# The Myriad Uses of Botulinum Toxin

Botulinum toxin (BTx) is an important therapeutic agent with widespread applications in neurologic and non-neurologic disease. One of the most potent neurotoxins known, BTx derives its name from the Latin word for sausage, *botulus*—referring to poisoning from badly prepared meat in the early 19th century. The toxin is a 150-kDa protein produced by *Clostridium botulinum* and composed of a heavy and light chain linked by a disulfide bond. When activated, the toxin targets peripheral cholinergic systems and prevents the release of acetylcholine. The heavy chain mediates binding to presynaptic cholinergic nerve terminals and internalization of the toxin into the cell. The light chain is a zinc endopeptidase responsible for its toxic effects and cleaves specific proteins needed for synaptic transmission (1). The first therapeutic use of BTx, purified and highly diluted, was as a treatment for strabismus in the 1970s (2). Seven serotypes of BTx have been identified, each with a specific mode of action at the molecular level. Currently, serotypes A (Botox [Allergan, Inc., Irvine, California]; Dysport [Ipsen, Ltd., Berkshire, England]) and B (Myobloc [Solstice Neurosciences, Inc., South San Francisco, California]) are available for clinical use. Over the past 25 years, BTx has proved to be remarkably successful in relieving spasms, unwanted movements, abnormal postures, and pain associated with many disorders (1).

Therapy with BTx has made it possible to control some neurologic conditions that once required systemic therapy and to avoid long-term consequences of muscle spasms and involuntary movements. Double-blind, placebo-controlled clinical trials have shown that BTx safely and effectively resolves excessive muscle contraction in dystonia (a condition characterized by sustained twisting and posturing movements that are usually directional in nature); hemifacial spasm and other hyperkinetic disorders (3); spasticity from stroke, cerebral palsy, brain trauma, or multiple sclerosis (4); and hyperhidrosis in autonomic disorders (5, 6). More recently, BTx has attracted additional interest for its effectiveness in other neurologic problems (7, 8), gastrointestinal and genitourinary dysfunction (9, 10), headache and pain disorders (11, 12), and cosmetic uses.

Therapy with BTx is a good option that produces an effect that lasts for several months, is temporary and self-limited, and has few side effects (1). Side effects mainly consist of unwanted weakness in the injected muscles or adjacent muscles. This adverse effect is particularly troublesome in eyelid injections (resulting in ptosis) and in bilateral neck injections (resulting in dysphagia). Excess weakness can be avoided by using low BTx doses and electromyography-guided injections. Electromyographic guidance is helpful for accurately localizing muscles, particularly for limb conditions such as writer's cramp. Systemic side effects, such as a transient flulike syndrome, are very rare. Long-term studies have shown that BTx continues to be effective and is safe after repeated use for 15 years or more (13).

The use of BTx to treat pain is intriguing. In this issue, Wong and colleagues (14) report that BTx was significantly more effective than placebo for reducing pain in lateral epicondylitis. The authors randomly assigned 60 patients (11 men, 49 women) with long-standing pain to receive 60 units of BTx (Dysport formulation) or placebo. At baseline, both groups had similar mean pain scores on a 100-mm visual analogue scale. All patients received injections at the same location relative to the lateral epicondyle. At 4 weeks and again at 12 weeks, pain scores were lower in the BTx group than in the placebo group. The difference at 4 weeks was 24.4 mm on the visual analogue scale; the 95% CI for this difference was 13.0 to 35.8, indicating that the smallest statistically probable difference was still much greater than 0. An interesting issue in this study was whether the mechanism of pain reduction was simply reducing muscle tension on the lateral epicondyle or whether BTx had direct analgesic effects. The authors measured weakness by using grip strength. Measurements did not change much for either group, implying that pain reduction might have been attributable to another cause, such as a direct analgesic effect from BTx. These findings are promising because BTx injections are less harmful than other therapies for lateral epicondylitis, such as corticosteroids or surgery, and BTx can provide long-lasting results.

In a similar randomized study, 40 patients with lateral epicondylitis (21 men, 19 women) were treated with 50 units of BTx (Botox formulation) injected 5 cm distal to the most tender region (15). No significant difference between the 2 groups was observed after 3 months. Although this report had fewer participants than the preceding study, the authors also used a visual analogue pain scale, grip strength, and quality of life as outcome measures. The treating physicians in both studies might have placed the BTx more precisely in the affected area if they had used electromyographic guidance to assist them in directing the needle. The outcomes of the 2 studies might have been more similar if the investigators had individualized the dose of BTx for each patient.

The effect of BTx on pain in lateral epicondylitis raises the possibility that BTx might provide pain relief in other conditions. Does BTx act through additional, as yet unknown pain-relieving mechanisms? Animal investigations found that BTx may alter pain physiology through modulation of substance P, glutamate, and calcitonin gene–related peptide (16). These substances are present at cholinergic nerve endings and are believed to play important roles in pain sensation. Anecdotal reports about the possible analgesic effect of BTx on conditions in which pain is the

predominant issue (such as migraine headache and nonneurologic musculoskeletal conditions [17]) have been mixed.

While new uses of BTx to relieve pain are being investigated, the mechanisms of well-established BTx therapeutic effects (that is, diminishing involuntary movement or reducing muscle tone) still are not fully understood. For example, BTx injections result in transient weakness, but the effects on muscle tone and involuntary movements usually last longer than the weakness does. This apparent paradox may be explained by evidence that BTx selectively blocks the most active neuromuscular junctions, which may preserve strength in other muscle regions (18). Another explanation is that BTx also affects the fibers that regulate muscle tone and the spinal stretch reflex, preserving strength while reducing tone (19). Finally, physiologic studies have shown that BTx indirectly improves the abnormal brain circuitry of dystonia even though it does not enter the central nervous system (20).

The number of BTx applications is expanding, as evidenced by the studies that demonstrate new therapeutic directions for BTx. Currently, physicians should consider BTx therapy for patients who have focused involuntary movements, such as hemifacial spasm, dystonia, or any other disorder in which muscle spasms and abnormal postures are prominent. In the future, pain syndromes, such as lateral epicondylitis, intractable daily headaches, and visceral pain, may become potentially new indications for BTx therapy. Improving our understanding of how BTx works may uncover even more applications for this most intriguing natural medication.

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