ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

Botulinum Toxin: Recent Advances in Treatment of Overactive Bladder

Tanmayee A Joshi*, Rohini S Chandratre, Minakshi Nehete and Prachi Mehendale

CU Shah College of Pharmacy, SNDT Women's University, Sir Vithaldas Vidya Vihar, Santacruz (W), Mumbai-400049.

ABSTRACT

Overactive bladder is characterized by increased urinary urge, incontinence, decreased bladder compliance, nocturia etc. This syndrome affects the quality of life tremendously. There are various approaches for the treatment of this syndrome such as anticholinergic drugs, drugs acting in CNS, Antidiuretic drugs with their own limitations. Use of Botulinum toxin is a comparatively new approach for the treatment, which is been tried recently, mostly in Europe and North America. Botulinum toxin inhibits release acetylcholine and thereby it decreases contractility. Using this property of Botox, there have been various studies conducted, showing results in favor of treatment by injections of botox in urinary bladder. This article discusses various pathophysiology of overactive bladder, various treatments for overactivity and case studies where botox has been used as main drug for the treatment.

Keywords: Botox, Bladder Overactivity, Idiopathic detrusor overactivity, Neurogenic detrusor overactivity, Incontinence.

Corresponding author

ISSN: 0975-8585

INTRODUCTION

Overactive bladder (OAB) refers to the common and bothersome group of storage lower urinary tract symptoms (LUTS). The International Continence Society (ICS) defines OAB syndrome as urgency with or without urge urinary incontinence (UUI), usually with frequency and nocturia. Prevalence rates for OAB are estimated to be approximately 12% in North America and Europe. Both men and women are equally affected by OAB, and the incidence rates increases with age OAB can be managed with bladder and behavioural training, biofeedback, electrical stimulation, pharmacologic treatments, or with a combination of therapies [1]

Anatomy of Lower Urinary Tract

The lower urinary tract has two main functions: storage and periodic elimination of urine. These two functions are regulated by a complex neural control system involving a central pathway located in the spinal cord, pons, and brain as well as by the peripheral autonomic and somatic neural pathways.

This control system functions like a switching circuit to maintain a reciprocal relationship between the bladder and outlet components of the lower urinary tract.

The storage and periodic elimination of urine depend on the reciprocal activity of two functional units in the lower urinary tract: a reservoir, the bladder, and an outlet represented by the bladder neck and the smooth and striated sphincter muscles of the urethra. During urine storage (Fig. 1), the bladder outlet is closed and the bladder smooth muscle is quiescent. This state allows intravesical pressure to remain low over a wide range of bladder volumes. During voluntary voiding (Fig. 2), the initial event is relaxation of the pelvic floor and striated urethral muscles, followed by a contraction of the detrusor muscle and opening of the bladder neck. This activity is mediated by three sets of peripheral nerves: parasympathetic (pelvic), sympathetic (hypogastric), and somatic (pudendal) nerves [2, 3].

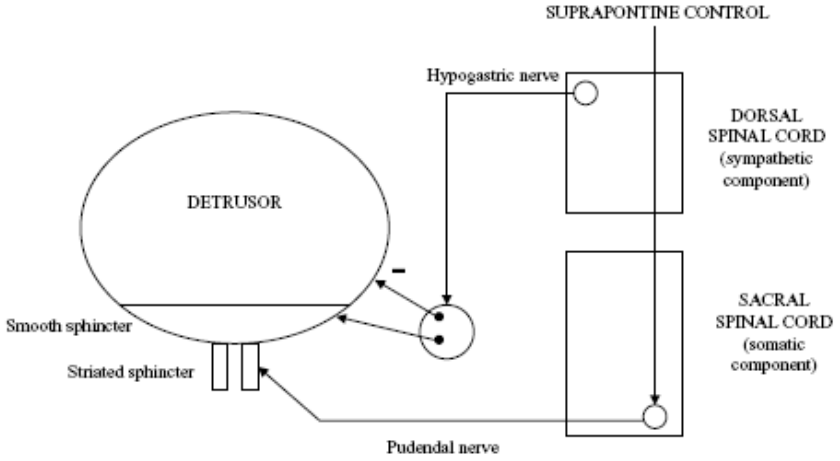

Figure1: Storage Reflexes [2]

