Long-Term Quantitative Benefits of Botulinum Toxin Type A in the Treatment of Axillary Hyperhidrosis

IB R. ODDERSON, MD, PHD

Department of Rehabilitation Medicine, University of Washington, Seattle, Washington, and Rehabilitation Services, Overlake Hospital Medical Center, Bellevue, Washington

BACKGROUND. **Although axillary hyperhidrosis is readily treated with botulinum toxin, the time course of benefits is not well established.**

OBJECTIVE. **To quantify the long-term effectiveness of botulinum toxin type A (BTX-A) for the treatment of axillary hyperhidrosis.**

METHODS. **This was a double-blind, placebo-controlled study. Eighteen patients received intradermal injections of either 100 U BTX-A (50 U/ml/axilla) or placebo. Sweating per surface area was quantified monthly for 5 months.**

RESULTS. **The BTX-A group had an average reduction in sweat production of 91.6% at 2 weeks (from 5.03 ml/min/m² to 0.42 ml/min/m², $P < .05$). The average reduction over 5 months was 88.2%. At the end of the study, only 1 of 12 BTX-A-treated patients had returned to baseline sweat production.**

CONCLUSION. **These quantitative results demonstrate that BTX-A is a safe and effective treatment for axillary hyperhidrosis and that the benefits last for at least 5 months.**

IB R. ODDERSON, MD, PhD HAS INDICATED NO SIGNIFICANT INTEREST WITH COMMERCIAL SUPPORTERS.

AXILLARY HYPERHIDROSIS is a disorder characterized by profuse sweating in excess of evaporation. The disorder affects both one's professional and personal life. Botulinum toxin type A (BTX-A) has been shown to be both effective and safe for focal hyperhidrosis. Recent studies have demonstrated that BTX-A injections into the axillae result in dramatic reductions in sweat production.[1–5] There are reports that this effect can last 4–7 months or longer. However, the methods for quantitating the sweat rate have varied and there are no standardized methods for sweat collection. Furthermore, comparison of studies is difficult due to the lack of standardized units for the sweat rate, as most studies have ignored the subject's size and area of sweat collection. This study was designed to document the time course and duration of benefit of BTX-A treatment for axillary hyperhidrosis, and to use rigid methods for sweat collection and a more precise description of sweat rates per surface area.

Methods

Study Design

The study was designed as a prospective, double-blind, placebo-controlled trial. The randomization of subjects was performed by a pharmacist, so that neither the treating physician nor the patient had any knowledge of the assignment of placebo versus BTX-A. The treatment allocation code was kept by the pharmacist and revealed only after each subject had completed the study. For each subject, the pharmacist prepared prior to treatment two 1 ml syringes with either placebo or BTX-A. After the study the placebo-treated subjects received a BTX-A injection.

Subjects

Individuals with symptoms of hyperhidrosis were recruited through advertisement and reports of the study in the media. Exclusion criteria were treatment with botulinum toxin within 3 months, known allergy or sensitivity to the study medication, presence of neuromuscular disease, concurrent use of medications that might interfere with neuromuscular transmission, infection at the injection site, pregnancy, nursing, or planning a pregnancy, or not using reliable birth control. The study was approved by the Human Subjects Division at the University of Washington and the subjects provided written informed consent.

Injection Protocol

The subjects were injected in both axillae with either BTX-A or placebo (saline). A 100 U vial of BTX-A was reconstituted by a pharmacist with 2 ml preservative-free saline and prepared as two 1 ml syringes (50 U/ml). Each patient received 1 ml of BTX-A or placebo per axilla distributed among 7–10 intradermal injection sites in the hair-covered area.

Address correspondence and reprint requests to: Ib R. Odderson, MD, PhD, Rehabilitation Services, Overlake Hospital Medical Center, 1035 116th Ave. NE, Bellevue, WA 98004.

ISSN: 1076-0512/02/$15.00/0 • Dermatol Surg 2002;28:480–483

utcome Measures

uantitative measurements of sweating were done once before injection and at monthly intervals over a 5-month period. Sweat collections were made from both axillae during a 15-minute resting period (30 minutes after the injection). The sweat was absorbed with discs of filter paper (grade 200, 5.5 cm diameter), covered by a 6 cm × 6 cm square of Parafilm (Figure 1), and secured in place by microfoam tape. To ensure contact of the filter paper with the skin, the subjects rested supine with their arms adducted during the collection period. After sweat collection, the discs were returned with a forceps to their screw-top plastic containers. The containers were weighed with the filter paper before and after sweat collection.

