

Chapter

6

Myriad Uses of Botulinum Toxin

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Introduction

Botulinum toxin (BTX) is an endotoxin produced by *Clostridium botulinum*, a gram-positive anaerobic bacterium¹. Seven serotypes of botulinum toxin (BonT) are known and these are labeled as types A, B, C (C₁, C₂, D, E, F, and G. These are structurally similar. BonT molecule is synthesized as a single chain (150 Kd) and then cleaved to form the dichain molecule with a disulfide bridge. The light chain (~50 Kd -with amino acids 1-448) acts as a zinc (Zn⁺⁺) 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 binding of the toxin to presynaptic receptors, and promotes light chain translocation across the endosomal membrane.

The discovery by Burgen et al, in 1949² that botulinum toxin blocks neuromuscular transmission provided theoretical foundation for the development of the toxin as a therapeutic tool. The clinical use of purified botulinum toxin (BonT) represents one of the most dramatic role reversals in modern medicine: a potential evil transformed into a health benefit and now used widely as a therapeutic agent in an expanding scope of human conditions. The discussion will focus on the myriad uses of BonT type A, the serotype commercially available for clinical use. Clinical experience is emerging also with BTX types B³ and F⁴.

Mechanism of Action

a. *Botulinum toxin muscular activity: Effect at the neuromuscular junction and muscle spindle*

BonT acts by binding presynaptically to high-affinity recognition sites on the cholinergic nerve terminals and decreasing the release of acetylcholine, causing a neuromuscular blocking effect. BonT induces weakness

of striated muscles by inhibiting transmission of alpha motor neurons at the neuromuscular junction. This has led to its use in conditions with muscular over activity, such as dystonia. Transmission is also inhibited at gamma neurons in muscle spindles, which may alter reflex over activity⁵. Recovery occurs through proximal axonal sprouting and muscle reinnervation by formation of new neuromuscular junction.

b. *Beyond muscular effects: Antinociceptive activity*

Because local muscle paralysis and reduction in overall muscle contraction do not fully explain the pain relief mechanism of BonT-A, it is postulated that BonT-A inhibits peripheral sensitization of nociceptive fibers, thereby indirectly reducing central sensitization. BonT-A inhibits both substance P and Ach-mediated response in cholinergic neurons in animal studies. It blocks the release of substance P, a molecule that is involved in pain perception, promotes vasodilatation, neurogenic inflammation and hence pain perception⁶. BonT also inhibits release of acetylcholine in all parasympathetic and cholinergic postganglionic sympathetic neurons thereby extending its spectrum of its use for various painful disorders. This has also fuelled interest in its use as a treatment for overactive smooth muscles (for example, in achalasia) or abnormal activity of glands (for example, hyperhidrosis).

Therapeutic Uses

a. *Focal dystonias* - Involuntary, sustained, or spasmodic patterned muscle activity

- Blepharospasm (eyelid closure)
- Cervical dystonia (spasmodic torticollis)
- Laryngeal dystonia (spasmodic dysphonia)
- Limb dystonia (writer's cramp)

- Oromandibular dystonia
 - Orolingual dystonia
 - Truncal dystonia
- B. Spasticity** - Velocity-dependent increase in muscle tone
- Stroke
 - Traumatic brain injury
 - Cerebral palsy
 - Multiple sclerosis
 - Spinal cord injury
- C. Non-dystonic disorders** of involuntary muscle activity
- Hemifacial spasm
 - Tremor
 - Tics
 - Myokymia and synkinesis
 - Myoclonus (tensor veli palatini muscle, causing tinnitus)
 - Hereditary muscle cramps
 - Strabismus (disorder of conjugate eye movement) and nystagmus
- D. 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
 - Freezing in Parkinson's disease
- E. Smooth muscle hyperactive disorders**
- Detrusor-sphincter dyssynergia
 - Achalasia cardia
 - Hirschsprung disease
 - Sphincter of Oddi dysfunctions
 - Chronic anal fissures
- F. Cosmetic use**
- Hyperkinetic facial lines (glabellar frown lines, crow's feet)
 - Hypertrophic platysma muscle bands
- G. Sweating disorders**
- Axillary and palmar hyperhidrosis

- Frey syndrome, also known as auriculotemporal syndrome (gustatory sweating of the cheek after parotid surgery)
- Sialorrhea in ALS and Parkinson's disease.

