DECEMBER 2000
VOLUME 123   NUMBER 6

ANNUAL MEETING
Denver, Colorado
September 9-12, 2001

Mosby

ORIGINAL ARTICLES

Botulinum toxin type A (BOTOX) for treatment of migraine headaches: An open-label study

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OBJECTIVE: The object of this clinical experience was to evaluate the correlation between pericranial botulinum toxin type A (BOTOX, Allergan Corp, Irvine, CA) administration and alleviation of migraine headache symptoms.

STUDY DESIGN AND SETTING: A nonrandomized, open-label study was performed at 4 different test sites. The subjects consisted of 106 patients, predominantly female, who either (1) initially sought BOTOX treatment for hyperfunctional facial lines or other dystonias with concomitant headache disorders, or (2) were candidates for BOTOX treatment specifically for headaches. Headaches were classified as true migraine, possible migraine, or nonmigraine, based on baseline headache characteristics and International Headache Society criteria. BOTOX was injected into the glabellar, temporal, frontal, and/or suboccipital regions of the head and neck. Main outcome measures were determined by severity and duration of response. The degrees of response were classified as: (1) complete (symptom elimination), (2) partial (≥50% reduction in headache frequency or severity), and (3) no response (neither (1) nor (2)). Duration of response was measured in months for the prophylactic group.

RESULTS: Among 77 true migraine subjects treated prophylactically, 51% (95% confidence interval, 39% to 62%) reported complete response with a mean (SD) response duration of 4.1 (2.6) months; 38% reported partial response with a mean (SD) response duration of 2.7 (1.2) months. Overall improvement was independent of baseline headache characteristics. Seventy percent (95% confidence interval, 35% to 93%) of 10 true migraine patients treated acutely reported complete response with improvement 1 to 2 hours after treatment. No adverse effects were reported.

CONCLUSIONS: BOTOX was found to be a safe and effective therapy for both acute and prophylactic treatment of migraine headaches. Further research is needed to explore and develop the complete potential for the neuroinhibitory effects of botulinum toxin. (Otolaryngol Head Neck Surg 2000;123:669-76.)

Migraine is an episodic neurologic disorder that affects roughly 17% of women and 6% of men. Disability from migraine is profound and affects functioning in the workplace with comorbidity including overlap with other major affective disorders. As such, migraine is a major stressor of the health care providing system.[1] Numerous current therapies have limited benefit and are often accompanied with significant adverse side effects.
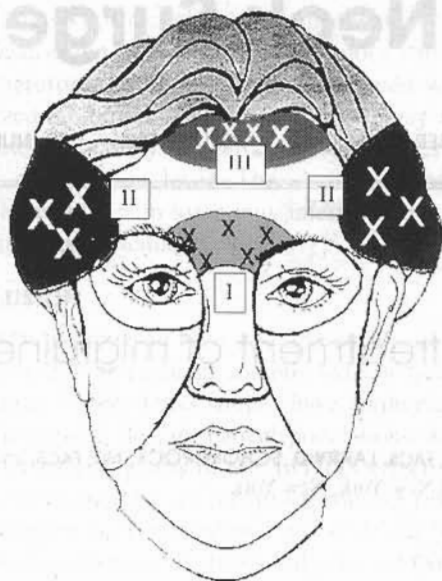
Fig 1. Injection sites for open-label study of BOTOX efficacy for treatment of migraine headache symptoms. Average number of injection sites given per area: glabella 3-5; temporal 2-4; forehead 3-6. Injections were also administered to the suboccipital area in 2 patients.

Given the known limitations of existing therapies, both acute and long-acting prophylactic therapy that is both effective and well-tolerated is needed.

