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Onabotulinumtoxin A in the Treatment of Migraine Headache

Carrie O. Dougherty, MD
Jefferson Headache Center, Philadelphia

Stephen Silberstein, MD
Jefferson Headache Center, Thomas Jefferson University

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Carrie O. Dougherty, MD and Stephen D. Silberstein, MD

Jefferson Headache Center, Thomas Jefferson University, Philadelphia, PA, USA

Reprint requests and correspondence should be addressed to:

Stephen D. Silberstein, MD, Jefferson Headache Center,

111 South 11th Street, Suite 8130, Philadelphia, PA 19107;

phone: (215) 955-2030; fax: (215) 955-6682;

e-mail: Stephen.Silberstein@jefferson.edu.

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Abstract

Recent trials have demonstrated that onabotulinumtoxinA is a safe and effective treatment for the prevention of chronic migraine headaches. Although the exact effect of the toxin on the pathophysiology of migraine is not clear, several in-vivo and in-vitro models have shown that onabotulinumtoxinA inhibits the release of neurotransmitters and neuropeptides involved in pain signaling pathways with resulting attenuation of both peripheral and central sensitization in migraine. Limited systemic adverse effects and physician administered treatments that eliminate concerns for patient compliance have made onabotulinumtoxin A an appealing alternative to oral prophylactic medications for migraine. This article is designed to provide an overview of current research into the mechanism of action of onabotulinumtoxinA in the pathophysiology of pain conditions including migraine, as well the current literature supporting its efficacy in migraine treatment.

In the 1820s, Justinus Kerner described the clinical syndrome of botulism as a foodborne illness after compiling 76 cases of lethal food poisoning that occurred following the ingestion of spoiled smoked sausages[1]. He isolated an extract that contained the purported toxin from the sausages and characterized its effects on animal models. His published reports proposed that the isolated toxin had potential therapeutic uses[1]. Kerner's ideas, though visionary, were not fully realized until the late 1970s, when ophthalmologist Alan Scott used onabotulinumtoxinA for the treatment of strabismus and blepharospasm[2].

Today, onabotulinumtoxinA (BoNT-A) is used in the management of several medical conditions, including dystonia, blepharospasm, and spasticity, and is the only FDA-approved medication for the prevention of chronic migraines. The observation of therapeutic benefit of BONT-A in the treatment of pain has incited research into the mechanism of action of BoNT-A outside of the neuromuscular junction. Although the pathophysiology is still not well understood, the use of BoNT-A in the prevention of chronic headaches, specifically chronic migraine, has proven to be an effective treatment modality, with few contraindications and minimal side effects.

Effect of Onabotulinumtoxin A on Cholinergic Neurons

The effect of BoNT-A on the neuromuscular junction is well described. When injected into the target muscle, the C-terminal of the heavy chain binds to ganglioside acceptor protein on the plasma membrane of the alpha motor neuron and mediates endocytosis of the toxin[3]. The acidic environment within the vesicle leads to conformational change of the toxin, and reduction of the linking disulfide bond separates heavy chain and light chain. The light chain is translocated from the endocytotic vesicle into the neuronal cytosol. Within the cytosol, the light

chain acts as a zinc endopeptidase and cleaves vesicular docking protein SNAP-25, a component of the SNARE complex that facilitates fusion of the membrane of the acetylcholine (ACh)-containing vesicle with the presynaptic membrane. The various botulinum toxins target different proteins in the SNARE complex. Toxins A/E/C target SNAP-25, B/D/F/G target VAMP (aka synaptobrevin), C also targets syntaxin. Cleavage of SNAP-25 inhibits Ach vesicle docking on the presynaptic membrane and inhibits ACh release into the neuromuscular junction. This results in partial chemical denervation and subsequent reduction in muscle activity. Recovery from chemical denervation involves sprouting of new nerve terminal and resumption of synaptic activity in the original terminal[4]. In clinical use of onabotulinumtoxinA in humans, this takes 2-6 months[5].