Blepharospasm

The first double-blind, placebo-controlled trial, reported in 1987, established the safety and efficacy of BonT in the treatment of this form of focal dystonia⁷. Numerous subsequent reports confirmed the beneficial effects of BonT when injected into the eyebrows and the orbicularis oculi⁸. The average dose of BonT-A is 10 U in each eyebrow, 10 U in the upper eyelid and 5 U in the lower eyelid. Over the years the technique has been gradually refined. For example, a controlled study showed that injection of BonT into the pretarsal, rather than the preseptal, portion of the orbicularis oculi is more effective and is associated with lower frequency of ptosis. Moderate to marked improvement is usually noted in over 90% of patients treated for blepharospasm. In addition to observed functional improvements, such as improved ability to read, drive, or watch TV, there is usually a meaningful amelioration of discomfort and quality of life also. The average latency from the time of the injection to the onset of improvement is approximately 4 days. The average duration of maximum benefit is 3 months, but the total benefit may last considerably longer, up to 6 to 8 months in some cases.

Only about 10% of patients experience complications, such as ptosis (most common), blurring of vision or diplopia, tearing, and local hematoma. Complications usually improve spontaneously in less than 2 weeks. Ptosis and other complications can usually be prevented by initially injecting only 5 U in the lateral portion of the upper lid and 5 U medially. Many authors have also demonstrated that unilateral injection improves bilateral blepharospasm, possibly via toxin spread but more likely as a result of some physiological mechanism peculiar to dystonia. In addition to idiopathic blepharospasm, BTX injections have been used effectively in the treatment of blepharospasm induced by drugs (e.g. levodopa in parkinsonian patients or neuroleptics in patients with tardive dystonia), dystonic eyelid and facial tics in patients with Tourette's syndrome, and in patients in whom blepharospasm has been associated with "apraxia of eyelid opening."

Oromandibular Dystonia

It is among the most challenging forms of focal dystonia to treat; it rarely improves with medications, and there are no surgical treatments. The masseter

muscles are usually injected in patients with jaw-closure dystonia (average dose = 30 U per muscle), and the lateral pterygoid and/or submental muscle complex is usually injected in patients with jaw-opening dystonia (average dose: 20 U). A meaningful reduction in the oromandibular-lingual spasms and an improvement in chewing and speech are achieved in more than 70% of all patients. The improvement is usually noted within an average of 5 days after the injection and lasts 3 months. Patients with dystonic jaw closure generally respond better than those with jaw-opening dystonia. Temporary swallowing problem is present in less than 20% of treatment sessions. BonT injections provide the most effective relief of oromandibular dystonia, and early treatment may prevent dental and other complications, including the temporomandibular joint syndrome and other oral and dental problems associated with persistent jaw clenching and bruxism⁹.

Laryngeal Dystonia (Spasmodic Dysphonia)

Until the introduction of BonT, the prospects for effective therapy of spasmodic dysphonia had been disappointing. The anticholinergic and benzodiazepine drugs only rarely provide meaningful improvement in voice quality. Unilateral transection of the recurrent laryngeal nerve, although temporarily effective in most patients, frequently causes unacceptable complications and the voice symptoms often recur. Several studies have established the efficacy and safety of BonT in the treatment of laryngeal dystonia, and this approach is now considered by most to be the treatment of choice for spasmodic dysphonia¹⁰. In adductor spasmodic dysphonia, the toxin is injected through a monopolar, hollow, Teflon-coated needle directed into the thyroarytenoid muscle. Irrespective of the technique, most investigators report about 75 to 95% improvement in voice symptoms. The dosage can be adjusted depending on the severity of glottal spasms and the response to previous injections. Adverse experiences include transient breathy hypophonia, hoarseness, and rare dysphagia with aspiration. Although technically more complicated, BonT injections into the posterior cricoarytenoid muscle, with the EMG needle placed posterior to the thyroid lamina, may be used in the treatment of the abductor form of spasmodic dysphonia. BonT produces variable results in the treatment of voice tremor and stuttering¹¹.

