Involuntary eyelid closure and orbicularis paralysis

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Blepharospasm

Blepharospasm occurs usually as a result of irritating disease such as keratitis or internal ocular inflammation. When it occurs in the absence of identifiable ocular causes, the diagnosis of neurologic blepharospasm must be suspected. Neurologic blepharospasm, defined as involuntary movements of the orbicularis oculi muscles, leads to loss of vision from episodes of forceful eyelid closure.

Within the ophthalmic literature, this condition has been defined as "essential blepharospasm" (Henderson, Trans Am Ophthalmol Soc 1956, 54:453–456). Essential blepharospasm has been known for a debilitating condition usually occurring in elderly patients. The condition is usually chronic and often interferes with routine daily activities.

The cause of this condition historically was thought to have an emotional basis; however, recent evidence has refuted this explanation for the problem (Jankovic et al., JAMA 1982, 248:3160–3164; Metz and Magee, Arch Ophthalmol 1960, 63:692–694; Jankovic and Nutt, in Jankovic and Tolosa, eds. Advances in Neurology, Vol. 49: Raven Press, 1988, pp 117–123).

Evidence of an organic cause for this condition includes: 1) the condition's strong familial association with other movement disorders, eg, essential tremor of the head and hand, spasmodic torticollis, spastic dysphonia, and various forms of spastic diseases within the jaw (Jankovic and Nutt, 1988), and the fact that the disease has been observed in identical twins (Borodic, Paper presented at Neurology Grand Rounds, Brigham and Womans Hospital, Boston, 1989); 2) its consistent constellation of symptoms, including blepharospasm and involuntary movements of the lower face, neck (torticollis), tongue, or jaw, which have been labeled Meige syndrome (Metz and Magee, 1960; Jankovic and Nutt, 1988; Nutt and Hammerstad, Ann Neurol 1981, 9:189–191; Irvine, Am J Ophthalmol 1968, 65:889[1–4]; 3) its chronic disease course over many years, without a tendency for spontaneous resolution; and 4) its high incidence of beneficial response to chemonervation (botulinum A toxin), which can be explained on a sound neurophysiologic basis.

Many patients with essential blepharospasm later develop involuntary movements of the lower face or spasms within other areas of the head and neck during the course of the disease. Specifically, torticollis, spastic dysphonia, tongue darting, and occasional difficulties with dysphagia can occur. Because patients with blepharospasm have a strong family history of other movement disorders of the head and neck, the condition is thought to have a hereditary basis (Borodic, 1989; Nutt and Hammerstad 1981; Irvine, 1968). In addition, patients with certain neurologic diseases, such as multiple sclerosis and cerebral vascular accidents (Jankovic, Arch Neurol 1986, 43:866–868), are occasionally noted to have a syndrome very similar to Meige disease and essential blepharospasm.

Recent developments in the treatment of facial movement disorders include the introduction of botulinum A toxin as an injectable agent that is capable of partially chemodenerverting facial muscles when injected in low doses (Scott et al., Arch Ophthalmol 1985, 103:347–350). This drug has provided a substantial improvement in the management of these conditions over the past 5 years.

Botulinum A toxin

Pharmacology

Botulinum A toxin is a protein with a molecular weight of approximately 150,000. The toxin is one of seven immunotypes produced by subspecies of the bacterium Clostridium botulinum. The toxin currently uses a freeze-dried form of a highly diluted protein and is measured in biologic units (international units). The international unit is equivalent to the lethal dose for a standard white mouse. The toxin is reconstituted from a freeze-dried form with nonpreservative-containing saline and is injected directly into the facial muscles in which denervation is desired. Once it is reconstituted, the toxin should be used within 4 to 5 hours to maintain potency.

