BOTULINUM TOXIN IN THE TREATMENT OF AUTONOMIC NERVOUS SYSTEM DISORDERS

ABIGAIL ARAD, MD, ANDREW BLITZER, MD, DDS

Botulinum toxin A has become a valuable tool in the treatment of neurological disorders and other disorders associated with acetylcholine such as excessive muscle contraction and hypersecretion of glands. It is the most potent neurotoxin, and over the past 20 years it has been shown to be very effective in many fields. As such, cholinergic autonomic parasympathetic and postganglionic nerve synapses may be treated with botulinum toxin in conditions involving excessive activity such as hyperhydrosis, Frey's syndrome, hyperlacrimation, and sialorrhea.

Botulinum toxin A (BTX) is a therapeutic agent used to inhibit cholinergic transmission. It blocks the presynaptic release of acetylcholine by destroying a protein complex, SNAP-25, which is necessary for the exocytosis of synaptic vesicles.[1] Local injections of BTX have been used successfully in treating motor disorders; BTX injections decreased motor activity for 3 to 5 months, after which reinnervation by collateral sprouting and repair of the SNAP-25 proteins re-established the former state.[2]

Neurogenic hyperactivity of the secretory glands results in hyperhydrosis, hypersalivation, or increased tearing. The principal terminal neurotransmitter involved in salivary glands, ecrine sweat glands, and lacrimal glands is acetylcholine, and therefore it may be the target of BTX.

HYPERHYDROSIS

Focal hyperhydrosis can be defined as excessive sweating of the palms, soles of the feet, axillae, and less commonly the head and neck region. The term "symptomatic hyperhydrosis" is used when hyperhydrosis occurs within endocrinological or neurological diseases, which can cause excessive adrenergic stimulation such as hyperthyroidism, diabetes mellitus, pheochromocytoma, lesions of sympathetic nerves as in carpal tunnel syndrome, and in spinal cord injuries.[3] Idiopathic hyperhydrosis is defined as excessive sweating without apparent pathological condition. Emotional, mental, and physical activity, as well as activating substances such as caffeine, may trigger this activity.

Local or systemic medical treatment is often unsatisfactory, and surgical procedures, eg, sympathectomy, may involve considerable risk. Intradermal injection of BTX has proved highly effective in abolishing focal sweating in idiopathic hyperhydrosis.[4,5] Boger et al[6] treated 12 men (aged 31-76) suffering from bilateral craniofacial hyperhydrosis with BTX (Dysport, Ipsen Ltd, Berkshire, UK). They injected half of the forehead and anterior temples after performing a Minor's iodine starch test. BTX was injected intracutaneously into the skin of the forehead with a dose of 0.1 ng of Dysport per injection. Depending on the size of the hyperhydrotic area, 25 to 40 injections were undertaken. Four weeks after the first series, the opposite side was injected. Physical examination at that time revealed mild weakness of the frontalis muscle. Two patients had a slight brow asymmetry that lasted 1 to 12 weeks but eventually completely resolved. Eleven patients reported complete resolution of their complaints. Sweating in most patients had not recurred at 27-month follow-up. One patient had a relapse after 9 months.

GUSTATORY SWEATING

An interesting variant is gustatory hyperhydrosis, in which excessive facial sweating starts after the intake of hot, spicy, or sour food. It may occur after parotid surgery or trauma (Frey's syndrome) or in polyneuropathies such as in diabetes mellitus. In Frey's syndrome,[7] there is an aberrant regeneration of postganglionic parasympathetic fibers feeding the parotid gland that are severed during parotidectomy. These cholinergic fibers seek out cholinergic receptors and find sympathetic receptors of the skin, causing sweating, flushing, and piloerection. In diabetic neuropathy, the sympathetic denervation that occurs in sweat glands might be compensated by reinnervation of aberrant parasympathetic fibers stemming from the minor petrous nerve and normally innervating the parotid gland, via the auriculotemporal and facial nerve, after being relayed in the otic ganglion. This causes facial scalp or neck sweating during or immediately after eating.

