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ORIGINAL ARTICLE

Diffusion characteristics of botulinum neurotoxin products and their clinical significance in cosmetic applications

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Abstract
Over the past decade, growth in the number and types of aesthetic procedures performed using botulinum neurotoxin has increased, along with the number of these products. As more options, along with emerging counterfeit agents, become available to clinicians, differences among preparations need to be considered in order to ensure optimal outcomes for patients. Once injected into the muscle, botulinum neurotoxin distributes within that tissue to produce the desired local effects. Diffusion, or the distribution of product beyond the target muscle, can be of concern because of the potential for local and systemic effects that result in muscle weakening away from the desired site. Several factors influence diffusion, including preparation characteristics (e.g. molecular size and structure), dosing and injection technique, and muscles injected. In this article, we discuss the accumulating preclinical and clinical data that differentiate botulinum neurotoxin agents with respect to their diffusion characteristics.

Key words: *botulinum neurotoxin, diffusion characteristics, injection techniques, safety margin, therapeutic margin*

Introduction

Since 1992, when the first article demonstrating the effectiveness of botulinum neurotoxin in reducing glabellar frown lines (1) appeared in the medical literature, the aesthetic use of the toxin has grown, both in the number and variety of procedures performed. Although BOTOX® (also known as Vistabel® and Vistabex®, Allergan, Inc., Irvine, CA, USA) remains the most studied agent, over the past decade several other products have been approved for therapeutic and/or aesthetic use in various countries. Our experiences with these preparations are based on those available in the areas in which we practice. For example, in Brazil and South America, the botulinum neurotoxin marketplace consists of BOTOX, Dysport® (Ipsen Limited, Slough, UK), and Prosigne (Lanzhou Institute of Biological Products, Lanzhou, China), all botulinum neurotoxin type A products. In Belgium and in Europe in general, BOTOX and Dysport are the available botulinum neurotoxin type A products, and Myobloc®, also known as NeuroBloc® (Solstice Neurosciences, South San Francisco, CA, USA), is the botulinum neurotoxin type B product. While effective for facial lines, botulinum neurotoxin type B is not as popular as type A for this indication because of its shorter duration of action (2,3). Xeomin® (Merz Pharmaceuticals, Frankfurt, Germany), another type A product, is available in Germany only.

Counterfeit or unapproved agents also have permeated the numerous markets worldwide, advertising both to clinicians and the general public. Unlike approved botulinum neurotoxins, these preparations are not supported by the medical literature, making claims of efficacy and safety impossible to verify. More importantly, clinicians who use these products may be placing patients at risk for potentially devastating consequences. The availability of unapproved or counterfeit agents highlights the issue of safety and raises important questions about the accuracy of information provided to physicians concerning botulinum neurotoxins and cosmetic use.

Each botulinum product is purified and manufactured using proprietary processes, resulting in unique, noninterchangeable agents that differ in such features as molecular weight, uniformity of toxin complex size, protein content, and the presence of inactive ingredients. These differences can manifest as variations in performance characteristics including potency; duration of effect; adverse

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event profile; and diffusion, which can further affect the product's adverse event profile. Indeed, it is well established that the various preparations are of different unit potencies, prohibiting equivalent dosing or conversion using a fixed dose ratio.

Of considerable pharmacologic interest among the botulinum neurotoxins are their varying diffusion, or migration, profiles; these have become the focus of much recent research (4–7). Once injected into a muscle, botulinum neurotoxin is distributed within that tissue for the desired pharmacologic effect. However, the potential exists for the neurotoxin to diffuse outward, away from the target tissue. Such diffusion can cause muscle-weakening effects outside of the desired targeted area, leading to unwanted local effects or possible leakage into the systemic circulation. For example, generalized muscle weakness of the limbs and other muscles has been reported following treatment of cervical dystonia using botulinum neurotoxin (8,9). In the case of aesthetic use of botulinum neurotoxin, diffusion away from the targeted muscle could potentially result in ptosis, heavy brow, or a frozen look. In this article, we discuss the accumulating body of evidence that characterizes the varying diffusion characteristics between the different botulinum neurotoxin products and the clinical application of neurotoxin diffusion in aesthetic practice.

