeated in 20 patients with dysuria or urinary retention due to detrusor underactivity and non-relaxing urethral sphincter, who were refractory to conservative treatment (Kuo, 2003). Spontaneous voiding resumed in 11 patients and significantly improved in 5. By contrast, another study found no significant improvement of micturition in 6 women who received transperineal BoNT treatment for voiding difficulties or complete urinary retention due to abnormal myotonic-like activity in the striated urethral sphincter (Leippold *et al.*, 2003). The inconsistency of reported outcome indicates that further studies are necessary to clarify the appropriate indications for BoNT injections in such cases.

Interstitial Cystitis

Some studies have examined whether BoNT has any effect on conditions of chronic inflammation and pain. A multi-institutional case series described the use of intravesical Botox or Dysport for the treatment of recalcitrant interstitial cystitis (13 patients) (Smith *et al.*, 2004). Overall, 9 out of 13 (69%) patients had subjective improvement from the treatment. Five out of seven responded to Dysport: urinary frequency and nocturia were reduced by 44% and 45% ($P < 0.05$), respectively. Pain, measured by a visual-analogue scale, decreased by 79% 1 month after treatment ($P < 0.05$). In addition, urodynamic parameters improved.

USE OF BONT IN DISEASES OF THE PROSTATE

Chronic Prostatic Pain

This is a common diagnosis confronting the practicing urologist. Different treatments have been tried, but long-term results have remained poor. Recently, four men with chronic non-bacterial prostatitis and poor bladder emptying associated with a non relaxing external urethral sphincter received bilateral injections of 30 Botox U (Maria *et al.*, 1998c). They had a mean duration of symptoms of 18 ± 3 months and had failed to respond to tamsulosin (0.4 mg once daily for at least 4 months). The patients were subject to fluxometry to assess the time of urinary flow (TQ), maximum urinary flow (Tqmax), maximum flow (Qmax), average flow (Qave), and the total urinary volume (Vcomp). An increased value of TQ and Tqmax, with a normal Qmax value, was taken as indicative of incomplete relaxation of the bladder neck. One week after treatment with BoNT, all patients had a striking improvement in voiding and none complained of urinary incontinence. Four weeks after treatment, three patients had continuing improvement that remained stable and unaccompa-

nied by incontinence until 8 weeks after treatment. The patients were followed up for an average of 12 months. No relapse occurred in the three patients who improved. Urodynamic tests showed a decrease in TQ and Tqmax values at 1, 4, and 8 weeks compared with baseline values.

Eleven patients with chronic prostatic pain were investigated with urodynamic tests, anorectal manometry, transrectal ultrasound examination and cystoscopy, before and after a transurethral perisphincteric injection of 200 Botox U. Nine patients had pain relief; their average pain level decreased on a visual-analogue scale from 7.2 to 1.6. Urodynamic measures showed a decrease of functional urethral length and of urethral closure pressure, a decrease of postvoidal residual volume and an increase of peak and average urinary flow (Zermann *et al.*, 2000). Injections of BoNT into the external urethral sphincter may reduce sphincter activity and improve LUT symptoms; but large controlled trials are needed for confirmation.

Benign Prostatic Hyperplasia

BPH is a non-malignant enlargement of the prostate that involves both the stromal and the epithelial elements of the gland (Oesterling, 1995; Hollander and Diokno, 1996; Djavan *et al.*, 1999; Clifford and Farmer, 2000; Barry and Roehrborn, 2001; Kaplan *et al.*, 2001; Roehrborn *et al.*, 2001). Symptoms are caused by the urethral obstruction and a gradual loss of bladder function, resulting in incomplete bladder emptying, which can lead to complications, including acute urinary retention (McConnell *et al.*, 1994; 1998; Clifford and Farmer, 2000). BPH rarely causes symptoms before age 40, but more than half of men in their sixties, and as many as 90% in their seventies and eighties, have some symptoms of this disease (Walsh, 1996). Goal of treatment is to reduce or alleviate LUT symptoms, and prevent complications by producing as few adverse effects as possible (Barry and Roehrborn, 2001). Few treatments are without unwanted reactions, and this is particularly true for BPH treatments, where the trade-off between benefits and side-effects is delicate (Walsh, 1996). There is a large palette of treatment options, including medical therapies and various surgical procedures (Oesterling, 1995; Djavan *et al.*, 1999; Clifford and Farmer, 2000; de la Rosette *et al.*, 2001); transurethral prostatic resection, which is the gold-standard treatment for symptomatic BPH, is completely satisfactory. Approximately 25% percent of patients who undergo surgical treatment do not have satisfactory long-term outcome (Lu-Yao *et al.*, 1994). Because of these problems, as well as the desire of patients to avoid surgery whenever possible, there has been much interest in alternative options (Walsh, 1996).