ISSN: 0975-8585

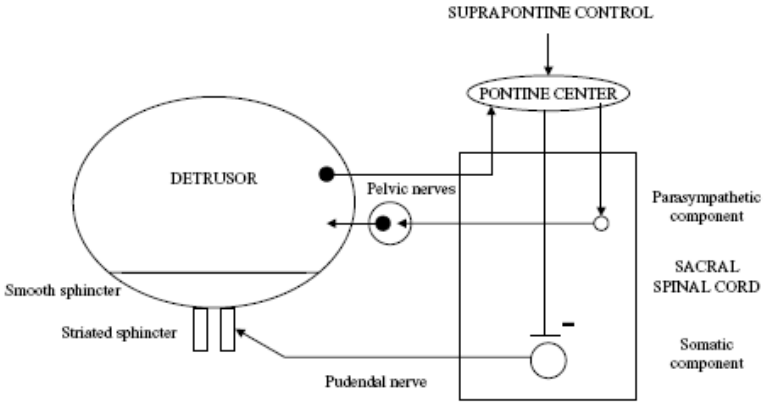

Figure 2: Voiding reflexes. [2]

These nerves also contain afferent axons that terminate in the lower urinary tract and are involved in initiating micturition.

Micturation Reflex

Micturation occurs via combination involuntary and voluntary muscle contractions. When the volume of urine in the urinary bladder exceeds 200-400 ml, pressure within bladder increases considerably, and stretch receptors in its wall transmit nerve impulses into spinal cord. These impulses propogate to micturation centre in sacral spinal cord segments S2 and S3 and trigger a spinal reflex called micturation reflex.

In the reflex arc, parasympathetic impulses from the micturation centre propogate to the urinary bladder wall and internal urethral sphincter. The main neurotransmitter released by the parasympathetic postganglionic nerve terminals is acetylcholine. The nerve impulses cause contraction of detrusor muscle. Sympathetic postganglionic terminals release norepinephrine, which acts on alpha-1 vesical and urethral receptors and beta-2 adrenergic detrusor receptors. The effect of norepinephrine on the former is a contraction of the bladder base and urethral smooth muscle. Simultaneously, the micturation center inhibits somatic motor neurons that innervate skeletal muscle in external urethal sphincter. Upon contraction of urinary bladder wall and relaxation of sphincters, urination takes place [3, 4].

Physiology of Continence

Norepinephrine, via an action of the Beta-2 receptors, can also relax the body of the bladder. Somatic afferent pathways that originate from the motoneurons in the Onuf nucleus of the anterior horn of the spinal cord from S2 to S4 innervate the external striated urethral sphincter muscle and the pelvic floor musculature. Somatic nerve terminals release acetylcholine, which acts on nicotinic receptors to induce a muscle contraction. The striated urethral sphincter also receives noradrenergic input from the sympathetic nerves. The

combined activation of the sympathetic and somatic pathways elevates the resistance of the bladder outlet and contributes to urinary continence [2-4].

Pathophysiology of overactivity of detrusor muscle

The parasympathetic system (S2, S3 and S4) is the motor nerve supply to the bladder and affects the intensity of detrusor contractions. The sympathetic innervation is derived from the hypogastric nerve and acts mainly on beta receptors resulting in relaxation of the detrusor muscles. While the pathophysiology of the overactive bladder is not yet fully understood, the two most widely accepted explanations are the myogenic and neurogenic theories. In the myogenic theory, partial denervation of the detrusor muscle is believed to alter of the properties of the smooth muscle, leading to increased excitability resulting in contractions of the detrusor muscle. Contractions are likely to occur as a result of acetylcholine release from the bladder. This is why anticholinergic medications suppress abnormal contractions but do not lead to paralysis of bladder contractions mediated through the pudendal nerve for voiding. The neurogenic theory involves changes in CNS pathways that inhibit bladder activity and/or over-sensitivity of the sensory nerve endings in the bladder. This is mediated by acetylcholine acting on muscarinic receptors at the level of the bladder. There are currently five recognized subtypes of muscarinic receptor; the M1, M2, and M3 subtypes are of interest in bladder activity. Muscarinic receptors are also found in other parts of the body (e.g. gut, salivary glands, tear ducts). In both theories, the outcome is over activity of the detrusor muscle [5].