Safety

Adverse events were monitored throughout the study period.

Statistical Methods

Data analysis was performed using StatView Student volume 1.0 software (StatView Student Abacus Concepts, Inc., Berkeley, CA). Differences in sweat rate were assessed by a way analysis of variance (ANOVA), and differences in age were assessed with a *t*-test. All means are expressed as ±1 SD and a value of $P < .05$ was considered significant.

Results

A total of 18 patients (7 females, 11 males) with a mean age of 32.2 ± 8.6 years (range 16–50 years) were enrolled in the study. There was no significant difference in age between the treated group (30.3 ± 8.3 years) and the control group (36.0 ± 8.4 years).

The preinjection sweat rate of the BTX-A group (5.04 ± 4.64 ml/min/m^2) was not significantly higher than for the control group (2.97 ± 1.68 ml/min/m^2). After 2 weeks (1–30 days) the sweat rate was significantly reduced for the treated group by an average of 91.6% (from 5.04 ± 4.64 to 0.42 ± 0.30 ml/min/m^2). After injection the sweat rate for the treated group remained significantly reduced throughout the study by an average of 88.2% compared to the preinjection sweat rate (0.59 ± 0.11 versus control 1.78 ± 0.34 ml/min/m^2). Only 1 of 12 subjects in the treated group had resumed a normal sweat rate at the end of the study. The control group temporarily experienced a mild average reduction in sweat rate, which was not statistically significant. The individual data for the control group also confirms the great inter- and intrasubject variability (Figure 2).

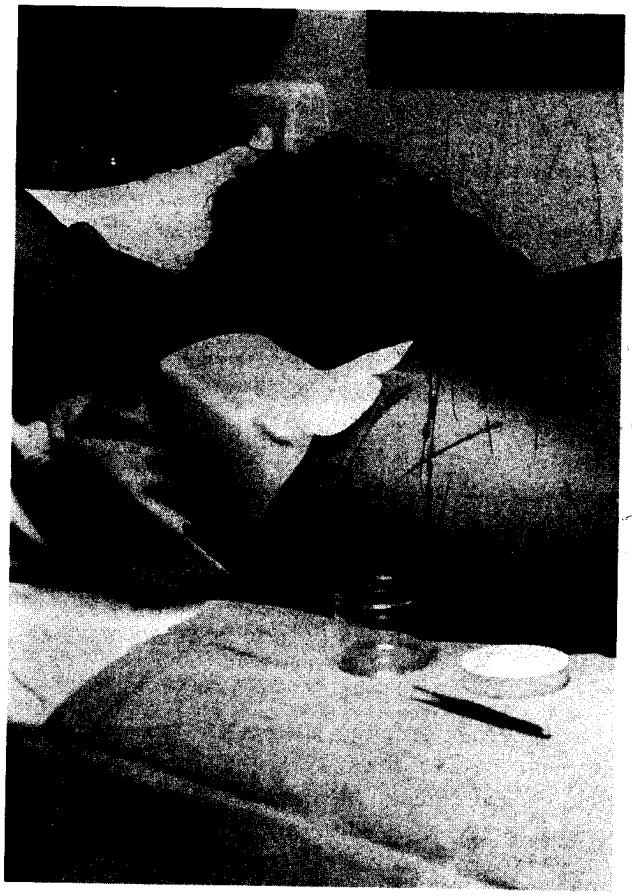

Figure 1. Technique used to quantitate the axillary sweat response (Odderson[16] with permission).

Safety Results

During the study only 1 of 18 patients reported an adverse event in the form of a localized, mild compensatory hyperhydrosis between her thighs.

Discussion

This study documents the time course of the long-term benefits of BTX-A in the treatment of axillary hyperhidrosis. The treatment is effective and the reduction in sweat production is dramatic and lasts for at least 5 months, which was the duration of the study. In one subject the benefits lasted beyond 6 months. BTX-A is a safe treatment for axillary hyperhidrosis and the adverse effects are rare and mild, with only one subject reporting possibly mild compensatory sweating on her thighs. The duration of benefits was in excess of the preferred minimum time for repeat injections.