Cervical Dystonia (Spasmodic Torticollis)

The efficacy and safety of BonT in cervical dystonia has been demonstrated in several open-label and double

blinded trials¹². In one double blind placebo controlled trial of 55 patients with cervical dystonia, 39% experienced moderate to marked improvement after BonT injection, but none had a similar degree of improvement after placebo¹². Open-label studies generally report improvement in 90% or more of patients. Proper dose and site of injection have been shown to be the most important determinants of a favorable response to treatment. The average latency between injection and the onset of improvement is about 1 week, and the average duration of maximum improvement is 3 to 4 months. On average, the injections are repeated every 4 to 6 months. Less than 5% of patients fail to improve after repeated injections. Results similar to those obtained with BonT-A have been obtained in patients treated for cervical dystonia with BonT type B. Up to 20% of patients experience complications such as swallowing difficulties and neck weakness. Dysphagia after injection into one or both sternocleidomastoid muscles is the most common complication and resolve spontaneously, usually within 2 weeks. Brachial plexopathy has been rarely reported after BonT injection for cervical dystonia¹³. EMG may be helpful in some patients with obese necks or in whom the involved muscles are difficult to identify by palpation.

Writer's Cramps and Other Limb Dystonias

Treatment of writer's cramps with medical and surgical therapies has all been disappointing. Several open¹⁴ and double blind trials¹⁵ have concluded that BTX injections into selected hand and forearm muscles provide the most effective relief in patients with these task-specific occupational dystonias. In one study of 19 patients with hand dystonia, some benefit was produced in 84%. The latency from injection to onset of effect averaged 6 days and the benefit lasted an average of 10 weeks. Temporary hand weakness, common complication, occurred in 54% of patients. In addition to improving writer's cramps, BonT may provide relief in other task-specific disorders affecting typists, draftsmen, musicians, sportsmen, and other people who depend on skilled movements of their hands. Local injection of BonT may benefit patients with foot dystonia as a manifestation of idiopathic torsion dystonia, and patients with parkinsonism who may experience foot dystonia as an early symptom of their disease, or more commonly, as a complication of levodopa therapy. BonT injections may not only alleviate the disability, pain, and discomfort, but improves gait. Whether BonT injections will play an important role in the treatment of recurrent painful physiologic foot and calf cramps has yet to be determined.

Hemifacial Spasm

Hemifacial spasm is not only annoying, but also socially embarrassing, and in some patients it causes blepharospasm that can interfere with vision. While microvascular decompression of the facial nerve has a high success rate, this surgical treatment also carries some serious risks, such as permanent facial paralysis, deafness, stroke, or death. Local injections of BonT into involved facial muscles offer a useful alternative to surgical therapy. Nearly all patients improve, the complications are minimal and transient, and the approach can be individualized by injecting only those muscles whose contractions are most disturbing to the patient. The average duration of improvement of hemifacial spasm is about 5 months, longer than the dystonic disorders.

Tremor

While propranolol, primidone, and other anti-tremor medications may be satisfactory, pharmacotherapy alone is usually not sufficient for a high-amplitude tremor. In some severe cases, neurosurgical treatment (thalamotomy or thalamic stimulation) provides satisfactory relief. Tremor accompanies dystonia in about half of all dystonic patients. The use of BonT specifically for tremor followed the observation that some patients treated with BonT for their focal dystonia also noted improvement in their tremor¹⁷. In a placebo-controlled study of 25 patients with essential hand tremor, 50 U of BTX injected into the wrist flexors and extensors of the dominant limb resulted in moderate but definite reduction in the amplitude of the tremor. Four weeks after injection, patients treated with BonT showed a significant improvement ($P < 0.05$) on the tremor severity rating scale as compared to placebo, and this effect was maintained for four weeks. Also after 4 weeks, 75% of BonT-treated patients vs. 27% of placebo-treated patients ($P < 0.05$) reported mild to moderate improvement, a result confirmed by accelerometric recordings. In an open trial, the average duration of improvement was 10.5 weeks.