Recent studies have reported that finasteride (a 5α-reductase inhibitor) and long-acting α_1-adrenergic antagonists (such as terazosin, doxazosin and tamsulosin) are safe and effective for treating BPH (Lepor *et al.*, 1996; McConnell *et al.*, 1998; Clifford and Farmer, 2000; Boyle *et al.*, 2001; Narayan and Lepor, 2001). It has also documented that the combination of terazosin and finasteride is no more effective than terazosin alone (Lepor *et al.*, 1996). Although these drugs represent an attractive option for men with BPH, they have adverse effects. A systematic review found that withdrawals attributed to adverse events were similar for alfusozin, tamsulosin, and placebo (Lepor, 1990; Boyle *et al.*, 2001; Narayan and Lepor, 2001). A higher withdrawal rate was found with doxazosin and terazosin.

Recently, it has been documented that the injection of BoNT into the rat prostate induces selective denervation and subsequent gland atrophy (Doggweiler *et al.*, 1998). RCT has been recently performed in men (Maria *et al.*, 2003). Thirty patients aged 50-80 years, who were symptomatic for BPH, were enrolled in the study. They were assessed with the American Urological Association symptom index (Barry *et al.*, 1992a,b) and underwent urodynamic tests; residual urinary volume was measured ultrasonographically (McConnell *et al.*, 1994; Barry *et al.*, 1995). Serum concentrations of prostate-specific antigen were measured, and prostatic volume was measured by transrectal ultrasonography (McConnell *et al.*, 1994). The primary end point was the evaluation of symptomatic improvement after treatment, as measured by the symptoms index and peak urinary flow rates. The secondary end points were the evaluation of prostatic volume, of serum PSA concentration, and of residual urinary volume. Fifteen patients were treated with 200 Botox U (4 ml solution) directly injected into the prostate gland, half in each lobe; fifteen age-matched control patients received an equal amount of saline solution; the procedure was well tolerated and no complications were encountered.

Two months after treatment, 13 patients in the BoNT group and 3 patients in the control group had symptomatic relief (P =0.0007). In the BoNT group, the symptoms index was reduced by 65% (P =0.00001) compared with base-line values, serum PSA concentration was reduced by 51% (P =0.00001) from baseline. In patients who received saline, the symptoms index and serum PSA concentrations remained unchanged. In treated groups, prostatic volume and residual urine volume were reduced by 68% (P =0.00001) and 83% (P =0.00001), respectively; whereas the mean peak urinary flow rate was significantly increased (P =0.00001). In the control group, there were no changes

from baseline.

Recently, BoNT has been used to treat patients with refractory BPH (Chuang *et al.*, 2005). Eleven men with symptomatic BPH refractory to medical treatment (at least one month of treatment with an α-blocker) were treated with 100 Botox U into prostate under transrectal ultrasound examination surveillance. They observed that the mean symptoms index and a quality of life index were improved after treatment. Furthermore, the maximum flow rate was significantly increased, although there were no changes in residual urine and prostate size.

These studies demonstrate that BoNT can be used to treat BPH. Multicenter trials are now underway in North America and in Europe, in order to confirm these monocentric data before proposing the use of BoNT as a minimally invasive treatment for BPH.

Prostatic growth has been considered to be controlled by endocrine means (Doehring *et al.*, 1996; McVary *et al.*, 1998; Farnsworth, 1999). However, the abundance of adrenergic and muscarinic receptors and nerve fibers suggests that the autonomic nervous system may play a role in the growth and secretory function of the gland (Gup *et al.*, 1990; Ruggieri *et al.*, 1995; McVary *et al.*, 1998; Farnsworth, 1999). It has been also found that a subtype of muscarinic receptors predominates in BPH and may stimulate gland growth (Ruggieri *et al.*, 1995). BoNT may block these muscarinic receptors, thus inducing denervation and atrophy in the human prostate. This hypothesis is in keeping with the finding that prostatic volume and serum PSA concentration are reduced in the treated patients. Furthermore, 40% of the cellular volume in the hyperplastic gland is made up of smooth muscle fibers (Farnsworth, 1999), whose contraction is mediated by α_1-adrenoceptors. BoNT may induce direct or NO-mediated smooth muscle relaxation.

