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Treatment of hyperhidrosis with botulinum toxin

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Focal idiopathic and episodic eccrine sweating of the axillae, palms, soles, and face troubles afflicted individuals with a social curse that can only be imagined by those whose hands or underarms dampen only occasionally. Although there is no accurate incidence in the epidemiology literature, it seems that about half of the patients who have presented to the author with this condition have at least one first-degree relative similarly affected. Social stigma, lack of understanding on the part of medical providers as to the cause and nature of the problem, and lack of effective therapy keeps most of these patients from seeking medical care. A larger social sampling is needed to measure accurately both the number of patients per 100,000 population who have the condition, and the exact nature of the genetic influence.

Gravimetric measurements of palmar sweating show that patients with hyperhidrosis easily exceed 12 to 30 time's normal rates of eccrine secretion from the palmar surface of the hands and fingers, and often the distal dorsal aspects of the fingers and sides of the hand and digits. Diagnostic rates are arbitrarily defined. In some patients perspiration may exceed 50 mg of sweat per minute in the axillae and 30 mg of sweat per minute on the palms [1–5]. Although many patients sweat on a more or less continuous basis, even while asleep, many if not most of the patients report that they suffer from sudden, inexplicable increases in sweating. These sweating attacks can be brought on by emotional stressors, such as public speaking or meeting new social contacts at work or leisure; high ambient temperature; and ingestion of stimulants like coffee. But they also report that they can be sitting relatively calm and cool and without situational stress and notice that suddenly and inexplicably their hands, underarms, soles, or faces begin to drip.

Many patients have covered this affliction up by resorting to elaborate behavior rituals, repetitively wiping their palms on clothes, wearing underarm absorbent pads, carrying towels and handkerchiefs at all times, and avoiding the dreaded handshake at all costs. Traditional therapies, such as topical aluminum chlorides salts in antiperspirants, anticholinergic drugs, and glutaraldehyde tinctures, are irritating, rife with side effects, and generally impractical for patients with this condition [6–8]. Direct excision of the affected skin has been proposed for treating axillary sweating [9,10] but cannot be performed on the palms. Liposuction curettage has been advocated for axillary hyperhidrosis [11–16], but is of no value in palmar sweating.

The standard surgical approach for palmar and facial sweating has been focused on neurosurgical techniques with elective thoracic sympathectomies at the T2-T3 level, performed with endoscopic approaches and minimal incisions, popular for some time [17–22]. The procedure provides unpredictable partial relief for axillary sweating and carries the risk of some significant postoperative complications, including Horner's syndrome, pneumothorax, and partial or incomplete response [23–26]. Worse, significant portions of patients treated by sympathectomy develop some degree of compensatory hyperhidrosis [27–29]. This condition affects the skin from the areolas caudally. The patients, although dry over the entire hand, arm, shoulder, neck and head, paroxysmally sweat profusely from mid-chest down. This is a highly distressing and irreversible condition and no known algorithm to predict its occurrence preoperatively has yet been described. When compensatory hyperhidrosis occurs, the result is that one intolerable sweating problem is traded for another.

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Botulinum toxin for sweating

There has been considerable interest in using selective, focal chemodenervation with botulinum neurotoxin to control problems of localized but severe sweating [30–36]. There are two commercially available forms of the A serotype complex: BOTOX® (Allergan, Irvine, CA) and Dysport (Speywood Pharmaceuticals, Maidenhead, Berkshire, UK). A third commercially approved product, a B serotype, was recently approved by the Food and Drug Administration for cervical dystonia and is marketed in the United States under the name Myobloc (Elan Pharmaceuticals, South San Francisco, CA) and in Europe as Neurobloc. The A serotypes have accumulated more clinical experience in treatment of hyperhidrosis. For the balance of this article, reference is made to BOTOX® unless otherwise specifically indicated.

