Botulinum toxin (BTX) is the most lethal naturally occurring toxin known to mankind. Injection of BTX into the urethral sphincter or bladder is an effective treatment for lower urinary tract dysfunction. We reviewed the literature on the mechanisms of action and clinical efficacy of BTX treatment in urologic diseases, with a focus on lower urinary tract dysfunction. Injection of BTX is safe and effective in the treatment of detrusor-sphincter dyssynergia, non-neurogenic pelvic floor spasticity, and refractory overactive bladder. Urodynamic assessment after sphincter injection with BTX reveals a decrease of bladder voiding pressure, urethral pressure profile, and post-void residual urine. An increase of the functional bladder capacity and a decrease of the bladder voiding pressure can be seen after bladder injection with BTX. Clinical improvement was found in a moderate percentage of treated patients in most reported series and lasted for 3 to 14 months without significant adverse effects. In addition, BTX-A treatment inhibits afferent-nerve-mediated bladder contraction. This analgesic effect may expand the application of BTX in the localized genitourinary tract pain syndrome, such as interstitial cystitis and prostatodynia. In conclusion, application of BTX is a promising treatment for lower urinary tract dysfunction with profound basic and clinical implications.

Key words: Botulinum toxin; Urethral diseases; Bladder
Acetylcholine release involves the ATP-dependent transport of the vesicle from the cytosol to the plasma membrane. Vesicle docking requires the interaction of various cytoplasmic, vesicle, and target membrane proteins, some of which are specifically targeted with clostridial neurotoxins. BTX-A, for example, cleaves the cytosolic translocation protein synaptosomal-associated protein (SNAP)-25, thus preventing vesicle fusion with the plasma membrane (Fig. 2 & 3).10

The median lethal dose (LD50) of BTX-A was estimated to be 40 U/kg, or about 3000 U in a 75 kg man.3,11 Low doses of BTX injected directly into the target muscle would rapidly and tightly bind to the local nerve terminals and little toxin would pass into the circulation to cause systemic effects.3,11 Systemic toxicity below the dosage of 300 U has not been reported.

**Clinical Uses of Botulinum Toxin**

Seven immunologically distinct neurotoxin types are known, and they are typically labelled from A–G. Botulinum toxin A (BTX-A) [Botox®, Allergan, Irvine, Calif.] received US FDA approval in 1989 for the treatment of strabismus, benign essential blepharospasm and disorders of the VIIth nerve. Since its introduction into clinical use in the 1980’s, BTX-A has been successfully used to treat various conditions including blepharospasm, strabismus, focal dystonias, muscle spasms and spasticity, axillary hyperhidrosis, and achalasia.12-16 More recently, the FDA approved a BTX-B complex preparation (Myobloc™, Elan) for clinical use in cervical dystonia patients.

**Fig. 1.** Depiction of the active, dichain polypeptide form of botulinum toxin. The parent chain is cleaved into a heavy chain (approximately 100 kDa) connected by a disulfide bond to a light chain (approximately 50kDa) with an associated zinc atom.

**Fig. 2.** Schematic diagram of a nerve terminal indicating the normal fusion of the synaptic vesicles with the plasma membrane. Ach = acetylcholine; SNAP = synaptosomal-associated protein; VAMP = vesicle-associated membrane protein.

**Fig. 3.** Schematic diagram of a nerve terminal indicating the blocking effect of seven types of botulinum toxin (BTX-A to -G) on normal fusion of the synaptic vesicles with the plasma membrane. Note: after blocking of the vesicle transport by botulinum toxin no acetylcholine release occurs, leading to muscle atrophy. Ach = acetylcholine; SNAP = synaptosomal-associated protein; VAMP = vesicle-associated membrane protein.
Sphincter application

Urologic applications of BTX-A have been primarily associated with cases of detrusor external sphincter dyssynergia (DESD). Management of spinal-cord-injured (SCI) patients was revolutionized with the development of clean intermittent catheterization (CIC) by Lapides in 1971. However, not all patients are capable of performing CIC and require an alternative that decreases outlet resistance and allows continuous bladder decompression. Various alternatives have been described, including external sphincterotomy, radical transurethral resection of the prostate, and various denervation procedures, e.g. dorsal rhizotomy. Unfortunately, these procedures are permanent and irreversible, and carry with them inherent risks (i.e. bleeding, stricture formation, fistulas).

