

# O Contemporary Ophthalmology

A Biweekly Publication for Continuing Medical Education in Ophthalmology

## Botulinum Toxin Pharmacology and Ophthalmic Applications With Introduction of the Blepharitis Application

Gary Borodic, MD

**Learning Objectives:** After reading this lesson, the participant should be able to:

1. Discuss the basic and theoretical aspects of botulinum pharmacology.
2. List the generally accepted indications for ophthalmic and related use.
3. Describe a new ophthalmic potential indication for botulinum, hypersecretion blepharitis, in relation to pharmacologic and pathologic principles and early clinical experience.

Botulinum toxin has become a major therapeutic tool across many specialties since its introduction to medicine for the treatment of strabismus in 1981 by Dr. Alan Scott of the Smith Kettlewell Institute<sup>1</sup> in conjunction with the scientific assistance of Dr. Edward Schantz from Food Research at the University of Wisconsin-Madison.<sup>2</sup> Many applications have been tried and proved scientifically effective over the past 23 years, while other applications have remained controversial lacking a consistent standard of proof based on double-blind, placebo-controlled trials, such as the migraine application.

Botulinum toxin is an extremely versatile agent. Regional biologic activity is contained within the anatomic region where it is injected without systemic spread, resulting in a very high safety record over the past two decades. The basic pharmacology of botulinum toxin involves binding at the presynaptic membrane of the neuromuscular junction, resulting in suppression of acetylcholine release coupled with motor nerve impulses. It also results in blockage of acetylcholine release at autonomic cholinergic ganglion synapses within ganglion and effector organs such as sweat glands. Other tissue effects, such

as direct action on sensory neurons, neuropeptides, cell membrane receptor expressions, and other neurotransmitters, have been postulated and are under investigation.

Unique features of botulinum toxin technology are related to its very low protein exposure per dosing unit, often below the sensitivity of the immune system.<sup>2,3</sup> Low protein exposures easily achieve biologic and clinical effects, making this technology less likely than other forms of protein-based pharmaceuticals to cause neutralizing antibodies. As the technology continues to mature, the differential pharmacology of various botulinum-based immunotypes and formulations is becoming a topic of increasing interest.

### Basic Pharmacology

Botulinum toxins used in clinical practice throughout North America fall into one of two categories: immunotype A (Botox [Allergan], Reloxin [Ipsen/Medicis]) and immunotype B (Myobloc [Elan Pharmaceuticals, Inc./Solstice Neurosciences, Inc.]). In nature, the toxin occurs as immunotypes A through G with minimal antigenic cross-reactivity. The type A botulinum toxins used to date in the United States consist of a protein complex composed of a pure neurotoxin, hemagglutinin protein, and a nonhemagglutinin, non-neurotoxin protein. The neurotoxin molecule takes the form of a molecular mass of 900,000 organized as a noncovalently bound tetramer. The so-called nonactive complexing proteins are produced within the fermentation process and are believed to stabilize the activity of the neurotoxin. Each botulinum toxin subunit consists of two light and two heavy

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Dr. Borodic has disclosed that he is/was a consultant/advisor for Mentor Corporation, and is a patent owner of botulinum-related technology.

Dr. Borodic has disclosed that the use of botulinum has not been approved by the U.S. Food and Drug Administration for the treatment of pain and blepharitis.

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chains bound by a disulfide bond. Like type A, type B neurotoxin is synthesized by fermentation. Unlike type A, however, type B neurotoxin is produced as a pro-toxin, requiring enzymatic cleavage with trypsin to potentiate pharmacologic activity.

When injected into tissues, the toxin binds rapidly to receptors on the presynaptic membranes of the neuromuscular junction through molecular interaction with its heavy chains, and undergoes cleavage into light and heavy chains followed by penetration of the light chain into the cytosol. The light chain of type A acts as a zinc-dependent endopeptidase interacting with synaptosomal associated protein (SNAP)-25, a protein involved in vesicular fusion. Light chains from other immunotypes interact with vesicular-associated membrane protein and syntaxin, cytoplasmic proteins involved with exocytosis.