Unlike the case with sympathectomy, the focal areas treated with BOTOX® are confined to the palms or axillae or the soles, and the total body surface area treated is less than 3%. In contrast the surgical section of the sympathetic chain at the T2-T3 level renders at least 20% of the body's surface anhidrotic. Thermoregulatory stress then creates the compensatory sweating, which has not been reported with focal chemodenervation with BOTOX®.

Documentation of problem

There are two methods used to document the magnitude and distribution of abnormal palmar sweating: gravimetric measurement and the Minor starch-iodine test [37]. Gravimetric testing uses filter paper that is held in contact with the palm for a fixed period of time and then weighed. This technique is useful largely as a research tool to document the magnitude of sweat reduction and identify the therapeutic dose range. The Minor starch-iodine test is performed by first wiping the skin with a colored iodine tincture (eg, an antibacterial iodine solution available in pharmacies). The iodine solution must be brown-orange in color. Decolorized iodine solution does not perform the colorimetric conversion properly. Several seconds are given to allow the iodine solution to dry. A small fan is useful for this purpose. The palm is then lightly dusted with ordinary baking cornstarch powder, available in any food store. As the eccrine sweat exits the skin onto the palmar surface a chemical reaction takes place between the iodide molecule and the starch present in the powder producing a colorimetric reaction as the powder turns deep purple in a matter of a couple of seconds (Figs. 1, 2). The exact location of the active sweating is then mapped and outlined with a marking pen before beginning injections.

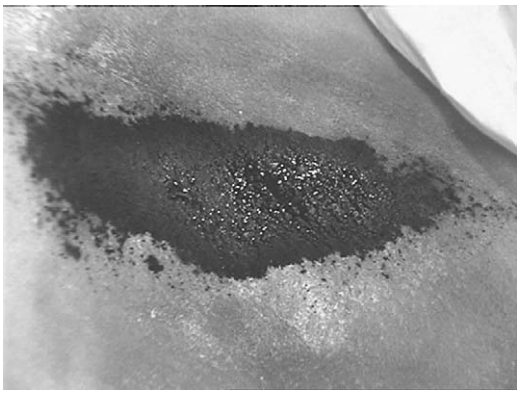

Fig. 1. Minor starch-iodine test of axilla before treatment with BOTOX®.

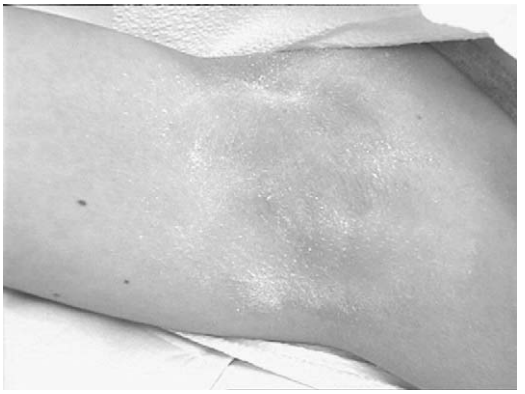

Fig. 2. Minor starch-iodine test of axilla 2 weeks after treatment with 50 U intradermal BOTOX® at a dilution of 2.5 mL/100 U.

One should take care to perform the starch-iodine test before applying any regional nerve blocks or before application of topical anesthetics like prilocaine or eutectic mixtures of lidocaine (EMLA) in wide use today. The vasoconstrictive effect of the topical anesthetics and the hyperemic response in the skin seen after regional wrist blocks both interfere with the amount of sweating and can give misleading results in the Minor starch-iodine test.

