Botulinum Toxin Treatment for Neurogenic Detrusor Overactivity

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BOTULINISM

Botulinum toxin is a neurotoxin of which there are 7 immunologically distinct types. Type A and type B are commercially available [1]. Most of our experience has been with Botulinum toxin type A (BoNT/A) for urological conditions.

RATIONALE FOR USE IN THE NEUROGENIC POPULATION

In order to understand this, one needs to be familiar with the underlying pathophysiology of neurogenic bladder function. In the neurologically intact bladder the sensation of bladder filling is mediated by A delta fibers. Signals are then sent via the spinal cord to the midbrain where the pontine micturition center is alerted to the state of bladder fullness. At appropriate bladder fullness, and at an appropriate time and place, under the influence of the cortex, signals are then sent back via the spinal cord to the sympathetic and parasympathetic pathways resulting in micturition (Fig. 1). With spinal cord disruption, there is a change in the population of the afferent fiber activity such that the unmyelinated C fiber becomes predominant [2]. This is responsible for the local spinal reflex resulting in neurogenic overactivity.

BoNT/A has been shown to affect both the afferent and efferent pathways. Which pathway is more important and whether there is an interaction between both mechanisms is yet to be established. However, we do recognize that the duration of the effect of BoNT/A in the bladder is much longer than we see in skeletal muscle, suggesting the presence of other pathways being affected in the bladder.

BoNT/A works by cleaving the translocation protein (specifically SNAP 25) that is responsible for the release of the neurotransmitter from within the nerve terminal. Therefore, any neurotransmitter reliant on this pathway may be inhibited from release (Fig. 2). The effect of BoNT/A in the muscle is, therefore, related to the inhibition of the release of acetylcholine. The effect, however, is not long lasting, with the appearance of new axonal sprouting that eventually regress with recovery of the original motor endplate.

Evidence for the role of BoNT/A affecting the afferent pathway comes from immunohistochemistry studies done on post injection bladder biopsy specimens. Popat et al demonstrated that in the neurogenic population there is an increase in the population of vallinoid sensitive and purinergic sensitive afferent fibers [3]. Following injection with BoNT/A there is a decrease in the expression of vallinoid and purinergic receptors on the afferent fibers [3]. Whether this effect is primary or secondary has not been fully established. Animal studies have, however, suggested that the instillation of BoNT/A into the spinal cord of injured rat model results in a decrease in the frequency of bladder contractions, suggesting a primary afferent role [4].

TREATMENT ALGORITHM

The indication for BoNT/A in the neurogenic bladder is not first line management predominantly due to the cost. It is, however, the treatment of choice for those patients who do not respond to anticholinergic medication or are intolerant of anticholinergic side effects. Most of these patients are left to either suffer incontinence or face the morbidity of major surgery i.e. enterocystoplasty.

Most experience with BoNT/A has been in the spinal cord injury group. There is, however, increasing knowledge related to its use in central pathology, including multiple sclerosis.

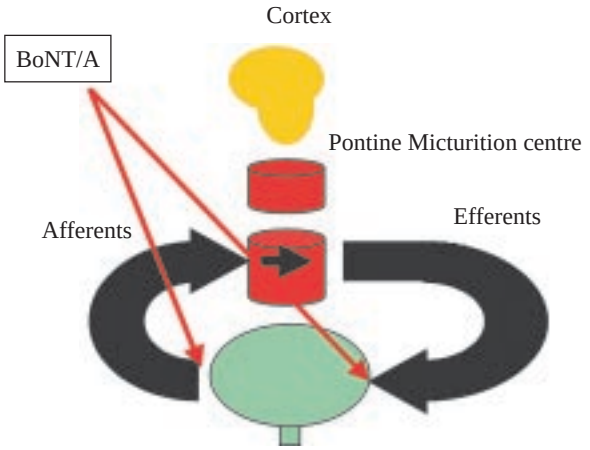

Fig. 1. The neurophysiology of micturition and Botulinum toxin A action sites.

