Botulinum toxin and the overactive bladder

Botulinum toxin is now a treatment for many conditions. It is undergoing increasing use in several different unlicensed urological clinical situations which are outlined in this article. The article discusses the available evidence relating to its use, effectiveness and safety.

Botulinum toxin (BTX) is the most potent naturally occurring neurotoxin known to man (Gill, 1982). First derived from *Clostridium botulinum* in cases of food poisoning (in this scenario known as 'botulism'), its toxicity led to development as a purified agent in biological warfare during World War II. From this purified agent Alan Scott, an ophthalmologist, successfully explored the use of BTX in experimental models of strabismus which heralded the start of its modern use in medical interventions (Scott et al, 1973).

It is known is that seven distinct botulinum toxins occur – designated types A–G (Simpson, 1986). BTX is a polypeptide chain which is then cleaved to consist of a heavy and light chain linked with a disulphide bond and non-covalent bonds. The heavy chain acts to prevent digestion by the gastrointestinal tract and also facilitates the toxin's endocytosis into the terminal button of the motor nerve. Once here the disulphide bond is cleaved and the light chain is freed. It is the light chain that confers the potent neurotoxic effects.

The light chain migrates out of the endosomes and cleaves a protein (in the case of BTX-A the protein cleaved is termed SNAP-25 (synaptosome-associated protein 25)) which is key in allowing vesicles containing the neurotransmitter acetylcholine (ACh) to exocytose into the synaptic cleft (*Figures 1* and *2*). The other types of BTX work on slightly different proteins (collectively called SNARE (soluble N-ethyl-maleimide sensitive factor attachment receptor and exocytosis) proteins) also involved in regulating the exocytosis of ACh-containing vesicles. Thus ACh release is selectively blocked and paralysis occurs. Effects take 48–72 hours to maximally evolve. Recovery from paralysis seems to arise not from BTX degradation but from nerve regrowth or sprouting from the terminal nodes of Ranvier, and preterminal axon of the motor nerve causing a reinnervation bypassing the blocked motor endplate. However, these new sprouts eventually degenerate and function returns to the original motor endplate (Meunier et al, 2002). Recovery times vary and probably relate to differences in the physiology of smooth (detrusor) and striated (sphincter) muscles.

Medical grade BTX – type A – is produced in the USA by Allergen (Botox), and in the UK by Ipsen Ltd (Dysport). Both are type A, and importantly have dif-

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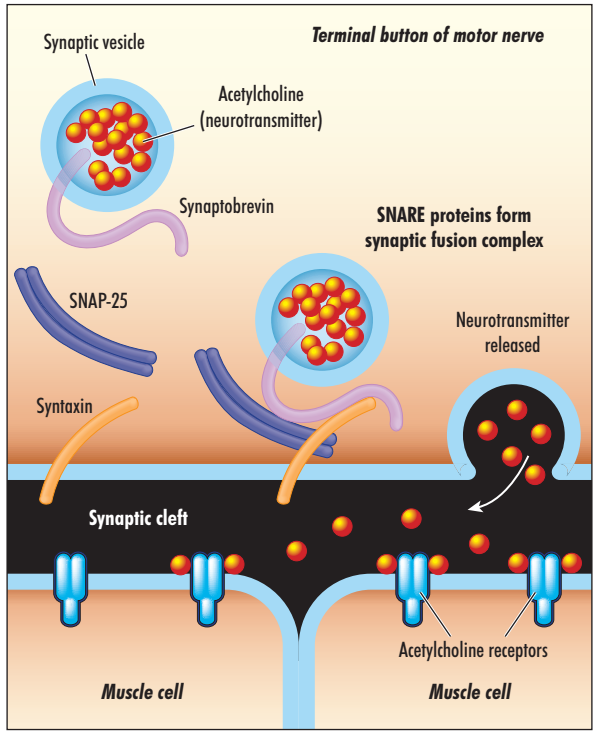
Figure 1. The normal functioning of the neuromuscular junction involves the SNARE (soluable N-ethyl-maleimide sensitive factor attachment receptor and exocytosis) proteins (SNAP-25 (synaptosome-associated protein 25), synaptobrevin, syntaxin) facilitating the fusion of vesicle and cell membrane allowing acetylcholine release.



ferent strengths. An approximate ratio with one unit of Botox equating in efficacy to around three units of Dysport has been established for skeletal muscle, but no recognized ratio has been established for smooth muscle. BTX-B is available from Elan (Myobloc or Neurobloc). BTX-B has been used to treat BTX type A resistance. Licensed indications for BTX-A include strabismus, blepharospasm, and spasticity in cerebral palsy. Unlicensed applications include cosmetic wrinkle reduction, reduction of hyperhydrosis, reduction of hypersalivation, and the urinary treatments detailed below.

