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REVIEW ARTICLE

Toxin which relieve your pain –a review

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Abstract

Drugs developed from biological toxins are new additions to the therapeutic armamentarium for pain control, cardiac diseases, cosmetic dentistry etc. Botulinum toxin, in the treatment of painful conditions associated with skeletal muscle. Purified Botulinum toxin Type-A (Botox) binds to the pre-synaptic nerve terminal to prevent the release of acetylcholine and thereby prevents neurotransmission. This extremely potent bacterial toxin is currently being used for the treatment of Myo-facial pain, various spasmodic neuromuscular disorders, and for cosmetic procedures etc. This article explains the mechanism and implication of drug worldwide in field of life sciences.

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INTRODUCTION

Diagnosis and treatment of painful muscle syndromes are difficult and frustrating task for any clinician. Typically, the mainstay of therapy for such conditions is therapeutic exercise, analgesics, and a tincture of time. Unfortunately, not all patients respond to this paradigm, and, despite heroic efforts on the part of the treating clinician, some conditions are refractory to this approach.

Reports have described the purported effectiveness of using a biologic neuromuscular blocking agent, botulinum toxin, in the treatment of painful conditions associated with skeletal muscle. While incompletely understood and at times controversial, use of botulinum toxin in the treatment of conditions associated with involuntary muscle contraction, such as focal dystonia and spasticity, is supported by prospective, randomized clinical research; however, while the volume of comparable studies in pain syndromes is growing, the number of clinical randomized trials is limited. Moreover, not all such reports have demonstrated clear efficacy of the use of botulinum toxin under all circumstances. Therefore, in view of our current understanding of the nature of muscle-induced pain and the paucity of prospective research regarding neuromuscular blockade and/or inhibition of nociception in such conditions, critical and careful analysis of the data and opinions presented in this section is appropriate.

The world's most potent biological toxin, botulinum toxin was first isolated in 1897 by Van Ermengem [1] Botulinum toxin (abbreviated either as BTX or BoNT) is produced by *Clostridium botulinum*, a gram-positive anaerobic bacterium. The clinical syndrome of botulism can occur following ingestion of contaminated food, from infant gastrointestinal tract, or from a wound infection.

Botulinum toxin is broken into 7 neurotoxins (labeled as types A, B, C [C1, C2], D, E, F, and G), which are antigenically and serologically distinct but structurally similar. Human botulism is caused mainly by types A, B, E, and (rarely) F. Types C and D cause toxicity only in animals.

The Botulinum toxin molecule is synthesized as a single chain (150 kD) and then cleaved to form the dichain molecule with a disulfide bridge (see Image 1). The light chain (~50 kD - amino acids 1-448) acts as a zinc (Zn^{2+}) endopeptidase similar to tetanus toxin with proteolytic activity located at the N-terminal end. The heavy chain (~100 kD - amino acids 449-1280) provides cholinergic specificity and is responsible for binding the toxin to presynaptic receptors; it also promotes light-chain translocation across the endosomal membrane.

History

The German physician and poet Justinus Kerner (1786-1862) first developed the idea of a possible therapeutic use of botulinum toxin, which he called "sausage poison." In 1870, Muller (another German physician) coined the name botulism. The Latin form is *botulus*, which means sausage. 1895, Professor Emile Van Ermengem, of Belgium, first isolated the bacterium *Clostridium botulinum*. 1928, Dr. Herman Sommer, at the University of California, San Francisco, first isolated in purified form botulinum toxin type A (BoNT-A) as a stable acid precipitate. 1946, Dr. Edward J Schantz succeeded in purifying BoNT-A in crystalline form–cultured *Clostridium botulinum* and isolated the toxin. 1949, Dr. Burgen's ASV group discovered that botulinum toxin blocks neuromuscular transmission. In the 1950s, Dr. Vernon Brooks discovered that when BoNT-A it blocks the release of acetylcholine from motor nerve endings. .The clinical use of BoNT-B has been studied, and several products currently are available commercially (eg, MyoBloc, in the United States; NeuroBloc, in Europe). MyoBloc was approved by the FDA on December 8, 2000, for treatment of cervical dystonia, to reduce the severity of abnormal head position and neck pain. Use of BoNT-F also is under investigation in patients who have become immunologically resistant to serotypes A and B.

