USE OF BOTULINUM TOXIN IN THE TREATMENT OF LOWER URINARY TRACT DISORDERS. CURRENT STATUS

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Summary.- The role of botulinum toxin in the treatment of lower urinary tract disorders has vastly expanded in the last few years. The indications list growing to include conditions ranging from detrusor sphincter dyssynergia, neurogenic and idiopathic detrusor overactivity, painful bladder syndrome and lower urinary tract symptoms consequent upon bladder outflow obstruction. This treatment is minimally invasive, shows a remarkable efficacy and has effects lasting up to one year. We review the latest evidence both basic science and clinical to address some of the key questions regarding this treatment modality. There is an abundance of evidence supporting the efficacy, safety and tolerability of this treatment. However, it is clear that much work is still required to understand the mechanism(s) of action of the toxin and more robust placebo controlled randomised trials need to be undertaken to answer the many remaining questions concerning this novel treatment. Nevertheless this treatment modality has remarkable efficacy and minimal side effects and thus will be a key future treatment option for a wide range of indications.

Keywords: Botulinum toxin. Detrusor overactivity. Urgency. Neurogenic bladder dysfunction. Idiopathic bladder dysfunction. Prostate.

Resumen.- El papel de la toxina botulínica en el tratamiento de los síntomas del tracto urinario inferior (STUI), ha aumentado enormemente en los últimos años. La lista de indicaciones crece hasta incluir condiciones que van desde la obstrucción por disinergia vesicouresinterna, hiperactividad neurogénica e idiopática del detrusor, síndrome de vejiga dolorosa y los STUI consiguientes a la obstrucción del flujo urinario. Este tratamiento es mínimamente invasivo, presenta una notable eficacia y sus efectos tienen una duración de hasta un año. Revisamos la evidencia más reciente tanto en ciencia básica como clínica para tratar algunas de las cuestiones fundamentales que atañen a esta modalidad de tratamiento. Existen abundantes pruebas que respaldan la eficacia, seguridad y tolerabilidad de este tratamiento. Sin embargo, está claro que todavía hace falta mucho trabajo para comprender el/los mecanismo(s) de la acción de la toxina y deben llevarse a cabo ensayos aleatorizados y controlados con placebo más sólidos para responder a las muchas preguntas aún pendientes.
INTRODUCTION

Produced by the bacterium Clostridium botulinum, botulinum toxins are amongst the most potent toxins known to man. The neurotoxin has for some years been known to decrease the release of Acetylcholine (ACh) from pre-synaptic membranes thereby blocking the transmission of impulses wherever ACh is the neurotransmitter. Kerner first conceived a possible therapeutic role for botulinum toxin. It was first used to treat conditions of hypertonicity in striated muscle. The first use in humans, in 1980, was for the treatment of strabismus and subsequently the drug administration agency approved its use for conditions such as strabismus, blepharospasm and hemifacial spasm in patients over 12 years old. Its indications have since expanded and it has been used successfully in many conditions characterised by muscle spasticity.

In 1996 Schurch first published the use of botulinum toxin-A (BTX-A), injected into the external urinary sphincter, to treat detrusor sphincter dyssynergia (DSD) in patients with spinal cord injury (1). This was followed by using local injections of BTX-A to treat neurogenic detrusor overactivity (NDO) (2). Efficacy approaching 100% has been described with over 600 patients treated for NDO and a further 200 with idiopathic detrusor overactivity (IDO) reported in the literature. Most groups reporting improvements in quality of life and symptoms of urgency, frequency and incontinence with concomitant improvements in urodynamic parameters. This review will discuss the postulated mechanism of action and the reported data regarding efficacy in the various disorders of the lower urinary tract.

