Br J Dermatol 2003 Nov;149(5):1041-5

2003112130

Therapeutics

A double-blind, randomized, comparative study of Dysport® vs. Botox® in primary palmar hyperhidrosis

M.SIMONETTA MOREAU, C.CAUHEPE,* J.P.MAGUES* AND J.M.SENARD†

*Fédération de Neurologie and *Département d'Anesthésie, CHU Purpan, place du Dr Baylac, 31059 Toulouse cedex, France*

†INSERM U317, Service de Pharmacologie Clinique, Faculté de Médecine, 37 allées Jules Guesde, 31073 Toulouse cedex, France

Accepted for publication 27 March 2003

Summary

Background Intradermal injections of type A botulinum toxin have been reported to reduce excessive sweating in patients with primary palmar hyperhidrosis. Two preparations are commercially available in Europe: Botox® (Allergan; 100 U per vial) and Dysport® (Beaufour Ipsen Biotech; 500 U per vial), which are not bioequivalent. A few studies have tried to find an appropriate conversion factor between the two preparations in dystonic patients but results remain controversial.

Objectives To compare the efficacy of Botox and Dysport in palmar hyperhidrosis using a conversion factor of 1 : 4.

Methods In a double-blind, randomized study, eight patients with severe primary palmar hyperhidrosis received in the same session intradermal injections of Dysport in one palm and Botox in the other, after regional median and ulnar nerve blocks. Quantification of sweat production was performed by Minor's iodine starch test at baseline, 1, 3 and 6 months after the treatment. Subjective assessment of sweat production was performed using a visual analogue scale.

Results The mean ± SD number of injection sites (28 ± 1), mean volume of reconstituted solution injected (2·8 mL) and mean sweating area at baseline (BSA) were similar in each palm group. The mean ± SD dose injected was 69·3 ± 3·1 U for the Botox-treated palms and 283·7 ± 11·3 U for the Dysport-treated palms (1 : 4). At 1 month, Minor's test revealed significant decreases in mean sweating area for each preparation (Dysport palms: −78·6% vs. BSA, $P = 0{\cdot}0002$; Botox palms: −56·6% vs. BSA, $P = 0{\cdot}003$). The percentage of decrease was more pronounced in Dysport palms compared with Botox palms but the difference did not reach statistical significance. At 3 months, the decrease in sweating area remained significant for Dysport palms (−69·4% vs. BSA, $P = 0{\cdot}008$) but not for Botox palms (−48·8% vs. BSA). Self-evaluation showed a similar amount of improvement in both palm groups at 1 and 3 months (77% and 75% for Dysport; 68% and 72% for Botox). Local side-effects were more frequent in Dysport palms (weakness of thumb–index pinch in four cases, lasting 8–30 days) than in Botox palms (weakness of thumb–index pinch in two cases, lasting 15–21 days). The mean duration of positive effect was similar: 17 weeks in Dysport (range 8–32) and 18 weeks in Botox palms (range 8–32).

Conclusions Using a conversion factor of 1 : 4, the efficacy of Botox and Dysport injections was similar. However, there was a trend towards a larger improvement after Dysport treatment but with a higher incidence of adverse effects.

Key words: botulinum toxin A, intradermal injections, palmar hyperhidrosis

Correspondence: Dr M.Simonetta Moreau.
E-mail: simonetta.m@chu-toulouse.fr

Primary palmar hyperhidrosis (PPH) is a common disorder characterized by excessive sweating of the palmar surface of the hands. It is a disabling condition causing not only social but also psychological and occupational problems. Based on several double-blind, placebo-controlled studies there is now strong evidence for intradermal injections of botulinum toxin (BT) being a treatment of choice in focal axillary hyperhidrosis and PPH.[1–4] Two BT type A preparations are available in Europe: Botox® (Allergan, Mougins Cedex, France; 100 U per vial) and Dysport® (Beaufour Ipsen Biotech, Paris Cedex, France; 500 U per vial), which are not bioequivalent. Some studies have tried to find an appropriate conversion factor between these two preparations in dystonic patients, but with controversial results.[5–10] The aim of this study was to compare the efficacy and tolerability of Botox and Dysport in PPH using a conversion factor of 1 : 4 in a double-blind, randomized design.

