

# Botox

More than just  
a pretty face

**15** ANSWERS  
TO YOUR LATEST  
CLINICAL QUESTIONS



PARKHURST  
EXCHANGE

## Botulinum toxin

More than just a pretty face

by Gordon D. Ko, MD

### CASE PRESENTATION

**Mrs. K., a 46-YEAR-OLD** church worker and married mother of two, was seen with fibromyalgic syndrome, irritable bowel syndrome, and migraine headaches. She was taking belladonna/ergotamine/phenobarbitol tablets, codeine, and pinaverium bromide. Supplements included ginger, echinacea, milk thistle, garlic, vitamin E, and coenzyme Q10. She had been abused in childhood by alcoholic parents and was an intravenous drug abuser (hepatitis C diagnosed in 1995). She was in a car accident in 1989, incurring whiplash and a right frozen shoulder.

Initial examination (June 2000) findings included: height = 163 cm, weight = 52 kilos, no anemia or jaundice, and BP 134/99 mm Hg. She was treated with hydrotherapy (in addition to active physiotherapy) and gabapentin (slowly up to 2,400 mg/day). She was weaned off codeine and belladonna/ergotamine/phenobarbitol.

On her September 2000 visit, she had a better appetite and her weight had increased to 54 kilos. In December 2000, she began receiving injections of botulinum toxin type A (BTX-A): 25 units for headaches (with supraorbital nerve blocks) and 75 units for upper trapezii and splenii cervicis. At the post-injection in January 2001 she described "an excellent response." Her headaches resolved (not to mention her wrinkles!) [see Table 1].

She returned in March 2001 for an injection of 300 units of BTX-A. Her 22nd set of injections was done on January 15, 2008 with 400 units as follows: 25 units (2:1 dilution) into bilateral pectoralis minor, pectoralis major,

**TABLE 1**  
Data from Mrs. K's case study

Outcome measure	Pre-injection	Post-injection	
	June 2000	September 2000	January 2001
PVAS	5/10	4/10	3/10
SFM	25/45	13/45	7/45
PDI	30/70	18/70	11/70
FIQ	57/100	—	14/100
TeP count	18/18	18/18	8/18

PVAS = Pain visual analog scale, SFM = short-form McGill Questionnaire, PDI = Pain Disability Index, FIQ = Fibromyalgia Impact Questionnaire, TeP = tender point

levator scapulae, upper trapezius muscles; 50 units (4:1 dilution) into bilateral subscapularis muscles; 10 units (2:1) into bilateral masseters, splenius capitis muscles and 60 units total into the frontalis, procerus, corrugator, occipitalis muscles (following the Silberstein protocol for migraine). With these treatments, she continues to work full-time, exercises 3x/week, and requires no oral anal-

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gesic agents. She has experienced no adverse effects over these past 9 years with regards to cardiac, liver, renal and endocrine function.

Botulinum toxin was first used in the 1950s by ophthalmologist Dr. Alan Scott (and subsequently approved by the FDA in 1989) for the treatment of eye movement disorders such as strabismus and blepharospasm. Its uses have subsequently expanded to include neurological movement disorders including focal muscle dystonia and spasticity. Botulinum toxin type-A (BTX-A) prevents spasticity through its prolonged blockade of acetylcholine. When injected into muscle, BTX-A binds with high specificity and affinity to presynaptic cholinergic axon terminals.

This inhibits calcium-activated release of acetylcholine, a blockade which leads to muscle relaxation or paralysis. Within 4 days, collateral terminal sprouting will occur, as the body attempts to reinnervate the neuromuscular junction. These temporary functional synapses bring partial recovery of muscle function after about 28 days. By about 2 months post-injection, the original nerve terminals will begin to recover their ability to release acetylcholine as original connections are restored. Sprouting then stops and the temporary synapses lose their function. Within roughly 3 months, the original neuromuscular junctions recover full, normal function.

