Michael B. Chancellor · Christopher P. Smith

Botulinum Toxin in Urology

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Foreword

Europe, North America and Asia

Professor Christopher Chapple

Dear Colleagues,

I would like to congratulate Michael Chancellor and Christopher Smith on this very interesting overview of the use of botulinum toxin in the treatment of urological disorders.

It is now clearly recognised that as a biological agent, the various formulations of botulinum toxin differ markedly in terms of their content, potency and potential site of action. There is no adequately controlled comparative data currently available contrasting one formulation of botulinum toxin with another. Most of the evidence base relating to the utilisation of botulinum toxin is from studies using onabotulinumtoxinA.

We have phase II dose ranging data for onabotulinumtoxinA in idiopathic detrusor overactivity and phase III data with its use in the treatment of neurogenic detrusor overactivity in both multiple sclerosis patients and spinal cord injury patients recently reported at international meetings.

This excellent overview comprehensively covers safety and general principles, aetiology and aspects of potential mechanisms of action and looks at the use of treatment for bladder, prostate and pelvic floor disorders. In addition there are interesting sections on the role of botulinum toxin in medicine, with a consideration of health economics.

Currently botulinum toxin proves to be enormously useful in the management of both idiopathic and neurogenic detrusor overactivity in our practice and we eagerly await the results of the phase III dataset with onabotulinumtoxinA.

Although we have limited evidence base as to the volume of injection to be used and the site of injection, it is our practice to use 0.5 ml injection, each containing 10 units of onabotulinumtoxinA and our standard therapy has been using 200 units, but in view of the recently reported dose ranging study with onabotulinumtoxinA in idiopathic detrusor overactivity, we are considering utilising 100 units as primary treatment of these patients and then up-titrating as necessary.

All of our patients at present are informed that the treatment is currently off-label and warned about the potential consequences of this therapy, in particular relating

to urinary retention, which seems to be the main potential side effect; symptoms of cystitis do occur but we routinely use antibiotic prophylaxis. We tend to inject onabotulinumtoxinA across the base of the bladder.

OnabotulinumtoxinA in our practice has been used for sensory bladder disorder with interesting early results when injected into the trigone. We have not utilised it for the management of benign prostatic obstruction or sphincteric or pelvic floor disorders.

In my view it has proved to be a very useful treatment for both idiopathic and neurogenic detrusor overactivity. The use of onabotulinumtoxinA still has to be adequately investigated in painful bladder syndrome, where there is very limited evidence base, and to date its use in other conditions, in my review, still remains within the realms of research rather than being considered appropriate for routine clinical practice.

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Professor Roger R. Dmochowski

Botulinum toxin use in urology has undergone substantial evolution over the last decade. Although not as yet approved in the majority of countries for indications in the lower urinary tract, rapid evidence is being accrued with appropriate levels of insight (randomized placebo controlled double blinded trials) which may meet regulatory criteria for approval for some lower urinary tract indications.

This book summarizes the evolution and journey of botulinum toxin in the management of lower urinary tract disease and is the work of two of the pre-eminent experts in the field of neurotoxin use in urology. The contribution of Michael Chancellor and Christopher Smith has not only been substantive from a clinical standpoint, but also from a mechanistic standpoint. Their studies have helped our understanding the actions of botulinum toxin on the lower urinary tract including affects on both afferent and efferent aspects of the reflexogenic activity of the lower urinary tract. Recent data would suggest that botulinum toxin has a complex mechanism of action, indeed affecting both aspects of the reflex arm controlling lower urinary tract function. Its role as an afferent modulator has only recently been appreciated and may underpin subsequent use of this toxin for an expanded group of indications in the lower urinary tract.

Questions regarding botulinum toxin use clinically remain legion. Appropriate dosing, administration, and patient selection being amongst the most problematic concerns; however, other issues related to repetitive administration such as potential changes within the lower urinary tract must be investigated as the medical community considers the use of botulinum toxin in the lower urinary tract.

As indicated in the table of contents this book summarizes essentially all of the lower urinary tract indications and reported uses of botulinum toxin. Again, for the majority of the world, these have not yet achieved regulatory approval, but ongoing studies exist across the areas indicated. Additionally, the book also summaries interesting uses of botulinum toxin (specifically neurogenic) and the health economic impact of this particular biologic entity which indeed may be substantive, at least initially. However, by reducing subsequent salvage related treatments costs, the overall impact may actually be beneficial.

