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Botulinum toxin—Beyond wrinkles

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Botulinum neurotoxin is produced by the bacterium, *Clostridium botulinum*. The neurotoxin inhibits acetylcholine at the neuromuscular junction, thus interfering with overall muscular contraction. Botulinum neurotoxin is commonly used for the following medical conditions: cervical dystonia, upper limb spasticity, blepharospasm, strabismus, and hyperhydrosis. However, the use of botulinum neurotoxin was recently approved for the prophylaxis of headaches in adults with chronic migraines. The proposed mechanism of botulinum neurotoxin is no longer solely limited to the inhibition of acetylcholine. There are new mechanisms emerging that involve inhibition of proinflammatory agents and neuropeptides involved in chronic pain. Consequently, there is a disruption of the overall sensory feedback loop involved in chronic pain, thus decreasing peripheral and central sensitization.

During the late 1700s, there were numerous deaths that occurred throughout Europe due to the mysterious "sausage poison." In 1822, the German physician, Dr Justinus Kerner, wrote and hypothesized early findings of how the sausage toxin interrupted both peripheral and autonomic nerve transmission and could actually serve a medical purpose in lowering sympathetic activity in movement disorders. He also was able to describe the clinical picture of botulism poisoning including dysphagia, respiratory failure, vomiting, mydriasis, and ptosis. It was not until 1895, after an outbreak of deaths had occurred following ingestion of contaminated meat, that Dr Emile Pierre van Ermengem determined the "mysterious sausage poison" to be "Bacillus Botulinus" found in contaminated foods. This term later became known as *Clostridium botulinum*.[1]

C botulinum, a Gram-positive anaerobic bacterium, produces a toxin known as botulinum neurotoxin (BoNT). There are 7 neurotoxin serotypes of BoNT: A, B, C (C1 and C2), D, E, F, and G. Strains A, B, E, and F can potentially cause human botulism with ingestion of contaminated food. Strains C and D cause botulism only in animals. Botulinum toxin A is currently US Federal Drug Administration (FDA) approved to treat the following medical conditions: cervical dystonia, blepharospasm, strabismus, upper limb spasticity, hyperhydrosis, and most recently, chronic migraines. The public most commonly recognizes BoNT to be used for cosmetic purposes for the treatment of wrinkles. There are 3 forms of BoNT-A: *Ona botulinum* toxin A (Botox), Abobotulinum toxin A (Dysport), and Incobotulinum toxin A (Xeomin). There is 1 form of BoNT-B, Rimabotulinum toxin B (Myobloc).[2] The medical benefit of BoNT is based on the acetylcholinergic mechanism of muscle relaxation through inhibition of the neurotransmitter acetylcholine (Ach) at the neuromuscular junction.[3,4] However, there are emerging mechanistic theories that occur both in conjunction with and independent of Ach inhibition. The inhibition of neuropeptides such as substance P, glutamate, and calcitonin gene-related peptide (CGRP) in sensory neurons may provide an explanation of the analgesic effects of botulinum toxin in various chronic pain conditions.[3,5]

Based on the acetylcholinergic mechanism, BoNT-A targets acetylcholine at the end plate on motor neurons. During normal skeletal muscle contraction, Ach docks at the presynaptic membrane of the end plate terminal of the motor neuron through the soluble N-ethylmaleimide sensitive fac-

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tor attachment protein receptor (SNARE) complex. Nerve signals cause mobilization of calcium to occur, which causes Ach to be released into the neuromuscular junction. Ach then binds to the postsynaptic membrane through nicotinic receptors. Nicotinic receptors are ionotropic, which allows sodium and potassium transport across the postsynaptic membrane. This initiates a depolarization of the cell membrane, which causes an action potential to occur leading to skeletal muscle contraction.[2-4]

