Current Evidence on the Unit Equivalence of Different Botulinum Neurotoxin A Formulations and Recommendations for Clinical Practice in Dermatology

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BACKGROUND   The unit equivalence between the two main Botulinum neurotoxin A (BoNTA) preparations, Dysport (Ipsen Ltd., Slough, Berkshire, UK) and BOTOX (Allergan Inc., Irvine, CA), is a matter of discussion. The UK assay used to test Dysport is more sensitive than the U.S. assay used for BOTOX, resulting in a different efficacy per unit in both formulations. Ratios ranging from 6:1 to 1:1 can be found in the literature, but the more recently published literature suggests that 1 unit of BOTOX is equivalent to approximately 2 to 4 units of Dysport (ratio 2:1–4:1).

OBJECTIVE   Because the number of BoNTA treatments is constantly increasing, these differences warrant a systematic review of published evidence about the unit equivalence of UK and U.S. formulations.

METHODS   The review is based on a detailed literature research in all relevant databases (MEDLINE, PubMed, Cochrane Library, specialist textbooks).

RESULTS   The present review supports the recent assumption that dose ratios of less than 3:1 (e.g., 2.5:1 or even 2:1) between Dysport and BOTOX are probably more suitable.

CONCLUSIONS   The current evidence is still insufficient, and further investigation of lower dose ratios is recommended.

The authors have indicated no significant interest with commercial supporters.

Even after 15 years of clinical experience, the difference between the potency units of the two main Botulinum neurotoxin A (BoNTA) products, Dysport (Ipsen Ltd., Slough, Berkshire, UK) and BOTOX (Allergan Inc., Irvine, CA), is a source of confusion. Early studies measured dosage in ng of toxin. The first double-blind study of the treatment of torticollis[1] employed 100 units of the original formulation of BOTOX, which was stated to be "equivalent to 40 ng of Botulinum-A toxin." Elston and Lee[2] first switched from BOTOX to Dysport on a 1:1 weight basis (0.312 ng in the extraocular muscles for the treatment of strabismus) and found an unacceptably high frequency of side effects (ptosis and involvement of other eye muscles). Reducing the dose to one-fifth (0.0625 ng) yielded "good effects." Quinn and Hallet[3] warned of the differences in

weight potency and biological potency between the two products in 1989, and Jankovic and Brin[4] stated that the "British toxin" was more potent (40 units/ng) than the American form (2.5 units/ng), which was associated with a higher incidence of side effects.

Progress was made when Schantz and Johnson[5] found that the weight of toxin used was not relevant and that a bioassay, the mouse unit (i.e., the LD50 for mice), ought to be employed. However, this did not solve the problem of comparability of the two products, and Brin and Blitzer[6] pointed out in 1993 that the crucial difference was that of unit potency between the two preparations. They stated that the reasons for this difference were unknown and suggested a dose equivalence of 4:1 to 5:1 mouse

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units based on "a discussion with our European colleagues." The reason for the disparity in relative efficacy (the difference in the diluents used in the mouse assays) was not published until 1994.[7,8]

For the mouse assays used to standardize each batch of Dysport, the toxin is diluted in a phosphate buffer containing gelatine that stabilizes low-concentration toxins, whereas for the BOTOX assay, saline is used as the diluent. Therefore, the assay used for Dysport is more sensitive than the one used for BOTOX. Hambleton and Pickett,[7,8] who measured different samples of BOTOX and Dysport using the two assays, first showed this in 1994. A BOTOX unit was 3.15 times more potent in the Dysport assay, and a Dysport unit was approximately 2.5 times less potent (activity declined to 39.7%) in the saline assay. In the Dysport assay, a unit of BOTOX was equivalent to 2.87 units of Dysport. In the saline assay, one Dysport unit was equivalent to a nominal 0.4 units of BOTOX, suggesting a potency ratio of 1:2.52.[7] The UK National Institute for Biological Standards and Control (NIBSC) organized an extensive international multicenter comparison of laboratory assays using three BoNTA compounds in 10 laboratories in five countries.[9] This independent work by NIBSC confirmed that the unit ratios are similar to those obtained for the marketed products as described by other authors,[7,8,10] but the interlaboratory variation remained substantial even when the same assay protocol was employed.

