CHAPTER 35

APPLICATIONS OF BOTULINUM TOXIN-A IN THE LOWER EXTREMITY

James H. Morgan, Jr., D.P.M.

The bacterium, *Clostridium botulinum,* is a gram positive, rod-shaped, anaerobic organism that produces a powerful exotoxin which causes botulism, a condition similar to food poisoning. Affected individuals develop signs and symptoms within hours of ingesting contaminated food. Early symptoms include visual disturbances and bulbar paresis, followed by generalized muscle weakness. Severe cases result in respiratory paralysis, leading to death.

The first study on the effect of botulinum toxin (BTX) as a therapeutic agent was published in 1973 by Dr. Alan Scott, an ophthalmologist in San Francisco. Scott was searching for an alternative to surgery for treatment of strabismus in children. His study revealed that BTX type A (BTX-A) induced transient weakness on lateral rectus muscles in monkeys, lasting several months without significant local or systemic side effects. In 1981, Scott published his results with the first application of BTX-A in humans suffering from strabismus. Scott then expanded his use of BTX-A to include treatment of blepharospasm in 1985. Mauriello et al. and Carruthers and Stubbs reported their results for treatment of hemifacial spasm.

After its establishment as an agent for cervical dystonia (Tsui et al.) the most common focal dystonia, the neurological applications of BTX have been extensive, including torticollis, kyphoscoliosis, limb dystonia, spasticity, oromandibular dystonia, laryngeal dystonia, tremor, tics, stuttering and palatal myoclonus. It has also been used in urology (detrusor-sphincter dyssynergia), gastroenterology (anismus and achalasia), and dermatology (facial wrinkles and frown lines). BTX may offer another treatment option to podiatric physicians for patients with dystonia or spasticity of the lower extremity.

MECHANISMS OF ACTION OF BOTULINUM TOXIN

Botulinum neurotoxin has seven unique serotypes: A, B, C, D, E, F, and G. BTX-A is the most commonly used serotype because of its longer duration of action. It has a molecular weight of 150,000 and consists of a heavy chain (MW 100,000) and a light chain (MW 50,000). The heavy chain is responsible for rapidly and strongly binding to presynaptic cholinergic nerve terminals at the neuromuscular junction. The toxin is then internalized via endocytosis and ultimately acts as a metalloendopeptidase and cleaves SNAP-25, a protein complex necessary for docking of acetylcholine vessicles to the cell membranes before they can be released (Fig. 1).

This inhibition is brought about by the light chain. Muscle treated with BTX-A loses junctional acetylcholine receptors at an accelerated pace. Within a few hours post-injection, paralysis and a nearly complete decline of miniature end-plate potentials occurs. A delay in onset of clinical effect may be due to spontaneous release of acetylcholine. Injected muscle becomes functionally

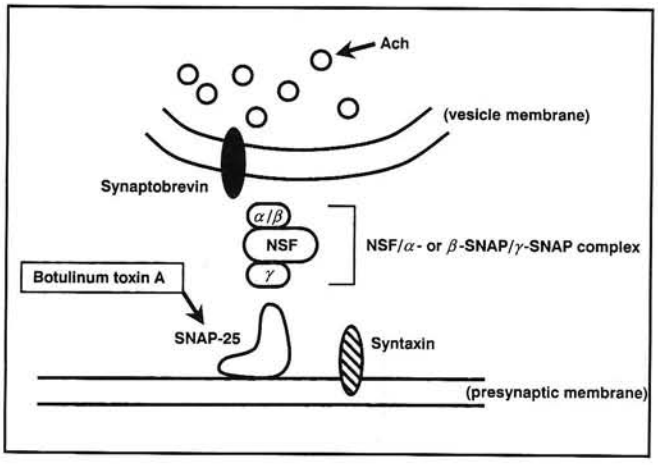

Figure 1. Botulinum toxin A cleaves the SNAP-25 receptor in the presynaptic membrane of the neuromuscular junction.

enervated, atrophies, and develops extrajunctional acetylcholine receptors. The axon terminal begins to sprout within two days after muscle exposure to the toxin. The proliferating branches then form new synaptic contacts on the adjacent muscle fibers. Functional recovery of the neuromuscular junction occurs in three to six months, while sprouting and remodeling can take place for up to three years.

BTX-A is quantified in mouse units (MU). One MU is the amount of toxin required to kill 50% of a batch of 18 to 20g female Swiss-Webster mice (LD50). The LD50 for humans, extrapolated from monkey experiments, is estimated to be 40 MU/kg or 2500-3000 MU for a 70kg man. This is not a perfectly accurate calculation of the toxic dose for humans due to species difference in sensitivity.