Other potential targets are cholinergic para-

sympathetic and postganglionic sympathetic nerve synapses of the autonomic nervous system. For example, intradermal injections of BTX-A leads to denervation of eccrine glands (useful for hyperhidrosis and sialorrhea).<sup>1</sup> Current research includes treatment of over-active bladders<sup>2</sup> and prostatic hypertrophy.<sup>3</sup>

Patients are usually advised that the onset of action occurs around day 3, and the peak effect (in muscle relaxation) after 3 weeks. The average duration of response is 3 months. Pain relief, however, may last longer than the muscle relaxation effect.<sup>4</sup> Injections are spaced at least 3 months apart to minimize the rare risk of antibody formation to the protein (as this would prevent BTX-A from working the next time).

Post-injection electrical stimulation of the injected muscle has been reported to augment the response. Targeted injections of the nerve terminal endplate (with electromyographic [EMG] guidance) appear to be more effective than anatomical approaches.

## The safety of botulinum toxins

Botulinum toxin type-A comes in vials of 100 units. A unit of BTX-A is defined as the lethal dose for 50% (LD-50) of mice. The LD-50 for monkeys is 39 U/kg. Extrapolated to a 70 kg human, this would mean a lethal dose is about 2,700 units. The typical maximum dose at one injection setting is 400 units.

BTX-A should be stored in the freezer and reconstituted with preservative-free normal saline. When stored in saline, it loses potency by 35% after one week and 44% after two weeks.

Reported side effects include post-injection muscle soreness, stiffness (typically lasting a week), and rarely, a flu-like illness, which may last a few days to a month. Inadvertent weakness is generally near the site of injection, e.g. eyelid ptosis for injections in the pericranial frontal muscles, and difficulty with swallowing for anterior neck muscle injections. Case reports of serious adverse effects have led to recent FDA and Health Canada safety reviews. Such incidents are largely dependent

TABLE 2

### Trigger points and myofascial pain syndrome criteria\*

#### Major criteria

- pain localized to region, usually unilateral, asymmetric tenderness
- taut band is palpable
- pain in known referred zone
- exquisite spot tenderness
- restricted range of motion due to tight muscle

#### Minor criteria

- reproduction of pain/altered sensation by pressure on TrP
- local twitch response on snapping the taut band
- pain alleviated by stretching muscle or by injecting TrP

Diagnosis requires all the major criteria and at least one minor criteria; TrP = trigger point.

\* Source: *Eur Urol* 2006;49:528-35.

on operator technique, e.g. concomitant general anesthetic, and dose used. A retrospective review of 929 patient encounters involving children with cerebral palsy documented no severe adverse effects or botulism.<sup>5</sup> Other supportive studies document safety and a meta-analysis has supported the overall safety of BTX-A.<sup>6</sup>

## **Contraindications to botulinum toxins**

Relative contraindications to BTX-A include generalized muscular weakness (myopathies and neuromuscular junction diseases such as myasthenia gravis), profound atrophy of the target muscle, aminoglycoside antibiotic therapy, nursing and pregnancy.

## **Botulinum toxin and headache**

It was first observed by Jankovic in work on cervical dystonia that there was a noticeable reduction in pain. Subsequent reports by the Carruthers (a Vancouver-based dermatologist-ophthalmologist couple who were the first to report the anti-wrinkle effects from blepharospasm treatment) documented relief of headaches with injections done for wrinkles.

Though there were earlier supportive studies for the use of botulinum toxin type-A for headache treatment (migraine, tension, and cervicogenic types), more recent, larger multi-centre trials found no good evidence for a role in tension-type headache. Results were more positive in specific subgroups of migraine and chronic daily headaches. But a recent neurology consensus panel did not find sufficient evidence at this time for headache.<sup>7</sup> The results of a large multi-centre phase III trial for migraine (PREEMPT), however, concluded this therapy was safe and effective.

## **Laboratory pain studies**

More recent lab research has also indicated that BTX-A may also have a more central effect in pain control by blocking calcium-mediated release of substance P in dorsal root ganglion neurons, as well as in the brain and

**TABLE 3****ABCD starting dose guidelines<sup>11</sup>**

**Active Trigger Point:** five to 10 units — if local anesthetic provides just short-term relief.

**Biomechanical approach:** 25 to 50 units, e.g. injecting tight pectorals to correct anterior shoulder protraction and head forward posture. Dosing may be titrated up higher for larger muscles, e.g. piriformis with 100 units, iliopsoas with 150 units.

