

Review Article

Approach to pharmacotherapy of botulinum toxin A in the field of urology

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Abstract. By altering discharge of neurotransmitter from the end of nerve, the strong toxin that is called botulinum toxin or BTX could results in paralysis of different muscles into the human bodies. However there are seven serotype of botulinum toxin, but only botulinum toxin A (BTX-A) was recommended as the most commonly prescribed of BTX by urologists. When treatment strategy based on use of simultaneous anticholinergics could not meet a satisfactory criterion for pharmacologist, urologist and patients, then it seems that BTX-A expressively could improve urinary incontinence symptoms, urodynamic, and quality of life in patients with both neurogenic and non-neurogenic detrusor activity. Related to its use in urological disorders, it seems that intravesical BTX-A injection is useful in inflammatory bladder disease such as chemical cystitis, radiation cystitis, and ketamine related cystitis. Dysuria and urinary retention could be mentioned as the maximum and minimum reported side-effects after injection. It is prescribed in urinary incontinence that could be a result of urethral underactivity (stress) or bladder overactivity (urge), or a combination of two urethral overactivity/bladder underactivity (overflow incontinence). Hematoma, pain at injection site, intractable headache, ptosis, diplopia and hyperactivity of the local antagonist muscle could be mentioned as the temporary side effects. Dry and red eye, space striving, dry mouth, abdominal turbulences, dysphagia, throatiness and lastly breathing difficulties could be specified as potentially serious events.

Keywords: Botulinum toxin-A, BTX-A, urology, bladder, pharmacotherapy

Introduction

The neurotoxic protein that is produced by the Bacterium Clostridium Botulinum was originally discovered by Emile Van Ermengem in the year 1895 and subsequently called botulinum toxin (BTX). However, there are seven serotype of botulinum toxin, but only botulinum toxin A (BTX-A) was recommended as the most commonly prescribed of BTX by urologists. In the year 1989, the Food and Drug Administration (FDA) approved Botox[®] for the pharmacotherapy of strabismus, blepharospasm, and cervical dystonias in population of patients with > 12 years old. The neurotoxins produced by the Bacterium Clostridium Botulinum are the mainly strong acute toxins and are the contributing agents of the neuroparalytic disease botulism. The toxins act mainly at peripheral cholinergic synapses by blocking the evoked discharge of the neurotransmitter acetylcholine [1]. The estimated human median lethal dose (LD50) is 1.3-2.1 ng/kg intravenously or intramuscularly and 10-13 ng/kg when inhaled [2]. A dose of 200 U for treatment of neurogenic detrusor overactivity (NDO) was recommended by FDA [3]. The general uses of BTX in medicine include; upper motor neuron syndrome, severe primary axillary

hyperhidrosis, belparospasm, strabismus, chronic migraine, bruxism, cervical dystonia, neuromuscular disorder of the head and neck, severe primary axillary hyperhidrosis, muscle spasm and overactive bladder (OAB). When injected in small amounts, it could weaken a muscle for a period of three to four months. As voiding dysfunctions are common problems in urological practice [4], efficacy and safety of repeated BTX-A injections for patients with drug refractory non-neurogenic overactive bladder (NOAB) seems to be important issue related to its prescription [5, 6]. In the year 2011, it was approved for urinary incontinence due to detrusor overactivity [7]. The efficacy of BTX-A in management of OAB has been recommended by previous publications. According to the definition by the International Continence Society, urgency with or without urge incontinence, usually with frequency or nocturia called over active Bladder (OAB) [8]. Related to its use in urological disorders, publications suggested that intra-detrusor injection of botulinum toxin may have beneficial effects in patients with medication refractory detrusor overactivity and may offer a new minimally invasive alternative to patients with severe overactive