Distribution and diffusion

The distribution of botulinum neurotoxins within the injected target muscle and, consequently, diffusion outside the target muscle depend on a number of factors, including the structure of the molecule, injection technique (i.e. volume of injection, dose, use of massage following injection), intrinsic properties of the formulation (e.g. protein load), and muscle injected (6,10). In this article, we focus on the factors that may influence distribution and diffusion of botulinum neurotoxins when used in the small muscles of the face.

Molecular size and structure

In culture, botulinum neurotoxins exist as 150-kDa toxins surrounded by nontoxic proteins, which impart stability and protect against degradation to form complexes (11). Botulinum neurotoxin type A forms complexes of 300 kDa, 500 kDa, and 900 kDa (11). The BOTOX product consists of uniformly sized complexes of 900 kDa (12). Conversely, Dysport is composed of a heterogeneous mixture of 500–900 kDa complexes (13). The toxin complex size of Myobloc has been determined to be approximately 700 kDa (14). In a recent review, Foster et al. (6) described the impact of botulinum neurotoxin complex size on diffusion potential. Based on the basic principle that larger proteins diffuse more slowly through an identical aqueous medium compared with smaller proteins, it would be predicted that botulinum neurotoxins of greater size or molecular weight will be less likely to diffuse outside the target tissue compared with those of smaller size. Thus, BOTOX, composed of uniform 900 kDa complexes, would be less likely to diffuse outside the target tissue compared with Dysport (a heterogeneous mixture of 500–900 kDa complex sizes) and Myobloc (700 kDa).

Product differences: preclinical observations

The diffusion potentials of BOTOX, Dysport, and Myobloc have been characterized in several preclinical studies that have considered the influence of dose on the extent of diffusion (4–6). The studies used the Digital Abduction Score (DAS) assay to determine the median effective dose (ED_{50}) of muscle weakening, defined as the dose of botulinum neurotoxin that produces 50% of its maximum weakening effect after injection into the gastrocnemius muscle. In these experiments, following botulinum injection, mice are suspended briefly by the tail to elicit a startle response, characterized by extension of the hind limbs and abduction of the hind digits. The amount of limb extension and digit abduction is scored on a 5-point scale (0=normal digit abduction to 4=maximum decrease in digit abduction) by an observer who is masked to the treatment condition. The ED_{50} is equal to a DAS of 2. In several sets of murine experiments, the ED_{50} was consistently 4- to 5-times greater for BOTOX compared with Dysport (Table I) (6). These studies also determined the LD_{50}, or median lethal dose (i.e. causing death in 50% of a population of mice), a measure of systemic toxic effects (5). Thus, the ratio

Table I. Pharmacologic parameters for intramuscular injection of BOTOX, Dysport, and Myobloc based on murine models of efficacy and local and systemic diffusion using digital abduction scoring after injection into the gastrocnemius muscle.

Product	ED_{50}	LD_{50}	Safety margin (LD_{50}/ED_{50})	Therapeutic margin (threshold dose/ED_{50})
BOTOX	3.5±0.58	69.2±2.89	19.8±3.38	6.8
Dysport	16.3±1.62	168±6.29	10.3±1.09	1.0
Myobloc	23.7±2.04	103±2.55	4.35±0.39	0.4

ED_{50}=median effective dose of muscle weakening; LD_{50}=lethal median dose causing death in 50% of the murine population. Adapted from Foster KA, Bigalke H, Aoki KR. Botulinum neurotoxin—from laboratory to bedside. Neurotoxicity Res. 2006;9:133–40 (6).

of ED_{50} and LD_{50} indicates the safety margin, or the separation between an effective dose and one that causes diffusion of toxin from the treated muscle to cause a systemic effect (6). Finally, the therapeutic margin, or ratio of threshold dose (i.e. the lowest dose causing atrophy compared with the contralateral quadriceps) to ED_{50}, was calculated as a measure of the tendency of the botulinum neurotoxin to diffuse outside the injected muscle. As shown in Table I, the safety and therapeutic margins were 2- and 5-fold greater for BOTOX compared with Dysport, respectively, signifying that BOTOX is less likely to cause the untoward systemic and local effects that can result from diffusion.