Botulinum toxin type A (BOTOX) is a paralytic neurotoxin that is approved therapy for blepharospasm, strabismus, and hemifacial spasm and has been safely used for dystonia, spasticity, tremor and other neuromuscular disorders of inappropriate muscular contraction. It is commonplace for use in the treatment of wrinkles and hyperfunctional lines of the face.[2,3] The inhibition of the vesicular release of the primary neurotransmitter, acetylcholine (Ach), at the neuromuscular junction is thought to be responsible for the chemodenervating action of botulinum toxin and the therapeutic effect causing muscle paresis or paralysis.[4] However, botulinum toxins are known to have a blocking action on the parasympathetic nervous system that may also inhibit the release of a number of neurotransmitters and neuropeptides other than Ach or produce a blocking role in the transmission of afferent neuronal impulses.[5]

While performing initial clinical trials of BOTOX treatment for hyperfunctional lines of the face, the senior author (W.J.B.) discovered a correlation between pericranial BOTOX and the alleviation of migraine headache symptoms. The use of BOTOX to reduce migraine pain was not immediately obvious because there is no clear cut mechanism of action that could explain its clinical effect. Consequently, the 3 other

Table 1. International Headache Society Criteria for Migraine

Diagnostic criteria for migraine without aura:
  At least 5 attacks fulfilling A to C below:
  A. Headache attacks lasting 4 to 72 hours (untreated or unsuccessfully treated).
  B. Headache has at least 2 of the following characteristics:
  • Unilateral location.
  • Pulsating quality.
  • Moderate or severe intensity (inhibits or prohibits daily activities).
  • Aggravation by walking stairs or similar routine physical activity.
  C. During headache, at least one of the following:
  • Nausea and/or vomiting.
  • Photophobia and phonophobia.
Diagnostic criteria for migraine with aura:
  At least 2 attacks fulfilling at least 3 of the following 4 characteristics:
  A. 1 or more fully reversible aura symptoms including focal cerebral cortical and/or brainstem dysfunction.
  B. At least 1 aura symptom develops gradually over more than 4 minutes or 2 or more symptoms occur in succession.
  C. No aura symptom lasts more than 60 minutes. If more than 1 aura symptom is present, accepted duration is proportionally increased.
  D. Headache follows aura with a free interval of less than 60 minutes (it may also begin before or simultaneously with the aura).

authors (M.F.B., A.B., L.D.S.) were contacted and asked to retrospectively review their patients who had received BOTOX for wrinkles or other dystonias. Patients with concomitant headache disorders as well as other patients requiring treatment only for headaches were then prospectively treated to determine whether the relationship between BOTOX treatment and the alleviation of migraine symptoms was meaningful and could be replicated by other physicians. We hereby report the results from our combined, multicenter, open-label study on the efficacy of BOTOX in both the acute and prophylactic management of migraine.

METHODS

Subjects considered for participation were authors' patients who (1) had received BOTOX injections for the treatment of hyperfunctional facial lines or dystonias who had concomitant headache disorders, or (2) were candidates for treatment specifically for headache disorders. Patients received treatment at cosmetic surgery, otolaryngology, and movement disorder/dystonia clinics. All patients included in the open-label study signed informed consent (based on the standard guidelines of dosing and administration of BOTOX for blepharospasm and hyperfunctional lines) and were permitted to continue chronic and rescue medications (other than

Table 2. Type of treatment administered and migraine classification of patients treated with BOTOX (n = 106)

Migraine classification*	Prophylactic	Acute	Both prophylactic and acute
True	69	2	8
Possible	15	2	1
Non	9	0	0

*Based on self-reported baseline headache histories and International Headache Society criteria for migraine with or without aura.

Table 3. Baseline characteristics of patients treated with BOTOX (n = 106)

Characteristics	All subjects (n = 106)† Number (%)	True migraine* (n = 79)† Number (%)
Gender		
Female	95 (90)	69 (87)
Male	11 (10)	10 (13)
Age		
21 to 35	27 (26)	17 (22)
36 to 45	36 (34)	25 (32)
46 to 60	36 (34)	30 (38)
61 to 74	7 (7)	7 (9)
Frequency/month		
<2	26 (28)	18 (26)
2 to 3	32 (34)	26 (37)
4 to 8	20 (21)	16 (23)
9 to 30	16 (17)	10 (14)
Severity		
Mild	3 (3)	1 (1)
Moderate	22 (21)	14 (18)
Moderate-severe	26 (25)	23 (29)
Severe	53 (51)	41 (52)

*Based on self-reported baseline headache histories and International Headache Society criteria for migraine with or without aura.
†Rows with characteristics that do not total the number of subjects are due to missing data.