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TABLE 1
PHARMACOLOGICAL PROPERTIES OF BOTULINUM TOXIN A

<p>Formula: $C_{6760}H_{1044}N_{1743}O_{2010}S_{32}$</p> <p>Molar mass: 150 kg/mol (150,000 g/mol)</p> <p>Route of administration: IM (approved), SC, Intradermal, into gland</p>
<p>Clinical Efficacy: An injection of 200 U (10 U/mL) at 20 sites with trigone sparing, significant increases in maximum cystometric capacity (MCC) from 182 mL to 313 mL were observed at 4 weeks. Reduced episodes of frequency (mean change from 15.44 to 7.93 times per day), urgency (mean change from 0.69 to 9.21 times per day) as well as UII (mean change from 4.98 to 1.9 times per day) at 4 weeks, and a significantly better improvement in quality of life as compared with placebo was noted by Brubaker L. et al., in 2008 [15].</p> <p>Dose-Relationship Effects: A durable efficacy for dose groups of 100 U or greater was reported by Dmochowski R, et al. in 2010 who performed a clinical trial related to doses of 150 to 300 U. In that study, doses greater than 150 U contributed minimal additional or clinically relevant improvement in symptoms and health-related quality of life [16].</p> <p>Side Effects: According to the meta-analysis of BTX-A in treating idiopathic detrusor overactivity patients, BTX-A significantly augmented post-void residual volume (32.77 vs. 2.01), proportions of urinary tract infection (19.69% and 5.94), and proportions of clean intermittent catheterization (8.41% and 0.46%) versus placebo [29]. As related to the age >61 years, low maximum flow rate, low voiding efficiency (a percentage of the voided volume compared to the prevoid bladder volume <90%), and large post-void residual volume at baseline has been reported as risk factors for these adverse events [30]. Hematoma, injection site pain, intractable headache, ptosis, diplopia and hyperactivity of local antagonist muscle could be mentioned as the temporary and benign side effects. Dry and red eye, space striving, dry mouth, abdominal turbulences, dysphagia, throatiness and lastly breathing difficulties could be specified as potentially serious events [1-30].</p>

IM: intramuscular, SC: subcutaneous.

bladder symptoms [1-8]. This study was designed in order to gather talented satisfying evidence, strong review articles and research in order to focus in BTX injections associated to urological-disorders.

Materials and Methods

United States National Library of Medicine (PubMed, NLM/ MEDLINE®) were searched. The main words relevant to; “1) butilinum toxin A, 2) butilinum toxin A efficacy and safety, 3) butilinum toxin A in clinical practice, 4) butilinum toxin A dosing 5) butilinum toxin A in urology, 6) butilinum toxin A in urological disorders were investigated. A total of: 1) 7649 (18 April 2016 to 17 May 1946), 2), 545 (29 February 2016 to February 1997), 3) 199 (29 January 2016 to 1998), 4) 121 (December 2015 to January 1996), 5) 446 (31 March 2016 to September 1998), 6) 735 (20 October 2015 to February 1997), manuscripts were recognized. Consequently, research papers appropriated to the pharmacotherapy management of BTX-A, in urology were selected and assessed entirely [9-12].

Results

Table 1 shows pharmacological properties of BTX-A, which could be categorized the novel treatment associated to a range of therapeutic domains. BTX-A has been established for the management of numerous lower urinary tract symptoms (LUTS), sexual dysfunctions such as OAB, detrusor-sphincter dyssynergia (DSD), benign prostatic

hyperplasia (BPH), interstitial cystitis/painful bladder disorder, long-lasting pelvic pain and more recently early ejaculation. It has expected guiding authorization for the use in NDO and OAB, but its' use remains unlicensed in other LUTs such as non-neurogenic LUTs in men with BPH, bladder pain syndrome and DSD [13].

