European Journal of Clinical Pharmacy
PrintISSN:2385-409X**OnlineISSN**:3105-0409
Website: https://farmclin.com/

Review: The Pharmacology of Botulinum Toxin Beyond Aesthetics

Article History:

Name of Author:
Ban M. Ali[1], Orooba M.S. Ibrahim[2] and Nibras Z Yahya[3]

Affiliation: *[1,2,3]Department of Physiology, Biochemistry and Pharmacology, College of Veterinary Medicine, University of Baghdad, Baghdad, Iraq,*

Corresponding Author:
Ban M. Ali

Received: 22-11-2025
Revised: 05-12-2025
Accepted: 19-12-2025
Published: 30-12-2025

Abstract: ***Background:*** Known as the "poison that heals," botulinum toxin (BoNT) has changed from being a common cosmetic agent to a multipurpose therapeutic tool utilized in many different medical specialties. Although BoNT has long been known for its cosmetic benefits in curing dynamic wrinkles, it is now becoming more well acknowledged for its ability to effectively treat a variety of non-cosmetic illnesses, such as migraines, face spasms, muscle hyperactivity disorders, and laryngeal dystonia. It works by preventing acetylcholine from being released at cholinergic nerve terminals, which relaxes muscles and reduces pain. BoNT's structure allows for selective cellular entry and function because it is a dimer made up of a heavy and light chain. The effectiveness and safety of the toxin are greatly influenced by its pharmacokinetics, which include absorption, diffusion, and distribution. Injection technique and formulation also have an impact on the results. BoNT use needs to be done carefully, especially in patients with neuromuscular problems, despite its encouraging outcomes. Recent developments also investigate its use in new delivery systems as mesobotox and scar therapy. Even if its cosmetic uses are still the most common, research is still being done to increase BoNT's therapeutic potential in a variety of fields.

Keywords: Botulinum, BoNT-A, Neuromuscular, Pain, and Aesthetic.

INTRODUCTION

The term "poison that heals," which is frequently applied to botulinum toxin (BT), is undoubtedly accurate. It is widely used in cosmetic treatments and has been shown to be helpful, especially for dynamic wrinkles [1]. BT's therapeutic benefits for non-cosmetic disorders have also been well-established since the FDA in the United States licensed it for use in cosmetic applications in 2002. Many other specialties, such as urology, otolaryngology, gynecology, ophthalmology, plastic surgery, neurology, and dermatology, now use it as a proven treatment, laryngeal dystonia, vocal tics, stuttering, blepharo-spasm, hemi-facial spasm, rhinitis, and facial nerve paresis are just a few of the problems in the head and neck that BT has been used to treat [2]. Pain control is one prominent therapeutic application of BT. Injections that target muscles innervated by the trigeminal and face nerves have been extremely successful in preventing migraines [3]. Other painful diseases like trigeminal neuralgia and masticatory myalgia have also been successfully treated with BT [2]. In addition to other surgical applications, BT has revealed potential in curing skeletal muscle hyperactivity issues and aiding in the rebuilding of abdominal wall and prosthetic breast [4].

2- Neurotoxin complex and BoNT molecule structure

Botulinum neurotoxin is a protein dimer made up of two separate chains: the heavy chain (H-chain) and the light chain (L-chain). Its molecular formula for is C6760H10447N1743O2010S32. By functioning as a proteases and blocking synaptic release, the L-chain

creates a catalytic portion of the BoNT molecule. In contrast, the translocation domain creates a channel in the cell membrane to let the light chain enter the cell, while the binding domain of the H- chain attaches to the receptors on the target cell surface [5]. This toxin is produced by bacteria and in a composition with various proteins. These include one non-toxic non-hemagglutinin protein and several hemagglutinins [5]. The non-toxic hemagglutinin and hemagglutinin proteins can combine to form a number of different multimeric complexes with BoNT. Each of these complexes, referred to as botulinum neurotoxin complexes, contains a single BoNT molecule that is liberated from the complex in response to changes in the surrounding medium's pH [6].