The larger therapeutic margin and safety margin values for BOTOX compared with Dysport indicate a broader range between therapeutic and toxic doses for BOTOX. Moreover, it is well established that there is a lack of dose equivalence between these agents (e.g. 3–5 U Dysport is required to achieve the same therapeutic or aesthetic effect as 1 U BOTOX) (15,16). According to the preclinical observations described here, when doses are titrated to provide similar efficacy between products, the result is a ratio of ED_{50} values of approximately 1:5 (BOTOX:Dysport). At this ratio, BOTOX has a lower risk of diffusion compared with Dysport. Conversely, when doses are adjusted to match safety using LD_{50} values, the relative dose would be reduced to approximately 2.5:1 (BOTOX: Dysport), a ratio that results in reduced efficacy for Dysport (17).

Injection technique

In one early small study in which ten patients received botulinum neurotoxin type A in the forehead (18), a 5-fold increase in dilution volume resulted in increased diffusion, with an area of muscle weakness that was 50% larger than with the lower injection volume. However, a second, larger study did not confirm these findings (19). In this later study, 80 women with moderate to severe glabellar lines were randomized to receive 30 U botulinum neurotoxin type A (BOTOX) in one of four dilutions: 100, 33.3, 20, or 10 U/mL. There were no significant differences in responder rate (subjects who achieved a wrinkle score of none or mild), relapse rate (subjects whose glabellar lines had returned to baseline), or improvement rate (subjects who had improved from baseline) among the different dilutions at either maximum frown or repose during the 48-week post-treatment evaluation. All dilutions were safe and well tolerated; swelling and puffiness appear to be the only dilution- and treatment-related adverse effect, occurring in 8 of 20 patients who received botulinum neurotoxin type A diluted 10 U/mL, 2 of 20 patients receiving 20 U/mL, and in 1 of 20 patients in each group receiving 100 or 33.3 U/mL. A consensus panel on the cosmetic application of botulinum neurotoxin type A recommends any convenient concentration to deliver the required units per injection site (20). For BOTOX, the manufacturer recommends reconstituting a 100 U vial with 2.5 mL sterile saline to yield 0.4 U per mL (21).

The precise placement of botulinum neurotoxin injections into the facial musculature is paramount in achieving desired effects free of complications. Recommendations for dosing as well as injection technique are well described in the literature (20). (For a detailed discussion on this topic, see *Facial rejuvenation with botulinum neurotoxin: an anatomical and experiential perspective* by Drs Fagien and Raspaldo in this supplement.)

Clinical studies of diffusion

Studies have shown marked differences in the diffusion of various botulinum neurotoxin products. A recent study compared the diffusion characteristics of BOTOX and Dysport in a clinical model designed to show diffusion differences in the face (7). Twenty subjects with forehead hyperhidrosis received two injections of BOTOX 3 U in one side of the forehead and two injections of Dysport in the other side of the forehead. For the Dysport injections, patients were randomly assigned to receive 7.5 U, 9 U, or 12 U per injection, corresponding to BOTOX:Dysport dose ratios of 1:2.5, 1:3, or 1:4. Identical volumes (0.06 mL) were used for all injections. For each treatment group, one injection was intradermal and the other was intramuscular. Using iodine/starch applications to the forehead, patients were photographed at baseline, after 24 hours, 1 week, 2 weeks, and monthly up to 6 months to assess anhidrotic halos, defined as the sum of the medial and lateral halo areas.

