Chapter 5
Botulinum Toxin for Migraine Headaches

David Stepnick

Introduction

About two decades ago, a local television news station ran a story about a "new" pharmaceutical being used for what to most viewers seemed to be a strange purpose —to decrease facial movement in the forehead thereby improving wrinkles associated with motion. "Why would some people have this substance injected into their bodies," the television reporter asked, "when a thimble full of this agent, in its pure form, could kill everyone in the state?" This teaser, perhaps somewhat sensationalized, was referring to botulinum toxin type A (BTX-A); the reporter ultimately was introducing this product and application to the public at a point when few people knew anything about it. BTX-A had been used by ophthalmologists for blepharospasm and strabismus since the early 1980s, but its use for cosmetic purposes, migraine, and a plethora of other indications began to expand as the general public and physicians became more aware of the product.

Improvement or elimination of migraine headaches with BTX-A were, at first, anecdotal accounts by patients who had BTX-A injected for other reasons (ophthalmologic or off-label cosmetic) or corrugator resection as part of upper facial rejuvenation surgery. Indeed, the author's first experience with BTX-A eliminating migraine headaches came in the same timeframe as did the above-noted news story. A patient handed me a sheet of paper on which was listed, in two columns filling the paper from top to bottom, a list of medications and interventions which had been tried by her and her neurologist to control her migraine headaches. "None of

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these things have really worked," she exclaimed, "but my headaches have been much better since the Botox®." My patient was receiving Botox® for her vertical glabellar creases but ultimately enjoyed elimination of what had been impossible-to-control migraines. Many thought that these reports were simply coincidences but eventually physicians and patients realized they were not isolated incidents, but rather reproducible effects that eventually led to the Food & Drug Adminstration (FDA) approval of onabotulinumtoxinA (Botox®) for chronic migraines.

BTX-A has been successfully used for a wide variety of disorders, including strabismus and nystagmus, migraine headache, smooth muscle hyperactive disorders, sweating disorders, disorders of localized muscle spasms and pain, focal dystonias, non-dystonic disorders of involuntary muscle activity, and spasticity. It is used for a variety of cosmetic purposes including for vertical glabellar creases, horizontal forehead lines, "crow's feet," to create a temporal browlift, for platysmal bands, horizontal neck lines, and by some for perioral rhytids.

History

Of the world's deadly toxins—tetanus toxin, shigella toxin, ricin toxin, aflatoxins and pufferfish toxin—botulinum toxin is the most acutely toxic substance known to man. The toxin, with a lethal dose of about 0.2–0.3 ng/kg (0.0000000002 g/kg), was first described in the 1820s by Dr. Justinus Kerner, a German physician and poet, when its toxic effects were observed after the deaths of several dozen Germans who had consumed improperly prepared blood sausages. Kerner recognized the link between the improperly prepared food and the neurological symptoms of food-borne botulism: ptosis, dysphagia, muscle weakness, and if untreated, paralysis and respiratory failure. He used the term "Wurstgift," or sausage poison [1, 2]. In 1870, another German physician, John Muller, coined the name "botulism" from the Latin term botulus, which means "sausage" or "black pudding" [3].

Dr. Emile Pierre van Ermengem, a Belgian microbiologist, first connected "the disease" botulism with a bacterium. Having discovered the bacterial causes of anthrax, tuberculosis, and cholera, he investigated three deaths and 23 cases of paralysis following a dinner at the annual gathering of the Music Society in the town of Ellezelles in Belgium. Van Ermengem's close friend had died after consumption of the salted pork dish responsible for tragedy, and his investigations led him to become the first person to isolate the microbe *Clostridium botulinum* from both the food and the postmortem tissue of victims who had died. He isolated a spore-forming gram-positive bacterium which produced the exotoxin [4]. While he named the bacterium *Bacillus botulinus*, it is now known as *C. botulinum* because of its characteristic appearance under the microscope: "kloster" meaning "spun yarn" or "thread that is twisted" in Greek.

During World War II, the US Academy of Sciences created a laboratory at Fort Detrick in Maryland for the investigation of biologic agents that could be used in

war. Potential biological weapons included botulinum toxin, already known to be the deadliest substance in the world. Supposedly, a batch of gelatin capsules filled with botulinum toxin was produced with the intent of having Chinese prostitutes slip the pills into the food and/or drinks of high-ranking Japanese officers. The project was abandoned before the plan was executed. In 1946, largely as a result of interest in botulinum toxin for biowarfare, researchers isolated a crystalline form of BTX-A [5]. This method was subsequently used by biochemist Dr. Edward Schantz to produce the first batch of BTX-A in the early 1950s.

Experimentation with the toxin continued. Physiologist Dr. Vernon Brooks discovered, in 1953, that injecting small amounts of BTX-A into a hyperactive muscle blocked the release of acetylcholine from motor nerve endings, causing temporary "relaxation" [6]. In the 1960s, Dr. Alan B. Scott, an ophthalmologist researching ways to treat strabismus, began injecting BTX-A into monkeys, theorizing that strabismus may be improved by the toxin's "muscle-relaxing effects" [7].

In 1972, President Richard Nixon signed the Biological and Toxin Weapons Convention that terminated all research on biological agents for use in war, in part responsible for the closing of Fort Detrick. Research into the use of botulinum and other food-borne toxins for medicinal use continued at the University of Wisconsin under the leadership of Dr. Edward Schantz. In 1979, he produced a "large" batch of BTX-A, named batch 79–11, which consisted of 200 mg of twice crystallized toxin. Alan Scott subsequently received FDA approval to inject small amounts of the botulinum toxin into human volunteers.

Scott published a number of studies including a 1981 paper in the *Transactions of the American Ophthalmological Society* concluding that BTX-A appeared to be "a safe and useful therapy for strabismus" [8–10]. Interestingly, as early as the 1980s, patients reported not only reduction in spasms, but improvement in facial lines. In the first half of that decade, further refinement of BTX-A as a therapeutic agent occurred as university-based ophthalmologists in the United States and Canada explored its potential. By 1985, a scientific protocol of injection sites and dosage had been empirically determined for treatment of blepharospasm and strabismus. Side effects were considered rare, mild, and treatable. The beneficial effects of the injection lasted 4–6 months.

Scott utilized a manufacturer and distributor for BTX-A which, in 1986, was not able to obtain product liability insurance. He (and others) were not able to obtain the drug and supplies of BTX-A were gradually consumed. For a period of four months, until liability issues were resolved, blepharospasm patients in the United States had to have their injections at eye centers in Canada. In 1988, Allergan acquired the rights to distribute Scott's batch of BTX-A, at that time known as Oculinum; one year later, the FDA approved its use for the treatment of both strabismus and blepharospasm. When Allergan's acquired Scott's company, it changed the drug's name to "Botox®."

Although ophthalmologists who used BTX-A for ophthalmologic indications had noticed that their patients had less severe or absent "frown lines," it was Carruthers who published a study in the *Journal of Dermatologic Surgery and Oncology* stating that, although temporary, "treatment with *C. botulinum*-A

exotoxin is a simple, safe procedure" for the treatment of brow wrinkles [11]. Still off-label in the mid-1990s, cosmetic use of Botox® increased rapidly and by 1997 the supply ran out. Once it became available again, it caught the attention of the New York Times which reported, "Drought Over, Botox is Back" [12].

