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INVESTIGATIVE REPORT

Equipotent Concentrations of Botox® and Dysport® in the Treatment of Palmar Hyperhidrosis

Alma RYSTEDT[1], Carl SWARTLING[2], Catarina FÄRNSTRAND[3] and Hans NAVER[1]
[1]Department of Neuroscience, Neurology, [2]Department of Medical Science, Dermato-Venerology, and [3]Department of Neuroscience, Clinical Neurophysiology, Uppsala University Hospital, Uppsala, Sweden

There are indications that the dilution of botulinum toxin affects dose-response. This must be considered when comparing different products. The aim of this study was to estimate a concentration of Dysport® in physiological saline that is approximately equivalent to Botox® 100 U/ml with respect to anhidrotic and muscular effect. Thirty-six patients with primary palmar hyperhidrosis were treated with multiple intradermal injections of 0.02 ml botulinum toxin. Botox® was injected in one hand and Dysport® in the other in a random order. The concentrations of Dysport® were 200 U/ml ($n=18$), 150 U/ml ($n=11$) and 100 U/ml ($n=7$). Muscular effect was measured as the reduction in compound muscle action potential in 3 muscles in the hand and anhidrotic effect was indicated by an iodine-starch test 4 weeks after treatment. Dysport® at 200 U/ml was more potent than Botox® at 100 U/ml with regard to both anhidrotic and muscular effect. The equipotent concentration of Dysport®, compared with Botox® 100 U/ml, was found to be in the range 100–150 U/ml. ***Key words; botulinum toxin; concentration; equipotent; hyperhidrosis; Botox; Dysport.***

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Hans Naver, Department of Neuroscience, Neurology, University Hospital, SE-751 85 Uppsala, Sweden. E-mail: hans.naver@akademiska.se

In recent years two products containing botulinum toxin (BTX) type A have been commercially available in Europe; Botox® (Allergan Inc., Irvine, California, USA) and Dysport® (Ipsen Biopharm, Slough, UK). According to a number of studies of muscular disorders, one unit of one product is not equivalent to one unit of the other when it comes to treating humans (1–3). This lack of an exact conversion factor between Botox and Dysport causes problems when changing from one product to the other.

The explanation for the divergence in dose-response between Botox and Dysport may lie in differences in formulation, such as albumin content and protein load, as well as dissimilar methods used in the mouse unit assay (4, 5).

We believe that the amount of saline added when diluting the BTX can play a significant role. Wohlfarth et al. (6) found no difference in effect between Botox and Dysport when tested *in vitro* and in muscles on volunteers. In that study, the products were diluted to the same BTX concentration and albumin was added to Dysport to produce the same albumin content as the Botox solution.

The volume injected at each site may also influence the spread of the toxin.

No systematically comparable dose-response studies have yet been carried out; this is understandable, because of the large volume of material necessary, and the problems of achieving objective and quantitative measures of dose-response, especially for dystonic disorders.

The usage of BTX in the treatment of focal palmar hyperhidrosis provides the opportunity to measure dose-response objectively. The amount of sweat can be measured by, for example, an iodine-starch test. Furthermore, the effect on muscles in the palm can be quantified by analysing electromyogram (EMG) signals after supramaximal stimulation of motor neurones (7).

This double-blinded study aimed to estimate the concentration of Dysport in physiological, unpreserved saline that was approximately equipotent with Botox at a concentration of 100 U/ml, with respect to muscular effect and anhidrotic effect, after intradermal injections of equal volumes in the palms of patients with primary hyperhidrosis.

MATERIALS AND METHODS

The study included 36 patients (25 women) with primary palmar hyperhidrosis, all of whom had given informed consent. The mean age was 30 (age range 14–52) years. The study was approved by the local ethics committee.

As a first step, Dysport at 200 U/ml was compared with Botox at 100 U/ml, in 18 patients; Dysport was injected in one hand and Botox in the other hand in a random order. The results were used to decide whether the next step would be to investigate the effect of Dysport in concentrations higher or lower than 200 U/ml.

The second step was thus to compare Botox at 100 U/ml with Dysport at 150 U/ml ($n=11$) and 100 U/ml ($n=7$). Botox was injected in one hand and Dysport in the other, again in a random order.

All 18 patients receiving Dysport at 200 U/ml and 8 of the patients receiving Dysport at 150 U/ml had been treated with BTX prior to the study; the other 10 patients were BTX-naive hyperhidrosis patients.

Multiple, intradermal injections of 0.02 ml BTX at a distance of 15 mm apart were made for all patients. The injections were

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made using templates, to ensure identical placement on the left and right hand. The study was double-blinded; the syringes were all identical in appearance, and were marked for left or right hand by a nurse. Neither the patient nor the physician performing the injections knew which hand was receiving Dysport and which receiving Botox until the measurements had been made at the control visit 4 weeks after the treatment.