The toxin acts by binding to the presynaptic membrane and impairing the release of acetylcholine at the myoneural junction. Although this action is an initial effect of the toxin, histologic evidence in animals (Duchen, J Physiol (Lond) 1969, 151:598–607) and humans (Holt and Anderson, Presented at the Seventh International Symposium of the Benign Essential Blepharospasm and Meige Disease Research Foundation, Columbus, 1989; Borodic and Ferrante, Presented at the American Academy of Ophthalmology, Las Vegas, 1988) has shown that collateral axonal sprouting from the preterminal axon follows within several weeks. This effect leads to growth and regeneration of motor end plates at
the level of muscle. During the process of denervation, a substantial amount of atrophy develops within muscle fibers which has been well demonstrated in animals (Duchen, 1969) and humans (Holt and Anderson, 1969; Borodic and Ferrante, 1988). The atrophy appears to be temporary because the reinnervation process occurs over a 3- to 5-month period. Muscle specimens taken from orbicularis oculi of patients who received multiple injections of botulinum for the treatment of essential blepharospasm do not appear to show any long-term muscle fiber damage (Borodic and Ferrante, Presented at the American Academy of Ophthalmology Meeting, Atlanta 1990).

The toxin is known to bind rapidly to the neuromuscular junctions, and local diffusion of the toxin has been associated with the production of adverse side effects. When the toxin is injected into the periocular region, ptosis may occur, as may epiphora (Scott et al., Arch Ophthalmol 1985, 103:347–350) and diplopia (Scott et al., 1985; Frueh et al., Am J Ophthalmol 1988, 106:45–47). The side effects are thought to result from unwanted spread of the toxin muscles within close proximity to the orbicularis oculi, ie, the levator palpebrae superioris muscle fibers (ptosis), extraocular muscles (diplopia), and a portion of the orbicularis oculi (nasolacrimal pump function [epiphora]). One case was reported of a patient’s developing angle-closure glaucoma several hours after botulinum toxin injection [5].

![Fig. 1. Typical injection points of botulinum A toxin for the treatment of blepharospasm.](image)

The injection format of the toxin into orbicularis oculi has become standard (Fig. 1). It is important that the injections be placed away from the midline and close to the eyelashes in the upper lid and laterally along the lower lid. This placement provides the maximum distance between injection sites and both the muscular portion of the levator palpebrae superioris muscle and the portion of the orbicularis oculi driving the nasolacrimal pumping apparatus. By injecting at these points, the common local side effects, including ptosis, diplopia, and epiphora, are usually avoided.

Because botulinum A toxin is a foreign protein, when it is injected over a period of many months and perhaps years, immunization may occur. In fact, the botulinum toxin antibodies have been demonstrated in patients who have received repeated injections for treatment of spasmodic torticollis (Jankovic, Personal Communication). Sensitization to botulinum A toxin results in loss of effectiveness with repeated injections of the drug. Although such antibodies have not been demonstrated as yet in the treatment of blepharospasm, it is fair to say that careful studies on patients receiving repeated injections of this drug with respect to possible immunization remain to be reported. Biochemical factors involved in toxin production may be important to its antigenicity.

Although botulinum toxin is lethal when injected in high doses, the current dose in ophthalmologic practice for the treatment of blepharospasm is far below the estimated lethal dose for humans. To date, no systemic side effects have been associated with the administration of botulinum toxin for the treatment of blepharospasm, although there has been electromyographic evidence of remote effects (Sanders et al., Neurology 1985, 35:271–272).

The current form of botulinum toxin used is processed from a culture broth and tested against biologic standards. Its sterilization process involves a microfiltration process. The toxin’s activity is known to deteriorate progressively through the process of sterilization; and in fact, the active drug probably has a greater percentage of inert protein by the time it reaches the final steps in this process. Although these steps are of course necessary to insure an adequate pharmacologic-grade material, a potential problem is that a substantial amount of the original protein may be converted to a toxoid. Because of this possibility, further investigations of the purification process for botulinum toxin may be useful with regard to the toxin’s application for blepharospasm and other movement disorders of the head and neck [6].

**Dose and duration of effect**

The average total dose per injection session for the treatment of essential blepharospasm and Meige syndrome is 40 to 80 IU. The average duration of effect with repeated injections is 3.1 months (Fig. 2). It is best to start with a total dose of 20 to 40 IU on the initial injection and to increase the dose after repeated injection because patients’ dose requirements may vary somewhat. Most patients are asked to return when they feel the involuntary movement is again becoming disabling. Patients with hemifacial spasm are clearly more sensitive to the drug and have a longer duration of effect. The starting total dose is 10 to 20 IU with a range of 15 to 25 IU with repeated injections (Fig. 3).

**Oculoplastic procedures**

Although the use of botulinum toxin is clearly the treatment of choice in patients with severe debilitat-