The author has found it useful to take a digital photograph of the starch-iodine test for the medical record and a Polaroid picture to give to patients. They can easily perform a starch-iodine test themselves in follow-up and ascertain the fractional response to therapy (Figs. 3–5). The photographs also help

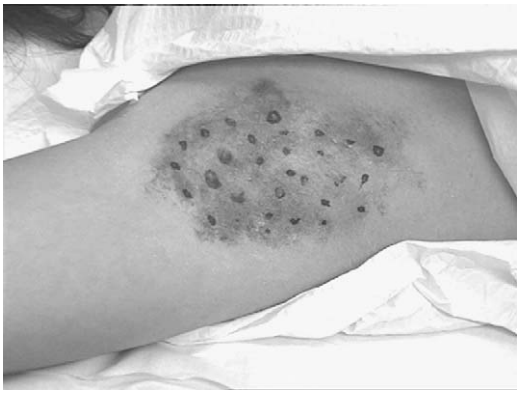

Fig. 3. By injecting through the starch-iodine, the small amount of moisture at each injection site readily demonstrates the scattered pattern of injections.

patients visualize the degree of the problem and their response to therapy after the BOTOX® injections are performed. Patients are psychologically traumatized by hyperhidrosis, and most are exquisitely sensitive to any persisting sweat after treatment. They are often reassured by comparing the before and after starch test pictures (Fig. 6). It reinforces their understanding of the effect of the drug and the therapy.

Anesthesia

Treating the axillary skin with intradermal injections of BOTOX® through a 30-gauge hypodermic needle can be accomplished easily without anesthesia, although topical anesthetics may be used after marking

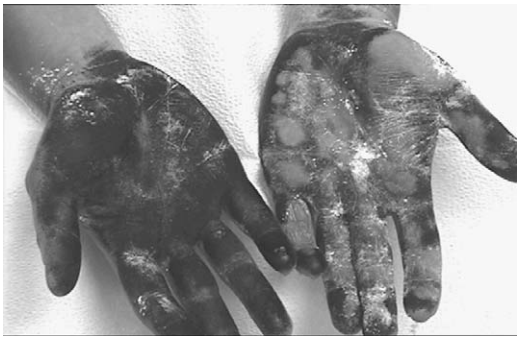

Fig. 4. Minor starch-iodine test. Right hand untreated. Left hand 2 days after treatment with BOTOX®. Notice areas of diffusion with anhidrosis developing circumferentially around injection sites. (*From* Glogau RG. Treating palmar sweating with neurotoxins. Semin Cutan Med Surg 2001; 20:103; with permission.)

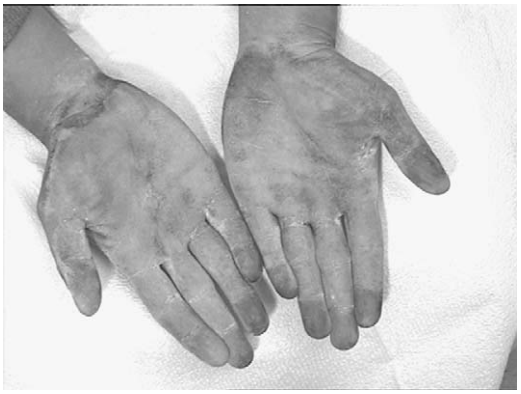

Fig. 5. Minor starch-iodine test. Two weeks after treatment of both palms with BOTOX®. (*From* Glogau RG. Treating palmar sweating with neurotoxins. Semin Cutan Med Surg 2001; 20:104; with permission.)

the area to be treated using the Minor starch-iodine test. Similarly, forehead or facial sweating can be treated without anesthetic.

A few stoic patients with palmar or plantar sweating may opt for simple topical anesthesia, such as ice, EMLA, ELA-MAX, and so forth, but few can tolerate the discomfort of 60 to 70 needle sticks per palm or sole without anesthesia. Most patients require regional nerve block anesthesia, such as wrist or ankle blocks, before undergoing palmar injection [38,39]. The occasional patient may require twilight anesthesia [40] or tourniquet limb anesthesia (Bier block) [41].