Dysport produced a larger area of anhidrosis than BOTOX in 93% of medial-medial or lateral-lateral comparisons of the two products at individual time points. The mean anhidrotic halos were larger with Dysport than with BOTOX at all dose ratios evaluated (Figure 1). The sizes of the halos were not affected by intramuscular or intradermal injection ($p=0.91$).

All patients also exhibited frontalis muscle relaxation on both sides of the forehead. However, in the 12 patients with relatively symmetrical forehead wrinkles at baseline, review by a blinded expert observer 4–6 months post-treatment indicated that in 25 of the available 29 photographic evaluations, BOTOX produced comparable or superior inhibition of muscle contraction compared with Dysport (7). This is particularly noteworthy because although BOTOX resulted in a smaller area of diffusion, as evidenced by anhidrotic halos, the efficacy in reducing contraction in the injected muscle was greater with BOTOX than with Dysport.

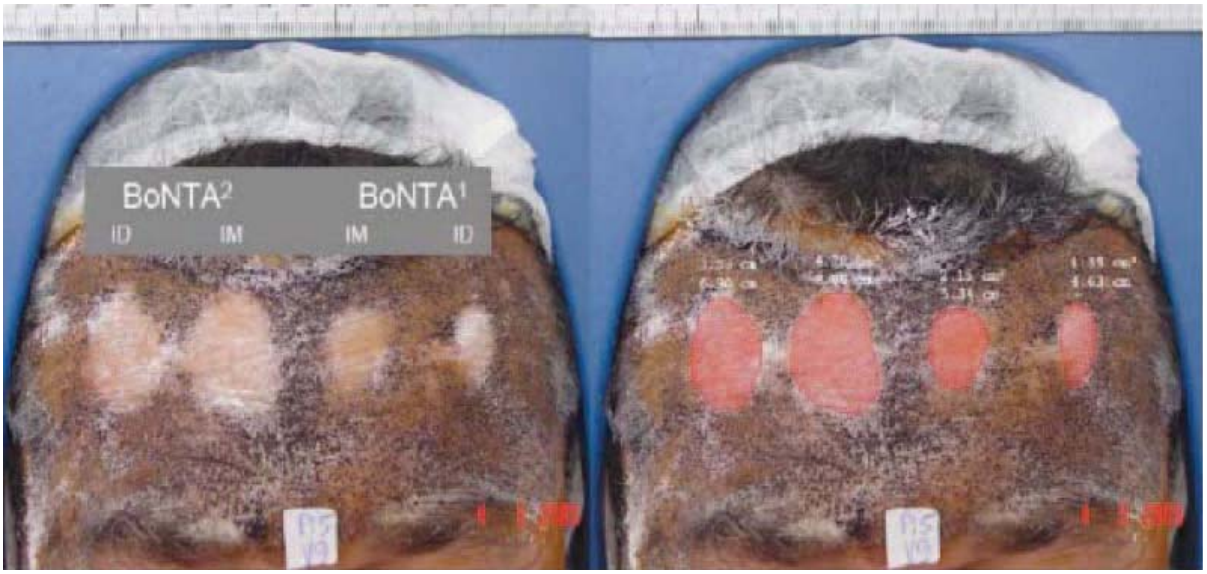

Figure 1. Areas of diffusion of BOTOX and Dysport when injected into the frontalis in models of forehead hyperhidrosis. BoNTA indicates botulinum neurotoxin type A; BoNTA^2=Dysport; BoNTA^1=BOTOX; IM=intramuscular injection; ID=intradermal injection. Reprinted from Trindade de Almeida AR, Marques E, de Almeida J, et al. Pilot study comparing the diffusion of two formulations of botulinum toxin type A in patients with forehead hyperhidrosis. Dermatol Surg 2007;33 special issue: S37–43. Published by Blackwell Publishing (7). Photographs courtesy of Ada Trindade de Almeida, MD.