The most obvious effect of injection of a botulinum toxin preparation into or in the proximity of muscle is neurogenic muscle fiber atrophy. The diameters of the fibers shrink considerably with fiber size variability, similar to motor nerve surgical denervation.<sup>4,5</sup> The neurogenic atrophy is accompanied by electromyographic (EMG) signs of neuromuscular blockage (jitter potentials on single fiber electromyography). The anatomic effect has its onset within 10 to 14 days, but the first clinical signs of weakness are seen in 3 to 4 days in 50% of people who have received the injection. The denervative effects usually last from 12 to 14 weeks, with complete recovery from weakness and complete reversibility of anatomic changes. Pre-axonal motor fiber sprouting has been studied with botulinum injections and also appears to be reversible. Precise placement of the injections can be critical to a beneficial result, because the toxin remains confined to the targeted region if given in lower doses.

The quantization of botulinum toxin therapeutics involves LD50 (the lethal dose in 50% of a cohort of 20- to 30-g white mice).<sup>2</sup> Other in vitro assays have been tried, but the mouse bioassay still remains the "gold standard" for determining dose units and has proved to be a reliable guideline when used with the same formulation of botulinum toxin. However, the LD 50 unit is not universal, and units are not interchangeable among various preparations.<sup>6</sup> For instance, treatment of blepharospasm with Botox (type A) requires a total dose of about 30 to 60 units per treatment, whereas treatment with Myobloc (type B) may require 2000 to 5000 units. Differences also have been noted with different formulations of the same immunotype. Reloxin requires about 120 to 250 units to treat blepharospasm, whereas Botox requires about one-fourth this amount. Clearly, the LD 50 unit is not a precise measure of denervation potential, and dose-response analysis must be carefully accomplished with any potentially new botulinum formulations.

The stability of botulinum toxin preparation is quite good for a protein-based drug. Current preparations require refrigeration and must be used within 4 hours of reconstitution. Newer preparations generally are more stable at room temperature prior to reconstitution. Care must be exercised to avoid higher temperatures during storage, because they may impact biologic activity labeled on the vials.

Specific activity of various preparations is defined by the unit of biologic activity over the amount of protein in the vials (in nanograms). This measurement indicates the purity of the preparation and the amount of nonactive protein in the vials. A lower specific activity can indicate deactivated or inactive protein in the preparation

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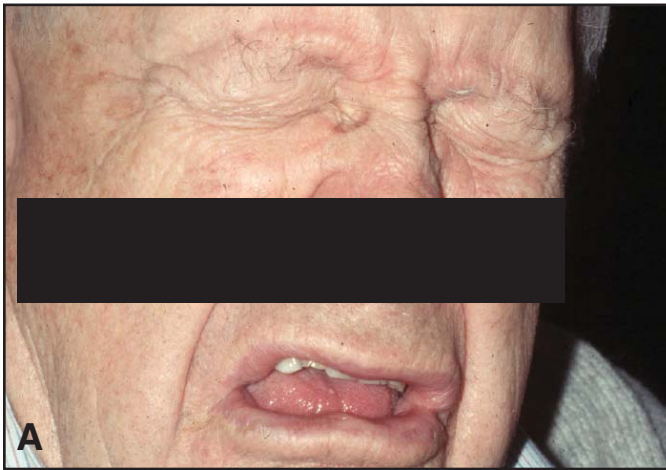
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**Figure 1.** A, Essential blepharospasm demonstrating severe involuntary eyelid closure with extension of involuntary movements to the lower face and neck region (Meige syndrome). Tremor of head and hand often is associated with this condition, in the patient or another family member. B, Hemifacial spasm is caused by involuntary and ectopic excitation of one facial nerve, causing synchronous contractions of muscles on one side of the face. Disfigurement and difficulty with communication are the major forms of morbidity.



and, possibly, toxoid accumulation. Earlier preparations of Botox contained a specific activity between 1.5 and 2.5, indicating deactivated protein in the preparation. After 1998, the specific activity was increased to 20, which appeared to decrease incidence of immune response for larger-dose indications such as cervical dystonia. Protein exposure (expressed as protein load per injection cycles) has been associated with an increased incidence of immunity.<sup>3</sup> The amount of protein needed to treat any indication depends on the units required for that indication and the specific activity of the preparation used. A decrease in the protein load has been associated with sustained response with less secondary resistance in cervical dystonia.<sup>7</sup>

The duration of action for botulinum toxin type A preparations is 12 to 14 weeks for most preparations studied. Increasing the dose can increase the duration of action to a point, but at the expense of diffusion away from the injection location and an increased incidence of diffusion-related complications such as ptosis or diplopia.