BOTOX) as needed. On the basis of self-reported baseline histories of headache episodes, subjects were classified into 1 of 3 groups: true migraine, possible migraine, and nonmigraine. "True migraine" subjects satisfied 4 of the International Headache Society (IHS) criteria for migraine with or without aura; "possible migraine" subjects satisfied 2 or 3 of the IHS criteria; all others fulfilling less than 2 IHS criteria were defined as "nonmigraine" subjects (Table 1).[6]

Prospective treatments were administered both prophylactically and for acute migraine episodes. Some subjects received both prophylactic and acute treatments; however, no subsequent treatments were administered until follow-up data had been collected for the preceding session. BOTOX was injected into glabellar, temporal, frontal and, in 2 patients, the suboccipital regions of the head and neck (Fig 1). Sites of injection, numbers of injections, and doses per injection were given according to the standards already determined for the treatment of hyperfunctional facial lines and facial dystonias.[2] All of the physicians were experienced injectors of BOTOX. Subjects injected specifically for headaches tended to receive larger doses as the study progressed. Length of follow-up varied by patient (corresponding with office visits or based on phone contact), ranging from 1 to 6 months (3 patients were evaluated at 3 weeks).

For each subject, treating physicians documented dose per injected site, total dose injected, area injected, and, at follow-up, self-reported treatment benefit and adverse effects. Subjects were asked to report both qualitative (degree of response) and quantitative (duration of response) assessments of treatment benefit. Degrees of response were categorized as: (1) complete response (elimination of headache symptoms), (2) partial response (at least 50% reduction in frequency or severity of headaches), and (3) no response (less than 50% reduction in frequency or severity of headaches). Subjects lost to follow-up were classified as nonresponders for analysis purposes. Standard forms were used by all treating physicians for collection of baseline and outcome data.

A *t* test was used to test differences in continuous variables (dose, age, duration of benefit) between baseline groups (frequent/severe migraines vs infrequent/mild migraines); approximate *t* tests were used when homogeneity of variance was violated.[7] Fisher's exact test was used to test differences in categorical variables (injection site, gender, treatment response) between baseline groups and to test differences in baseline characteristics (gender, age, headache frequency, and severity) among migraine classification groups; for the later, age and headache frequency were categorized with approximate quartiles as cutpoints based on distributions among all subjects. Analysis of variance was used to test for differences in response by dose, injection site, age, and gender; analysis of covariance was used when adjustment for baseline characteristics was necessary. Ninety-five percent confidence intervals (CI) were calculated for proportions of responders by assuming a binomial distribution. All tests were 2-sided with a 0.05 significance level.

RESULTS

Treatment response data were obtained on 106 subjects: 93 received prophylactic treatment, 4 received
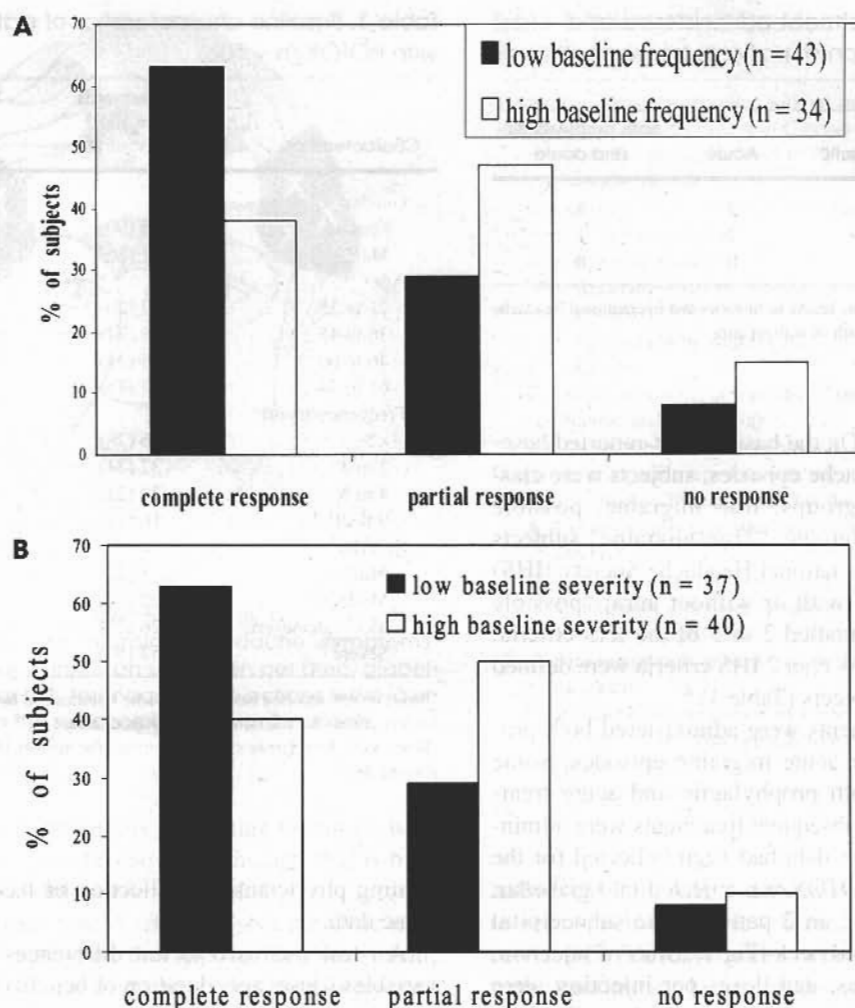
A