In 2000, Botox® was approved for the treatment of cervical dystonia. Botox Cosmetic® was approved in 2002. Probably largely due to the attention Botox® received as a result of its cosmetic uses and the public's intrigue with a simple, non-invasive treatment for facial aging, the sales and use of Botox® skyrocketed. Physicians explored other applications for this drug, and soon the list of indications was long. These indications eventually included the treatment of overactive bladder, certain types of urinary incontinence, chronic migraine [prophylaxis in patients with migraine ≥ 15 days per month with headache lasting 4 h a day or longer], spasticity, severe axillary hyperhidrosis as well as blepharospasm and strabismus [13]. It has been used "off-label" in many different situations including for facial tics, hemifacial spasm, spasmodic dysphonia, piriformis syndrome, thoracic outlet syndrome, Parkinson's disease, myofascial pain syndrome, and for ischemic digits, among others.

Other neurotoxins were released by other pharmaceutical companies, including Myobloc®, Dysport®, and Xeomin® but none currently are indicated for migraine headaches. An FDA alert was released 8/2009 that said: "Changes to the established drug names to reinforce individual potencies and prevent medication errors. The potency units are specific to each botulinum toxin product, and the doses or units of biological activity cannot be compared or converted from one product to any other botulinum toxin product. The new established names reinforce these differences and the lack of interchangeability among products" [14].

As the number of anecdotal cases of migraineurs whose headaches improved after having BTX-A injected for aesthetic reasons accumulated, clinicians began to investigate using BTX-A in the migraine population. On October 15, 2010, Botox® was approved for treatment of adult patients with chronic migraine [15]. Botox® and Botox Cosmetic® officially became knowns as OnabotulinumtoxinA.

Pharmacology

Botulinum toxin is produced by *C. botulinum*, a Gram-positive spore-forming anaerobic bacterium. There are seven structurally similar but antigenically and serologically distinct neurotoxins: types A, B, C [C1, C2], D, E, F, and G. Human botulism is caused mainly by types A, B, E, and (rarely) F. The molecule is synthesized as a single 150 kD chain which is then cleaved to form a dichain molecule joined by a disulfide bridge. An approximately 50 kDa light acts, similar to tetanus toxin, as a zinc endopeptidase with its proteolytic activity located at the N-terminal end. The $\sim$100 kD heavy chain provides cholinergic specificity; it is responsible for binding the toxin to presynaptic receptors. The heavy chain also promotes light-chain translocation across the endosomal membrane.

The process of neuromuscular transmission begins with neuronal stimulation. This initiates a cascade of events that leads to the fusion of neurotransmitter-containing vesicles with the nerve membrane, a process that requires a group of proteins that are part of the SNARE complex (SNARE—an acronym from SNAP REceptor) (SNAP—an acronym for Synaptosomal Associated Protein). Membrane fusion results in the release of acetylcholine by exocytosis into a synapse. Acetylcholine diffuses across the cleft and eventually binds to receptors on the muscle, leading to muscle contraction.

BTX-A acts by presynaptically binding to high-affinity recognition sites on the cholinergic nerve terminals thereby decreasing the release of acetylcholine, causing a neuromuscular blocking effect. The effect of the toxin is permanent—the toxin does not "wear off" as it may seem to do clinically. Recovery occurs by proximal axonal sprouting and muscle re-innervation and formation of a new neuromuscular junction.

The process by which BTX-A blocks neuromuscular transmission is actually a four-step process. These steps include binding, internalization, translocation, and blocking. First, the dichain toxin complex *binds* to the presynaptic terminal, a process which takes about 30 min. Next, mediated by the heavy chain, the neurotoxin is *internalized* into the nerve cell by receptor-mediated energy-dependent endocytosis. The nerve cell actually invaginates around the toxin molecule. The toxin is then *translocated*, the disulfide bond is cleaved, and the toxin is released into nerve cell cytoplasm. The final step of BTX-A action, the *blocking* step, involves prevention of fusion of the neurotransmitter vesicle with the nerve membrane by light-chain proteolysis of SNAP-25, a cytoplasmic protein required for the attachment of acetylcholine-containing vesicles onto the nerve membrane, thereby preventing acetylcholine exocytosis.

Botulinum Toxin Preparation

Botox® is prepared by laboratory fermentation of *C. botulinum*. The toxin is harvested, purified, and crystallized. The crystallized Botox® is then diluted with human serum albumin, lyophilized, and bottled. Each vial contains 50 or 100 U of BTX-A (the human lethal dose is estimated to be approximately 3000 U). Vials should be stored in a freezer at or below 58 °C.

A 100 U vial of Botox® is usually reconstituted with saline just before use. Package insert instructions specify using saline that does not contain a preservative as the diluent, but many physicians prefer to use saline with preservative, as it seems to cause less discomfort when injected and it has the added benefit of the preservative. Solutions may be prepared with 1–4 ml/100 U vial, depending on physician preference, creating concentrations of anywhere from 25 to 100 U/ml. Once reconstituted, it should be stored at 2–8 °C. It is claimed that agitation can easily denature the Botox®, so the diluent should be gently injected onto the inside of the wall of the vial and swirled gently rather than shaken. The reconstituted

solution should be refrigerated and optimally used within 24 h. However, many physicians will use the Botox®, properly refrigerated, for several weeks. A multicenter trial, suggested that reconstituted Botox® could be effectively used for up to 6 weeks [16, 17].

Contraindications

- Patients with preexisting neuromuscular conditions (e.g., myasthenia gravis or Eaton-Lambert syndrome).
- Patients who are pregnant or actively nursing.
- Patients on medications such as such as aminoglycosides, calcium channel blockers, penicillamine, and quinine (these can potentiate the effects of botulinum toxins).

Migraine Headache

Headache is one of the most common patient complaints in a neurology office, many of these patients carrying the diagnosis of migraine headache. Headache is also among the most common complaints reported by patients visiting the emergency department [18, 19], responsible for 3 million visits in 2000, and representing an annual cost between $600 million to nearly $2 billion [20]. Estimated annual costs as a result of migraine are between $13 billion to $17 billion in the United States [21]. It has been estimated that pain costs employers more than $60 billion annually mostly from diminished job performance [22]. An estimated 6% of men and 15–17% of women in the United States have migraine headache (about 28–36 million people), causing significant disability and an impaired quality of life.

The "International Classification of Headache Disorders" describes the specific criteria necessary for the diagnosis of the many different types of headaches. For example, the diagnosis of migraine without aura must fulfill the following criteria:

(A) At least five attacks fulfilling criteria B–E
(B) Attacks lasting 4–72 h, untreated or successfully treated
(C) Headache has at least two of the following characteristics—unilateral location, pulsating quality, moderate or severe pain intensity, aggravation by or causing avoidance of routine physical activity (e.g., walking or climbing stairs)
(D) During headache at least one of the following—nausea and/or vomitting, photophobia, and phonophobia
(E) Not attributable to another disorder [23].

Migraine with aura has a similar set of specific characteristics used to make the diagnosis. It is very important to make sure that the headache is not attributable to

another disorder. This requires the participation of a neurologist whose expertise allows exclusion of other potential causes of headache.