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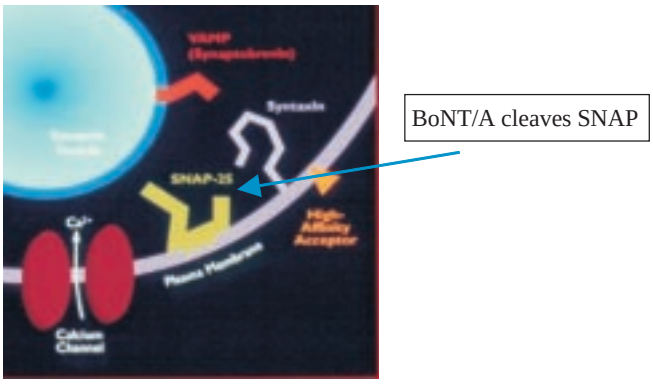

Fig. 2. BoNT/A works by cleaving the translocation protein (specifically SNAP 25) that is responsible for the release of the neurotransmitter from within the nerve terminal.

The algorithms for management of spinal cord pathology and multiple sclerosis/other central neurogenic pathology are shown in Fig. 3 and Fig. 4.

EVIDENCE

There have been more than 20 published trials looking at the use of BOTOX® in the neurogenic bladder. In total more than 600 patients have been injected. Although we now have level 1 evidence, most of the trials provide at best level 3 evidence.

The largest series has been a retrospective review published by Reitz et al involving 200 cases from 10 centers across Europe [5]. Patients included had predominantly spinal pathology but also meningomyelocoele and multiple sclerosis. The dose used was 300 units in 30 mL, with 1 mL injections to the detrusor muscle but sparing the trigone. At 12 weeks, 132 of the 180 patients, who were incontinent prior to injection of BoNT/A, reported complete continence. In regards to urodynamic parameters, there were significant improvements in maximum cystometric capacity (272 mL to 420 mL) and in maximum detrusor pressure (60 to 30 cmH_2O).

The largest single center experience has been that of Grosse et al who injected 277 patients with a total of 481 treatments (120 patients with multiple injections). Data published on the reinjection group suggested that there was no reduction in efficacy with repeated injections [6].

Schurch et al published a prospective multicenter randomized placebo controlled trial looking at the use of 200 and 300 units [7]. Fifty-nine patients with spinal pathology, meningomyelocoele and multiple sclerosis were included. Incontinence episodes decreased by approximately 50% and the difference remained significant until 6 months [7]. Quality of life (QoL) also showed a significant change from pre-BoNT/A, with an improvement of 40%-50% in the incontinence QoL value. Similarly, urodynamic parameters (cystometric capacity, reflex volume and maximum detrusor pressure) improved significantly [7]. The difference between the 200 and 300 unit groups, however, was not consistent and may be a result of small sample size.

Unpublished data from my center comparing 200 and 300 units in a prospective randomized double blind trial showed that 300 units had a greater duration of effect on urodynamic parameters than 200 units - reflex volume and maximum detrusor pressure. Reflex volume at 12 months was still approximately 80% greater than the pre-BoNT/A state in the 300 unit group compared to 30% in the 200 unit group [8]. Maximum detrusor pressure decreased by 65% in the 300 unit group compared to 40% in the 200 unit group. Cystometric capacity demonstrated an increase of 100% (300 units) cf 30% (200 units) but the difference was not statistically significant [8]. The difference, however, was less apparent at the earlier time points.

TECHNICAL ASPECTS

Patient selection (neurogenic group)

In order to improve outcome and also improve health care costs, one must be selective in finding suitable cases for the use of BoNT/A. The criteria I used for the neurogenic population were as follows:

1. Urodynamic evidence of detrusor overactivity.
2. Intolerant of anticholinergics or continued problems despite anticholinergics.
3. Self catheterizing or accepts the risk and is able to perform self catheterization.
4. Stable disease process (esp. in reference to multiple sclerosis).
5. Infection free at time of injection.

Dose

The accepted dose for the neurogenic population who are self catheterizing is 300 units. The dilution and volume of each injection, however, varies in the literature. Dilution may be between 15 mL to 30 mL of normal saline, with injection volume being 0.5 mL to 1 mL. The efficacy between these variables is not established and it is essentially physician preference. A lower dose of 100 to 200 units may be preferable for patients who are not self catheterizing.