BoNT-A is a large molecule with a molecular weight of 900 kDa, comprising a single chain with a heavy and light chain. Upon injection of BoNT-A, the molecule migrates toward the nerve terminal and attaches to it via the C portion of the heavy chain. Endocytosis occurs, causing the BoNT-A vesicle to be internalized and enter the nerve terminal. Next, the light chain portion of the BoNT-A detaches from the molecular vesicle and enters the cytoplasm. The light chain targets and cleaves the SNAP-25 protein of the SNARE complex, resulting in inhibition of Ach release. This in turn causes decreased muscular contraction.[4] In addition, it is hypothesized that substance P and CGRP release are inhibited at the sensory afferent nerve. Glutamate, an excitatory neurotransmitter at the presynaptic membrane, is also inhibited. The inhibition of glutamate in turn further decreases the release of substance P and CGRP. Wide dynamic neuron activity is believed to be diminished, thus interrupting the overall sensory feedback mechanism. The inhibition of these neuropeptides involved in pain transmission and the overall interruption in the sensory feedback mechanism is hypothesized to be the cause of antinociceptive effects in chronic pain and ultimately the reduction of both peripheral and central sensitization.[5] In vitro studies have shown BoNT-A to inhibit capsaicin-induced substance P release at the dorsal root ganglion in embryonic rat specimens.[6,7] BoNT-A has been shown to inhibit evoked CGRP in trigeminal rat ganglia.[8] Additional in vivo rat models have shown a decrease in edema formation and a decrease in glutamate expression and wide dynamic range neuron activity with pretreatment of BoNT-A.[9]

Based simply on the acetylcholinergic mechanism, one can rationalize that myofascial pain syndromes may benefit from BoNT-A injections. Myofascial pain is regional in location and commonly involves muscular trigger points (MTPs). Trigger points are characterized by focal areas of muscular tissue that are taut and ropy to palpation. MTPs are not only tender to palpation, but also may "trigger" pain distant from the actual site, known as "referred" pain. A "twitch response" of the palpated trigger point is commonly seen. The mechanism of pain is believed to be due to a dysfunctional motor end plate causing an excess of Ach release leading to excessive muscular contraction and spasm.[3,4] MTPs are commonly treated with local injections of anesthetic but also have benefited from dry needling alone. BoNT-A appears to be a reasonable injectate; however, there are inconclusive results in the literature. Ho and Tan performed a systematic review of randomized controlled trials of BoNT-A injections vs saline for trigger-point myofascial pain. Four of the 5 studies included in their criteria did not support the use of BoNT-A for treatment of MTPs as there was no significant difference between botulinum toxin A and saline for analgesic relief. They were unable to perform a quantitative review due to methodology variability in performing the trigger point injections.[10] On the contrary, Freund and Schwarz showed a significant benefit in analgesia and improved range of motion from BoNT-A injections into MTPs for chronic myofascial neck pain.[11] BoNT-A has been shown to provide relief in pain and improvement in function for patients with chronic low back pain due to muscular dysfunction.[12-15] There is no consensus as to the dosing of BoNT-A for myofascial pain disorders.

Additional off-label uses of BoNT-A injections for myofascial pain disorders include plantar fasciitis and piriformis syndrome. Plantar fasciitis is a common pain syndrome involving the plantar fascia characterized by exquisite tenderness over the medial aspect of the calcaneal tuberosity, which is exacerbated upon weight-bearing. The pain mechanism of plantar fasciitis is believed to involve hypertrophy and microtears of the plantar fascia with secondary inflammation and spasm of the underlying foot musculature. Plantar fasciitis is commonly treated with physiotherapy, orthotics, and at times steroid injections. Babcock et al showed a significant benefit in analgesia with BoNT-A injections vs placebo.[16] However, there is insufficient research comparing the efficacy of steroid injections vs BoNT-A for plantar fasciitis. Next, piriformis syndrome is a common diagnosis and cause for buttock pain that refers pain in a sciatic distribution in the absence of lumbar discogenic findings. Patients usually present with exquisite pain upon piriformis palpation that is exacerbated with hip flexion combined with hip internal rotation. There are variable anatomic findings of the sciatic nerve in relation to the piriformis. Upon spasm and tightening of the piriformis muscle, it is believed to irritate the sciatic nerve, thus imitating lumbar discogenic referred pain. There are limited studies for BoNT-A injections for piriformis syndrome; however, Childers and colleagues did show analgesic benefit from BoNT-A injections into the piriformis under electromyography and fluoroscopy guidance.[3,17]

