

Treatment of focal hyperhidrosis with botulinum toxin type A: long-term follow-up in 61 patients

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Accepted for publication 12 April 2001

Summary

Background The blocking action of botulinum toxin type A (BTX-A) on cholinergically innervated sweat glands has been used successfully to treat patients with focal hyperhidrosis.

Objectives To investigate the long-term efficacy and safety of intradermal injections of BTX-A.

Methods We performed an open-label study in 61 patients treated over a period of 3 years for axillary or palmar hyperhidrosis. A total dose of 400 mU BTX-A (Dysport®) was injected into both axillae or 460 mU BTX-A (Dysport®) into both palms. The injections were repeated after relapse. Objective quantification of sweat production was performed using digitized ninhydrin-stained sheets.

Results Four weeks after BTX-A treatment the median reduction in sweat production was 71% compared with baseline ($P < 0.001$) in the axillary group and 42% ($P = 0.005$) in the palmar group. Subjective assessment of sweat production by the patients using a visual analogue scale (0, no sweating; 100, the most severe sweating) showed a significant reduction in both the axillary ($P < 0.001$) and palmar groups ($P < 0.001$). Secondary disturbances due to focal hyperhidrosis interfering with daily activities were markedly improved in both groups. The median time interval between the sets of injections was 34 weeks for axillary hyperhidrosis and 25 weeks for palmar hyperhidrosis. The treatment of palmar hyperhidrosis was complicated by transient but not disabling weakness of the small hand muscles in nine of 21 patients.

Conclusions Repeated intradermal injections of BTX-A in patients with axillary and palmar hyperhidrosis are as effective as first treatments.

Key words: botulinum toxin type A, focal hyperhidrosis

Botulinum toxin type A (BTX-A) acts primarily at peripheral cholinergic synapses, inhibiting the release of acetylcholine.¹ Its therapeutic effect was used initially to block the neuromuscular junction in order to relieve increased muscle tone in patients with focal dystonic and spastic syndromes.^{2,3} In the last few years the blocking action of BTX-A on cholinergically innervated sweat glands has been used successfully to treat patients with focal hyperhidrosis of the axillae and palms.^{4–13} So far, there has been no general agreement concerning the duration of the anhidrotic effect and the

need for repeated injections. Additionally, the optimal treatment regimen concerning injection technique, dosage and dilution has still to be determined.

The development of neutralizing antibodies against BTX-A with secondary non-response has been described in up to 10% of patients treated with BTX-A for dystonia and blepharospasm over a 10-year period.^{14–16} To our knowledge, clinical resistance to BTX-A has not yet been described in hyperhidrosis. We do not know at present if intradermal application, the high number of injection sites and the younger age of the patients treated is associated with a greater risk of developing antibodies. The purpose of this study was to

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evaluate the duration of the anhidrotic effect after repeated treatments with BTX-A, as well as its long-term efficacy and safety in patients with axillary and palmar hyperhidrosis.

Materials and methods

Patients

Sixty-one patients (33 women, 28 men; age range 21–53 years, mean \pm SD 33.7 \pm 9.6) with focal hyperhidrosis (40 axillary and 21 palmar) were included over a period of 3 years for this trial. In the first year 23%, in the second year 39%, and in the third year 38% of the patients were included. During the study 148 sessions of injections were performed. All patients were unresponsive to any conventional conservative treatment (local antiperspirants containing aluminium salts in axillary and palmar hyperhidrosis, iontophoresis in palmar hyperhidrosis) and were socially handicapped by their symptoms.¹⁷ Before treatment, patients underwent a pretreatment examination to exclude secondary hyperhidrosis. We excluded patients younger than 19 years of age, pregnant women and those with systemic diseases causing hyperhidrosis. The study was approved by the Ethics Committee of the Medical Faculty of the University of Vienna. Informed consent was obtained from all patients following a full written and oral explanation.

Study design

The study was designed as an open-label study for patients with axillary and palmar hyperhidrosis. All patients underwent a pretreatment evaluation consisting of clinical assessment, objective quantification of sweat production (ninhydrin test) and subjective rating of the individual sweating profile. A clinical examination and objective quantification of sweat production were performed 1 month after the first treatment. The patients were instructed to evaluate the necessity of BTX-A reinjection themselves. Before the first treatment they were informed about the potential risk of the production of neutralizing antibodies following long-term treatment with BTX-A. To minimize this risk, reinjection was never performed earlier than 3 months after the previous treatment. When the patients concluded that a relapse of their condition was as marked as previously, they were to request reinjection.