BTX-A represents a viable option in the treatment of DESD. The toxin acts at the neuromuscular junction of the external sphincter to block vesicle transport of acetylcholine; in essence, producing a chemical denervation. The clinical effects begin within 2–3 days and are reversible as terminal nerve sprouting occurs within 3–6 months. Injection of BTX-A into the external urethral sphincter indicated denervation of 5 men with SCI and DESD. Electromyography of BTX-A injection into the external urethral sphincter of mice has been shown to induce the formation of terminal nerve sprouts from the parent terminal. The sprouts form functional synapses with the muscle but eventually regress at a time when the parent nerve terminal regains the ability to release neurotransmitters. It remains to be seen whether similar processes occur in autonomic nerves innervating the lower urinary tract.

Dykstra investigated the effects of BTX-A injection in two studies of SCI patients with DESD. In the first study, published in 1988, all 10 patients who were evaluated by electromyography after injection showed signs of sphincter denervation. Urethral pressure profile decreased by an average of 27 cm H₂O and post-void residuals decreased by an average of 146 mL after BTX-A injection. Later, Dykstra published a double-blind, placebo-controlled study of BTX-A injection into the external urethral sphincter of 5 men with SCI and DESD. Electromyography of the external urethral sphincter indicated denervation in the three patients who received toxin injections. The urethral pressure profile decreased an average of 25 cm H₂O, post-void residual decreased an average of 125 mL and bladder pressure during voiding decreased to an average of 30 cm H₂O. Parameters were unchanged from baseline in the two patients who received normal saline injections.

We performed a prospective study on 21 patients referred to our clinic with voiding dysfunction. All patients were evaluated with videourodynamics. Follow-up ranged from 3–16 months. Following urethral injection of BTX-A, voiding pressures decreased by an average of 38%. Sixty-seven percent of patients reported improvement in voiding patterns. No complications or side effects were noted. Our results are consistent with the largest series to date treating DESD with BTX-A. In that study, Schurch et al treated 24 patients with SCI and DESD with BTX-A injection. Significant improvement in DESD was noted in 21/24 patients (88%), with decreased post-void residuals in most patients. The effects lasted 3–9 months, with no adverse events reported. Thus, BTX-A toxin injections are a safe and efficacious treatment option for DESD.

The clinical success of BTX-A is supported by laboratory research demonstrating marked decreases in the release of labeled norepinephrine and acetylcholine in BTX-A-injected rat urethral sphincters. While the therapeutic effect of inhibiting acetylcholine release is obvious, blockage of norepinephrine release may provide clinical benefit by inhibiting sympathetic transmission and smooth muscle dyssynergia.

In addition to classic neuropathic DESD, we have expanded the indications for use of BTX-A to include patients with a variety of bladder outlet obstructions, excluding those patients with obstruction secondary to fibrosis. We have successfully used BTX-A to treat voiding dysfunction in multiple sclerosis patients with DESD, patients with pelvic floor spasticity, and even in an acontractile multiple sclerosis patient who wished to void by valsalva. Recently, we reported a case of functional urethral obstruction and detrusor acontractility following pubovaginal sling surgery that was successfully treated by BTX-A urethral sphincter injection.

We perform Botox® urethral sphincter injections by mixing one vial (100 units) of Botox® with 10 mL of saline just prior to injection. It is important not to shake the vial as this may break the disulfide linkage between the light and heavy chains and render the toxin ineffective. Using a collagen injection needle, injections of 2.5 mL each are made at the 12, 3, 6, and 9 o’clock positions at the level of the striated sphincter. Injections must be directed deeper than collagen injections in order to target nerve terminals innervating skeletal muscle. The needle should also be flushed with 0.2 mL of saline at the end of the procedure to ensure that no toxin is wasted.

Bladder application

Data has been accumulating on the clinical application of BTX-A to detrusor muscle in hyperreflexic

Botulinum Toxin for Urethral-Bladder Dysfunction
bladders of SCI patients. A preliminary study by Schurch et al in 31 patients with detrusor hyperreflexia demonstrated a significant increase in mean maximum bladder capacity (296 to 480 mL, \(p < 0.016\)) and a significant decrease in mean maximum detrusor voiding pressure (65 to 35 cm H\(_2\)O, \(p < 0.016\)) in patients injected with BTX-A. A follow-up, long-term study completed by the same investigators in 87 patients with detrusor hyperreflexia corroborated the efficacy of intravesical botulinum toxin injection demonstrated in their earlier work. In addition, they reported that clinical responses lasted 4–14 months, and observed no adverse effects with treatment. Detrusor muscle injections were performed in over 30 sites with either 300 units of Botox\(^\text{®}\) or 500–750 units of Dysport\(^\text{®}\) (Porton Down, Salisbury, UK). The trigone was spared, presumably to avoid the potential complication of vesicoureteral reflux.