In addition, the dilution artefact in the saline assay is higher for Dysport than for BOTOX. Presumably this is because a vial of Dysport contains less human serum albumin (0.125 mg) than a vial of BOTOX (0.5 mg) (for comparison of BoNTA products, see Rzany and Zielke[11]). This excipient is added to prevent adsorption of the toxin molecule on syringe surfaces and elsewhere. At high dilutions, Dysport loses more potency than BOTOX,[12] relatively speaking, and this effect can be neutralized by adding serum albumin.[13,14] These complicated and subtle effects remind us that caution should be exercised when interpreting the results of experiments done with nonstandard dilutions and extrapolating them to the clinical situation, especially when they are not relevant to clinical use per se.

The clinical literature on dose equivalence is extensive but confusing, and many published studies are not of high quality. A recently published review[15] identified just four key articles on head-to-head comparison of Dysport and BOTOX that are of sufficient quality to fulfill the criteria of evidence-based medicine. In these studies, unit ratios of 4:1 and 3:1 were tested in patients with blepharospasm or torticollis, and the joint conclusion was that 3:1 is more appropriate than 4:1 but that the two products are not equivalent at this ratio. Despite this, ratios of 4:1 or even higher are still accepted, and articles supporting higher ratios have been published recently,[16,17] although these are not head-to-head controlled trials.

A sound understanding of dosage relationships between Dysport and BOTOX is required to optimize treatment in terms of efficacy and safety, and the repercussions of these relationships are substantial. Therefore, we decided to analyze the current literature to find evidence of the most appropriate dosage ratio of the two BoNTA formulations under discussion.

Methods

This review is based on a detailed literature research in all relevant databases: MEDLINE (National Library of Medicine), PubMed (National Library of Medicine), the Cochrane Library, and specialist textbooks. Selected key words were: "BONTA" or "BOTULINUM TOXIN TYPE A" and "POTENCY" (11 hits), "BONTA" or "BOTULINUM TOXIN TYPE A" and "DYSPORT" and "BOTOX" (13 hits), "BONTA" or "BOTULINUM TOXIN TYPE A" and "DOSE-RESPONSE RELATIONSHIP" and "COMPARATIVE STUDY" (64 hits). Published material on the question of dosage equivalence of Dysport and BOTOX was weighed according to the standards of evidence-based medicine as outlined by Sackett and

TABLE 1. Level of Evidence (According to Sackett et al.[18]) of the Studies Quoted in ''Results''

Evidence level	Explanation	Studies
Ia	Systematic review (SR) of randomized controlled trials (RCTs) with homogeneity	Sampaio et al.[15], Rzany and Nast[23]
Ib	RCT with narrow confidence interval	Carruthers et al.[19,27,28,30], Karsai et al.[21], Monheit et al.[24], Ascher et al.[26], Rzany et al.[29], Ranoux et al.[31], Odergren et al.[33], Poewe et al.[34], Simonetta-Moreau et al.[38], Talarico-Filho et al.[40], Wohlfarth et al.[43]
IIa	SR of cohort studies (CS) with homogeneity	Sesardic et al.[9], Poewe,[32] Rosales et al.[45]
IIb	Individual CS or low-quality RCT	Bihari,[16] Lowe et al.[22], Brisinda et al.[35], Sampaio et al.[36], Nüßgens and Roggenkämper,[37] Trindade de Almeida et al.[39], Hexsel,[41] de Almeida et al.[42]
IIc	''Outcomes'' research	Marchetti et al.[17], Heckmann and Schön-Hupka,[25] Van den Bergh and Lison,[44] Rosales et al.[45]
V	Expert opinion	Hambleton and Pickett,[7] Rzany and Zielke,[11] Sommer et al.[20]

SR, systematic review; RCT, randomized controlled trial; CI, confidence interval; CS, cohort study.

colleagues.[18] (Results of a randomized controlled trial with a valid blinding scheme will be considered more meaningful than simple outcome observations or expert opinions.) The level of evidence of the studies quoted in "Results" is shown in Table 1.

Results are briefly reviewed in chapters dealing with the different indications of BoNTA treatment.

