Migration Characteristics of Botulinum Neurotoxins

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Botulinum neurotoxin products are originated, manufactured, and formulated by different methodologies; thus, these different agents cannot be used interchangeably. One difference resulting from these manufacturing and formulation differences is the size and consistency of botulinum neurotoxin complexes, with some products exhibiting higher and more consistent molecular weight than others. Molecular weight is physiologically related to product migration or diffusion: all other factors being equal, the higher the molecular weight, the lower the rate of diffusion. This may have clinical implications in terms of efficacy (ie, products staying concentrated where placed) and safety (ie, the potential for products to leak into surrounding untargeted tissues or into the systemic circulation).

A number of different therapeutic botulinum neurotoxin type A (BoNTA) products are available worldwide. These include Botox® Cosmetic, available in the United States and Europe; Dysport®, available outside the United States; Xeomin®, available only in Germany; and Chinese BoNTA, available in some countries around the world and marketed as Prosigne® in South America. No studies have been published on the aesthetic use of Xeomin or Prosigne. Myobloc® is a botulinum neurotoxin type B agent that is approved for therapeutic use but not for aesthetic indications in the United States; it is sold as NeuroBloc in other countries. These products—even those of the same serotype (eg, BoNTA)—are not generic equivalents and are not interchangeable; instead, each is unique with its own individual profile.[1,2]

A number of factors contribute to the distinctive quality of each botulinum neurotoxin (BoNT) product. Different bacterial strains and purification and manufacturing procedures are used.[2] In addition, varying potency assessments are used in determining units of activity.[2] These differences in manufacturing and assay procedures have the potential to directly affect the potency, antigenicity, and migration of each agent.[2] Efforts to develop a simple dose ratio for converting products have been problematic, with different clinical studies identifying different dose ratios.[1,2]

In North America, only one BoNTA product is currently available for cosmetic indications (Botox), but others are seeking regulatory approval, are under investigation, and are in development. Given the future availability of additional products, it is beneficial to cosmetic dermatologists to understand the differences among agents and how they relate to clinical outcomes based on current evidence.

DIFFERENCES IN MIGRATION CHARACTERISTICS

Preclinical studies in the gastrocnemius muscles in mice have demonstrated that the various BoNT products have different propensities to migrate from the site of injection and cause muscle weakening.[1,3,4] These studies suggest that the safety margins (separation between an effective dose and one that leaks from the treated muscle to cause a systemic effect) and diffusion margins (ratio of threshold dose [the lowest dose causing quadriceps muscle atrophy compared with the contralateral quadriceps] to median effective dose) of the various BoNT agents are as follows: those of Botox are greater than those of Dysport, which in turn are greater than those of Myobloc.[1] Thus, at least experimentally, at doses causing desired muscle-weakening effects, Botox is less likely to migrate from the site of injection (ie, gastrocnemius) than Dysport or Myobloc. When one extrapolates these findings to human facial use, migration away from the site of BoNT injection in facial aesthetics may result in the development of adverse effects (AEs) such as lid ptosis. Clinical observations relating to the migration potential

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of BoNTs in dermatologic models are discussed in the following section.

CLINICAL STUDIES OF MIGRATION

Trindade de Almeida et al[5] recently reported the results of a double-blind, randomized, intrapatient-controlled pilot study comparing the diffusion characteristics of 2 BoNTA formulations in patients with forehead hyperhidrosis (N=20). Patients received 2 Botox injections (1 medial and 1 lateral) at a dose of 3 U per injection administered to one randomly selected side of the forehead, and 2 Dysport injections (1 medial, 1 lateral) at a Botox:Dysport dose ratio of 1:2.5, 1:3, or 1:4 (Dysport doses of 7.5, 9, or 12 U/injection) administered to the other side of the forehead. Volume was constant across all injections (0.06 mL). Iodine and starch were used to delineate the area of anhidrosis, with quantitative measures determined through standardized photography (identical camera settings, lighting, and patient positioning with a stabilizing headset and centimeter rule) and computer software (Canfield Mirror DPS Imaging System).