Mechanisum of action

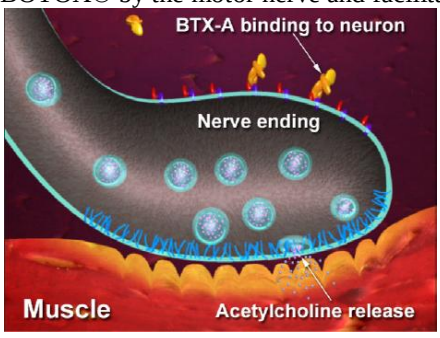
BOTOX® (Botulinum Toxin Type A) contains a protein complex purified from the bacterium *Clostridium botulinum*. A component of this complex, Botulinum Toxin Type A is the important active ingredient. Type A is one of the seven distinct botulinum toxins produced by different strains of the bacterium. BOTOX® decreases muscle activity by blocking overactive nerve impulses that trigger excessive muscle contractions or glandular activity. In addition, BOTOX® is believed to reduce neck pain associated with cervical dystonia by relaxing the muscles and possibly through its influence on the pain sensory system (e.g., inhibiting the release of neurotransmitters involved in the transmission of painful sensations), although the exact mechanism of action is unknown.

Phase I – Nerve-Muscle Communication is blocked

BOTOX® blocks the transmission of overactive nerve impulses in targeted muscle by selectively preventing the release of the neurotransmitter acetylcholine (ACh) at the neuromuscular junction, temporarily preventing muscle contraction. This is primarily a local effect. BOTOX® may also prevent the release of pain-stimulating neuropeptides in peripheral nerves.

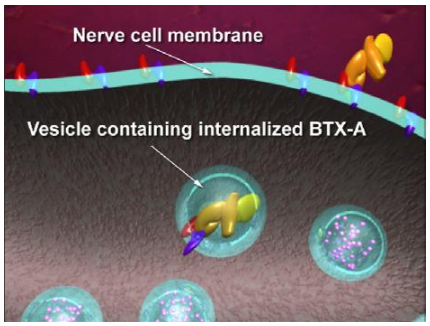
A) Binding:

The heavy chain portion of the active ingredient in BOTOX® binds to the cell membrane of the motor nerve via an unidentified high-affinity "acceptor" molecule. This high-affinity binding action allows for efficient uptake of BOTOX® by the motor nerve and facilitates selective, targeted treatment at the injection site



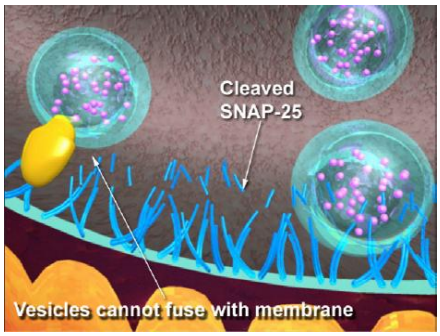
B) Internalizing:

After binding, the BOTOX® protein molecule passes through the cell membrane of the motor nerve into its cytoplasm via a process called endocytosis. It is here that the enzymatic component (light chain) of the BOTOX® protein molecule is activated.



C) Blocking:

Inside the motor nerve, the light chain of the BOTOX® protein molecule cleaves apart a protein (called SNAP25) that enables vesicles which store the neurotransmitter acetylcholine to attach to the cell membrane. Cleaving SNAP25 prevents these vesicles from fusing with the membrane and prevents the release of acetylcholine into the neuromuscular junction (the space between the motor-nerve and the muscle). Thus, nerve impulses that control muscle contractions are blocked decreasing muscle activity.



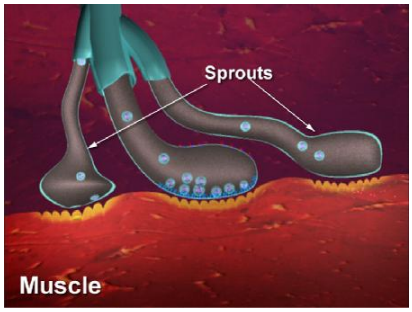
Cleaving SNAP25 also blocks release of neuropeptides involved in the transmission of painful sensations (including substance P, glutamate and calcitonin gene-related peptide, or CGRP), theoretically reducing pain sensitization of peripheral nerves. This may be how BOTOX® reduces the neck pain associated with cervical dystonia, although the exact mechanism of action is unknown.

Phase II – Nerve-Muscle Communication is Restored

The effect of BOTOX® is generally temporary. Previous nerve impulse activity and associated muscle contractions resume over the course of a few to several months, depending on the individual patient and the indication for which they are being treated.