B

Fig 2. Proportion (95% CI) of self-reported complete, partial, and nonresponders among 77 true migraine subjects treated prophylactically by (**A**) baseline headache frequency (high frequency, at least 3 times/month) and (**B**) severity (high-severity, severe) open-label study of BOTOX efficacy on migraine headache symptoms.

treatment for an acute migraine episode, and 9 additional patients treated acutely were also followed prophylactically and included in both categories for analysis (Table 2). Seventy-nine (75%) subjects were classified as having true migraine, 18 (17%) as having possible migraine, and 9 (9%) as having nonmigraine headaches. Most subjects were female (90%), 36 to 60 years old (68%), and reported severe symptoms (51%) 2 to 3 times per month (34%) (Table 3). Headache severity but not frequency differed by migraine classification ($P = 0.03$); nonmigraine subjects were more likely than possible or true migraine subjects to report less severe headaches. Gender and age were similar among migraine classification groups.

Prophylactic Treatments

The mean (SD) dose of BOTOX administered among 102 subjects treated prophylactically was 31.0 (17.5) units (range, 5 to 110). True migraine subjects with self-reported high baseline frequency (at least 3 times/month) received higher total doses than those with low baseline frequency (mean [SD] dose = 35.5 [20.7] vs 27.7 [11.3]; $P = 0.06$) and were more likely to receive temporal injections ($P = 0.01$); however, neither dose nor injection site depended on self-reported baseline migraine severity. Both age and gender were unrelated to baseline frequency and severity.

Among 77 true migraine subjects treated prophylactically, 51% (95% CI, 39% to 62%) reported complete
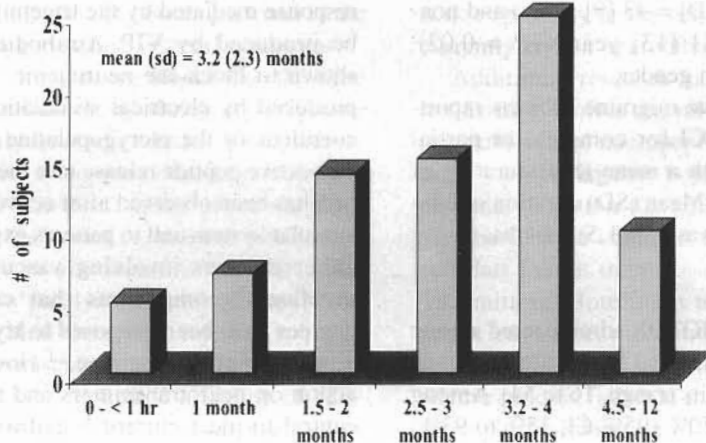
Fig 3. Self-reported duration of treatment response among 77 true migraine subjects treated prophylactically.
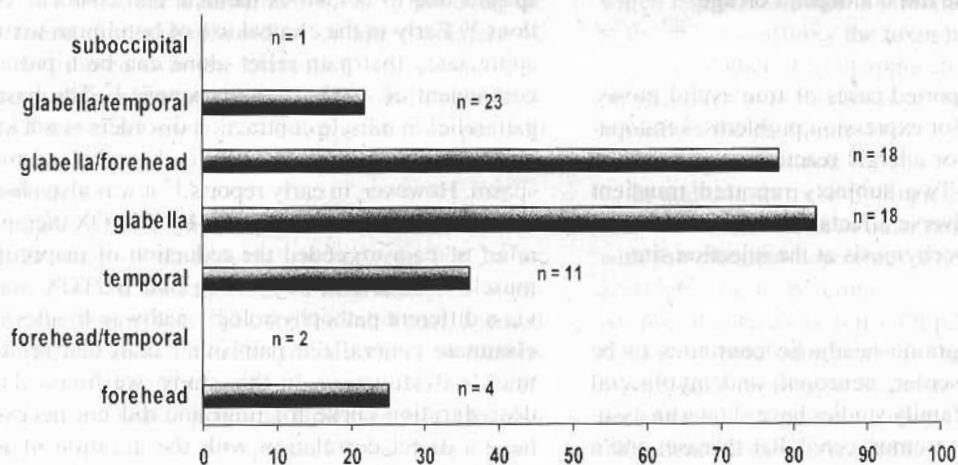
Fig 4. Proportion (95% CI) of self-reported complete responders among 77 true migraine subjects treated prophylactically by injection site.