Rationale for botulinum toxin based on past experiences

The introduction of BTX in the treatment of detrusor overactivity was based on the supposition that it would block the efferent neural pathway, thereby decreasing the involuntary detrusor smooth muscle contractions characteristic of detrusor overactivity. However this is unlikely to represent the whole picture. The precise mechanism of action in bladder storage disorders is unknown. It is unlikely to be acting primarily via the efferent pathway. The toxin is injected into both the suburothelial layer and detrusor muscle. The supposition of causing localised islands of detrusor muscle paralysis could potentially abolish the overactivity associated with OAB but how could this mechanism explain the efficacy achieved in treating painful bladder syndrome/interstitial cystitis (PBS/IC) where the pathophysiology is unlikely to involve detrusor overactivity? Furthermore, it does not explain the relief of the symptom of urgency, unless urgency is postulated to result as a consequence of detrusor overactivity propelling urine into the proximal urethra thereby stimulating urethral afferents. Below we discuss the mechanisms of action including current theories to explain its effects.

Mechanism of action

There are 7 serotypes of the toxin; BTX-A to BTX-G, the most commonly used being BTX-A (botulinum toxin A). However; BTX-B has also recently been licensed due to some reports of efficacy in those resistant to BTX-A. The other known serotypes are not currently licensed for clinical use. The neurotoxin causes a highly specific neuromuscular blockade of vesicular ACh release at somatic and autonomic pre-synaptic nerve terminals (3). BTX is a protein consisting of a heavy chain (50kDa) and a heavy chain (100kDa) bound together by a labile disulphide bond. The heavy chain binds to complex gangliosides located in the presynaptic nerve terminals at the neuromuscular junction and mediates the internalisation of the light chain, the neurotoxic component. The light chain is then thought to work by cleaving SNARE proteins SNAP-25, VAMP and syntaxin which causes inhibition of vesicular SNARE dependent ACh release from the presynaptic terminal of the motor end plates (3). This prevents vesicular release of ACh causing a sustained flaccid paralysis of the innervated muscle. It is highly selective and this supplies the basis for its potency. Clinical effects appear 24-72 hours after injection, the reason for this delay being unknown (4).

The various toxins disrupt different parts of the SNARE complex with BTX-A acting against SNAP-25 and BTX-B against VAMP (3). The defective SNARE complexes have a prolonged life within the nerve terminal, which may account for the sustained action. This action is not permanent as neuronal death does not occur and the toxins are eventually inactivated and removed. Histological assessments show...
the intoxicated nerve terminals degenerate and it is thought re-sprouting of axons leading to new synaptic contacts occurs forming new functional synapses and may presumably account for the return to muscular function which occurs after a number of months (3). Unnecessary sprouts are gradually eliminated.

Moreover, local injection leads to local flaccidity but due to its tissue specificity very little has any systemic effect and therefore minimal side effects are reported. Indeed, even with the most potent of substances no fatalities have been reported. The effect of the toxin lasts for a number of months and repeat administration has been demonstrated to have reproducible efficacy. A small number of patients after repeated doses have however been noted to develop an immune response forming antibodies that neutralise its effect.

New concepts on the action of BTX include the release of neurotransmitters including ATP (5), Ach and substance P from the Urothelium. Once thought to be inert the urothelium is in fact a complex organ, involved directly in bladder storage (6). It has been shown that ATP is released due to stretch stimulating the suburothelial purinergic neuronal receptors (7). In summary the urothelium acts as an intermediary in transduction of urothelial stretch to the reflex and afferent nerves, possibly modulating the signal. This transmission giving rise to bladder sensations and ultimately activating the micturition reflex (6).

The importance of the afferent innervation in overactive bladder disorders (OAB) and urinary incontinence is becoming clear (8). Elevated levels of ATP have been demonstrated in patients with urgency (9) and following spinal cord injury (10). Moreover, elevated levels of ATP have been found to induce detrusor overactivity (DO) (11) and the expression of purinergic ATP activated receptors is up-regulated in DO (12).