In October of 2010, the FDA approved the use of BoNT-A for prophylactic treatment of chronic migraines characterized by greater than or equal to 15 migraines per month, lasting longer than 4 hours per day. The PREEMPT (Phase III Research Evaluating Migraine prophylaxis Therapy) studies showed significant results of decreased frequency of migraine headaches with BoNT-A injections vs placebo. The recommended dosing of BoNT-A injection is 155-195 U dispersed among 7 pericranial and cervical regions. The BoNT-A is diluted with preservative-free normal saline 0.9% in a 2:1 ratio (2 mL of normal saline mixed with 100 U of BoNT-A). The BoNT-A is dispersed among the following muscles: Frontalis 20 U, corrugator 10 U, procerus 5 U, occipitalis 30-40 U, temporalis 40-50 U, trapezius 30-50 U, cervical paraspinals 20 U. The recommendation is

to repeat the injections every 3 months. The injections do not require nor is the use of electromyography recommended for needle guidance. The antinociception mechanism is based not on the acetylcholinergic mechanism but rather on the inhibition of neuropeptides involved in pain: substance P, CRGP, and glutamate at afferent nerve endings. In turn, neurogenic inflammation is inhibited, thus decreasing peripheral sensitization and indirectly overall central sensitization.[18-21] For specific injection recommendations, refer to the PREEMPT trials literature.

Osteoarthritis (OA) is the most common form of arthritis that affects primarily large weight-bearing joints such as the knees and hips, but also affects the spine, hands, and shoulders. OA is commonly treated with physiotherapy, oral anti-inflammatory medications, and intra-articular steroid joint injections. Rheumatoid arthritis (RA) is an autoimmune disease that affects smaller joints typically the hands and feet and targets the synovial lining of the joints producing chronic inflammation. RA can also affect one systemically with multiorgan involvement. RA is typically treated with anti-inflammatory medications, disease-modifying antirheumatic drugs, steroids, and physiotherapy. Mahowald and colleagues performed intra-articular BoNT-A injections on patients with OA and RA who were refractory to oral anti-inflammatory and analgesic agents. All the patients had a history of either intra-articular steroid or viscosupplement injections with no significant benefit. BoNT-A intra-articular injections included the knees, ankles, and shoulders. Results showed a significant reduction in pain as well as improved active range of motion.[22]

Joint pain and articular damage activate peripheral terminals of the polymodal C fibers and Delta A fibers of the joint. C fibers are found throughout the synovium of the articular capsule and Delta A fibers are found throughout the articular and peri-articular ligaments. Upon joint damage due to mechanical trauma or thermal trauma, various chemicals are produced including hydrogen, potassium, adenosine triphosphate, bradykinin, serotonin, histamine, and prostaglandins. This ultimately initiates an action potential along the afferent sensory nerve up to the dorsal root ganglion. Neuropeptides are then released from the dorsal root ganglion including substance P, glutamate, CGRP, dynorphins, and enkephalins, which travel to the dorsal horn. Substance P indirectly stimulates inflammatory mediators that contribute toward pain transmission. An antidromic efferent signal is sent back to the periphery, causing increased release of these neuropeptides. Neurogenic inflammation occurs in the articular cartilage. This creates a sensory feedback loop contributing toward ongoing pain transmission and peripheral and ultimately central sensitization.[22,23] Again, BoNT-A is hypothesized to inhibit the release of these neuropeptides involved in the transmission of pain. Consequently, there is a disruption in the sensory reflex loop resulting in an overall decrease in pain sensitization.

Other off-label, non-FDA uses of botulinum toxin injections for joint-related pain was shown by Dykstra and colleagues with injections of either BoNT-A or BoNT-B into cervical facets and lumbar facets for facet mediated pain, sternoclavicular joint injections, sacroiliac joint injections, and even C2 nerve root injections. Overall, the results showed improved pain scales that were superior to intra-articular steroid injections.[24]

Botulinum toxin has also been applied to a variety of neuropathic pain conditions. Diabetic neuropathy is 1 of the most common neuropathies seen today. Diabetic neuropathy usually affects the distal extremities starting with the feet and hands, affecting both sensation and potentially motor function. Symptoms may be characterized by the following: paresthesias, numbness, burning, shooting lancinating pain, weakness, and impaired proprioception. Standard treatments of symptoms include anticonvulsants such as gabapentin or pregabalin, antidepressants such as amitriptyline, and analgesics. The pathophysiology of neuropathic pain is complex and is hypothesized to involve local tissue damage in the periphery resulting in damage to the afferent C fibers and A-delta fibers. Consequently, nociceptor thresholds are diminished and neuroplasticity occurs including increased sodium channels and an upregulation of the N-methyl-D-aspartate receptors involved in neuropathic pain transmission. Furthermore, sympathetic nerve terminals are altered in neuropathic pain states, while proinflammatory agents and neuropeptides involved in pain transmission are increased in the periphery. Upon modification of the nervous system, characteristics of neuropathic pain may occur including hyperalgesia (increased pain perception by noxious stimuli), hyperesthesia (exaggerated sensory pain perception), and allodynia (pain perception by nonnoxious stimuli).[5,25,26] In a double-blind crossover trial, Yuan and colleagues showed a reduction in pain upon injection of BoNT-A vs placebo into the dorsum of the feet of patients with diabetic neuropathy.[26] Gazerani and colleagues showed improved blood flows, decreased skin temperatures, and improved levels of pain with BoNT-A injections in capsaicin-induced trigeminal pain.[27-29] It is postulated that BoNT-A inhibits substance P, glutamate, and CGRP at the afferent nerve terminals. Consequently, there is less transmission of neuropeptides at the postsynaptic membrane N-methyl-D-aspartate receptors, in turn theoretically diminishing central sensitization. In addition, BoNT-A has been shown to block $P2X_3$ receptors involved in adenosine triphosphate transmission in sensory neurons involved in chronic pain. BoNT has also been shown to block the transient receptor potential vanilloid receptor, TRPV1, in peripheral nociceptors involved in pain transmission.[26]