ANATOMY AND PHYSIOLOGY OF THE ANORECTUM

The complex anatomy and physiology of the anal canal and rectum account for their important role in continence and for their susceptibility to diseases. The anorectal angle measures bending of the rectum by the sling-shaped fibers of the puborectalis muscle at the level of the anorectal junction; the angle is maintained between 80 and 110 degrees to warrant gross fecal continence (Brisinda *et al.*, 2002a,b; 2003b). Physiologically, continence is maintained by the tonic contraction of the internal anal sphincter (IAS) and of the puborectalis muscle, which wraps around the anorectum. During defecation, pelvic-floor muscles (including the puborectalis) relax, allowing the anorectal angle to straighten by at least 15 degrees, and the perineum to descend by 1-3.5 cm. The external anal sphincter (EAS) also relaxes to reduce pressure onto the anal canal. A fecal bolus in the rectum causes reflex relaxation of the IAS, the so-called rectoanal inhibitory reflex. This is a local intramural reflex mediated by NO.

At the anal level, the sphincter complex consists of two overlapping sphincters. The EAS, forming the outer layer, is composed of a voluntary, skeletal, muscle. The internal sphincter is the involuntary, smooth, muscle component, being in a state of continuous maximal contraction to provide a natural barrier to the involuntary loss of stool and gas. This action is exerted by a combination of intrinsic myogenic and extrinsic autonomic neurogenic properties (Albanese *et al.*, 2001). The internal sphincter is responsible for 50-85% of resting anal tone. Being of visceral origin, it is supplied both by sympathetic and parasympathetic fibers. Noradrenergic sympathetic nerves are excitatory whereas parasympathetic fibers are inhibitory. The latter do not act directly, but rather form synaptic connections with neurons whose cell bodies are in the intrinsic gastrointestinal tract ganglia. The neurotransmitter is acetylcholine acting on nicotinic receptors (Albanese *et al.*, 2001). Continence and defecation rely heavily on the appropriate functioning of the puborectalis muscle, the internal and the EAS, although other factors play important roles. The latter include stool consistency, volume and delivery of colon contents to the anorectum, rectal storage capacity, anal and rectal sensations and cognitive and behavioural variables.

The evaluation of patients complaining of difficult defecation should include detailed history and physical examination, to be supplemented by appropriate diagnostic tests whenever necessary. Defecation difficulty may arise as a result of disordered movement through the colon or the anorectum. There are two major causes of constipation, which may coexist in patients: slow transit and outlet dysfunction. In slow transit constipation there is failure of coordinated motor activity to move luminal contents through the colon; this may be associated with dietary factors, such as caloric deficiency, medications altering motility or a variety of neurological, metabolic and endocrine diseases. Other patients with slow transit constipation have enteric nerve abnormalities. By contrast, disorders of the anorectum and pelvic floor cause outlet type dysfunction, where the primary difficulty is an inability to completely evacuate contents from the rectum.

TABLE III Studies utilizing botulinum toxin injections into the puborectalis muscle.

Design	Outcome	Reference
Open. 7 patients (BoNT-A)	Anal pressures decreased Anorectal angle increased	Hallan *et al.,* 1988
Open. 4 patients (BoNT-A)	Bowel movement increased	Joo *et al.*, 1996
Open. 15 patients (BoNT-A)	Anal pressures decreased Anorectal angle increased	Shafik and El-Sibai, 1998
Open. 4 patients (BoNT-A)	Anal pressures decreased Anorectal angle increased	Maria *et al.*, 2000a,b
Open. 25 patients (BoNT-A).	Anal pressures decreased Anorectal angle increased	Ron *et al.*, 2001
Open. 14 female patients with anterior rectocele (BoNT-A).	Anal pressures decreased Anorectal angle increased Rectocele depth and rectocele area decreased	Maria *et al.*, 2003
Open. 10 patients with Parkinson's disease (BoNT-A).	Anal pressures decreased Anorectal angle increased	Albanese *et al.*, 2003

