Urol Colomb. 2016;25(2):72–74

SCU Sociedad Colombiana de Urología®

REVISTA UROLOGÍA Colombiana

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EDITORIAL

What is the role of onabotulinumtoxinA for the management of the overactive bladder symptom complex in 2016?

¿Cuál es el papel de la onabotulinumtoxina para el tratamiento del complejo de síntomas de vejiga hiperactiva en 2016?

Christopher Chapple[a,b,c,d]

[a] *Royal Hallamshire Hospital, United Kingdom*
[b] *Honorary Professor, University of Sheffield, United Kingdom*
[c] *Visiting Professor, Sheffield Hallam University, United Kingdom*
[d] *Secretary General, European Association of Urology, United Kingdom*

Is all 'botox' the same?

The bacterium *Clostridium botulinum*, produces several serotypes of botulinum toxin (BTX-A to BTX-G). The most commonly used and studied is BTX-A, which consisting of a light chain (50 kDa) and a heavy chain (100 kDa) bound together by a labile disulphide bond. Different formulations of BTX-A exist due to different isolation, extraction and purification processes by manufacturing companies. These include, Botox® (Allergan Pharmaceuticals, Irvine, CA), Dysport® (Ipsen Biopharm Ltd, Slough, UK), Xeomin® (Merz Pharmaceuticals UK Ltd, Herts, UK), Prosigne® (Lanzhou Biological Products, Lanzhou, China) and PurTox® (Mentor Corporation, Madison, USA). Despite being the same serotype the efficacy and safety of each formulation varies and the formulations cannot be considered as generic equivalents.[1,2] To reflect this, the FDA has defined new terminology for the different formulations of BTX and Botox® is termed ''onabotulinumtoxinA'', Dysport® is termed ''abobotulinumtoxinA'' and Xeomin ''incobotulinumtoxinA''. This commentary will review latest developments relating to onabotulinumtoxinA as none of the other agents are currently licensed for us in treating bladder overactivity.

How does it work?

Classical opinion is that BTX-A acts by blocking the transmission in nerve impulses wherever acetylcholine (Ach) is the principal neurotransmitter leading to muscle paralysis. The heavy chain binds to complex gangliosides located in

DOI of original article: http://dx.doi.org/10.1016/j.uroco.2016.06.001
E-mail address: c.r.chapple@sheffield.ac.uk

http://dx.doi.org/10.1016/j.uroco.2016.06.002

the presynaptic nerve terminals at the neuromuscular junction and facilitates the internalisation of the neurotoxic light chain. This then cleaves the 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] The defective SNARE proteins remain in the nerve terminal for a number of months and may account for the sustained duration of activity. More recent work has suggested that in fact the desired therapeutic efficacy is achieved by an action on the sensory afferent system. Laboratory evidence has shown that BTX-A also blocks other neurotransmitters such as ATP, substance P, $P2X_3$ and TRPV1 receptors and recent functional studies looking at afferent signalling after the application of botulinum toxin in an animal model has lend support to an effect on the afferent system being of fundamental importance.[4,5]

What is the clinical evidence for an effect on overactive bladder (OAB)?

A great deal of work has centred on the most appropriate dose of onabotulinumtoxinA for the treatment of OAB, one unit (1 U) is defined by the LD50 for mice, although a laboratory based assay is now used. The phase 11 data with onabotulinumtoxinA suggested that a dose of 15 U probably provided the best efficacy, with higher doses just leading to a higher retention rate with no additionally increased efficacy.[6] A number of randomised controlled trials have assessed onabotulinumtoxinA use in patients with OAB, using onabotulinumtoxinA, but the two placebo controlled registration studies of 548 and 557 patients respectively have demonstrated increased efficacy over placebo at a dosage of 100 U[7,8] and provided the basis for licensing by the MHRA and FDA. Patient inclusions were >3 urinary incontinence episodes in 3 days and more than 8 micturitions per day. Co-primary end points were changes from baseline in number of incontinence episodes per day and patient reported benefits on the treatment benefit scale (TBS) at 12 weeks. Other reported parameters were changes in urgency, frequency, nocturia and QoL assessments. Both studies reported a decrease in incontinence episodes by 2.6–3 episodes per day compared to placebo which decreased by 1 episode per day ($P < 0.001$). This represents a 62–64% reduction in incontinence episodes. A quarter of all patients became completely dry. Also, two thirds of patients reported a positive treatment response on the TBS scale. Secondary end-points also showed improvements, with 18, 45 and 25% reductions in frequency, urgency and nocturia episodes respectively. Quality of life improvements assessed with the I-QoL and KHQ questionnaires also revealed significant benefits with onabotulinumtoxinA over placebo ($P < 0.001$). The risk of urinary tract infection (UTI) is reported in 21% of patients included in randomised controlled trials. The need for temporary intermittent self catheterisation (ISC). This was required, in 12% of patients in RCT's. Initial reports reported a higher rate of ISC and it must be recognised that the PVR which instigated catheterisation was lower in those studies 100 ml vs. 200 ml.[2] It must be borne in mind that clinical practice does not suggest such a high clinically evident infection rate and that the threshold value for starting ISC is dependent on the views of the treating clinician.

