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The Unusual History and the Urological Applications of Botulinum Neurotoxin

Key Words

Botulinum neurotoxin • Detrusor overactivity • Detrusor-sphincter dyssynergia • Historical aspects • Prostate • Urology

Abstract

Introduction: Botulinum neurotoxin (BoNT) is probably the most potent biological toxin that can affect humans. Since its discovery by Justinus Kerner, BoNT has seen use in a wide range of cosmetic and non-cosmetic conditions such as cervical dystonia, cerebral palsy, migraines and hyperhidrosis. We tried to trace its history from its inception to its recent urological applications. **Materials and Methods:** Historical articles about botulinum toxin were reviewed and a Medline search was performed for its urological utility. We hereby present a brief review of historical aspects of BoNT and its applications in urology. **Results:** In 1793, the first known outbreak of botulism occurred due to 'spoiled' sausage in Wildebade, Germany. The German physician and poet Justinus Kerner published the first accurate description of the clinical symptoms of botulism (sausage poison). He was also the first to mention its potential therapeutic applications. In urology, BoNT has been used in bladder and urethral lesions with varying degree of success. Recently, BoNT applications were explained for prostatic disorders. BoNT applications in urology are in the treatment of detrusor external sphincter dyssynergia, detrusor overactivity, detrusor underactivity, spastic conditions of the urethral sphincter, chronic prostate pain, interstitial cystitis, non-fibrotic bladder outflow obstruction (including benign prostatic hyperplasia) and acute

urinary retention in women. **Conclusion:** Justinus Kerner is the godfather of botulism research. The role of BoNT in urology has evolved exponentially and it is widely used as an adjuvant in voiding dysfunction. In the future, its utility will broaden and guide the urologist in managing various urological disorders.

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Introduction

Though the existence of botulinum neurotoxin (BoNT) has been known for centuries, its positive effects have been appreciated in recent decades. At present, BoNT is in use or under study in more than 70 countries worldwide. We have aimed to describe the transition of BoNT from a poorly understood poison to an actively researched novel therapeutic agent. This article reveals an interesting history of the evolution of BoNT from poison to a healing agent and summarizes the current practice of this exciting agent within the urologic community [1].

Materials and Methods

A Web-based search was performed for the historical aspects of BoNT and its applications in the medical field. Historical manuscripts from medical and pharmaceutical journals were cross-referenced. Concerning general applications, various articles were reviewed to assess the utility of BoNT in other medical specialties. Concerning urological applications, a Medline search was performed to obtain the application of BoNT in urology.

Fig. 1. Justinus Kerner (godfather of BoNT research).

Many manuscripts were reviewed to define the use of botulinum toxin in detrusor overactivity, underactivity and detrusor-sphincter dyssynergia. In addition, its efficacy in treating prostatic disorders was evaluated.

Results

Botulism-like illness was described by the ancient Greeks and Egyptians. Emperor Leo IV, Byzantium (886–911 AD), banned the ‘blood sausage’ as it caused fatal illness. The journey of BoNT from toxin to therapy is thought-provoking and its urology timeline is inspiring (tables 1, 2).

In 1793, the first documented outbreak of botulism occurred in Wildebad, Germany. Johann Heinrich Ferdinand Autenreith, a medical professor at the University of Tübingen, was one of the first people to begin researching the sausage poison. He requested family practitioners and health officers to report cases of food poisoning. One of the medical officers that responded to Autenreith’s request was Justinus Kerner and together they published their observations in 1817 in the *Tübingen Papers for Natural Sciences and Pharmacology* [2].

Justinus Kerner (fig. 1) is often referred to as the godfather of BoNT research, as he devoted a great deal of his life to exploring the nature of this sausage poison. In 1820, Kerner [3] published his first monograph on sausage poisoning entitled ‘New observations on the lethal poisoning occurring so frequently in Württemberg