USE OF BoNT ON PELVIC FLOOR DYSFUNCTIONS

Constipation Due to Pelvic Floor Dysfunction

Pelvic floor dysfunction is associated to a failure of the puborectalis muscle to relax during efforts to defecate, or to its paradoxical contraction; therefore, the anorectal angle does not straightens and the anal canal does not open. The diagnosis is confirmed by the observation of a persistent impression of the puborectalis muscle on the posterior surface of the anal canal during attempted evacuation of barium paste and by EMG evidence of increased electrical activity in the puborectalis muscle during straining. Prolonged efforts to empty the rectum may aggravate the condition. It has been suggested that paradoxical puborectalis contraction during straining represents a focal dystonia (Mathers *et al.*, 1988).

BoNT-A has been used to selectively weaken the extrernal anal sphincter and the puborectalis muscle in patients with constipation (Joo *et al.*, 1996; Ron *et al.*, 2001). BoNT-A is capable to relax the puborectalis muscle (Hallan *et al.*, 1988; Shafik and El Sibai, 1998); this allows sufficient increase of the anorectal angle during straining and makes it possible to evacuate. The limitation to this approach is that, despite good results, the effects are fairly short term (Table III).

Outlet-type constipation may occur in Parkinson's disease (Albanese *et al.*, 2003). We performed a prospective study to identify the prevalence of this condition among out-patients. In a population of 138 patients with Parkinson's and chronic constipation, 18 (13%) had isolated or prominent outlet-type constipation. Ten of these patients received a total of 100 Botox U in the puborectalis muscle (two sites one on each side) under transrectal ultrasonographic guidance. At one month follow up, anal tone during straining was reduced to 40.7 ± 11.5 mm Hg from 97.4 ± 19.6 mm Hg at baseline, in absence of reductions of resting anal tone and maximum voluntary contraction. Two months after the treatment the anorectal muscle increased from a mean of 99 ± 7.9 to 122.2 ± 15 degrees, while no further change was observed at anorectal manometry. This observation indicates that outlet obstruction is the main cause for constipation in a minority of PD patients and provides evidence that BoNT-A may be an effective therapeutic option for them. The duration of efficacy of the injections remains to be measured, and repeated treatments are probably necessary (Albanese *et al.*, 1997). The optimal BoNT dose also remains to be determined.

Anterior Rectocele

Rectocele is a hernia of the anterior rectal wall into the lumen of the vagina (Sailer *et al.*, 1998; Maria *et al.*, 2001). It has been suggested that in some instances the rectocele is caused by failure of relaxation or paradoxical contraction of the puborectalis muscle occurring during attempted evacuation, but the reason for its establishment is yet unclear. A wide variety of surgical approaches have been proposed with the aim of assuring rectal emptying by reducing the dimension of the rectocele. However, the results of surgery are often disappointing with regards to emptying difficulties. Surgical repair, either vaginal, transperineal, or

transanal, does not always alleviate symptoms, and in some patients it causes impaired fecal continence. Furthermore, transanal repair may compromise anal sphincter pressures and an alternative approach should be considered when the anal sphincter is lax. Recently, 14 women were treated with a total of 30 Botox U evenly divided into three sites, two on either side of the puborectalis muscle and the third anteriorly in the EAS (Maria *et al.*, 2001). At two months follow up, symptomatic improvement was detected in nine patients; at the same time defecography showed reduction of rectocele depth from 4.3 ± 0.6 cm to 1.8 ± 0.5 cm and decrease of rectocele area from 9.2 ± 1.3 cm^2 to 2.8 ± 1.6 cm^2. According to these results, anorectal manometry demonstrated decreased anal tone during straining at one and two month evaluation.

USE OF BoNT ON DISEASES OF THE ANAL CANAL

Chronic Anal Fissure

A chronic fissure is a cut or crack in the anal canal or anal verge. The fissure can be seen as the buttocks are parted. It is often suspected because there is marked spasm of the anus making examination difficult. A spasm of the IAS has been noted in association with chronic fissure and for many years treatment has focused on alleviating this hypertonia. The IAS of patients is fibrotic, compared to that of controls (Brown *et al.*, 1989). Albeit the cause of the spasm remains obscure, it has been consistently found that resting anal pressure is higher in patients than in controls, suggesting that high resting pressure may be related to IAS hypertonus. The fissure may also be caused by insufficient blood supply to the anal canal, as a consequence of IAS hypertonus (Schouten *et al.*, 1996; Lund *et al.*, 1999). Consequently, a decrease in anal pressure causing increase of blood flow to the mucosa and relief of ischemia could produce fissure healing.