As the clinical use of BoNT-A increased following Dr. Scott's work in strabismus, providers made a number of curious observations about the effects of the medication after it was injected for involuntary movements. Reports included descriptions of bilateral and distant effects after unilateral injection for spasticity and dystonia, decrease in muscle spasm strength and muscle spasm frequency, and alleviation of sensory symptoms, such as neck tenderness in spasmodic torticollis and light sensitivity in blepharospasm[6]. Giladi cites a number of examples where the improvements in sensory symptoms were disproportionate to the degree of muscle weakness or outlasted the duration of muscle weakness[6]. These observations suggested that BoNT-A had effects in addition to those on motor neurons.

A possible explanation for the effect on neurons distal to the injection site was proposed after it was shown that onabotulinumtoxinA undergoes retrograde transport in motor neurons[7]. Antonucci et al. demonstrated BoNT-A truncated SNAP-25 at distal projections from both peripheral and central BoNT-A injections. The transport of SNAP-25 was inhibited by

colchicine, indicating microtubule-dependent axonal transport. BoNT-A also inhibits gamma-motor neurons innervating intrafusal fibers in muscle spindles[8]. Information about muscle stretch is transmitted from muscle spindles to the CNS via 1a afferents. It has been proposed there is some degree of pain relief from the resulting reduction in afferent input of tonic muscle contractions[9]. However, it is difficult to extrapolate this hypothesis to the mechanism of action of BoNT-A on headache because facial muscles contain very few muscle spindles[6].

BoNT-A inhibits cholinergic neurotransmission in the autonomic nervous system. Several neurotransmitters and neuropeptides, including enkephalins, substance P, neurotensin, somatostatin, ATP, vasoactive intestinal protein (VIP) , neuropeptide Y, and NO, co-localize with ACh in autonomic neurons[10,11]. BoNT-A may inhibit the release of substances other than ACh that are released through a common vesicular docking mechanism[12]. Some authors also postulate that the inhibition of autonomic transmission by BoNT-A may suppress neurogenic inflammation[11].

The potential of BoNT-A in the treatment of migraine was first reported by Binder et al in 2000, after observations that patients treated for hyperfunctional facial lines reported alleviation of migraine symptoms[5]. The effect was unexpected and prompted further research into the pathophysiology of BoNT-A in the transmission of pain-signaling pathways.

Effect of Onabotulinumtoxin A on Afferent Neurons

Several in vivo and in vitro studies have demonstrated that BoNT-A inhibits the release of neurotransmitters and neuropeptides involved in inflammatory pain such as glutamate[13], substance P[14, 15], and CGRP[16]. A rat model for inflammatory pain with the injection of formalin solution into the hindpaw results in characteristic behaviors associated with pain, such a licking

the injected paw. The typical behavioral response is biphasic, with an early response evoked by peripheral sensitization of nociceptors, followed by decrease in pain-associated behaviors attributed to descending inhibition, and finally a recurrence of pain-associated behaviors that reflect the development of peripheral inflammation and central sensitization. Peripheral injection of BoNT-A reduced the second phase of formalin-induced nociceptive behavior in a dose dependent manner[13]. BoNT-A also resulted in dose-dependent reduction in mechanical allodynia and thermal hyperalgesia in an animal model of peripheral neuropathic pain[17].

The effect of BoNT-A on migraine is postulated to involve inhibition of both peripheral and central sensitization. A rat model of migraine via sensitization of dorsal horn neurons in the trigeminal nucleus caudalis showed that chemical irritation of the dura results in a 2- to 3-fold increase in extracellular glutamate. However, there was no significant change in extracellular glutamate in rats pre-treated with periorbital injection of BoNT-A[18]. In a rat model of trigeminal neuropathy due to infraorbital nerve constriction, Kitamura et al demonstrated that BoNT-A resulted in reduction of both exaggerated neurotransmitter release in from trigeminal ganglia neurons and pain-associated behavior[19]. Matak et al. recently demonstrated that BoNT-A truncated SNAP-25 in the trigeminal nucleus caudalis after peripheral injection, suggesting retrograde axonal transport of BoNT-A analogous to that described in alpha motor neurons. The antinociceptive effect of peripherally injected BoNT-A was inhibited by colchicine, suggesting that retrograde axonal transport and central action are obligate parts of the mechanism of action of BoNT-A on pain sensation[20].