The two commercially available BTX-A preparations are Botox , prepared by Schantz in 1979 and marketed by Allergan Inc., Irvine, CA; and Dysport, supplied by Speywood Pharmaceuticals, England. One nanogram of Botox is equivalent to 2.5 MU, and one Botox MU is equivalent to 3-5 Dysport MU. Botox is supplied in 100 MU vials. The vials are diluted in 1 mL, 2 mL, 5 mL, or 10 mL of normal saline to produce concentrations of 10 MU, 5 MU, 2 MU or 1 MU per 0.1 mL, respectively.

Larger muscles require larger doses of toxin; therefore, more concentrated solution injections can be performed with less volume. The toxin is injected with a tuberculin needle into the muscle belly frequently with EMG guidance to insure placement only in the desired muscle. Theoretically, the smallest dose and volume delivered precisely at the motor endplate is the best technique. Injections should only be performed by someone who is experienced with this technique.

Improvement of symptoms usually occurs after a 1 to 14 day latent period post-injection. Peak effect is reached in about 2 to 6 weeks. Effects wear off after 10 to 12 weeks. Muscle atrophy is noted within two weeks after treatment, and muscle mass returns to 70%-80% of original bulk after three months.

CLINICAL APPLICATIONS IN THE LOWER EXTREMITY

Foot Dystonia

Foot dystonia is the most frequent initial symptom of focal dystonia in childhood, and it usually progresses to a generalized dystonia. In adults, it is not progressive and rarely begins in an isolated manner in the legs. It can occasionally be observed in untreated Parkinson's disease, and more commonly is seen in advanced stages of the disease related to chronic levodopa therapy in approximately one-third of parkinsonian patients treated for more than three years. Symptoms usually occur during the "off" period especially in the afternoon or early in the morning before the first dose is taken, or late at night when levodopa levels are low. This phenomenon is related to an underlying dopaminergic central dysfunction. Foot dystonia predominates on the side most affected by parkinsonism and becomes worse when the patient attempts to walk. The foot assumes a plantarflexed and inverted position. Injections of 50 to 150 MU into the tibialis posterior muscle may relieve painful foot dystonia for months, and may improve gait.

Muscle Cramps

Patients with inherited benign cramp-fasciculation syndrome, an autosomal dominant disorder, experience frequent muscle cramps that can be very distressing and disabling. Treatment consists of quinine, carbamazepine, phenytoin, or diazepam. Because these are otherwise healthy patients, these drugs often cause unwanted systemic side effects, have potential toxicity, require daily administration, and frequently provide inadequate relief. These patients have lower cramp threshold frequency. When treated with BTX-A, these patients show relief of symptoms with no weakness or fatigability of injected muscles.

Spasticity

Spasticity, a velocity-dependent resistance to passive movement, can be caused by any disease of the cerebral cortex, brainstem, or spinal cord. It is associated with other upper motor neuron symptoms such as motor weakness, increased tone, hyper-reflexia with release of cutaneomuscular

reflexes, and impairment of voluntary control. Spasticity results in joint stiffness reducing range of motion. Intermittent spasms may also be seen. Ultimately, contractures will develop. Conventional treatments include spasmolytic agents, various surgical techniques (rhizotomy, tenotomy, tendon transfer, and osteotomy), phenol injections, and intrathecal baclofen. A large number of patients are not relieved by conventional therapy.

Patients with chronic multiple sclerosis can develop "spastic ankles" where in addition to weakened dorsiflexors, producing footdrop, they may have spasticity of the gastrocnemius and soleus muscles. This lack of mobility of the ankles makes walking and application of splints difficult. Flexibility of the ankle can be increased with BTX-A injections.

Post-stroke spasticity is another potential application for BTX-A. Premature calf muscle activation in the terminal swing phase of gait has been shown by kinematic EMG to be an important cause of equinovarus deformity after stroke. Doses of 50 MU to 150 MU are suggested for gastrocnemius, soleus, and tibialis posterior. Early trial results are encouraging, according to Tsui and O'Brien, who report two-thirds of ten patients with functional improvement and all patients having relief of spasticity. Dengler et al. and Hesse et al. noted reduction in tone, increase in passive ankle range of motion, and improved gait after injecting patients with spastic dropfoot deformity. Hesse et al. also noted improvement in gait, reduction of clawtoe deformity, decrease in ankle clonus, and more normal EMG patterns after injection of tibialis posterior, soleus, and gastrocnemius in post-stroke patients. Burbaud et al. reported improvement in patients with hemiparetic foot spasms. Timing is imperative when treating patients with post-stroke spasticity because treatment is useless once contractures have developed. Ideally, injections should begin within three to nine months after stroke to enhance physiotherapy and rehabilitation.