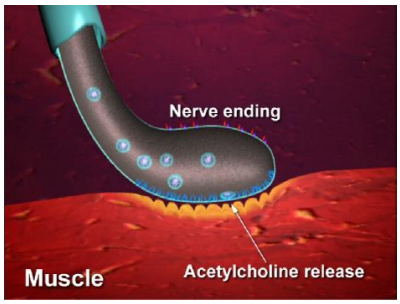
A) Nerve Sprouting:

New nerve endings sprout and connect to the muscle after the original nerve ending is blocked, renewing the ability of the nerve to cause muscle contractions.



B) Original Nerve Connection Re-established:

Eventually, the new nerve sprouts retract and the original nerve ending regains its function, suggesting that treatment with BOTOX® does not permanently alter the neuromuscular junction.



Therapeutic uses of botulinum toxin injection

- Focal dystonias - Involuntary, sustained, or spasmodic patterned muscle activity
  - Cervical dystonia (spasmodic torticollis)[2,3]
  - Blepharospasm (eyelid closure)
  - Laryngeal dystonia (spasmodic dysphonia)
  - Limb dystonia (writer's cramp)
  - Oromandibular dystonia
  - Orolingual dystonia
  - Truncal dystonia
- Spasticity - Velocity-dependent increase in muscle tone
  - Stroke
  - Traumatic brain injury
  - Cerebral palsy
  - Multiple sclerosis
  - Spinal cord injury
- Nondystonic disorders of involuntary muscle activity
  - Hemi-facial spasm
  - Tremor
  - Tics
  - Myokymia and synkinesis
  - Myoclonus (tensor veli palatini muscle [middle ear], causing tinnitus)
  - Hereditary muscle cramps
- Strabismus (disorder of conjugate eye movement) and nystagmus
- Disorders of localized muscle spasms and pain
  - Chronic low back pain
  - Myofascial pain syndrome
  - Temporomandibular joint disorders associated with increased muscle activity
  - Tension headache
  - Migraine headache
  - Cervicogenic headache
  - Improving gummy smile
- Smooth muscle hyperactive disorders
  - Detrusor-sphincter dyssynergia
  - Benign prostatic hypertrophy
  - Achalasia cardia
  - Hirschsprung disease
  - Sphincter of Oddi dysfunctions
  - Following hemorrhoidectomy
  - Chronic anal fissures[5]
- Cosmetic use
  - Hyperkinetic facial lines (glabellar frown lines, crow's feet)
  - Hypertrophic platysma muscle bands
- Sweating disorders
  - Axillary and palmar hyperhidrosis

- Frey syndrome, also known as auriculotemporal syndrome (gustatory sweating of the cheek after parotid surgery)

Different studies on the use of BoNT in the management of different pain disorders are listed in Table 1.

Table 1. Studies on the Use of Botulinum Toxin in Pain Management

Author(s) (Year)	Clinical Condition	Study Type	N	Results
Zwart et al (1994)	Tension headache	Open-label	6	Unilateral temporal injection not effective
Wheeler et al (1998)	Myofascial pain [34]	Randomized, double-blind, controlled	33	No significant difference, second injection effective?
Wheeler (1998)	Tension headache	Open-label	4	Effective in 4 patients
Schulte-Mattler et al (1999)	Tension headache	Open-label	9	Effective in 8 of 9 patients
Freund et al (1999)	Temporomandibular disorders	Open-label	15	Effective
Freund et al (2000)	Temporomandibular disorders	Open-label	46	Effective
Silberstein et al (2000)	Migraine headache	Double-blind, vehicle-controlled	123	Effective prophylaxis
Rollnik et al (2000)	Tension headache	Double-blind, placebo-controlled	21	Not effective
Freund et al (2000)	Cervicogenic Headache	Randomized, double-blind, placebo-controlled	26	Effective
Freund et al (2000)	Whiplash associated with neck pain	Randomized, double-blind, placebo-controlled	26	Effective
Barwood et al (2000)	Severe postoperative pain and spasm in cerebral palsy	Randomized, double-blind, placebo-controlled	16	Effective prophylaxis
Porta (2000)	Chronic myofascial pain syndrome	Randomized, controlled, comparative	40	BOTOX® better than methylprednisolone

Conclusion :

Many interesting research questions remain regarding BTXs effects. However, one cannot deny the ingenuity of man in transforming the lethal toxin of Clostridium botulinum into a modern-day therapeutic medicine.

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