Botulinum Toxin: Beyond Cosmesis

BOTULINUM TOXIN A has virtually revolutionized the minimally invasive approach to cosmetic enhancement of the upper face. Nevertheless, the road to its present cosmetic and noncosmetic applications could certainly be considered a journey of serendipity. In 1895, Emile P. Van Ermengem first isolated the evil microbe *Clostridium botulinum* from food and the postmortem tissue of victims who had died in Ellezelles, Belgium, after consuming raw, salted pork. Additionally, he was aware that this disease process was caused by a toxin produced by this bacterium. Nevertheless, it was not until 1946 that the toxin produced by this organism was first isolated in crystalline form by Edward J. Schantz at Camp Detrick in Maryland.

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One of the most pivotal individuals in the history of the medicinal use of botulinum toxin was Dr Alan Scott, whose search for a nonsurgical treatment for strabismus brought him into contact with Schantz and his purified toxin. While Scott had been evaluating alternative treatments to pharmacologically weaken extraocular muscles since the early 1970s, it was his union with Schantz and Schantz's purified type A toxin that would ultimately make nonsurgical treatment of strabismus possible. Indeed, the batch prepared by Schantz and used extensively by Scott (batch 79-11) was still in use as Botox (Allergan Inc, Irvine, Calif) until December 1997.[1,2]

Scott's use of the toxin to treat the fine muscles of the eye inevitably led to experimentation with larger muscle groups. It quickly became recognized that botulinum toxin A was effective in the treatment of dystonias, the disordered tension of skeletal muscle seen in a wide variety of neuromuscular disorders. While dystonias were obviously the first arenas that Botox successfully entered, it was the seminal observation in 1987 of ophthalmologist Jean Carruthers and her dermatologist husband, J. Alastair Carruthers, that frown lines disappeared following the use of Botox to treat patients for blepharospasm that ignited the explosive cosmetic application of this product today. Jean Carruthers was making regular visits to Scott's laboratory and had observed the effect of Botox on the vertical glabellar creases in patients who were treated for blepharospasm. She shared the observation with Alastair. The Carruthers were aware of the potential cosmetic applications when Scott indicated that he had used the preparation for such purposes in the mid-1980s. Indeed, while Botox was approved as an orphan drug for the treatment of strabismus, blepharospasm, and certain hemifacial spasms by the Food and Drug Administration (FDA) in 1989, the Carruthers' abstract in 1990,[3,4] presentation in 1991,[5] and ultimately their article of 1992[6] set the stage for its appearance enhancement applications, which have been virtually revolutionary.

While the ability of this toxin to produce cosmetic improvement was also noted by the Columbia group led by Mitchell Brin, their findings were not published until after the Carruthers' reports. Indeed, the Carruthers have produced a legion of faithful followers since 1992. From the Carruthers' energetic educational efforts coupled with observations by their dermatologic disciples as well as those of investigators from other fields, it has become apparent that the glabellar frown as well as horizontal forehead lines, crow's feet, nasal flare, eyebrow (elevation/shaping), and chin (dimpling) are sites where the product is incomparable.[1,6-15] Additionally, the suborbital area, platysma, and possibly lip lines and labiomandibular grooves are other facial locales where Botox therapy holds great promise.[8,13-17] Indeed, at the present time, Botox is as necessary as an antiherpetic medication to provide optimal results with laser resurfacing, in which the prolonged immobility during the healing and collagen-remodeling phases prevents the untimely early reappearance of folding and creasing that diminish the smoothing and tightening effect achieved around the crow's feet and eyes.[13] In addition to its previously noted off-label cosmetic indications, Botox, in all likelihood, will be shown to be safe and effective for a wide range of medical conditions, including achalasia, dysphonia, cervical dystonia, cerebral palsy, chronic anal fissures, migraines, and, of course, hyperhidrosis.[18-24]

The bacterium *C botulinum* has 8 serotypes (A, B, C alpha, C beta, D, E, F, and G) that produce 7 serologically distinct exotoxins. While the intracellular targets of the toxins are variable, they all ultimately prevent release of acetylcholine and thus produce chemical denervation and the desired effect. This chemical denervation is effective for both striated muscle and, needless to say, eccrine glands. Type A, the most potent of the toxins, is the form currently approved for use in the United States and internationally and is commercially available as Botox and Dysport (Speywood Pharmaceuticals Ltd, London, England). Dysport is primarily used in Europe. It should be noted that while Botox and Dysport are both type-A exotoxins, they differ in formulation, potency, and manufacturing process. Each Botox vial contains approximately 100 U, whereas the Dysport vial has about

500 U. Furthermore, IU of Botox is the equivalent in potency of 3 to 5 U of Dysport.[24,25] A highly concentrated type-B toxin developed by Athena Neurosciences, Foster City, Calif, and manufactured by Elan Pharmaceuticals (Dublin, Ireland) is presently under consideration by the Food and Drug Administration.[26]

