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Hyperhidrosis and Botulinum Toxin A: Patient Selection and Techniques

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Abstract. *Focal idiopathic excessive eccrine sweating presents most commonly as an affliction of three anatomically distinct area: the axillae, the palms and soles, and the upper face. The true incidence is not known, but about half of the patients referred to us with this condition have at least one first-degree relative similarly affected. Only a fraction of patients afflicted are thought to seek medical care because of the social stigma, lack of understanding on the part of medical providers as to the cause and nature of the problem, and, until now, lack of effective nonsurgical therapy. A large social sample is required to accurately measure both the incidence and the exact nature of the genetic influence.*

For diagnostic purposes, sweating rates are arbitrarily defined. Gravimetric measurements of palmar sweating show rates of sweating that exceed 12-30 times normal. 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 patients report that they suffer from sudden, inexplicable onsets of sweating. These sweating attacks can be triggered by emotional stressors such as public speaking, meeting new social contacts, high environmental temperature, and stimulants like caffeine. Patients also complain that they can be both calm and cool, without situational stress, and suddenly and inexplicably, their hands, underarms, soles, or faces begin to drip.

Many patients attempt to conceal this affliction by elaborate behavior rituals, eg, repetitively wiping their palms on clothes, wearing underarm absorbent pads, carrying towels and handkerchiefs at all times, and avoiding the dreaded handshake. Traditional therapies such as topical aluminum chlorides salts in antiperspirants, anticholinergic drugs, glutaraldehyde tinctures, and tap water iontophoresis are irritating, cumbersome, and generally impractical for patients with this condition.[6,7] Direct excision of the affected skin has been proposed for treating axillary sweating[8,9] but this procedure cannot be performed on the palms. Liposuction curettage has been advocated for axillary hyperhidrosis,[10–15] but this is of no value in palmar sweating.

Surgical Approaches to Hyperhidrosis

The standard surgical approach for palmar and facial sweating has been a neurosurgical technique with elective ablation of the thoracic sympathetic ganglia at the T2–T3 level, performed with endoscopic approaches and minimal incisions. These endoscopic thoracic sympathectomies have been popular for some time.[16–21] The procedure provides predictable complete anhidrosis for the palm, hand, and arm but unpredictable and partial relief for axillary sweating. The procedure carries the risk of some significant postoperative complications, including Horner's syndrome, pneumothorax, and partial or incomplete response.[22–25] The most significant postoperative complication, however, is that portions of the patient's skin treated by sympathectomy can develop some degree of compensatory hyperhidrosis.[26–28] This condition affects the skin from the areolas caudally. The patients, though dry over the entire hand, arm, shoulder, neck, and head, will paroxysmally sweat profusely from midchest down. This is a highly distressing and irreversible condition, and no algorithm to predict its occurrence has yet been described. When compensatory hyperhidrosis occurs, the result is that one intolerable sweating problem is traded for another.

Botulinum Toxin A for Sweating

Selective, focal chemodenervation with botulinum neurotoxin can control localized severe sweating.[29–35] At present in the United States, there is one commercially available form of the A serotype complex, Botox® (Allergan, Inc., Irvine, California). A second form of the A serotype is available in Europe (Dysport®, Speywood Pharmaceuticals, Inc, Maidenhead, Berkshire, United Kingdom). A third commercially approved product, a B serotype, is approved by the U.S. Food and Drug Administration for cervical dystonia and is marketed in the United States under the name Myobloc® (Elan Pharmaceuticals, South San Francisco, California) and in Europe as Neurobloc®. The A serotypes have accu-

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mulated more clinical experience in treatment of hyperhidrosis. For the balance of this discussion, 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, axillae or 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® to date.

Documentation of the Problem

There are two methods used to document the magnitude and distribution of abnormal sweating: gravimetric measurement and the Minor starch-iodine test.[36] Gravimetric testing utilizes 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 will 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 skin is then lightly dusted with ordinary baking cornstarch powder, available in any food store. As the eccrine sweat exits the skin onto the 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 few seconds (Fig 1). The exact location of the active sweating is then mapped and can be outlined with a marking pen before beginning the injections.

There are two caveats using either gravimetric or starch testing in the presence of anesthesia. First, the starch-iodine test should be performed before using 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.