It is difficult to explain the remarkable efficacy of BTX by simple Ach blockage causing detrusor paralysis alone. Surely this paralysis would cause a higher rate of urinary retention? BTX has interestingly been found to have analgesic properties in conditions such as interstitial cystitis, signifying its role in altering sensory pathology (13) (14). In hyperactive neurons BTX-A has been found to reduce pathologically raised neurotransmitters, including ATP in the urothelium (15). Also BTX A treatment lead to a decrease in the number of suburothelial afferent neurons expressing purinergic receptors (16), in particular the P2X3 and TRPV1 receptors (10) (17). In addition to that BTX decreases nerve growth factor which may result in reduced afferent C-fibre hyperexcitability and thus a decrease in DO (18). In conclusion, clinically it may mean autonomic hyperactivity in detrusor overactivity may be susceptible to blockade by BTX yet the lower frequency normal parasympathetic detrusor is unaffected permitting normal voiding (16).

Role in management of

Detrusor Sphincter Dyssynergia (DSD)

Dykstra et al. (19) and Schurch et al. (20) first used BTX-A to treat DSD in patients with spinal cord injuries. A paralytic effect was described affecting the external urethral sphincter, either by injection transurethrally or transperineally. The latter study concluded an improvement in 21 out of 24 patients with the effect lasting between 3 to 9 months. In the former study the urethral pressure profile was decreased, electromyography showed signs of sphincter denervation and PVR volumes were down by an average of 146mls. In addition to this there was a decrease in autonomic dysreflexia in some patients.

This was later echoed by Petit et al. (21) using 150u of Dysport, the therapeutic effect (of the low dose) lasting 2 to 3 months. Later Kou et al. reported using Botox in 29 patients with DSD resulting in improvements in 80% of patients lasting 4 months (22). De Seze et al. compared 100u of Botox against 0.5% lidocaine injected into the urethral sphincter via a transperineal approach and found only patients in the former group had a significant decrease in PVR and maximum detrusor pressure (23). More recently, after investigating patient quality of life (QoL) scores and urodynamic assessments, Kou reported mixed results of satisfaction in patients with DSD (24). The study reported that 60% of patients were satisfied with the outcome, the remainder being dissatisfied due to resulting incontinence. This calls for careful patient selection.

Indications for BTX have been further expanded to include patients with non-relaxing urethral sphincter and detrusor underactivity who wish to void via the valsala manoeuvre (25) (26). In 6 females with chronic idiopathic retention, Fowler et al. found no improvement in symptoms and 3 out of 6 patients developed stress incontinence (25). Phelan et al. reported better results in 8 patients with a non-relaxing urethral sphincter showing improved PVR and voiding pressures (26). Kuo et al. injected 50-100u of Botox into the external sphincter of 30 patients with a non-relaxing urethral sphincter. Significant improvement was seen in 89% of patients both subjectively and on urodynamic parameters (22). Better results were seen in patients with detrusor underactivity (27). Overall
stress incontinence rates were 7%; and 3% developed nocturnal urinary incontinence.

**Neurogenic detrusor overactivity (NDO)**

NDO commonly occurs in patients with spinal cord injury, multiple sclerosis and myelomeningocele principally due to a disruption of the descending pathways providing the inhibitory input to the sacral micturition centre. This loss of inhibition leads to involuntary contractions and, frequently, incontinence. In addition to this, uncoordinated contraction of the sphincter (DSD) leads to structural bladder damage, vesicoureteric reflux and consequent renal impairment due to elevated bladder pressures. Clean intermittent self catheterisation (CISC) has been the mainstay of treatment supplemented with anticholinergic preparations. These lead to autonomic side effects and preclude usage at a sufficient dose to improve the condition significantly.

Over 600 patients are reported in the literature with neurogenic overactivity. Notable improvements have been seen in the urodynamic parameters of maximal cystometric capacity and the reflex volume (volume at the start of the first hyperreflexive contraction) thereby increasing bladder storage. Many patients are reported to have no involuntary contractions following treatment thus reducing symptoms of urgency and frequency and many patients gaining complete continence (28). In addition to this many patients have a lower maximal detrusor pressure on voiding, offering protection to the upper tracts. Treatment benefit lasts 3-14 months and only short lived side effects are reported.