Investigation of the use of BTX-A in children with cerebral palsy (CP) is currently underway. Koman et al. noted tone reduction, improved positioning, and improved gait after injecting paraspinous and lower limb muscles in both non-ambulatory and ambulatory children with CP. Chutorian and Root reported improvement in gait pattern and range of motion in sixteen children with spastic diplegic CP who were injected in the gastrocnemius muscles. Cosgrove et al. injected lower limb muscles in twenty-six children with CP and dynamic lower limb contractures, and noticed improvement in ambulation and reduction in tone that persisted even after the effects of the toxin wore off. Sutherland et al. injected the gastrocnemius muscle in eight children with CP and documented improvement in gait using motion analysis. Gooch and Sandell reported temporary improvement in gait in a three-year-old child who received injections and underwent serial castings to correct a plantarflexed and in-toeing foot. The major drawback to BTX-A therapy in children with CP is the cost of multiple repeat injections and the potential for developing antibodies to the toxin, rendering it useless. Therefore, patient selection and goals of therapy are of major importance.

Patients with brain or spinal cord injury could receive the greatest benefit cost-wise. A single injection of BTX-A into affected muscles has been shown to greatly improve function and reduce spasticity in this patient group. Due to success with merely one injection, BTX-A is an attractive choice compared to daily medication or surgery.

ADVERSE REACTIONS

No serious adverse reactions have been reported with the use of BTX-A injections. All side effects are transient because the effects of the toxin are reversible. Poor injection technique is the most probable potential cause of more serious complications. Systemic effects include fever, malaise, fatigue, and flu-like symptoms; however, these effects have been seen as frequently in placebo injections. Excessive weakness in target muscles can result in difficulty in function. Effects of the toxin have been seen to a lesser degree in neighboring muscles. No cases of hypersensitivity reactions have been documented. Resistance due to antibody formation varies from center to center, but is estimated at 0% to 10%. This usually occurs with higher doses, more than three years of treatment, and frequent booster injections. Patients with resistance to BTX-A have been treated successfully with BTX-F, although the effects lasted only three to four weeks.

Aminoglycosides or other drugs that interfere with neuromuscular transmission can potentiate the action of BTX-A; therefore, concomitant use should be avoided. Injections should be avoided during

pregnancy (pregnancy category C). Use in children under age twelve has not been approved by the FDA, although studies recommend ranging dosages from 3 to 5 MU to 8 to 10 MU per kilogram of body weight. Careful consideration should be given before using BTX-A in neuromuscular disorders (ALS, myasthenia gravis, and Eaton Lambert syndrome).

CONCLUSION

Botulinum toxin is a symptomatic treatment and not a cure for the conditions it is used to treat. Injections are usually repeated in three to four months. There is no clear toxic dose, although it is generally accepted that total doses of less than 400 MU may be given per treatment session. Because muscles of the lower extremity require higher doses, it may be difficult to treat all muscles requiring therapy in one visit without going over the toxic dose. Conditions such as chronic multiple sclerosis, cerebral palsy, and stroke are associated with significant muscle weakness in addition to spasticity. Reduction of spasticity does not guarantee improvement in function. Extreme care must be taken when selecting the appropriate patients for treatment, with indications and objective made very clear. With all of this taken into consideration, botulinum toxin can be used to improve the lifestyle in certain patients with lower limb spasticity and dystonia.

BIBLIOGRAPHY

Bertolasi L, Priori A, Tomelleri G, Bongiovanni LG, Fincati E, Simonati A, De Grandis D, Rizzuto N: Botulinum toxin treatment of muscle cramps: a clinical and neurophysiological study. *Ann Neurol* 41: 181-186, 1997.

Borodic G, Johnson E, Goodnough M, Schantz E: Botulinum toxin therapy, immunologic resistance, and problems with available materials. *Neurology* 46:26-29, 1996.

Burbaud P, Wiart L, Dubos JL, Gaujard E, Debelleix X, Joseph PA, Mazaux JM, Bioulac B, Barat M, Lagueny A: A randomized, double blind, placebo controlled trial of botulinum toxin in the treatment of spastic foot in hemiparetic patients. *J Neurol Neurosurg Psychiatry* 61:265-269, 1996.

Carruthers JDA, Stubbs HA: Botulinum toxin for benign essential blepharospasm, hemifacial spasm, and age-related lower eyelid entropion. *Can J Neurol Sci* 14: 42-45, 1987.

Childers M, Stacy M, Cooke DL, Stonnington HH: Comparison of two injection techniques using botulinum toxin in spastic hemiplegia *Am J Phys Med Rehabil* 75:462-469, 1996

Chutorian AM, Root L: Management of spasticity in children with botulinum-A toxin. *Int Pediatrics* 9:35-43, 1994.

