Botulinum Toxins
Botulinum Toxins

Cosmetic and Clinical Applications

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About the Companion Website

Don’t forget to visit the companion website for this book:

www.wiley.com/go/cohen/botulinum

This site hosts valuable video materials to enhance your learning:

Dr Cohen and Dr Ozog present several patient cases, focusing on patient evaluation, preparation for toxins, and specific injection techniques. Each patient is appraised carefully and optimal injection techniques are discussed, along with methods for avoiding adverse effects, and ways to minimize injection points and related bruising. One week follow up videos will highlight optimization of results.
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Sausage Poisoning

In the late 1700s in Europe, outbreaks of a deadly illness from contaminated foods swept across the continent, fueled in part by the poverty from the Napoleonic War (1795–1815) that led to unsanitary food production [1]. The primary source of food-borne illness of the time: smoked blood sausages. One of the biggest outbreaks occurred in 1793 in Wildebrad, Southern Germany; by 1811, the Department of Internal Affairs of the Kingdom of Württemberg named “prussic acid” as the culprit in sausage poisoning [2]. Intrigued, the district medical officer and poet, Dr. Justinus “Würst” Kerner (1786–1862), began what would become a lifelong quest to uncover the mysteries of the poison. He would later be considered the godfather of botulinum toxin (BoNT) research for his early, intensive work. In 1817 and 1820, Kerner identified and described the first accurate descriptions of botulism (a term coined in 1871 from the Latin *botulus*, meaning “sausage”) [2, 3]. In 1822, he compared contaminated sausage ingredients and concluded that the toxin must occur in fat, leading him to call the suspicious substance “sausage poison,” “fat poison,” or “fatty acid,” and published the first complete monograph of the “fatty toxin” from blood sausages [2].

In his monograph, Kerner described the symptoms of botulism – including vomiting, intestinal spasms, mydriasis, ptosis, dysphagia, and respiratory failure – and recommended methods for the treatment and prevention of food poisoning. Through animal and self-experimentation, Kerner observed that the toxin developed under anaerobic conditions and was lethal in small doses. Since the effects of this blood poison were similar to atropine, scopolamine, nicotine, and snake venom, Kerner surmised that sausage poison was likely biological in nature – remarkable in that microscopic pathogens had not yet been discovered at that time – and interrupted signal transmissions within the peripheral and autonomic nervous system. Indeed, some would call Kerner prophetic: he suggested that small amounts of this sausage poison might be used to lower sympathetic nervous system activity associated with movement disorders (i.e., treat St. Vitus’ dance or Sydenham’s chorea, a disorder characterized by jerky, uncontrollable movements, either of the face or of the arms and legs) and hypersecretion of bodily fluid, as well as to treat ulcers, delusions, rabies, plague, tuberculosis, and yellow fever [4].
Identification of C. botulinum

Microbiologist Professor Emile Pierre van Ermengem (1851–1922) trained under Robert Koch, who discovered anthrax, tuberculosis, and cholera and was the first researcher to prove that microorganisms could cause disease in animals [5]. In 1897, Van Ermengem identified the bacterium Clostridium botulinum (originally called Bacillus botulinus) as the causative agent of botulism after examining postmortem tissue of patients in Belgium who had contracted gastroenteritis and died from eating raw, salted pork [6]. Over the next twenty years, different strains of the bacterium that produced serologically distinct types of toxins were recognized; these were eventually classified alphabetically into seven serotypes (A, B, C1, D, E, F and G) [7]. In 1928, Dr. Herman Sommer (University of California, San Francisco) isolated the most potent serotype – BoNT type A (BoNTA) – in purified form as a stable acid precipitate, paving the way for future studies [8].

Biological Weapon of Warfare

During the First World War, Germany unsuccessfully attempted to produce chemical and biological weapons. As World War II approached, the American government learned that multiple countries were engaged in bio-warfare programs. In response, and on orders from President Franklin Roosevelt, the US National Academy of Sciences and Fred Ira Baldwin, chairman of the bacteriology department of the University of Wisconsin, gathered bacteriologists and physicians in a laboratory named Fort Detrick (Maryland). The purpose of Fort Detrick: the investigation of dangerous infectious bacteria and toxins to use as offensive and defensive biological weapons [1].