Table 1. Timeline for BoNT

886 AD	Emperor Leo IV	banned ‘blood sausage’ as it caused fatal illness
1822	Justinus Kerner	sausage poison (possible therapeutic use)
1870	Müller	botulism (Latin: botulus) for sausage
1895	Van Ermengem	<i>Clostridium botulinum</i> (causative agent of botulism)
1919	G.S. Burke	minimum lethal dose: guinea pigs
1928	Herman Sommer	BoNT (purified) isolation
1946	Carl Lamanna Edward Schantz	LD50 test: neurotoxin activity BTA in crystalline form
1949	Arnold Burgen	neuromuscular transmission blockade
1950s	Vernon Brooks	BTA: blockade of acetylcholine from motor nerve endings
1960s	Schantz/Scott	strabismus: monkeys
1980	Scott	strabismus: humans
1984	FDA	designates BTX for blepharospasm in adults
1986	FDA	designates BTX for cervical dystonia
1987	–	cosmetic benefit
1988	Allergan	Oculinum (BTA): clinical trials
1989	FDA Allergan	Oculinum (BTA): strabismus, blepharospasm and dystonia buys Oculinum and renames as BTX
1993	–	SNAP-25: molecular target of botulinum toxin type A
2000	FDA	approves BTX for cervical dystonia
2001	–	BTX for cosmetic procedures (Canada and New Zealand)
2002	FDA	approves BTX for cosmetic therapy BTX (Australia, Switzerland, Taiwan and Singapore)
2003	–	BTX as VISTABEL® (France)
2004	FDA	BTX for primary axillary hyperhidrosis

through the consumption of smoked sausages’. Later on he began animal experiments and even experiments on himself to isolate the unknown toxin from sausages which he referred to as ‘sausage poison’ or ‘fatty acid’. These results were published in a second monograph in 1822 en-

Table 2. Urology timeline for BoNT

1988	Dykstra et al. [10]	first to describe BTX-A in spinal cord injury and detrusor sphincter dyssynergia patients
1996	Schurch et al. [11]	transperineal injection of botulinum toxin
1998	Doggweiler [45]	Botox-induced prostatic involution
1998	Wheeler et al. [26]	BTX-A injections for voiding dysfunction following spinal cord injury
2000	Zermann et al. [36]	perisphincteric injection of BTX-A for chronic prostatic pain
2001	Phelan et al. [24]	BTX-A in voiding dysfunction
2002	de Seze et al. [27]	double-blind lidocaine-controlled study of BTX-A in detrusor sphincter dyssynergia
2002	Smith et al. [1]	Botulinum toxin treatment of urethral and bladder dysfunction
2003	Kuo [15]	treatment of voiding dysfunction due to detrusor underactivity
2003	Maria et al. [37]	randomized, placebo-controlled study in benign prostatic hyperplasia
2004	Flynn et al. [17]	BTX-A in severe urge urinary incontinence
2004	Reitz et al. [14]	BTX-B for management of type A resistant neurogenic detrusor overactivity
2006	Chuang et al. [40]	intraprostatic injection of BTX-A relieves bladder outlet obstruction in humans

titled ‘The fat poison or the fatty acid and its effects on the animal organism, a contribution to the examination of the substance which acts toxically in bad sausages’ [4].

The most exciting of all Kerner’s work with the sausage poison were the experiments he carried out on himself. He placed a few drops of the toxin-containing extract on his tongue and reported that the toxin tasted sour and caused drying out of the palate and pharynx. These experiments were stopped after a warning from his former teacher, Professor Autenreith. In spite of failure to isolate or synthesize pure toxin, Kerner was able to speculate on the nature of the toxin and the pathophysiology of sausage poisoning, and suggested that the toxic substance is in the fat. Kerner also reported that the effects of this poison were similar to other known poisons such as atropine (anticholinergic) and snake venom. He therefore con-

cluded that the fat poison was most likely biological [4]. He inferred that the toxin acts by interrupting the signal transmission within the peripheral and autonomic nervous system. In his writing, Justinus Kerner gave a remarkably complete and accurate description of clinical botulism: its symptoms, time course and the physical findings that the tear fluid disappears, the skin is dry, the eye, gut and somatic muscles are paralyzed, and mucus and saliva secretion is suppressed [4].

Major conclusions made about the sausage poison by Kerner were the etiology of sausage poisoning, in that the toxin develops in spoiled sausages under anaerobic conditions. As a result, he suggested that sausages should be boiled long enough and stored under aerobic conditions. He also mentioned that the toxin is lethal in small doses. Kerner also discussed the idea of a therapeutic use of this toxin and concluded that in very small doses, the toxin could decrease or block the hyperactivity of the sympathetic nervous system, which at the time covered all nervous functions [4].