Results

Cosmetic Applications (Hyperfunctional Lines)

The majority of clinical trials recommend a unit equivalence of 3:1 based on the aforementioned Cochrane review.[15] This ratio consistently yields favorable results with low toxicity in the treatment of forehead wrinkles.[19,20]

In a randomized controlled double-blind "split-face" trial,[21] a dosage scheme of 3:1 yielded more pronounced effects of Dysport than of BOTOX in the treatment of hyperfunctional forehead lines. At this ratio, the inhibition of electromyographic activity and the clinical effect were more prolonged after treatment with Dysport. This makes studies on lower conversion ratios of 2.5:1 or even 2:1 appro-priate and promising. Also, the manufacturer's recommended doses in Germany (50 U for Dysport and 20 U for BOTOX) suggest that a 2.5:1 dose conversion ratio is more appropriate.

By contrast, Lowe and colleagues recently published a study in which the effect of Dysport was less sustained than that of BOTOX in a 2.5:1 dosage regimen.[22] However, there are some points in this study that render its results questionable. The effect of BOTOX apparently *increased* later in the observation period, which has not been observed in any other study or in clinical practice. This might not be a drug-related effect but could instead be due to variability of the clinical scoring method used, and this weakens the conclusions of Lowe and colleagues substantially.[23]

According to a Phase II Food and Drug Administration trial of Dysport in the treatment of glabellar lines, a dosage of as low as 20 U is effective in most cases, supporting a unit equivalence of 2.5:1.[24] These results are in accordance with a previous independent trial;[25] nonetheless, higher dosages of 50 U have been employed frequently (e.g., Ascher and colleagues[26]). According to dose-ranging studies by Carruthers and colleagues,[19,27,28] the minimum

effective dosage of BOTOX is 20 U in women and 40 U in men, supporting a possible unit equivalence below 2:1.

Basically, whatever the rating method or product used, the results of all published studies are remarkably similar.[24,26,29,30] Peak effect was seen 2 to 4 weeks after injection, followed by a slow decline over the next 12 to 16 weeks. It has also been clearly demonstrated that, for a variety of indications, a conversion ratio of at least "no more than 3:1" may be assumed for Dysport.[31–35]

Diseases with Muscle Hypertonus

In an early study on the treatment of blepharospasm and hemifacial spasm, Sampaio and colleagues[36] found no difference between efficacy and safety of Dysport and BOTOX in a 4:1 dosage ratio; other ratios were not tested. The more extensive crossover (each patient receiving both treatments) study of Nüßgens and Roggenkämper[37] showed that the effect of BOTOX at this 4:1 ratio lasted marginally longer (not significant) but that this was at the cost of statistically significantly more side effects, particularly ptosis ($P = .01$).

Odergren and colleagues[33] investigated a 3:1 dose ratio in patients with cervical dystonia. The differences in responder rates, duration of effect, and assessment of efficacy rates were not statistically significant, and the authors concluded that 3 Dysport units were equivalent to 1 BOTOX unit in clinical use.

More recently, Ranoux and colleagues[31] treated 60 cervical dystonia patients in a double-blind, randomized crossover study with 4:1 and 3:1 dose ratios. Dysport was significantly more effective than BOTOX not only at 4:1 (Tsui score, Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) pain score, duration of action) but also at 3:1 (Tsui score, TWSTRS pain score). Side effects, particularly swallowing disturbances, were higher with Dysport, significantly so ($P = .03$) for the 4:1 dose. The

authors and Poewe[32] concluded that the conversion ratio between the two products should be less than 3:1 in clinical use.

These four studies are the only ones that fulfilled the Cochrane criteria for evidence-based medicine. Although the authors of these studies all concluded that the effects of the two products were equivalent, the effects and side effects of Dysport were consistently higher in all four studies and at both dose ratios. These differences were not statistically significant but strongly suggest that even 3:1 is still too high a conversion ratio. Sampaio and colleagues themselves concluded that 3:1 was more appropriate than 4:1 but that the products were not equivalent at this ratio.