An interesting finding was that reported by Rovner, who noted that improvements in urodynamic parameters and clinical outcomes generally trended together following onabotulinumtoxinA treatment. Key urodynamic parameters in patients with idiopathic OAB and UUI, with no differences in outcomes between those with and those without baseline detrusor overactivity (DO). Concluding that successful treatment of OAB with onabotulinumtoxinA does not appear to be related to urodynamically proven DO.[9] This is important as only 40–60% of female patients and 60–90% of male patients without and with OAB respectively have DO.

The randomised controlled studies use a very standardised protocol and another question which have been raised is what is the optimum position at which to inject botulinum toxin and what volumes to use; issue which deserve further research.

How does onabotulinumtoxinA compare to other therapies for OAB?

Two recent randomised studies funded by NIH have contrasted onabotulinumtoxinA to anticholinergic therapy[10] and sacroneuromodulation.[11] The ABC study[10] was a double-blind, double-placebo-controlled, randomised trial involving women with OAB ($\geq$5 UI episodes on a 3-day diary. Initially over a 6-month period, participants were randomly assigned to daily oral anticholinergic medication (solifenacin, 5 mg initially, with possible escalation to 10 mg and, if necessary, subsequent switch to trospium XR, 60 mg) plus one intra detrusor injection of saline or one intra detrusor injection of 100 U of onabotulinumtoxinA plus daily oral placebo. The primary outcome was the reduction from baseline in mean UUI per day over the 6-month period. Secondary outcomes included complete resolution of urgency urinary incontinence, quality of life, use of catheters, and adverse events. 249 women underwent randomisation and 247 were treated, and 241 had data available for the primary outcome analyses. The mean reduction in UUI per day over the course of 6 months, from a baseline average of 5.0 per day, was 3.4 in the anticholinergic group and 3.3 in the onabotulinumtoxinA group ($P = 0.81$). Complete resolution of UUI was reported by 13% and 27% of the women, respectively ($P = 0.003$). Quality of life improved in both groups, without significant between-group differences. The anticholinergic group had a higher rate of dry mouth (46% vs. 31%, $P = 0.02$) but lower rates of catheter use at 2 months (0% vs. 5%, $P = 0.01$) and urinary tract infections (13% vs. 33%, $P < 0.001$). The conclusion was that anticholinergic therapy and onabotulinumtoxinA produced a similar reductions in the frequency of daily episodes of urgency urinary incontinence. The group receiving onabotulinumtoxinA was less likely to have dry mouth and more likely to have complete resolution of UUI but had higher rates of transient urinary retention and urinary tract infections, Whilst this study demonstrated an increase effect on UUI with a higher rate of complete resolution it is of note that nearly60% of patients had been on prior anticholinergic therapy and the design did not mimic the situation in clinical practice where onabotulinumtoxinA therapy tends to be used as second line therapy after failure of anticholinergic therapy. It was not clear what the status of patients was and whether they were responders to anticholinergic therapy

as in real life clinical practice, patients treated with onabotulinumtoxinA are non-responders to this therapy.

The Rosetta trial reported its design recently in 2014.[11] This was conducted as a randomised, open-label, active-control trial comparing the effectiveness of 200 units of onabotulinumtoxinA (Botox A®) versus sacral neuromodulation (InterStim®) therapy for refractory UUI. This trial was designed to compare changes in UUI episodes over 6 months, as well as other lower urinary tract symptoms, adverse events and cost effectiveness in women receiving these two therapies. Eligible participants had previously attempted treatment with at least 2 medications and behavioural therapy. The initial results from this were reported at the recent American Urology Association meeting.[12] 386 women with at least six UUI episodes per day were randomised to either onabotulinumtoxinA injection or sacral neuromodulation. The mean age in the study cohort was approximately 63 years, onabotulinumtoxinA 200 U was injected. In the neuromodulation group, a two-stage procedure was used. The rate of clinical response at one month (defined as a reduction of at least 50% in urgent urinary incontinence episodes on a 3-day bladder diary) was similar in the injection and neuromodulation groups (83% vs. 84%). At 6 months, the change in the mean number of UUI episodes from baseline, was greater in the injection group than in the neuromodulation group (−3.9 vs. −3.3 episodes/day; $P = .01$). More patients in the injection group than in the neuromodulation group achieved complete symptom resolution at 6 months (20% vs. 4%; $P < .0001$). Treatment satisfaction was better in the injection group than in the neuromodulation group ($P = .01$), as was endorsement, assessed with the Overactive Bladder Satisfaction of Treatment Questionnaire ($P = .0009$). The rate of urinary tract infection was higher in the injection group (35% vs. 11%; $P < .0001$). as was intermittent catheterization; seen in 8% of patients at 1 month, by 4% at 3 months, and by 2% at 6 months versus 3% of patients required surgical revision or removal in the stimulation group.

The Rosetta trial raises some interesting questions as the dose used was twice that of the FDA approved dose and resulted in a lower retention rate than seen in many studies. In addition the patient age group was a little older than seen in many OAB studies and the sustained benefit of onabotulinumtoxinA seen at 6 months was also noteworthy. As is often the case this well conducted study has raised a number of questions.

Disclosures

Consultant, researcher, speaker and trial participant for Allergan, Astellas, Recordati. Researcher for Ono, Pfizer.

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