response with mean (SD) duration of benefit of 4.1 (2.6) months. Subjects with low baseline frequency were more likely to report complete response than subjects with high baseline frequency ($P = 0.06$); similarly, subjects with low baseline headache severity (less than severe) were more likely to report complete response than subjects with high baseline severity ($P = 0.07$). However, the proportion of subjects reporting improvement (complete or partial response) did not depend on baseline frequency or severity (Fig 2). Overall response levels, mean (SD) self-reported duration of response was 3.2 (2.3) months (Fig 3). Response duration did not differ by baseline frequency, either overall (mean [SD], 3.2 [2.8] and 3.0 [1.4] months for low and high baseline

frequency, respectively) or among complete responders (mean [SD], 4.2 [3.3] and 4.0 [1.0] months for low and high baseline frequency, respectively). Complete responders with severe baseline headaches had somewhat longer response durations (mean [SD], 4.6 [3.1] months) than those with less than severe baseline headaches (mean [SD], 3.7 [2.3] months).

After adjustment for baseline frequency, there was no evidence of dose-response; however, injection site was a significant predictor of complete response. Glabellar injections were more likely to produce complete responders than any other site or combination of sites ($P = 0.01$; Fig 4). Complete responders were significantly older (mean [SD] age, 48 [12] years) than

partial responders (mean [SD] = 43 [9] years) and non-responders (mean [SD], 41 [13] years) (P = 0.02). Response did not depend on gender.

An additional 38% of true migraine subjects reported partial response (95% CI for complete or partial response, 79% to 95%) with a mean (SD) duration of benefit of 2.7 (1.2) months. Mean (SD) duration of benefit among nonresponders was 1.3 (1.5) months.

Acute Treatments

The mean (SD) dose of BOTOX administered among 13 subjects, all females, treated for acute migraine episodes was 31.6 (15.2) units (range, 16 to 54). Among 10 true migraine subjects, 70% (95% CI, 35% to 93%) reported complete response, and all responders experienced improvement 1 to 2 hours after treatment. The most common injection site was the glabella, either alone (39%) or combined with injections in the forehead (31%). Response did not depend on age.

Adverse Events

There were no reported cases of true eyelid ptosis, diplopia, facial nerve or expression problems, keratopathy, or idiosyncratic or allergic reactions as a result of BOTOX treatment. Two subjects reported transient brow ptosis; other adverse effects were limited to transient local pain and ecchymosis at the injection site.