The first multicentre RCT of 59 patients randomised to either 200 units, 300 units or placebo found, on average, incontinence episodes were reduced by 50% (p< 0.05). The maximal cystometric capacity, maximal detrusor pressure and residual volume were all improved (29). The efficacy of treatment was maintained for the 6 months of the study. Quality of life assessment also improved (p<0.002). No dose differences were demonstrated; however the sample size was small. Those with severe detrusor overactivity appeared to have greater benefit than those with less severe detrusor overactivity. Approximately 25% of patients developed a UTI (including placebo group).

Reitz et al. describe the largest collection of patients with NDO; 231 from 10 centres. Using 300u in a trigone sparing technique, they found significant improvements in bladder capacity, reflex volume and voiding pressure. Many patients even stopped taking their anticholinergic prescriptions (30). No side effects were reported in this study. From the clinical point of view 73% of patients achieved full continence between CISC and at 9 months the majority still experienced significant urodynamic and clinical improvement.

Del popolo et al. reported on the use of Dysport in 93 patients with NDO refractory to anticholinergics using CISC. They found improvements in mean bladder capacity and mean maximum detrusor pressure. The average length of effect was 1 year. Patients receiving 1000u, with complete cord transection were more prone to develop hyposthenia in suprallesional muscles, which occurred in 5% of patients.

The other major benefit of BTX injections in NDO patients is the reduction in urinary infections-pyelonephritis, orchitis, and prostatitis commonly observed in NDO patients. The reason for this decrease is most likely associated with a reduction in detrusor pressure, PVR and vesico-ureteric reflux and consequent protection of the upper tracts (31,32). Consequently, recent analysis in the UK and Germany have shown BTX to be cost effective, although the cost in the UK per BTX injection and follow up was high (£874.62) in neurogenic patients. This was less than the standard cost of care for these patients (33). Similarly in Germany the cost of incontinence aids and urinary infection treatments meant a drop in cost by 50% (34). With all these benefits and little by the way of adverse events, to be licensed BTX treatment still requires completion of robust randomised controlled studies, some of which are already underway.

**Paediatric NDO**

BTX has been used to treat NDO in a number of studies using 4-12u/Kg Botox (35) (36) (37). Results are comparable to adult studies, with significant improvements in urodynamic parameters and symptom scores with side effects being rare. Duration of effect was 6 months; which may be due to a bias towards a selective population with conditions such as myelomeningocele having a less well developed autonomic nervous system.

**Idiopathic detrusor overactivity**

Following the remarkable efficacy seen with BTX in NDO, a number of authors have investigated its use in patients suffering from intractable IDO, when all other non-surgical treatment modalities have failed. Results show similar efficacy and tolerability in IDO as NDO. Radziszewski and Borowski conducted...
the first clinical trial using Dysport in 18 patients with IDO and found increase in bladder capacity and return of continence without any side effects (38). Popat et al. compared BTX-A in non randomised neurogenic patients (300 units, 30 sites) with idiopathic patients (200 units, 20 sites); the lower dose given to reduce the risk of the need for CISC. Both groups showed improvements in symptoms and urodynamic parameters with no differences between the two groups (39). Chancellor et al. reported similar efficacy between the 2 groups with injections involving the trigone and no patients affected by urinary retention or vesico ureteric reflux (40).