For palmar anesthesia 1% to 2% lidocaine plain, without epinephrine, is placed by superficial, subcutaneous injections at the wrist to produce blocks of the

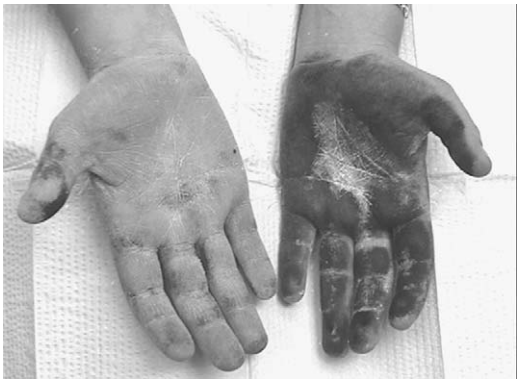

Fig. 6. Minor starch-iodine test. Right hand treated 2 weeks previously. Left hand untreated. (*From* Glogau RG. Treating palmar sweating with neurotoxins. Semin Cutan Med Surg 2001;20:105; with permission.)

median, ulnar, and radial nerves. The median nerve is blocked by injecting between the palmaris longus tendon and the flexor carpi radialis tendon at the proximal flexion crease of the wrist. Injecting between the ulnar artery and the flexor carpi ulnaris tendon blocks the ulnar nerve. The superficial radialis is blocked by injecting in the ''anatomic snuff box'' on the dorsal-medial aspect of the base of the thumb.

Once the injections are placed, usually a half-hour wait ensues to allow for the diffusion of anesthetic into the nerves to produce sufficient anesthesia. The disadvantage of using wrist blocks is that the patient's reactive hyperemia that develops increases the tendency to bleed from each small injection site, which may increase loss of material from the injection site and decrease the relative effectiveness of each injection. Warning patients off aspirin before treatment is probably wise for the same reason.

For plantar anesthesia, adequate anesthesia of the sole of the foot can be achieved with two injections [39]. The first is a medial ankle block of the tibial nerve at the level of the medial malleolus posterior to the posterior tibial artery, in-between the Achilles tendon and the medial malleolus. The second injection is a lateral ankle block of the sural nerve, between the Achilles tendon and the superior border of the lateral malleolus with the needle pointed perpendicular to the skin.

Wrist and ankle blocks are usually performed without significant trauma if 30-gauge needles are used and if injection pressure is kept slow and steady. Occasional reflex neuropathy can be encountered as a rare complication.

Injection syringes

The dosage of drug used and injection method has not been standardized. There are a variety of dosages reported in the literature [35,38,42–44]. For all areas to be treated, the author's technique is to use a dilution of 2.5 mL per 100 mouse units, dividing the whole bottle among five Ultrafine II 50-U insulin syringes (Becton-Dickinson Franklin Lakes, New Jersey). Each syringe holds 0.5 mL and has the 30-gauge needle swaged directly into the chamber of the syringe, eliminating the dead space that occurs with a needle hub. This minimizes the waste of expensive botulinum toxin. The syringes are filled by popping the metal cap and rubber stopper from the bottle and drawing up the BOTOX® by aspirating with the needle inside the bottle. This is done to avoid needlessly dulling the 30-gauge needle passing through the rubber stopper.

Injection technique

Each syringe then holds 0.5 mL of solution that is 20 U; it is relatively easy to read the graduations on the syringe and place either 2 U (0.05 mL) or 4 U (0.1 mL) in each site. With practice, one can generate about 10 to 12 injections with each syringe.

To treat the axillae, one bottle of 100 U of BOTOX® is diluted with 2.5 mL of sterile saline with preservative and then divided into five 0.5-mL insulin syringes. Following a spiral pattern, 50 U of BOTOX® are injected in 0.05 mL to 0.01 mL (2 to 4 U) amounts intradermally raising tiny wheals spaced approximately 1.5 to 2.0 cm apart, beginning at the periphery of the hair-bearing skin and circling into the center of the axillary vault (see Fig. 3). The skin being rather thin in this area, care is taken to avoid injecting the material subcutaneously where it could go beyond the targeted glands. Keeping the needle bevel up and more parallel to the skin surface and advancing the needle 2 mm before injecting helps prevent backflow of the BOTOX® from the injection tract, which minimizes any loss of the toxin.