The first reports from Germany[8-10] on intracutaneous injections of BTX to treat gustatory sweating led others to try this treatment.[11] We reported our experience in 7 patients,[12] and Restivo et al reported the same method in 14 diabetic patients.[13] After performing a Minor's starch iodine test (Figure 1), a grid was made with 1- to 1.5-cm markings through the affected area. BTX (2.5 U Botox by us or 5 U Dysport by Restivo et al) was injected intradermally at each intersection of the grid pattern, allowing 5 to 10 mm of diffusion around each injection (Figure 2). The skin was then cleaned and patients were asked to return in 2 to 4 weeks. The Minor's starch iodine test was then repeated and additional BTX injected if needed. The dia-

From the Parkinson's and Movement Disorders Clinic, Department of Neurology, Chaim Sheba Medical Center, Tel Hashomer, Israel; Department of Clinical Otolaryngology, Columbia University, New York; New York Center for Voice and Swallowing Disorders, New York; and New York Center for Clinical Research, New York, NY.

Address reprint requests to Andrew Blitzer, MD, DDS, Department of Clinical Otolaryngology, Columbia University, 425 W. 59th Street, New York, NY 10019. E-mail: Ab1136@aol.com

1043-1810/04/1502-0011$30.00/0
doi:10.1016/j.otot.2004.01.010

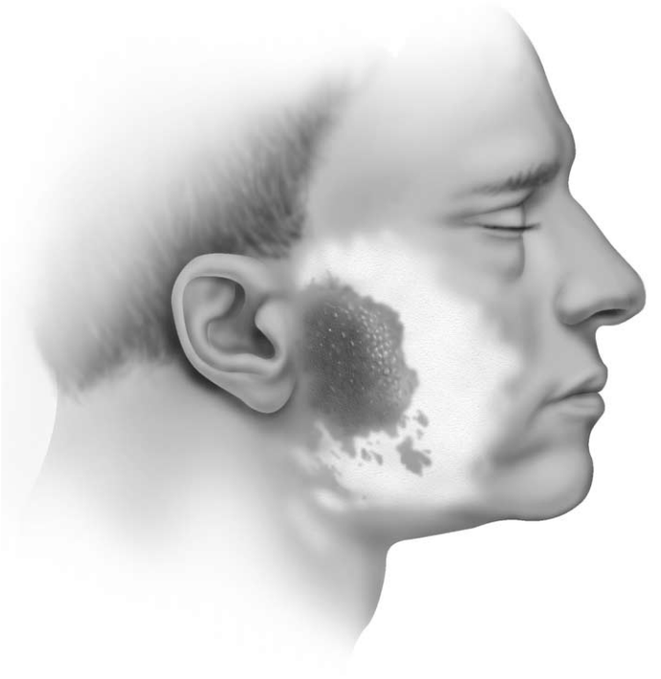

FIGURE 1. Patient who had a parotidectomy 5 years previously and developed significant gustatory sweating. The starch iodine test shows areas of abnormal sweating with stimulation by lemon juice.

betic patients were followed for 24 weeks and no patients needed to be treated subsequently. Our patients were all free of symptoms at 8 to 24 months (mean 12.3 months) post-treatment.

No evidence of major adverse effects has been shown in any of the reports, except for a temporary slight weakness of the upper lip in one of our patients.

BTX has a longer lasting therapeutic effect on secretory function in hyperhydrosis than on the neuromuscular system. This long duration of effect has been previously demonstrated in other cutaneous districts than the facial ones[14] and in Frey's syndrome.[11] Laskawi et al[15] suggested 3 mechanisms that could be responsible for this observation. The long duration of chemical denervation may partially or completely abolish sweat gland function. These autonomic nerve fibers, once chemically denervated, are generated feebly or not at all. Therefore, some patients will not complain of any symptoms, although the Minor's starch iodine test will show some positive areas. And lastly, postsurgical or post-traumatic local changes in the tissue may compromise axon regenerating potential.

We conclude this section with a strong recommendation for the use of intradermal injections of BTX for treating hyperhydrosis and Frey's syndrome. It is safe, well tolerated, and effective for the treatment of craniofacial idiopathic and gustatory sweating.