The incidence of immunity after repeated injections (secondary immunity, secondary nonresponse) still is unknown for many botulinum toxin indications.<sup>8</sup> Although immunity rates for the neck dystonia applications have been evaluated, the incidence of neutralizing antibody formation has not been determined for cosmetic application or blepharospasm.<sup>8</sup> Secondary immunity causing loss of beneficial effect has been reported for blepharospasm, cosmetic rhytid reduction in the glabellar area, hemifacial spasm, and spasmodic dysphonia.<sup>9,10</sup> There continues to be a lack of large, well-designed studies for detection of immunity rates for botulinum-based products currently in use in ophthalmic and cosmetic practice. A further problem in determining the immunity rate for lower-dose applications used in ophthalmology is the lack of a sensitive assay for the detection of clinically significant antibodies.

Antibodies are classified as *neutralizing*, meaning that the antibody blocks the bioactivity of a lethal mouse injection, and *non-neutralizing*, measured with enzyme-linked immunosorbent assay (ELISA) or Western blot assays that measure antibodies that bind to the botulinum toxin protein antigen but do not necessarily neutralize the lethal activity of the toxin. Neutralizing antibodies are correlated with poor clinical responses to botulinum. Attempts to use non-neutralizing antibodies to predict clinical outcome have produced inconsistent results, although Western blot assays recently have been validated against the mouse neutralization assay. The antibody issue will continue to be of concern for this therapeutic technology, as repeated injections over many years are necessary to treat chronic ocular conditions such as essential blepharospasm and hemifacial spasm as well as many other neurologic diseases. Given the wide-scale use of botulinum in the cosmetic domain, further defining and preventing this complication will be important for maintaining the viability of this agent for future therapeutic use.

After repeated doses of botulinum toxin pharmaceuticals over many years, tachyphylaxis (i.e., reduced efficacy) may develop. The cause of this phenomenon is still not clear, but it may be immunologic. This complication is seen in about 15% of patients with chronic essential blepharospasm and hemifacial spasm treated for over 5 years.

## Ophthalmic Applications

### Cosmetic

The most publicized application for botulinum toxin-based pharmaceuticals is the cosmetic facial application. Injection in point doses ranging from 1.25 to 10 U (type A), for a total dose of 20 to 40 U, can efface and depress dynamic and static lines and furrows within the glabellar region, lateral orbital region smile lines, and transverse forehead creases. Multiple injection points are necessary to spread the effects evenly and balance the facial dynamics during active facial expression. This effacement provides a consistent, reproducible effect and can be administered quickly and conveniently with little to no recovery time for patients. The easy administration and

ergonomics offset the need for repeated injections, and patients view the tradeoff as tolerable. In addition to their use for minimizing upper facial dynamic lines, injections have been used for reduction of neck bands caused by platysmal muscle contraction, square faces, (i.e., jowl shrinkage), and modest reduction of lower face bulging. Botulinum toxin type A is the preferred agent because it is less painful than botulinum type B (Myobloc), and it has lower immunogenicity, lower diffusion potential (ptosis-diplopia rate), and a generally longer duration of action.

### Essential Blepharospasm and Hemifacial Spasm

Since its introduction in 1983, botulinum toxin has become the virtual therapeutic backbone for treatment of essential blepharospasm and hemifacial spasm (Figure 1). This therapy has given many patients with these afflictions an opportunity for a normal life. The botulinum toxin technology has replaced surgical procedures such as facial neurectomy and orbicularis myectomy. Neurologic drugs such as clonipin and trihexyphenidyl (Artane; American Cyanamid Company) are not very effective as primary therapy, with response rates of less than 30%. Surgical procedures such as myectomy can be disfiguring and often require supplementation with botulinum toxin injections. Facial neurectomy can affect facial expression and often offers only temporary relief. Although the surgical procedures are not appropriate as first-line therapy, they can be useful in patients refractory to botulinum toxin injections.

Essential blepharospasm is defined as bilateral involuntary eyelid closure, affecting virtually all visual function. In extreme cases, patients become housebound, unable to ambulate independently because of visual disability. Repeated botulinum injections result in increased eyelid control, allowing for improved and often normal visual function. The dosage can vary from 20 to 80 U per injection cycle. Injections are split equally, usually among four injection locations per eye. Injections in the upper lid should be kept close to the lash line along the lateral and medial extremes of the upper eyelid to avoid diffusion of toxin into the levator muscle. In the lower lid, injections should be placed laterally, avoiding the medially located inferior oblique muscle, which lies close to the skin surface. The most common complications of the injections include ptosis and diplopia. Correct placement of the injections at proper doses mitigates against these complications.