The Botulinum Toxin Type A—Migraine Connection

After sporadic anecdotal observations of migraine relief in the early 1990s by physicians who were using BTX-A for cosmetic and ophthalmologic indications, by the middle of the decade many other physicians were making the same observations. Studies began to emerge that independently suggested that BTX-A is useful for the prevention/treatment of chronic migraines in adults: patients had fewer headache days, less headache-related disability, and improved quality of life.

Silberstein et al. [24] performed a double-blind, vehicle-controlled study of 123 patients with two to eight migraines per month, randomized to receive vehicle or BTX-A. Pericranial injection of BTX-A significantly reduced migraine frequency, severity, acute medication usage, and associated vomiting.

Otolaryngologists began to investigate the effect of BTX-A on headache patients in the same era. Binder et al. performed a non-randomized study at four test sites. In these 106 patients, 77 were true migraine patients. 51% of the patients reported complete elimination of symptoms; 38% reported partial response. The authors concluded that BTX-A was safe and effective for both acute and prophylactic treatment of migraine headaches [25].

Blumenfeld's study suggested that dosage was important and concluded that positive results were found when the mean BTX-A dose was 63.2 units, for a mean total treatment time of 8.6 months, during which patients received an average of 3.4 treatments [26]. Another study compared BTX-A to placebo in 60 patients. The primary efficacy point was the number of headache-free days. Statistically significant improvement in headache-free days was seen in the BTX-A group from week 8–12 [27].

Two large, random double-blind, placebo-controlled trials were published in 2005 with 702 and 571 patients, respectively, studied over a period of 11 months. There was a statistically significant decrease in the number of headache days per month in the BTX-A group compared to placebo in both studies. To see the benefit, 180 days of treatment may be necessary in some patients [28, 29].

Mathew designed an 11-month randomized, double-blind, placebo-controlled study using 13 test sites in which headache patients who had 16 or more headache days per month were treated with BTX-A. They found that botulinum toxin type A-treated patients had a decrease from baseline of 50% or greater in the frequency of headache days per month at day 180 with patients having, on the average, approximately seven more headache-free days per month [28]. Silberstein examined toxin dosages and concluded that the most benefits (compared to placebo groups) were found when patients received 150 Units of BTX-A per treatment [29].

355 patients with migraine or probable migraine were randomized in a study published by Dodick et al. in 2005. These patients were not taking other

prophylactic medication and were included in their analysis. They found, after two injection sessions, that the maximum change in the mean frequency of headaches per 30 days was −7.8 in the BTX-A group compared with only −4.5 in the placebo group ($P = 0.032$). The between-group difference favoring BTX-A treatment continued to improve to 4.2 headaches after a third injection session ($P = 0.023$) and BTX-A treatment at least halved the frequency of baseline headaches in over 50% of patients after three injection sessions compared to baseline. They concluded that BTX-A "is an effective and well-tolerated prophylactic treatment in migraine patients with CDH who are not using other prophylactic medications" [30].

Relevant Anatomy

Largely through the work of Bahman Guyuron, four "peripheral" sites have been identified that appear to be associated with and act as migraine triggers [31–37]. The first site is the glabella and forehead region, where the supraorbital and supratrochlear nerves provide sensory input implicated as a migraine trigger. The muscles in this region are primarily the corrugator muscles and secondarily the procerus and frontalis muscles. The second site is in the temporal region associated with the zygomaticotemporal branch of the trigeminal nerve and its compression from surrounding musculature. The third site is intranasal: it is the only site of the four that has no correlation with muscle tension or improvement with BTX-A. As such, this chapter will not discuss this site further. The fourth and final site is in the occipital region of the neck. The trapezius muscle and the semispinalis capitis muscles and sometimes small arteries compress or stimulate the greater occipital nerve and occasionally the lesser occipital or third occipital nerves. As with the first two sites, BTX-A injected into these muscles can weaken them ultimately resulting in improvement of migraine headaches.

Understanding the anatomy of each of these muscles is important, as placing the BTX-A in the proper position results in the desired effect while, at the same time, not causing side effects.

Vertical glabellar creases result from the action of the depressor muscles of this region: the corrugator superciliaris, the medial portion of the orbicularis oculi, and the depressor supercilii. The corrugator muscle is a brow adductor which moves the brow medially and downward. It arises from the nasal bone just above the medial orbital rim. It extends upward and laterally and inserts in the skin above the area of the middle of the eyebrow. The medial fibers of the orbicularis oculi also originate from the medial orbital rim, but anterior to the origin of the corrugator. Its fibers interdigitate with fibers of the corrugator, procerus, and frontalis muscles. The depressor supercilii muscles originate from the nasal process of the frontal bone; they insert into the skin at the medial aspect of the eyebrow. These muscles can stimulate the supraorbital and supratrochear nerves as they exit their notch or foramen and course superiorly.

The zygomaticotemporal nerve has been identified as another peripheral trigger for migraine in certain patients. The zygomatic branch of the trigeminal nerve (V_2) originates in the pterygopalatine fossa, enters the orbit through the inferior orbital fissure, travels along the lateral orbital wall, and bifurcates into zygomaticotemporal and zygomaticofacial branches (V_2 is completely sensory, emerging from the trigeminal ganglion). The zygomaticotemporal nerve passes through the deep temporal fascia about 2 cm above the zygomatic arch providing innervation to skin of the temporal area. It exits the skull in a shallow depression easily palpable about 17 mm posterolateral and 6.5 mm cephalad to the lateral orbital canthus. It communicates with the auriculo-temporal nerve and it may have accessory branches.

Another primary trigger site is the occipital region. The greater occipital nerves are the primary target of BTX-A therapy, although the lesser occipital and third occipital nerves may play a role in some patients. The greater occipital nerves are the continuation of the medial branch of the C2 dorsal root. They emerge through the semispinalis capitus in an area approximately 1.5 cm in diameter, 3 cm inferior to the occipital protuberance and 1.5 cm lateral to the midline. Janis et al. describe multiple compression points along the course of the nerve: between the semispinalis and the obliquus capitis inferior, near the spinous process; at its entrance and exit into the semispinalis; at the entrance of the nerve into the trapezius muscle, where the nerve exits the trapezius fascia insertion into the nuchal line and in the distal region of the trapezius fascia where the occipital artery often crosses the nerve [37]. Peripherally, the nerve arborizes in the subcutaneous tissue above the superior nuchal line.

Proposed Mechanisms by Which Botulinum Toxin Affects Headache

The exact mechanism by which BTX-A prevents headache has not been clearly established and still is the subject of debate. In broad terms, the development of a migraine can be thought to be a cascade of events that that ends with the headache itself. It appears that in persons who are genetically predisposed to migraines (evidence for which is accumulating), this cascade of events can be triggered by stimulation of peripheral sensory nerves which can relay pain messages to the brain.

Welch identified four components that he believed were integral to the development of migraine, of which (1) peripheral activation of the trigeminal nerve and (2) progressive central sensitization have relevance to the mechanism by which BTX-A is postulated to affect headache [38]. Central sensitization of trigeminovascular neurons appears to be an integral factor in the development, progression and maintenance of migraine headaches [39]. The headache itself is thought, to be caused by dilation of large vessels innervated by the trigeminal nerve in a cascade of events that includes release of calcitonin gene-related peptide, substance P, and neurokinin A, found in the cell bodies of trigeminal neurons [40–43].