The science of botulinum toxin no doubt will continue to evolve as experience with this toxin increases. More importantly, our ability to select or de-select groups of patients based upon primary pathology as causative for detrusor overactivity will clearly allow targeted use of not only botulinum toxin but other appropriate interventions for lower urinary tract disease. It is clear from this book, that the journey has started but is nowhere yet complete. As I read the contents of this book, I was reminded of Sir Isaac Newton's comments regarding the fact that all of us stand on the shoulders of those who go before us. The broad shoulders of Drs. Chancellor and Smith have clearly provided a foundation for the subsequent investigation and possible use of botulinum toxin in an expanded role for the lower urinary tract.

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Professor Hann-Chorng Kuo

In this past decade, advances in functional urology have made great progress. Bench investigations have provided evidence for new clinical diagnosis and novel treatment options. Such progress has enabled physicians to revisit the traditional concept of lower urinary tract dysfunction, interstitial cystitis/painful bladder syndrome, and overactive bladder syndrome.

One of the most important advances achieved is the application of botulinum toxin for lower urinary tract dysfunction, which has allowed clinicians to effectively treat patients with neurogenic or non-neurogenic voiding dysfunctions and benign prostatic hyperplasia in high risk patients. I have witnessed reduction of prostatic volume and improvement of lower urinary tract symptoms as well as improved voiding function after prostatic botulinum toxin injections. In my experience, injecting 100 U onabotulinumtoxinA into the urethral sphincter not only can reduce the urethral resistance and facilitate spontaneous voiding, but also provide a chance of recovery of detrusor contractility in patients with idiopathic detrusor underactivity.

Decrease of bladder pain after botulinum toxin injection into the bladder also extends the therapeutic indication to interstitial cystitis/painful bladder syndrome (IC/PBS). Increased apoptosis and decreased proliferation of urothelium are recently found to be the possible pathophysiology of IC/PBS. These urothelial dysfunctions are closely linked to the chronic inflammation in IC/PBS. After botulinum toxin injection, we have found that maximal bladder capacity increases and the glomerulation grade after hydrodistension was reduced, suggesting the inflammation process was interrupted and that urothelial homeostasis was restored. Thus, intravesical botulinum toxin injection may reduce chronic inflammation of the bladder in IC/PBS, and improve bladder pain as well as increase bladder capacity. Botulinum toxin might play a role by eliminating central sensitization in IC/PBS. Repeated botulinum toxin injections may be necessary for symptom relief and long-term disease cure.

In my experience, intravesical injection with 100 U of onabotulinumtoxinA provides therapeutic effect on decreasing urgency incontinence episodes, urgency severity score and improved quality of life in patients with overactive bladder. I have noted that bladder base injection is as effective and safe as bladder body injection. However, high adverse event rates including dysuria, urinary tract infection, and acute urinary retention in the first one month remain problems, although they usually resolve by three months. Before one determines the appropriate dose, injecting sites, and depth of injection, careful patient selection is necessary. Informing the possible adverse events to patients who wish to be treated by botulinum toxin is mandatory before bladder injection for refractory overactive bladder. Nevertheless, the occurrence of adverse events has not influenced our final results and long-term success rate.

In the journey of botulinum toxin treatment of lower urinary tract dysfunctions, Michael Chancellor and Christopher Smith are the true pioneers. Their earliest works encourage many young researchers to devote themselves into this exciting field. The application of botulinum toxin in urology opens a window for urologists and urogynecologists to see an interesting garden.

Through the treatment results of more clinical trials, we learn more about how to apply botulinum toxin as a therapeutic agent in the treatment of lower urinary tract disorders. There are still many unknown phenomena of botulinum toxin treatment in lower urinary tract dysfunctions that deserve future investigation. The publication of this book provides a fundamental platform for the future research of botulinum toxin application in urology.

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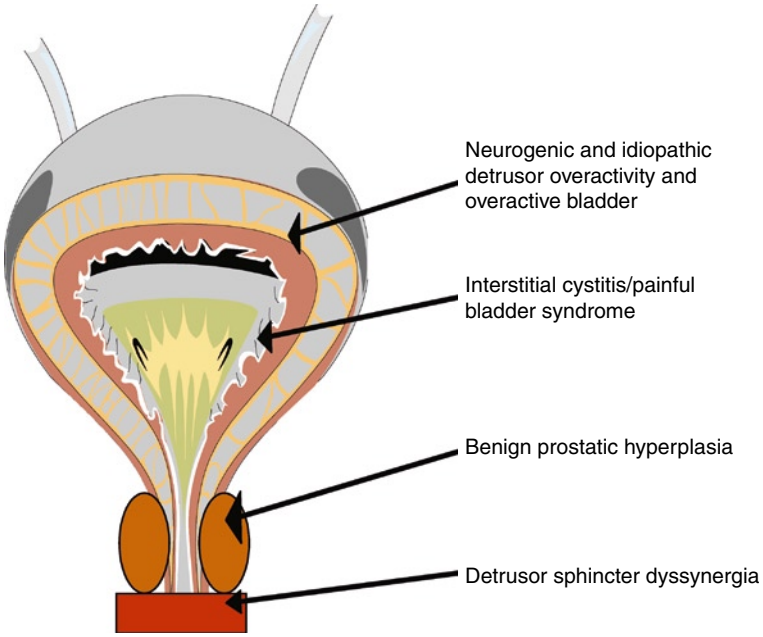
Introduction