BoNT-A inhibits peripheral sensitization by blocking the release of pain-related neurotransmitters and neuropeptides from peripheral nerve endings. The resulting reduction of afferent input into the CNS indirectly inhibits central sensitization. Additionally, BoNT-A

undergoes retrograde transport into central trigeminal neurons and has been shown to decrease centrally mediated neurotransmitter release, which directly inhibits central sensitization.

Clinical Results of OnabotulinumtoxinA in the Prevention of Episodic Migraine

Although initial results on the use of BoNT-A in the treatment of episodic migraine were positive, subsequent trials failed to show a significant improvement in migraine frequency or severity. In the first study following Binder and colleagues' initial observations, 123 subjects with 2 to 8 migraines/month were randomized to placebo, 25U, or 75U BoNT-A. Injections sites included bilateral frontalis, temporalis, procerus, and corrugator muscles. There was a significant decrease in migraines/month in the 25U but not the 75U group, compared with placebo. The lack of effect in the higher-dose group was attributed to lower mean migraine frequency in the baseline group characteristics; 4.3 in the 25U group compared with 4.0 in the 75U group[21].

Subsequently, Evers et al evaluated differences in response to frontal versus neck muscle injection sites. Sixty-six subjects with 2 to 8 migraines/month were randomized to either 100U in the frontalis, temporalis, SCM, trapezius, splenius capitus, and semispinalis, or 16U in the frontalis and temporalis and placebo in the neck muscles, or placebo in all muscle groups. There was no significant difference in migraine frequency among the three treatment groups. However, there was a significant decrease in migraine-associated symptoms in the 16U, but not the 100U, treatment group[22].

Elkind et al evaluated 418 subjects with 4 to 8 migraines/month in three sequential four month trials with re-randomization at each stage. Subjects were treated with 7.5U, 25U, or 50U BoNTA. There were no significant differences in migraine frequency between the two groups[23].

Aurora et al evaluated the "follow-the-pain" injection protocol in episodic migraine. Fixed-dose injections were given in the occipitalis, with the remainder of the injections and doses chosen based on the severity and distribution of the subject's pain rather than fixed doses in predetermined muscles (the "fixed-site, fixed-dose" paradigm). The study randomized 369 subjects with ≥ 4 migraines but ≤ 15 headache days/month to three treatments with 110 to 260U BoNTA or placebo every 90 days. There was no statistically significant difference between the two groups. However, subgroup analysis of subjects with a baseline migraine frequency of ≥ 12 headache days/month did show a significant decrease in headache episodes compared with placebo at the Day 180 endpoint, -4 versus -1.9 ($p=0.48$)[24].

In an effort to better characterize BoNTA responders with episodic migraine, Relja et al divided subjects into placebo responders (n=173) and placebo nonresponders (n=322) and then randomized to 75, 150 or 225U BoNTA or placebo every 90 days for 6 months. Subjects on concomitant preventive migraine medications were excluded. Injections were fixed-site, fixed-dose into the frontalis, corrugator, temporalis, trapezius, splenius capitus, semispinalis, and occipitalis muscles. There was no significant difference in headache frequency between the two groups at the Day 180 primary endpoint[25].

Saper et al evaluated the effect of different injection sites and dosing amounts in 232 subjects with 4 to 8 migraines/month. Subjects were randomized to four different injection site patterns: frontalis (10U), temporalis (6U), glabellar (9U), or all three sites combined (25U). There was no significant difference in headache frequency at the Day 60 primary endpoint[26]. The authors supposed that one of the reasons for the negative results may have been due to the low doses of BoNT-A.

Clinical Results of OnabotulinumtoxinA in the Prevention of Chronic Daily Headache and Chronic Migraine

