Botulinum toxin type A therapy for palmar and digital hyperhidrosis

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Objective: We evaluated the efficacy of subepidermal injections of botulinum toxin type A on recalcitrant palmar and digital hyperhidrosis.

Methods: Twenty patients with recalcitrant palmar and digital hyperhidrosis were treated with subepidermal injections of botulinum toxin. Nineteen patients completed the 12-month study. Injections were performed in 3 stages. The total dose of toxin for each hand, which included the palm, thenar eminence, and digits, was 165 units. Patients were followed up on a monthly basis.

Results: Botulinum toxin significantly reduced sweat production in the treated areas. Anhidrosis lasted 9 months in 3 patients, 8 months in 3 patients, 7 months in 8 patients, 6 months in 3 patients, 5 months in 1 patient, and 4 months in 1 patient. Reduced sweating of the palm and digits continued in all patients for the 12-month evaluation period, with the greatest reduction of sweating in the nondominant hand. Mild weakness of the thumb occurred in 4 patients at a mean duration of 3 weeks, with the greatest duration being 6 weeks.

Conclusion: Botulinum toxin provides a safe and efficacious alternative in the treatment of recalcitrant palmar and digital hyperhidrosis. (J Am Acad Dermatol 2000;42:1026-9.)

Palmar and digital hyperhidrosis can cause physical, psychologic, social, and occupational debilitation. Topical or systemic treatments are not effective in all patients. Transthoracic sympathectomy can alleviate the hyperhidrosis, but can cause concomitant morbidity.[1-4] Botulinum toxin therapy has recently emerged as an effective, non-indicated treatment of focal hyperhidrosis.[5-13] The toxin acts by blocking the release of acetylcholine from the presynaptic cholinergic nerve fibers innervating sweat glands.[14] We describe our experience with botulinum toxin in patients with recalcitrant palmar and digital hyperhidrosis.

PATIENTS AND METHODS

Twenty patients were enrolled in this study after ethical approval was obtained. Inclusion criteria included patients with palmar (thenar eminence included) and digital hyperhidrosis who stated the hyperhidrosis interfered with their daily activities, and who did not respond to appropriate topical and iontophoresis therapy. Exclusion criteria consisted of age younger than 18 years, pregnant women, patients with known systemic diseases that cause hyperhidrosis, and patients receiving systemic medications that may interfere with neuromuscular activity. A total of 14 men and 6 women from 18 to 55 years of age participated in the study.

Hyperhidrotic areas can be evaluated by several means. We evaluated areas by placing a patient's hand on butcher-type paper for 60 seconds. Butcher-type paper can effectively and expeditiously localize the extent of the areas of hyperhidrosis with minimal cost and inconvenience. Patients were also evaluated subjectively on a monthly basis as to their response to the treatment. Before treatment, cold packs were placed on the area to be treated for 15 minutes or liquid nitrogen was sprayed on the injection site for 5 seconds before the injections. EMLA cream was used in 8 patients. Botulinum toxin type A (Botox, Allergan, Irvine, Calif, 100 U per vial with diluent of 2.0 or 4.0 mL of 0.9% sterile preservative-free, normal saline added for a resulting dose per 0.1 mL of 5.0 or 2.5 U) was injected subepidermally in 3 stages. First, an average of 26 sites were injected with 2.5 U at each site on the nondominant hand, except in the central cup area of the palm. It was this area that pro-

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duced significant amounts of sweat according to pretests. Therefore an average of 10 sites in the central cup area were injected with 5.0 U at each site. Next, 2 weeks later, an average of 20 sites were injected with 2.5 U at each site on the nondominant digits and thenar eminence. Also, the dominant palm was treated as in the first stage. Finally, 2 weeks later, an average of 20 sites were injected with 2.5 U at each site on the dominant digits and thenar eminence.

Injections were performed with a 30-gauge needle. On the basis of pretests, 2.5-U injections were spaced approximately 1.0 cm apart except in digit areas where 5.0-U injections were spaced approximately 1.5 cm apart (Fig 1). Patients were instructed to restrict activity for 24 hours after receiving their injections.

RESULTS

Of the 20 patients enrolled, 1 was lost to follow-up after the first stage of treatment. Of the remaining 19 patients, anhidrosis occurred in 15 of 19 patients (79%) by 1 week and in the remaining patients by 2 weeks. Patients were assessed on a monthly basis. Anhidrosis lasted 9 months in 3 patients, 8 months in 3 patients, 7 months in 8 patients, 6 months in 3 patients, 5 months in 1 patient, and 4 months in 1 patient. Reduced sweating of the palm and digits continued in all patients for the 12-month evaluation period. In particular, on a scale of 0, 25%, 50%, 75%, 90%, or 100% of reduction of sweating as compared with sweating before the injections, 4 of 19 patients (21%) experienced a 90% reduction, 8 of 19 (42%) experienced a 75% reduction, and 7 of 19 (37%) experienced a 50% reduction by 12 months. Evaluations were performed by patient subjectivity and by the butcher paper test. Of note, recurrence initially was noted at the sites of the digits in 18 of 19 patients (95%). In addition, the dominant hand was the initial site of recurrence in 15 of 19 patients (79%). At 12 months, both hands demonstrated an equal, albeit reduced, amount of recurrence of hyperhidrosis.