In treatment of anal fissures, Brisinda and colleagues[35] found no difference in efficacy and toxicity of Dysport and BOTOX in 100 patients employing a 3:1 unit equivalence. By contrast, Bihari[16] found a higher efficacy of BOTOX after a switch from Dysport at a 4:1 or even 5:1 dosage ratio in a cohort of 48 patients with blepharospasm, cervical dystonia, or hemifacial spasm. Quite astoundingly, the rate of side effects was higher with Dysport. A few methodological questions have to be mentioned in a critical light: First, the patients were a sample from a population of undefined size. The background of the study was the temporary nonavailability of Dysport in Hungary, and patients were offered the choice of switching to BOTOX or waiting until Dysport became available again. The number of patients who opted for the latter is undisclosed, as is the number of patients who opted for BOTOX but refused to participate in the study. Moreover, the absolute point differences in TWSTRS pain score are analyzed without information about the baseline values, making it hard to judge the extent of improvement objectively. Clinical improvement was exclusively scored according to the patients' subjective assessment.

In the "REAL DOSE" study,[17] the switch between both BoNTA preparations in treatment of cervical

dystonia and blepharospasm followed a conversion ratio of less than 4:1 in only 21% of 114 cases, and a ratio of less than 3:1 was not reported; the average ratio was 4.7:1. The dose ratios, however, varied remarkably between participating centers, ranging from 5.3:1 (UK) to 3.8:1 (Czech Republic) for cervical dystonia and from 4.5:1 (Poland) to 2.8:1 (Norway) for blepharospasm, indicating substantial variation in dosage-finding strategies.

Hyperhidrosis

Based on a 4:1 conversion factor, Simonetta-Moreau and colleagues[38] found a higher efficacy of Dysport in palmar hyperhidrosis. This was paired with a somewhat higher toxicity (weakness of thumb-index pinch), indicating that a lower ratio would be preferable.

A recent study analyzing the anhidrotic area in 20 patients with forehead hyperhidrosis[39] suggested a greater diffusion area of Dysport, possibly hindering the exact localization of the desired effect. As an "accompanying result," the study failed to demonstrate differences in efficacy between both formulations at ratios of 2.5:1, 3:1, and 4:1, suggesting that a ratio of 2.5:1 is at least equipotent.

Finally, Talarico-Filho and colleagues[40] found no difference in efficacy at a 3:1 ratio in the treatment of axillary hyperhidrosis in 10 patients.

Experimental Evidence

Preliminary data on "action halos"[41,42] (i.e., anhidrotic circles around the site of injection) seen in the forehead of human subjects support a ratio of less than 3:1. This is also the case in another human model, the Extensor Digitorum Brevis compound action potential, on which an extensive series of comparative measurements was recently performed.[43] These data have only been published as abstracts, but they suggest a dose conversion ratio of 2:1 or less.

The mouse assay data also generally corroborate a dose conversion ratio of less than 3:1. Calculating

dose ratios across all studies cited[7,9,44] yields dose ratios of between 1.7 and 3.2:1. Experiments performed by the manufacturers of BOTOX using the mouse Digital Abduction Score (DAS) model have found the LD50 ratio to be approximately 2:1. In these experiments, the efficacy ratio was higher— approximately 4:1. This has been interpreted as showing different safety margins for the two products, but these results have not been confirmed independently. Rosales and colleagues[45] did DAS experiments in rats and found a ratio of 2.5:1 for efficacy and diffusion into the thigh muscle.

Discussion

The effect of BoNTA as a muscle-relaxing agent is undisputed in cosmetic and medical settings. As outlined in the introduction, once physicians realized that there was a difference in unit potency between the two BoNTA assays, a conversion factor of 4 to 5:1 was assumed. This thought has proved surprisingly persistent, despite the fact that extensive comparison of the assays in different laboratories and comparative clinical trials conducted in accordance with Cochrane standards of evidence-based medicine suggest that 3:1 is a more appropriate conversion ratio. However, lower ratios have not yet been tested in such head-to-head trials, and the data from these studies indicate that 3:1 is still too high. The overwhelming majority of published studies support this ratio as a "ceiling," and it should not be exceeded. Instead, a lower ratio of 2.5:1 or even 2:1 deserves further research, because present evidence suggests that this is probably sufficient in terms of efficacy and should therefore be preferred because of lower treatment cost and a broader safety margin. Also, a meta-analysis[15] has shown that the two formulations are not bioequivalent regardless of the dose relationship and that Dysport and BOTOX have intrinsic differences that need to be elucidated in further studies.