Since botulinum neurotoxin was initially approved for clinical use by the Food and Drug Administration in 1989, it has become a powerful therapeutic tool in the treatment of a variety of neurologic, ophthalmic, and other disorders manifested by abnormal, excessive, or inappropriate muscle contractions. The use of botulinum toxin has expanded to include gastrointestinal, orthopedic, dermatologic, secretory, cosmetic, and urinary tract disorders. Botulinum toxin has also been applied in the clinical management of pain in a number of areas, including myofascial pain disorders, migraine headache, low back pain, and other chronic pain syndromes including pain in the areas of the bladder, prostate, and the pelvic floor.

In using this practical book, we urge the health care professional to recognize the need for appropriate injection technique. This includes careful identification both of appropriate patients and of the muscles or regions that are to be injected, along with

an awareness of the potential side effects of botulinum toxin therapy. We have included three appendices to highlight the practical operational nursing aspects of successfully and safely utilizing botulinum toxin in the urinary tract.

Tied to the successful use of botulinum toxin is the need to educate patients about the limitations of treatment, including the delay between treatment and the appearance of benefits, and the re-appearance of symptoms as the effects of botulinum toxin dissipate.

I started using botulinum toxin in 1998. I remember the frustration I felt back then having three female patients suffering from multiple sclerosis with high residual urine, recurrent urinary tract infections, and dyssynergia of the urethral sphincter. Nurse Margie O'Leary and me tried our best but were just unable to teach them to self-catheterize because of poor hand dexterity. After a consultation with the neurologists the patients were willing to try botulinum toxin instead of indwelling catheters or reconstructive surgery. The neurology clinic taught me how to prepare the toxin for injection and we went ahead with the procedure.

The procedures were uneventful and all three patients did very well after the sphincter botulinum injection. All three were able to void with significantly lower residual urine and there was no stress incontinence. I did some more research and discussed it with Professor William (Chet) de Groat at our lab meeting. Dr. de Groat was intrigued with the idea and recommended that we should pursue the study further in our lab. With de Groat's positive feedback I thought about bench top studies. At this time Christopher Smith started his National Institute of Health K12 Physician Scientist fellowship in Pittsburgh at the endorsement of his Mentor Dr. Tim Boone in Houston. Chris was looking for a new project to start and liked the concept of botulinum toxin research immediately. Working with Dr. George Somogyi, who led the neurotransmitter release and muscle contractility laboratory in the neurourology program, Chris and I quickly found that botulinum toxin not only effectively relaxed urethral strips but also detrusor muscle strips. We further found that botulinum toxin not only effectively blocked acetylcholine release from bladder and urethral strips but also norepinephrine release. Now this was something new and interesting.

As the cliché goes, the rest is history and led to a wonderful journey that started more than a decade ago since I took the first step.

We wish to express my most sincere gratitude to pioneers such as Dr. Dennis Dykstra and Professor Brigitte Schurch who opened up the field to urologists and urogynecologists.

Michael B. Chancellor, M.D.

Christopher P. Smith, M.D., M.B.A.

Acknowledgment

There are many other friends and colleagues who have helped us along the path from 1998 to today. Too many that we are sure to leave out important people. A few examples of additional people who worked directly with us include Chet de Groat, Naoki Yoshimura, George Somogyi, Piotr Radziszewski, Janet Erickson, Margie O'Leary, Sara Marx, Cindy Young, Darnetta Young, Tracy Cannon-Smith, Christopher Chermansky, Jill Bishoff, Timothy Boone, Alvaro Munoz, Mohit Khera, Pradeep Tyagi, Vikas Tyagi, Kenneth Peters, Ananias C. Diokno, Hsin-Tzu Liu, Wendy Leng, Teruhiko Yokoyama, Dae Kyung Kim, Hann-Chorng Kuo, Fernando de Miguel, Michele Anthony, Jonathan Kaufman, Maureen Cooney, Michelle Lajiness, Yao-Chi Chuang.

