## Aims of course/workshop

Botulinum toxin-A is an effective treatment option for treating refractory overactive bladder and detrusor overactivity. This workshop will provide an overview of the published literature on the subject but will focus on level I evidence. Its use in neurogenic bladder, bladder oversensitivity and painful bladder syndrome will also be discussed. Current knowledge on mechanism of action will be presented. The workshop will deliver practical points, technical aspects of drug delivery, tips and tricks which will be helpful to both new and established users.
Botulinum Toxin-A for refractory Overactive Bladder: Efficacy, Mechanism of action and Practical Tips and Tricks

Formulations and terminology – Arun Sahai

FDA approved products and updated terminology (from FDA website)

<table>
<thead>
<tr>
<th>Trade Name*</th>
<th>NEW Drug Name</th>
<th>OLD Drug Name</th>
<th>Indication</th>
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<tbody>
<tr>
<td>Botox</td>
<td>OnabotulinumtoxinA</td>
<td>Botulinum toxin type A</td>
<td>Cervical dystonia, Severe primary axillary hyperhidrosis, Strabismus, Blepharospasm</td>
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<td>Botox Cosmetic</td>
<td>OnabotulinumtoxinA</td>
<td>Botulinum toxin type A</td>
<td>Temporary improvement in the appearance of moderate to severe glabellar lines</td>
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<td>Dysport</td>
<td>AbobotulinumtoxinA</td>
<td>Botulinum toxin type A</td>
<td>Cervical dystonia, Temporary improvement in the appearance to moderate to severe glabellar lines</td>
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<td>Myobloc</td>
<td>RimabotulinumtoxinB</td>
<td>Botulinum toxin type B</td>
<td>Cervical dystonia</td>
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* The marketed trade names and the product formulations have not changed.

Botulinum Toxin – Mechanism of Action  CH FRY

Botulinum toxin (BoNT) is produced mainly by the gram-postive anaerobic bacterium Clostridium botulinum. There are at least seven serologically distinct forms (BoNT-A to BoNT-G) with similar effects. BoNT is expressed as single polypeptide (≈150 kDa), with several functional sections (Fig 1-1). BoNT binds to a receptor on the surface membrane (e.g. SV2) or the target cell where it is internalised and cleaved to generate an active light chain that prevents fusion of neurotransmitter vesicles to the surface membrane. This it achieves through cleavage of proteins of the SNARE complex that facilitate vesicle fusion (Fig 1-2). The precise steps will be discussed in the workshop. Although most discussion concerns the action of BoNT at cholinergic neuromuscular junctions, there is in principle no reason why a similar action should not occur at other cells capable of vesicular exocytosis.

BoNT receptors have been identified on the surface membranes of several cell types – such as neurons and epithelia. Their differences will be discussed as a means to develop tissue specific toxins that may be of clinical use.
In the context of management of bladder dysfunction with BoNT a number of questions arise that will be addressed in turn during the workshop:

i) What is the extent of the distribution of BoNT after injection
ii) Does BoNT act on parasympathetic cholinergic nerves to reduce efferent activation of detrusor smooth muscle
iii) Does BoNT act on the sensory arm of the micturition reflex to reduce afferent function.
iv) If there is evidence for BoNT acting on the sensory arm does it act on afferent nerves.
v) If there is evidence for BoNT acting on the sensory arm does it act on urothelium.

There are data from urodynamic measurements as well as investigative laboratory studies. The latter include results from animal experiments to investigate the fundamental modes of action of BoNT as well as from human tissue obtained from bladders that have previously been treated with BoNT. The above questions will be addressed as follows.

i) BoNT distribution after injection has been assessed by measuring the appearance of SV2 and SNARE complex fragments, indicative of a biological action. The data suggest that there is a considerable area of distribution.
ii) BoNT can affect nerve-mediated bladder contractions. Points to be discussed in the workshop will be its efficacy of action in this context and if it affects equally the release of all excitatory neurotransmitters
iii) There is urodynamic evidence that BoNT affects the sensory arm of the micturition reflex and this will be discussed in the workshop
iv) Experimental evidence indicates that BoNT can alter afferent nerve firing during filling. Does BoNT have a primary effect on afferent nerves or is afferent function modulated due to the action of BoNT on sensory transducers that influence afferent firing.
v) During physical and chemical stresses to the bladder wall the urothelium releases several substances that may act as sensory mediators. The evidence that BoNT can influence the release of these modulators will be discussed.

The bladder wall also releases inflammatory mediators that may be measured in the urine, and thus are potential biomarkers of underlying conditions that cause bladder dysfunction. The release of such mediators may be altered by BoNT. The value of this observation to be discussed in the workshop is that we can understand more about the control of release of such mediators.