Problems with long-term management include decreasing efficacy after repeated botulinum injections. The decreasing response rate was estimated to be 15% of patients in one survey taken at the regional meeting of the Benign Essential Blepharospasm Research Foundation, Boston, 2006, of about 100 patients treated for over 5 years. Reasons for decreasing response rates include progression of disease, immunity to botulinum toxin with development of neutralizing antibodies, tachyphylaxis to the drug, and the development of aggravating factors (e.g., sleep disturbances, entropions, ptosis, ocular surface allergy, anxiety, or depression). The progression of benign essential blepharospasm often accompanies involuntary movements of other regions of the

head, with grimacing, lip smacking, dysphonia, head and hand tremor, torticollis, and bruxism.<sup>1</sup>

Hemifacial spasm is a facial nerve condition characterized by involuntary firing of one facial nerve with synchronous contractions of muscles on one side of the face, causing closure of eyelids, elevation of nasolabial folds, elevation of the brow, and lip ectropion. Sometimes thumping sounds are heard by patients from stapedius contractions on the side of facial nerve involvement. Because the blepharospasm in hemifacial spasm is unilateral, vision often is not severely decreased. Morbidity results from severe disfigurement, impairment in natural facial expressions, and difficulty in "face to face" communications. Partial denervation of facial muscle is seen on the involved side. The syndrome is chronic and often progressive and is believed to be caused by an irritating compression from aberrant tortuous blood vessels in the proximity of the facial nerve at the cerebellar pontine angle. Current effective therapy has included microvascular neurosurgical decompression via posterior craniotomy and botulinum injection into the eyelids. Microvascular decompression has the potential to effect long-term suppression and cure<sup>11</sup>; however, this surgical approach can be associated with complications including hearing loss, intractable vertigo, and possible vascular compromise to brain stem structures. Botulinum toxin injections must be administered repeatedly; however, morbidity is minimal compared to that of the neurosurgical procedures. It is important to administer botulinum at lower doses than are used for essential blepharospasm because of pre-existing weakness associated with the partial facial motor nerve damage from intracranial facial nerve compression. For most patients, a total dose of 15 U is sufficient to suppress involuntary eyelid movement for 3 to 4 months. Because of associated partial facial palsy associated with hemifacial spasm, paralytic lagophthalmos is a more common complication than other forms of facial dyskinesias.

Another form of hemifacial spastic disease is aberrant facial nerve regeneration. The syndrome occurs after facial paralysis from Bell's palsy, Ramsay Hunt syndrome, traumatic facial nerve injury, or surgical intervention (often as a result of acoustic neuroma resection). The condition is characterized by synkinetic involuntary closure of the eyelids with lower facial movements during the recovery period after facial injury. Reflex tearing (so-called crocodile or gustatory tearing) can result from aberrant autonomic regeneration in the lacrimal gland, and, more rarely, reflex sweating can result from aberrant regeneration within exocrine sweat glands along facial regions (Frey syndrome). Sometimes, involuntary movements of the lower face are noted to occur with blinking. Patients often demonstrate an appearance of increased facial tone with upwardly contracted nasolabial fold and a sensation of increased facial tension. Botulinum toxin injection for this condition can be helpful to relieve involuntary blinking, reflex tearing, and reflex sweating, if present. Dosing is similar to that for hemifacial spasm, using about 15 U total dose in four or five injection locations. Paralytic lagophthalmos can be aggravated by botulinum toxin, so patients suffering concomitant dry eye or surface exposure keratitis must be treated with caution. Punctal plugs

can be useful to reduce dry eye symptoms and increase tolerance in selected patients.

Apraxia of eyelid opening is another syndrome involving involuntary eyelid closure. This condition is associated with gentle closure of the eyelids, not with forceful spasm. The condition is seen in the setting of degenerative brainstem diseases such as progressive supranuclear palsy, Parkinson disease, or other forms of central nervous system pathology. Generally, botulinum toxin injections are less effective for eyelid apraxia, but nevertheless can be tried.