HYPERLACRIMATION

Increased tearing during eating, known as the "crocodile tears" syndrome, is observed after facial nerve lesions such as Bell's palsy or Ramzy–Hunt syndrome and after salivary gland transplant for severely dry eyes[16]

Secretomotor fibers of the facial nerve innervate the lacrimal gland through the greater superficial petrosal nerve. After a facial palsy, an aberrant connection of the visceromotor fibers, originally innervating the salivary gland to the fibers of the lacrimal gland, may develop and cause a hyperlacrimation whenever the patient salivates. Aberrant regeneration of fibers of the facial nerve after facial palsy may produce an involuntary synkinesis between the orbicularis oculi and orbicularis oris muscle, leading to closure of the eye during lip movement. Before the introduction of BTX treatment, there was no effective medical or surgical therapy for these troublesome symptoms.[17,18]

BTX injected into lacrimal gland and orbicularis oculi muscle was first described by Boroojerdi et al.[19] Ten patients with facial palsy were treated. An average dose of 75 U (range 40-120) of Dysport was injected at 4 points in the orbital part of the orbicularis oculi muscle. In 2 patients, an extra dose of 20 U was injected into the lacrimal gland. For the latter injection, the patients were asked to look to the contralatral side, and the toxin was injected 2 to 3 mm subcutaneously into the lateral part of the frontopalpebral sulcus into the palpebral part of the lacrimal gland. In 4 patients, the lacrimal gland was not injected, despite suffering from "crocodile tears" syndrome, because there was a moderate to good effect on the hyperlacrimation after local injections to the lateral part of the orbicularis oculi muscle. The treatment effect on the hyperlacrimation was assessed with a Schirmer test both before and 2 to 4 weeks after treatment. There was a good clinical effect on synkinesis in 91% of patients and a moderate effect in 9% of patients. The average duration of the effect was 23.9 (range 13-40) weeks. The 2 patients with hyperlacrimation who were injected in the lacrimal gland had a nearly complete recovery from this symptom. The 4 patients with hyperlacrimation who were injected only into the orbicularis oculi muscle showed a moderate to complete recovery, probably because of local diffusion of BTX to the gland area.

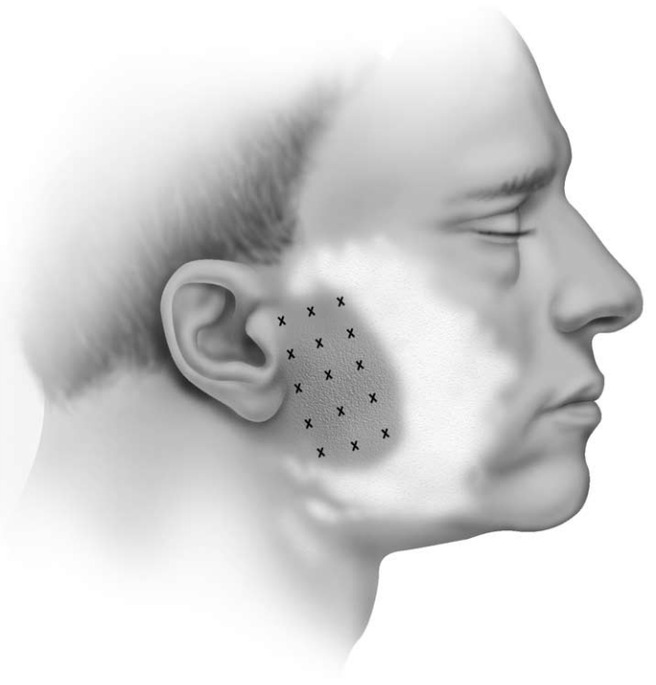

FIGURE 2. After the starch iodine test is complete, a grid is marked with sites 1 cm apart within the area of the positive test site. Intradermal injections are then performed at each of these markings. We use 2.5 U per 0.1 mL at each mark.

Six patients had adverse effects that lasted between a few days and 2 weeks; these included incomplete lid closure, ptosis, double vision (1 case), and conjunctivitis. Only the higher doses of BTX (100-120 U) caused adverse effects; doses of 60 to 80 U produced no side effects. The doses and effects are comparable with other studies regarding synkinesis[20,21] and hyperlacrimation.[22-24] In conclusion, subcutaneous toxin injections into the lateral part of the orbicularis oculi muscle may have a beneficial effect on hyperlacrimation in most cases. In the case of suboptimal response to treatment, injection of BTX into the lacrimal gland may be more effective.