Sahai et al. recently published a single centre, randomised, double blind, placebo controlled trial of patients with IDO. Participants received 200units BTX-A or placebo via a trigone sparing flexible cystoscopic approach. Significant improvements were seen in QoL scores with benefits lasting the 6 months of the study (41). Using 100 units of BTX no cases of urinary retention were noted and the effect on the post void residual was short lived; however 2 of 26 women were not affected by the treatment (42). Similarly Brubaker et al. compared 200u Botox with placebo. Approximately 60% of women receiving BTX-A had a significant improvement in lower urinary tract symptoms with a median duration of 373 days. However 43% of women had a transient increase in PVR and 75% of these had urinary tract infections (43). Schmid et al. injected 100u of Botox in 100 patients with IDO, more than 80% of patients' incontinence symptoms had resolved and temporary incontinence was reported in 4% (44). In a recent randomised dosing study comparing 100u to 150u BTX no difference was found in urodynamic or QoL results suggesting the lower dose may be the starting point, increasing as the need arose (45).

In response to the increased understanding of the urothelium in OAB, Kuo gave BTX injections sub-urethrally (46). Although this method was found to be more effective than detrusor injections, bladder sensations and voiding efficiency were impaired. 30% of patients required catheterisation and 75% reported voiding difficulty. Thus suggesting that detrusor blockade was higher through sub-urothelial sensory fibres than neuromuscular junctions or a small amount of diffusion occurs from the detrusor to the sub-urothelium following detrusor injection.

BTX has also been used in patients with refractory OAB symptoms, with no evidence of DO on urodynamics, with significant improvements in symptom scores, bladder diary and urodynamic parameters (47,48). The decrease in urgency may be due to the effect on the afferent detrusor innervations.

Even with a dose of 300u of BTX no increase in post void residuals or need for CISC was noted; possibly because all these patients had 50-75u of BTX injected into the external sphincter concurrently. This did not lead to increased rates of stress incontinence.

It is increasingly likely BTX will play an increasingly important role in the management of IDO, filling the void between unsuccessful pharmacotherapy and invasive surgical therapy. Initial studies have been supportive, often in patients with intractable symptoms. Unfortunately many unanswered questions remain which must be resolved before mainstream acceptance of this treatment modality.

Paediatric IDO

Hoebke et al. describe BTX use in a paediatric population with IDO with a response rate of 80%, with a significant proportion of patients continuing with a response 12 months following treatment (49). Of the 21 patients, 4 had transient side effects including retention and VUR. Peeren et al. retrospectively analysed paediatric patients treated with BTX and found after 18 months 33% had continued symptom control, which is higher than other sub-groups (50).

Painful bladder syndrome/ Interstitial cystitis (PBS/IC)

Giannantoni et al. (51) reported success with the use of 200u BTX-A in 12 out of 14 patients with PBS/IC at 1 and 3 months follow up, 2 patients reported incomplete bladder emptying. BTX-A lead to significant improvements in urodynamic parameters, urinary frequency and bladder pain. Continuing this on to one year they found, at the 5 month mark, 26.6% of patients reported beneficial effects to have lasted and at 12 months pain had recurred in all 15 patients (52). All the patients in the above study were given intra-trigonal injections. Smith et al. also reported benefit in 9 out of 13 patients with PBS/IC given 100-200u BTX into the trigone and floor of the bladder (53). More recently Kuo and Chancellor reported a randomised trial of suburothelial injections of either 200u or 300u of BTX followed by hydrodistension or hydrodistension alone (54). They found that subjective improvements occurred in both groups, more so in the former group. Urodynamic parameters were significantly improved only in the BTX group. Given the lack of evidence for the use of BTX in PBS/IC it should still be considered an experimental treatment.

In men with chronic pelvic pain syndrome (chronic prostatitis) BTX injection decreased pain and
improved voiding symptoms (55). Three out of four patients were satisfied with the treatment and none complained of urinary incontinence. This adds weight to the theory of anti-nociceptive actions of BTX (56,57).