It could be prescribed in patients with urinary urgency and frequency, urge incontinence and nocturia those suffer from OAB [7]. The first randomized, double-blind, placebo-controlled trial to compare the efficacy of BTX-A versus placebo in treating patients with refractory IDO of either sex was reported by Sahai et al. in 2007 [8, 14]. In another study performed by Brubaker L. et al., in 2008, 200 U (10 U/mL) was injected at 20 sites with trigone sparing. Significant increases in maximum cystometric capacity (MCC) from 182 mL to 313 mL were observed at 4 weeks. BTX-A also reduced episodes of frequency (mean change from 15.44 to 7.93 times per day), urgency (mean change from 11.69 to 9.21 times per day) as well as UII (mean change from 4.98 to 1.9 times per day) at 4 weeks, and a significantly better improvement in QOL as compared with placebo was noted. The beneficial effects persisted for at least 24 weeks. Brubaker et al. also compared 200 U intradetrusor BTX-A injection at 15 to 20 sites versus placebo in women with refractory idiopathic UII [8, 15]. A durable efficacy for dose groups of 100 U or greater was reported by Dmochowski R, et al., in 2010 that was performed a clinical trial related to doses of 150 to 300 U. In that study doses more than 150 U contributed

negligible advance or clinically pertinent improvement in signs and health-related quality of life [16].

In patients with intractable OAB non-responsive to anticholinergics drugs, it seems to be trust worthy management. Inoculated into the detrusor muscle, BTX-A toxin is well tolerated with negligible threat of systemic side effects. A recent study showed that the injections of 100 units of BTX-A in the submucosal coating of the bladder are ineffective in those with over active bladder (OAB), while additions in the detrusor indicate to an imperative improve in signs of urgent and recurrent urination for six months [8]. BTX-A is a strong neurotoxin that could discriminately modulate neurotransmitter discharge from the end of nerve, that could consequences to muscular paralysis. Due to its' possible effect on sensory nerve it could have anti-inflammatory effect [18]. Study performed in women with medication-resistant, urodynamic-confirmed idiopathic detrusor overactivity showed an improvement in the median scores from baseline to one month on the incontinence impact and Urogenital Distress Inventory [19]. Results of meta-analysis performed by Duthie et al., in 2011 specified that however, the administered doses of 100 to 150 units of BTX-A, seem to demonstrate beneficial effects, but prescription of 300 units of BTX-A might have more effective and longer lasting, but with more side-effects. Related to the type and doses of BTX-A, its' effect might be last after 6-12 months. Repeated injections of BTX-A, do not seem to become refractory to BTX-A [20].

Diagnosis and treatment for bladder pain syndrome/interstitial cystitis (BPS/IC) seems to be puzzling. Neuhaus et al., in 2012 studied intravesical treatments of BPS/IC and suggested that as a second line of therapy, BTX-A injection, intravesical sodium hyaluronate instillation and DMSO instillation suggested to be the best-performing managements [21]. Pinto et al., in 2013, studied persistent therapeutic effect of repeated injections of onabotulinum toxin a in refractory bladder pain syndrome/interstitial cystitis. It was mentioned that mean decrease in pain score (compared to baseline 5.9 ± 1.8), O'Leary-Sant score (associated to baseline 28.8 ± 6.3), and urinary frequency (related to baseline 16.4 ± 5.3) and mean increase in voided volume (likened to baseline 112 ± 42 ml) and superiority of life were comparable after each management. Individual symptom relief lasted 6 to 12 months with an average duration of 9.9 ± 2.4 months [22].

Study related to repeated injections of BTX-A (Dysport) for 33 women with intractable detrusor overactivity was performed by Abeywickrama et al. in 2014. In this study mean duration between the first and second injections was 15.2 ± 7.2 months, whereas between the second and third was 19.2 ± 10 months ($P=0.025$). Two women developed UTI and required clean intermittent self-catheterization. Three women required dose escalation to 750 units. Longer duration of subjective quality of life improvement was stated among the second and third BTX-A injections paralleled to period among the first and second injections [23]. A comparison between Abo-BTX-A and control patients at baseline and at 3 months of follow-up performed by Manning et al., in 2014.