Types of Overactive Bladder Syndrome

A) Neurogenic Detrusor Overactivity (NDO)

Involuntary detrusor contractions, as a result of neurologic pathway interruption, are the hallmark of the neurogenic bladder dysfunction. As a result of these uninhibited contractions, pressures in the bladder can rise to dangerous levels, predisposing patients to infection, causing incontinence and, if severe, causing vesico ureteral reflux and renal damage.

B) Idiopathic detrusor overactivity (IDO)

It is usually idiopathic in origin. Much like neurogenic bladder dysfunction, this condition is characterized by frequent uninhibited contractions of the bladder but due to the intact ability to void with urge; this does not usually result in dangerous pressure elevations within the bladder [6, 7].

TREATMENT APPROACHES FOR OVERACTIVE BLADDER
Anticholinergic agents

In the treatment of the OAB syndrome, the following antimuscarinic atropine-like drugs are the most commonly used.

Oxybutynin

Oxybutynin has a direct spasmolytic effect along with anticholinergic properties. The dosage must often be adapted to the individual patient in relation to her tolerance. Its systemic antimuscarinic action, with effects on the gastroenteric tract and on the lachrymal glands, is the major cause for the therapy having been abandoned. Oxybutynin is usually prescribed at the dosage of 5 mg twice a day with the possibility to increase up to 10 mg three times a day. The use of slow release systems of oxybutynin could improve patient compliance when compared to the immediate release formulation, although some data are controversial [8].

Trospium chloride

Trospium chloride is an antimuscarinic drug with a variable absorption. It lacks selectivity for the bladder and the clinical evidence for its efficacy and tolerance in treating OAB syndrome is still poor [8].

Tolterodine

Tolterodine is the newest antimuscarinic on the market at present with an efficacy of 50% in the treatment of OAB syndrome. It is characterised by a greater selectivity for the lower urinary tract compared to oxybutynin; this determines a significant decrease in side effects allowing a better treatment compliance in the long term, even when slow release formulations are compared, maintaining an effective treatment aound 50%. This allows improved compliance for long term pharmacologic therapy [8].

Limitations of Antimuscarinic drugs

Antimuscarinic drugs lack selectivity for bladder receptors. The non bladder actions can contribute to adverse effects. For example, in salivary glands, both M1 and M3 receptor subtypes control secretion. In the cardiovascular system, the postjunctional M2 receptor subtype can produce parasympathetically mediated bradycardia and a decrease in cardiac output, which is due mainly to a reduction in the rate of contraction of the atria. In the brain, the role of postsynaptic cortical M1 receptors in cognitive processing is well documented, and M1-receptor blockade centrally would be expected to compromise CNS functions. For gastrointestinal motility, M3 receptors are especially important [9].

Drugs to decrease contractility

Imipramine

Imipramine is a tricyclic antidepressant which inhibits the re-uptake of noradrenaline and 5-idrossitriptamine in the presynaptic membranes, increasing their action in this way. It has a relaxing effect on the bladder and increases urethral resistance to flow. It also has anticholinergic and local anaesthetic properties. Imipramine is used in the treatment of

nocturnal enuresis and nocturia but it is limited by its anticholinergic and cardiac side effects [8].

Antidiuretic drugs

1-Desamino-8-D-arginin-vasopressina (DDAVP)

1-Desamino-8-D-arginin-vasopressina (DDAVP) is a long acting synthetic analogue of vasopressine, prescribed by intranasal spray. It has an antidiuretic effect and it is useful in the treatment of nocturia and nocturnal enuresis. It is a drug with proved long term safety, although it must be used with caution by patients with coronary heart disease, hypertension, cardiac insufficiency or epilepsy [8].