The technique for palmar injections is similar, but injections must be spaced closer together because of the smaller zone of radial diffusion produced in palmar skin (Fig. 7). The needle must enter the palmar skin at an oblique angle. Mechanical needle flanges have been advocated, which provide a method for assisting the depth of the injection [38,45]. But if the needle enters perpendicular to the skin surface, there is usually a significant amount of backflow of material that leaks out of the injection tract. Because the volumes of

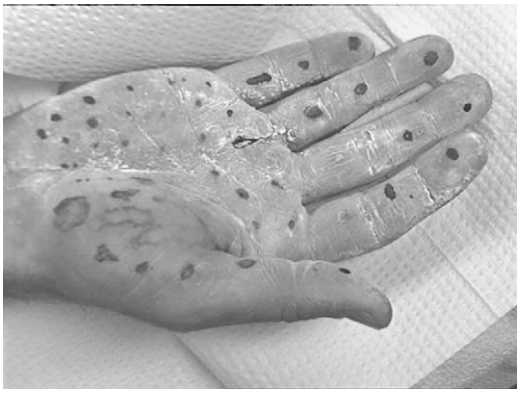

Fig. 7. Minor starch-iodine test. Immediately after placing injections in the right palm. Note how minimal backflow was achieved in most, but not all, injection sites. (*From* Glogau RG. Treating palmar sweating with neurotoxins. Semin Cutan Med Surg 2001;20:105; with permission.)

BOTOX® are typically small, this backflow significantly impacts the effectiveness of the injections.

In axillary skin each injection is placed to produce a wheal. The palmar skin is comparatively stiffer, however, and usually a wheal cannot be raised under any circumstances. It is desirable, however, to produce a small zone of visible blanching, indicating that the material is in the deep dermis. One should take care with each injection to remove the thumb from the plunger and allow a second or two for the pressure to normalize before withdrawing the needle from the skin or else the fluid flows back out the injection tract directly.

Injection pattern and dosage

A representative sample of the dosage regimens, pattern of injection, and indications for the botulinum toxin are presented in Table 1. Injection of the axilla usually involves placement of 10 to 20 individual intradermal injections of BOTOX® about 2.5 cm apart to cover the area of the axillary vault that stains darkly with Minor starch-iodine test. These can be performed quickly with minimal discomfort and virtually no sequelae.

Sweating of the upper forehead and anterior crown can be approached in a similar fashion, by injecting 2 to 4 U of BOTOX® every 2 cm along the anterior hair line from sideburn to sideburn, and an additional shorter row in the anterior crow about 2 cm behind the anterior hairline, and another horizontal row in the upper third of the forehead skin. These are also performed easily without anesthesia and well tolerated (Figs. 8, 9).

In the author's technique palmar injections are placed approximately every 1.5 cm across the palmar surface. On the fingers the volar pad of each phalanx receives its individual dose. The fingertips usually receive two: one in mid pad and another at the very tip, because this is a very problematic sweating area for people with hyperhidrosis. The dominant or writing hand also receives an extra row of injections along the ulnar side, midway between the palm and dorsal surface, to provide maximum dryness for writing. Occasionally extra injections can be placed on the distal dorsal fingers or in the webs depending on the patient's complaints. The goal is to place the injections in a pattern so that diffusion provides overlapping coverage for the entire palmar surface. One needs to minimize the number of injections that arrive subcutaneously because this increases the likelihood of diffusion of drug into the intrinsic muscles of the hand.