Another study investigated the diffusion of BOTOX relative to Myobloc (22). To compare the rate of onset and radius of diffusion between BOTOX and Myobloc, patients with symmetrical moderate to severe forehead wrinkles at full contracture (n=8) were treated with an intramuscular injection of BOTOX 5 U on one side of the frontalis and Myobloc 500 U (1:100 BOTOX:Myobloc dose ratio) on the other side. Myobloc consistently produced a greater radius of toxin diffusion, as measured by a wrinkle reduction area calculated using a digital micrometer on traced scanned images. In another comparative study between BOTOX and Myobloc, Matarasso (3) reported that patients treated for crow's-feet reported a greater sensation of tightness, or freeze, when injected with Myobloc than with BOTOX, and speculated that increased diffusion may be one possible explanation for this observation.

Clinical implications

Few head-to-head studies exist in the medical literature comparing BOTOX with Dysport in their efficacy and safety for aesthetic use (16,17). In a clinical trial in which 20 Korean patients received either BOTOX (n=14, doses ranged from 5–20 U/site) or Dysport (n=6, doses ranged from 20–80 U), patients were evaluated prior to injection and at a follow-up assessment at least 6 months after injection (16). While the efficacy in ameliorating facial lines was similar between groups, adverse events occurred three times more often with Dysport than with BOTOX (in 100% (6/6) of patients versus 35.7% (5/14) of patients; $p<0.05$). The adverse events were indicative of diffusion outside of target tissue and included lagophthalmos in three subjects (15%), tingling sensations in three subjects (15%), and temporary lid swelling in five subjects (25%) (16). Similarly, in a crossover study in which 212 patients with blepharospasm were randomized to receive double-blind BOTOX or Dysport at a respective dose ratio of 1:4, the duration of effect was similar between treatments. Dysport, however, was associated with a significantly greater incidence of adverse events compared with BOTOX (in 24.1% (51/212) of patients receiving Dysport versus 17.0% (36/212) of patients receiving BOTOX; $p>0.05$) (23). Specifically, ptosis was observed in 1.4% (3/212) of BOTOX-treated patients compared with 6.6% (14/212) of Dysport-treated patients ($p<0.01$).

In a recently completed double-blind, comparative study in glabellar lines (n=62) (17), the efficacy and safety of BOTOX 20 U, the dose recommended in the prescribing information (21), was compared with Dysport 50 U, the dose previously recommended as optimal in a large placebo-controlled trial (24). At this BOTOX:Dysport dose ratio of 1:2.5, the duration of effect of BOTOX in reducing glabellar line severity and in measures of patient satisfaction was more prolonged compared with Dysport. Specifically, both products produced similar improvements from baseline at 8 and 12 weeks post-treatment, but significant differences between products emerged at 16 weeks post-treatment in favor of BOTOX. Both products were well tolerated, and there were no differences in the adverse event rates between groups.

Taken together, these clinical studies indicate that at a BOTOX:Dysport dose ratio of 1:2.5, BOTOX is more efficacious than Dysport, with both products being equally tolerable. At a BOTOX:Dysport dose ratio of 1:4, Dysport is associated with similar efficacy outcomes as BOTOX, but at a significantly increased adverse event rate (16,23). Thus, it appears that at doses needed to achieve Dysport efficacy comparable to that of BOTOX, safety is compromised and effects related to unwanted diffusion emerge. Indeed, these results confirm the predictions of the preclinical data.

Several clinical studies have compared the effects of BOTOX and Myobloc on various facial lines (2,3,25). All these studies have observed that the effects of botulinum neurotoxin type B on facial lines are not as long-lasting as those of type A, thereby limiting the overall clinical utility of botulinum neurotoxin type B.