**Botox in prostatic obstruction**

Another new role for botulinum toxin is in the management of LUTS arising from benign prostatic enlargement. This potential was first explored in animal studies (58), where the prostate was seen to undergo atrophy after injection. This was subsequently reported in man by Maria et al (59,60). Intraprostatic injections of 200u BTX have been compared to an injection of an equivalent volume of saline in two randomised groups consisting of 15 men. Injections were made through the perineal route under transrectal ultrasound guidance. No side effects were noted from treatment. The AUA symptom index score halved in the BTX arm but not in the placebo arm. This was supported by a significant increase in peak flow and decrease in PVR. Interestingly the prostate size and PSA level also decreased by 51% (60). It is difficult to explain this phenomenon completely without adequate histology; but it may be due to gland atrophy due to toxin action locally or due to blockage of autonomic nerve fibres. Injecting small prostate glands (<30 mls) has been found to cause a reduction of 13% (61), whereas injection of larger prostates (>70 mls) has been found to cause a reduction of 40% volume (62).

Chaung et al. reported similar improvements in subjective symptoms starting at one week and lasting up to 6 months. Two of these patients underwent prostatic biopsy and were found to have increased apoptotic activity in both glandular and stromal components of the prostate (61). Other authors have noted improvements in voiding in patients with prostatic obstruction who are too unfit for more invasive procedures. Improvements usually commence at 1 week (presumably time taken for the prostate to atrophy significantly enough for improvement to be noted). Improvements are noted in Qmax and PVR, also prostate volume and PSA decrease and patients with long term catheters may start spontaneously voiding (62). At a mean follow up of 9 months, Kuo et al. found none of their cases with previous urinary retention had recurrence of their retention (63). Silva et al. continued their 6 month study described above (62) in 11 patients and found the prostate volume began to recover from 6 months onwards to return to baseline at 18 months. The PSA, Qmax, IPSS and QoL scores did not change significantly from the 3 month scores (64).

The use of botulinum toxin in obstructive conditions of the prostate still needs much work both scientifically and clinically with longer follow up periods. No consensus exists upon the favoured route; whether it be perineal, urethral or transrectal? Also the dose of toxin to be used needs investigating as does the number of injections and in to which zones? Like all new applications it will take time for the true answers to become apparent.

**Preparations and dose**

BTX-A was the first licensed serotype in clinical use under the name Botox, however another brand of BTX-A called Dysport is also available but has not been used or studied as widely in the lower urinary tract. Although these two products are the same serotype, their dose, efficacy and safety profile are different enough for them not be considered as generic equivalents (65). Furthermore, BTX-B products have been licensed for use and have a different efficacy, diffusion, duration of effect, immunogenicity profile and mechanism of action and again the two must not be considered clinically alike (66). BTX-B has been reported to have more side effects. 1u of BTX-A is approximately equal to 50-100units of BTX-B (67) and 3-5u of disport (4,68,59).

Dysport has been described in 12 patients with IDO, who were all given 300u. All patients had a return of continence and improvements in maximum cystometric capacity and frequency without any adverse events (38). Del Popolo et al. showed a significant increase in maximum cystometric bladder capacity, decreased detrusor pressures and subjective improvements in continence and QOL with primary and repeat injections. Also no differences were found between three different Dysport doses (69).

In patients with NDO Truzzi et al. compared 100 to 300 units of Botox. Although some patients became continent with just 100u, the results were better with 300u (70). This raises the need to identify those in whom 100u would suffice. In IDO patients Gousse et al. randomised patients to receive 100 or 150u of BTX-A. They found that the lower dose was equally effective in frequency, voided volume, QoL and PVR, suggesting that lower doses could be used. However no mention was made of duration of action (71). The issue of dose requires further robust study.

A couple of case reports describe the continued efficacy of BTX-B in cases where resistance has developed to BTX-A (59,72). The different target proteins for these toxins may explain why there is confi-
nued efficacy. However one must be wary of cross-reactive antibodies which may limit this use.