Second, the hyperhidrotic phenomenon is frequently episodic, ie, there are periods when the skin is quite dry. We have noticed that patients coming from environmentally warm weather into the cooler climate of San Francisco, for example, may be too dry to produce either an abnormal starch test or elevated gravimetric measurements of sweating. We have had to resort to raising the ambient temperature, forced exercise, or even caffeine stimulants to provoke a degree of sweating that can be reliably measured and documented. The import of a strongly positive test is unquestioned; the meaning of a negative test is less clear. Certainly, a negative test with a negative history is confirmatory of therapeutic success. A negative test, however, can be seen in patients who report episodic breakthrough sweating, and in addition, there are patients who truly suffer from hyperhydosophobia—a disorder not dissimilar from other body dysmorphophobias.

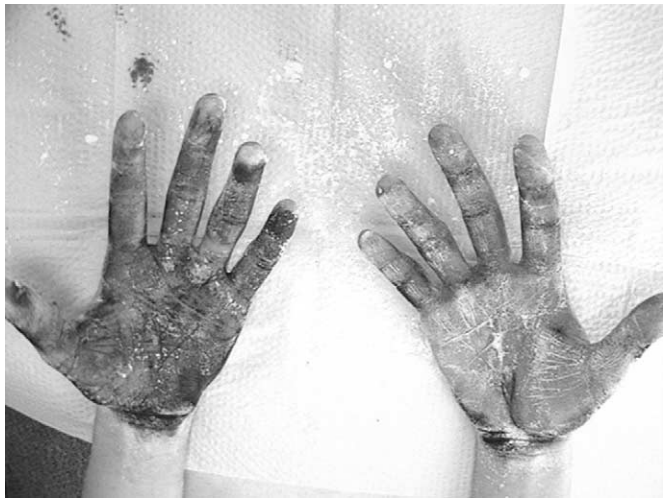

Figure 1. *Minor starch-iodine test. Left hand untreated. Right hand injected with 100 U botulinum toxin A complex (Botox®, Allergan, Inc., Irvine, California) 7 days earlier.*

We have found it useful to take a digital photograph of the starch-iodine test for the medical record and a Polaroid™ picture to give to the patients. They can easily perform a starch-iodine test themselves in follow-up and evaluate partial responses to therapy (Fig 2). The photographs also help the 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. In fact, most patients with hyperhidrosis object to the presence of any sweating and do not recognize or tolerate degrees of sweating that unaffected individuals tolerate. They are often reassured by comparing the before and after starch-test pictures. It reinforces their understanding of the effect of the drug and the therapy and may increase their tolerance for normal degrees of sweating.

Anesthesia

Treating the axillary skin with intradermal injections of Botox® through a 30-gauge hypodermic needle can be accomplished easily without anesthesia, although topi-

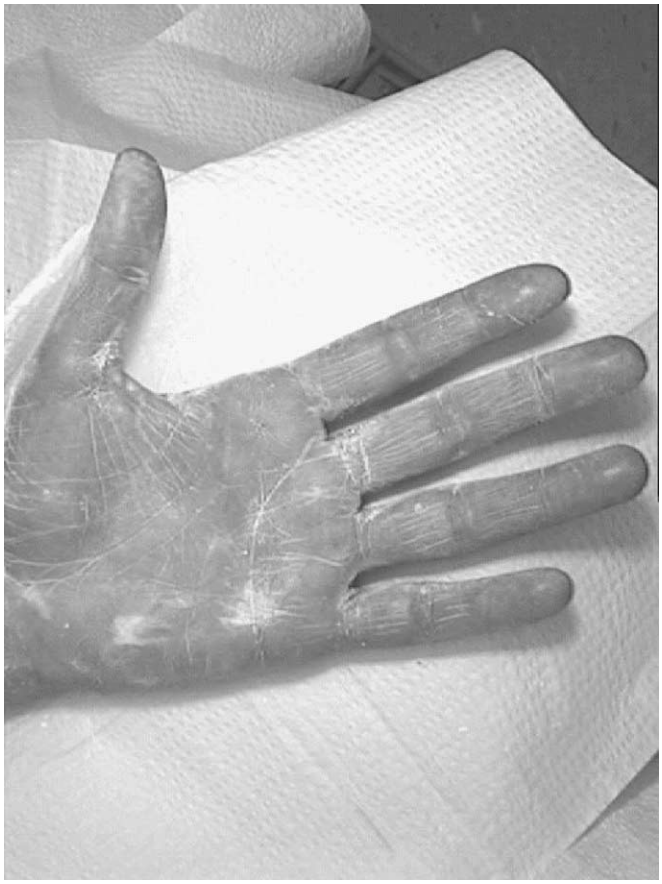

Figure 2. *Minor starch-iodine test. Same patient as in Fig 1. Right hand 2 weeks after injection with 100 U botulinum toxin A complex (Botox®, Allergan, Inc., Irvine, California).*

cal anesthetics may be used after marking the area to be treated after 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®, etc., but few can tolerate the discomfort of 60-70 needle sticks per palm or sole without anesthesia. Most patients will require regional nerve block anesthesia, such as wrist or ankle blocks, before undergoing palmar injection.[37,38] The occasional patient may require twilight anesthesia[39] or tourniquet limb anesthesia (Bier Block).[40]