Patients and methods

Patients

Eight patients (three men and five women), age range 23–37 years (mean ± SD 30 ± 2) entered the study after informed consent was obtained. The study was approved by the Toulouse II Ethics Committee. All patients had had severe PPH since childhood and were socially and/or professionally handicapped.

Study design

The study followed a double-blind, randomized, comparative design. Each patient received intradermal injections of Botox into one palm and of Dysport into the other in the same session. The 'Botox' and 'Dysport' palms were randomized. Both the patients and the physician performing the injections and follow-up were unaware of the Botox and Dysport sides until the end of the study. The efficacy and tolerability of the two preparations were assessed 1 (M1), 3 (M3) and 6 (M6) months following injection. Allergan and Beaufour Ipsen Biotech supplied the BT but did not design the study, collect, analyse or interpret the data and did not write any part of this report.

Botulinum toxin injections

BT was diluted in 0·9% saline solution to achieve a concentration of 2·5 U per 0·1 mL for Botox and 10 U per 0·1 mL for Dysport preparations, with a 1 : 4 conversion factor. After regional median and ulnar nerve block BT was injected intradermally in 28 ± 1 sites (mean ± SD) in each palm, in the same session, using 1-mL tuberculin syringes and 27G needles. The number of injection sites was similar for each palm in a given patient.

Sweating assessment

To quantify baseline sweating and to compare the effect of Botox and Dysport injections, Minor's iodine starch test[11] was performed prior to (D0) 1 (M1), 3 (M3) and 6 months (M6) following BT injections. A digital photograph of both hands was taken 5 min after powder application and the size of the area that turned purple was measured (i.e. palm sweating area, PSA). Patients were also asked to quantify the intensity of decrease in sweat production using a visual analogue scale of 100 points for each palm (0 = no effect of the treatment on sweating; 100 = total anhidrosis) at M1 and M3 visits (global assessment of treatment satisfaction). Side-effects were documented by a questionnaire.

Results

Comparison of baseline values

No substantial differences were found at baseline between Dysport and Botox palm groups. The mean ± SD PSA (68·4 ± 11·3 cm^2 vs. 70·4 ± 8 cm^2), the mean ± SD number of sites injected per palm (28 ± 1 in both groups) and the mean ± SD volume of solution injected (2·8 ± 0·1 mL in both groups) were similar in Dysport- and Botox-treated palms. The mean ± SD dose injected per palm was 69·3 ± 3·1 U for Botox and 283·7 ± 11·3 U for Dysport, respecting the 1 : 4 ratio.

Objective rating

One month (M1) after BT injection, Minor's test revealed a dramatic decrease in the size of excessive sweating area for each preparation in most patients. The decrease in mean PSA was 76·8% (mean ± SD 14·6 ± 4·6 cm^2) of baseline sweating area (BSA) for the Dysport-treated palms ($P = 0·0002$, paired t-test) and 56·6% (mean ± SD 30·5 ± 9·5 cm^2) of BSA for the Botox-treated palms ($P = 0·003$). The percentage of decrease was more pronounced in the Dysport