Tics

Tics are rarely disabling and usually improve with anti-dopaminergic drugs. Some patients, however, have troublesome tics that may cause functional blindness or local discomfort. In a study of 10 patients, 5 with disabling blinking and blepharospasm and 5 with painful dystonic tics involving the neck muscles showed moderate to marked improvement after BonT injection in all patients¹⁸. The improvement lasted 2 to 20 weeks and, except for transient ptosis in 2 patients, there were

no other complications. BonT injections into the vocal cords, in the manner similar to the technique used for spasmodic dysphonia, have been found useful in the treatment of loud phonic tics and coprolalia.¹⁸

Spasticity and Other Disorders of Muscle Tone

Intramuscular injections of BonT have been found to be useful in the treatment of spasticity in multiple sclerosis (MS), cerebral palsy (CP)¹⁹, stroke²⁰, traumatic brain injury (TBI), and spinal cord injury (SCI). Different studies have shown the effectiveness of BonT-A injection in the management of spasticity. It was shown to improve gait pattern in patients with cerebral palsy with progressive dynamic equinovarus and equinovalgus foot deformities. Treatment of children with cerebral palsy during the key early years when functional skills in walking are being developed improves the outcome and may help to avoid surgery for contracture and bony torsion²¹. In multiple sclerosis the toxin can relieve contractions of thigh adductors that interfere with sitting, positioning, cleaning, and urethral catheterization. It can also reduce muscle tone and increase range of movement in upper extremity spasticity or in spastic foot drop after a stroke. Whether this translates into functional improvement has yet to be substantiated.

Strabismus and Other Ocular Motility Disorders

The idea behind using BonT A in disorders of ocular motility is to shorten the non-injected antagonist muscle in order to align the visual axes. In patients with concomitant strabismus, who have compromised or absent binocular fusion, treatment is cosmetic as permanent ocular realignment cannot be expected. In secondary strabismus resulting from transient monocular vision loss (such as posttraumatic cataract), toxin injections can help to establish whether binocular cooperation is still present. If so, the patient would be a candidate for surgery to restore ocular function. BonT has also proved useful when surgery has over or under corrected strabismus. Paralytic strabismus is due to weakness of extraocular muscles. Injections into the ipsilateral antagonist can prevent contracture of this muscle. In restrictive causes of strabismus, for instance in dysthyroid eye disease, BonT can help to realign the eye before more definitive surgery. Complications include transient ptosis, subconjunctival hemorrhage, and transient vertical deviations of the globe.

Pain Management

Use of BonT A in the management of different pain disorders is being also studied. At this time, indications

for the use of BonT in managing muscle pain disorders still are controversial. The exact mechanism of action of BonT in causing analgesic effect is not known; however, a recent study by Purkiss and colleagues shows that BonT inhibits calcium-dependent release of substance P in embryonic dorsal root ganglia. Hence, a mechanism of analgesic effect may be due to peripheral inhibition of C and A delta fibers by blocking the release of substance P. In a recent double-blind randomized placebo-controlled study, Foster et al showed efficacy of 200 U of botulinum toxin type A injection, 40 U/site at 5 lumbar paravertebral levels on the side of maximum discomfort in chronic low back pain patients. Different studies have shown effectiveness of BonT in the management of different painful disorders, tension headache, myofascial pain²², fibromyalgia pain²³, pain secondary to temporomandibular joint disorders²⁴.