A unique feature of this study is the technique for sweat collection and the expression of the sweat rate in relation to the surface area from which the sweat

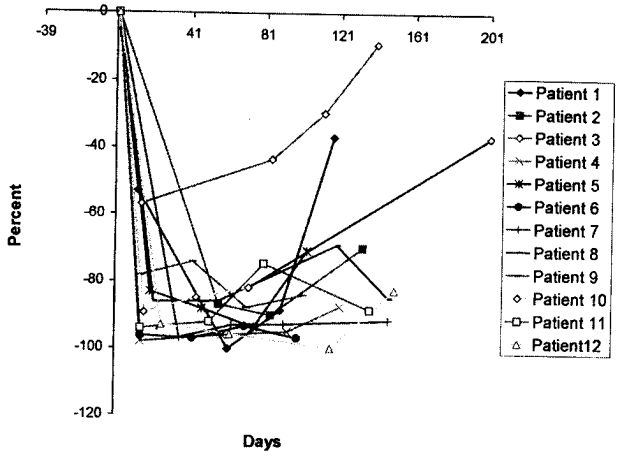

Figure 2. Percent change in axillary sweat rate after BTX-A injection. In most patients, the maximum reduction in sweat production occurred within the first 30 days. At the end of the study, only 1 of 12 patients had returned to pretreatment sweat production. At day 100, all but two patients still had sweat production levels that were approximately 70% below baseline.

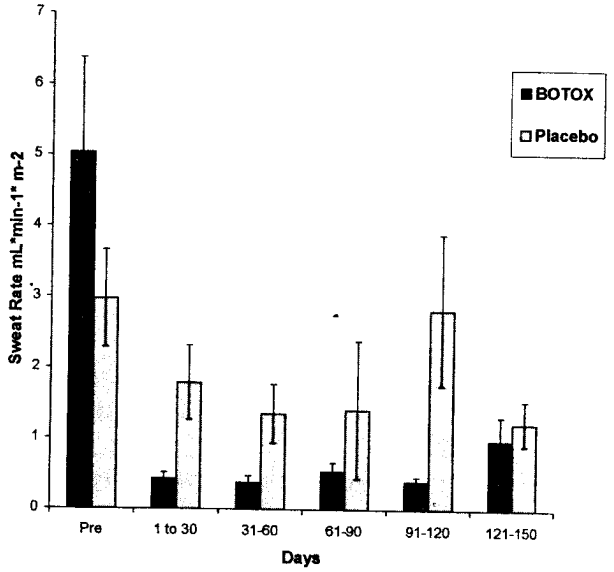

Figure 3. Change in axillary sweat rate following BTX-A. At week 2, average reduction in sweat production was 91.6%. Throughout the 5-month study period, the average reduction in sweat production was 88.2%. Average sweat production remained far below baseline at 5 months, suggesting that the benefits of treatment may last considerably longer than 5 months. Values are means ± SE.

was collected. In previous studies a variety of methods have been used to assess sweating. Frequently, gravimetric measurements have been used to quantitate sweating, since this technique primarily requires an accurate scale.[1,5–7] Other nonvolumetric techniques have been used, such as visual inspection with starch-iodine,[3,8,9] planimetry of hyperhydrous areas identified with iodine-starch,[2] digital image analysis of ninhydrin-stained sheets,[10] and evaporimeter[3] and subjective evaluation.[3,11] However, the sweat collection techniques have been inaccurate, as the time for collection has been brief (1 minute), which increases the variability of measurements,[1,3,6,7] or the time period not described.[10] Furthermore, sweat has been collected from both sides of the filter paper and allowed to evaporate before and during weighing.[1,5] Measurements of sweating by evaporimeter tends to underestimate sweat production when it exceeds evaporation, which is often used as a definition for hyperhidrosis.

The technique used in this study was designed to minimize evaporation immediately after sweat collection by returning the filter paper discs with a forceps to the screw-cap container. The plastic container was weighed before and after sweat collection. In addition, the collection periods have been longer (15–30 minutes) to minimize fluctuations in sweat rate. In order to reduce measurement errors, several discs of filter paper were used to increase the weight of the discs.

Efforts have also been made to relate the sweat rate to the surface area. Sweat was collected on discs covered by parafilm, thus limiting sweat collection to only one side of the filter paper. In addition, the parafilm was placed to prevent sweat from the surrounding area from running down the axillae and being absorbed by the filter paper.

