Review

Botulinum neurotoxin (BoNT) in Urology - An overview of current and emerging uses

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Abstract: *Background:* Botulinum neurotoxin (BoNT) is produced by the anaerobic organism *Clostridium Botulinum*. BoNT has increasingly diverse uses in medicine due to its ability to relax muscles by inhibiting the release of acetylcholine. There are now a number of established and emerging uses for BoNT. *Objective:* This article provides an overview of the current therapeutic uses of BoNT in urology. *Discussion:* BoNT is now used in the treatment of a number neurogenic and non-neurogenic lower urinary tract disorders. The efficacy of BoNT, combined with its low risk profile, makes it a promising alternative when conservative medical therapies fail and surgical management is not appropriate. At present the use of BoNT in urology is '*off label*'. It is anticipated that within the next 12 months, the United States Food and Drug Administration (FDA) will approve BoNT use in neurogenic bladder overactivity.

Key words: Botulinum neurotoxin (BoNT); Urologic disease; Neurogenic bladder; Benign prostatic hyperplasia; Pelvic pain

INTRODUCTION

Botulinum neurotoxin (BoNT) is produced by the anaerobic bacteria *Clostridium Botulinum*. The toxin was first discovered in 1897.[1] Although scientists recognized the ability of BoNT to block nerve transmission in 1949, it was not until the 1980s that the toxin was used in a clinical setting. Produced within the cytosol of the bacteria, BoNT is released as a polypeptide chain. It consists of a light (50kDa) and heavy (100kDa) chain linked by a disulphide bond.[2] The structure of BoNT is pivotal to its ability to act on the cholinergic neuromuscular junction.[3] There are seven serotypes of BoNT, each produced by a distinct strain of the bacteria. Designated type A, B, C1, D, E, F or G, each BoNT serotype has individual characteristics. However, only types A (Botox®, Allergan, Inc., CA, USA; Dysport, Ipsen Ltd, Berkshire, UK) and types B (Myobloc®, Elan Pharmaceuticals, Inc., Princeton, NJ, USA) are commercially available.[4] In urology, type A BoNT is most commonly used.

MECHANISMS OF ACTION

BoNT exerts its clinical effects of paralysis by preventing the release of acetylcholine at the cholinergic nerve terminals. The key cellular steps leading to the inhibition of neurotransmitter release are binding, translocation and cleavage.[5]

The heavy chain of BoNT binds to a specific receptor on the parasynaptic nerve terminal (Figure 1). The BoNT/receptor complex is then endocytosed into the nerve terminal. The light chain is translocated into the cytosol where it is able to cleave one or two of the pre-synaptic proteins (Figure 2).[2] These proteins are responsible for the docking and release of vesicles containing neurotransmitters.[6] It is the cleavage of these pre-synaptic proteins (SNAP 25) that results in the inability for acetylcholine to be released and exert its action (Figure 3).[7] Eventually the light chain within the cytosol deteriorates, allowing turnover of parasynaptic vesicles.[7] The effects of BoNT tend to last from 3 to 12 months.[8]

INDICATIONS

Neurogenic bladder

Detrusor sphincter dyssynergia

Detrusor sphincter dyssynergia (DSD) was the first and remains the most common urologic application of BoNT.[8] DSD has been defined as a detrusor contraction concurrent with an involuntary contraction of the urethral and⁄or periurethral striated sphincter muscle (rhabdosphincter), which prevents adequate voiding. The impact of DSD can be significant and is associated with a substantial burden of disease.[9] The management of DSD relies heavily on clean intermittent self-catheterisation (CISC). Patients unable to perform CISC require an alternative means to decrease outlet resistance.[10] In addition, low functional bladder capacity may mean that very frequent CISC is required and/or leakage may be difficult to prevent. Whilst other surgical procedures have been used, they are associated with significant complications including bleeding and stricture disease.[8,11] BoNT injections into the external sphincter are most useful in tetraplegics where clean intermittent self-catheterisation is often impossible and in whom one wants to avoid long-term catheterisation as a means of drainage due to risks of inherent catheter-related problems.