Hyperhidrosis

Primary hyperhidrosis is defined as excessive, uncontrollable sweating without any discernible cause. It commonly involves the axilla, palms, and soles. Severely affected patients have skin maceration and secondary microbial infections and drenching of clothes, especially from axillary hyperhidrosis. Though not life-threatening, it is socially embarrassing. Therapies that have been shown to reduce the rate of sweat production include iontophoresis, topical application of aluminum chloride and administration of anticholinergic agents and beta-blockers. For axillary hyperhidrosis, however, iontophoresis is cumbersome. Application of aluminum chloride often must be discontinued because of skin irritation. Anticholinergic agents and beta-blockers may have substantial side effects. In certain instances, the surgical removal of sweat glands may be considered. Sympathectomy is of limited benefit for isolated axillary hyperhidrosis. Recently, the intradermal injection of botulinum toxin A has been shown to be effective in patients with gustatory sweating (pathologic sweating in response to the tasting of food, also known as Frey's syndrome) and those with axillary sweating²⁵ palmo-plantar sweating, or compensatory sweating (sweating in a circumscribed area because of lack of sweating in other areas). Mechanism proposed for this is that BonT-A blocks neuronal acetylcholine release at the neuromuscular junction and in cholinergic autonomic neurons. Open label, multicenter trial of BonT-A in 145 patients showed improvement after BonT injection²⁶.

Sialorrhea in Amyotrophic Lateral Sclerosis (ALS)

Sialorrhea is a disabling symptom in patients with bulbar amyotrophic lateral sclerosis (ALS) affecting up

to 20% of patients with ALS²⁷. The use of oral anticholinergic drugs is often limited by lack of efficacy or by unacceptable adverse effects with higher doses. BonT-A blocks the release of acetylcholine in motor and autonomic nerve terminals. In animals, immunohistochemistry studies have shown a significant reduction of acetylcholinesterase in the salivary glands and a reduction of saliva production after local treatment with BoNT-A. Inhibition of secretion of salivary glands by local application of BonT-A could therefore be considered as a therapeutic approach for sialorrhea in patients with bulbar ALS. In a study of five patients BonT-A ameliorated sialorrhea and improved quality of life. It was concluded that BTX may be safe and effective treatment for sialorrhea in selected patients.

Migraine and Tension-type Headache

Historically while conducting initial clinical trials of BonT-A for the treatment of facial lines, Binder et al noted improvement of migraine headache symptom^{28,29}. Based on these findings multicenter open label and randomized trials had been conducted. Mauskop and Basedo reviewed record of 27 patients treated for migraine prophylaxis with BonT-A²⁹. A decrease in headache frequency and severity was reported in 85% (n=23) of patients. Eross and Dodick evaluated the effect of BonT-A (25 to 100 units) on reducing disability in 48 patients with either episodic or chronic migraine. 58% reported decrease in migraine associated disability. Recently, Ondo et al²¹ conducted double blind placebo controlled parallel clinical trial of BonT-A on patients with chronic daily headache, including chronic tension headache and chronic migraine. At 24 weeks patients who had received 2 BonT-A injections had significantly fewer headache days over the second 12 week period than those receiving one injection (40 versus 19 days, $p < 0.05$) showed greater efficacy with repeated dosage.

The most common sites of injections include glabellar, frontal, temporal and occipital regions. BonT-A is administered either as a fixed injection or at sites of maximum pain or tenderness (follow the pain) or a combination of both. The total dosage administered ranges between 25 and 300 units over several injection sites. BonT-A has a long duration of action that may last longer than 3 months with no systemic or serious adverse events observed.

Miscellaneous Uses

In addition to the movement disorders, other involuntary muscular contractions are now successfully treated with BonT which include palatal myoclonus, achalasia, gustatory sweating, tennis elbow, sphincter disorders such as detrusor-sphincter dyssynergia³⁰,

anismus associated with intractable constipation caused by spasm of the rectal sphincter, and vaginismus. There has been growing interest in the use of BTX in cosmetic applications, such as correction of wrinkles and frown lines.

The safety, effectiveness, specificity, and reversibility of BTX make it a powerful and versatile tool in a wide variety of neurological disorders, and it is likely that the applications of BTX therapy will continue to expand in the future. Gratifyingly, less than 5% of those treated for cervical dystonia and only rare patients treated for other disorders have become resistant through development of blocking antibodies²⁶. Some of these patients have benefited from injections by different preparations of BonT-A or BonT types B and F.

CONCLUSION

Botulinum toxin has now become an important tool in the management of a variety of neurological and non neurological disorders. Its safety and drawbacks including side effects are well studied and hence we now know how to avoid them. In future newer indications may be found where BonT may be useful.

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