For palmar anesthesia, 2% lidocaine plain, without epinephrine, is placed by superficial, subcutaneous injections at the wrist to produce blocks of the 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, etc., 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.[38] 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.

Dilutions and Volumes

The dosage of drug used and injection method has not been standardized. There are a variety of dosages reported in the literature (Table 1). 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). Each syringe holds 0.5 mL and has the 30-gauge needle swaged directly into the chamber of the syringe, thus 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. Each syringe then holds 0.5 mL of solution that is 20 U; therefore, 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 10-12 injections with each syringe.

Injection Technique

To treat the axillae, 50 mouse units of Botox® are injected in 0.05-mL amounts *intradermally,* raising tiny wheals spaced ~1.5-2.0 cm apart, beginning at the periphery of the hair-bearing skin and circling into the center of the axillary vault (Figs 3 and 4). Because the skin is 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

Table 1. Sample of Dosage Regimens and Patterns of Injections for Treatment of Hyperhidrosis with Botulinum Toxins

Author	*Dilution (mL/100 U)*	*Dose Botox® unless otherwise labeled*	*Distance or total sites per area treated*	*Diagnosis*
Naumann, 2003[74]	4.0	50 per axilla	10–15 sites/axilla	Axillary
Lowe, 2003[75]	4.0	50 per axilla	10–15 sites/axilla	Axillary
Odderson, 2002[43]	2.0	50 per axilla	7–10 sites/axilla	Axillary
Heckmann, 2002[76]	4.0	50 per axilla	2.5 per site	Axillary
Naumann, 2002[46]	4.0	50 per axilla	10 per axilla	Axillary
Salmanpoor, 2002[42]	?	125 per axilla Dysport®	10 per axilla	Axillary
Naumann, 2001[49]	4.0	50 (3–5 per site)	10–15 sites/axilla	Axillary
De Almeida, 2001[37]	2.0	5 per site	1.0 cm	Palmar
Heckmann, 2001[51]	5.0	200 (Dysport)	10 sites/axilla	Axillary
Dulguerov, 2000[77]	2.0	5 per site	1.0	Frey's
Karamfilov, 2000[53]	1.0	200 per axilla	Single dose	Axillary
Naver, 2000[54]	?	2 per site	4.0 cm^2	Axillary/palm
Solomon, 2000[65]	2.0	2–4 per site	1.0 cm	Palmar
Birch, 1999[78]	4.0	7.5 per site	6 cm^2	Frey's
Schnider, 1999[55]		33.3 per axilla	2–3 cm	Axillary
Glogau, 1998[35]	2.0	2 per site	1.5 cm	Axillary
Heckmann, 1998[56]		400 (Dysport)	1 cm	Axillary
Naumann, 1998[57]		3	2 cm	Axillary, palm
Odderson, 1998[58]		100 (Botox)		Axillary
Shelley, 1998[64]		2	1 cm	Palmar
Schnider, 1997[34]		20 units	6 sites	Palmar
Bushara, 1996[29]		20–50	Single dose	Axillary
Cheshire, 1996[31]		1 unit	1.5 cm	Forearm
Drobik, 1995[79]		0.5 unit	1.0 cm	Frey's

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 due to the smaller zone of radial diffusion produced in palmar skin. The needle must enter the palmar skin at an oblique angle. Mechanical needle flanges have been advocated that provide a method for assisting the depth of the injection.[37,41] If the needle enters perpendicular to the skin surface, however, there is usually a significant amount of backflow of material that leaks out of the injection tract. Because the volumes of Botox® are typically small, this backflow significantly impacts the effectiveness of the injections.