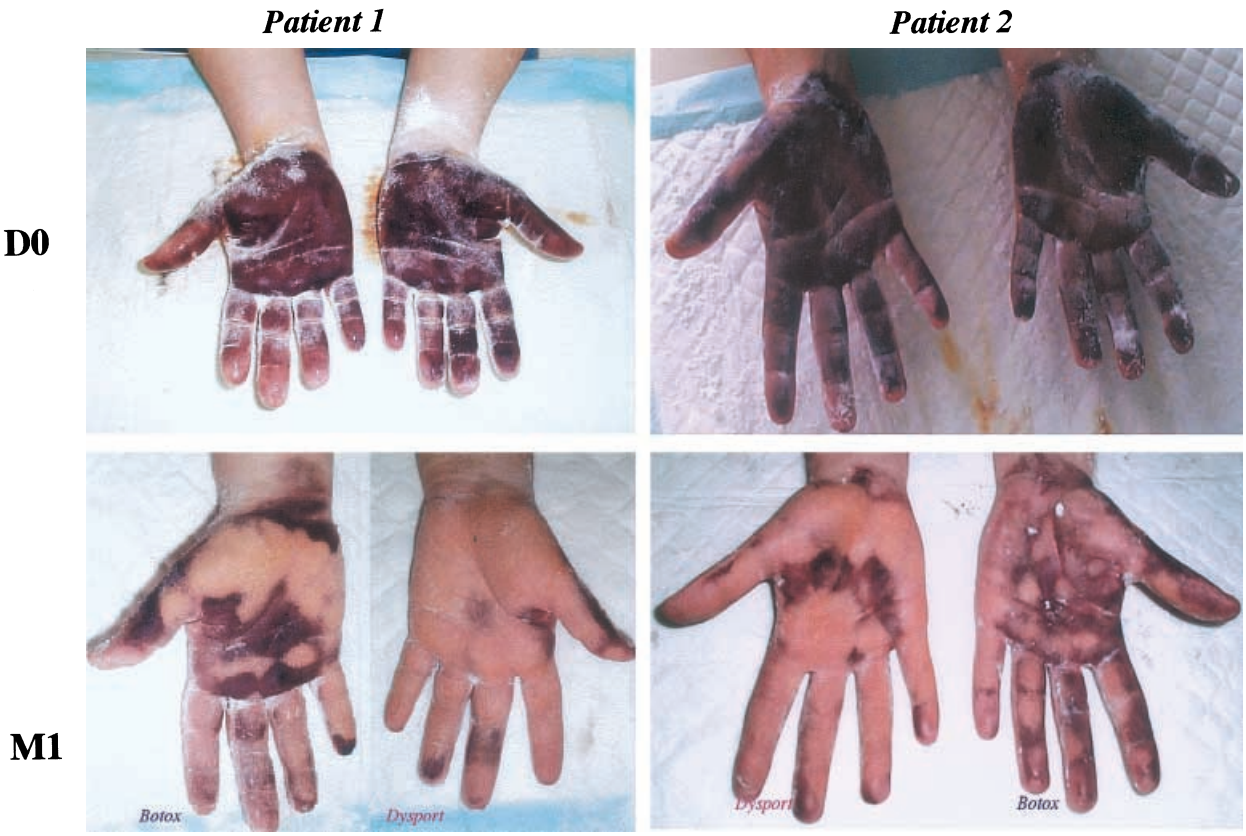

Figure 1. Minor's iodine starch test before (D0) and 1 month (M1) after comparative injections of Botox vs. Dysport type A botulinum toxin. Digital photographs from two patients.

palms compared with the Botox palms but the difference did not reach statistical significance (ANOVA). Digital photographs obtained from the left and right palms of two patients at the baseline (D0) and M1 visits are shown in Figure 1.

Three months (M3) after treatment, the decrease in mean PSA remained significant in Dysport-treated palms (−69·4% vs. BSA, mean ± SD 20·9 ± 11·2 cm^2, $P = 0{\cdot}008$) but not in the Botox-treated palms (−48·8% vs. BSA, mean ± SD 36 ± 16 cm^2, not significant). The difference between the two groups did not reach significance. At the M6 visit, a persistent complete anhidrotic effect was observed bilaterally in two patients, and a partial relapse occurred in two other patients, with a larger percentage of persistent decrease in PSA for the Dysport-treated palm (−85·3%) than for the Botox-treated palm (−37%) in one case and a similar percentage in the other case (−33% and −43%, respectively). Two other patients returned to baseline values and the remaining two patients did not return at the M6 visit. In the six patients who performed Minor's test at M6, the decrease in mean PSA remained significant in the Dysport-treated palms (−56·6% vs. BSA, mean ± SD, 29·7 ± 14·2 cm^2, $P = 0{\cdot}05$) but not in the Botox-treated palms (−51% vs. BSA, mean ± SD, 34·8 ± 14 cm^2, not significant). Results are illustrated in Figure 2.

Subjective rating

Patient satisfaction showed a similar amount of mean improvement at the M1 and M3 visits, regardless of the preparation injected (Fig. 2). The subjective percentage of mean decrease in palm sweating was 77% and 75% (range 20–100%) in the Dysport-treated palms and 68% and 72% (range 20–100%) in the Botox-treated palms at the M1 and M3 visits, respectively. A subjective assessment of the duration of beneficial effect was obtained from all the patients and was similar in both hands: 17 weeks (range 8–32) for Dysport and 18 weeks (range 8–32) for Botox-treated palms.