3- Botulinum toxin absorption and distribution

Both healthy and damaged tissues can allow botulinum neurotoxin (BoNT) to enter the body. BoNT type-A (BoNT/A) medicines are usually injected as close to the target cells as feasible for therapeutic objectives. Though they are not currently in Phase III clinical trials, BoNT/A formulations that can be administered without causing skin damage are still being developed [6]. BoNT normally enters the body through intact epithelium membranes and has the ability to cause botulism by systemic action. The toxin must first penetrate epithelial barriers and enter the general circulation—a process called as absorption—in order to get to its target cells. Transcytosis and the paracellular pathway are the two main ways that BoNT can enter the intestinal or pulmonary epithelium.

During transcytosis, BoNT attaches itself to cell surface ganglioside receptors, internalizes by endocytosis, and travels into the epithelial cell in vesicles. This differs from neuronal uptake in that the toxin is not released into the cytosol nor undergoes structural modifications during this process [7]. The paracellular pathway, on the other hand, entails hemagglutinin proteins attaching to E-cadherin at intercellular junctions. BoNT can enter circulation as a result of the connections being disrupted [8]. BoNT can interfere with gut motility and secretion by binding to cholinergic and serotoninergic neurons in the enteric nervous system after it has passed through the intestinal wall. This has a role in the early signs of newborn and alimentary botulism, including constipation [9].

BoNT enters the general circulation after passing through the epithelial barrier and is dispersed throughout the body's extracellular fluid compartments, with the exception of the central nervous system. BoNT enters the extravascular space from the intravascular compartment and subsequently travels to the intercellular fluid. By entering the extravascular compartment (or intravascular compartment if injected into a blood artery) close to the target cells, BoNT avoids the absorption phase when used therapeutically through local injections. After entering the intercellular space, BoNT attaches itself to receptors at the cholinergic nerve endings on the periphery, where it starts to work as a medication.

4- Neuromuscular transmission

Acetylcholine (ACh) synthesis, storage, release, binding, breakdown, and recycling are the six essential processes involved in cholinergic neuromuscular transmission. First, sodium ions and choline are carried into the cell. Acetylcholine is created inside the neuron by the enzymatic conversion of choline and acetyl-CoA, and it is then stored in synaptic vesicles. These synaptic vesicles fuse with the cell membrane when calcium ions enter the neuron in response to a nerve impulse that reaches the neuromuscular junction. Acetylcholine is released into the synaptic cleft as a result of this fusion. Muscle contraction is the result of a sequence of events that are started when the released acetylcholine attaches to nicotinic receptors on the muscle fibers. Then, acetylcholinesterase enzyme rapidly breaks down acetylcholine, splitting it in to choline and acetate. To keep the neuromuscular transmission functioning continually, the choline is recycled back to the neuron to creates new acetylcholine [10].

5- Mechanism of action

The primary mechanism of action of botulinum toxin is chemical denervation Chemical denervation, which prevents the release of acetylcholine into the synaptic cleft. When BT is injected in to the skin or muscle, its heavy chain binds to receptors on cholinergic nerve terminal. This contact causes the BT molecule to be endocytosed in to the nerve terminal where the light and heavy chains are separated. After then, the light chain binds to a collection of proteins called the soluble N-ethylmaleimide-sensitive fusion (SNARE) complex, which is involved in vesicle fusion. Synaptobrevin (VAMP), synaptosome-associated protein (SNAP-25), and syntaxin are the three essential proteins that make up the SNARE complex. SNAP-25 is cleaved by botulinum toxin type A (BoNT/A), whereas synaptobrevin is cleaved by boNT type B (BoNT/B). cholinergic is not released into the synaptic cleft because BT cleaves these proteins, which prevents cholinergic vesicles from fusing with the neuronal membrane [11].

Both smooth and striated muscles are affected similarly by BT, which causes less muscular growth and even atrophy after repeated injections. The results, however, are not always constant and can

differ. Although not always predicted, there is a link between duration and dose. Higher dosages tend to plateau after roughly three months, while lower doses usually provide effects that last less time. Despite this plateau, the impact is greater at larger doses. Nonetheless, some benefit is still seen even at smaller dosages [12].