In 1946, Carl Lamanna and James Duff developed concentration and crystallization techniques for the toxin that were subsequently used by Dr. Edward J. Schantz, a young US army officer stationed at Fort Detrick to produce the first BoNTA lot for human use (the basis of the later clinical product) [9, 10]. The US Office of Strategic Services (OSS) developed a plan using Chinese prostitutes to assassinate high-ranking Japanese officials via gelatin capsules containing the newly purified BoNTA. The government abandoned the plan when test donkeys that received the capsules survived [1]. Ironically, though BoNT today is considered one of the deadliest poisons in the world – 1 g has the potential to kill 1 million people – the toxin is not an ideal biological weapon, since large amounts must be ingested and mortality rates vary).

In 1972, President Richard Nixon signed the Biological and Toxic Weapons Convention, effectively putting an end to all investigations on biological agents for use in war. Schantz took his research to the University of Wisconsin, where he produced a large amount of BoNTA (batch 79–11) that remained in clinical use until December of 1997 [11].

Human Experimentation

Clinical use of the toxin began in the late 1960s and early 1970s, when Dr. Alan Scott (Smith-Kettlewell Eye Research Foundation, San Francisco; Figure 1.1) began experimenting with BoNTA, supplied by Dr. Schantz, and other chemical agents in monkeys, with the hope that one of the compounds could be used for the nonsurgical treatment of strabismus in humans [12, 13]. Scott published his first primate studies proving that BoNTA could weaken extraocular muscles in 1973, and postulated that the toxin could be used for a wide variety of musculoskeletal disorders and spasticity, even before conducting any human studies [13, 14]. In 1978, Scott received Food and Drug Association (FDA) approval to begin testing small amounts of the toxin (then named Oculinum) in human volunteers; his landmark paper, published in 1980 [15], showed that intramuscular injections of BoNTA could correct gaze
misalignment in humans. In 1989, one year after manufacturer Allergan Inc. (Irvine, CA) acquired the rights to distribute Scott’s Oculinum in the United States, BoNTA was approved for the nonsurgical correction of strabismus, blepharospasm, hemifacial spasm, and Meige’s syndrome in adults, and clinical use expanded to include the treatment of cervical dystonia and spasmodic torticollis [13, 16, 17]. Shortly thereafter, Allergan bought Scott’s company and renamed the toxin. Botox® was born.

The Cosmetic Connection

In the mid-1980s, Dr. Jean Carruthers, an ophthalmologist in Vancouver, Canada, noticed that her patients injected with BoNTA for blepharospasm experienced a reduction in glabellar rhytides, and discussed the findings with both Scott and her dermatologist spouse, Dr. Alastair Carruthers, who was attempting to soften the forehead wrinkles of his patients using soft-tissue augmenting agents available at that time. Intrigued by the possibilities, the Carruthers used the toxin experimentally in their receptionist’s forehead and subsequently published the first report of BoNTA for the treatment of glabellar frown lines in 1992 [18] (Figure 1.2). Other reports soon followed [19, 20], including the first double-blind, placebo-controlled study for the treatment of hyperkinetic facial lines [21].

Properties, Mechanism of Action, and Clinical Effect

Clostridium botulinum is a rod-shaped, gram-positive anaerobic bacterium. Of the seven serotypes, A, B, and E are commonly involved in human botulism [22]. BoNT is a high-molecular-weight protein of 150,000 daltons with noncovalent proteins protecting it from digestive enzymes, making it a lethal cause of food poisoning [1]. The symptoms of botulism include disturbances in vision, speech, and swallowing, with asphyxia and death sometimes occurring 18–36 hours after ingestion (mortality rate: 10–65%) [22].

Researchers gained an understanding of mechanism of action in the late 1940s, when they discovered that BoNT blocks neurotransmitter release at the neuromuscular junction [23]. The follow-up discovery in the mid-1950s that BoNT blocks the release of acetylcholine from motor nerve endings when injected into hyperactive muscles led to a renewed interest in the neurotoxin as a potential therapeutic agent [3].