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 the midpad and the other at the very tip, as 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 will provide overlapping

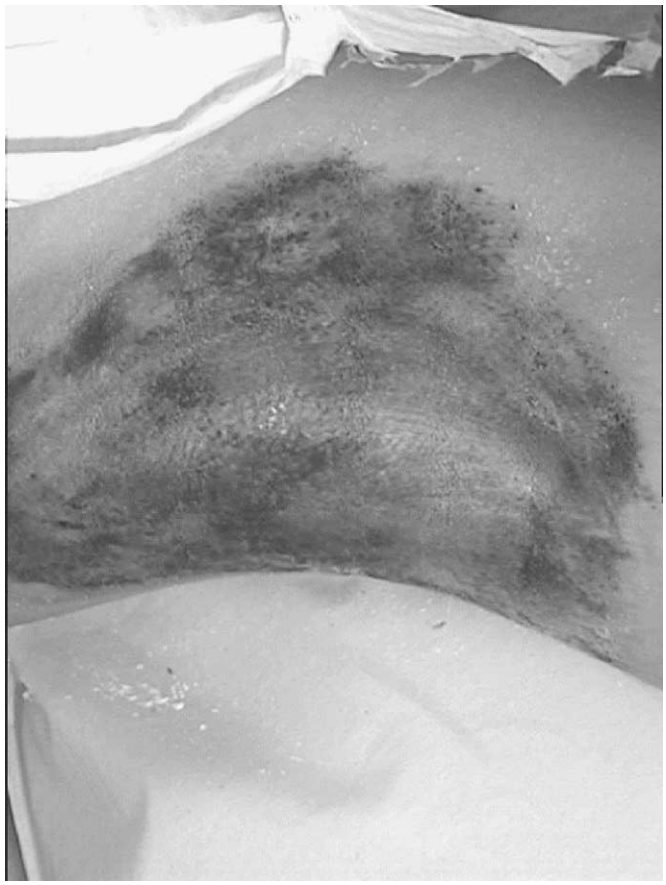

Figure 3. *Minor starch-iodine test. Right axilla before treatment.*

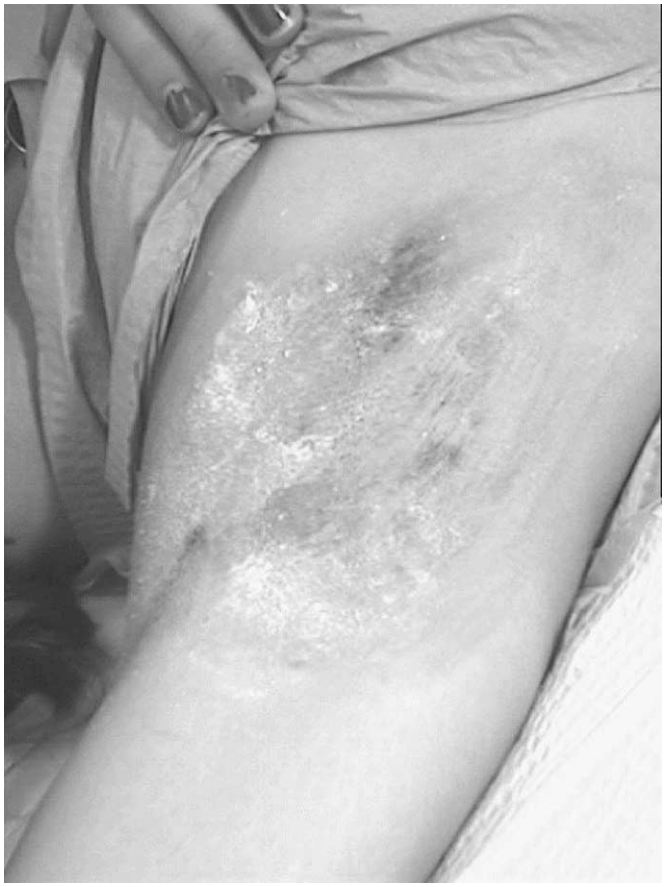

Figure 4. *Minor starch-iodine test. Right axilla 1 week after treatment with 60 U botulinum toxin A complex (Botox®, Allergan, Inc., Irvine, California).*

coverage for the entire palmar surface. One needs to minimize the number of injections that arrive subcutaneously, as this will increase the likelihood of diffusion of drug into the intrinsic muscles of the hand.

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

In axillary skin, each injection is placed to produce a wheal. The palmar skin, however, is comparatively stiffer, 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. 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 will flow back out the injection tract directly.

