

Botulinum Toxin: An Elegant Therapeutic Tool

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Abstract

Botulinum toxin, an exotoxin produced by *Clostridium botulinum*, causes botulism by inhibiting the release of acetylcholine from vesicles at the neuromuscular junction. However, physicians are recognizing its vast potential as a therapeutic agent to treat conditions where muscle paralysis is desirable such as dystonia, spasticity and bladder dysfunction. Botulinum toxin has some limitations in that it only provides symptomatic relief for a duration of several months but it is still more effective than most of the other treatments available for these conditions since it is longer-lasting and allows physicians to target the site of interest accurately.

HISTORY

Although food borne botulism was recognized as a threat in the tenth century by Emperor Leo VI of Byzantium, it was a German physician Kerner who in 1820, published the first accurate clinical description of botulism.

Kerner documented not only flaccid paralysis but also the key autonomic symptoms such as dry mouth and absence of secretion of sweat, tears, and ear wax. Remarkably, he envisaged the use of botulinum toxin for treatment of hyperkinetic movements and conditions such as excessive sweating.

Following isolation of the toxin, Dickson and Shevsky characterised how the toxin acts upon the nervous system. They demonstrated that the toxin worked by binding to receptors at the neuromuscular junction, which was then followed by flaccid paralysis. One hundred and fifty years after Kerner's original vision Scott demonstrated the use of botulinum toxin (serotype A) for treatment of strabismus, first in monkeys and then in humans.

The toxin received FDA approval in 1989 to treat strabismus, hemifacial spasm, and blepharospasm in patients younger than 12 years of age. Botulinum toxins have now been widely accepted for treatment of various muscle pain disorders, spasticity and cervical dystonia to reduce the severity of neck pain and abnormal head position.¹

Physiological Mechanisms

There are seven distinct serotypes of the toxins (serotypes A-G) which are all produced by *Clostridium botulinum*. All types have a light and a heavy chain, the heavy chain is important for

endocytosis whereas the light chain acts intracellularly to prevent acetylcholine release (Figure 1). Types A, B, E and rarely F and G are associated with human botulism whereas the human nervous system is resistant to types C and D.²

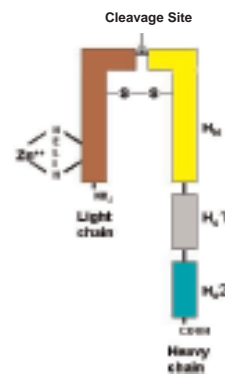


Figure 1. Molecular structure of Botulinum toxin, showing the relationship between heavy and light chains.³

Although oral ingestion of the toxin in improperly preserved food is the most common cause of botulism, the toxin can also be inhaled. Both routes require penetration across an epithelial layer, absorption into the circulatory system and eventual uptake by a nerve terminal at the neuromuscular junction.

Once at the neuromuscular junction the first step is internalisation of the toxin into cholinergic neurones. The toxin's heavy chains bind to high affinity areas in the presynaptic nerve terminals. Endocytosis of plasma membrane containing toxin-receptor complexes introduces the toxin within endosomes into the presynaptic neurone. Once internalised, the disulfide bond between light and heavy chains is cleaved and the light chain of the toxin is translocated across the endosomal membrane into the cytoplasm of the nerve terminal. The light chain of serotypes A and E cleave the cytoplasmic synaptosomal-associated

protein (SNAP-25 protein) required to dock the acetylcholine vesicles on the inner side of the nerve terminal plasma membrane (Figure 2). Serotypes D, B and F impede the release of acetylcholine into the synaptic cleft by preventing the vesicles associated membrane protein/synaptobrevin protein complex. Serotype C acts by cleaving a target membrane protein called syntaxin.⁴

By preventing release of acetylcholine into the synapse, the toxin prevents the neuromuscular end plate from depolarising and the muscle from contracting. The result is decreased muscle tone. This is the therapeutic effect sought when using botulinum toxin to treat muscle spasticity or dystonia.

Therapeutic Uses

Botulinum toxin is used to treat spasticity associated with neurological disorders such as Parkinson's disease, multiple sclerosis, stroke-related neurologic sequelae and cerebral palsy. The mechanism behind spasticity is poorly understood, but is most likely due to an imbalance of inputs from reticulospinal and other descending pathways, such as the corticospinal system from the brain to interneuronal circuits of the spinal cord. This leads to involuntary muscle contractions and increased muscle tone. Patients suffering from spasticity appear to shake excessively since the muscles are overactive and readily spasm. Spasticity can strike at any time and is exacerbated by stress, temperature, pain and position.⁶

Many dystonias are now successfully being treated by botulinum toxins. In this debilitating condition, certain parts of the body are forced into abnormal and often painfully awkward positions. Some of the most important forms of dystonia, treated with the toxin, include blepharospasm, torticollis, writer's cramp, oromandibular dystonia and laryngeal spasms.