Coffield JA, Bakry N, Zhang R-d, Carlson J, Gomella LG, Simpson LL: In vitro characterization of botulinum toxin types A, C and D action on human tissues: combined electrophysiologic, pharmacologic and molecular biologic approaches. *J Pharmacol Exp Ther* 280:1489-1498, 1997.

Cosgrove AP, Corry IS, Graham HK: Botulinum toxin in the management of the lower limb in cerebral palsy. *Dev Med Child Neurol* 35:379-85, 1994.

Dengler R, Neyer U, Wohlfarth K, Bettig U, Janzik HH: Local botulinum toxin in the treatment of spastic drop foot. *J Neurol* 239:375-378, 1992.

Duarte J, Frech FA, Sempere AP, Martinez E, Coria F, Mataix AL, Claveria LE: Isolated idiopathic adult-onset foot dystonia and treatment with botulinum toxin. *J Neurol* 242:114-115, 1995.

Gooch JL, Sandell TV: Botulinum toxin for spasticity and athetosis in children with cerebral palsy. *Arch Phys Med Rehabil* 77:508-511, 1996.

Grazko MA, Polo KB, Jabbari B: Botulinum toxin A for spasticity, muscle spasms, and rigidity. *Neurology* 45:712-717, 1995.

Hesse S, Krajnik J, Lucke D, Jahnke MT, Gregoric M, Mauritz KH: Ankle muscle activity before and after botulinum toxin therapy for lower limb extensor spasticity in chronic hemiparetic patients. *Stroke* 27:455-460, 1996.

Hesse S, Lucke D, Malezic M, et al.: Botulinum toxin treatment for lower limb extensor spasticity in chronic hemiparetic patients. *J Neurol Neurosurg Psychiatry* 57:1321-1324, 1994.

Jankovic J, Brin MF: Therapeutic use of botulinum toxin. *N Eng J Med* 324:1186-1194, 1991.

Jankovic J, Schwartz K: Response and immunoresistance to botulinum toxin injections. *Neurology* 45:1743-1746, 1995.

Koman LA, Mooney JF, III, Paterson S: Botulinum toxin: potential role in the management of cerebral palsy during childhood. In Jankovic J, Hallett M, eds. *Therapy with Botulinum Toxin* New York;Marcel Dekker Inc:1994;511-522.

Mauriello JA Jr, Coniaris H, Haupt EJ: Use of botulinum toxin in the treatment of one hundred patients with facial dyskinesias. *Ophthalmology* 94:976-979, 1987.

Mezaki T, Kaji R, Kohara N, Kimura J: Development of general weakness in a patient with amyotrophic lateral sclerosis after focal botulinum toxin injection. *Neurology* 46:845-846, 1996.

Oguma K, Fujinaga Y, Inoue K: Structure and function of clostridium botulinum toxins. *Microbiol Immunol* 39:161-168, 1995.

Pacchetti C, Albani E, Martignoni E, Godi L, Alfonsi E, Nappi G: "Off" painful dystonia in parkinson s disease treated with botulinum toxin. *Mov Disord* 10:333-336, 1995.

Pullman SL, Greene P, Fahn S, Pedersen SF: Approach to the treatment of limb disorders with botulinum toxin A: experience with 187 patients. *Arch Neurol* 53:617-624, 1996.

Scott AB: Botulinum toxin injection of eye muscles to correct strabismus. Trans Am Ophthalmol Soc 79: 734-770, 1981.

Scott AB, Rosenbaum A, Collins CC: Pharmacologic weakening of extraocular muscles. *Invest Ophthalmol Vis Sci* 12:924-927, 1973.

Sloop RR, Escutin RO, Matus JA, Cole BA, Peterson GW: Dose-response curve of human extensor digitorum brevis muscle function to intramuscularly injected botulinum toxin type A. *Neurology* 46:1382-1386, 1996.

Sutherland DH, Kaufman KR, Wyatt MP, Mubarak SJ: Effects of botulinum toxin on gait of patients with cerebral palsy: preliminary results (abstract). *Dev Med Child Neurol* 70:11, 1994.

Tsui JK: Botulinum toxin as a therapeutic agent. *Pharmacol Ther* 72:13-24, 1996.

Tsui JK, O Brien CF: Clinical trials for spasticity. In Jankovic J, Hallett M, eds. *Therapy with Botulinum Toxin* New York;Marcel Dekker Inc:1994;523-533.

Tsui JK, Eisen A, Mak E, Carruthers J, Scott A, Calne DB: A pilot study on the use of botulinum toxin in spasmodic torticollis. *Can J Neurol Sci* 12:314-316, 1985.

Tsui JK, Eisen A, Stoessl AJ, Calne S, Calne DB: Double-blind study on the use of botulinum toxin in spasmodic torticollis. *Lancet* ii:245-247, 1986.