Over the 6-month observation period, the area of anhidrosis (the sum of medial and lateral halo areas) was larger with Dysport than with Botox in 92.9% (195 of 210) of medial-medial or lateral-lateral comparisons of the 2 products.[5] The area by which the mean halo area with Dysport exceeded the mean halo area with Botox from 1 week to 6 months posttreatment was significantly greater for all dose ratios ($P \leq .01$ with 1:2.5 ratio and $P \leq .001$ for the 1:3 and 1:4 dose ratios) (Figure 1).

The smaller area of anhidrosis with Botox appeared to be independent of inhibition of muscular contraction (eg, frontalis muscle relaxation).[5] In the 12 patients with relatively symmetrical forehead wrinkles, the smaller area of anhidrosis with Botox did not compromise its efficacy in inhibiting contraction of the frontalis muscle.

Cliff and Judodihardjo[6] recently completed a study similar in design to the one by Trindade de Almeida et al.[5] The results of the former support the findings of the latter. Fourteen days following injection of Botox 4 U and Dysport 12 U into different sides of the forehead in 12 healthy volunteers, significantly larger mean halo areas were observed with Dysport than with Botox ($P<.005$).[6] Areas in the center of the forehead injected with saline control exhibited no anhidrosis.

The migration characteristics of Botox were compared with those of Myobloc in 8 patients with symmetrical moderate to severe forehead wrinkles at full contracture.[7] Patients received Botox 5 U intramuscularly on one side of the frontalis and Myobloc 500 U on the other side (1:100 Botox: Myobloc dose ratio). The radius of toxin diffusion,

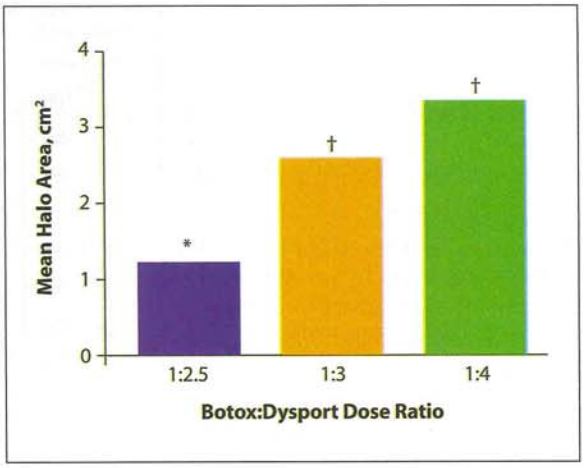

Figure 1. Comparison of the migration patterns of 2 types of botulinum neurotoxin type A in a model of forehead. Area by which the mean halo area with Dysport® exceeded the mean halo area with Botox® Cosmetic (from week 1 to month 6) is shown. Asterisk indicates $P<.01$; dagger indicates $P<.001$ versus no difference in halo area. Reprinted from Trindade de Almeida AR, Marques E, de Almeida J, Cunha T, Boraso R.[5] Pilot study comparing the diffusion of two formulations of botulinum toxin type A in patients with forehead hyperhidrosis. *Dermatol Surg.* 2007;33(1 Spec. No.):S37-S43, with permission from Blackwell Publishing.

measured calculating the wrinkle reduction area by digital micrometer on traced scanned images, was consistently larger with Myobloc. The onset of action was faster with Myobloc than with Botox. Other studies have noted a shorter duration of effect with Myobloc—about half as long as that of Botox—and that Myobloc is associated with more discomfort on injection; these factors limit the overall clinical utility of Myobloc for aesthetic purposes.[8-10]

CLINICAL STUDIES OF BoNTA IN FACIAL REJUVENATION

Few clinical trials have compared the efficacy and safety of different BoNTA formulations for the aesthetic treatment of facial lines.[11,12] In a recent study (N=62), patients with moderate to severe glabellar lines were randomized to receive double-blind 20 U Botox or 50 U Dysport (Botox:Dysport dose ratio of 1:2.5).[11] All injections were 0.1 mL in volume. Five injection points were used, with 20% of the dose injected into the procerus (1 injection) and 80% injected into the corrugator muscles (2 injections/side). At each visit, patients were photographed, and the severity of glabellar lines during maximal attempted muscle contraction was subsequently graded by blinded investigators on a 4-point scale ("none," "mild," "moderate," or "severe").