6- The classification of aesthetic indications according to the targeted nervous system

Botulinum toxin type A (BoNT-A) has been used extensively in several areas of aesthetic medicine since Carruthers and Carruthers initially showed its cosmetic potential in 1992 [13] by treating glabellar wrinkles. BoNT-A was first developed to reduce wrinkles on the face, but it is now commonly used for treatments like contouring the lower face, altering the neckline and calf, and treating focal hyperhidrosis in places like the scalp and axilla [14]. Also used in facial contouring, BoNT-A causes muscular atrophy from repeated injections, which can alter larger muscles including the calf, masseter, and trapezius [15]. BoNT-A has also been used to treat salivary gland atrophy by preventing parasympathetic innervation, especially in the parotid and submandibular glands, which helps to define the jawline. By relaxing the platysma and depressor anguli oris (DAO) muscles, it also helps in the treatment of gummy smiles by targeting the levator labii superioris alaeque nasi muscle [16].

By altering fibroblast activity, encouraging apoptosis, and modifying inflammatory pathways, BoNT-A has demonstrated promise in treating scars and keloid formation in addition to its effects on muscle modulation. In a systematic study, BoNT-A was found to be more effective than corticosteroids or a placebo in treating keloids and scars [17].

Mesobotox (sometimes called microbotox) is a new treatment that uses superficial, diluted BoNT-A injections to improve skin texture, acne, pore size, and face flushing while also softly relaxing muscles [18]. Even though these innovative uses are becoming more and more popular, more thorough scientific research is required to confirm their efficacy and safety.

7- Factors influencing safety and efficacy

The three main processes of Botulinum Toxin A (BoNT-A) distribution—diffusion (passive spread within tissues), spread (physical movement influenced by the injection technique), and migration (distant effects via nerve or blood transport)—are crucial to its clinical efficacy and safety [19]. However, formulations vary, research shows that Botox, Dysport, and Xeomin have comparable diffusion [20], however RT002 has been shown to have less diffusion and longer-lasting effects [21].

BoNT-A may return via neural pathways and have an impact on the central nervous system (CNS) due to its limited retrograde axonal transport. Through its ability to control neurotransmitter release, BoNT-A may be able to explain some of its therapeutic advantages in disorders including neuropathic pain and chronic migraine [22].

Flu-like symptoms and autonomic side effects are examples of systemic effects of BoNT-A that raise the risk of hematogenous dissemination, or spread through the circulation, especially when combined with BoNT-B [23]. The results are greatly influenced by the injection strategy, including dilution, volume, speed, and depth. For instance, limiting undesired distribution and improving results can be achieved by giving several little injections close to motor endplates [19]. Because BoNT-A increases the risk of worsening weakness, it should not be used in people with neuromuscular conditions including myasthenia gravis or Lambert-Eaton syndrome [24].

CONCLUSION

Botulinum toxin, frequently referred to as "a poison that heal" has evolved from a primarly cosmetic agent to a very versatile therapeutic tool utilized in a variety of medical specialist because of its strong neuro-modulatory effects. BoNT is effective because it inhibits the release of acetylcholine at cholinergic nerve terminals, which eases pain and relaxes muscle. The toxin selective cellular entry and subsequent intracellular activities are made possible by its light and heavy chains structure. Its distribution throughout the body depends on the several complex factors, including injection technique, volume, diffusion and migratory pathways. Plus, BoNT has a several therapeutic benefits beyond looks, while being most commonly utilized for cosmetic objectives such as wrinkle reduction, facial contouring, and the treatment of hyperhidrosis. It has shown effective in treating pain syndrome, muscular hyperactivity issues and even scar formation.

It is essential to understand the pharmacokinetics of botulinum toxin, adhere to precise dosing guidelines, give injection accurately, and be aware of contraindications in order to optimize results. Additionally, even though BoNT established uses are widely known, more research is necessary to validate its effectiveness in more recent and emerging indications.

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