In contrast, Del Popolo noted hypostenia in 5/61 patients treated with high-dose intravesical BTX-A injections (300 units of Botox, or 1000 units of Dysport\(^\text{®}\)). The suprapresional weakness was transient in nature, disappearing 2–4 weeks after injection, and was abolished with lower dosage injections (500 units of Dysport\(^\text{®}\)). The dose and the volume injected appear to play a significant role in inducing systemic toxicity with BTX-A. Multiple injections of lower doses would be expected to have a more localized and less systemic effect. However, the main disadvantage of intravesical BTX-A injections for many urologists is the need for repeated cystoscopy and toxin injections that are necessary to maintain clinical results.

BTX-A injections have extended beyond use in the treatment of neurogenic bladders to the treatment of non-neurogenic voiding and storage disorders. Radziszewski et al reported favorable effects of intravesical BTX-A injections in a pilot study of patients with either idiopathic bladder overactivity or functional outlet obstruction. Following intravesical or sphincteric BTX-A injections, patients demonstrated resolution of incontinence and improved voiding efficiency. Zermann et al reported the results of intravesical BTX-A injection in 7 patients with severe urgency-frequency-syndrome refractory to anticholinergic therapy or electrical stimulation. In contrast to other studies involving intravesical injections of BTX-A, these authors targeted the trigone and bladder base with 5–7 injections of 50, 100 or 200 units of BTX-A. Four of seven patients responded to treatment with decreases in frequency and increased bladder capacity. Vesicoureteral reflux was not reported as a complication of treatment in their study.

Chancellor and Smith recently reported a single surgeon’s experience using Botox\(^\text{®}\) in the bladder and urethra for a variety of dysfunctions over a three-year period. Between October 1998 and October 2001, 50 patients (19 men and 31 women, age range 31–84 yr) were injected with botulinum toxin into the bladder (n = 10) or urethra (n = 40). Voiding dysfunctions were a result of both neurogenic and non-neurogenic conditions and included the following: multiple sclerosis, spinal cord injury, cerebral vascular accident, overactive bladder, interstitial cystitis, and dysfunctional voiding. Procedures were performed using light sedation. Patients were treated with either 100 units of Botox\(^\text{®}\) divided in equal doses into the four quadrants of the external sphincter, or via injection into the bladder base using 100–300 units of botulinum toxin diluted in 20 mL of sterile saline. Fifteen of these patients underwent further injections (as many as 4) at intervals of 6 months or more.

Maximal efficacy of botulinum injection was achieved within 7 days post-injection. Forty-one of 50 patients (82%) reported a decrease or absence of incontinence as well as a significant decrease in voiding symptoms. Sleep quantity and quality increased in more than 50% of patients. Follow-up of these patients indicated that effects lasted up to 12 months. No patient developed stress incontinence or urinary retention.

These latest clinical findings are supported by other studies demonstrating the efficacy of BTX on autonomic nerves. Our previous study found significant decreases in the release of labeled noradrenaline, epinephrine and acetylcholine in BTX-A-injected rat bladder.

**Research Developments**

**Botulinum toxin isoforms**

An interesting side effect in patients with cervical dystonia injected with BTX-B was the development of dry mouth. A rare occurrence following BTX-A treatment, dry mouth was unexpected because the salivary glands were farther from the injection site than relatively unaffected lingual or lower facial muscles. This implies that BTX-B may have a greater affinity for cholinergic nerves innervating the salivary gland rather than lingual or lower facial muscles or, alternatively, that there are a higher number of BTX-B receptors in salivary gland compared to muscles of the lower face and tongue. Future studies should clarify whether similar effects are seen in parasympathetic cholinergic nerves innervating the lower urinary tract.