### Strabismus

Strabismus was the first FDA-accepted indication for the use of botulinum toxin. Although botulinum treatment is effective for horizontal forms of strabismus, the effects often are temporary and require repeated injection under EMG guidance. Toxin diffusion also is a problem, with relatively higher rates of vertical deviations and ptosis as complications of botulinum toxin injection. For many practical considerations, botulinum toxin is not a primary therapy for eso- or exotropia. Nevertheless, botulinum toxin may be used as an adjunct to surgical procedures such as muscle transpositions for sixth nerve palsies.

Oscillopsia is another ocular motor condition for which botulinum toxin has been advocated. This syndrome is characterized by acquired involuntary movements of the eyes from multiple sclerosis or other forms of brainstem pathology. The involuntary eye movement causes a deterioration in vision, most often in those persons with multiple neurologic deficits. Injections are given under EMG direction into the muscles involved in causing involuntary movement. Improvement in acuity in one eye has been documented repeatedly. The major pitfall is diplopia, which often is caused by extraocular muscle weakness caused by the injections, often requiring patching of the contralateral eye. Patients often have little desire for repeated injection.

### Protective Ptosis

Botulinum toxin has been known to cause ptosis as a complication from periocular injections for blepharospasm, cosmetic applications, and strabismus. In situations where a tarsorrhaphy may be useful, one alternative is to administer a small quantity of botulinum toxin into the muscular portion of the levator palpebrae superioris muscle to create a temporary weakness resulting in a protective ptosis. Generally 5 to 20 units are injected into the superior sulcus of the eyelid, with the needle bevel pointed toward the orbital roof. After 5 to 7 days, ptosis results, and lasts from 4 to 6 weeks. Such an approach may be most useful for situations calling for temporary tarsorrhaphy, such as corneal epithelial erosions. Reduced Bell's phenomenon has been cited as a drawback but has not, in any practical sense, been a major problem for this application. Ptosis may obstruct vision completely, however, as a variation in the degree of ptosis can not be readily predicted by dose.

### Headache Syndromes

In 1994, it was reported that botulinum toxin could be useful for the treatment of primary pain disorders in the context of the syndrome of myofascial pain and tension headaches.<sup>12</sup>

This conclusion was based on the theory that pain was the most botulinum toxin-responsive component of the spasmodic torticollis syndrome (>90%) and that other muscle-based pain syndromes also could be treated, such as myofascial pain<sup>12</sup> (cervicogenic headache). The application spread to include migraine because of a serendipitous observation that botulinum toxin injections given for cosmetic rhytides coincidentally relieved migraine headaches.<sup>13</sup>

An extensive industrial and academic effort has ensued to explore and validate the use of botulinum toxin for treatment of headache.<sup>13-19</sup> Response rates as high as 80% in open-label trials for migraine and tension headaches were cited. The pharmacologic advantage includes a long duration of action, which would make botulinum toxin a good prophylactic agent for episodic severe headaches and one that would be effective with limited side effects. Unfortunately, the evidence of its efficacy has not been convincing in double-blind placebo-controlled trials, which have produced inconsistent results.<sup>15-21</sup> Well-controlled and reproducible data supporting a migraine application have not yet been obtained, despite variations in dose, injection placement, and patient selection criteria, and despite multiple attempts by industrially sponsored multicenter clinical trials. In a recent trial for use in patients with a combination of chronic daily headaches (chronic tension headaches) with episodic migraine, migraine patients with chronic daily headaches who were not using other prophylactic medications did experience improvement.<sup>20</sup> In addition to myofascial tension and migraine headaches, botulinum toxin injections have been found useful in treating temporal mandibular joint dysfunction (pain with bruxism), trigeminal neuralgia, headaches associated with sinusitis, and postoperative pain syndromes. Other syndromes have included various forms of low back pain.

When responding to the diagnosis of multiple kinds of pain, what could be the mechanism of action? The answer is unclear. However, a number of theories have been advanced, including but not limited to suppression of neuropeptide release, suppression of histamine release and other forms of sensitizing autocooids, blockage of N-methyl-D-aspartate (NMDA) receptor expression, decreasing neurogenic inflammation, and relaxation of muscle tone. To date, no primary pain approval has been issued by the FDA.