Several studies have shown that BoNT can be used to treat anal fissure, particularly in patients at risk of incontinence (Maria *et al.*, 1998a,b; 2000a,b; McCallion and Gardiner, 2001; Tilney *et al.*, 2001; Minguez *et al.*, 2002; 2003; Brisinda *et al.*, 2003a,b; Madoff and Fleshman, 2003; Nelson, 2003;). The doses used are 30-50 Botox U or 100-150 Dysport U; injections are placed into the IAS, although injections in the EAS are also efficacious. Side-effects are usually mild and include transient incontinence for flatus or feces, rarely perianal thrombosis or hematoma (Tilney *et al.*, 2001). In the authors' experience (based on a series of over 1,000 patients so far injected), the procedure is safe (Brisinda *et al*, 2003a), well tolerated, and more effective than other medical options (Brisinda *et al*, 1999). However, this view has been challenged by other observations based on smaller series, providing inferior evidence of efficacy. The results of some studies are so disappointing that it led Nelson (2004) to conclude a Cochrane review stating that ".,.medical therapy for chronic anal fissure... may be applied with a chance of cure that is only marginally better than placebo..". We think that such conclusion is too pessimistic, and welcome further multi-center trials with appropriate methodology (intention-to-treat based selection of patients, doses, and injection technique) and adequate follow-up, to ascertain the safety and efficacy of the technique in a multi-center setting.

Chronic Idiopathic Anal Pain

This is one of a rather ill-defined group of disorders termed chronic idiopathic perineal pain, also encompassing proctalgia fugax and coccygodynia. No objective abnormalities are found on clinical examination, and the distinction between the three types of perineal pain is based on the patient's description of pain and on the location of tenderness by palpation. A feeling of obstructed defecation may also occur. The etiology and pathogenesis are unknown. There is no satisfactory treatment for anal pain: anal stretch and lateral internal sphincterotomy re-used in selected patients based on the assumption that pain might be supported by a hypertonic IAS. Recently, injections of Botox (20 units placed intersphincterically in four quadrants or at the lower rim of the puborectalis muscle under ultrasonographic guidance) yielded improvement in 4 patients with chronic anal pain that persisted during a follow up of 12 to 24 months (Christiansen *et al.*, 2001).

Hirschsprung's Disease

BoNT injections have been placed into the IAS for either diagnostic or therapeutic purposes after pull-though surgery for Hirschsprung's disease, based on the assumption that IAS spasm can cause persistent obstructive symptoms. A prospective study evaluated 18 children who received BoNT treatment (total dose 15-60 U Botox) in 4 quadrants of the sphincter (Langer and Birnbaum, 1997; Minkes and Langer, 2000). Twelve patients (67%) improved for at least 1 month and 5 improved beyond 6 months. Based on this observation it has been proposed that BoNT is not only an alternative to myectomy, but can also serve as a diagnostic tool to detect the persistence of symptoms despite a decrease in sphincter pressure, suggesting another etiology for the constipation.

Hemorrhoids and Pain After Hemorrhoidectomy

Pain after hemorrhoidectomy is multifactorial and depends on individual tolerance, anesthesia, postoperative analgesia, and surgical technique. A spasm of the IAS probably plays an important role. The efficacy of BoNT in reducing pain after hemorrhoidectomy has been assessed in a double-blind study on 50 consecutive patients undergoing Milligan Morgan operation who were assigned to an IAS injection of 0.4 ml of solution containing either 20 Botox U or saline. Patients treated with BoNT had significantly less pain by the end of the first week after surgery (Davies *et al.*, 2003). Reduction of IAS spasm is the presumed mechanism of action.

CONCLUSIONS

Lower urinary and pelvic floor disorders provide an increasing number of new indications for the use of BoNT. A number of RCT have shown the efficacy of BoNT for neurogenic bladder dysfunctions, benign prostatic hyperplasia, and anal fissure, but much research needs to be done in this area of medicine.

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