Treatment with botulinum toxin type A

Patients with axillary hydrosis were injected with a dose of 200 mU BTX-A (Dysport[®], Ipsen Pharma Ltd) at 10 sites on each side. One vial of BTX-A containing 500 mU was diluted with 1.25 mL 0.9% sterile saline. A dose of 230 mU BTX-A (Dysport[®]) was injected at 30 sites on each side (16 sites for the palm and 14 sites for fingers) in patients with palmar hyperhidrosis. Distance between the injection sites ranged between 15 and 25 mm. For these patients, one vial was diluted with 2.5 mL 0.9% sterile saline.

We performed the injections intracutaneously using a G26 \times 1/2, 0.45 \times 1/2 gauge needle. Anaesthesia was not given to patients treated in the axillae. In patients with palmar hyperhidrosis, anaesthesia of the plexus brachialis was performed twice and blocks of the medial and ulnar nerves were carried out three times. In other cases we used ethyl chloride BP cooling spray liquid (Chloroethyl DR Henning[®]).

Objective measurement

Analogous to the ninhydrin sweating procedure as described by Moberg for the palm, we performed ninhydrin sweat tests on both axillae and palms, before and 4 weeks after the first set of BTX-A injections, in a room with a constant temperature of 22 °C and a relative humidity of 65%.¹⁸ Moist palms pressed against paper (quality copy paper) left a print that can be dyed with a ninhydrin solution. The paper is dried and warmed for a few minutes at about 60 °C in an incubator. Objective quantification of sweat prints was performed using digital image analysis. The ninhydrin-stained sheets were digitized and transferred on to an IBAS 2000 image analysis workstation (Zeiss-Kontron, Germany). The stained area was quantified using a standardized algorithm.

Subjective measurement

All patients completed questionnaires recording subjective impressions of sweat production before and after treatment with BTX-A at weekly intervals for the duration of the study. The patients were asked to quantify the intensity of sweat production using a visual analogue scale (VAS) of 100 points (0, no sweating; 100, most severe sweating). Furthermore, the individual satisfaction with this treatment was rated on a semiquantitative scale (1, none; 2, poor; 3, moderate; 4, good; 5, very good). Before treatment, the

patients raised one or more individual problems related to their hyperhidrosis that were included in their individual questionnaire. After each treatment, improvement of these items was rated on a semi-quantitative scale (1, worse; 2, unchanged; 3, mild improvement; 4, moderate improvement; 5, marked improvement).

Side-effects

Side-effects were documented by a structured check-list attached to the questionnaire. Muscular power was monitored in the palmar group before and 4 weeks after each set of injections. The sustained muscle power of the hand muscles was tested for three different movements by squeezing a blood pressure cuff between thumb and index finger, and thumb and little finger, and by measuring hand grip.

Statistical analysis

Continuous data are given as the mean \pm SD, or as the median and the 25th and 75th percentiles, as appropriate. All statistical analyses were performed according to the intention-to-treat principle. Continuous measures were compared by using the Kruskal-Wallis test or repeated-measures analysis of variance, as appropriate. Duration of effect was evaluated using Kaplan-Meier tables. Comparison of the duration of effect between groups was performed with the log-rank test. Statistical analyses were two sided, and $P < 0.05$ was regarded as indicating statistical significance. SPSS (SPSS 6.0, Chicago, IL, U.S.A., 1993) software was used for all analyses.

Results

General data

A 3-year clinical follow-up was performed in 61 patients treated with intracutaneous injections of BTX-A for axillary or palmar hyperhidrosis. The patients received between one and six sets of injections. Sixteen patients received one set of injections, 22 received two sets, 15 received three sets, and eight patients received more than three sets. The median time interval between the sets of injections was 34 weeks (25th-75th percentile 29-46 weeks) for axillary hyperhidrosis and 25 weeks (25th-75th percentile 21-38 weeks) for palmar hyperhidrosis.