Anhidrotic effect was indicated by an iodine-starch test (Minor's test) (8). The palms were painted with a 5% iodine alcohol solution (iodium 5 g, potassium iodide 3.5 g, spiritus fortis 83 g, aqua sterilisata ad 100 g) and then pressed against a white, starch-containing sheet of paper (45 g/m^2) for one minute. The paper stained black where sweating had occurred (Fig. 1). Residual sweating was quantified by scanning the imprint into a computer program (Adobe® Photoshop 5.0), and counting the number of coloured pixels in the greyscale picture (9).

Muscular effect was measured as the reduction in compound muscle action potential (CMAP) in *m. abductor pollicis brevis* (APB), *m. abductor digiti minimi* (ADM), and *m. interosseus dorsalis I* (IOD). Stimulation was performed with surface electrodes over the median and ulnar nerves at the level of the wrist. Stimulus strength was more than 25% above that giving maximal response. Stimulus duration was set to 0.1 ms. Surface electrodes were placed over the respective muscle for recording, according to standard procedure (10). Amplitude (baseline to negative peak) was measured, and analysis was performed automatically using commercial equipment (Keypoint, Medtronic, Copenhagen, Denmark).

CMAP was measured before the treatment and at the control visit 4 weeks after the treatment. To ensure that the position of the surface electrodes was the same at each measuring session, pen marks were made at the spots where the surface electrodes were placed at the first CMAP test. After the measuring procedure, the hand with the marks was copied on a photocopier. In addition to the photocopy, the distance between a predetermined spot on the wrist and the measuring points on the hand was measured and documented.

At the control visit, patients were asked to describe the subjective effect, in terms of both muscle strength and anhidrotic effect. An iodine-starch test was also performed at this time. Four of the patients receiving Dysport at 200 U/ml and 3 of the patients receiving Dysport at 150 U/ml were not able to perform the iodine-starch test 4 weeks after treatment.

A paired *t*-test was used to compare differences in reduction in CMAP and differences in residual sweating between the Botox-treated hands and the Dysport-treated hands.

RESULTS

Objective measurements

Compared with Botox at 100 U/ml:

- Dysport at 200 U/ml resulted in a significantly greater reduction in CMAP of APB ($p < 0.01$) and ADM ($p < 0.01$) (Fig. 2), and less residual sweating of the palms ($p < 0.05$) (Figs 1 and 3).
- Dysport at 150 U/ml gave a significantly greater reduction in CMAP in APB ($p < 0.01$) but not in ADM ($p = 0.08$) (Fig. 2), with no difference in anhidrotic effect (Fig. 3).
- Dysport at 100 U/ml produced no significant differences in effect on CMAP (Fig. 2), and a greater area of residual sweating ($p < 0.05$) (Fig. 3).

Subjective reports

Among the patients receiving Dysport at 200 U/ml, 5 experienced no difference between the products concerning muscle power in the hands, 12 felt weaker in the Dysport-treated hand, and one felt weaker in the Botox-treated hand. In terms of the anhidrotic effect, 14 patients experienced no difference between the products, 3 felt that the Dysport-treated hand was drier, and one felt that the Botox-treated hand was drier.

Among the patients receiving Dysport at 150 U/ml, 8 experienced no difference between the products concerning muscle power in the hands, one felt weaker in the Dysport-treated hand, and one felt weaker in the Botox-treated hand. In terms of the anhidrotic effect, 8 patients experienced no difference between the products, and 2 felt drier in the Dysport-treated hand. One patient in this group did not report any subjective effects.

Among the patients receiving Dysport at 100 U/ml, 5 experienced no difference between the products con-