Such careful techniques for sweat collection and sweat rate reporting are now more important, as dose-response relationships are being researched and comparisons of BTX-A and BTX-B are undertaken. If the sweat rate is not expressed per unit surface area, a large male with a normal sweat rate may meet the definition of hyperhidrosis, while a small-statured woman with hyperhidrosis may not meet the criteria unless the sweat

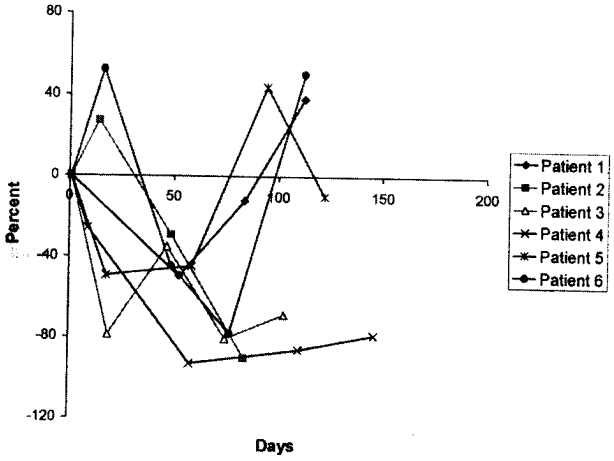

Figure 4. Percent change in axillary sweat rate in the control group. Sweat production in the placebo-treated patients was highly variable throughout the study period. Only patient 4 demonstrated a consistent reduction in sweat production.

is expressed per time unit and surface area. Such sweat rate expressions will also make a quantitative definition of hyperhidrosis more meaningful.

The gold standard for sweat rate assessment is by resistance hygrometry. With this method, sweating is measured by passing dried air through a capsule affixed to the skin. The humidity of the air leaving the capsule is measured using resistance hygrometry.[12,13] However, such techniques exceed the capacity of most clinical settings. The method used in this study provides a practical alternative. The use of capsules with filter paper may provide an even better and still practical way to collect sweat. The capsules would prevent sweat from surrounding areas to penetrate to the collection site.[14,15]

The starch-iodine technique is commonly used to identify the area of hyperhidrosis prior to injection of botulinum toxin.[9] However, such marking technique was not used in this study. It has been the experience of the author that the area of hyperhidrosis in the axillae is confined to only part of the hair-covered area. Thus only the hair-covered area was injected.

In order to reduce the number of injection sites, a relatively high concentration of botulinum toxin was used (5 U/0.1 ml).[16] The distance between injection sites of 2 cm was based on earlier studies where injections of 1.0 and 2.0 U of botulinum toxin resulted in anhydrous circle of 1.5 cm and 1.3 cm in diameter, respectively.[17,18] This technique has been reported to reduce the sweat rate by more than 70%.[16]

The anhydrous response to BTX-A of more than 5 months is consistent with other reports. In these studies the doses have ranged from 19 to 200 U/axillae (50–250 U of Dysport) lasting 4–10 months.[1–3,5–8,10,11,16,19] With lower doses (15–20 U of Dysport), no effects were reported and a reduced response was seen with 30 U of Dysport.[8]

The sweat rates were significantly suppressed beyond 5 months. Since 3 months is the preferred minimum time interval for repeat injections, axillary hyperhidrosis can be treated effectively with BTX-A injections.[4] The treatments can likely be spaced further apart, such as two times per year, thus minimizing the risk of neutralizing antibody formation.

It is of particular interest that one subject approximately 20 years prior to the study had been hospitalized with botulism when he served in the U.S. military in Germany. His symptoms at that time included severe nausea, vomiting, abdominal pain, and generalized weakness. However, the subject did not remember this event until after the study. His anhydrous response did not differ from the other subjects (Figure patient 8, Figure 4), and his sweat rate remained suppressed for more than 6 months.

Conclusion

These results demonstrate that BTX-A is a safe and effective treatment for axillary hyperhidrosis and that the benefits last for at least 5 months. The anhydrous response lasts the minimum time preference for repeat botulinum toxin injection of 2–3 months. This condition is thus readily managed with repeat injections of BTX-A. By reporting the sweat rate per time unit and surface area, meaningful comparisons can be made between studies and may provide a tool for a quantitative definition of hyperhidrosis.

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