Sweating of the upper forehead and anterior crown can be approached in a similar fashion, by injecting 2-4

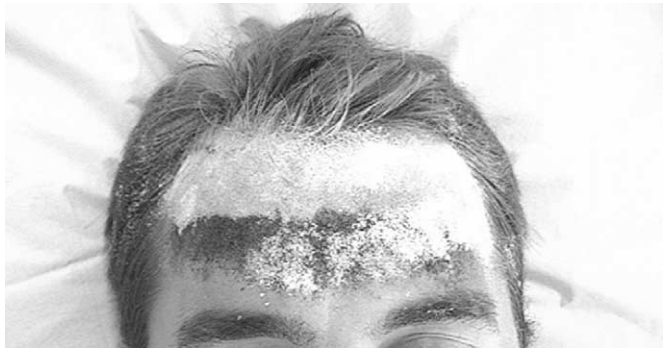

Figure 5. *Minor starch-iodine test. Upper forehead and anterior scalp 1 week after treatment with 60 U botulinum toxin A complex (Botox®, Allergan, Inc., Irvine, California).*

U of Botox® every 2 cm along the anterior hairline from sideburn to sideburn, an additional shorter row in the anterior crow ~2 cm behind the anterior hairline, and another horizontal row in the upper third of the forehead skin. These are also easily performed without anesthesia and are well tolerated (Fig. 5).

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 for the palms. Using the Minor starch-iodine test as a guide, however, and relying on ankle blocks for anesthesia, the same satisfactory outcome can be achieved. Duration of effect appears to be identical to that achieved in the palms.

Duration of Effect

Reported response times for duration of anhidrosis in the axillae range from 4-10 months in numerous studies, depending on dosage and technique.[3,29,35,42–59] Similar responses are seen in the treatment of forehead sweating.[50,60–62] We have routinely seen patients with dryness lasting 10-12 months and have many patients now on annual injection schedules.

There is a broader range of responses to palmar treatment, varying from ~3 months to 12 months.[33,34,51,54,57,63–65] The average in our hands is ~6 months. Interestingly, the effect does not seem to last as long as it does with axillary hyperhidrosis. This may be a problem of backflow from the injection sites, the smaller diffusion distance in thicker palmar skin, a higher number of cholinergic nerve endings in the palmar skin as opposed to axillary skin, or a differential recovery rate between the nerves of the palm and those in the axilla.

On average, patients seem to require treatment about twice a year to maintain reasonable control of 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 an acceptable end point. 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. Obviously, this changes the treatment intervals and dosages, but further work on patient tolerance as it affects dosing intervals needs to be undertaken.

To date, 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 down side, of course, is 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.

Further Considerations in Scheduling Palmar Treatments

Almost every patient who undergoes this treatment will develop a transient period of weakness and instability of the lumbrical muscles of the hand, which is predictably spontaneously reversible.[1,33,34,54,63–65] Tasks such as shoving a button through a tight button hole, holding heavy objects with chop sticks, or opening a stuck lock with a key, will become problematic about 5-7 days after treatment and will remain so for 3-5 weeks. Patients can write, type, and eat without difficulty, but opening a tight jar lid, etc., will pose problems for a few weeks.

For this reason, if the patient has ready access to the treating physician, it may be preferable to stagger the treatments. If the patient elects to treat the hands separately, the right hand, since it is the one used in social greetings, is usually treated on the first visit. After waiting several weeks, the left hand is treated, with any needed touch-up injections of the right hand on the second visit, and a third visit is scheduled to touch up the left hand. By doing so, one can stagger the onset and duration of hand weakness to make it easier on the patient.

Multiple visits, however, often are logistically impossible, and we have no objection to treating both palms simultaneously, so 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, to allow the patient to choose to schedule future treatments together or staggered according to their own experience. Clearly, the majority of patients elect to treat both hands at the same visit initially. It does not appear at this time that doing so promotes any meaningful antibody response, since the overwhelming majority of patients continue to respond to future treatments as expected.

Quality of Life Considerations

There are several studies[62,66–68] that document in a reproducible way what investigators have intuitively known about the use of botulinum toxin in hyperhidrosis: the results can be not only clinically gratifying but also truly life altering. Although a similar impact can be achieved with surgical interventions,[19,20,69,70] there can be little doubt that botulinum toxin can provide significant relief from the psychosocial burden of hyperhidrosis.

Future Directions

Work on injection delivery devices has stimulated some investigators, and further enhancements to the delivery system[37,71] may optimize the treatment for many patients. Comparative studies utilizing the two commercially available forms of A serotype toxin may be useful. Further investigation of the genetic pattern of the disorder may give further clues to possible therapies.[72,73] Until then, many patients can benefit from truly life-altering therapy with this amazing neurotoxin complex.

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