Drugs Targeting CNS

Naftopidil, an α-adrenergic receptor, may inhibit bladder activity in rats by targeting the lumbosacral cord. The antidepressant reboxetine , a selective NE reuptake inhibitor (selective NRI), which has minimal affinity for muscarinic ACh receptors and therefore causes less dry mouth, is being tested in a phase 2 trial for mixed urinary incontinence by Pfizer and it might be another alternative agent. The CNS opioid receptor system is a potential target of pharmacologic research because morphine and analogues have profound inhibitory effects on the micturition reflex. Tramadol, a opioid receptor ligand, which inhibits NE and serotonin reuptake, has promising effects on micturition in preclinical studies. In rats it inhibits cerebral infarctioninduced detrusor overactivity and counteracts the excitatory effects of apomorphine in other animals [10].

Evidence from laboratory studies on the potential of drugs acting on the serotonin receptor system is controversial. In humans, exposure to selective serotonin reuptake inhibitors (SSRIs) is associated with increased risk of urinary incontinence especially in elderly users of sertraline. Fluoxetine, a widely prescribed SSRI for depression, seems to inhibit detrusor activity. Capeserod hydrochloride, a 5-hydroxytriptamine 4 (5-HT4) receptor agonist, which has been tested as treatment for Alzheimer's disease, is under investigation by Sanofi-Aventis as therapy for urgency urinary incontinence in humans. To date, no convincing evidence exists to show SSRIs are effective in the treatment of OAB. Duloxetine, a serotonin-NRI, is approved by the European Medicine EvaluationAuthority (EMEA) for the treatment of female stress urinary incontinence (SUI) [10].

Intravesical Treatment

Intravesical agents appear to be, in some cases, alternatives to oral medication. All these local treatments resulting in bladder paresis are only recommended for patients performing intermittent catheterization.

Vanilloids drugs such as capsaicin and resiniferatoxin have showed some promising results. Capsaicin-sensitive bladder afferents contribute to hyperactivity of the bladder in neurogenic and nonneurogenic detrusor overactivity. Capsaicin is a specific neurotoxin that desensitizes afferent C-fibers that may be responsible for the signals that trigger detrusor overactivity. Resiniferatoxin is a less pugent agent that desensitizes capsaicin afferent C-fibers but fails to depolarize nerves. It may be associated with fewer local side effects than capsaicin, which is associated with pain. This type of temporary deafferentation is contraindicated in case of residual urine volume or vesicoureteric reflux. The efficacy of vanilloids has been shown, particularly in patients with detrusor hyperreflexia related to multiple sclerosis but also in patients with idiopathic detrusor hyperactivity [2].

USE OF BOTOX IN TREATMENT OF OVERACTIVE BLADDER DUE TO OVERACTIVE DETRUSOR MUSCLE

Botulinum toxins are synthesized within the bacterial cytosol as single chain peptides with a molecular weight of around 150 kDa. Proteolytic cleavage of parent chain results in a dichain polypeptide form, consisting of 100 kDa heavy chain and a 50 kDa light chain that remains linked by a non-covalent protein interaction and a disulphide bond, essential for neurotoxicity. Seven serologically distinct Botulinum neurotoxin types A–G have been isolated. However, only type A and B are commercially available and in clinical use. BTX-A is available as Botox1 (Allergan, Inc., Irvine, CA, USA) in the USA and Dysport1 (Ipsen Ltd., Slough, Berkshire, UK) in the UK [11].

The heavy chain of the toxin is particularly important for targeting the toxin to specific types of axon terminals. The toxin must get inside the axon terminals in order to cause paralysis. Following the attachment of the toxin heavy chain to proteins on the surface of axon terminals, the toxin can be taken into neurons by endocytosis. The light chain is able to cleave endocytotic vesicles and reach the cytoplasm. The light chain of the toxin has protease activity. The type A toxin proteolytically degrades the SNAP-25 protein, a type of SNARE protein. Normally at the neuromuscular junction, motor nerve endings contain acetylcholine-filled synaptic vesicles which fuse with the neuronal cell membrane through a 'docking' process. It is facilitated by a complex of proteins known as soluble N-ethylmaleimide sensitive factor attachment receptor (SNARE) proteins. These proteins anchor the synaptic vesicles membrane to the neuronal cell membrane by forming a complex known as a synaptic fusion complex. It releases acetylcholine into the synaptic space which binds to the receptors on the muscle cells to cause contractions. The SNAP-25 protein is required for the release of neurotransmitters from the axon endings. Botulinum toxin specifically cleaves these SNAREs, and so prevents neuro-secretory vesicles from docking/fusing with the nerve synapse plasma membrane and releasing their neurotransmitters [11].