The proper diluent with which to reconstitute the crystalline Botox deserves special mention. While the package insert recommends the use of unpreserved saline,[27] others have observed no loss of potency with preserved saline.[28] In fact, some have used lidocaine as a diluent and observed no compromise in activity. Once reconstituted, the insert suggests use within 4 hours, but there are now good data to support the stability of the reconstituted refrigerated product for up to 7 days (N. Grondhuis, BS, Allergan Inc, written communication, December 1999). Others have even reported that there is no decrease in activity after a 30-day period.[28] What should be avoided is the repeated thawing and freezing of the diluted vial, since denaturation of the toxin occurs with fracture of the molecule by ice crystals[29] (R. Aoki, PhD, written communication, December 1999). As for the ideal recommended volume of diluent, a recent survey of large cosmetic users of Botox found the mean to be 2.5 mL.[30]

The possibility of antibody production with resulting immunoresistance has always been a concern with the use of Botox.[31] For this reason, it was recommended that no more than 100 U be used at treatment sessions that occur at not less than monthly intervals with the original Allergan Inc batch 79-11.[32] Nevertheless, antigenicity of a foreign material is almost uniformly proportional to protein load, and the vastly decreased amount of protein present in the currently used batches of Botox, 91223US and BCB2024, may allow for the application of larger doses of the product per treatment session without fear of immunogenicity. Indeed, animal studies have supported the decreased formation of neutralizing antibodies with these new batches.[27]

In regard to frequency of injection sessions, many authorities employing Botox for cosmetic indications will give additional treatment when indicated 2 weeks after initial treatment (A. Carruthers, MD, oral communication, May 1999). With the small doses (<100 U) used for almost all cosmetic procedures, the limitation of injection interval does not appear to be crucial.

Hyperhidrosis is a subject the discussion of which could fill a textbook rather than a commentary. The anhidrotic effects of botulinum toxin were noted in 1994.[33] What followed were reports of its application for gustatory sweating in Frey syndrome. These observations then laid the framework for its use in almost all fields of hyperhidrosis.[34] Indeed, the report of its efficacy in the treatment of axillary hyperhidrosis occurred within a year of the account of its efficacy for gustatory use.[35] It has now been shown to effectively address this problem at palmar, plantar, axillary, and facial/scalp sites as well as any body locale in which an overactive eccrine gland exists.[11,36-39] Specifically regarding axillary hyperhidrosis, many individuals have evaluated the use of Botox for this indication.[11,35,40-43] Nevertheless, the required dose per site as well as depth of injection has always remained unknown. In regard to the axilla, we agree with Karamfilov et al[44] that a starch-iodine test is always necessary, since the hair-bearing area does not always delineate the area of eccrine activity. The critical concept is that in hyperhidrosis, unlike the situation with functional lines of expression, the surface area of skin, not muscle mass, is the determinant of dose. Given the ability of the drug to diffuse radially in the axilla skin in an area 1.5 cm in diameter, the task of the physician is to first identify the surface area of involvement using the starch-iodine test and then to place intercurrent doses of intradermal botulinum toxin spaced at intervals to allow overlap of the diffusion patterns, thus maximizing the paralytic effect on the eccrine units while minimizing the total dose needed to achieve dryness. Any drug that is injected into the subcutaneous space is probably less effective, may diffuse less predictably, and exposes the individual to unnecessarily high and potentially antigenic doses.

In addition, the authors do not convincingly present evidence that a dose of 200 U per axilla will result in increased duration of efficacy. Because high-dose therapy may result in resistance, we prefer the following approach for the axilla: inject the involved area as revealed by starch-iodine testing in a spiral pattern at 2.5 to 5 U/cm^2 with 50 U or, at most, in larger individuals, 100 U per axilla. Remember that this is a dose per unit area of gland. Injections are always placed as superficially as possible so that the toxin will easily diffuse to the depth of the eccrine gland and resulting unnecessary wasteful loss of the toxin in the subcutaneous tissue is limited. Using this approach, we have not seen resistance and have obtained a 12-month response in more than 100 patients. What is really needed is a study that addresses the dose response of axillary hyperhidrosis comparing 50, 100, and 200 U per axilla.[11,45] Such a protocol would have to show a dramatic increase in longevity of response to justify the expense and possible antigenic risk of the doses the authors recommend.

Treatment of the palmar skin requires modifications in technique using regional wrist anesthesia blocks, anticipated decrease in grip strength, a more limited range of diffusion capacity away from the injection sites, and possibly a shorter duration of action. Facial sweating in the upper forehead and anterior crown and nape of the neck appears to be dramatically relieved by a technique similar to the axillary methods. We remain unconvinced that a higher dose is necessary for the axilla. Nevertheless, of one thing we are convinced: for axillary hyperhidrosis, Botox works!

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