Table 1
Sample of dosage regimens and patterns of injections for treatment of hyperhidrotic conditions with botulinum toxins

Author	Dilution mL/100 U	Dose BOTOX® unless otherwise labeled	Distance or total sites per area treated	Diagnosis
Odderson, 2002 [57]	2	50 per axilla	7–10 sites/axilla	Axillary
Heckmann 2002 [73]	4	50 per axilla	2.5 per site	Axillary
Naumann and Hamm, 2002 [52]	4	50 per axilla	10 per axilla	Axillary
Salmanpoor and Rahmanian, 2002 [58]	?	125 per axilla Dysport	10 per axilla	Axillary
Naumann and Lowe, 2001 [53]	4	50 (3–5 per site)	10–15 sites/axilla	Axillary
De Almeida et al, 2001 [38]	2	5 per site	1 cm	Palmar
Heckmann et al, 2001 [48]	5	200 (Dysport)	10 sites/axilla	Axillary
Dulguerov et al, 2000 [72]	2	5 per site	1	Frey's
Karamfilov et al, 2000 [50]	1	200 per axilla	Single dose	Axillary
Naver et al, 2000 [54]	?	2 per site	4 cm2	Axillary/palm
Solomon and Hayman, 2000 [44]	2	2–4 per site	1 cm	Palmar
Birch et al, 1999 [70]	4	7.5 per site	6 cm2	Frey's
Laccourreye et al, 1999 [74]		2.5 per site	1 cm2	Frey's
Schnider et al, 1999 [59]		33.3 per axilla	2–3 cm	Axillary
Glogau, 1998 [32]	2	2 per site	1.5 cm	Axillary
Heckmann et al, 1998 [49]		400 (Dysport)	1 cm	Axillary
Naumann et al, 1998 [42]		3	2 cm	Axillary, palm
Odderson, 1998 [56]		100 (BOTOX®)		Axillary
Shelley et al, 1998 [43]		2	1 cm	Palmar
Schnider et al, 1997 [35]		20 U	6 sites	Palmar
Bushara et al, 1996 [30]		20–50	Single dose	Axillary
Cheshire, 1996 [31]		1 U	1.5 cm	Forearm
Drobik et al, 1995 [71]		0.5 U	1 cm	Frey's

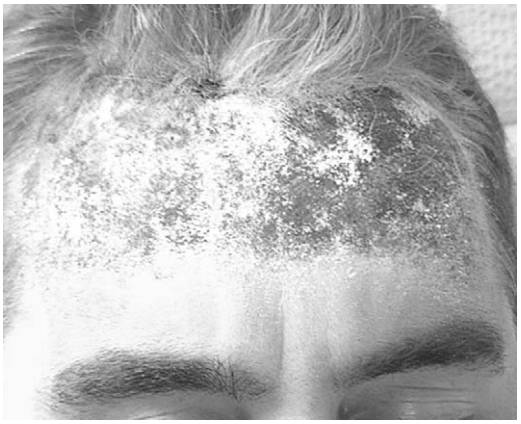

Fig. 8. Minor starch-iodine test on upper forehead showing broad area of excessive sweating.

The total amount of drug used per hand is dependent on the surface area of the hand. Patients with large shoe sizes have correspondingly larger hands and require more injections and larger total dosage. A man with a size 13 shoe (US) requires up to 150 U per palm, whereas a woman with a size 6 shoe (US) requires as little as 75 U to cover the palm. The average dose in the author's patients was about 120 U per palm.

Injection of the soles of the feet follows the same technique and pattern as the palms. The difficulty arises from the necessity of treating a much larger surface area, so doses usually exceed those of the palms. Using the Minor starch-iodine test as a guide, and relying on ankle blocks for anesthesia, the same satisfactory outcome can be achieved. Duration of effect seems to be identical to that achieved in the palms.

Duration of effect

Reported response times for duration of anhidrosis in the axillae range from 4 months to 10 months in numerous studies depending on dosage and technique [1,30,32,42,46–62]. Similar responses are seen in treatment of forehead sweating [51,63–65].