Investigators have linked stimulation of peripheral nerves to various headache syndromes. Bartsch found a large number of neurons that had convergent input from both the dura as well as cervical cutaneous and muscle territories. Their findings support a functional continuum between the caudal trigeminal nucleus and upper cervical segments involved in cranial nociception [44]. They conclude that "The facilitatory effect of greater occipital nerve stimulation on dura stimulation suggests a central mechanism at the second order neurone level" and "this mechanism may be important in pain referral from cervical structures to the head and therefor have implications of most forms of primary headache" [44].

There probably are several mechanisms by which BTX-A controls migraine headaches. One mechanism appears to be by blocking the release of acetylcholine thereby preventing the contraction of the muscle, which stops the mechanical stimulation of potentially sensitized peripheral nerves [45].

There is also evidence that BTX-A affects not only the SNARE proteins but also decreases the release of pain mediators including substance P, calcium gene-related peptide (CGRP), and glutamate [46]. There appears to be a direct effect as the toxin blocks both substance P from trigeminal sensory afferent terminals and the release of CGRP from autonomic vascular terminals. Additionally, BTX-A inhibits the release of glutamine (which stimulates the release of substance P and CGRP [47, 48]. These pain mediators produce neurogenic inflammation and result in sensitized pain receptors, creating a feedback circuit for continuing inflammation, pain, hyperalgesia, and allodynia [47].

A third mechanism appears to be that BTX-A appears to cause an analgesic effect without paralysis when it is conjugated with lectin and applied to dorsal root ganglion cells, selectively affecting the nociceptive sensory afferents, C fibers. In the study, BTX-A attenuated nociceptive transmission in vitro and in vivo for at least 24 days [47].

BTX-A, therefore, may reduce migraine pain by alleviating painful muscle contraction, blocking the pain neurotransmitters, and interrupting the nociceptive sensory afferents.

BTX-A and Surgical Treatment of Migraine Headaches

Today, while only a handful of physicians across the United States have the training to perform migraine surgery, with its approval by the FDA, BTX-A has taken a position among neurologists in their armamentarium for control for migraines. Guyuron observed that many of his patients who carried the diagnosis of migraine headache that underwent forehead rejuvenation (which included removal of the corrugator supercilii muscles) had improvement in their headaches after the surgery. Over the past decade and a half, he has done extensive work with migraine patients and published extensively on the peripheral trigger sites and surgical treatment of migraine headache. In his early study of 314 patients who underwent this surgery, 39 carried the diagnosis of migraine. 31 of these 39 patients experienced either

complete elimination or significant improvement in their migraine headaches ($p < 0.001$) over an average follow-up period of 47 months [31]. A prospective pilot study supported the findings of the retrospective study: 55% of patients whose corrugators were injected had complete elimination of their headache and 28% had significant improvement [35]. Further anatomic investigations by Guyuron et al. led to the identification of additional peripheral trigger sites, including not only sensory nerves of the face and neck but also sinonasal trigger(s).

Guyuron proposed that it may be the mechanical stimulation of the potentially hyperexcited peripheral sensory nerves that initiates the migraine cascade and notes that in three of his [initially] four trigger sites, the sensory nerves traverse muscles, ultimately the target of BTX-A injections [31]. Guyuron analyzed his outcomes for surgical treatment of these trigger sites at 5 years and found that 88% of the 69 patients appeared to benefit from surgery after 5 years: 29% reported complete elimination and 59% noticed a significant decrease in migraine headache ($p < 0.0001$) [36].

Work-Up

Regardless of the specialty of the physician who injects BTX-A for migraines, it is important for the primary evaluation and management of these patients to be done by a neurologist. It is critical to have a firm diagnosis and to exclude other causes of headache.

As with any condition, evaluation for BTX-A injection begins with a complete history. A number of headache-specific questions should be asked including the number of migraines and headaches per month, how long they last, how painful they are, where they begin and radiate and if they are unilateral or bilateral. Additionally, questions should include at what age the headaches began, their quality (e.g., throbbing, band-like, stabbing), what makes them worse and better, and their association with other symptoms such as eyelid droop, nausea and vomiting, loss of vision, or speech difficulty. In females, whether there is a relationship between the headache and the menstrual cycle is important to establish. Family history of migraine and whether the patient had a head or neck injury are other important pieces of the history. The location where the pain *begins* can help identify the trigger site(s).

In addition to other components of a physical examination, identification of trigger sites should be attempted with specific attention to sensory asymmetries. Three of the four main trigger points are related to the trigeminal nerve (including the intranasal trigger site, which is not treated with BTX-A) and one is associated with the greater and lesser occipital nerves from C2 and C3.

Patients who describe pain over the corrugator and/or procerus can be considered candidates for BTX-A injection in the glabellar region. Those who describe pain in the region of the temporalis muscle or the zygomaticotemporal branch of the trigeminal nerve can be injected in the temporal site. These patients may also

describe puffy eyes and/or ptosis. Pain in the occipital region supplied by the greater occipital nerve may benefit from occipital injections of BTX-A. These patients may describe retro-orbital pain or "runny nose." A positive response is defined as a 50% reduction in headaches following BTX-A injection.

Nerve blocks may be used to evaluate whether or not a patient is likely to benefit from BTX-A injections (or surgery). 1.5 cc of Marcaine 0.5% plain ±1.5 cc of Kenalog-10 is placed along an approximately 2 cm line over the trapezius insertion point horizontal line, centered about 4 cm from the midline. Patients can typically point to this spot when asked where the pain is most intense.

Injection Technique

When the FDA approved Botox® for use in chronic migraine patients in October of 2010, it did so based on the placebo-controlled double-blinded PREEMPT study. As such, the approval for general use is a fixed dose protocol based upon the location of injections used by investigators in this study. Of note, chronic migraine is defined as having more than fifteen headache days per month over a three month period, of which more than eight of the headaches are migrainous, in the absence of medication overuse. "On label" use of Botox® for chronic migraines an injection of 155 units in 31 sites and will be discussed later in this chapter.

The author's technique is considered "off label" use, but it limits the amount of BTX-A used in each patient, decreases the number of sites injected and, as such, is quicker, and probably less invasive and more cost effective. Improvement in the migraine is delayed until at least the 3–10 days it takes for the muscle to be weakened but when a patient is initially being treated with BTX-A, it may take longer for the sensory nerves to become desensitized.

The Author's Injection Protocol

Glabellar Site

After providing informed consent, the patient is placed in a comfortable supine position. The patient is asked to frown or "scowl" which allows the position and extent of the corrugator to be seen as it moves the medial brow and skin creating wrinkling. The skin is wiped with an alcohol wipe. A 3 cc syringe attached to a 30 gauge 1-inch long needle is used, with a BTX-A concentration of 50 U/1.0 ml. The needle is inserted at the lateral extent of the corrugator 1 cm or more above the brow, and is passed along the belly of the muscle, becoming deeper medially near the periosteum. 0.5 ml (25 U) is injected into each side as the needle is withdrawn (Fig. 5.1). More dilute mixtures of BTX-A necessarily require higher volumes to deliver the same number of units, increasing the chances of brow depression or ptosis and are, as such, not recommended. Pressure is held briefly over the injection site.