BoNT injections into the external sphincter can be performed by either a transurethral or transperineal approach. The former approach is more common. BoNT is injected transurethrally via a cystoscopic needle at the level of the striated sphincter.[12] Transperineal BoNT injections are performed by inserting a spinal needle on each side of the urethral meatus in women 10 and it requires electromyographic (EMG) guidance.[8, 10]

Over the past 20 years, a number of small prospective studies have evaluated BoNT therapy in DSD. In 1998 Petit et al. demonstrated success rates as high as 88%, with a reduction of residual urine by more than 50%.[13] The success of BoNT in DSD has been echoed by the other studies.[12, 14] BoNT therapy is safe, reversible and effective, making it a valuable treatment option in DSD.

Neurogenic Detrusor overactivity

Neurogenic Detrusor overactivity (NDO) is involuntary detrusor contraction due to a neurological condition, often resulting in incontinence.[15-16] NDO may be due to conditions such as spinal cord injuries, multiple sclerosis and spina bifida.[17] This condition is often managed by anticholinergic medications, however these drugs are not effective in all individuals with NDO and are associated with a number of side effects.[18]

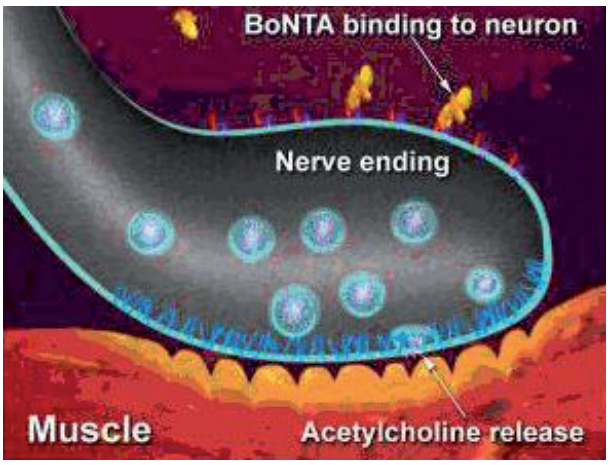

Figure 1. – BoNT Mechanism of Action - Binding.

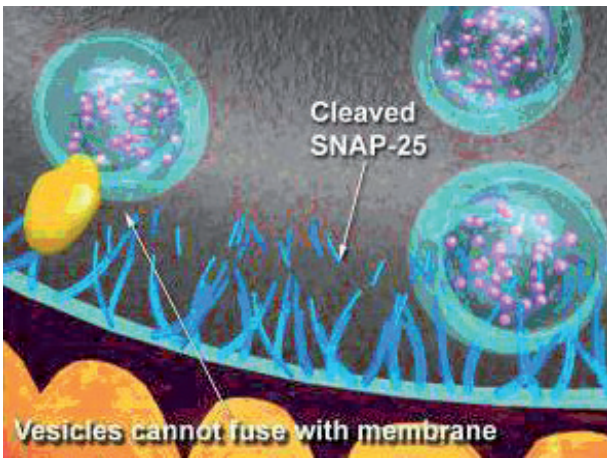

Figure 3. – BoNT Mechanism of Action – Cleavage.

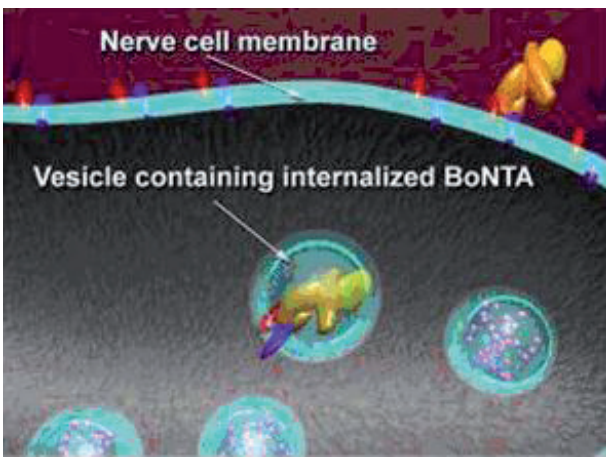

Figure 2. – BoNT Mechanism of Action - Translocation.