SIALORRHEA

Sialorrhea is a common symptom of many neurological disorders. It is seen in amyotrophic lateral sclerosis, cerebral palsy, mental retardation, post-traumatic encephalopathy, and Parkinson's disease (PD). It often results from a disturbance in the coordination of swallowing rather than from real hypersalivation. The condition affects about 10% of patients with these chronic neurological diseases.[25] Persistent sialorrhea creates major hygienic and psychological difficulties for patients and their caregivers. These include maceration of the skin around the mouth, chin, and neck. In addition, sialorrhea can interfere with speech and feeding and thus contribute to embarrassing and disabling social problems, which result in a decreased quality of life.

Salivary glands are controlled by the autonomic nervous system, and are primarily under parasympathetic cholinergic control. The paired parotid, submandibular, and sublingual glands account for 95% of the 1.5 L of saliva produced each day.

Treatment options are limited and often unsatisfactory; the adverse effects of standard treatments with anticholinergic medications, such as blurred vision, cardiac arrythmia, and urinary retention[26] often preclude their use, whereas irradiation[27] of salivary glands may produce local damage and increase the risk of malignancy. Surgical intervention[28] is invasive and may be contraindicated.

Several reports indicate that BTX injections to salivary glands are a safe and effective treatment for sialorrhea. Bushara[29] gave "blind" intraparotid injections of BTX to treat sialorrhea, followed by others in a couple of preliminary studies[30,31] who reported a reduction in salivary secretions with minimal side effects. Glickman et al[32] described his methods of injecting BTX to parotid glands. With the patient placed in lateral decubitus, the skin inferior to the tragus is lifted off the deeper structures and a 21-gauge needle is inserted through the skin into the cavity created and advanced until the tip lies at the anterior border of the masseter. The noninjecting hand is placed flat against the cheek, with the base of the extended thumb at the angle of the mandible and the index finger running to the angle of the mouth. This limits the cavity inferiorly and posteriorly to prevent dispersion of toxin. Toxin is injected while withdrawing the syringe to the angle of the mandible. A second injection is performed that is aimed at the zygomatic arch. He recommended that the cavity limiting fingers should be kept in place for 5 minutes and then the other side can be injected. In this technique, they injected up to 150 U of Dysport (or 40 U of Botox) with a good response.

In a randomized trial, Lipp et al[33] injected placebo and 18.75 U, 37.5 U, and 75 U of BTX (Dysport) into each parotid gland in 32 patients, one injection to the mass of the parotid gland and another into the adjacent part above the masseter muscle. Drooling was assessed pre-injection and every 4 weeks postinjection by the weight of dental rolls placed into the patient's mouth as well as by a questionnaire given to the patient once a month. The primary endpoint was achieved with 75 U of BTX, where a reduction of 50% was observed. The other BTX-treated patients counted less drooling, but only the high-dose-treated patients reached significance compared with the placebo group. The benefit lasted up to 3 months after injection.

In 2 other reports,[34,35] 5 U of BTX (Botox) were injected "blindly" into the parotid glands of 9 children and 11 PD patients. Drooling was assessed by bibs and dental rolls, respectively, in addition to questionnaires. In the children's group, there were 3 good responders (75-100% reduction in drooling frequency), 2 moderate responders (27-46%), 1 poor responder, and 4 nonresponders. Follow-up was scheduled at 16 weeks, and drooling was assessed at week 4. In 9 of 11 PD patients, scores on the questionnaire decreased after BTX injections, and the average secretion of saliva decreased in 9 patients, remained unchanged in 1 patient, and increased in 1 patient. The duration of benefit was ~6 weeks.

To improve the accuracy of injections and improve results, 2 more recent studies used ultrasound-guided BTX injections into both parotid and submandibular glands. Porta et al[36] treated 10 patients. BTX (Botox) was injected bilaterally into the parotid and submandibular glands with an ultrasound probe to avoid areas of hypervascularization. Two separate injections were performed in each parotid gland (total 15-40 U, mean dose 27.7 U), and a single site was selected for each submandibular gland (10-15 U, mean dose 11.9 U). The reduction in the rate of salivation was first noted 3 to 8 days after injection, and the response was maintained for 4 to 7 months (mean 4.7). No adverse effects occurred, except in one patient who complained of a mildly dry mouth after receiving 100 U of BTX.