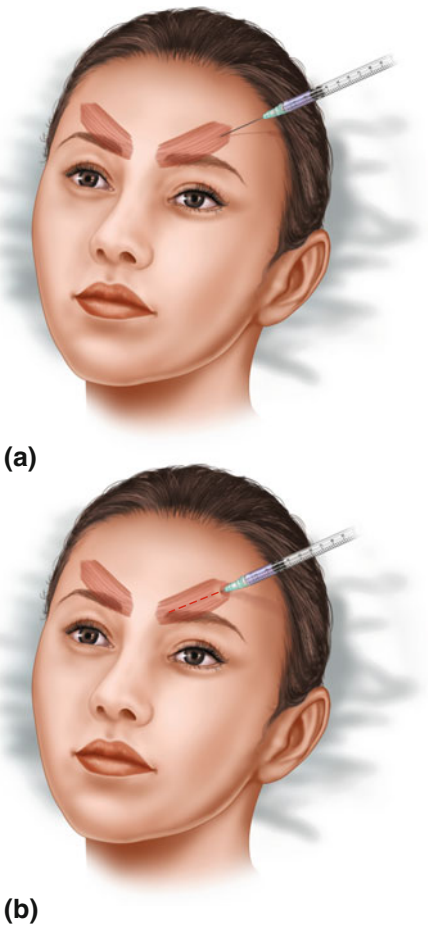

Fig. 5.1 Linear injection of the corrugator muscles is accomplished by inserting the needle at the lateral aspect of the corrugated muscle at least 1 cm above the brow, progressing deeper towards the periosteum medially, and slowing injecting the BTX-A as the needle is withdrawn

Temporal Site

As with the frontal site, the patient is placed in a comfortable supine position and, once again, a 30 gauge 1-inch long needle is used. BTX-A concentration is the same (50 U/1 ml). For the right temple, for a right-handed person, the left index finger is placed at the hollow where the nerve emerges from the deep temporal fascia, about 16–17 mm lateral to the lateral canthus. The needle is inserted about 2 cm posterior and lateral to the index finger just in front of the temporal hairline and advanced into the underlying muscle, using the entire length of the needle (Fig. 5.2). There is increased resistance as the needle pierces the deep temporal fascia and the injector should make sure that this depth is achieved. Muscle contraction may be felt. 0.5 ml of BTX-A is injected along this trajectory then cephalad, caudally, and posteriorly in an attempt to distribute the BTX-A throughout the muscle. Note that the tip of the needle should be well away from

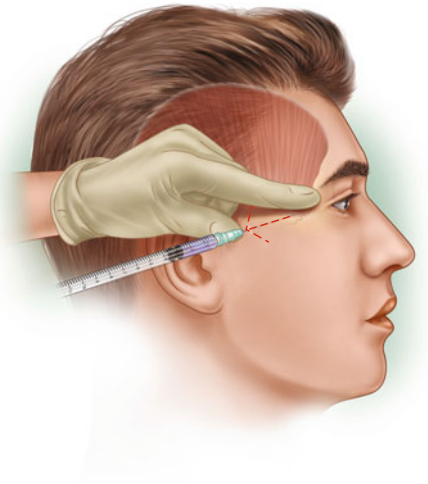

Fig. 5.2 Injection of the temporal area is accomplished by inserting the needle just in front of the hairline, passing it through the skin and fascia in a trajectory towards the shallow depression where the zygomaticotemporal branch exits. This landmark should be palpated with the opposite hand during the injections, which are fanned out above and below this initial trajectory to disperse the BTX-A in the temporalis muscle

the lateral orbital wall. Paralysis of those fibers of the temporalis muscle closest to the zygomaticotemporal branch of the trigeminal nerve is obviously most important.

Occipital Site

The patient is placed in a comfortable prone position, with the clenched fists acting as a pillow for the patient's forehead. The patient should tuck their chin which facilitates access to the occipital area. The fixed landmarks are the occipital protuberance and the posterior hairline. The patient is asked to point out, with one finger, where the pain begins; this roughly guides the site of injection. The greater occipital nerve exits 3 cm inferior and 1.5 cm lateral to the occipital protuberance and often is the site where the patient points when asked to define the origin of pain. A total of 50 U (1.0 ml) is injected 3 cm inferior and 1.5 cm lateral to the occipital protuberance, 0.5 ml per side. One is able to feel resistance as the needle passes through the trapezius fascia. It is important to use the full length of the needle, and the BTX-A should be injected in multiple passes at various angles fanning it out into the underlying muscles and almost to midline. Note that the needle is not completely withdrawn from the skin; it is almost fully withdrawn but the vector is changed, the needle is again inserted almost its full length, and this maneuver is repeated (Fig. 5.3). The depth of the posterior neck muscles are much greater than the muscles in the glabella, forehead, and temporal region and the BTX-A reaches these muscles using the 30 gauge 1-inch needle whereas it may not be using on-label techniques.

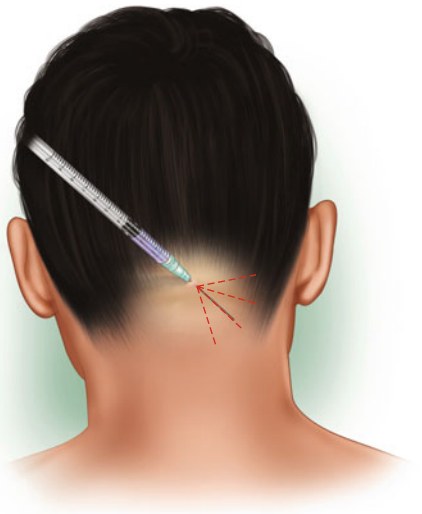

Fig. 5.3 Injection of the occipital area is done with the patient comfortably lying in a prone position, using the occipital protuberance as a landmark. An additional landmark is obtained by having the patient point to the area where pain begins. The muscles are relatively deep, so it is important to fan out the injections using the entire length of the needle

"On-Label Protocol" Injections

The PREMPT protocol involves injection of 155 U of BTX-A in 31 sites across seven specific areas of the head and neck [49, 50]. Patients undergo a trial of two treatments 12 weeks apart with subsequent treatments, if they experience improvement, every 12 weeks. Each injection is 5 U (0.1 ml). The most superficial part of the muscle should be injected, with the bevel pointing up. The entry point of the needle is not always the delivery point, as the clinician should attempt to place the BTX-A in the muscle which can be defined by inspection and palpation as the patient activates it. For bilateral sites, one side should be injected, then the contralateral site, at which point the next area is injected.

Each corrugator is injected with 5 U (0.1 ml) near the medial aspect of the brow, about 1.5 cm above the orbital rim (C—Fig. 5.4). Furrowing the brow shows the position of the corrugator as it moves the brow inferiorly and medially. Note that the corrugator originates deeply medially and becomes more superficial laterally as it inserts into the skin.