Later, a German physician named Müller referred to the sausage poisoning as ‘botulism’ from the Latin word *botulus*, which means sausage. Prof. Emile Pierre van Ermengem, of Ellezelles, Belgium identified the bacterium *Bacillus botulinum*, later named *Clostridium botulinum* [5]. In the 1920s, Dr. Herman Sommer at the University of California, San Francisco [6], was the first to isolate the BoNT type A in a purified form as stable acid precipitate. This provided the raw material for future studies. The glory of purifying BoNT type A in crystalline form goes to Edward J. Schantz and colleagues [7] in 1946. Dr. Vernon Brooks discovered the temporary paralysis of hyperactive muscle by blocking the release of acetylcholine from motor nerve endings [7]. This breakthrough sparked new interest in BoNT as a potentially valuable therapeutic agent. In the past two decades, growing interest in the medical use of BoNT has been fueled by the demonstration of its therapeutic usefulness and safety.

General Applications

In the 1960s and 1970s, Dr. Schantz and Alan B. Scott tested BoNT in monkeys to determine its use in ocular strabismus [7, 8]. Later, Scott [8] reported its use to correct strabismus in humans. Since then, BoNT-A has been used in the treatment of neurologic and non-neurologic disorders. BoNT-B is under trial to assess its clinical effectiveness around the globe. In 1989, the FDA approved Oculinum for strabismus, blepharospasm and hemifacial spasm in patients older than 11 years. Other uses of BoNT range from palatal myoclonus, achalasia, gustatory sweating,

Table 3. Current and potential applications of BoNT [44]

Urethra	Bladder
Detrusor sphincter dyssynergia	Detrusor overactivity
Pelvic floor spasticity	Neurologic detrusor overactivity
Post bladder neck suspension retention	Detrusor underactivity
Prostatitis	Sensory urgency
Benign prostatic hyperplasia	Interstitial cystitis
Bladder neck obstruction and dyssynergia	

tennis elbow and cervical dystonia. There has been growing interest in the use of BoNT in cosmetic applications, such as correction of wrinkles and frown lines. Dodick et al. [9] showed that BoNT-A is an effective and well-tolerated prophylactic treatment in migraine patients with chronic daily headache who are not using other prophylactic medications. Finally, BoNT is being increasingly used in the treatment of focal hyperhidrosis. The safety, effectiveness, specificity and reversibility of BoNT make it a powerful and versatile tool in a wide variety of neuromuscular disorders, and it is likely that the applications of BoNT therapy will continue to expand in the future.

Urology Applications of BoNT

In urology, BoNT is being used for idiopathic and neurogenic detrusor overactivity. Presently, there are various studies to assess the effectiveness of BoNT types A and B in voiding dysfunction (tables 2, 3). Dykstra et al. [10] were first to describe the injection of BoNT serotype A into the external urethral sphincter in men with spinal cord injury and detrusor-sphincter dyssynergia. Over the next two decades, there was rapid progress in the research to assess the urological application of BoNT. Schurch et al. [11] reported the application of BoNT-A in detrusor-sphincter dyssynergia and neurogenic detrusor hyperactivity in spinal cord injury patients.

Bladder and Urethra

Detrusor Overactivity. Detrusor overactivity is a major cause of urinary incontinence in patients with spinal cord injury, multiple sclerosis, myelomeningocele and spina bifida. Available treatment options for these patients range from simple anticholinergics with clean intermittent self-catheterization to bladder augmentation or urinary diversion [12, 13]. BoNT-A injections into the detrusor muscle provided beneficial clinical and urodynamic results with reduction of detrusor overactivity and restoration of urinary continence in most of these patients. In

a large multicentre study, Reitz et al. [14] showed good improvement of bladder function and subjective satisfaction following BoNT-A injections in patients with detrusor overactivity. Also, they confirmed that this new treatment is safe and valuable.

Detrusor Underactivity. Kuo [15] investigated the effectiveness of botulinum A toxin in the treatment of various types of lower urinary tract dysfunction and showed that urethral injections of 50 or 100 units of BoNT-A effectively decreased urethral sphincter resistance in patients. Furthermore, the same group demonstrated the effectiveness of BoNT-A in patients with detrusor underactivity and difficult urination [16]. Flynn et al. [17] reported a decrease in urge urinary incontinence and improved quality of life for 3 months following injection of BoNT in patients with severe urge urinary incontinence. Mokhless et al. [18] evaluated BoNT injection into the urethral sphincter in children and concluded that it was a reliable treatment modality in children with neurogenic bladder after the failure of conservative therapy. Schurch et al. [19] demonstrated that BoNT-A injections are well tolerated and can provide improvements in urinary incontinence caused by neurogenic detrusor overactivity of spinal cord origin. Giannantoni et al. [20] showed clinical and urodynamic improvement in continence (88%) following BoNT-A intradetrusorial injections for refractory neurogenic detrusor overactivity in spinal cord injury patients. Various researchers [21–23] have suggested that repeat intradetrusor BoNT-A injections are a safe and valuable option for neurogenic detrusor overactivity.