There is a broader range of responses to palmar treatment, varying from about 3 months to 12 months [34,35,42–44,48,54,66]. The average in the author's hands is about 6 months. Interestingly, the effect does not seem as long as it is with axillary hyperhidrosis. Speculative reasons for this may be the problem with backflow, the smaller diffusion distance in thicker palmar skin, the higher number of cholinergic nerve endings in the palmar skin, or a differential recovery rate between the nerves of the palm and those in the axillary skin. On average, patients seem to require treatment about twice a year to maintain reasonable control of the palmar sweating. Patients are usually expecting complete anhidrosis as an end point, at least with their initial treatment. It may take several treatments before they recognize less than total response as successful. They are generally unfamiliar with normal palmar moisture, and at least initially are intolerant of anything but a totally dry hand as a measure of success. With time and release from the mental anguish of unreliable palmar sweating, many do seem to change their therapeutic end point goals, and are comfortable with control as opposed to total ablation of palmar sweating. This changes the treatment intervals and dosages, but further work on patient acceptance needs to be undertaken.

There have been no known reports of compensatory hyperhidrosis from the focal use of botulinum toxin in the palms or axillae. This is an important theoretical and practical advantage of the botulinum toxins in the management of hyperhidrosis. The downside relates to the fact that the botulinum effect is neither permanent nor inexpensive. Properly informed patients may elect to pursue the surgical alternative, however, and referral should be made to neurosurgical or thoracic surgical practices with expertise in this method.

Scheduling palmar treatments

Almost every patient who undergoes this treatment develops a transient period of weakness and instability

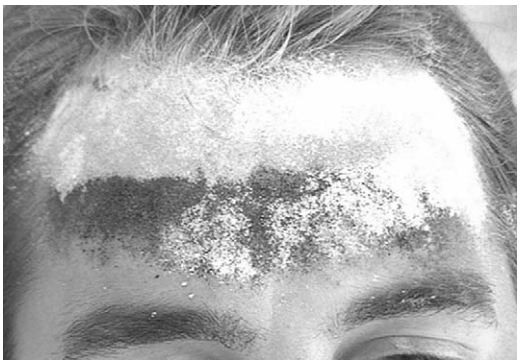

Fig. 9. Minor starch-iodine test after treatment with 60 U of BOTOX®. Note that only the upper portion of the forehead was treated to avoid inactivation of lower frontalis and secondary disturbance of normal brow elevation. Treatment also was extended back into the anterior hairline where some of the most intense staining was visualized before treatment.

of the lumbrical muscles of the hand, which is predictably spontaneously reversible [2,34,35,43,44,54,66]. Such tasks as shoving a button through a tight button hold, holding heavy objects with chop sticks, or opening a stuck lock with a key, become problematic about 5 to 7 days after treatment and remain so for 3 to 5 weeks. Patients can write, type, and eat without difficulty, but opening up a tight jar lid, for example, poses problems for a few weeks.

For this reason, if the patient has ready geographic access to the treating physician, it may be wise to offer to stagger the treatments apart. Beginning with the right hand on the first visit, the author often waits a couple of weeks and then treats the left hand with any needed touch up injections of the right hand on the second visit, and schedules a third visit to touch up the left hand. By doing so, one can stagger the time line of weakness to make it easier on the patient. Multiple visits often are logistically impossible, however, and the author has no objection to treating both palms simultaneously as long as the patient is aware of the implications. One successful strategy has been to offer to treat the hands separately the first time, but depending on the muscle weakness, let the patient choose to schedule future treatments together or staggered according to their own experience.

Future directions

Further work is needed to optimize the dilution and units per square centimeter. Introduction of a botulinum toxin of the B serotype (Myobloc, Neurobloc, Elan Pharmaceuticals, Dublin, Ireland) may present an alternative molecule to the A serotypes currently in use. No data exist on the behavior of this molecule in the hyperhidrosis model [67,68]. Work on injection delivery devices has stimulated some investigators and further enhancements to the delivery system [38,69] may optimize the treatment for many patients. Further investigation of the genetic pattern of the disorder may give clues to possible therapies. Until then the patients can benefit from truly life-altering therapy with this amazing molecule.

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