5 U (0.1 ml) are injected into the procerus, slightly beveling the needle as it is inserted, avoiding periosteum, midway between the corrugator injections (P—Fig. 5.4). The frontalis muscle is then injected, 5 U (0.1 ml) per injection in four sites, two medial injection points and two lateral injection points each side. The medial site is located by drawing a vertical line upwards from the medial inferior edge of the orbital rim in the upper one-third of the forehead, at least 1.5 cm above the corrugator site. The paired lateral injections are parallel to the medial sites, at least 1.5 cm lateral to the medial site and lining up with the lateral limbus (F—Fig. 5.4). When injections into the frontalis are too low, medial brow ptosis and/or lateral brow elevation may occur, especially in patients with some degree of

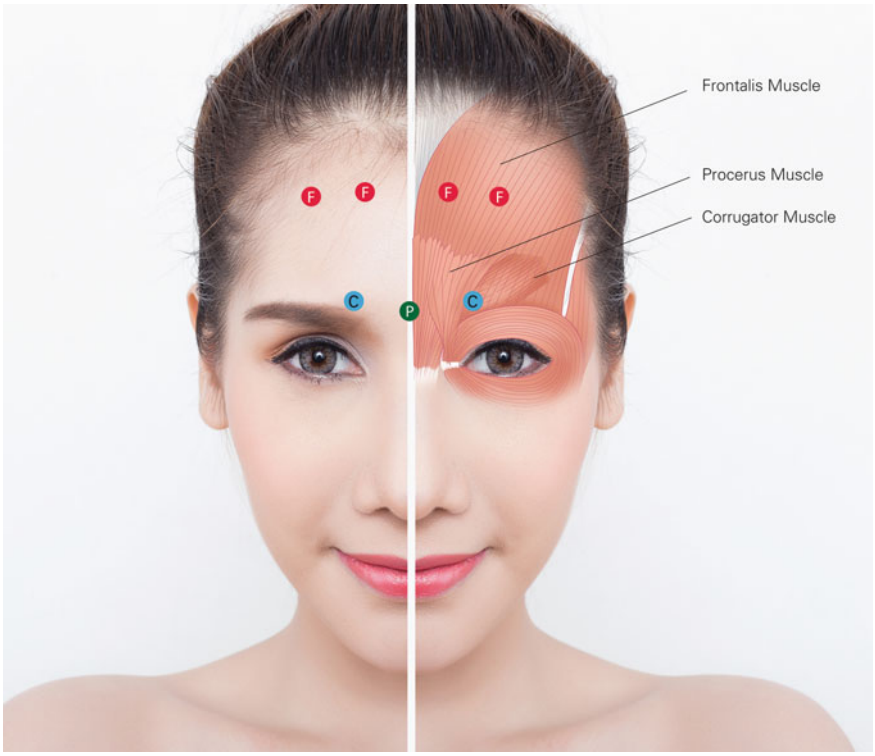

Fig. 5.4 On-label injection of the glabella region and the forehead targets the corrugator, procerus and frontalis muscles. Each injection site is injected with 5 U (0.1 ml), with a total of 10 U in the corrugators, 5 U in the procerus, and 20 U in the frontalis muscles. Details are described in the body of the text

preexisting brow ptosis. The tissues overlying the forehead are thin, as is the frontalis muscle. Injections should be superficial enough that wheal is seen after the injection.

The temporalis area receives 5 U (0.1 ml) per injection site and there are four injection sites (20 U) per side. The first site is 3 cm directly above the tragus. The second site is 1.5–3 cm directly above the first temporalis region injection site. The third site is halfway between the first and second sites, but 1.5–3 cm anteriorly (toward the face). The fourth site is 1.5 cm back from the second site, in vertical alignment with the highest point of the ear (1–4, Fig. 5.5). Prior to each injection, negative pressure on the syringe helps to insure that the needle is not within a vessel. The needle must pierce the fascia overlying the temporalis muscle, which often is felt by the injector and heard by the patient. Having the patient clenching their teeth activates the muscle and helps localize it. Pressure should be applied briefly to minimize bleeding. Note that the facial nerve is not at risk if the muscle is injected properly, as the action of BTX-A is at the neuromuscular junction;

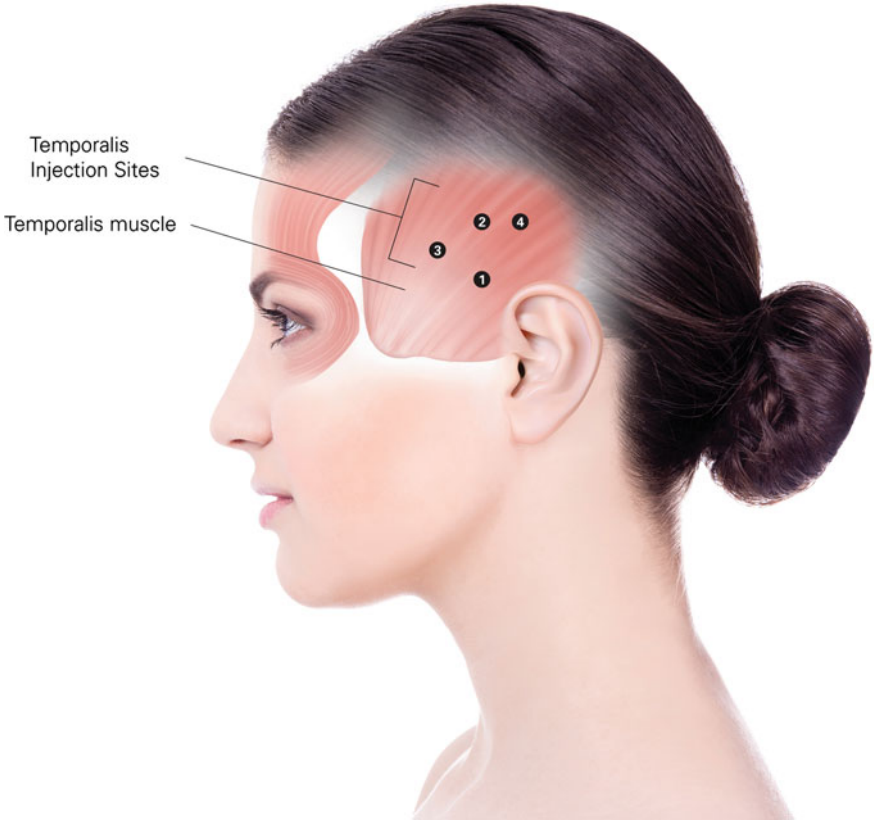

Fig. 5.5 On-label injection of the temporal region targets the temporalis muscle. As with the glabella/forehead site, each injection is with 5 U of BTX-A (0.1 ml): 20 U per side for a total of 40 U. Details are described in the body of the text

neuromuscular junctions of muscles innervated by the facial nerve are not located in this area, only the branching facial nerve itself.

Posterior injections are made in the occipitalis muscles, cervical paraspinal muscles, and in the trapezius. As with the other sites, each injection is 0.1 ml (5 U). The occipitalis receives a total of 15 U per side (three injections per side). The occipital protuberance and the mastoid process are palpated and the distance between the two is divided in half. The first injection is just above the [easily palpable] nuchal ridge at this midpoint. The second line is 1.5 cm from the first injection, along a vector from the first injection site toward the helix of the ear. The third injection is also 1.5 cm from the first injection site, on a vector medially which mirrors the lateral vector used for the second injection (O1–O3, Fig. 5.6). According to the protocol, the injections should be upwards, away from the neck, just under the dermis (which is relatively thick in this region). The cervical paraspinal muscles receive 10 U in two injection sites per side, for a total of 20 U.