Overall, this section of the workshop will seek to improve our understanding of the mode of action of botulinum toxin in the bladder wall and how this knowledge may be used to control more effectively bladder dysfunction.
Slide 1

Botulinum toxin in NDO

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ICS Barcelona August 2013

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Case scenario
• 48, female
• Secondary Progressive multiple sclerosis- 10 years
• Optic neuritis, paraparesis
• Urgency, frequency, incontinence
• Hesitancy, straining, double voiding

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• Bladder scan- PVR 180 mL
• Urine dipstick- normal
• Urodynamics- DO
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Slide 6

History

Botulinum toxin for the first time in the lower urinary tract


- urethral pressure ↓
- post void residual ↓
Literature overview: 2000 to 2007 (Q4)

Search PubMed: botulinum AND bladder NOT sphincter NOT prostate
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Results: Urgency Incontinence

Reduction in number of UI episodes compared to baseline (%)

Schurch. J Urol, 2005

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Results: Urodynamics – MCC

Mean increase in MCC from baseline (ml)

Schurch. J Urol, 2005

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Results: Quality of Life

Increase in Total I-QoL Score from baseline (%)

Schurch. J Urol, 2005
Single injection improves bladder symptoms and QoL in MS

Kalsi et al., 2007

Success of Repeat Detrusor Injections of Botulinum A Toxin in Patients with Severe Neurogenic Detrusor Overactivity and Incontinence

Grosse et al., 2005

Fig. 1: Interstitial cystitis 12, 24, 36 months after injection.
There is no significant difference between the groups.
Grosse et al., 2005
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Urogenital symptoms in MS (n=112)

UDI6 Scores

PreBoNT/A 1 PostBoNT/A 1 PreBoNT/A 2 PostBoNT/A 2 PreBoNT/A 3 PostBoNT/A 3 PreBoNT/A 4 PostBoNT/A 4 PreBoNT/A 5 PostBoNT/A 5

0 20 40 60 80

p<0.001 p<0.001 p<0.001 p=0.016 p<0.001

Khan et al. Poster BAUS, 2009

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Incontinence

IIQ7 Scores

PreBoNT/A 1 PostBoNT/A 1 PreBoNT/A 2 PostBoNT/A 2 PreBoNT/A 3 PostBoNT/A 3 PreBoNT/A 4 PostBoNT/A 4 PreBoNT/A 5 PostBoNT/A 5

0 20 40 60 80

p<0.0001 p<0.0001 p<0.0001 p=0.136 p=0.0003

Khan et al. Poster BAUS, 2009

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Median inter injection interval (NDO/MS)

Interval 1 Interval 2 Interval 3 Interval 4 Interval 5 Interval 6

0 10 20 30 40

p=0.6; 12.6 months

(n=112, MS) Khan et al. Poster BAUS, 2009
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**Botulinum toxin for NDO (n=112)**

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<tr>
<th>ADVERSE EVENTS</th>
<th>12.1%</th>
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<th>1.5%</th>
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<td>FLULIKE SYMPTOMS</td>
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</tbody>
</table>

Khan et al. Poster BAUS, 2009

**Slide 20**

**Open label study of 137 MS patients**

- Bladder emptying before 3.5 weeks after Botox.


**Slide 21**

**Efficacy and Safety of Oumabimemastat in Patients with Ectopic Pressurized Bladder in Overactive Bladder:**

- Efficacy and Safety of Oumabimemastat in Patients with Ectopic Pressurized Bladder in Overactive Bladder

*THE JOURNAL OF UROLOGY* 2011
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- Time to retreatment: 254 vs. 256 vs. 92 days
- Initiating ISC: 42% vs. 35% vs. 10%
- Commonest adverse effects: UTI, retention

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**Inferences**

- Onabotulinum toxin A significantly improves symptoms
- Likelihood of ISC: dose dependent
- No clinically relevant benefit in efficacy or duration for 300 U over 200U

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**Botulinum toxin in Parkinson’s disease?**

Giannantoni et al. 2011

MCC
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Post void residual

Giannantoni et al. 2011

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Patient Perception - Before

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Patient Perception - After
Annual increase in workload

"botulinum toxin A is the 21st century penicillin for the bladder"
Cost effectiveness

The Costs plotted against the QALYs of each intervention

Net benefit and duration in the model

Net Benefit of each intervention compared with age

AC, JTOA/MAC, JTOA, RTX, No Rx
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Blepharospasm
Cervical dystonia (spasmodic torticollis)
Chronic migraine prophylaxis
Focal spasticity stroke
Urinary Incontinence (NDO)
Focal spasticity paediatric CP
Equinus deformity
Glabellar lines
Hemifacial spasm
Cervical dystonia (spasmodic torticollis)
Axillary hyperhidrosis
Focal spasticity stroke: hand