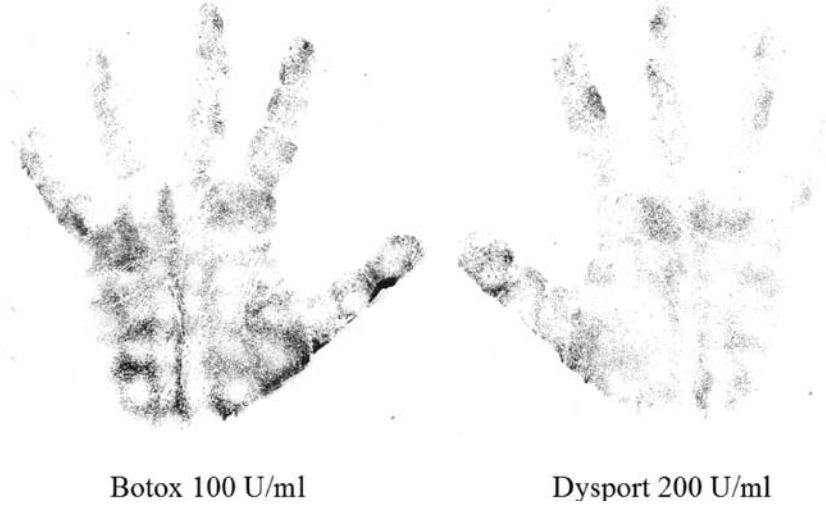

Fig. 1. Example of an iodine-starch test performed 4 weeks after injections of botulinum toxin. The imprint of the left hand, treated with Botox at 100 U/ml, shows more residual sweating compared to the imprint of the right hand, treated with Dysport at 200 U/ml.

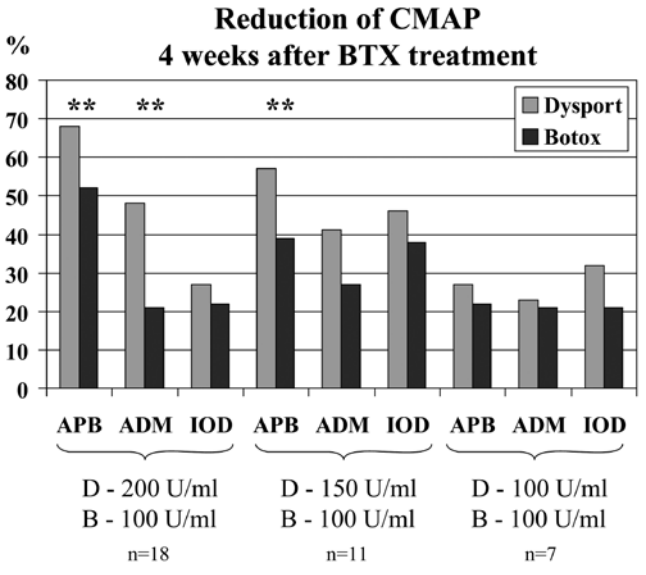

Fig. 2. The reduction in compound muscle action potential (CMAP) in *m. abductor pollicis brevis* (APB), *m. abductor digiti minimi* (ADM) and *m. interosseus dorsalis I* (IOD) 4 weeks after botulinum toxin (BTX) treatment. D: Dysport; B: Botox. Significant differences between the products are marked with asterisks.

cerning muscle power in the hands, and 2 felt weaker in the Botox-treated hand. In terms of the anhidrotic effect, 6 patients experienced no difference between the products, and one felt drier in the Botox-treated hand.

DISCUSSION

The results from the measurements on muscular effect are congruent with the results from the measurements on sudomotor effect.

Based on the measurements 4 weeks after intradermal injections, it can be concluded that Dysport at 200 U/ml is more potent than Botox at 100 U/ml with regard to anhidrotic effect, neuromuscular effect, and the effect on subjective experience.

The CMAP measurements imply that the concentration of Dysport that is equipotent to Botox at 100 U/ml is close to 100 U/ml, while the iodine-starch test indicates a Dysport concentration closer to 150 U/ml. There was, however, no large difference in objective effect between Dysport at 150 U/ml and Dysport at 100 U/ml in comparison with Botox at 100 U/ml, which would suggest that Botox at 100 U/ml is equipotent to Dysport in a concentration somewhere between 100 U/ml and 150 U/ml. The results of the subjective assessments also support this. However, the number of patients in the study group was too small to estimate a more exact dose conversion factor.

For the patient groups receiving Dysport at 200 U/ml and 150 U/ml, the muscles seemed to be affected more in both the Botox-treated and the Dysport-treated hand, compared with the group receiving Dysport at 100 U/ml. All patients receiving Dysport at 200 U/ml and 8 patients receiving Dysport at 150 U/ml had been treated with BTX before the study, while all patients receiving Dysport at 100 U/ml and 3 patients receiving Dysport at 150 U/ml were BTX-naive patients, who had never previously been treated with BTX. It is conceivable that the muscles of the patients who had been treated with BTX before the study were more sensitive to BTX, due to induction of sprouts forming functional synapses. The line of reasoning would then be that less BTX might be needed to paralyse a sprout compared with an original nerve ending.