CASE STUDIES

Various parameters are measured to determine effectiveness of drug, in case of treatment of overactive bladder.

Bladder Reflex Volume: It is the volume when first inhibited contraction occurs.

Maximum Cystometric Bladder Capacity (MCBC): The volume at when a patient with normal sensation, feels that he/she can no longer delay micturation.

Functional Bladder Capacity: Largest single volume voided during 24 hour period.

Bladder Compliance: Change in volume of bladder for a given change in pressure.

In a study reported by Vinay Kalsi et.al. 24 patients with mean age of 45, were evaluated in which 16 were suffering from NDO and 8 were suffering from IDO. Dose used for NDO patients was 300mu whereas for IDO patients it was 200mu. After 4 weeks it was found that for IDO patients urgency decreased from 8.1 to 2.6, day time frequency decreased from 9.9 to 5.7 and nocturia decreased from 1.5 to 0.5. For IDO patients' urgency decreased from 9.3 to 1.9, day time frequency decreased from 9.9 to 6.3 and nocturia decreased from 1.7 to 1.2 [12].

Another small study is reported by Heinrich Schulte et.al. 7 women with mean age of 61.1 were evaluated and 300U of Botox were injected. In a period of 6 months it was found that urgency decreased from 8.1 to 7.4, daytime frequency decreased from 8.1 to 7.4 and nocturia decreased from 1.9 to 2.7 [13].

A study on 20 patients was performed by Andre Reitz et al, in which there were 13 males and 7 females with mean age of 41.1 years. 300 units of botulinum toxin were injected. Reflex volume was found to be increased from 195 to 252, bladder capacity increased from 216.5 to 500, and overactivity percentage decreased from 1 to 0.25 [14].

A large study was performed on 200 patients in various European medical centers by Andre Reitz et.al. 300 units of botulinum toxin were injected. After 12 weeks it was found that MCBC increased from 272 ml to 420 ml, reflex volume increased from 236 ml to 387 ml and bladder compliance increased from32 ml/cm H_2O to 72 ml/cm H_2O. For 99 patients bladder a second follow up study was performed , in which it was found that bladder capacity increased from 272 to 352, reflex volume increased from 236 to 291, voiding pressure decreased from 61 cm of H_2O to 44 cm of H_2O. For second follow up 72 patients out of them reported complete continence whereas 27 reported recurrent incontinence, after 36 weeks [15].

Mohanty et al performed a study on 39 patients with mean age of 52; dose of Botox was 200 units. After a period of 9 months it was found that urgency disappeared in 80% of the patients, frequency of urination decreased from 15 to 6, bladder capacity increased from 205 ml to 290 ml and detrusor pressure decreased from 61 cm H_2O to 40 cm H_2O [16].

Giulio et al performed study on 199 patients suffering from NDO with mean age of 42.5 years; dose of botox was 750 IU. Within 3 weeks they observed that MCBC increased from 226 ml to 380 ml, reflex volume increased from 201ml to 297 ml and bladder compliance increased from 26.7 ml to 41 ml [17].

ISSN: 0975-8585

Another study was performed by Grosse et.al on 66 patients suffering from NDO with mean age of 38.5 years, 300 IU of botox was injected. It was found that continence volume increased from 220 ml to 500 ml, functional bladder volume increased from 300 ml to 420 ml, maximal bladder volume increased from 380 ml to 610 ml, MCBC increased from 300 ml to 420 ml, reflex volume increased from 200 ml to 380 ml and bladder compliance increased from 280 ml to 450 ml [18].

Above case studies are depicted below in tabular format.