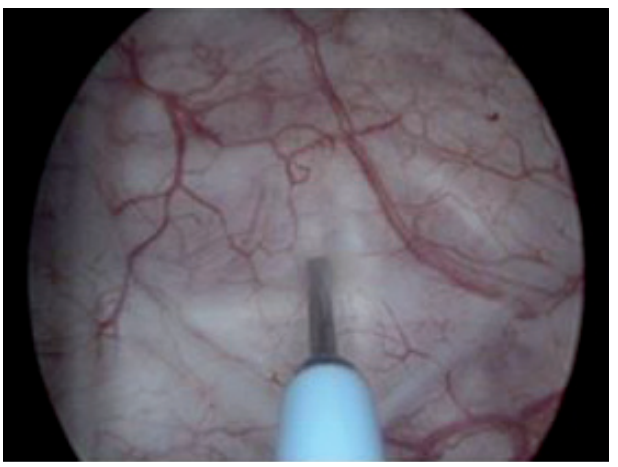

Figure 4. – BoNT injection under cystoscopic guidance into the bladder.

Multiple injections into the detrusor muscle or sub endothelial layer of the bladder can be performed using a cystoscope through which a long thin injection needle can be passed (Figure 4).[8] Most doctors perform 10-30 injections and the urinary trigone is generally avoided.[10]

The largest prospective study to date found that 73% of the 200-person cohort maintained complete continence 12 weeks after treatment.[19] In 2007, a review of clinical evidence by Dmochowski and Sand reported a continence rate between 50-90% in NDO after BoNT therapy.[17] Patient satisfaction was also deemed to be high in those with NDO treated with BoNT therapy.[17] It is anticipated that within the next 12 months, the United States Food and Drug Administration (FDA) will approve BoNT use in neurogenic bladder overactivity.

Non-neurogenic Lower Urinary Tract Dysfunction

Non-Neurogenic (Idiopathic) Detrusor Overactivity

Idiopathic detrusor overactivity (IDO) is represented often by involuntary detrusor contraction during bladder filling where no defined cause is found. It often causes overactive bladder (OAB) symptoms of urgency, frequency and/or nocturia, with or without urge incontinence. 16 For individuals with idiopathic OAB, traditional management options such as solifenacin (Vesicare™), oxybutinin (Ditropan™, Oxytrol™), tolterodine (Detrusitol™), or darifenacin (Enablex™) are not always effective or well-tolerated.[20]

BoNT is often administered as a day-surgery procedure, in a similar fashion to patients with neurogenic detrusor overactivity, except doses are often lower to prevent side effects, such as temporary urinary retention which may require a period of clean intermittent self-catheterisation or indwelling urethral catheterisation. All potential injection candidates are made aware of this risk during the informed consent process.

A number of cohort and randomised control trials (RCT) have been carried out in the last 10 years to assess the success of BoNT in refractory idiopathic OAB. Continence rates in the cohort studies ranged from 33-91% in patients treated with BoNT.[17] The combined result of three RCTs found the individual treated BoNT had 3.88 fewer episodes of incontinence compared with the placebo group and had an improved quality of life.[21-24]

Benign prostatic hyperplasia

Benign prostatic hyperplasia (BPH) is due the proliferation of transitional zone prostate tissue that results in enlargement and clinically manifests as lower urinary tract symptoms (LUTS). The gold standard therapy in BPH is considered transurethral resection of the prostate (TURP), however 15-25% of men who undergo this procedure have a poor long-term outcome.[25] BoNT has been found to relieve the symptoms produced by BPH by varying degrees.[25-27]

BoNT may be administered to the prostate by one of three routes; transurethral, transrectal or transperineal.[25-28] The transrectal approach is performed using transrectal ultrasound (TRUS) guidance.[29]

Current studies have demonstrated a 34-86% decrease in prostate volume at first follow-up.[28-29] The mechanism of action of BoNT in BPH is not fully understood. It is thought to relate to the toxins ability to relax smooth muscle and increase apoptotic activity in the prostate.[29-30] It may be useful in the drug-refractory patient group where TURP is contraindicated (e.g. in anaesthetically unfit patients). While BoNT therapy has the ability to reduce prostate size and BPH symptoms, larger randomised clinical trials are required before the clinician knows which patient groups are suitable for it to be considered in everyday clinical practice.