The differences in reduction in CMAP between the 3 groups receiving Dysport at 200 U/ml, 150 U/ml, and 100 U/ml do not affect our conclusions, since Dysport and Botox were compared intra-individually and within the groups. Because of these intra-individual comparisons it was found unnecessary to have a wash-out period between the original treatment and the study treatment

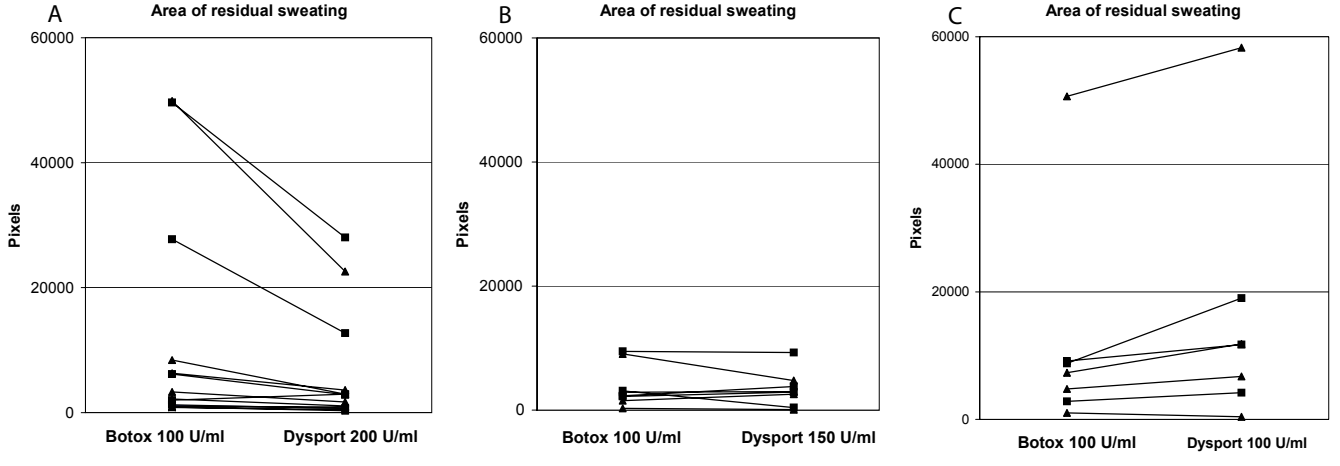

Fig. 3. Area of residual sweating expressed as the number of coloured pixels present on each patient's iodine-starch imprint. (A) Imprints from patients receiving Botox® 100 U/ml in one hand and Dysport® 200 U/ml in the other hand ($n=14$) ($p<0.05$). (B) The same results but from patients receiving Botox® 100 U/ml vs. Dysport® 150 U/ml ($n=8$). (C) The same results but from patients receiving Botox® 100 U/ml vs. Dysport® 100 U/ml ($n=7$) ($p<0.05$).

for the patients who had received BTX before. Furthermore, it appeared unethical not to treat the patients when needed.

It was found that CMAP was reduced in a higher degree in APB compared with ADM for the patients, which can be explained by differences in skin thickness. The skin covering ADM is thicker than that covering ADB, consequently leading to a larger distance for BTX diffusion.

Variability in CMAP due to measuring technique was minimized by securing identical placement of the surface electrodes. Measurements were made before and after BTX treatment to consider intra-individual differences in CMAP between the hands.

The results regarding muscular effects cannot be directly applied in situations where the toxins are administrated straight into muscles. In this study the toxins were injected intradermally and muscular effects were due to diffusion into underlying muscles. However, if diffusion in muscles reflects the diffusion in skin, the results may also be valid when treating muscular disorders.

We decided to evaluate the anhidrotic effect using a planimetric method (iodine-starch test) which measures sweating from the entire palm. A gravimetric test result would also have been useful, but this was declined due to the patients variation of hidrosis between distinct parts of the hand, consequently leading to a risk of misleading results depending on the placement of the measuring probe. The iodine-starch test was not performed before the BTX treatment, since the large amount of sweat produced by many of the patients when untreated would result in only very small differences between the hands concerning the quantity of coloured pixels on the imprints (9). After the BTX treatment, the coloured pixels were fewer, making it possible to distinguish differences in effect between the hands. In conclusion; based on evaluation 4 weeks after intradermal injections, Dysport at 200 U/ml is more potent than Botox at 100 U/ml with regard to anhidrotic effect, neuromuscular effect, and the effect on subjective experience. When treating palmar hyperhidrosis, Botox at 100 U/ml seems to be equipotent to Dysport in a concentration somewhere between 100 U/ml and 150 U/ml. The duration of effect was, however, not investigated and this should be studied further.

Conflict of interest

The drugs used in this study were not sponsored by any company. The patients paid a standard fee at the hospital before treatment. HN has previously received unrestricted grants from Allergan and Ipsen and he has been a member of advisory boards regarding treatment of hyperhidrosis for both companies.

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