Current therapeutics used to treat spasticity and dystonia include dopaminergics, anticholinergics, benzodiazepines (GABA-A antagonists) and baclofen (GABA-B agonist). However, these treatments prove to be less than effective and have more side effects than botulinum toxin.⁶ One of the key advantages of botulinum toxin is that it is injected directly into the target group of spastic muscles, therefore localizing the treatment and avoiding systemic effects. Deep muscles for example, laryngeal muscles, require the use of

electromyography to guide the administration of the toxin.⁷

Successful treatment of urinary complications such as bladder dysfunction or urinary incontinence has also been shown with botulinum toxin. In a study of 50 patients suffering from various forms of bladder incontinence investigators evaluated the effect of direct botulinum toxin injection into the urethra or ureter. The results showed that two thirds of patients reported an absence of incontinence while the remaining one third of patients experienced reduced incontinence with results lasting up to six months. Other treatment options include anticholinergics to weaken the bladder muscles or alpha-adrenergics to strengthen the sphincter. Botulinum toxin proved more effective in comparison to these agents as a result of its ability to be localised to bladder muscles and was associated with fewer side effects.³

Botulinum toxin is proving useful for various ophthalmologic conditions, including strabismus, nystagmus and blepharospasm. The toxin is injected into various ocular muscles or the orbicularis oris in the case of blepharospasm, thus avoiding surgically invasive treatments.⁹ Botulinum toxin has also been demonstrated as a non-invasive alternative to surgery for problems such as hyperhidrosis, vaginismus, achlasia, and excessive salivation.^{10,11}

The use of botulinum toxin for these and other conditions related to muscle spasticity is not considered curative and must be repeated every few months to continue providing effective relief. Results are usually evident in three to 10 days, peak by two to six weeks and fade three to six months later.¹²

The major adverse effects are bleeding at injection site and headaches. Rarely, severe complications have been reported such as pain, oedema, flu like symptoms, and allergic reactions. Botulinum toxin is contraindicated in patients with prior allergic reactions, neuromuscular disorders such as myasthenia gravis and should be avoided while pregnant or breast-feeding.¹²

Therapeutic Challenges

Patients may fail to respond to a first dose of botulinum toxin due to inadequate injection, denatured toxin, variations in synaptic docking proteins or previous subclinical exposure

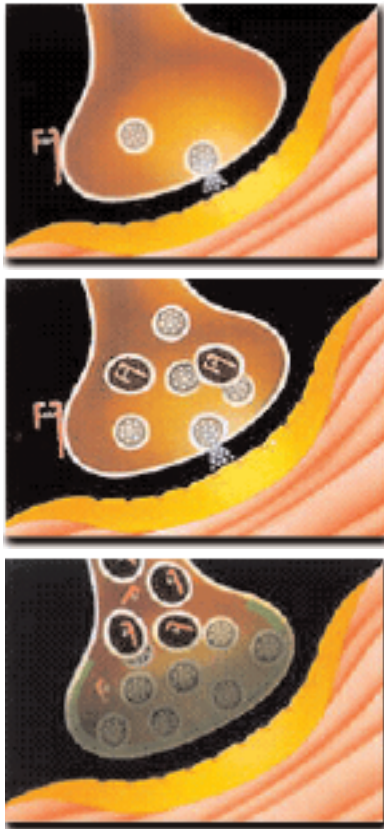


Figure 2. The mechanism of Botulinum toxin at the neuromuscular junction. The toxin binds to the neuronal membrane before entering the neuron by endocytosis. Once endocytosed, the light chain enters the cytoplasm and prevents the vesicles releasing acetylcholine into the synapse.³

immunizing the patient. These patients are termed primary non-responders. Secondary non-responders are patients who initially responded to toxin but due to development of antibodies

against the toxin, do not achieve response on subsequent injection. In most cases, symptomatic relief lasts for approximately three months, necessitating repeat injections in most chronic conditions.

It is obviously desirable to avoid secondary nonresponse and various risk factors for this have been identified. They include injection of a dose higher than required to treat symptoms and booster injections given within a one month period. In cases of nonresponsiveness due to neutralising antibodies, switching the toxin to a different serotype may provide a way to evade antibodies.¹³

One of the most important issues in the use of

botulinum toxin involves appropriate dose titration. Two to three injections, administered on separate visits are often required before symptomatic relief is accomplished. Inevitably some patients elect not to continue after the first injection fails to meet their expectations. However, a recent evidence based review on the use of botulinum toxin A in treatment of a variety of disorders showed 85 percent of studies demonstrate an improvement in quality of life, 91 percent demonstrate improvement in impairment and patients report high rates of satisfaction with the treatment.¹⁴

CONCLUSION

Botox has become one of the most talked about drugs in recent years, second perhaps only to Viagra in terms of column inches glossy magazines have dedicated to its wondrous anti-ageing benefits. What has not been so well documented is that long before this recent interest, botulinum toxin has been gaining approval in a much less glamorous niche. The last fifteen years has seen botulinum toxin proven effective and gaining acceptance in the treatment of dystonias and spasticity. The toxin has been shown to be highly satisfactory for patients and is associated with an improved quality of life. This outcome is particularly gratifying given the poor outcome of alternative treatments.

Greater standardisation of toxins and improved technique will doubtlessly result from widespread use in cosmetic surgery, as paying customers demand a safer and more effective treatment. So ironically the use of botulinum toxin in cosmetic surgery may in the future prove beneficial to those using it for dystonias and spasticity. Indeed many future treatments for wrinkles and ageing may also prove effective for neuromuscular disorders and so cosmetic surgery may someday repay neurology for this tool.

This simple toxin which previously featured in the annals of history as a threat to health has turned its' fate around and looks to play an important role as safe therapy for many suffering debilitating dystonias and spasticity.

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