Although all seven serotypes block neuromuscular motor transmission by binding to receptor sites on motor nerve terminals and inhibiting the release of acetylcholine, producing temporary chemodenervation of the muscles, each differs with regard to cellular mechanism of action and clinical profile [24, 25]. The commercially available subtypes – type A (BoNTA) and type B (BoNTB) – are both 150 kDa dichain polypeptides
comprising heavy and light chains linked by disulfide bonds. The light chain of BoNTA cleaves to a 25 kDa synaptosomal associated protein (SNAP-25), a protein integral to the successful docking and release of acetylcholine from vesicles situated within nerve endings, while the light chain of BoNTB cleaves to vesicle-associated membrane protein (VAMP or synaptobrevin). This difference may be responsible for some of the differences witnessed in the clinical effect of the subtypes [12]. When injected intramuscularly at therapeutic doses, BoNT produces temporary chemical denervation of the muscle, resulting in a localized reduction of muscle activity. The process of cellular recovery after injection of BoNT is only partially understood. Initial recovery of muscle contraction is accompanied by collateral sprouting of active terminal buds near the parent terminal. However, research indicates that these new sprouts are only transitory; neurotransmission is eventually restored at the original nerve ending, accompanied by the elimination of the dispensable sprouts [26], suggesting that treatment with BoNT does not permanently alter the neuromuscular junction. Recommended doses of injected neurotoxin do not result in systemic clinical effects in patients without other neuromuscular dysfunction. Studies of human and animal tissue show that in the first 2 weeks postinjection with BoNTA, the target muscle begins to atrophy, with changes in individual muscle fibers [27]. The paralytic effect of the toxin is dose-related, with initial effects occurring within 2–3 days and peaking approximately 1–2 weeks after treatment [28]. Atrophy continues for approximately 4 weeks before stabilizing; clinical recovery of function occurs 3–6 months posttreatment [29]. There is an area of denervation associated with each point of injection due to toxin spread of about 1–1.5 cm (diameter, 2–3 cm). Repeated injections can extend the clinical effect for up to 12 months [29]; it is possible

Figure 1.2 The Carruthers’ first patient treated in the glabella area for cosmetic reasons alone. Seen (a) before frowning; (b) after frowning; (c) before at rest; (d) after at rest.
that over the course of treatment, individuals alter their habitual use of muscles that cause expression lines. Long-term remodeling of the dermis and epidermis that helps to sustain the cosmetic effects also occurs in most individuals, because the tissue is no longer subjected to the same forces of muscle contraction.

A Multitude of Formulations

Until recently, one product – at least for cosmetic purposes – dominated the market: onabotulinumtoxinA (Botox®/Botox Cosmetic®/Vistabel®/Vistabex®; Allergan, Inc., Irvine, CA). Now, however, a host of other agents have joined the original formulation to fight the signs of aging. Of the formulations of BoNTA available or in development, the original, onabotulinumtoxinA, is the most recognized and discussed in peer-reviewed literature. Botox Cosmetic, which was approved by the US FDA in 2002 for the treatment of glabellar rhytides [30], has gone on to receive approval for 20 indications in more than 75 countries [31]. Now three formulations of botulinumtoxin type A are approved for cosmetic use in North America. The original onabotulinumtoxin A has been joined by abobotulinumtoxinA (Dysport®) and IncobotulinumtoxinA (Xeomin®). Initially approved in over 65 countries for therapeutic indications (Dysport®; Ipsen Ltd., United Kingdom/Medicis, Scottsdale, AZ; and Azzalure® in 15 European countries; Galderma, France), abobotulinumtoxinA received FDA approval for cosmetic applications in North America in 2009 (Dysport®; Ipsen Ltd). Although produced from the same serotype, abobotulinumtoxinA differs from onabotulinumtoxinA in purification procedures, dosing, injection schedules, and clinical effect [32]. Units of abobotulinumtoxinA are less powerful than those of onabotulinumtoxinA; most cosmetic injectors use a multiple of two to three times the number of units. Overall, abobotulinumtoxinA is safe and well tolerated [33, 34]. A third BoNTA (Xeomin®/NT-201; Merz Pharmaceuticals, Frankfurt, Germany) is approved for therapeutic indications in Germany and other European countries, the United States, Canada, Mexico, and Argentina, and has been approved for the treatment of glabellar rhytides in Argentina and the United States. Clinically, Xeomin and onabotulinumtoxinA appear to behave in a similar fashion, with equal levels of potency, safety, and duration of effect [35–40]. Xeomin is free of complexing proteins, which some believe may result in purer formulations with greater efficacy and a reduced risk of sensitization and antibody formation [37]. One formulation of BoNT type B (BoNTB) is also available in North America. RimabotulinumtoxinB (Myobloc®/NeuroBloc®; Solstice Neurosciences Inc./Eisai Co., Ltd.) was FDA-approved in 2000 for the treatment of cervical dystonia but has been used off-label to treat facial wrinkles with some success [41–44]. BoNTB works faster than but does not last as long as BoNTA [45], although duration has been shown to be dose dependent [46]. BoNTB tends to diffuse more widely than BoNTA and injections can be more painful and may lead to additional side effects [45]; however, a close examination of several doses found all to be safe and effective for cosmetic use [46].