Pelvic Pain

The use of BoNT in the treatment of pelvic pain is still emerging, however the anti-noceptive mechanism of the toxin is not entirely understood.[15] BoNT therapy in the symptomatic treatment of interstitial cystitis has been explored in two small cohort studies with varying outcomes. Smith et al, found 69 % of patients experienced a decrease in symptoms such as pain, urinary frequency and nocturia; while the second study reports that there was no significant improvement in pain.[31-32] In 2000, Zermann et al. found a decrease in pain severity in 82% of male subjects with chronic pelvic pain syndrome (CPPS) after BoNT treatment into the perisphincteric area.[33] BoNT has also been shown to reduce pelvic pain and pressure in women with pelvic floor hypertonicity,[34] which is a condition associated with CPPS in its presentation. The evidence to support the analgesic effects of BoNT is promising but limited. Further studies are required before BoNT can be used in the routine treatment of pain-related urological conditions.

CONTRAINDICATONS

BoNT therapy is contraindicated in individuals who have a peripheral neuropathy (e.g. amyotrophic lateral sclerosis) or pre-existing disease of the neuromuscular junction.[10] BoNT treatment should be avoided during pregnancy, when breastfeeding and when taking medications that interfere with neuromuscular transmission (e.g. aminoglycosides).[10, 35]

TABLE 1. – Unwanted effects of BoNT.

Local	**Systemic**
Urinary retention	Decreased sensitivity
Haematuria	Dysphagia
Haematoma	Respiratory compromise
Urinary tract infection	Generalised weakness
	Diminished sensation
	Death

TABLE 2. – Summary of BoNT therapy in Urology

Benefits	**Risks /Limitations**
Clinical effects last a number of months	'Off Label' applications of the drug
Low risk profile	Rare but lethal side effects
Minimally invasive route of delivery	Repeated use may lead to sensitisation
Improved quality of life	Long term safety has not been
Improves symptom in a numbe of urological conditions	Limited high power clinical evidence

UNWANTED EFFECTS

BoNT therapy is considered safe, however it may be associated with a number of adverse effects (Table 1).

Local

BoNT injections have been associated with transient urinary retention, haematuria, local haematomas and an increased risk of urinary tract infections.[22, 35]

Systemic

Systemic effects are rare, as it requires the migration large quantities of BoNT into the blood stream. The lethal BoNT dose is considered 2000-3000 units, well above the therapeutic dose of 150-300units used in lower urinary tract dysfunction.[10] Repeated BoNT treatments may lead to the formation of neutralising antibodies that may reduce the efficacy of the toxin.[32] Other rare potential systemic effects include dysphagia, respiratory compromise, short term generalised weakness and diminished sensation.

CONCLUSION

BoNT has been shown to have a number of diverse urological applications, with new uses still emerging. At present, clinical evidence has demonstrated that BoNT is effective, safe and improves the quality of life in a number of conditions (Table 2). With respect to OAB, at the present time, BoNT should be reserved for anti-cholinergic-refractory cases only. Further robust clinical evidence is required before it can be used as a first line or standard treatment. Current research now focuses on better patient selection to maximise efficacy, improving and standardising injection protocols, and even less invasive delivery methods (e.g. bladder instillation with liposome-encapsulated BoNT). Due to its efficacy, low risk profile, duration of action and minimally invasive route of delivery, BoNT should surface in the very near future to become an integral part of the armamentarium in the treatment of a number of drug-refractory lower urinary tract conditions to improve quality of life.

KEY POINTS

- BoNT exerts clinical effects: paralysis and analgesia
- Shown to be beneficial in a range of urological conditions, especially overactive bladder (OAB)
- BoNT has a low risk profile
- BoNT therapy should be considered when standard treatments fail

Conflict of interest: A/Prof Prem Rashid has been a visitor to the American Medical Systems (AMS) US manufacturing facility undertaking a cadaveric dissection clinic and observed operative procedures by high volume implant urologists affiliated with AMS during that time. He also has acted as a consultant for Coloplast, Astra Zeneca, Ipsen, Hospira and Abbott pharmaceuticals, as well as, the Neotract Corporation. He was a Preceptor in Advanced Laparoscopic Urology with Professor Inderbir S. Gill, (then) Head of the Section of Laparoscopic and Robotic Surgery and Chairman, Glickman Urological Institute, Cleveland Clinic Foundation via a 2006 grant from the Australasian Urological Foundation. No commercial organization initiated or contributed to the writing of the article (apart from providing images for use where indicated).

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