Detrusor-Sphincter Dyssynergia. Phelan et al. [24] demonstrated subjective improvement in voiding following BoNT-A injection into urethra in voiding dysfunction patients and concluded that BoNT injection should be considered for complex voiding dysfunction. Gallien et al. [25] described the treatment by transperineal injections of BoNT for detrusor sphincter dyssynergia, and

showed an increase of functional detrusor capacity and a decrease of maximal detrusor pressure during voiding. Since then, various studies have demonstrated the use of BoNT in detrusor sphincter dyssynergia [26–28]. Cruz and Silva [29] concluded that urethral BoNT injections may improve bladder emptying in patients with dysfunctional voiding problems besides detrusor external sphincter dyssynergia. Injection of BoNT is safe and effective in the treatment of detrusor-sphincter dyssynergia, non-neurogenic pelvic floor spasticity and refractory overactive bladder. Urodynamic assessment after sphincter injection with BoNT reveals a decrease of bladder voiding pressure, urethral pressure profile and post-void residual urine. An increase of the functional bladder capacity and a decrease of the bladder voiding pressure can be seen after bladder injection with BoNT. In addition, BoNT-A treatment inhibits afferent-nerve-mediated bladder contraction. BoNT is a promising treatment for lower urinary tract dysfunction with profound basic and clinical implications [30]. Pannek et al. [31] demonstrated the long-term efficacy of BoNT-A in neurogenic detrusor overactivity. On the contrary, Schulte-Baukloh et al. raised the important subject of BoNT-A antibodies and therapy failure after long-term use of BoNT-A [32].

Interstitial Cystitis and Painful Bladder Syndrome. Smith [33] explored the role of BoNT in interstitial cystitis and reported on phase II and phase III clinical trials as a therapeutic agent in overactive bladder and benign prostatic hyperplasia. Kuo and Chancellor [34] produced improved results with intravesical injections of BoNT-A followed by hydrodistension than with hydrodistension alone in patients with interstitial cystitis/painful bladder syndrome. Giannantoni et al. [35] demonstrated medium-term efficacy of BoNT-A in patients with painful bladder syndrome.

Prostate

Zermann et al. [36] demonstrated subjective and urodynamic improvements following transurethral perisphincteric injection in patients with chronic non-bacterial prostatitis with lower urinary tract symptoms due to external sphincter spasticity. More recently Maria et al. [37] concluded that BoNT injection into the prostate is a promising approach for the treatment of benign prostatic hyperplasia. It is safe, effective and well tolerated. A prospective study by Kuo [38] concluded that it is an effective alternative treatment with minimal adverse effects for patients with benign prostatic obstruction who are poor surgical candidates or in whom medical treatment has failed. Chuang et al. [39] showed remarkable increases in

maximal flow rate by injection of BoNT-A in patients with small prostates and symptomatic benign prostatic hyperplasia, and demonstrated an increase in apoptotic activity. Also, BoNT-A injection into the prostate alters cellular dynamics by inducing apoptosis, inhibiting proliferation and downregulating α (1A) adrenergic receptors. It might be a potential drug with dual action both on the static and dynamic components of benign prostatic hyperplasia [40]. Silva et al. [41] used BoNT in frail elderly patients with refractory retention and showed prostate volume reduction and marked symptomatic improvement. Intraprostatic injection of BoNT-A improved lower urinary tract symptoms due to refractory benign prostatic hyperplasia [42, 43].

Conclusion

The history of BoNT from poison to a healing agent is intriguing. BoNT is the most poisonous substance known to man (LD50). The research in this area has seen a shift from characterizing the toxic substance to understanding its clinical efficacy. In 1822, Justinus Kerner, the godfather of botulism research, first realized the clinical potential of this toxin and hypothesized that in small doses, the agent responsible for ‘sausage poisoning’ would decrease or eliminate the hyperactivity of the sympathetic nervous system. BoNT therapy promises a number of novel therapeutic applications in addition to improved drug formulations for reduction in the adverse effects. BoNT therapy represents an expanding opportunity for adjuvant interventions and will provide urologists with increasing options for addressing difficult challenges in voiding dysfunction.

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