We are indebted to the experts from around the world whose help made urological development of botulinum toxin possible and for contributing to Chap. 11. We thank Professors Markus Naumann and Pankaj Jay Pasricha for sharing their perspectives on non-urological uses of toxin with genitourinary insight in Chap. 9. We appreciate very much Professor Yao-Chi Chuang's insight to the ideal BPH candidate for BoNT therapy in Chap. 8. Margie O'Leary, Michelle J. Lajiness and Mary Dierich were so wonderful with aiding us on the practical nursing appendixes. We want to especially thank Professors Christopher Chapple, Roger R. Dmochowski and Hann-Chorng Kuo for their friendship and writing a forward for our book. Thank you all.

We would finally like to thank our departments for their support for our research and our family for allowing us to take time out to write this book on an important topic we are passionate about.

Disclosure: Doctors Chancellor and Smith have both been consultants and investigators with the application of botulinum toxin in urology with Allergan, Inc Irvine California and have received financial compensation.

Michael B. Chancellor, M.D.

Christopher P. Smith, M.D., M.B.A.

Contents

Part I

Rationale and Safety for BoNT

Safety and General Principles of Botulinum Toxin Therapies: Pearls From Across Medical Fields

1

1.1 Introduction

Since the initial trials and approval of the medicinal use of botulinum toxin in the 1980s, therapeutic applications of botulinum neurotoxins have come from virtually every medical specialty. Table 1.1 is a list of applications of botulinum toxin (BoNT) and the list continues to expand. In this chapter, we hope to summarize some of the general treatment principles that have been learned from other specialties, especially neurology and rehabilitation medicine who both have been using BoNT for much longer than urologists and gynecologists, in order to help us better treat our patients.

1.2 Considerations for the Safe Use of BoNT

Healthcare professionals should be aware that a boxed warning has been added to the prescribing information of BoNT in the United States to highlight that BoNT can spread from the area of injection to produce symptoms consistent with botulism. Box 1.1 summarizes general notices by public health officials on key facts regarding botulism. The US Food and Drug Administration (FDA) in 2009 issued a new warning that botulinum toxin must carry warning labels explaining that the material has the potential to spread from the injection site to distant parts of the body – with the risk of serious difficulties, like problems with swallowing or breathing.

Symptoms of botulism include unexpected loss of strength or muscle weakness, hoarseness or trouble talking (dysphonia), trouble saying words clearly (dysarthria), loss of bladder control, trouble breathing, trouble swallowing, double vision, blurred vision, and drooping eyelids.

Swallowing and breathing difficulties can be life-threatening and there have been reports of deaths related to the effect of spread of BoNT. Be aware that children treated for spasticity are at greatest risk of these symptoms, but symptoms can also occur in adults treated for spasticity and other conditions. Realize that cases of toxin

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Table 1.1 Expanding therapeutic applications of botulinum neurotoxin

Focal dystonias
• Blepharospasm
• Oromandibular-facial-lingual dystonia
• Cervical dystonia
• Laryngeal dystonia (spasmodic dysphonia)
• Focal dystonias: involuntary, sustained, or spasmodic patterned muscle activity
• Task-specific dystonia (occupational cramps, e.g., writer's cramps and other limb dystonias)
• Other focal dystonias
Other involuntary movements
• Voice, head, and limb tremor
• Palatal myoclonus
• Hemifacial spasm
• Tics
Other inappropriate contractions
• Smooth muscle hyperactive disorders of the gastrointestinal and genitourinary systems
• Strabismus
• Nystagmus
• Stuttering
• Painful rigidity
• Temporomandibular joint disorders associated with increased muscle activity
• Muscle contraction headaches
• Lumbosacral strain and back spasms
• Radiculopathy with secondary muscle spasm
• Spasticity (e.g., stroke, head injury, paraplegia, cerebral palsy, multiple sclerosis)
• Achalasia
• Urinary sphincter dyssynergia
• Pelvic and rectal spasms (anismus, vaginismus)
• Achalasia cardia
• Hirschsprung disease
• Sphincter of Oddi dysfunctions
• Following hemorrhoidectomy
• Chronic anal fissures
Other applications
• Protective ptosis
• Sweating disorders
• Axillary and palmar hyperhidrosis
• Frey syndrome, also known as auriculotemporal syndrome (gustatory sweating of the cheek after parotid surgery)
• Cosmetic
• Hyperkinetic facial lines (glabellar frown lines, crow's feet)
• Genitourinary track dysfunctions including bladder and prostate
• Migraine and tension headache
• Pain
• Myofascial pain syndrome