The incidence of at least 1-grade improvement versus baseline in glabellar line severity was highest at 8 weeks posttreatment in both groups (Figure 2).[11]

The duration of this improvement, however, was significantly longer with Botox than with Dysport (Figure 2). Both Botox and Dysport were well tolerated, with no significant between-group differences in terms of AEs. However, the small sample size limits the broader applicability of results to the general population.

An even smaller and uncontrolled study compared the effects of Botox with those of Dysport at a 1:4 dose ratio in 20 patients for various facial lines.[12] Fourteen patients received Botox 5 to 20 U, and 6 received Dysport 20 to 100 U. Wrinkle reduction was similar between groups during the posttreatment follow-up period, although the rate of AEs was significantly greater with Dysport (all patients) than with Botox (5 of 14 [35.7%]; $P<.05$). No lid ptosis occurred during treatment, and no patients complained of an "unnatural look."

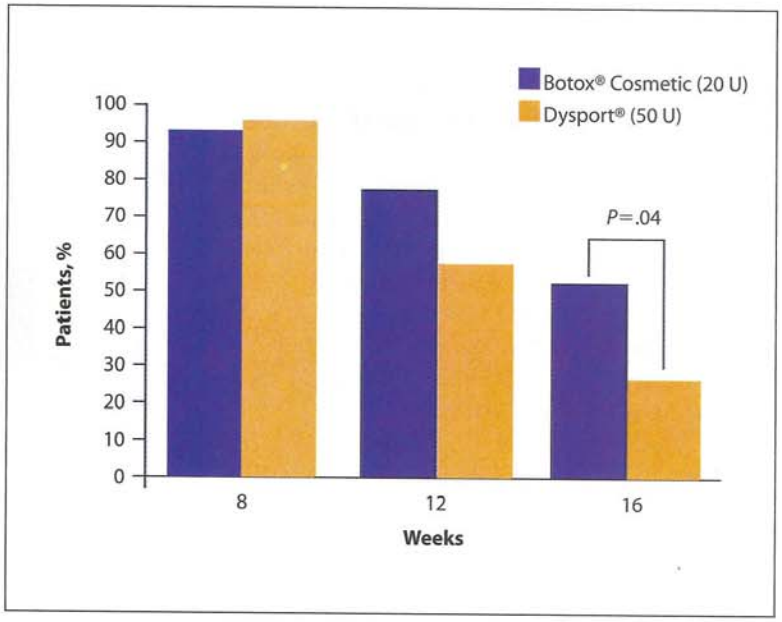

Figure 2. Incidence of at least 1-grade improvement from baseline in glabellar line severity at maximum contraction for patients treated with botulinum neurotoxin type A. Reprinted from *J Am Acad Dermatol,* vol. 55, Lowe P, Patnaik R, Lowe N,[11] Comparison of two formulations of botulinum toxin type A for the treatment of glabellar lines: a double-blind, randomized study, Copyright (2006), with permission from the American Academy of Dermatology, Inc.

The comparable efficacy but higher AE rate also was observed when Botox was compared with Dysport in a randomized, double-blind comparison for the treatment of essential blepharospasm.[13] In this study, 212 consecutive patients received 1 injection of Botox (average dose, 45.4 U) and 1 injection of Dysport (average dose, 182.1 U) at 2 separate treatment sessions (the order of product administration was randomized).[13] Thus, the Botox:Dysport patient dose ratio was 1:4. The duration of effect was similar between groups (8 weeks; $P=.42$).[13] However, there were significantly fewer AEs with Botox than Dysport treatment. This was true both for total AEs (lid ptosis, blurred vision, double vision, hematoma, and foreign body sensation; $P<.05$) and for lid ptosis alone ($P<.01$).