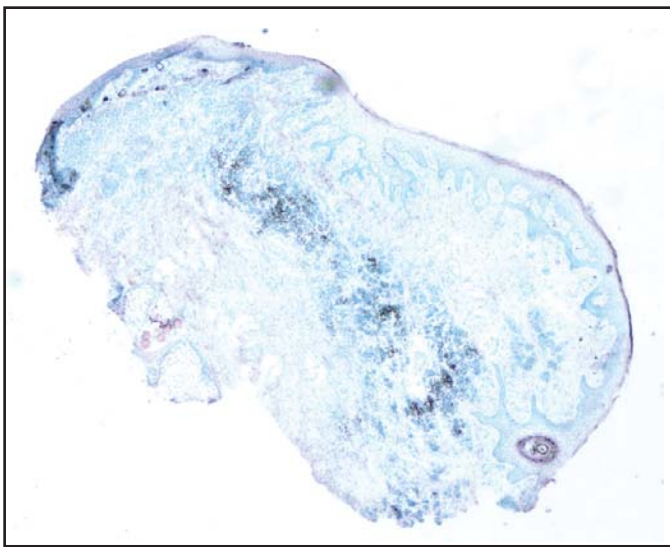
### Application of Botulinum Toxin for Chronic Hypersecretion, Blepharitis, and Recurrent Chalazia-Hordeola

Botulinum toxin recently has been approved for treatment of hyperhidrosis syndrome, based on cholinergic suppression of exocrine sweat glands. Exocrine glands are under cholinergic control, even though they are innervated by component of the sympathetic autonomic nervous system. The effect of the injections lasts for more than 3 months, and it is regional.

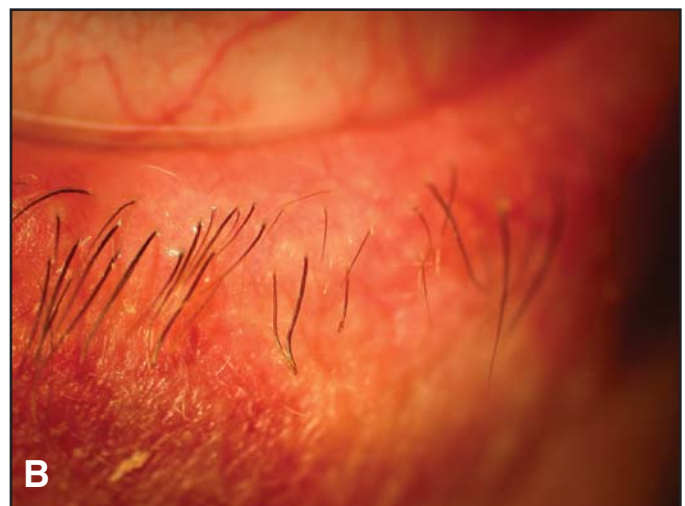
Cholinesterase has been identified in close proximity to the meibomian glands, suggesting that secretion of meibum, much like that from the sweat glands, may be under cholinergic control. This hypothesis is based on the heavy cholinesterase staining associated with portions of the meibomian glands (Figure 2). Acetyl cholinesterase, the enzyme

catalyzing acetylcholine transmission, is a marker for tissue locations for cholinergic neurotransmission. The notion that cholinergic transmission may have an influence on meibomian secretion is founded on this observation and on clinical experience.

The clinical findings and the pathophysiology of blepharitis involve hypersecretion from the meibomian glands, which may serve as culture medium for staphylococcal overgrowth and inspissation of the glands. Clogging of the gland orifices with debris or associated glandular epithelial changes or an inability to clear these oily secretions leads to accumulation of meibum deposits within tissues, further leading to foreign body granulomatous inflammation, which accounts for formation of chalazia and hordeola. Acne rosacea, seborrhea, and atopic dermatitis may contribute to the process.



**Figure 2.** Full-thickness section through the lower eyelid demonstrating cholinesterase staining within the tarsal plate surrounding the meibomian glands, indicating cholinergic mediators in proximity to structures producing eyelid margin secretions.



**Figure 3.** Blepharitis treatment with botulinum toxin. *A*, Blepharitis often is associated with meibum hypersecretion and inspissation, causing lid margin and tarsal plate inflammation. Hypersecretion of meibum has been associated with bacterial overgrowth and complicating infections. *B*, Injection of botulinum toxin into the lid margin can reduce meibum secretion and reduce tissue accumulation of fatty glandular secretion and associated foreign body-related granulomatous inflammation.

Based on projected cholinergic effect, a series of 27 patients with evidence of gland hypersecretion and blepharitis were treated with low-dose botulinum toxin injections along the eyelid margin, receiving between 0.6 and 5 U per injection site. Seventy-two percent of patients reported a significant improvement in subjective symptoms of irritation and chronic discharge (personal observation). This is demonstrated in Figure 3. The patient was unresponsive to conventional antibiotic eyedrops and lid hygiene, but did respond to botulinum injection at the lid margin. The author has found this treatment to be useful for chronic, recurrent chalazia and hordeola.

