Injectable and topical neurotoxins in dermatology

Basic science, anatomy, and therapeutic agents

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Learning objectives
After completing this learning activity, participants should be able to discuss the history, science, safety profile, and new indications of neurotoxins in clinical and cosmetic practice; describe the mechanisms of action of currently available neurotoxins; and explain how to use a more standardized approach to their neurotoxin injection protocol to help minimize complications.

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Botulinum toxin is a potentially deadly anaerobic bacterial toxin that acts by inhibiting release of acetylcholine at the neuromuscular junction, thereby inhibiting contraction of the exposed striated muscle. There are currently 4 botulinum toxin preparations approved by the US Food and Drug Administration (FDA): onabotulinumtoxin, abobotulinumtoxin, incobotulinumtoxin and rimabotulinumtoxin. While significant overlap exists, each product has unique properties and specifications, including dosing, diffusion, and storage. Extensive physician knowledge of facial anatomy, coupled with key differences of the various neurotoxin types, is essential for safe and successful treatments. The first article in this continuing medical education series reviews key characteristics of each neurotoxin, including new and upcoming agents, and provides an anatomic overview of the most commonly injected cosmetic sites. (J Am Acad Dermatol 2017;76:1013-24.)

Key words: abobotulinum; anatomy; botulinum toxin; *Clostridium botulinum*; incobotulinum; lower face; neuromodulator; neurotoxin; new indications; onabotulinum; properties; rimabotulinum; RT001; RT002; upper face.

HISTORY

In the early to mid-1800s, "sausage poison," now known as botulism, was a major and lethal source of food poisoning in Europe.[1] In 1989, after much investigation and scientific research, *Clostridium botulinum*'s bacterial toxin was approved for a variety of medical uses, including hemifacial spasms, strabismus, and blepharospasm.[1] A serendipitous discovery by ophthalmologist Jean Carruthers in the late 1980s recognized reduced facial wrinkles in

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patients with benign essential blepharospasm who were treated with injectable botulinum toxin.[2] This was first reported at the American Society for Dermatologic Surgery (ASDS) annual meeting in 1991 (Fig 1). Initially met with skepticism, this was closely followed by 2 confirmatory clinical trials of safety and efficacy.[2,3] In 2002, it received approval by the US Food and Drug Administration (FDA) for "temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity."[4] Subsequently, there has been a rapid acceptance and widespread investigation into additional cosmetic and therapeutic usages for this previously "deadly" toxin that ultimately revolutionized aesthetic medicine.

BASIC SCIENCE

Key points

- **Botulinum toxin has 7 serotypes purified from the anaerobic, Gram-positive, spore-forming *Clostridium botulinum***
- **Botulinum toxins are 150-kDa proteins that are distinguished by the variations in their light chains**
- **Incobotulinumtoxin is free from complexing proteins**
- **The mechanism of action involves toxin cleavage of the SNARE protein complex with resultant dysfunction of acetylcholine release at the neuromuscular junction**

Seven serotypes (A through G) of botulinum toxin have been identified and purified from differing strains of the anaerobic, Gram-positive, spore-forming *C botulinum*.[5] Type A is the most potent, with types B and F closely following.[2] Types A, B, and E are known causes of food poisoning, and types C and D do not appear to affect the human nervous system.[1,5] Type F is implicated in food poisoning less often, and type G has not been linked to human botulism.[6]

Botulinum neurotoxins are 150-kDa polypeptides that consist of a 100-kDa heavy chain linked with a 50-kDa light chain via heat-sensitive disulfide bonds and noncovalent forces.[5] Different toxin serotypes are distinguished by variations in their light chains.[7] The toxins can be complexed with hemagglutinin and "nontoxic molecule" then dimerized to form a larger compound: 900 kDa for onabotulinum toxin and 500 kDa for abobotulinum toxin.[2,4]

Incobotulinum is free from complexing proteins, weighing 150 kDa.[4] The final active forms act on the peripheral nervous system to inhibit the release of acetylcholine from the neuromuscular junction

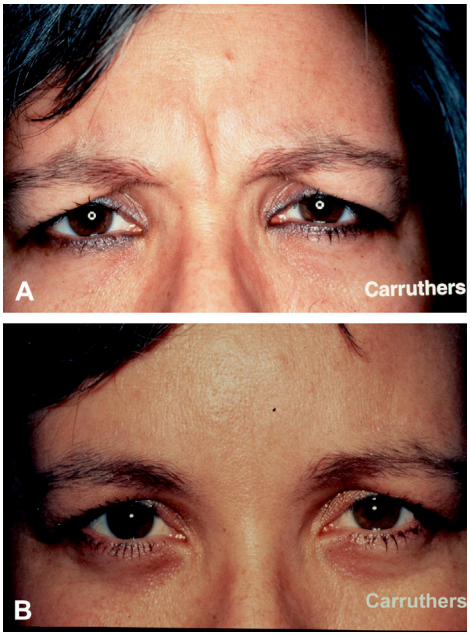

Fig 1. The first cosmetic patient treated with botulinum toxin to the glabellar region. **A**, Pretreatment. **B**, Post-treatment. (Courtesy of Jean Carruthers, MD.)

(NMJ).[5] The most common site of action is the presynaptic terminal; however, binding to the autonomic cholinergic ganglia with resultant autonomic effects has been reported in very large doses.[5,8,9]

Once injected, it irreversibly binds to a receptor on the presynaptic terminal of the NMJ, termed synaptotagmin.[5] Through receptor-mediated endocytosis, internalization of the toxin-receptor complex occurs, and the disulfide bond linking the heavy and light chains is cleaved. The light chain then translocates to the cytoplasm, fuses with a toxin-specific protein isoform, soluble NSF attachment protein receptor (SNARE), and cleaves the protein isoform utilizing a zinc-dependent endopeptidase.[5,7] The synaptic fusion complex consists of three main SNARE proteins, synaptobrevin/vesicle-associated membrane protein, 25-kDa synaptosomal-associated protein, and syntaxin.[7] Type A botulinum toxins, most commonly used, cleave 25-kDa synaptosomal-associated protein, while type B toxins catalyze the breakdown of synaptobrevin/vesicle-associated membrane protein (Fig 2). This disrupts the docking, fusion, and release of acetylcholine vesicles into the NMJ, thereby inhibiting muscular contraction.[5]

It has also been suggested that acetylcholinesterase activity is altered with botulinum toxin.[2] While typically confined to the NMJ, staining patterns in treated muscle have shown acetylcholinesterase activity spanning over most of the sarcolemma.