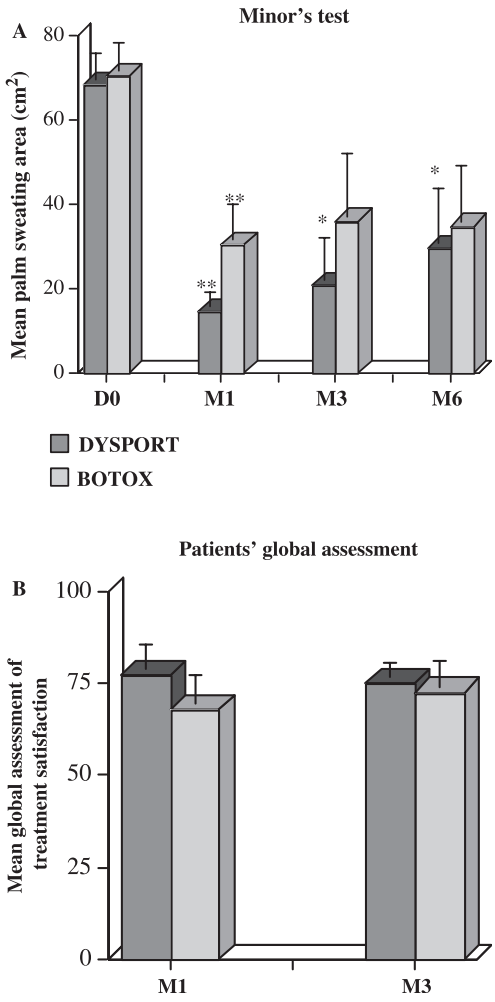

Figure 2. (A) Comparative Botox vs. Dysport mean ± SD palm sweating area (cm^2) assessed by iodine starch test before (D0) and 1 (M1), 3 (M3) and 6 (M6) months after type A botulinum toxin injections. Asterisks indicate the level of significance for the comparison between M1, M3, M6 and baseline (D0), respectively: $^{**}P < 0{\cdot}01$, $^{*}P < 0{\cdot}05$. Differences between Dysport and Botox at M1, M3 and M6 did not reach statistical significance. (B) Comparative Botox vs. Dysport mean ± SD patients' global assessment of treatment satisfaction at M1 and M3 visits (0 = no effect; 100 = complete anhidrosis).

Side-effects

Four patients reported transient thumb–index pinch weakness lasting between 1 and 4 weeks. This side-effect was bilateral in two cases, more pronounced in the Dysport-treated palm in one case and of similar intensity in the other case. Two other patients complained of thumb–index weakness pinch only on the Dysport-treated palm and not on the Botox-treated palm. Another patient complained of right upper limb heaviness lasting 8 days on the side of Dysport injections.

Discussion

Type A BT significantly decreased PPH for at least 2 months in all the patients, regardless of the preparation used. This was demonstrated by objective measurements as well as subjective ratings and confirms the effectiveness of local intradermal injections of BT in reducing PPH. Until now there is no consensus concerning appropriate dose, which ranges from 50 to 240 U per palm for Botox,[4,12,13] and is poorly documented for Dysport in this indication (120–240 U per palm according to Schnider *et al.*[3,14]). The doses used in this study are in the low range of Botox doses previously reported as effective and are higher than those reported for Dysport. Nevertheless, the mean reduction of sweat production area and the patients' satisfaction were in the same range as previously reported (higher than 50%). The range of subjective assessment of duration of beneficial effect was very large (8–32 weeks) among the patients included in this study, but the mean duration of action of 4–5 months was similar to that previously described. The most frequent side-effect (transient minor thumb–index pinch weakness) reported here with an incidence of 50% was similar to that reported in previous studies. The study of Saadia *et al.*[4] suggests that the incidence of hand weakness could be dose dependent. In our study, hand weakness was more frequent in the Dysport-treated palms than in the Botox-treated palms. The higher incidence of adverse effects in the Dysport-treated palms cannot be related to differences in the number of injection sites or in the volume of solution injected in each palm as they were similar in both groups. This greater incidence of side-effects could be due to a higher tendency of Dysport to diffuse within tissues, as suggested by Ranoux *et al.*[10] and Moore.[15]