Objective measurement

Objective measurements before and after the first set of injections were available for 44 patients (29 axillary, 15 palmar). We have included only 44 patients because in 11 patients the prints of the axillae were not conclusive, and in six patients the palms were too moist at baseline and we used a low-quality paper unsuitable for image analysis. After the first BTX-A treatment, the median reduction in sweat production compared with baseline was 71% (25th-75th percentile 52-92%, $P < 0.001$) for axillary hyperhidrosis and 42% (25th-75th percentile 3-60%, $P = 0.005$) for palmar hyperhidrosis.

Subjective measurement

Four weeks after BTX-A treatment of axillary hyperhidrosis, the median subjective rating for sweat production (VAS) was 0.5 points (25th-75th percentile 0-10), which was significantly different from the baseline values (median 90 points, 25th-75th percentile 80-100, $P < 0.001$). For palmar hyperhidrosis, the median subjective rating 4 weeks after BTX-A treatment was 22.5 points (25th-75th percentile 10-40), which was also significantly different from the baseline values (median 90 points, 25th-75th percentile 75-95, $P < 0.001$). The median duration of maximum effect as evaluated by subjective rating was 28 weeks (25th-75th percentile 20-38 weeks) for axillary hyperhidrosis and 11 weeks (25th-75th percentile 6-20 weeks) for palmar hyperhidrosis ($P = 0.005$, Fig. 1). The median individual satisfaction after treatment was 5 (range 3-5) in patients with axillary hyperhidrosis and was also 5 (range 2-5) in those with palmar hyperhidrosis.

The patients with axillary hyperhidrosis mentioned the following as individual problems due to hyperhidrosis: the necessity to change their clothes frequently (85%), nervousness (24%) and social isolation (15%). The patients with palmar hyperhidrosis mentioned embarrassment when shaking hands (86%), trouble working with paper (17%) and professional handicaps (15%). The median improvement of the individual handicap was 5 (range 1-5) in patients with axillary hyperhidrosis and was also 5 (range 1-5) in those with palmar hyperhidrosis.

Repeated sets of injections

For patients who received repeated sets of injections, subjective ratings of sweat production before and after

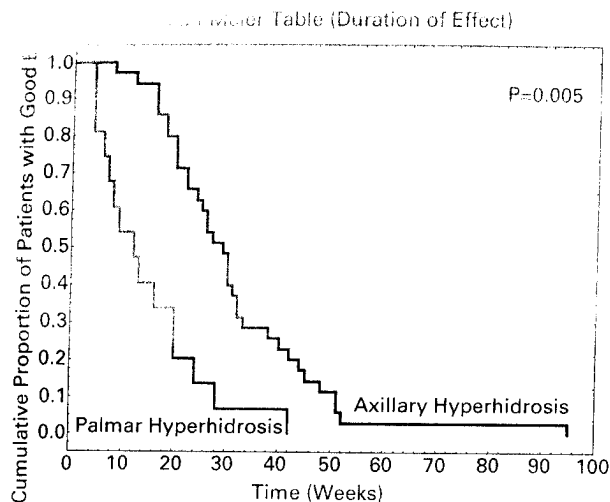


Figure 1. Duration of the maximum anhidrotic effect after the first set of botulinum toxin type A injections in patients with axillary and palmar hyperhidrosis.

the first, second and third sets of injections were available for eight patients (Fig. 2). In these patients, we observed no difference with regard to the subjective efficacy between the first, second and third sets of injections ($P = 0.68$ for differences between the sets of injections). Similarly, there was no statistically significant difference in the duration of effect between the first (median 19 weeks), second (median 18.5 weeks) and third sets (median 20 weeks) of injections ($P = 0.69$).

Safety evaluation and side-effects

The BTX-A treatment was well tolerated by all patients. Patients treated for axillary hyperhidrosis reported local itching after injections with a mean duration of 2.5

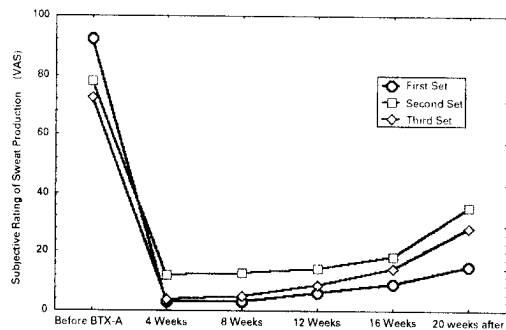


Figure 2. Subjective ratings before and after the first, second and third sets of botulinum toxin type A (BTX-A) injections in patients receiving repeated courses of treatment ($n = 8$). VAS, visual analogue scale.

weeks (three patients), and compensatory sweating in other areas with a mean duration of 12 weeks (four patients). One patient reported compensatory sweating after each treatment with a mean duration of 13 weeks and the others only discrete compensatory sweating with a duration ranging from 3 to 7 weeks. This side-effect was not as incapacitating as the treated condition and the affected patients asked for further treatment.