These clinical data are in line with those of preclinical and clinical models of migration by further supporting the notion that the BoNTAs behave differently and cannot be easily converted from one dose to another using a simple dose ratio. Additional data and experience are needed to determine whether any meaningful differences exist among agents in terms of outcomes in the aesthetic clinical setting.

RATIONALE FOR VARYING MIGRATION CHARACTERISTICS: POTENTIAL ROLE OF MOLECULAR STRUCTURE

Differences in the migration characteristics of the various BoNT agents may be the result of their unique purification and manufacturing processes, which give rise to varying physicochemical attributes. It has been postulated that the size and uniformity variations in the BoNT complex among the products may account for the migration findings.[1,14] In culture, all BoNTs exist as 150-kDa toxins surrounded by nontoxin proteins to form complexes ranging in size from 300 kDa to 900 kDa (Figure 3).[15] Botox is composed of a uniform mixture of 900-kDa complex sizes.[3,16] Published studies suggest that Dysport exhibits more heterogeneity, with toxin complex sizes ranging from 500 to 900 KDa.[14,17] The toxin complex size of Myobloc has been estimated at 700 kDa.[18]

One of the basic physicochemical tenets of diffusion is that the greater the molecular weight of the particle, the more slowly it diffuses through an equivalent aqueous medium (assuming that charge, temperature, and general molecular structure remain constant), as the larger size is a hindrance to diffusion.[1] Thus, it would be expected that different BoNTs would differ in their diffusion rates according to molecular weight (ie, those with toxin complex sizes of higher molecular weights would diffuse out of the targeted tissue to a lesser degree than those with toxin complexes of lower molecular weights).[1] According to this theory, Botox would be less likely to migrate from the site of injection than Myobloc or Dysport. This theory remains to be confirmed with other BoNT formulations.

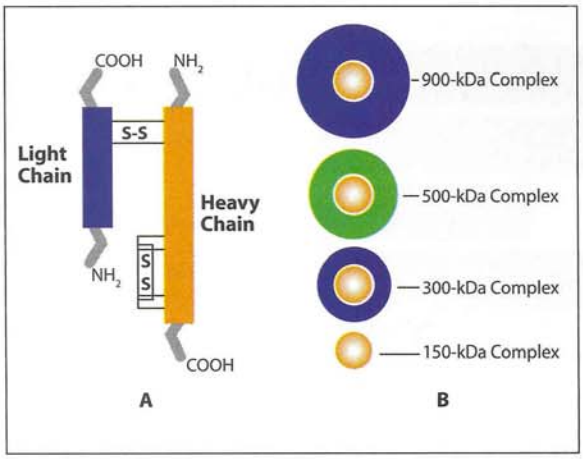

Figure 3. Schematic representation of the botulinum toxin molecule (A). It exists as a 150-kDa structure surrounded by nontoxin proteins to form complexes (B). Toxin complexes range in size from 300 kDa to 900 kDa.

COMMENT

BoNT products are not interchangeable; rather, each should be treated as a unique entity with its own dosing parameters, migration potential, and duration of effect. Both the bulk drug substance and formulation of each BoNT agent differ in a number of ways, such as size and consistency of size of the BoNT complex, excipients used in the formulation, and pH. These differences may influence the clinical profile of the product, in terms of both efficacy and safety.

Differences in migration characteristics among the BoNTA products are likely attributable to differences in size and uniformity of size of the toxin complexes, with higher and more uniform molecular weight complexes physicochemically associated with a slower and more predictable diffusion pattern. This notion remains to be confirmed with other BoNT formulations. These issues may be of interest when selecting BoNTA preparations for cosmetic dermatology applications.

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