Previous studies conducted in neurological patients proposed conversion factors between Botox and Dysport ranging from 3 to 6, and this question still remains debated. To date only three randomized controlled studies have tried to answer the question, giving conversion factors of 1 : 4,[8] 1 : 3[9] and < 1 : 3.[10] Palmar hyperhidrosis represents a good model to perform such Botox/Dysport comparative studies in a double-blind, randomized manner and in which each patient acts as his/her own control. With a 1 : 4 ratio, the efficacy of Botox and Dysport injections assessed by Minor's test and subjective ratings was not statistically different, although there was a trend towards a larger improvement after Dysport treatment but with a higher incidence of side-effects. This suggests

that to achieve similar efficacy without differences in incidence of side-effects, either a lower dose of Dysport or a higher dose of Botox should have been used. A conversion factor of 1 : 3·5 or 1 : 3 may be more appropriate than 1 : 4 to obtain more precisely the same amount of decrease of hyperhidrotic area with the same duration of beneficial effect for Botox in comparison with Dysport.

Acknowledgments

This study was supported by grants from Allergan, Beaufour Ipsen Biotech and Toulouse Hospital (no. 0100 203).

References

1 Naumann M, Lowe NJ. Botulinum toxin type A in treatment of bilateral primary axillary hyperhidrosis: randomised, parallel group, double blind, placebo controlled trial. *Br Med J* 2001; **323**: 596–9.
2 Heckman M, Ceballos-Baumann AO, Plewig G. Botulinum toxin type A for axillary hyperhidrosis (excessive sweating). *N Engl J Med* 2001; **344**: 488–93.
3 Schnider P, Binder M, Auff E *et al.* Double blind trial of botulinum A toxin for the treatment of focal hyperhidrosis of the palms. *Br J Dermatol* 1997; **136**: 548–52.
4 Saadia D, Voustianouk A, Wang AK, Kaufmann H. Botulinum toxin type A in primary palmar hyperhidrosis. Randomized, single-blind, two-dose study. *Neurology* 2001; **57**: 2095–9.
5 Brin MF, Blitzer A. Botulinum toxin: dangerous terminology errors. *J R Soc Med* 1993; **86**: 493–4.
6 Marion MH, Sheehy M, Sangla S *et al.* Dose standardisation of botulinum toxin. *J Neurol Neurosurg Psychiatry* 1995; **59**: 102–3.
7 Durif F. Clinical bioequivalence of current commercial preparations of botulinum toxin. *Eur Neurol* 1995; **2**: 17–18.
8 Sampaio C, Ferreira J, Simoes F *et al.* DYSBOT: a single-blind, randomized parallel study to determine whether any differences can be detected in the efficacy and tolerability of two formulations of botulinum toxin A—Dysport and Botox—assuming a ratio of 4 : 1. *Mov Disord* 1997; **12**: 1013–18.
9 Odergren T, Hjaltason H, Kaakkola S *et al.* A double-blind, randomized parallel group study to investigate the dose equivalence of Dysport and Botox in the treatment of cervical dystonia. *J Neurol Neurosurg Psychiatry* 1998; **64**: 6–12.
10 Ranoux D, Gury C, Fondarai J *et al.* Respective potencies of Botox and Dysport: a double blind, randomized, crossover study in cervical dystonia. *J Neurol Neurosurg Psychiatry* 2002; **72**: 459–62.
11 Sato KT, Richardson A, Timm DE, Sato K. One-step iodine starch method for direct visualization of sweating. *Am J Med Sci* 1988; **295**: 528–31.
12 Solomon BA, Hayman R. Botulinum toxin type A therapy for palmar and digital hyperhidrosis. *J Am Acad Dermatol* 2000; **42**: 1026–9.
13 Swartling C, Naver H, Lindberg M. Botulinum A toxin improves life quality in severe primary focal hyperhidrosis. *Eur J Neurol* 2001; **8**: 247–52.
14 Schnider P, Moraru E, Kittler H *et al.* Treatment of focal hyperhidrosis with botulinum toxin type A: long-term follow-up in 61 patients. *Br J Dermatol* 2001; **145**: 289–93.
15 Moore AP. General and clinical aspects of treatment with botulinum toxin. In: *Handbook of Botulinum Toxin Treatment* (Moore P, ed.). Oxford: Blackwell Science, 1995: 28–53.