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Review Article

Botulinum toxin in Urology

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ABSTRACT

Introduction: Botulinum toxin is a neurotoxin produced by Clostridium botulinum species of bacteria. This powerful toxin, which is the most poisonous substance known to mankind, has been used in highly dilute concentrations in urology. This review examines the various applications of botulinum toxin sub-type A (BTA) in the field of Urology.

Material and methods: Recent literature with respect to the use of BTA in Urology was examined with specific reference to clinical applications.

Results: Intradetrusor injection of BTA has a wide and expanding role in Urology. Intradetrusor BTA injections lead to a significant increase in cystometric capacity and reduction in detrusor pressure in patients with neurogenic detrusor overactivity. In patients with idiopathic detrusor overactivity, there is significant reduction in urgency and frequency. There is also evidence to support the use of BTA in overactive bladder without detrusor overactivity, bladder pain syndrome, detrusor sphincter dyssynergia and dysfunctional voiding. Initial studies support the continued investigational use of intravesical catheter instillation of liposomal BTA. Evidence with regard to benign prostatic hyperplasia is conflicting and this treatment is not recommended for regular clinical use.

Conclusions: There is good quality evidence to support the use of intradetrusor BTA in patients with detrusor overactivity both neurogenic and idiopathic as well as in overactive bladder and bladder pain syndrome. The evidence with regards to detrusor sphincter dyssynergia, dysfunctional voiding and benign prostatic hyperplasia is less robust. Liposomal BTA delivery may present an attractive future option in Urological disorders.

1. Introduction

Botulinum toxin is the most powerful poison known to mankind. Just a teaspoon of concentrated toxin could wipe out all of humanity. However, just like several other poisons such as digitalis or snake venom, when used in the right concentration, poisons often transform into powerful medicines. Botulinum poisoning and its link with poorly preserved meat was possibly noted for the first time in 1793 in Germany after an outbreak of poisoning with symptoms of paralysis. Perhaps the earliest account of Botulinum on Pubmed is from the year 1916 when Lancaster reported strabismus following suspected Botulinum poisoning.[1] Van Ermengen, a microbiologist in Belgium was the first to isolate the Clostridium botulinum bacteria which produces the toxin and reported it in 1897 following an outbreak of the poisoning after a meal at a funeral.[2]

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The first medical use of Botulinum was reported by Alan Scott for strabismus in 1981 who used Botulinum toxin A, the serotype of toxin that is currently in common use.[3] The first urological experience was reported in 1988 by Dykstra who injected it into the striated urethral sphincter for the treatment of detrusor sphincter dyssynergia.[4]

2. Material and methods

A Pubmed search was conducted with terms botulinum toxin, detrusor overactivity, overactive bladder, bladder pain syndrome, dysfunctional voiding, detrusor sphincter dyssynergia and benign prostatic hyperplasia. Recent literature was reviewed and conclusions were made with regards to clinical application.

3. Pharmacology of botulinum toxin A (BTA)

Botulinum toxin is a neurotoxic protein produced by *Clostridium botulinum*. There are seven types of toxins (Type A–G) of which Type A has the longest duration of action and has been in common clinical use. Botulinum toxin A (BTA) has two chains, a light chain of about 50 KDa size and a heavy chain of about 100 KDa size held together by a disulfide bond.[5]

There are four different sub-types of BTA known with a 15% variation in the amino acid sequence.[6] The light chain is a zinc-dependent endopeptidase responsible for the toxicity while the heavy chain has three distinct parts, H_N, H_{CN} and H_{CC}. These assist in the internalization and translocation of the toxin.[5] BTA can be complexed to different proteins with consequential differences in its pharmacokinetic profile. Hence, one must differentiate between these various commercial types of BTA. Onabotulinum toxin A is most commonly in use (Botox, Allergan Inc; Neuronox, Medytox Inc). Abobotulinum toxin A (Dysport, Ispen Biopharm Limited) and Incobotulinum toxin A (Xeomin, Merz Pharmaceuticals) are some other preparations that are commercially available.

3.1. *Mechanism of action*

The heavy chain of BTA binds to receptors on the pre-synaptic cholinergic neuronal endings with consequent internalization of the toxin. In the cytoplasm, the toxin is cleaved into its light and heavy chains. The light chain then interferes with SNARE proteins that are responsible for the binding of acetylcholine vesicles to the neuronal membrane. This prevents the binding of vesicles and subsequent release of acetylcholine. There are various types of SNARE proteins which are targeted by different sub-types of botulinum toxin. SNAP 25 protein is targeted by types A, C and E. VAMP (or synaptobrevin) is targeted by types B, D, F and G while Syntaxin is targeted by type C. This binding is permanent and cleaved SNAP 25 can be noted in human nerve terminals upto 11 months following an injection. The effect wears off as new nerve endings sprout.[5,7]

SNAP 25 is expressed almost universally by parasympathetic fibers and by about half of the sensory and sympathetic fibers in the bladder wall. It is also expressed by preganglionic parasympathetic nerve endings in ganglia located at the bladder wall.[5] On injection of the toxin into bladder wall, there is rapid spread across the detrusor. This is dependent on the volume of injected fluid as well as the number of injected sites. Cystoscopic injection into the bladder wall leads to reduced acetylcholine expression by parasympathetic efferents at the detrusor neuromuscular junction. This is accompanied by reduced release of other neurotransmitters associated with acetylcholine release such as ATP and Vasoactive intestinal peptide (VIP). There is also reduction in expression of muscarinic and purinergic receptors in the detrusor, urothelium and sub-urothelium which are important for both Aδ as well as C fibers.[8]

In the afferents, there is a reduced expression of neurotrophic factor with impairment of nociceptive impulses from the bladder wall. Hence there is an analgesic effect. Sympathetic fibers show a decrease in norepinephrine release by the trigone by a poorly understood mechanism.[9] In the urothelium, BTA reduces ATP and NO release. ATP is important in bladder activity. There is also increased cleaving of SNAP 23, which might be important in ATP release.[5] Repeated injections have not been shown to increase fibrosis. On the contrary, there is some evidence to show that fibrosis might be reduced in patients who are injected.

Intraprostatic injection can induce apoptosis with involution in size of the prostate although this finding has not been consistently seen. There is also decrease in smooth muscle contraction in the prostate.[10,11]

4. Clinical applications in Urology

4.1. *Neurogenic detrusor overactivity*

The first line management of patients with neurogenic detrusor overactivity is antimuscarinic medication. However, in patients with unsafe storage pressures despite medication, or in those with intolerance to antimuscarinic agents, the options are limited. The time-tested solution is an augmentation cystoplasty. However, augmentation is a major surgical reconstruction and carries a metabolic consequence. It cannot be offered in patients with significant reduction in glomerular filtration rate due to the side effects related to solute reabsorption and acidosis. Botulinum toxin injection offers an attractive solution in these patients.[12]

BTA has been found to be highly effective with significant reduction in storage pressures and increase in capacity.[13] This can potentially minimize risk to the upper tracts in patients at risk. The effect lasts for 6–12 months. The injections need to be repeated indefinitely and while the effects seem to be steady at more than five injections, the truly long term or life long consequences of bladder injections remains uncertain. Some studies suggest that patients who undergo injections might in fact, have less long term bladder wall fibrosis compared to those that are not injected. The effect does seem to be sustained, however, the numbers of patients studied with long term injections remains small. In a recent review, intradetrusor BTA injections were noted to lead to a significant improvement in incontinence, maximum cystometric capacity and maximum detrusor pressures of −63%, +68% and −42%, respectively (all $p < 0.01$).[14]