Using 5000u of BTX-B (neurobloc) injected in 20 sites, Hirst et al. found good efficacy but the duration of action was less than 10 weeks in 52% of patients and no patients had benefit lasting to 6 months (73). However Dykstra et al. reported a dose escalation study on 15 patients showing a significant correlation with dose and duration of effect \((p<0.001)\), with the longest effect being with doses >10 000u. A burning pain was noticed on initial injections; however this was relieved with dilution of the toxin with lidocaine. At the highest dose of 15 000u, 2 out of 3 patients noticed mild general malaise and dry mouth (74).

Ghei et al. performed a randomised cross over trial using 5000u of BTX-B. The study was done at 6 weeks and there was some evidence of carry over effects in the placebo group at the time. Statistically significant results were demonstrated in voided volume, frequency and incontinent episodes with the treatment but 2 patients developed AUR and left the study and 2 other patients had some transient autonomic side effects suggesting some systemic absorption (75).

**Administration**

Initially the administration of BTX was via a rigid cystoscope but with improvements in fine bore injection equipment, flexible cystoscopes are utilised more frequently. This has lead to many studies using only intra-urethral local anaesthetic gel instead of the previously used general or spinal anaesthesia. If a rigid cystoscope is used the anterior bladder wall is spared from treatment (76).

Variability in the number and volume of injections may affect the diffusion characteristics and efficacy of BTX treatment as well the possibility of adverse events. No change in efficacy, safety or QoL was found by Karsenty et al. when comparing 300u given at 30 sites or 10 sites. This provides indirect evidence that a dose dependant diffusion of BTX-A activity occurs (77). This may allow the for fewer injection sites thus simplifying the procedure. In our experience injecting 0.5ml containing 10u is effective.

Controversy exists regarding injecting the trigone. There is concern that injecting close to the ureteric orifices may lead to vesicoureteric reflux, particularly in susceptible patients with NDO. Moreover in awake patients, injecting the trigone, which is known to contain a rich plexus of nerves, is postulated to cause pain at the time of injection (78). Rapp et al. injected 300u in the bladder and trigone in 35 patients from which 7 complained of haematuria, pelvic pain or dysuria, all resolving within 3 days (48). However knowing the trigone contains this rich plexus of adrenergic, cholinergic, and nonadrenergic noncholinergic fibres may make it a chief site for injection (79). Indeed Zermann et al. injected the trigone and bladder base and reported no complications with a 57% improvement in frequency and bladder capacity (80). Recently Karsenty et al. showed no induction of vesico-ureteric reflux in patients that have trigonal injection (81).

**Failure of treatment**

Patients with severe diminished bladder compliance (<1.8l) have been found to be non responders to treatment (82). Despite improving compliance in some studies BTX treatment may not overcome very poor bladder compliance. The minimum level of acceptable compliance is unknown.

**Adverse events**

The adverse events reported with BTX have been very small with no serious events or fatalities reported. Patients must be counseled of the need to perform CISC, if not regularly done, if there is difficulty voiding post procedure. Patients in whom de novo voiding difficulty has occurred, it has been short lived. In larger series the rate of CISC post BTX treatment lies between 0-5% (44) (80), although higher rates of up to 36% have been reported (83) (84). In IDO patients, Schulte-Baukloh et al. reported injecting BTX into the sphincter if patients were found to have more than 15 mls PVR. This was compared to a group that had just injection into the bladder. On comparison of the 2 groups the PVR was distinctly higher in the detrusor only group \((p<0.05)\), but was unchanged in the detrusor and sphincter group, suggesting that concurrent injection will provide protection against developing a high PVR and requiring CISC following BTX for IDO. One would postulate a higher incidence of stress incontinence with this strategy but this was not found during this study (29).

No reports of generalised muscle paralysis have been reported. However there are reports of transient mild muscular weakness in the upper limbs, particularly in patients with high cervical lesions, given the maximum dose of 300u Botox (85) or 1000u Dysport (86).