The first site is 3 cm inferior to the occipital protuberance and 1 cm lateral to the midline. The second site is 1.5 cm from the first site, along a line defined by the first injection site and the helix (P1–P2, Fig. 5.6). The patient should be positioned upright, with the head neither flexed nor extended. Injections should not be lower than 3 cm inferior to the occipital protuberance and injections should be angled 45° superiorly. Finally, the trapezius is injected with 15 U per side, given in three injection sites. A line is drawn between the necklace line and the acromioclavicular joint; the first injection is in the midline of this line at the highest point of the shoulder/neck region as viewed from posteriorly. The second injection is halfway between injection site one and the acromiclavicular joint and the third injection is halfway between injection site one and the necklace line (T1–T3, Fig. 5.7).

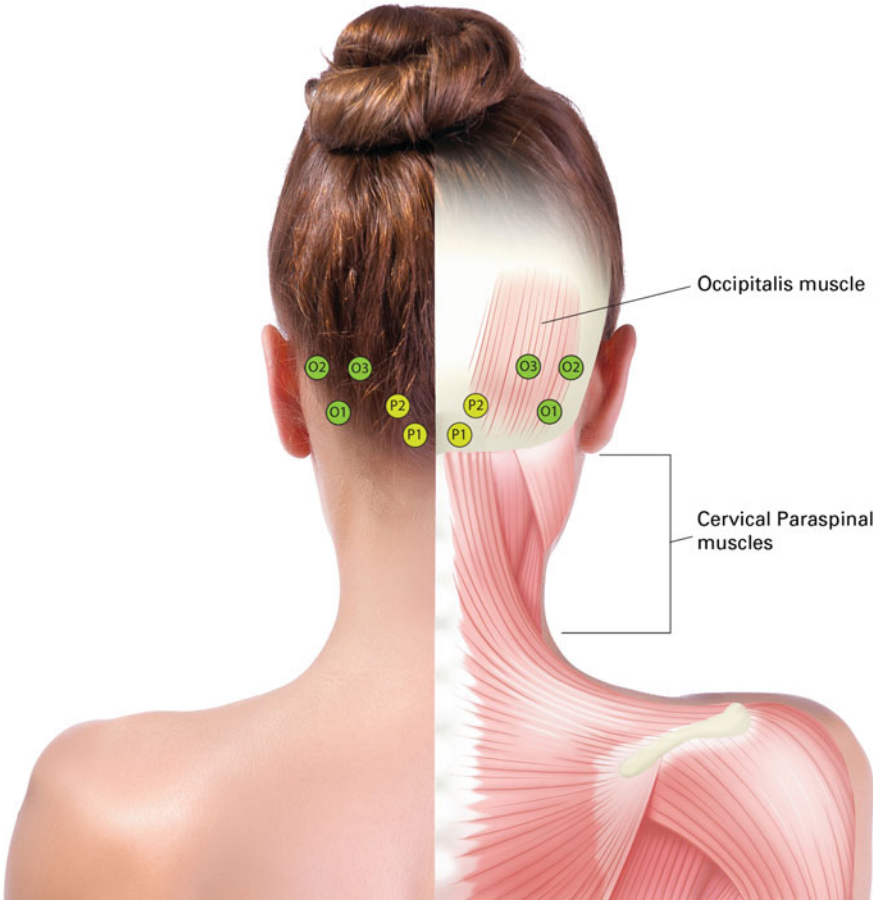

Fig. 5.6 On-label injection of the temporal region targets the occipitalis muscles and the cervical paraspinal muscles. Once again, each injection is 0.1 ml (5 U). The former muscles are injected with a total of 30 U (15 U per side) and the latter are injected with 20 U (10 U per side). Details are described in the body of the text

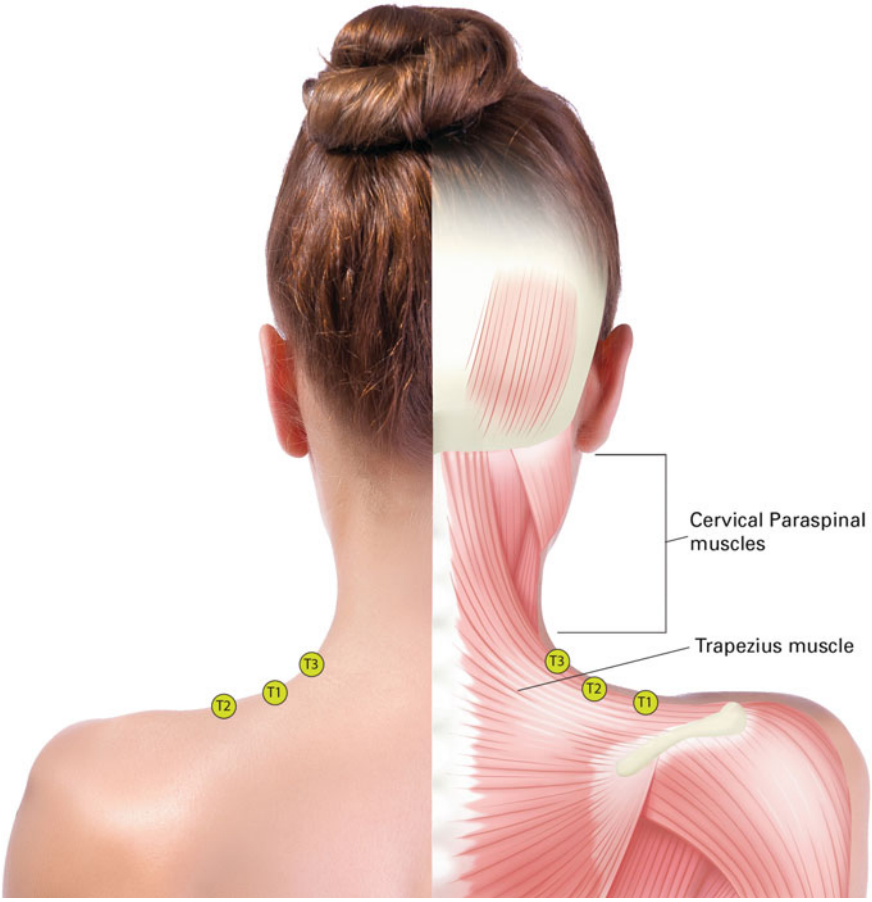

Fig. 5.7 On-label injection of the neck/shoulder region targets the trapezius muscles. As with all of on-label injections, 5 U (0.1 cc) in each site. A total of 30 U is injected into the trapezius (15 U per side)

Weakness may occur, especially in patients with small frames or patients with preexisting weakness of the neck or shoulder. Injections should be horizontal to the muscle.