Urological uses of botulinum toxin

BTX has been investigated for the treatment of various types of urinary tract dysfunction. Principal targets for the treatment are the detrusor (smooth) muscle and the (striated) external urethral sphincter (EUS). The clinical scenarios most widely treated with BTX are those of neurogenic detrusor overactivity (NDO), idiopathic detrusor overactivity (IDO) and detrusor sphincter dyssynergia (DSD) (*Figure 3*).

Detrusor overactivity is the presence of involuntary detrusor contractions during the filling phase of cystometry that the patient cannot completely suppress. Clinically, patients may present with symptoms of an overactive bladder, i.e. increased frequency and urgency with or without urinary incontinence, but symptoms correlate notoriously poorly with urodynamic findings (Umstad and Glenning, 1991). In the absence of factors explaining these signs the condition is described as idiopathic. If an attributable neurological cause is known the condition is termed NDO. When used in the detrusor the most commonly used protocol is to undertake 30 separate injections methodically distributed through the bladder but avoiding the trigone (Schurch et al, 1996).

DSD occurs in patients with neurological disease and causes simultaneous urinary sphincter contraction with detrusor contraction – so preventing adequate emptying of the bladder, and also generating dangerously high intravesical pressures which can lead to progressive renal impairment.

Medical treatment forms the mainstay of managing detrusor overactivity and DSD. Drug therapy includes anticholinergic agents, calcium-channel blockers and tricyclic antidepressants which decrease the pressures able to be generated by the detrusor. However, significant proportions of patients suffer intolerable side effects, or do not respond adequately to these medicines. Thereafter without BTX, surgery becomes the next (and irreversible) treatment option.

Botulinum toxin and neurogenic detrusor overactivity

Schurch et al (2000) were the first to use BTX for patients with refractory NDO in a non-randomized

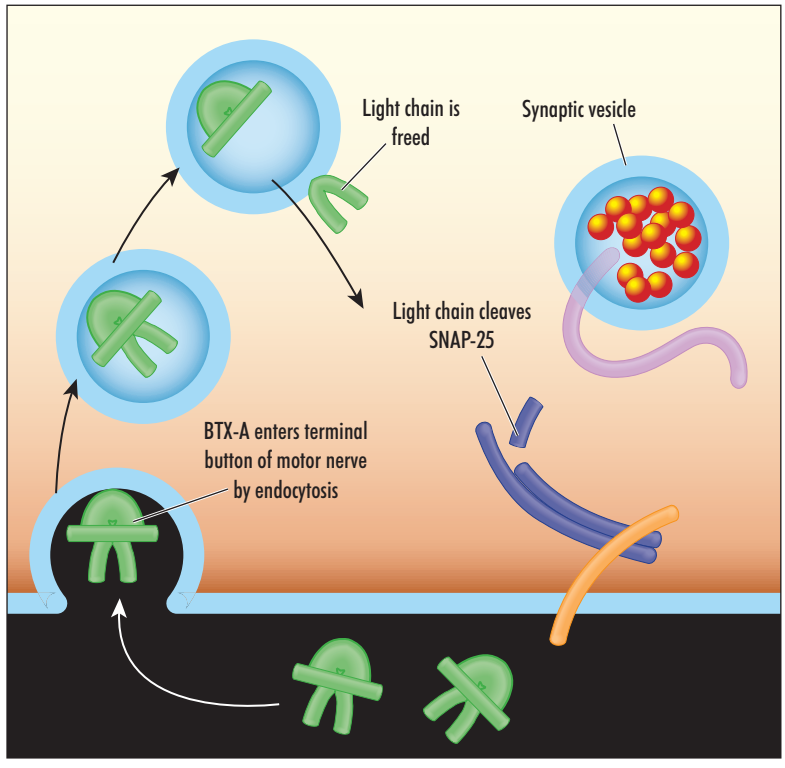
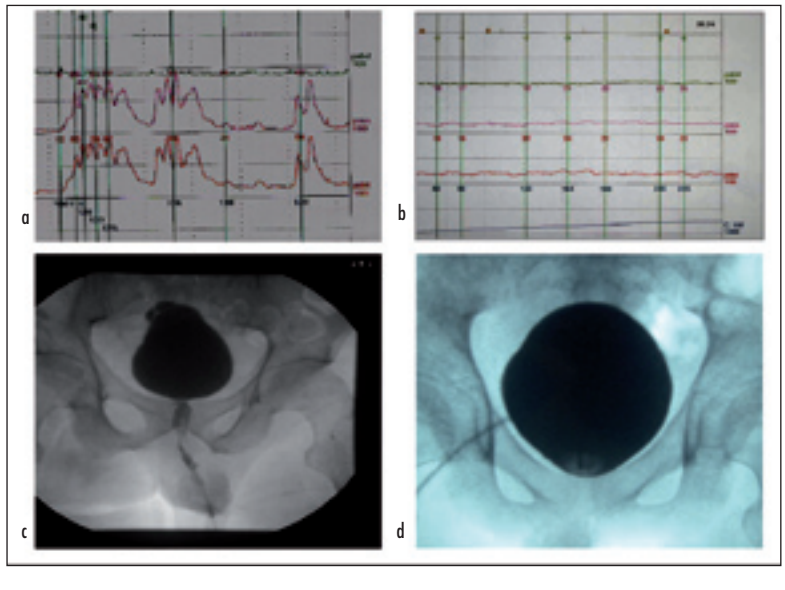