Based on their report, OLS questionnaires exhibited upgrading at 3 months. Only the O'Leary-Sant questionnaire consists of problem (OLS-PI) was improved in the AboBTXA group ($p=0.04$). At 3 months, no difference was found in either Leary-Sant questionnaire consisting of problem and symptom (OLS-SI) or total OLS score. Twelve patients had urinary tract infection (UTI) treated during the follow-up period, which confounded results. In the 38 patients without UTI, there was improvement in total OLS score ($p=0.02$), OLS-PI (0.08), and OLS-SI ($p=0.008$) for the Abo-BTX-A group at 3 months. Only five Abo-BTX-A compared with two control patients had a 50% reduction in OLS score [24].

Discussion

In recent years, there has been an augmented consideration in the use of BTX-A to treat medical conditions that were intractable to conservative management. According to publication by Dhaked et al. in 2010, botulinum neurotoxin approaches a main bioweapon hazard because of: 1) its dangerous strength and lethality, 2) its easiness of production, 3) carriage and waste, and 4) the need for protracted concentrated maintenance between pretentious individuals. A single gram of crystalline toxin, calmly spread and inhaled, can kill more than one million people. The source of the remarkable power of botulinum toxin is enzymatic. The toxin is a zinc proteinase that slashes neuronal vesicle related proteins accountable for acetylcholine release into the neuromuscular junction. A valuable feature of BTX study in modern years has been expansion of the strongest toxin into a molecule of important therapeutic usefulness. It is the first organic poison which is approved for dealing with human diseases [6]. Previous published articles suggested that BTX-A, could be effectual in cautiously selected group of patients and has negligible side effects profile and usually well accepted by numerous patients. BTX-A is the most commonly used for treatment of LUTs. Botox[®] is the onabotulinum toxin A (available in a 100 U or 200 U vials) that is available in United States. Dysport[®] is the abobotulinum toxin A (available in a 3000 unit or 5000 U vials) that is available in the Europe. 1 unit of onabotulinum toxin A is equivalent to approximately 3 to 5 unit of abobotulinum toxin A [2]. Under cystoscopic management, an injection of 300 units of Botox[®] (ranged from 100 to 400 units) in 30 injection sites (ranged from 15 to 40) of 10 units/ml (ranged from 6.7 to 25 units/ml) in the bladder, usually sparing the trigone has been reported by Karsenty et al, in 2008 [25]. Streeper et al. in 2016 based on periureteral injection of BTX-A for stone passage in the porcine model, stated that, BTX-A may offer a simple, office-based endoscopic management possibility for ureteral stones [26]. Investigation performed by Shim et al, in 2016, showed no differences in efficacy compared with placebo and also showed no difference in procedure-related adverse events occurred after BTX-A injection for LUTs/BPH (benign prostatic hyperplasia) [27]. El-Enen et al., in 2015 noted that BTX-A could be used as the more effective option in patients with small prostate and short symptom duration and could be prescribed for

management of patients with refractory chronic prostatitis-associated chronic pelvic-pain syndrome [28]. According to the meta-analysis of BTX-A in treating idiopathic detrusor overactivity patients, BTX-A significantly augmented post-void residual volume (32.77 vs. 2.01), proportions of urinary tract infection (19.69% and 5.94), and proportions of clean intermittent catheterization (8.41% and 0.46%) versus placebo [29]. Related to the age >61 years, low maximum flow rate, low voiding efficiency (a percentage of the voided volume compared to the pre-void bladder volume <90%), and large post-void residual volume at baseline were risk factors for these adverse events have been reported [30]. Finally clarification and recognition of patients signs with over active bladder that not well-managed with more traditional treatments need a talented decision to achieve the precise approach for the use of BTX-A injections. Additional investigations in Iranian population with such disorders seem to be advantageous.

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Conflict of Interest

The authors declare no conflicts of interest.

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