



## Botulinum toxin in overactive bladder and BPH

### Workshop 5

### Monday 23 August 2010, 09:00 – 12:00

Time	Time	Topic	Speaker
09.00	09.05	Introduction and aim of the workshop	Brigitte Schurch
09.05	09.35	Mechanisms of action of botulinum type A in the bladder and prostate	Paulo Dinis
09.35	10.00	Neurogenic OAB treatment with BonT/A: facts and questions	Brigitte Schurch
10.00	10.20	Best indications for BonT/A in OAB according to present knowledge	Emmanuel Chartier-Kastler
10.20	10.30	<b>Questions</b>	
10.30	11.00	Break	
11.00	11.25	BonT-A to treat BPH: where are we?	Gilles Karsenty
11.25	11.45	Safety	Jacques Corcos
11.45	11.55	<b>Questions</b>	
11.55	12.00	Discussion	All

#### **Aims of course/workshop**

To have an overview of current knowledge on the mechanism of action and safety profile of the botulinum toxin type A in urology.

#### **Educational Objectives**

*General objective:* To have an overview of current knowledge on the mechanism of action and safety profile of the botulinum toxin type A in urology

*Specific objectives:* At the end of the session, participants will be able to:

- understand mechanisms of action of botulinum toxin and prostate
- discuss algorithms of treatment of OAB and BPH
- define the best indications for BonT A in urology according to present knowledge
- list safety issues and their prevention



## **Botulinum toxin in overactive bladder and BPH**

### **Workshop 5. Monday 23 August 2010 9.00-12.00**

#### **Summary of the presentations**

##### *Mechanisms of action of botulinum toxin type A in bladder and prostate. Paulo Dinis (Porto, Portugal)*

Of the seven subtypes of botulinum toxin (BONT). BONT-A is the most relevant clinically. BONT-A acts by cleaving SNAP25, one of the N-ethylmaleimide-sensitive factor attachment protein receptor (SNARE) proteins in pre-synaptic nerve endings, thereby inhibiting the fusion of neurotransmitter-containing synaptic vesicles with the neuronal membrane, an event essential for the release of neurotransmitters. The reduction or absence of neurotransmitters in the synaptic clefts causes a natural interruption of neuronal transmission that affects both the efferent and the afferent branches of the micturition reflex. In cholinergic nerves of skeletal muscle, the gradual accumulation of synaptic vesicles in the pre-synaptic terminals has been shown to cause their rapid degeneration. This in time is followed by the formation of transient pre-synaptic sprouts until full regeneration of the original terminal was complete. Data on bladder cholinergic nerves seem to indicate a similar mechanism of SNAP-25 cleavage. However the recent demonstration of BONT-A action on first and second order neurons of the motor pathway, due to the presence of intramural ganglia, may contribute to explain a longer effect of BONT-A at this location. BONT-A also affects sensory transmission. BONT-A reduces the release of glutamate and substance P from sensory neurons and this reduces sensory input transmission by these cells. Moreover, BONT-A reduces the release of neuropeptides from the peripheral terminals of bladder sensory neurons, and after BONT-A application, there is a reduction of sensory fibers immunoreactive to P2X3 and TRPV1 in the bladder of neurogenic patients treated with the neurotoxin. Another possible neuronal mechanism occurring during BONT-A application has recently been described in sensory neurons. There is co-localization of SNARE proteins and TRPV1 in these cells. BONT-A prevents the SNARE protein-dependent TRPV1 trafficking from cytoplasm stores, where the receptor is inactive, onto the surface of sensory neurons, where it can be targeted by ligands. At least at the prostatic level, neuromediator release hindrance also occurs in the sympathetic peripheral nerve fibers. When injected into the prostate BONT-A will induce a long lasting inhibition of sympathetic fibers. This abolition of sympathetic tone has been shown to induce stromal cell apoptosis in turn reducing prostate size as well as symptoms related to Benign Prostatic Hyperplasia. In summary the central effect of BONT-A - blockade of SNARE proteins - at the bladder and prostate levels might translate into different clinical effects according to main type of peripheral nerve fibers targeted at each injection area.

Injection of the bladder dome will act mainly on parasympathetic fibers, thus its proven effect on detrusor overactivity. The bladder base and trigonal area contain most of sensory fibers identified in the human bladder. Thus injection at this site possibly has an effect on afferent transmission perhaps explaining effect of BONT-A on pain and hypersensitive



overactivity. The bladder base and trigonal area contain most of sensory fibers identified in the human bladder. Thus injection at this site possibly has an effect on afferent transmission perhaps explaining effect of BONT-A on pain and hypersensitive overactive bladder. This rationale also applies to prostatic BONT-A injection

*Neurogenic detrusor overactivity treatment with BoNT/A: facts and question. Brigitte Schurch (Zürich Switzerland)*