Figure 2. Botulinum toxin serotype A cleaves SNAP-25 (synaptosome-associated protein 25) and prevents vesicles from being exocytosed.

prospective series of 21 patients following up patients at 6, 16 and 36 weeks. At 6 weeks 17 of 19 patients examined were continent with reduced or stopped anticholinergic treatment. Mean maximum detrusor pressure (MDP) had decreased, and mean maximum cysto-

Figure 3. Videourodynamic studies on the same patient before and after intradetrusor botulinum toxin injections. Before injection (a) classical 'sawtoothing' pressure profile of neurogenic detrusor overactivity is seen, and (c) the X-ray shows detrusor sphincter dysynergia, leakage and asymmetrical bladder contraction. Following injection (b) the urodynamic trace is flat reflecting low pressures, and (d) the bladder outline is smooth and no leakage is evident.



metric capacity had increased significantly. Subsequent follow up showed that benefits continued to 36 weeks. Similarly Bagi and Biering-Sorensen (2004) found that 87% of 15 patients with NDO refractory to anticholinergics became continent with 300 U Botox 6 weeks following treatment. Patki et al (2006) prospectively reported an 82% continence rate using 1000 U Dysport and reported an associated 86% reduction in or cessation of anticholinergic usage in the population successfully treated.

In the largest study to date Reitz et al (2004) reported on 231 cases with NDO and injected with BTX in the same manner as Schurch et al (2000). Cases were retrospectively identified, however, from ten European centres in five countries. No data were described to determine how patients were selected for inclusion or exclusion and follow up cystometric measures were not uniform in timing at first follow up (mean 12 weeks standard deviation (SD) 29 days), i.e. 95% of measures were between 4 and 16 weeks. At second follow up (mean 256 days SD 51 days) only 99 of 200 patients had results available for analysis. Although they suggest an ongoing improvement in cystometric parameters like increased capacity, increase in reflex volumes and decrease in mean voiding pressures, a potentially large selection bias is possible. No complications were reported (Reitz et al, 2004).

In 2005 Schurch et al reported a randomized, placebo-controlled trial comparing Botox 200 U *vs* Botox 300 U *vs* placebo in 59 patients with urinary incontinence caused by NDO refractory to anticholinergic therapy. They reported significant decreases in incontinence episodes in BTX-A groups but not in the placebo group. The BTX-A groups, as assessed by urodynamics and quality of life measures, showed significant improvements. They observed benefits from week 2 to the end of the 24-week study and throughout no safety concerns were raised. The study did not demonstrate a clear difference in clinical effect between the 200 and 300 U BTX-A groups. While probably the most rigorous reported paper to date the studied numbers remain low, and no data were presented regarding the concomitant use and/or adjustment of anticholinergics which were reported to be continued through out the follow-up period.