DISCUSSION

The cause of migraine headache continues to be speculative with vascular, neuronal, and myofascial hypotheses.[8] Recent family studies have shown an association with essential tremor, cerebellar disease, and a presumed channelopathy in the hemiplegic form of the disease, suggesting that migraine is a heterogeneous and often genetic disorder.[9,10]

The trigeminoneurovascular theory of migraine proposes a reflex whereby afferent trigeminal neurons transmit pain sensation back to the central nervous system triggering autonomic pathway activation via the facial nerve, involving the pterygopalatine and otic ganglia and resulting in vasodilation.[11] This mechanism sets up a cycle triggering pain via trigeminal neurons and the efferent parasympathetic pathway producing feedback vasodilation. Vasodilation is thought to be mediated by the release of potent vasodilatory compounds from parasympathetic neurons innervating the pericranial vasculature. One of these vasoactive peptides, vasoactive intestinal peptide (VIP), has been histologically identified at nerves associated with large cerebral arteries and extracranial vessels supplying the tongue, salivary gland, nose, and eyes. In cats, Goadsby and Shelly[12] proposed that the neurogenic vasodilator response mediated by the trigeminovascular reflex may be produced by VIP. Antibodies to VIP have been shown to block the neurogenic vasodilatory response produced by electrical stimulation of either the locus coeruleus or the pterygopalatine ganglion in cats, and vasoactive peptide release into the extracerebral circulation has been observed after activation of the trigeminovascular system and in patients experiencing migraine.[13] Other theories involving vascular, supraspinal, and myofascial components that contribute in varying degrees have been proposed to try to explain the symptom complex of migraine.[14] However, pharmacologic action on neurotransmitters and their sites of action is central to most current 5 hydroxytryptamine agonist-like (sumatryptan) treatment regimens to stop the ongoing migraine cycle.[15]

Local injections of botulinum toxin into excessive muscle contraction have been successful in relieving spasms due to numerous medical and cosmetic conditions.[16] Early in the clinical use of botulinum toxin, we appreciated that pain relief alone can be a prominent component of its therapeutic benefit.[17] The basis for pain relief in muscle contraction disorders is not known and was assumed to be due to the relief of muscle spasm. However, in early reports,[17] it was also observed that after treatment of torticollis by BOTOX therapy, the relief of pain exceeded the reduction of inappropriate muscle contraction, suggesting that BOTOX may act via a different pathophysiologic pathway to alleviate or eliminate generalized pain other than that related to muscle dysfunction. In this study, we found that the dose-duration curve for migraine did not necessarily have a direct correlation with the duration of action associated with flaccid paralysis of muscles. We also observed that in some patients muscle function had returned after 3 months, but the effects of the drug on the elimination of the headaches had persisted longer.

Although there have been recent reports on the use of BOTOX providing symptomatic relief in tension headache, it has also been shown that tension-type headache sufferers do not reliably exhibit either abnormal resting levels of pericranial electromyographic activity, or abnormal levels of electromyographic activity in response to stress.[18] Should migraine be precipitated by cranial muscle contraction, then BOTOX would prophylax against this inciting factor. However, the properties exhibited by BOTOX in its inhibitory effect on the acute and chronic relief of migraine pain and other symptomatology such as nausea and vomiting, visual disturbances, photophobia, and phonophobia argues against this as the only simple explanation and infers alternative mechanisms of action. Until this report, we have found no other referenced citation doc-

umenting a localized injection of botulinum toxin to the head and neck reducing systemic visceral symptoms.

In the acute cases treated, we found that the time required for the elimination of the acute migraine attack was consistently between 1 and 2 hours, whereas the time required for a complete flaccid paralysis to occur is approximately 3 days. Other anecdotal findings were: (1) in a few cases, a smaller amount of BOTOX was required to eliminate the headache than that required to cause paralysis of the muscle; (2) in some patients, pericranial sites were injected subcutaneously and not intramuscularly; (3) during long-term follow-up, several patients described a feeling of "disconnection," whereby they felt as if a migrainous episode was present but did not experience the accompanying pain; (4) in 1 case, a temporary reduction in pain was noted in tic douloureux; and (5) the average dose per patient in these early findings was approximately 31 units per treatment. Recently, however, we have found that a minimal dose of approximately 50 units distributed over the glabella (5 injection sites), bitemporal (3 injection sites per side), and upper forehead (4 injection sites) at a dilution of 4 cc per 100 units has become the most frequent dose/volume/site ratio used.