In patients with neurologic disorders, bladder dysfunction associated with detrusor overactivity (DO) constantly impairs quality of life (QoL) and often poses a threat for the upper urinary tract (UUT). Therefore, it represents a major health problem in this population. Oral antimuscarinic agent have been widely used as first line treatment for patients with NDO or neurogenic OAB (NOAB). However, they are ineffective in some patients or can cause troublesome systemic side effects such as dry mouth, constipation, and blurred vision. Intravesical treatment strategies may provide alternatives to achieve a profound inhibition of NDO and to avoid high systemic drug levels. The use of BONT-A in the treatment of patients with NDO aims to improve urinary symptoms, to reduce UUT risk and to improve QoL. It has been developed as a second-line treatment option (ie, intolerance or failure after treatment and evaluation with an appropriate dose and for an appropriate period of antimuscarinics for patients with NDO with urinary incontinence able and willing to perform clean intermittent (self)-catheterisation (CIC). Recently European expert panel consensus conference was convened with main aims to evaluate the evidence and clinical considerations for the use of BoNTs in the treatment of urological and pelvic floor disorders, and to propose relevant recommendations. The quality of evidence from fully published English language literature in the PubMed and EMBASE databases was assessed using the European Association of Urology (EAU) levels of evidence (LoE). Recommendations were graded and approved by a unanimous consensus of the panel. Evidence synthesis: The use of BoNT/A is recommended in the treatment of intractable symptoms of neurogenic in adults (Grade A). The depth and location for bladder injections should be within the detrusor muscle outside the trigone (Grade C). Dosage in children should be determined by body weight, with caution regarding total dose if also being used for treatment of spasticity, and minimum age (Grade B). The use of BoNT/A in the LUT with the current doses and techniques is considered overall safe (Grade A).

*Best indications for BoNT/A in NDO and OAB according to present knowledge. Emmanuel Chartier Kastler (Paris, France)*

The treatment with botulinum neurotoxin A gained its level of great evidence for neurogenic detrusor overactivity (DO) since studies have been published regarding dose, effect, and lack of placebo effect on neurogenic patients suffering incontinence related to DO.

In the same period, randomized placebo-controlled and non-randomized uncontrolled trials started to use BoNT/A at a very low dose to treat the overactive bladder syndrome (OAB) in a non-neurogenic population.



The main difference among these two populations is the fact that non-neurogenic patients are voiding spontaneously, opposite to neurogenic patients using CISC because of the spinal cord trauma and/or disease.

The aim of this presentation will be to go through published studies to review results, main side effects, duration of effect and quality of life improvement. Contraindication will be discussed as well as currently running placebo-controlled trials.

As the use of BoNT/A is still off-label in neurogenic and non-neurogenic patients, we will also have to focus on good practice recommendations if available.

Guidelines, as published by ICI, have also to be discussed as the use of BoNT/A in OAB is still out of any label and should not be recommended, except controlled studies. Real life seems to be different from one country to another, or from one team to another. It is our own responsibility to differentiate clinical evaluation of new treatments and routine use with regards to other available treatments.

#### *BoNT-A to treat BPH: where are we? Gilles Karsenty (Marseille, France)*

When injected within rat, dog and human prostate botulinum toxin type A (BONT-A) reduces volume of glandular and fibromuscular (FMS) components. It also reduces prostatic tissue contractility. Since BONT-A is able to act on the static and dynamic components of BPH related bladder outlet obstruction it appears as a potential new treatment avenue of lower urinary tract symptoms due to BPH.

The aim of this presentation will be:

- To review current basic and clinical knowledge that supports a role of BTA in BPH treatments.
- To define the need for future studies to bridge the gap between efficacy clues to proven effectiveness of BONT-A in BPH treatment.

BONT-A induces apoptosis of the glandular prostatic epithelium as well as of the fibromuscular component of the gland. BONT-A also decrease contractility of smooth muscle fibres of the FMS. These effect are long lasting. The mechanism of apoptosis induction is not fully understood. There is some evidence for a safety of prostatic BONT-A injection regarding the risk of neoplastic lesion promotion or induction. BONT-A has the properties to treat all stages of BPH consequences. It may challenge medical treatment as well as ablative therapy. Actual duration of BONT-A effect after a prostatic injection is currently the question to be solved to precise the place of BONT-A future in BPH treatment algorithm. Prostatic injection of BONT-A is candidate to enter soon the BPH treatment algorithm.

#### *Safety of Botulinum toxin. Jacques Corcos ( Montreal Canada)*

Botulinum toxin (BonT) kills. Kerner in 1860 described a deadly consequence of consumption of sausages carrying the toxin. It is only a century later that Scott et al reported on the medical use of this toxin with extreme efficacy.

Bont-A has been used in urology since Schurch et al reported their initial experience in neurogenic bladders in 1999. Mainly indicated in neurogenic bladders, BonT- A is now widely used for OAB, BPH and obviously neurogenic bladder and dysfunctional external urinary sphincter. Presently BonT-A is not FDA approved for any indication in urology.



According to Cote et al, BonT used for cosmetic indications has never caused any deaths while it's therapeutic use caused 28 deaths. Among other adverse effects noted with BonT the most common are dysphagia, muscle weakness, allergic reactions, flu-like syndrome, injection site trauma, arrhythmia and MI. Several causes have been suggested to explain the occurrence of these adverse effects however none have been identified as a main cause. After injections, immunization has been clearly demonstrated; however it's clinical implications are presently questionable. Among all AE reported with Botox the most inconvenient for the patient is urinary retention, which occurs in 10 to 30 % of cases. In most cases no predictor of such an event can be identified, however a poor voiding detrusor pressure or significant chronic retention should be a contra-indication for BonT injection. Besides these relatively frequent events, BonT seems to be a safe drug which can be used quite freely in urology.