Botulinum toxin and idiopathic detrusor overactivity

With its success in the treatment of NDO the use of BTX was expanded to include patients with IDO. Werner and colleagues (2005) prospectively assessed 26 females with IDO and treated with BTX. They found that at 4 weeks just over 50% (14/26) were dry. These effects seemed to persist until 12 weeks follow up with 13 out of 20 being dry at this time. Longer follow up suffered from a high drop out.

Kessler et al (2005) also prospectively studied the comparative efficacy of BTX (300 U Botox) between anticholinergic refractory patients with NDO (n=11, mixed aetiology) and IDO (n=11), finding that in both groups there were significant and comparable results. Measures used included day and night voiding frequency, pad use, bladder compliance, and maximum cystometric capacity at 7–10 days post injection. Both groups also suffered similar rates of inadequate voiding with 10 of 22 (47%) requiring a change of management to self catheterization or a suprapubic catheter.

Botulinum toxin and the external urethral sphincter

In 1988 Dykstra et al published a study of the use of BTX in the EUS in 11 men with spinal cord injury and DSD with the aim to reducing the obstructive effects of the DSD to urinary outflow. They found that post-void residual urine volume decreased in 76%, and that episodes of autonomic dysreflexia were decreased. Petit et al (1998) (n=17) and Schurch et al (1996) (n=24) have similarly injected the EUS and have shown that urethral pressure, and bladder pressures during voiding, and post-void residual urine volume have decreased. Regardless of technique used for injection around 87% of patients show improvements.

Phelan et al (2001) used BTX to inject patients with voiding dysfunction as a result of neurogenic DSD (n=12), pelvic floor spacitity (n=8), or hypoactive bladder (n=1). All but one patient were able to discontinue the self catheterization following the procedure. No stress incontinence was observed, and postoperative post-void residual urine volume had decreased by 71%. Subjective improvements were reported in 67% of patients.

Kuo (2003) injected 20 patients with detrusor underactivity. Following treatment 11 could void using abdominal straining. Again voiding pressure and post-void residual urine volume decreased in 90% of patients. Patients reported an improvement in quality of life measures as recording at 3 months.

Botulinum toxin and the paediatric population

The use of BTX has expanded to encompass the paediatric population who suffer from NDO and IDO. Anticholinergics are the mainstay drug treatment in this population; however, large (and unlicensed) doses are often required to adequately control symptoms. Little work has been done to assess the long-term outcome of using these medications in developing children. Cognitive impairment is commonly reported while on this medication so it remains a concern as to the long-term effects on cognitive development. Given this BTX is a very attractive option.

Schulte-Baukloh and colleagues (2003) used BTX injections in children with hyper-reflexive detrusor muscle and high bladder pressure, over 40 cmH_2O despite anticholinergic therapy Follow-up cystometric

measurements were taken 2–3 weeks and 3–6 months after injection. Significant improvements were seen in reflex volume at 4 weeks and 3 months; and in bladder capacity at 4 weeks, 3 months and 6 months. A decrease in the MDP was seen at 4 weeks and 3 months.

Riccabona et al (2004) injected 15 patients with myelomeningocele and NDO refractory to anticholinergic treatment at 10 U/kg BTX (up to 360 U). After the first treatment bladder reflex volume, capacity and compliance all increased significantly, and MDP decreased significantly with 13 out of 15 patients becoming completely dry with clean intermittent catheterization. Results appeared to persist up to a mean 10.5 months follow up.

Schulte-Baukloh et al (2005) assessed 10 children looking at the efficacy of repeated BTX-A detrusor injections in children with neurogenic bladder. While only a few patients were assessed the efficacy seemed to persist over time in all the urodynamic measures assessed (reflex volume, bladder capacity, compliance and MDP). Also no evidence of drug tolerance was found (Schulte-Baukloh et al, 2005).

Adverse effects of botulinum toxin in urology

Since its first use in humans in the 1980s the incidence of reported adverse events following its urological use has remained low considering the toxicity of the drug. The total injected dosage used in urological contexts is estimated to be approximately 1000th of that predicted for lethality in a 70 kg man (Scott and Suzuki, 1988). Indeed very few authors commented on the presence or otherwise of adverse effects following injections of BTX.

Side effects can be divided into those directly attributable to the toxicity of BTX, and those related to an immunological reaction to the injected drug.