Mancini et al[37] performed a double-blind placebo-controlled study in 20 PD and multisystem atrophy patients. Under ultrasonographic guidance, he injected 146.25 U of BTX (Dysport) into each parotid gland and 78.75 U of BTX (Dysport) into each submandibular gland. The placebo group was injected with similar volumes of 0.9% saline. The effect of BTX on drooling in this study lasted ~1 month, which is less than the usual duration of its effect on muscle hypertonia or hyperhydrosis. The authors mentioned that in a previous study, lower doses injected into the parotid without ultrasound guidance were found to be ineffective.

It is noteworthy that these studies are hard to compare, and it is impossible to come to conclusions regarding this treatment modality, because they were performed in a small number of patients, with a large variability in BTX doses, methods of application, and evaluation criteria. Future controlled studies with larger sample sizes are needed to establish improved localization and spread of BTX in the gland, the ideal therapeutic dose, and the optimal number of glands to be injected.

CONCLUSIONS

Botulinum toxin A is of potential benefit in some autonomic disorders. These indications are still "off-label" uses. More carefully designed studies in larger groups are still required to address specific questions related to its use for many of those conditions where experience is still limited. Only then can treatment guidelines be effectively recommended.

More research will also define BTX-induced morphological alterations in the injected tissues, duration of action, neutralizing antibody formation, and possible long-term effects.