Evidence from Carpenter’s experiments in the late 1960’s as well as our laboratory suggests that rat
bladders are significantly more sensitive to the effects of BTX-D than BTX-A. In fact, Carpenter found that parasympathetic blockade with BTX-D occurred before somatic neuromuscular blockade. It remains to be seen whether these effects are merely due to differing sensitivities of various cholinergic nerve endings to different toxins, or whether BTX-D’s greater efficacy in the bladder is due to an effect on non-cholinergic transmission. Currently, there are no data on whether these same differences in rat bladder sensitivity to toxin isoforms exist in the human bladder.

**Afferent nerve effects**

Several investigators have demonstrated *in vitro* evidence of an afferent effect of botulinum toxin. Welch et al reported that neuropeptide release from rat dorsal root ganglia was inhibited by various botulinum toxins (BTX-A, -B, -C1, and -F), while Purkiss et al noted that incubation of rat dorsal root ganglia with BTX-A inhibited release of radioactively labeled glutamate. The inhibition of transmitter release from nociceptive neurons could impair mechanisms involved with central sensitization and position botulinum toxin as a therapeutic agent in conditions such as chronic pain. Recent *in vivo* studies support a role for BTX-A in relieving nociceptive pain. In a model of pain associated with formalin-induced inflammation, rats were pretreated in the hind paw with BTX-A prior to injection with formalin. Formalin provokes pain via a direct stimulation of nociceptors (phase I) and, subsequently, by inflammation (phase II). Formalin was injected 5 and 12 days after BTX-A injection. Surrogate markers of pain included paw-licking and paw-lifting behavior. Pretreatment with BTX-A significantly reduced pain at 5 and 12 days post-injection. These results support clinical observations that BTX-A has an antinociceptive effect that is independent of its effects on the neuromuscular junction.

Our previous results suggest that BTX-A treatment inhibits afferent-nerve-mediated bladder strip contractions, presumably by blocking neurotransmitter release from peripheral afferent nerve terminals in the bladder. BTX-A treatment significantly decreased afferent-nerve-mediated contractions to both electrical and chemical stimulation by 44.6% and 35.1%, respectively, compared with saline-treated animals (*p* < 0.05).

In addition, we treated a 42-year-old female patient suffering from recalcitrant IC with BTX-A. Under light sedation, following hydrodistension with saline (80 mL) for 5 minutes, 100 units of Botox®, diluted in 100 mL of saline, was instilled in the bladder and held for 30 minutes. The patient was discharged home the same day and followed up over the ensuing 6 months. One week following Botox® treatment, the patient noted marked improvement in her voiding symptoms, characterized by decreased frequency, urgency and urge incontinent episodes. Nocturia decreased 4-fold and painful bladder symptoms diminished greatly as evidenced by a 50% decrease in oral pain medication usage. On a visual analog scale, the patient’s bother score decreased from a 10 to a 5 following BTX-A treatment. Maximal therapeutic effects lasted 3 months, with some improvement still noted at 6 months post-treatment. Our preliminary findings may lead to new therapeutic applications of BTX-A, such as treating conditions associated with increased afferent nerve excitability (i.e. SCI, chronic inflammation).

Clearly, BTX-A has a much wider spectrum of application within the urologic field than merely the treatment of detrusor hyperreflexia and DESD in SCI patients. Treatment should be extended to other fields including the multiple sclerosis population and patients with non-neurogenic voiding and storage disorders. Our evidence that BTX-A inhibits norepinephrine release in the rat bladder and urethra suggests the need for studies investigating the effects of botulinum toxin on disorders of increased sympathetic activity (e.g. functional bladder neck obstruction, detrusor internal sphincter dyssynergia and benign prostatic hyperplasia). Finally, if afferent nerve transmission is impaired by botulinum toxin, a significant patient population with hypersensitive bladder may benefit from this treatment (Fig. 4).
Conclusions

Since the 1980’s, injection of botulinum toxin has been shown to be a safe and effective therapy for a variety of somatic and autonomic motor disorders. Clinical success with urethral and bladder BTX-A injections in the treatment of detrusor-sphincter dyssynergia, non-neurogenic pelvic floor spasticity, and refractory overactive bladder has also been reported. Many interesting research questions remain regarding the effect of BTX on the neural pathways of the lower urinary tract. However, one cannot deny the ingenuity of man in transforming the lethal toxin of Clostridium botulinum into a modern day therapeutic medicine.

References