Author	No of patients	Mean age	Dose	Results	Period of Observation
Vinay Kalsi et.al	24 in which 16 NDO and 8 IDO	45	300 mu for NDO and 200 mu for IDO	Urgency decreased by 68% for NDO patients and by 80% for IDO patients. Daytime frequency decreased by 42% for NDO patients and by 36%. Nocturia decreased by 66.6% for NDO patients and by 29.4% for IDO patients.	Four Weeks
Heinrich Schulte et.al	07	61.1	300U	Urgency decreased by 8.6 %, Daytime frequency decreased by 8.6%, and Nocturia decreased by 85.7%	Three Months
Andre Reitz et.al.	20	41.1	300U, Repeat dose study	Reflex volume increased by 29%, Bladder capacity increased by 130% and overactivity decreased by 25%.	-
Andre Reitz et.al	200		300U	MCBC increased by 29%, reflex volume increased by 25%, voiding pressure decreased by 28%.	Twelve Weeks
Mohanty et.al	39	52	200U	Urgency disappeared in 80% of patients, frequency decreased by 60%, bladder capacity increased by 60% and detrusor pressure decreased by 34.4%.	Nine Months
Giulio et.al	199 with NDO	42.5	750IU	MCBC increased by 68%, reflex volume increased by 48% and bladder compliance increased by 53.5%.	Three Weeks
Grosse et.al	66 with NDO	38.5	300IU	Continence volume increased by 127%, functional volume increased by 40%, maximal volume increased by 60%, MCBC increased by 40%, reflex volume increased by 90% and compliance increased by 60.7%.	Three Weeks

CONCLUSION

Current management of both idiopathic and neurogenic detrusor overactivity is focused on either medical management with anticholinergic medications or more invasive measures such as bladder augmentation and nerve stimulation to decrease the debilitating symptoms of detrusor dysfunction. However, when medical management fails and surgery seems excessive, alternative treatment options are needed. In the search for alternative measures, Botulinum toxin-A has emerged as a promising option. Studies to date have shown that not only is this treatment effective at decreasing urinary symptoms and incontinence, as well as improving potentially dangerous urodynamic measures, but it is also minimally invasive, reversible and safe.

ISSN: 0975-8585

REFERENCES

[1] Steers WD. Eur Urol Suppl 2002; 1: 3-10.
[2] Vignes JR, Gimbert E, Sessay M, Seze MD, Guerin. G, Joseph PA. Oper Tech Neurosurg 2005; 7: 163-174
[3] Sugaya K, Nishimuja S, Miyazato M, Ogawa Y. J Smooth Muscle Res 2005; 3 (41):117-132.
[4] Tortora JG, Derrickson BH, The urinary system In Principles of anatomy and physiology, John Wiley & Sons Inc;2009.p. 1019-1061.
[5] Foon R, Toozs-Hobson P, Detrusor overactivity, Obsterics, Gynaecology and Reproductive Medicine 2009; 7(9): 255-260.
[6] Casanova N, McGuire E, Fenner, DE. Int J Gynaecol Obstet 2006; 95: 305-311
[7] Smith CP. Toxicon 2009;54:639-646
[8] Salvatore S, Soligo M, Proietti F, Citterio S, Artibani W, Milani R. Eur J Obstet Gynecol Reprod Biol 2005; 120: 129-133
[9] Anderson KE. The Lancet Neurology 2004; 3: 46-53.
[10] Lazzeri M, Porena M. EAU-EBU Update Series 2007; 5: 205-258.
[11] Sinha D, Karri, K, Arunkalaivanan AS. Eur J Obstet Gynecol Reprod Biol 2007; 133: 4-11
[12] Kalsi V, Apostodilis A, Gonzales G, Elneil S, Dasgupta P, Fowler C. Eur Urol 2008; 54: 181-187
[13] Schulte-Baukloh H, Weiss C, Stolze T, Sturzebecher B, Knispel H. Urology 2005; 66: 82-87.
[14] Reitz A, Denys P, Fermanian C, Scurch B, Comperat E, Chartier-Kastler E. Eur Urol 2007; 52: 1729-1735.
[15] Reitz A, Stohrer M, Chartier-Kastler E, et.al. Eur Urol 2005; 45: 510-515.
[16] Mohanty NK, Nayak RL, Alam M, Arora RP. Indian J Urol 2008; 24: 182-185.
[17] Popolo DG, Filocamo MT, Marzi VL, et.al. Eur Urol 2008; 53: 1013-1020.
[18] Grosse J, Kramer G, Stohrer M. Eur Urol 2005; 47: 653-659.