Due to the antigenicity of BTX a small number of patients mount an immune response with the formation of neutralising antibodies. To minimise the small
risk of BTX resistance, most investigators currently recommend waiting at least 3 months between treatments, avoiding the use of booster doses and using the smallest dose that achieves the desired clinical effect (59). The newer formulations of Botox used after 1998 is thought to have drastically reduced the occurrence of resistance (87).

### Reinjection

The action of BTX is naturally reversed by neural regeneration and therefore repeat injections become necessary. Grosse et al. found repeat injections of Botox 300u or Dysport 750u were as effective as the first injection; with patients receiving up to 7 injections. The interval between the treatments remained the same. No drug resistance was encountered (68). This was found by Karsenty et al. in 17 neurogenic patients who had a mean of 5.4 injections. The reinjections were as efficacious as the first injection and did not have an effect on compliance or side effects (88). In both studies tolerance which may be anticipated due to enhancement of pathological innervation following repeat injection did not occur. Over a period of 6 years, Del Popolo and colleagues injected 49 patients with at least 5 injections of Dysport and found no change in the efficacy of repeat injections both subjectively and objectively (69). Giannantoni et al. re-iterated these findings recently (31).

There was concern repeated injections may cause detrusor atrophy or bladder wall fibrosis. This has been found not to be the case and in fact in NDO patients repeat injections have not caused a decrease in bladder compliance (69,89). In both NDO or IDO patients no inflammatory change, fibrosis or dysplasia has been seen (90-92).

### Further research

The potential of BTX in disorders of the lower urinary tract has only been touched upon. There is considerable research required for this novel treatment. There is a paucity of data coming from well designed randomised placebo controlled studies answering questions such as the optimum dose for each preparation to give the longest duration of efficacy with the least side effects; needing systematic dose ranging studies. Also we need to identify the most appropriate method of administration including the number and volume of injections and whether we should include the trigone. The timing of repeat injections needs clarification as does the need to inject the sphincter in cases at risk of retention.

More work needs to be done on the different serotypes; the efficacy, safety and dose ranges to allow us to consider use if resistance develops. There may even be a role for synergistic therapy with the use of 2 or more serotypes. Moreover patients in most studies are highly selective, often those with the severest symptoms (and possibly needing the treatment the most) being excluded. BTX in patients with reflux disease and subsequent renal impairment may demonstrate a different efficacy and have a different threshold of toxicity. Also sub-groups of patients such as those with intractable DO but no DO on urodynamics should be included. Finally all these studies need to be assessing the quality of life in those treated with BTX as this is the measure of greatest clinical significance to most patients.

### CONCLUSIONS

BTX is a minimally invasive outpatient procedure which may be given under local anaesthetic that has shown remarkable efficacy with effects lasting up to a year after a single treatment. Adverse events are rare. There is no doubt botulinum toxin has a promising future in management of lower urinary tract disorders. However considerable work, both basic science and clinical, still needs to done if we are to answer the remaining questions with regards to this treatment option. Many questions still remain unanswered; what is the appropriate dose range for optimal efficacy? What is the best method of administration? What is the optimal number and site of injection? Should we include the trigone or the external sphincter during injection- if so by how much? Should we use and/or combine different serotypes? And what is the effect of long term treatment?

The results of ongoing placebo controlled randomised controlled trials are awaited with much interest. Hopefully these and other case control studies in real life clinical practice may provide us with information on health related quality of life data and cost effectiveness of this novel treatment modality. Currently all BTX use for urological reasons is off-label and not licensed, therefore caution should be exercised until future large randomised licensing studies are reported.

### REFERENCES AND RECOMMENDED READINGS

(*of special interest, **of outstanding interest)


34. Boy S, Seif P, Braun: Retrospective Analysis of treatment outcomes and medical care of patients with neurogenic detrusor overactivity (NDO) receiving BOTOX therapy; 2008.


continence (NDOI) - A prospective randomized study to compare 30 vs. 10 injection sites; 2005.