In the highly elective environment of forehead line treatment, clinical trials should be designed to be on the safe side in terms of treatment tolerability. It is certainly more acceptable to achieve a less-than-

perfect effect than to induce side effects, which can be substantial with a biologically highly active substance such as BoNTA. This further supports the aforementioned recommendation of future trials with dosage ratios of 2.5:1 or even 2:1.

Proper use of Dysport involves a learning curve even (or especially) for experienced BOTOX injectors, which will slow its implementation on a large scale unless the cost difference significantly favors Dysport. Studies sponsored by the manufacturers of BOTOX tend to support higher ratios, and those sponsored by the manufacturers of Dysport consistently support lower ratios. The reason for this bias might simply be financial: The higher the ratio, the lower the cost benefit when Dysport is used instead of BOTOX. Because cosmetic treatment is not covered by any health care system but is paid for by the patient, the price of the drug is an important issue. This is especially true because the huge American market—to date the domain of BOTOX, which has FDA approval for "temporary improvement in the appearance of moderate to severe glabellar lines in adult patients ≤65 years of age"[46] —may soon be opened to Dysport, whose approval is still pending (The product is commonly referred to as Reloxin in the United States and Dysport for medical and aesthetic markets outside the United States.) Bearing this in mind, published results have to be discussed carefully and critically, especially in studies that are affiliated with the manufacturers of either product.

Whatever the product or indication, the BoNTA dosage applied is critical. The dose efficacy curve is a classic parabola,[47] and at the top of this curve, administering more toxin will not create a proportionately greater effect. The excess toxin will, however, diffuse away from the site of application and increase the risk of side effects. The principle of "as much as needed, but as little as possible" should always be borne in mind. This approach maximizes therapeutic efficacy, reduces the risk of side effects and antibody formation, and last but not least, minimizes treatment costs.

Finally, we should ask whether the results in the treatment model of frown lines and wrinkles are applicable to use in other indications, such as dystonia. There are several factors that should be taken into consideration: tolerances of potencies of the vials (as discussed), different potencies in muscles and in skin, differences in dose-response curves between small doses per injection site (cosmetic indications, blepharospasm, and hyperhidrosis) and high doses (spasticity, torticollis). In our opinion, however, the dose conversion ratio between the two products is primarily a function of the different assays used, and there must be a single ratio within the limits of experimental error. It should always be kept in mind that the permitted tolerances for the potency of a BoNTA preparation is ± 20% to 25% according to the European Pharmacopeia. Given this standard, any differences in ratios for different muscle groups might be due to suboptimal application techniques—and the evidence that such ratios actually exist is spurious. The best dilution and positioning of the injections are all factors that should be optimized for any target muscle group. It has also been claimed that the two products have different diffusion characteristics,[39] but in our opinion, this is a dosing artefact due to the continued tendency to give relatively high doses of Dysport, presumably because of the historical development outlined above. A recent review of head-to-head, randomized controlled trials[15] concluded that Dysport tends to have greater efficacy, longer duration, and greater frequency of adverse effects—a possible indication that relatively high doses of Dysport are being used. To resolve this matter, the current approach to titrating dosage—which the majority of trials follow —is not suitable. Randomized controlled double-blind head-to-head comparisons employing fixed dosage schemes (e.g., 3:1, 2.5:1, 2:1) are needed.

Further head-to-head controlled trials comparing dose ratios lower than 3:1 certainly appear to be justified according to the current evidence, and we recommend the double-blind split-face study design (as employed by Karsai and colleagues[21] recently) as an easily accessible human model that is nearer the

clinical situation than the DAS test and easier to perform than the Extensor Digitorum Brevis compound action potential test.

For the time being, the avoidance of side effects may dictate an individual dosing scheme starting with the lowest possible dose and upward titration (if necessary) until reliable information of dosage ratios between Dysport and BOTOX becomes available.

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