Systemic weakness as a result of systemic spread of the toxin is usually mild and transient but can be of significance to individuals with limited motor function where even small loss of power is potentially important. Wyndaele and Van Dromme (2002) reported two cases of otherwise unexplained general or peripheral motor weakness following injection with BTX for NDO. Dykstra et al (1988) reported three of five men with high spinal cord injury treated for DSD who had generalized weakness lasting 2–3 weeks following injection in a blinded trial. Grosse at al (2005) commented on transient muscle weakness in trunk and extremities in four of 66 patients but did not report that side effects were specifically enquired after in all patients. Del Popolo et al (2003) reported reduced muscle force in five of 61 patients injected for NDO using both Botox and Dysport.

Fever and refractoriness to treatment are results of an immunological response to BTX. Kuo (2005) reported one of 20 patients injected periurethrally had unexplained high fever for 2 weeks.

Long-term outcomes

What happens to the injected BTX is also subject to uncertainty. The longest reported series of repeated injections in a single individual for urological reasons is seven (Grosse et al, 2005). At high concentrations BTX is retrogradely transported to the spinal cord and may exert some of its effects via a direct effect of the neurotoxin in the motor neuron and/or its synaptic inputs. Concerns should also exist regarding the long-term outcomes of patients in which repeated dosings of a potent neurotoxin is undertaken – especially when little certainty exists regarding the natural degradation process of the neurotoxin.

Grosse et al (2005) (using both Dysport and Botox) reported that repeated injections of BTX-A were as effective as the first dose, and that inter-dose intervals did not significantly reduce over time. However, criteria used for judging the timing for retreatment varied from patient to patient, Interestingly 18% of patients were reported as treatment failures from outset, 70% still required anticholinergics, and 40% of those taking anticholinergics gained no reduction in anticholinergic treatment. Patki et al (2006) are the only other authors to report on absolute treatment failures from outset (i.e. those gaining no improvement at all) quoting failure at 17%.

Haferkamp et al (2004) assessed the histological changes in bladder biopsies of patients with NDO before and after injection with BTX (up to 22 months). They noted no significant histopathological changes in the bladders biopsied before and after BTX injections.

Discussion

The scope and common usage of BTX is increasing within the world of urology. Undoubtedly the patients who are treated with BTX are delighted by the potential to decrease the dosage of anticholinergics (along with the accompanying side effects), and improve continence at the same time. In its favour there seems to be an accruing amount of evidence to suggest that BTX is able to improve many cystometric parameters in a beneficial way.

However, these papers need to be interpreted in the light of their methodological quality too. Very often papers are retrospective, or have enrolled only small cohorts. Follow-up periods often remain short. The use of concomitant anticholinergics through studies is universal, mostly not systematic, and the data regarding their use are underreported. There is the need for a well-controlled double-blinded placebo-controlled trial.

The cost implications of this treatment have still to be fully assessed. BTX per treatment has been calculated at costing £846 per treatment using flexible cystoscopy as

an outpatient (Kalsi et al, 2006). The cost of a one-off surgical treatment (such as clam cystoplasty) might be initially higher but in the long term will compare favourably to the costs of serial repeat BTX injection. The extra workload burden for the urologist needs to be factored as well.

The evidence to suggest how the body metabolizes (if at all) BTX remains sparse. Will retrograde axonal transport eventually produce central effects? Will repeated injections cause histopathological changes with time? What are the consequences of developing tolerance to BTX? Only time will tell.

Conclusions

Intradetrusor BTX definitely has a role in treating detrusor overactivity that is otherwise refractory to anticholinergic medications. For those who are uncontrolled by anticholinergics, or are reluctant or unfit to undergo irreversible and major surgical procedures there is a treatment option that works with a high degree of success. In the authors' experience 61% of patients will stop anticholinergics at 1 year, 69% become continent following BTX, and 80% of patients are satisfied with the treatment. Moreover it provides an effective temporizing intervention that allows patients time to consider their options. **BJHM**

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Conflict of interest: none.

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KEY POINTS

- Intravesical botulinum toxin injection is a safe and effective treatment for drug-resistant neurogenic detrusor overactivity and idiopathic detrusor overactivity patients.
- It provides a temporizing treatment for patients unfit for or contemplating major reconstructive surgery.
- The quality of evidence to date is consistent with positive effects but long-term outcomes have not yet been adequately assessed.