Two complaints were encountered. All patients experienced pain during the injection. EMLA cream under occlusion was tried on 2 patients without providing significant relief. Therefore we used cryo treatment, which was mildly effective. Mild muscle weakness of the abductor pollicis brevis muscle was noted in 4 of the 19 patients (21%) within 2 weeks of injection; 3 of these experienced weakness only in their dominant hand, and 1 had weakness in both hands. We tested the motor strength of the thenar eminence muscles as measured by opposition strength, which was uniformly graded as 4/5, 5/5 being normal and 3/5 being anti-gravity. We also asked the patient's own subjective experience. Weakness lasted an average of 3 weeks, with the greatest duration being 6 weeks.

Fig 1. Palm and finger sites of 2.5 U botulinum toxin injections spaced approximately 1.0 cm apart. Central palm cup area sites of 5.0 U toxin injections spaced 1.5 cm apart.

DISCUSSION

Our study confirmed the efficacy of botulinum toxin in reducing palmar hyperhidrosis and presented new data for digital hyperhidrosis. As with other studies, pain during injections was one of the main disadvantages of this therapy, especially with subepidermal injections into "free nerve-endings."[5] We chose such sites, as opposed to subcutaneous,[15] because we thought the toxin would be in greater proximity to the sweat glands.[5] Interestingly, muscle weakness occurred primarily in the dominant hand. This may be a function of reliance on that hand and greater appreciation of disparity between normal and weak strength. Also, reliance on the use of the dominant hand may have dispersed the toxin to a greater extent than the nondominant hand.

Regarding the initial recurrence of sweat, this also occurred primarily in the dominant hand. Digits

recurred initially, possibly because of the concentration of the toxin used over an expanded area as compared with the palm concentration per area. Initial recurrence of sweating in the dominant digits and palm may be, once again, a function of their constant use in manual manipulation as compared with the nondominant hand.

The potential for antibody production in the use of doses greater than 200 U in a 1-month period has been raised in patients with strabismus and blepharospasm. One study demonstrated that the rate of antibody formation was directly proportional to the cumulative dose of toxin received.[16] Such antibodies may make further treatment ineffective for an indefinite period. We believe, as do others, that the immune response is not necessarily directed against the toxin, but rather determined by the protein contents of the preparation. The new bulk toxin preparation that became commercially available in December 1997 was used in this study. It has a 5-fold reduction in the neurotoxin complex protein as compared with the previous botulinum toxin.[17] With a reduced protein load there is a smaller potential for antigenicity and subsequent antibody formation and untoward reactions.[18] In a preliminary study using rabbit models, no antibody formation was noted after 6 months of treatment in 3 rabbits using the new preparation, which was used in this study, whereas 4 of 4 rabbits treated with the antecedent botulinum toxin developed antibodies by the fifth month.[17]

In our study, we used higher and total doses greater than the few reported studies dealing directly with this issue because we treated the digits and thenar eminence (50 U/hand) in addition to the palm (115 U/hand). It was our belief, as well as that of our patients, that treating the palm without concomitant treatment of the hyperhidrosis of the digits and thenar eminence did little to alleviate the debilitation of hyperhidrosis. Our patients had longer periods of anhidrosis and greater lengths of reduced sweat than did patients in other published reports in which lower doses were used. Furthermore, we believe that repeated injections may instill sufficient antigen to eventually reach an amount that may trigger neutralizing antibodies. The potential for antibody formation with the new preparation is an issue that must be evaluated in future studies. An isolated case reported that a total of 92 U of the old botulinum toxin triggered antibody production.[19] Patients should be made aware of the possibility of such occurrence and physicians may decide to treat only focal hyperhydrotic areas identified by the multitude of sweat collection methods or the patient's own subjective advice. We treat some patients by injecting their dominant hand only because that is the hand that predominantly is involved in social and occupational encounters. Furthermore, as evidenced by this and other studies, length of results can vary from patient to patient. Future studies are necessary because patient discriminatory factors, as well as injection spacing and dilution techniques, have not yet been standardized.

An issue not previously addressed is the cost for such treatment. Patients with recalcitrant hyperhidrosis suffer from physical, psychologic, social, and occupational debilitation. The medication is expensive. Even with a lower total dosage protocol, reimbursement for treatment of hyperhidrosis could be greater than for a flap excision of a malignant melanoma. In today's health care climate, reimbursement for such treatments may become an issue. If denied, many potential patients may choose to undergo reimbursable surgical intervention with its concomitant morbidity and possible compensatory hyperhidrosis. In our study, 8 patients entertained the alternative of undergoing transthoracic sympathectomy before undergoing the botulinum toxin injections. Of the 8, 6 indicated that they would self-pay to have botulinum toxin therapy repeated in the future to avoid surgery. Two patients were undecided.

Our study demonstrates that botulinum toxin can cause anhidrosis for palmar and digital hyperhidrosis recalcitrant to other therapeutic modalities for as long as 9 months and a reduced sweat production in all patients for the 12-month study period.

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