Research in both migraine and botulinum toxin therapeutics suggests an association between botulinum toxin and the theoretical bases of migraine. The literature on botulinum toxin has, for the most part, focused on its original known mechanism of action that inhibits the release of the neurotransmitter acetylcholine (Ach) at the neuromuscular junction. However, BOTOX also denervates autonomic nerves, and it has been shown that different neuronal components and systems have different susceptibilities to botulinum toxin.[19,20] In addition, botulinum toxin has been shown to have a direct effect on afferent fibers also suggesting that it may block the sensory system as well.[20]

Shaari et al[19] directed the use of botulinum toxin to block parts of the autonomic nervous system for clinically beneficial effects. In these cases, botulinum toxin was used to denervate autonomic nerves either directly or topically, as opposed to its known denervating cholinergic action on skeletal muscle. It was determined that the parasympathetic postganglionic neurons that innervate the canine submandibular glands are susceptible to the anticholinergic effect of botulinum toxin types A and D; different autonomic systems may have different susceptibilities to the toxin; and BOTOX exerts an anticholinergic effect when applied topically to the nasal mucosa. This provided evidence that the administration of BOTOX either by injection or by diffusion may have an effect on other important sites of action (possibly at the cellular level) in addition to the currently known neuroeffector sites.

Additional research has suggested that botulinum toxins may inhibit the release of a number of neurotransmitters and neuropeptides other than Ach.[21] Dolly et al[21] proposed that botulinum toxin may have the potential to inhibit the release of any substance that is distributed by a common vesicular release mechanism and thus inhibit the release of several different neurotransmitters. Botulinum toxins are metalopeptidases that cleave specific proteins involved in vesicular release. This may explain a common target in the release process found in many if not all nerve endings. Through the inhibition of vesicular release, botulinum toxin may inhibit neuropeptides, transmitters, or other neuronally released substances that normally modulate neuromuscular, neurosecretory, or neuroregulatory activity. The selectivity of action of the toxins with respect to which neurotransmitter is inhibited may also be related to the receptor affinity the toxin has on particular nerve terminals. Other clinical applications, such as its action on reducing hyperhydrosis as well as on the smooth muscle of the gastrointestinal and urinary tract, are not completely understood.[22]

In addition to these findings, Suzuki et al[23] in 1990 found a colocalization of other neuropeptides associated with the classical neurotransmitter norepinephrine and acetylcholine to be common in both the central and peripheral nervous systems. Of particular interest to the actions of botulinum toxin is that both VIP and neuropeptide Y were also found to be colocalized with acetylcholine in parasympathetic nerves originating in the sphenopalatine, otic, and internal carotid ganglia, all of which innervate cerebral arteries. Sala et al[24] used immunohistologic techniques to provide evidence that botulinum toxin may inhibit the release of calcitonin gene-related peptide from motor nerves in rats.[24]

These observations provide a possible link between the actions of botulinum toxin at cholinergic nerve terminals and its possible antivasodilatory as well as antiinflammatory properties. After injection of BOTOX into the muscles of the temple or forehead, it is possible that BOTOX recognizes the cholinergic (parasympathetic) neurons innervating the extracranial vasculature causing a disruptive effect on the vesicular release of Ach and Ach-like neuropeptides. BOTOX blockade of these neuropeptides may also inhibit neurogenic inflammation, which is thought to play a role in migraine. This sterile inflammation may be due to the release of neuropeptides from sensory (trigeminal) nerves innervating both the intracranial and extracranial vasculature. The parasympathetic neurons that innervate the vasculature may be a likely site of action for botulinum toxin

because of its known cholinergic component and possible colocalization of the other vasodilatory neuropeptides. Therefore, botulinum toxin, associated with its generalized inhibition of vesicular release, may inhibit the release of a variety of neuroactive substances at the sensory nerve (V-1) level. These correlations may explain how botulinum toxin may interrupt the viscous trigeminal-neurovascular cycle.

CONCLUSION

BOTOX is shown to be a safe and beneficial therapeutic agent in both the acute and prophylactic treatment of migraine. Double-blind studies have commenced to determine optimal dosing, patient populations, and the benefits for patient quality of life. BOTOX effectiveness might be explained by an inhibitory role on selective sensory trigeminal nerve endings, the vesicular release of neurotransmitters, or on the vasculature and extracranial inflammatory process currently thought to contribute to the symptoms during the course of migraine.

We honor the memory of Dr Larry Schoenrock with the publication of these findings.

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