### New Botulinum-Based Products

Botox has been the only botulinum type A toxin available in the United States. This product is an immunotype A toxin with a specific activity of about 20. Specific activity is an index of purity and was improved in this product in 1998. This material is a protein complex, meaning that inactive protein material is present within the vials. Human serum albumin from pooled human blood sources is used for stabilization. Reloxin also is a protein complex type A neurotoxin. The specific activity is higher than that of Botox, but the number of units needed to achieve an effective dose is higher with this product. A smaller amount of pooled human serum albumin is used as a stabilizer. Myobloc is an immunotype B botulinum neurotoxin formulated with human serum albumin in liquid state at a low pH (5.6). This material has been associated with higher unit requirement to treat various disorders and with a poor immunity profile after repeated injections compared to available type A toxin. Because of the high dose requirement and increased antigenic protein burden per injection cycle, this formulation is very unattractive as a first-line agent.

Newer botulinum formulations in clinical trials include type A toxins that are highly purified (Mentor, Merz). Decreased protein exposure available in these formulation may further improve immunity and resistance rates. Further studies and experience are warranted.

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1. Which of the following statements is/are true about botulinum type A toxins?
  - A. Botox is a type A toxin.
  - B. Antibodies to botulinum type B would not be expected to neutralize type A botulinum toxins.
  - C. Type A botulinum toxins bind to a specific receptor on presynaptic membranes.
  - D. Synaptosomal associated protein (SNAP) 25 is a cytoplasm substrate for the light chain.
  - E. All of the above
2. Hemifacial spasm differs from essential blepharospasm in relation to botulinum toxin in that
  - A. botulinum toxin is somewhat less effective for hemifacial spasm
  - B. hemifacial spasm requires relatively fewer units because of preexisting motor denervation
  - C. involuntary movements are more incapacitating
  - D. all of the above
3. In Meige syndrome essential blepharospasm
  - A. surgical intervention with myectomy and possible facial neurectomy is appropriate initial treatment
  - B. a hereditary predisposition is rare
  - C. the botulinum response rate is about 60%
  - D. blepharospasm is accompanied by other involuntary movements of the head and neck
4. Botulinum toxin application for migraine headache
  - A. is an accepted indication that has been approved by the U.S. Food and Drug Administration
  - B. requires doses 5 times the usual facial application
  - C. demonstrates conflicting data in controlled trials
  - D. represents the only pain indication which botulinum toxin has been reported effective
5. Botulinum toxin units refer to
  - A. specific activity of the preparation
  - B. nanogram quantities within each dose
  - C. LD 50 for Swiss Webster white mouse
  - D. a universal standard on medicinal quantification among varying immunotypes
6. Botulinum toxins are expected to work for reflex tearing in aberrant facial nerve regenerations because
  - A. the lacrimal gland is under adrenergic control
  - B. the lacrimal gland is under cholinergic control
  - C. botulinum toxin blocks substance P
  - D. botulinum toxin blocks basal tear secretion
7. Ptosis is a complication of periorbital botulinum toxin because
  - A. allergy occurs to the human serum albumin in the vials
  - B. diffusion of the toxin can spread into the orbit
  - C. venous drainage into the cavernous sinus can cause nuclear third nerve palsy
  - D. blepharospasm causes levator disinsertion
8. Botulinum toxin may be beneficial for blepharitis because
  - A. inflammatory neuropeptides may be suppressed
  - B. histamine may be suppressed
  - C. meibum secretion may be suppressed
  - D. all the above
  - E. none of the above
9. The presence of acetylcholinesterase staining near a glandular structure suggests
  - A. botulinum toxin activity
  - B. neuropeptide activity
  - C. cholinergic neurotransmission
  - D. neuromuscular junctions
10. Which one of the following statements regarding immunity to botulinum toxin after repeated injections is *false*?
  - A. The rate of immunity for the cosmetic indication has been well established.
  - B. Immunity can destroy the beneficial results of the therapy.
  - C. The immunity profile for immunotype B is less desirable than type A toxins available.
  - D. Testing methods are not very sensitive.
  - E. Repeated injections are necessary to develop secondary resistance.