While the aforementioned authors were evaluating the efficacy of BoNT-A in episodic migraine, Mathew et al. reported a positive outcome in a heterogeneous patient population with chronic daily headache (CDH)[27]. CDH is a broad category that includes any primary headache disorder that occurs with a frequency of 15 days/month or more. In this randomized, double-blind, placebo- controlled trial, 355 subjects with headache ≥ 15 days/month were divided into placebo responders (n=76) and nonresponders (n=279) and treated with 105 to 260U in a "follow-the-pain" distribution every 90 days for three treatment cycles. Although there was no significant difference for the primary endpoint of the number of headache-free days at Day 180, there were significant differences in several secondary endpoints. The BoNTA treatment group had a larger percentage of subjects with a ≥50% reduction in headache frequency and a greater mean change from baseline headache frequency at Day 180[27]. A subgroup analysis that excluded subjects taking preventive migraine medication found that the BoNTA treatment group had a statistically significant decrease in headache frequency compared to placebo after the second and third treatments[28]. A similar randomized, placebo controlled trial by Silberstein et al that evaluated 702 subjects with CDH did not meet the primary endpoint of mean reduction in headache frequency at Day 180[29]. However, subjects receiving 150U and 225U of BoNT-A had a greater decrease in headache frequency at day 240 that those taking placebo. These results, combined with Aurora et al's significant difference in subgroup analysis of migraine patients experiencing ≥ 12 headache days/month[24], prompted further investigation into the efficacy of BoNT-A in chronic migraine (CM).

The PREEMPT clinical program confirmed the efficacy and safety of BoNT-A in the preventive treatment of adults with CM. Two phase-3, multicenter studies (PREEMPT 1 and PREEMPT 2), which each had a 24-week, double-blind, parallel-group, placebo-controlled phase followed by a 32-week open-label phase, enrolled 1384 patients with CM. All patients received the minimum dose of 155 U of BoNT-A administered to 31 injection sites across seven head and neck muscles using the fixed-site, fixed-dose injection paradigm. A modified follow-the-pain approach with ≥ 40 U BoNT-A, administered to eight injection sites across three head and neck muscles, was also allowed. There were statistically significant reductions from baseline for frequency of headache days after BoNT-A treatment compared with placebo treatment in both PREEMPT 1 and PREEMPT 2 ($P = 0.006$; $P < 0.001$). There was also statistically significant improvement from baseline headache frequency after BoNTA treatment compared with placebo treatment in PREEMPT 2 ($P = 0.003$). Pooled analysis demonstrated that BoNT-A treatment significantly reduced mean frequency of headache days (−8.4 BoNT-A, −6.6 placebo; $P < 0.001$) and episodes (5.2 BoNT-A, −4.9 placebo; $P = 0.009$). Additionally, significant between-group differences favoring BoNT-A existed for several other secondary endpoints including migraine episodes, migraine days, moderate or severe headache days, cumulative hours of headache on headache days, and proportion of patients with severe disability. The PREEMPT results showed significant improvements in multiple headache symptom measures and demonstrated improvement in patients' level of functioning, psychological distress, and overall quality of life. Multiple treatments of 155 U up to 195 U per treatment cycle administered every 12 weeks were shown to be safe and well tolerated[30, 31, 32].

Comparative Efficacy of OnabotulinumtoxinA in Chronic Migraine

A few trials have been conducted that compared the effectiveness of BoNT-A to oral medication in migraine headache prevention . Mathew et al randomized 60 CM patients to either BoNT-A (100U fixed-site and 100 U follow-the-pain) and oral placebo or topiramate and placebo injections. Subjects received two rounds of injections at study start and month 3, whereas the topiramate group continued medication until study completion at 9 months. Only 36 subjects completed the study: 24.1% in the topiramate group dropped out due to adverse effect compared with 7.7% in the BoNT-A group. At the 9 month endpoint, a similar number of patients reported a ≥50% decrease in headache/migraines days in the BoNT-A and topiramate groups, 40.9% and 42.9% respectively[33]. Cady et al also evaluated BoNT-A to topiramate in a randomized, double-blind, placebo-controlled study of 59 CM patients over 12 weeks[34]. There was significant reduction in the number of headache days per month within but not between the two groups.

A trial of 59 patients randomized to 100U BoNT-A and oral placebo or 250mg divalproex sodium BID and placebo injections showed similar improvement in migraine disability and reduction in headache days. There were a greater percentage of adverse effects and discontinuation in the divalproex group[35]. Another study of CM patients showed that treatment with 250U BoNT-A had similar efficacy as 25mg or 50mg amitriptyline[36].

These studies suggest that BoNT-A has similar efficacy and a superior side effect profile compared to available oral medications for prevention of CM. Physician-administered injections every three month also reduce concerns for compliance with a daily dosing regimen.