REFERENCES

1. DePiva AS, Ashton AC, Foran P, et al: New observations regarding the auriculotemporal syndrome. Neurology 17:1159-1168, 1993
2. Bushara KO, Park DM, Jones JC, et al: Botulinum toxin—A possible new treatment for axillary hyperhydrosis. Clin Exp Dermatol 21:276-278, 1996
3. Champion RH: Disorders of sweat glands, in Champion RH, Burton JZ, Ebling FJG (eds): Rook/Wilkinson/Ebling Textbook of Dermatology, 5th ed. Oxford, UK, Blackwell, 1995, pp 25-30
4. Naumann M, Hofmann U, Bergmann I, et al: Focal hyperhydrosis: Effective treatment with intracutaneous botulinum toxin. Arch Dermatol 134:301-304, 1998
5. Schnider P, Binder M, Auff E, et al: Double-blinded trial of botulinum A toxin for the treatment of focal hyperhydrosis of the palms. Br J Dermatol 136:548-552, 1997
6. Boger A, Herath H, Rompel R, et al: Botulinum toxin for the treatment of craniofacial hyperhydrosis. J Neurol 247:857-861, 2000
7. Frey L: Le syndrome du nerf auriculotemporal. Rev Neur (Fr) 30:97-104, 1923
8. Drobik C, Laskawi R: Frey-syndrom: Behandlung mit botulinum toxin. HNO Aktuell 2:142-144, 1994
9. Drobik C, Laskawi R: Frey-syndrome: Treatment with botulinum toxin. Acta Otolaryngol (Stockh) 115:459-461, 1995
10. Drobik C, Laskawi R, Schwab S: Therapy of Frey Syndrome with botulinum toxin A. Experiences with a new method of treatment. HNO 43:644-648, 1995
11. Naumann M, Zellner M, Toyka KV, et al: Treatment of gustatory sweating with botulinum toxin. Ann Neurol 42:973-975, 1997
12. Arad-Cohen A, Blitzer A: Botulinum toxin treatment for symptomatic Frey's syndrome. Otolaryngol Head Neck Surg 122:237-240, 2000
13. Restivo DA, Lanza S, Patti F, et al: Improvement of diabetic autonomic gustatory sweating by botulinum toxin type A. Neurology 59:1971-1973, 2002
14. Naumann M, Lechenecker P, Brocker EB, et al: Botulinum toxin for palmar hyperhydrosis. Lancet 349:252, 1997
15. Laskawi R, Drobik C, Schonebeck C: Up-to-date report of botulinum toxin type A treatment in patients with gustatory sweating (Frey's syndrome). Laryngoscope 108:381-384, 1998
16. Geerling G, Bastian G-O, Sieg P, et al: Autologous transfer of the submandibular gland as treatment for most severe cases of keratoconjunctivitis sicca. Ophthalmology 105:327-333, 1998
17. Putterman AM: Jaw winking blepharoptosis treated by the Pasanella-Servant procedure. Am J Ophthalmol 75:1016, 1973
18. Guerrissi JO: Selective myectomy for postparetic facial synkinesias. Plastic Reconstr Surg 87:459, 1991
19. Boroojerdi B, Ferbert A, Schwarz M, et al: Botulinum toxin treatment of synkinesia and hyperlacrimation after facial palsy. J Neurol Neurosurg Psychiatry 65:111-114, 1998
20. Roggenkamper P, Laskawi R, Damenz W, et al: Involuntary lid closure caused by defective healing of facial paralysis and its treatment with botulinum toxin. Klin Monatsbl Augenheilk 198:268-270, 1991
21. Borodic GE, Pearce LB, Cheney M, et al: Botulinum A toxin for treatment of aberrant facial nerve regeneration. Plast Reconstr Surg 91:1042-1045, 1993
22. Montoya FJ, Riddell CE, Caesar R, et al: Treatment of gustatory hyperlacrimation (crocodile tears) with injection of botulinum toxin into the lacrimal gland. Eye 16:705-709, 2002
23. Keegan DJ, Geerling G, Lee JP, et al: Botulinum toxin treatment for hyperlacrimation secondary to aberrant regenerated seventh nerve palsy or salivary gland transplantation. Br J Ophthalmol 86:43-46, 2002
24. Riemann R, Pfennigsdorf S, Riemann E, et al: Successful treatment of crocodile tears by injection of botulinum toxin into the lacrimal gland: A case report. Ophthalmology 106:2322-2324, 1999
25. Smith RA, Goode RL: Current concepts: Sialorrhea. N Engl J Med 283:917-918, 1970
26. Lew KM, Younis RT, Lazar RH: The current management of sialorrhea. Ear Nose Throat J 70:99-105, 1991
27. Borg M, Hirst F: The role of radiation therapy in the management of sialorrhea. Int J Radiat Oncol Biol Phys 41:1113-1119, 1998
28. O'Dwyer TP, Conlon BJ: The surgical management of drooling: A 15 year follow up. Clin Otolaryngol 22:284-287, 1997
29. Bushara KO: Sialorrhea in amiotrophic lateral sclerosis: A hypothesis of a new treatment—Botulinum toxin A injections of the parotid gland. Med Hypotheses 48:337-339, 1997
30. Pal PK, Calne DB, Calne S, et al: Botulinum toxin A as treatment for drooling saliva in PD. Neurology 54:244-247, 2000
31. Bhatia KP, Munchau A, Brown P: Botulinum toxin is a useful treatment in excessive drooling of saliva (letter). J Neurol Neurosurg Psychiatry 67:697, 1999
32. Glickman S, Deaney CN: Treatment of relative sialorrhea with botulinum toxin A: Description and rationale for an injection procedure with case report. Eur J Neurol 8:567-571, 2001
33. Lipp A, Trottenberg T, Schink T, et al: A randomized trial of botulinum toxin A for treatment of drooling. Neurology 61:1279-1281, 2003
34. Bothwell JE, Clarke K, Dooley JM, et al: Botulinum toxin as a treatment for excessive drooling in children. Pediat Neurol 27:18-22, 2002
35. Friedman A, Potulska A: Quantitative assessment of parkinsonian sialorrhea and results of treatment with botulinum toxin. Parkinsonism Relat Disord 7:329-332, 2001
36. Porta M, Gamba M, Bertacchi G, et al: Treatment of sialorrhea with ultrasoung guided botulinum toxin type A injection in patients with neurological disorders. J Neurol Neurosurg Psychiatry 70:538-540, 2001
37. Mancini F, Zangaglia R, Cristina S, et al: Double-blind, placebo-controlled study to evaluate the efficacy and safety of botulinum toxin type A in the treatment of drooling in Parkinsonism. Mov Disord 18:685-688, 2003