Possible Complications/Adverse Effects

The clinician needs to be aware of the potential adverse effects of BTX-A before using it in their practice. Most importantly, one should be aware of the FDA'S "black box warning." The FDA warns that botulinum toxin may spread

systemically and cause asthenia, generalized muscle weakness, diplopia, blurred vision, ptosis, dysphonia, dysarthria, urinary incontinence, and life threatening swelling and breathing difficulties, hours to weeks after injection. Even though this warning accompanies each vial of the product, the FDA itself reminds us that there "has not been a confirmed serious case of spread of toxin effect when Botox® has been used at the recommended dose to treat chronic migraine, severe underarm sweating, blepharospasm, or strabismus, or when Botox Cosmetic® has been used at the recommended dose to improve frown lines" [14].

Serious adverse events have been seen with the use of unlicensed preparations that are not manufactured by Allergan. A case series of four patients with symptoms consistent with food-borne botulism had been injected with a highly concentrated, unlicensed preparation of BTX-A was published in 2006 [51]. These patients may have received doses over 2800 times the estimated human lethal dose by injection. While clinicians may be tempted to use unlicensed botulinum toxin products because of cost savings, the laboratory-confirmed cases of botulism demonstrate that without exception, it cannot be emphasized enough that only Botox® produced by Allergan should be injected.

More common adverse effects can be divided into two main categories: generalized and specific. "Generalized" effects include nausea, fatigue, malaise, flu-like symptoms, and rashes at sites distant from the injection. There have not been reports of weakness away from the injection site or central nervous system effects. "Specific" effects include injection site problems such as pain, edema, erythema, ecchymosis and short-term hypesthesia. Despite the fact that BTX-A is used for the treatment of chronic migraine, headache has been described as an adverse effect of BTX-A in injections. Discomfort is usually minimal and well-tolerated, but it can be decreased using topical anesthetics (not usually done by the author) or using small gauge needles. Discomfort can also be reduced by pinching the skin together with the underlying muscle, slowly inserting the needle bevel up and then slowly injecting the solution. Ice immediately after injection can further reduce pain, erythema, and edema. Bruising is not common but occurs most frequently in patients taking Vitamin E, NSAIDs, Plavix, or warfarin. Bruising can be minimized by patients avoiding these agents, limiting the number of injections, and applying gentle post-injection pressure. Headache is usually treated successfully by over-the-counter analgesics.

The most common complication in treating the glabellar complex is upper lid ptosis, caused by diffusion of the toxin through the orbital septum and affecting the levator palpebrae muscle. Maneuvers that help prevent ptosis include injecting at least 1 cm above the eyebrow and not injecting lateral to the mid-pupillary line. Digital pressure on the supraorbital ridge beneath the injection site can reduce extravasation inferiorly. Patients should be instructed not to push on the area that has been injected, and to remain in an upright position limit exercise for 3–4 h.

Treatment of Ptosis

When ptosis occurs, patients can be treated with Apraclonidine 0.5% eyedrops, an alpha 2—adrenergic agonist. Apraclonidine causes contraction of the Müller muscles thereby raising the lid. Ophthalmic Phenylephrine (Neo-Synephrine) 2.5% may also be used if Apraclonidine is not available.

Causes of Therapeutic Failures

In patients who have never been treated with BTX-A, failures may occur if there is a secondary headache disorder such as cervicogenic or TMJ-related headache. There may be other sites of compression. Patients may have medication overuse headache, opoid hypersensitization, abuse or addition, or even gluten intolerance.

There are a variety of reasons, in patients who previously have had headache relief from BTX-A, for therapeutic failures. Probably the most common reason is improper technique, if the injector does not have the needle in the proper intramuscular position or does not distribute the toxin throughout the muscle. The toxin may be less active, as a result of improper handling (not kept at proper temperature before or after mixing or shaking too vigorously) or error in dose or volume of the solution. A "bad batch" is theoretically possible, but probably unlikely. Circulating neutralizing IgG anti-BTX-A antibodies were thought to be important causes of failure, with earlier estimates as high as 5–15% of patients developing these antibodies; many now feel that this greatly overestimates the number of patients who are nonresponders. Risk factors for antibody production are patients who get repeat "booster" treatments after the primary injection or in patients who receive high doses (>200 U/session) of BTX-A. Tetanus toxin antibodies share homology in amino acid sequence with botulinum antibodies, so theoretically these antibodies may react with the BTX-A; cross-reactivity between the two may occur.

Marketing

There are several ways that physicians can establish themselves as clinicians who treat migraine headaches with BTX-A. The least expensive and often highest yield technique is by making established patients aware that BTX-A injections are a service you offer. Referrals by neurologists, primary care providers, and specialists such as allergists or other otolaryngologists are an important source of patients. Direct fact-to-face conversations or presentations at Departmental meetings or Grand Rounds can be useful. Patients who return to their referring physicians who have achieved relief of their migraine are likely to stimulate further referrals. Many neurologists are uncomfortable injecting BTX-A because the specialty is generally

not a procedure-oriented specialty; some neurologists are more comfortable if someone else physically performs the BTX-A injections. One cannot simply expect a neurologist to send all of their migraine patients to someone else to inject; a good relationship with mutual communication is critical.

Many neurologists are still skeptical about using BTX-A for migraines and it is important not to be lured into successfully treating headaches in a patient that has not been thoroughly, adequately, and properly worked-up. Always ensure that proper neurologic evaluation and work-up has excluded other headache sources.

Summary

Botulinum toxin type A, one of the world's most deadly toxins, once considered as a potential weapon for biological warfare, has become a commonly used pharmaceutical for a myriad of medical problems, with its list of indications growing each year. Migraine headache is a common, debilitating disease; the degree of debilitation is usually poorly understood by those not afflicted with headaches. No universally successful treatment is available so, while many other medical conditions are relatively easily controlled, migraine headache remains a difficult problem for the patients and their physicians alike. BTX-A emerged, in middle of the last decade of the last century, as a rather unlikely treatment for chronic migraine sufferers who had only achieved suboptimal control on other regimens. Since then, much has been learned about chronic migraines and BTX-A; yet, there is still a rather incomplete understanding of how botulinum toxin relieves or prevents headaches in this population. A number of investigators feel that the primary mechanism of action is by blocking the mechanical stimulation of the potentially hyperexcited peripheral sensory nerves that are involved in and initiate the migraine cascade which leads to the headache. This theory would explain the highly successful outcomes in patients who undergo surgical treatment of migraine headaches which primarily are procedures that decompress these sensory nerves. Yet, several studies have been published in the literature that offers insight into what might be additional mechanisms of action for BTX-A in patients with migraine headaches.

As experience has grown, some clinicians follow the on-label recommendations derived from the PREEMPT studies while others, through personal experience use their on off-label paradigms which have a number of advantages as detailed herein.

Recommendations

Physicians that would like to incorporate BTX-A injections for chronic migraine in their practice should always be sure that their patients have been properly evaluated and worked-up by a neurologist and have appropriate training for use of this agent. In a physician's practice that already utilizes BTX-A for other indications (e.g.,

cosmetic uses, blepharospasm, or facial spasm), it is fairly easy from a technical standpoint to adapt the injections for use in chronic migraine patients. It is more difficult to understand the "disease process" than it is to learn how to perform the injections. Those who are novice injectors probably should follow on-label recommendations and inject patients as defined for the PREEMPT study, but as experience is gained physicians may find it better to use the author's protocol detailed in this chapter. It is imperative that the physician understand how to avoid adverse events/complications and be familiar with their treatment should they occur.

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