Techniques for Onabotulinumtoxin-A Injection in the Prevention of Chronic Migraine

The injection protocols commonly used are: (1) the fixed-site, fixed-dose approach, which uses fixed, symmetrical injection sites and predetermined doses; (2) the follow-the-pain approach, which often employs asymmetrical injections and adjusts the sites and doses depending on where the patient feels pain and where the examiner can elicit pain and tenderness on palpation of the muscle; and (3) a combination approach, which uses injections at fixed frontal sites, supplemented with follow-the-pain injections (this approach typically uses higher doses of BoNT-A)[37].

The PREEMPT clinical trials used a modified follow-the-pain injection paradigm[30, 31]. OnabotulinumtoxinA (155 U) was administered as 31 fixed-site, fixed-dose injections across seven specific head and neck muscle areas using a sterile 1 ml Luer Lock syringe with a 30-gauge 0.5 inch needle. OnabotulinumtoxinA is available in single-use 50U, 100U or 200U vials. The 100U vial is reconstituted with 2mL sterile saline and the 200U vials with 4mL sterile saline for a final concentration of 5U onabotulinumtoxinA per 0.1 mL. Each injection in the fixed-dose paradigm is 0.1 mL (5U). Up to 40 U of additional onabotulinumtoxinA can be administered, using a follow-the-pain strategy, into the temporalis, occipitalis, and/or trapezius muscles, with a maximum dose of 195 U administered to 39 sites (Figures 1-4). When deciding on dose and location of additional onabotulinumtoxinA, the location of the patient's predominant pain and the severity of palpable muscle tenderness should be considered. Figure 1 lists recommended anatomical sites of injection for headache and the onabotulinumtoxinA (BOTOX®) dose per site used in the PREEMPT trials. The injections are typically administered every 12 weeks.

The most commonly reported side effects following injection of onabotulinumtoxinA for the treatment of chronic migraine include neck pain (9%), headache (5%), eyelid ptosis (4%), migraine (4%), muscle weakness (4%) and muscle stiffness (4%)[38]. The safety of

onabotulinumtoxinA has not been determined in women who are pregnant or lactating. It is currently FDA pregnancy category C. It is contraindicated in patients with neuromuscular disorders, such as myasthenia gravis. When used for indications other than CM, instances of systemic symptoms resembling botulism due to distant spread beyond the area of injection have been reported. For this reason, the FDA requires all botulinum toxin products to carry a boxed warning of distant spread of toxin effect[38].

Conclusion

Clinical studies suggest that BoNT-A is a safe and effective treatment in the prevention of CM. A favorable side effect profile and dosing schedule make it an attractive alternative to available oral medications, which are limited by adverse effects and the potential for noncompliance with dosing regimens. Further research is needed to understand the mechanism of action of BoNT-A on the pathophysiology of CM and fully evaluate its potential in the treatment of primary headache disorders.

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Figure 1: (A) The corrugator injection sites (bilateral) are above the medial superior edge of the orbital ridge (bony landmark). (B) The procerus site is above and midline to the medial superior aspect of the orbital ridge (bony landmark) of each eye. (Figures 1-4 reprinted with permission[39])

Figure 2: The frontalis injection sites (bilateral) are located just beneath the skin surface of the central and forehead regions.

Figure 3: (A) The first injection site is located in the anterior aspect of the temporalis muscle. The second and fourth sites are within the medial aspect and the third site is located in the posterior aspect of this muscle. These injections should be repeated symmetrically on the contralateral side for a total of 8 injections. Additional injections can be distributed between the right and left temporalis muscles in areas of maximal tenderness and/or pain. (B) The 6 occipitalis muscle injection sites are located superior to the supranuchal ridge on either side of the occipital protuberance. In the areas of maximal tenderness and/or pain, up to 2 additional injections can be distributed across the right and left occipitalis muscles.

Figure 4: (A) The first cervical paraspinal injection site is lateral to the midline and inferior to the occipital protuberance. The second site is lateral and superior to the first injection. These injections should be repeated symmetrically on the contralateral side for a total of 4 injections. (B) The first of the 3 trapezius muscle injection sites is located in the lateral aspect of the muscle. The second site is within the mid-portion of the muscle and the third site is within the superior aspect of the muscle. Symmetrical injections should be repeated on the contralateral side for a

total of 6 injections. Up to 4 additional injections can be distributed between the right and left trapezius muscles, in the areas identified as having maximal tenderness.