**Combination of the above:** care must be taken to not over-inject trigger points that are in weakened muscles under biomechanical tension.

**Dystonia:** higher starting doses are administered and often with electromyographic guidance.

trigeminal nerve ending. Lab studies suggest that botulinum toxin type-A may also inhibit other pain neurotransmitters. It reduces capsaicin-evoked pain and neurogenic vasodilation in human skin as well.

In our clinic, we've observed effectiveness in focal neuropathic pain control with intradermal injections of BTX-A. This may also apply for the 27% to 38% of fibromyalgia (FMS) patients with marked skin allodynia, in whom there are higher levels of cytokines in the skin. Patients with marked hypersensitivity should first try intradermal injections (using a 4:1 dilution), as they may actually have generalized neuropathic pain disorder and are more likely to flare up if injected too deeply and in too many areas initially. BTX-A can be initiated successfully in fibromyalgia patients who suffer from migraine headaches and lower back pain.

### **Botulinum toxin and myofascial pain/fibromyalgia**

One proposed theory for such pain relief is that BTX-A resolves muscle trigger points [TrPs]. It's important to distinguish trigger points from fibromyalgia tender points. The criteria for trigger points are listed in Table 2. Studies are conflicting on the use of BTX-A in myofascial pain. Successful randomized trials were published for chronic piriformis pain syndrome and chronic mechanical back pain.

It's been reported that 72% of FMS patients have trigger points.<sup>8</sup> Tender points don't

usually respond to injections of local anesthetic, but trigger points in fibromyalgia do.<sup>9</sup> Current theories as to the pathophysiology of TrPs include the dysfunctional motor endplate where excessive acetylcholine is released and where higher levels of inflammatory mediators have been found. Such mediators are often co-localized with acetylcholine and may explain how BTX-A works for recalcitrant TrPs.

One previous published study on BTX-A for FMS found it to be ineffective.<sup>10</sup> This was a small study of 10 patients who underwent alternate injections of lidocaine or BTX-A solely into the upper trapezii muscles. Only one patient reported relief of pain for two weeks with lidocaine. In our experience, injections into the trapezius may exacerbate pain in FMS patients, particularly in the presence of a head-forward posture with depressed scapula and TOS symptoms (painful paresthesias in the arm). Weakening this scapula elevator will aggravate the tension on the brachial plexus. Instead, injections into the tight pectoralis minor/levator scapulae muscles combined with daily stretching of these muscles and scapular stabilization exercises — strengthening the trapezii and rhomboids — results in a much better clinical response.

### **Botulinum toxin and other painful conditions**

Studies have also been published demonstrating effectiveness for other conditions including:

- TMJ pain syndrome
- tendinopathies (tennis elbow)
- plantar fasciitis
- osteoarthritis, rheumatoid and psoriatic arthritis
- post-motor vehicle accident whiplash syndrome
- cancer pain, including post-radical neck dissection and radiation fibrosis syndrome
- surgical wound healing
- post-amputation and phantom limb pain
- sports overuse injuries

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## PERSPECTIVES ON PAIN BOTULINUM TOXIN

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We recommend when injecting BTX-A for pain to use the ABCD recommendations, found in Table 3.

Patients who comply well with their exercise regimen (strengthening of weak core muscles and daily stretching of injected tight muscles), often seem able to go for longer periods in between BTX-A injections. Treatment should always be integrated with lifestyle changes, including adequate physical activity level, stress management, detoxification, and sleep hygiene. An interdisciplinary care and polypharmacy approach will be required for more complex chronic pain patients, in which BTX-A helps to contribute to the overall rehabilitation. **PE**

For more information:

- Dr. Ko's physician education website at [www.NeuropathicPain.ca](http://www.NeuropathicPain.ca)
- General education website at [www.DrKoPRP.com](http://www.DrKoPRP.com)
- For physician training, contact the Canadian Society for Neurotoxins in Pain

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For a complete list of references, please go to [parkhurstexchange.com](http://parkhurstexchange.com) and click Botulinum toxin on the May 2010 contents pages.