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Licensed Indications (Luxembourg)
Glabellar lines
Chronic migraine prophylaxis
Blepharospasm
Hemifacial spasm
Cervical dystonia (spasmodic torticollis)
Axillary hyperhidrosis
Focal spasticity stroke: hand

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Multiple indications

Ensuring patient safety when botulinum toxin is used for different indications

- Multidisciplinary teams
- Communication between teams
- Timing & dosing per indication
- Timing & total dosing per patient case

Conclusion

- Botulinum toxin is safe and effective in the management of NDO- level 1 evidence
- Attributes for the neurological patient- minimally invasive, minimal side effects, duration of effect
- Potential need for catheterisation
A large phase III, placebo controlled study was carried out involving 557 patients with OAB and urge urinary incontinence (UUI) who were refractory to antimuscarinic therapy and were treated with 100 U OnabotulinumtoxinA (1). Patients did not have to have IDO to be included. Outcome measures included measurement of daily UUI episodes, scoring on the treatment benefit response scale, and health related QoL scores. At 12 weeks post treatment, significant improvements were seen for these measures in those that received BTX-A, with 22.9% of BTX-A patients achieving continence versus 6.5% in placebo. Some of the results are summarised below. De novo CIC rates in this population have traditionally been a concern but in this study was only required in 6.1%.

BTX-A treatment has also been directly compared in a head to head study with antimuscarinic therapy (2). In this double blind, placebo controlled randomised trial, 247
patients with UUI were randomised into either a daily antimuscarinic tablet (solifenacin / trospium chloride) and an intradetrusor injection of saline, or an intradetrusor injection of OnabotulinumtoxinA (100 U) and a daily oral placebo tablet. In both arms significant improvements were seen at 6 months follow up. Both groups had a reduction of incontinence episodes from 5.0 per day to 3.4 and 3.3 for antimuscarinics and BTX-A, respectively. The BTX-A arm had significantly higher rates of complete resolution of UUI than the antimuscarinic arm (27% vs 13%). QoL also improved in both groups, without significant differences between the two arms. The antimuscarinic group had a significantly higher rate of dry mouth, but had significantly lower CIC rates and UTI episodes (2).

Long term effects of the toxin are largely unknown with regards to continuing efficacy, antibody formation and its effects on bladder function. However, medium term efficacy and discontinuation rates have recently been reported in a prospective study of 100 patients who had repeated injections of OnabotulinumtoxinA to treat refractory IDO (6). For those who
had up to five injections, there was statistically significant improvement in OAB symptoms and QoL compared to baseline, with a mean inter-injection interval of 322 days. The main reasons for those who dropped out of treatment were poor efficacy in 13%, and CIC related issues in 11% (6). Dropout rates were highest in the first 2 years following treatment and then very rare. Other studies have confirmed the efficacy of repeated injections in this patient population (7, 8).

However, Mohee et al., in their retrospective study noted different outcomes with BTX-A, in a predominantly OAB / IDO population (although some patients with NDO were included) (9). In 137 patients with at least 3 years of follow up approximately 60% had discontinued treatment mainly as a result of CIC related issues or UTI. Limitations include lack of antibiotic use and outcomes were based on patient reported factors as opposed to specific instruments or diaries and the retrospective nature of the study. Interestingly many of the patients had reverted back to conservative treatments and antimuscarinic therapy to which they were initially refractory (9).
Botulinum toxin injections into the detrusor: Technique and practical tips

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University of Zürich

Workup

- Medical history & physical examination
- Bladder diary
- Urine analysis / urine culture
- Urinary tract ultrasonography
- Urethro-cystoscopy / bladder washing cytology
- Urodynamics
Patient selection / information

- Refractory overactive bladder syndrome
- Potential need for catheterization
- Temporally limited effect → repeat injections
- Legal issues

- Flu-like symptoms / muscle weakness
- Haematuria

Equipement & technique
Postoperative care

• Outpatient setting
• Effect after 5-10 days (not immediately)
• Spontaneous voiders: PVR after 2 weeks
• Catheterization: PVR >150mL & LUTS
• Follow-up urodynamics
  • in selected patients (high-pressure, reflux)
  • before repeat injections

Tips & tricks

• Informed consent procedure (→ PVR)

• Ultrafine single-use needles → injections safe
  • under oral anticoagulation
  • under antiplatelet treatment

Tips & tricks

• Caution: potentiated effect in case of
  • aminoglycoside antibiotics
  • neuromuscular blockers

• Caution: spinal cord injury at / above T6
  • continuous cardiovascular monitoring
  • anaesthesiological stand-by