Carroll and colleagues showed longer antinociceptive effects with BoNT-A in the use of lumbar sympathetic blocks for complex regional pain syndrome vs injection of anesthetic alone.[30] Complex regional pain syndrome (CRPS) is a chronic pain condition that typically develops after some type of trauma with or without nerve damage. It is characterized not only by neuropathic features including allodynia and hyperalgesia, but also includes vasomotor and

sudomotor changes. Diagnostic criteria include edema, temperature differences compared to the contralateral limb, skin color changes, and autonomic changes such as increased perspiration. In addition, trophic changes may occur including loss of hair growth, nail changes, motor dysfunction, and even bone loss. The underlying pathophysiology of CRPS is not completely understood but believed to be at least in part sympathetically mediated with associated neurogenic inflammation and increased cytokine release.[30] BoNT-A, as described, targets cholinergic nerve terminals. Sympathetic preganglionic nerves are cholinergic as well. Sympathetic fibers exist within the neuromuscular junction. BoNT-A has been shown to prolong sympathetic blockade on surgically exposed sympathetic chains.[5] Furthermore, Argoff has described the relationship between myofascial pain, specifically trigger points, and neuropathic pain. CRPS is usually associated in conjunction with myofascial pain. MTPs may present with similar neuropathic pain characteristics. It has been hypothesized that MTPs may involve the autonomic nervous system with increased prostaglandin release due to activation of noradrenergic sympathetically mediated fibers in the affected muscle. Studies have shown the relationship of adrenergic receptor involvement in pain transmission in sympathetically mediated pain. BoNT-A is believed to affect autonomic function while also targeting the cholinergic nerve terminals inhibiting Ach as well as inhibiting noncholinergic neuropeptides: substance P, CGRP, and glutamate.[5]

Finally, there are numerous other chronic pain conditions in which BoNT has also been reported to show analgesic benefit, of which all are off-label use. Dykstra and Presthus demonstrated analgesic benefit of BoNT-A injections for the treatment of vulvodynia.[31] Research at the University of Minnesota School of Veterinarian Medicine is being done on intra-articular joint injections with BoNT in helper dogs with pain due to joint dysplasia. Several other chronic pain conditions that have been reported to benefit from BoNT include but are not limited to the following: burn pain, anal fissure pain, postherpetic neurologic pain, prostatic pain, temporomandibular joint pain, phantom pain, chronic pelvic pain, and neuroma-associated pain.[32,33]

Conclusions

C botulinum produces a neurotoxin that is termed botulinum neurotoxin (BoNT). There are 7 serotypes of botulinum neurotoxin. The most commonly used form of BoNT is type A. There are 6 medical conditions that are FDA approved for the use of BoNT: cervical dystonia, blepharospasm, strabismus, upper limb spasticity, hyperhydrosis, and most recently chronic migraines. The acetylcholinergic mechanism of BoNT is well documented in the literature of acetylcholine inhibition at the neuromuscular junction, thus causing an inhibition of muscular contraction. However, several new mechanisms have been proposed for BoNT in the use of chronic pain conditions that occur in conjunction and independent of acetylcholine inhibition. These new mechanisms include inhibition of neuropeptides and inflammatory chemicals involved in pain as well as an interruption in the overall sensory pain feedback loop. Consequently, there is a decrease in overall pain sensitization, thus providing analgesic benefit.

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