Patients treated for palmar hyperhidrosis reported mild reduction in finger power (after nine treatment sessions) and transient pain at the injection site for more than 12 h (one patient). The reduction in finger power was present and measurable after 4 weeks by means of a strength test in seven patients (after the first treatment session in five patients, and after two treatment sessions in two patients). The mean duration was 5.7 weeks (range 4–8). Two patients reported a subjective reduction in finger power and hand grip for 12 and 14 days, respectively, with a normal strength test after 4 weeks. When muscle weakness was detected, the dose of BTX-A was reduced by half at injection sites above the thenar eminence during further treatment sessions.

Discussion

Our data confirm that intradermal injections of BTX-A improve significant focal hyperhidrosis of the palms and axillae, which is resistant to conventional conservative treatment. The median duration of the maximum effect as evaluated by subjective rating was 28 weeks for axillary hyperhidrosis and 11 weeks for palmar hyperhidrosis, and the median time interval between the sets of injections was 34 weeks for axillary hyperhidrosis and 25 weeks for palmar hyperhidrosis. The duration of the anhidrotic effect has been assessed in different ways in the literature:^{8,12,13} either as the duration of anhidrosis identified by objective measurements (ninhydrin test, Minor test) or as assessed subjectively by the patients. Patients usually observe a fairly anhidrotic plateau phase, followed by a slow recurrence of hyperhidrosis over a period of several weeks. There are only very few data investigating the duration of anhidrosis and the effect of repeated injections in a large number of patients. After 2 years of investigation, Naver *et al.* reported a median duration of 10 months (range 3 to > 14 months) after injecting a mean total dose of 60 mU Botox[®] (range 32–100 mU) in 55 patients with axillary hyperhidrosis and a dose of 170 mU Botox[®] (range 120–220 mU) in 94 patients with palmar hyperhidrosis.¹² The use of the

different commercial preparations poses questions as to the comparability of the results. Assuming that 4 mU Dysport® is equivalent to 1 mU Botox®, we used a somewhat higher dose in axillary hyperhidrosis but a lower one in palmar hyperhidrosis in comparison with the dosages used by Naver *et al.*¹² and Brin.¹⁴ The difference in duration of anhidrotic effect in their study could be due to several factors, such as supplementary small injections into islands of skin where patients still experienced residual sweating after the first injections, as well as the lack of specific data for the two groups of patients (palmar and axillary). Regional anaesthesia by means of medial and ulnar nerve blocks was used regularly in patients with palmar hyperhidrosis in their study and it is therefore likely that more accurate injections were performed. We were cautious in offering nerve blocks because nerve blockade repetition, in particular, may possibly induce neural damage caused in turn by ischaemic, mechanical or chemical damage.¹⁹

Our data show that repeated BTX-A injections over a period of 3 years were just as effective as the first set of injections, suggesting that the production of neutralizing antibodies did not play a major role after three treatment sessions. After several years' experience, it seems wise to accept the general recommendations for minimizing the risk of antibody formation stated for BTX-A treatment of neurological disorders.^{15,16} The most appropriate dose that achieves the greatest efficacy while minimizing the risk of antibody formation is recommended. Booster injections between treatments should be avoided and an interval of at least 3 months between treatments should also be considered.^{15,16}

Secondary disturbances due to focal hyperhidrosis interfering with daily activities also improved markedly, which explains the patients' great satisfaction with this new treatment. This was true for both the palmar and the axillary group. The only serious side-effect was transient, mild weakness of the small hand muscles in the palmar group. A reduction of the BTX-A dose applied in the thenar area minimized the risk of muscle weakness during subsequent treatment sessions. The most appropriate method of anaesthesia for repeated injections in palmar hyperhidrosis has yet to be determined.

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