Summary

Injections of botulinum neurotoxin for cosmetic use are targeted injections delivered into small muscles to produce a precise treatment effect. Meticulous placement of the toxin and other injection-related factors, as well as the diffusion potential of the preparation used, can affect the ability to produce both desired and unwanted effects. An accumulating body of evidence suggests that some of the botulinum agents have different diffusion characteristics. The potential for diffusion by product (ranging from lowest to highest) appears to be BOTOX < Dysport < Myobloc. These observations have important clinical implications for aesthetic use, where unwanted diffusion may result in ptosis or a frozen look. Patients who pursue facial rejuvenation with botulinum neurotoxin generally seek a natural and relaxed look; therefore, these adverse outcomes are quite contrary to their intentions. Because each botulinum product is developed from distinct purification and manufacturing procedures and have varying toxin complex sizes and structures, physicians must understand the differences between these agents in order to achieve the best possible outcomes.

Discussion

The meeting on which this supplement is based allowed for a discussion period following each presentation. Following are the highlights based on the presentations by Drs Trindade de Almeida and De Boulle.

Shape of the halos

Boris Sommer, MD: Does the Trindade de Almeida study suggest that all our cosmetic patients always get anhidrosis? Previously, we believed that injecting botulinum neurotoxin type A intramuscularly did not cause anhidrosis. However, these results indicate that it doesn't matter whether botulinum neurotoxin type A is injected intramuscularly or subcutaneously—anhidrosis will occur either way.

Ada Trindade de Almeida, MD: Yes, anhidrosis occurred when botulinum neurotoxin type A was injected either way into the frontalis. We cannot be sure if this would be the case in other areas.

Koenraad De Boulle, MD: What do you think is the reason for the oval shape (versus round) of the anhidrotic halos? Was it the result of pressure or could it have something to do with muscle contraction?

Ada Trindade de Almeida, MD: We exerted a little pressure equally on all injected areas.

Nicholas Lowe, MD: An interesting point, because previously we had done some similar work in hyperhidrosis where we injected intradermally one bilateral axilla with starch iodine and found a circular pattern of anhidrosis. So it may be a muscle-dependent effect.

Steven Fagien, MD: Perhaps this type of study should be conducted in the glabellar region, specifically with treatment to the corrugator muscles, where there is nearly a 90-degree change in the force of the muscle contraction (vertical versus horizontal striations of the forehead). If the results showed wide ovals versus tall ovals, it would support that this phenomenon is muscle dependent.

Timothy Flynn, MD: In the Myobloc versus BOTOX trial, we also saw vertical oval halos after injection into the frontalis, and we did not apply pressure.

Ada Trindade de Almeida, MD: The pattern of diffusion was equally up as well as down from the injection point.

Differences in diffusion: BOTOX versus Dysport

Timothy Flynn, MD: I was very intrigued by the fact that the statistical significance became greater with increasing doses of Dysport. The clinician who may attempt to get more longevity by using higher doses of Dysport may have to consider this increased diffusion effect.

Joel Cohen, MD: In all our injections, we try to avoid the inferior aspect of the frontalis. Did you evaluate whether patients complained of an architectural change to the brow position or shape, and if so, did that correlate with the Dysport side having a greater diffusion pattern leading to brow ptosis or (unlikely) even lid ptosis?

Ada Trindade de Almeida, MD: We did not specifically study it, nor did we evaluate any complaints of adverse effects, such as brow

heaviness. But we may be able to refer to photographs to see if there was any architectural change to the shape and the positioning of the brow. However, in general, my findings have led me to change the injection patterns I would use if I injected Dysport. With Dysport I would inject higher up in the frontalis than I do with BOTOX.

Disclosures

Dr Trindade de Almeida is a consultant for Allergan, Inc.

Dr de Boulle is a consultant for Allergan, Inc., and has consulted for Johnson & Johnson, Q-Med AB, Mentor Corporation, Colbar LifeScience Ltd, and Inamed Aesthetics.

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