Method of injection

The injection may be performed by a variety of methods using either flexible cystoscopy or rigid cystoscopy. If performed on the conscious patient, flexible cystoscopy is preferable with prior instillation of lignocaine solution into the bladder.

There are a variety of needles used for the injection: (1) flexible cystoscope (Olympus flexible injection needle), (2) rigid cystoscopy (rigid injection needle, Williams cystoscopic needle).

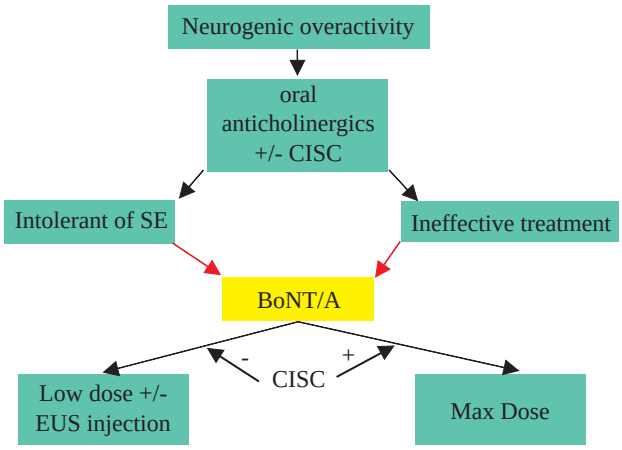

Fig. 3. The algorithms for management of spinal cord pathology.

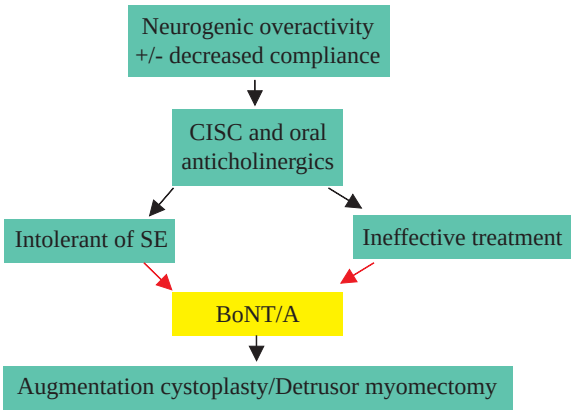

Fig. 4. The algorithms for management of multiple sclerosis / other central neurogenic pathology.

Depth of injection

Thus far the majority of trials involving the neurogenic population have been done using intradetrusor injections. It is unknown, however, whether submucosal injections as described by Kuo would be of any greater benefit [9].

The best description of the injection technique is by Chris Smith: "We inject ... in a manner that allows one to see the bladder wall rise with each injection but not so superficial that a blistered appearance developed."

Place of injection

For neurogenic patients, the 30 injections are distributed evenly around the bladder but sparing the trigone. The reason for sparing the trigone is related to the theoretical risk of developing reflux. Smith CP and Chancellor MB, however, have described a limited template for injection, involving the bladder base and trigone, with good efficacy and no clinical evidence of reflux [1].

When to reinject

As mentioned above, multiple repeated injections have not demonstrated development of tolerance to BoNT/A [6]. Injections should not be performed within 3 months due to the risk of autoantibody formation. After this time period, however, it is feasible to reinject based on the recurrence of symptoms provided all other clinical factors are stable. The average duration of effect is 8 months. It has, however, been recognized that these patients can be reintroduced to anticholinergic medication at a lower dose once there is evidence of diminishing Botulinum effects. This may then prolong the time between injections and thus reduce medical costs.

COMPLICATIONS

Specific complications related to the use of BoNT/A are uncommon. The most concerning of these is the potential risk of generalized muscular weakness presumed secondary to absorption of the toxin into the vascular system. Review of the literature suggests contributing factors to be injection technique, dosage, rapid reinjection and the specific commercial form of BoNT/A [6,10]. In total, approximately 14 cases have been described in the literature but over 1,500 cases have been injected with BoNT/A.

CONCLUSION

In summary, BoNT/A is a useful adjunct in the management of the neurogenic overactive bladder. There is level 1 evidence supporting its use in the neurogenic population. We now have a treatment that fits perfectly between oral medication and major surgical intervention.

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