Cosmetic Applications

Hyperkinetic lines result from the repeated contraction of muscles perpendicular to the wrinkles. Weakening or relaxing these muscles with BoNTA can smooth these lines, including horizontal lines on the forehead (from frontalis contraction), vertical lines in the glabellar region between the eyebrows (caused by the corrugator muscles), horizontal creases across the bridge of the nose (from procerus contraction), “crow’s feet” and lateral lines along the lower eyelid (caused by contraction of the lateral orbicularis oculi), and perioral lines (from contraction of the orbicularis oris). Deep grooves or folds
elsewhere that are exacerbated by muscle activity are also amenable to treatment. Patients 30–50 years of age may be most responsive to BoNTA, because their wrinkles are more likely to be caused by muscle activity than by the loss of skin elasticity that occurs during aging. Clinicians now use the neurotoxin to treat a variety of hyperkinetic facial lines in the upper face, including crow’s feet, horizontal forehead lines, and glabellar rhytides, as well as folds and lines in the lower face, neck, and chest with a high level of efficacy and patient satisfaction [12, 47–52].

**Facial Sculpting**

Facial rejuvenation with BoNT has expanded to involve a more artistic shaping and sculpting of the face. Now, in addition to targeting simple dynamic rhytides, careful injection of the toxin can be used to lift and shape the brow [53], widen the eyes [12, 54], correct facial asymmetry due to nerve palsies [55], dystonias [17, 20], surgery [56], or trauma [57], and to reduce muscle thickness of the jaw in patients with masseteric hypertrophy (Figure 1.3) [58–61].

**Adjunctive Therapy**

BoNT is used increasingly in combination with other facial rejuvenation procedures, such as soft-tissue augmentation [28, 62–66] and laser or light-based therapies [12, 28, 67–71], particularly for the treatment of deeper, more static rhytides and folds. BoNT is also used during surgery to prolong or enhance the aesthetic results and as an aid in wound healing and minimizing scars (Figure 1.4) [12, 73–77].
Therapeutic Applications

Intramuscular injections of BoNTA have become the treatment of choice for a number of disorders characterized by muscular hyperactivity, such as strabismus [15], blepharospasm and hemifacial spasm [17], cervical dystonia [78], focal dystonia (writer’s cramp) [79], and spasticity due to stroke [80, 81], and cerebral palsy [82]. In addition, the ability of BoNT to block acetylcholine release from autonomic nerve endings innervating glandular tissue or smooth muscle has led to investigation of its use for other indications, including Frey’s syndrome [83] and hyperhidrosis [84–89], as well as various gastrointestinal, genitourinary, and sphincter disorders [90], dyshidrotic hand eczema [91, 92], and allergic rhinitis [93, 94]. Flushing of the face and chest can be successfully treated with BoNT due to its ability to regulate blood vessel constriction [95, 96]. Clinicians continue to investigate the use of BoNT for the treatment of chronic pain disorders, including chronic lumbar [97], temporomandibular dysfunction [98], myofascial [99], and neuropathic pain [100], although the toxin’s efficacy in the treatment of headache disorders is under debate [101]. More recent research includes applications of BoNT to relieve the pain of arthritis [102, 103].

Future Directions

It is interesting to note that what once began as a potential – rather daring – treatment for a single disorder has translated into a worldwide phenomenon. And one cannot help but wonder what Justinus Kerner would think of his “sausage poison” now that so consumed his time and became his life’s research. BoNT has become the treatment of choice for smoothing hyperkinetic lines and shaping the face, alone or in combination with other rejuvenating procedures. Therapeutic applications include a variety of movement, pain, autonomic nervous system, and gastrointestinal and genitourinary disorders, among others. Current recruitment for clinical trials includes everything from arthritis and clubfoot to acne and depression, with new products emerging or on the horizon. Indeed, BoNT seems to have invaded nearly every aspect of clinical medicine, at least in some way, and there is no doubt that the range of indications will only continue to expand.

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