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Practical Applications of a
New Botulinum Toxin

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Practical Applications of a New Botulinum Toxin

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ABSTRACT

The injection of *Clostridium botulinum* type A neurotoxins is among the most commonly performed cosmetic procedures, both in the U.S. and worldwide. The U.S. Food and Drug Administration (FDA) approval of a new botulinum neurotoxin type A in April 2009 (BoNT-A, Dysport®, Medicis, Scottsdale, AZ—hereafter referred to as “Dysport”) has broadened the neurotoxin market and provides new therapeutic alternatives to practitioners. The introduction of this product raises questions about how to best use it. In this supplement, the authors address critical similarities and differences between onabotulinumtoxinA (Botox®, Allergan, Irvine, CA—hereafter referred to as “Botox”) and abobotulinumtoxinA (Dysport). The authors also provide practical guidelines for the use of Dysport based on clinical experience and peer-reviewed, published clinical trials. In the authors’ opinion, Botox and Dysport can be used for similar “on-” and “off-label” applications. Judicious use of either product requires an understanding of how the two products differ in order to avoid side effects and achieve optimal results.

Common Questions:

- Are these two toxins the same or different and how?
- How are inter-product “unit” conversions addressed?
- Does injection technique differ?
- Does one product result in greater adverse events?
- Does one product last longer or “diffuse” better than the other?
- What other toxins can be expected on the market in the future?

INTRODUCTION

Injection of *Clostridium botulinum* (*C. botulinum*) type A neurotoxin is performed millions of times per year, and comprises a major component of the cosmetic market in the U.S. The number of procedures increased by 8% in 2008, reaching 5 million per year.¹

The development of new type A botulinum toxins broadens the range of therapeutic and cosmetic options available to practitioners. The introduction of multiple toxins requires that physicians become familiar with the similarities and differences between these products. The following is the result of a roundtable discussion among experts in the U.S. and abroad highlighting practical approaches in the use of Botox® and Dysport®. The discussion of other commercially available botulinum types A and B neurotoxins is limited in order to present a focused overview of the clinical opportunities provided by the introduction of Dysport to the U.S. market.

Breaking Down the Botulinum Neurotoxin Complex

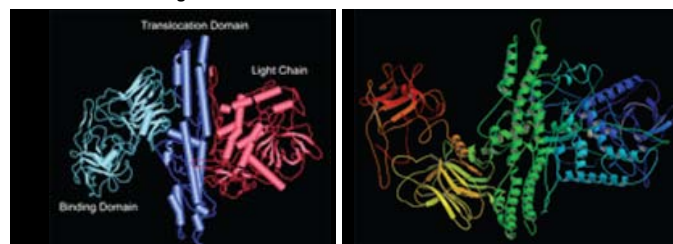
Clostridium botulinum, an anaerobic, Gram-positive, spore-forming bacterium, produces seven serologically distinct neurotoxins (i.e., A, B, C1, D, E, F and G) that block cholinergic neurotransmission at the neuromuscular junction in skeletal muscle. Only five of these toxins have known effects on humans (i.e., A, B, E, F and G). Commercially produced botulinum toxins consist of a core translocation domain flanked by

a light chain and a binding domain (Figure 1). Different toxin serotypes are distinguished by variations in their light chains,² which serve to cleave specific Soluble NSF Attachment Protein REceptor (SNARE) proteins at the neuromuscular junction.

Botulinum toxin is among the most deadly toxins and is lethal at doses as low as several nanograms/kg.³ Further, the seven serotypes of botulinum neurotoxin are known to have distinct biological potencies in vivo. Type A and G toxins are thought to be the most potent toxins at the neuromuscular junction, closely followed by the type B and F toxins.⁴ However, to date, only types A and B botulinum neurotoxins are available for clinical use.

The paralytic effect of botulinum neurotoxins results from disruption of the synaptic fusion complex at the neuromuscular

FIGURE 1. Structure of the botulinum type A toxin onabotulinumtoxinA (Botox) on left; abobotulinumtoxinA (Dysport) on right (courtesy of Medicis and Allergan).



junction. The synaptic fusion complex consists of three SNARE proteins: synaptobrevin/VAMP (vesicle associated membrane protein), SNAP-25 (25-kDa Synaptosomal-Associated Protein) and syntaxin. Type A toxins catalyze the breakdown of SNAP-25 proteins, while type B toxins catalyze synaptobrevin (VAMP) breakdown. The effect of protein cleavage is failure of fusion of acetylcholine-containing vesicles at the pre-synaptic cleft of the neuromuscular junction (NMJ), resulting in chemical denervation of skeletal muscle.

Several preparations of botulinum type A neurotoxin are currently available for clinical use worldwide: Botox/Vistabel®, Dysport/Azzalure®, BTXA®/Prosigne®, Neuronox® and Xeomin®. They differ in their fermentation technique, their additives and in the absence or presence of specific stabilizing proteins. For example, while Botox, Dysport, BTXA® and Neuronox® are all 900 kD complexes of the 150 kD neurotoxin non-covalently bound to stabilizing proteins (a non-toxin non-hemagglutinin, NTNH, and several toxin-associated Hemagglutinin proteins), Xeomin® is produced as a naked 150 kD toxin. Further, while Botox contains human serum albumin and sodium chloride, Dysport also contains lactose. BTXA contains bovine serum albumin (gelatin) as well as dextran and sucrose. Each of these additives is thought to subtly influence the physical properties of these toxins in vivo. Head-to-head trials are needed to determine if these differences significantly influence clinical outcomes.

The Unit Question

One of the most common questions among users of botulinum type A neurotoxins is how to safely and effectively interconvert

units of each toxin. The concept of “units” of toxin, as opposed to “mass” of toxin, is the direct result of the potency of the drug. Medications are usually measured and dosed by mass-grams or milligrams. However, botulinum toxin is so potent that dosing may be less than a nanogram, making units of mass impractical. In developing a dosing scheme for clinical use Allergan developed a proprietary mouse assay to determine the quantity of toxin required to reach lethality in 50% of mice (LD50) exposed to Botox by intraperitoneal injection. The mouse assay performed to determine the LD50 of Dysport differs from that used for Botox, such that it requires 2.5–3 U of Dysport to reach LD50.⁵ This is the result of technical aspects of the assay—the use of saline versus gelatin, containing phosphate buffer, for instance, and not necessarily because Dysport is less potent. If anything, clinical use and recent unpublished studies suggest that 2.5 U of Dysport is slightly more potent than 1 U of Botox.⁶ Studies comparing unit or dose-equivalence between Botox and Dysport have reported numbers ranging from 6:1-1:1.⁷ It is noteworthy that higher doses (4-6:1) have been used primarily in neuromuscular applications⁸ and cause potential side effects related to overdosing when used cosmetically. It is our consensus that a ratio of 2.5:1 between Dysport and Botox is an appropriate conversion for most upper face applications, while a ratio of 2:1 may be more appropriate for lower face use.⁹ This is of particular importance if published Botox doses are being used as the dosing reference.

Overview of Available and Emerging Botulinum Toxins

Worldwide there are currently five botulinum toxins available for clinical use (Table 1). Botox/Botox Cosmetic and Vistabel (Allergan Inc., Irvine, CA), Azzalure and Dysport 500 U/Dysport

TABLE 1.

Type A Botulinum Toxins Currently in Use Worldwide

Trade Name	Botox®/BotoxCosmetic	Dysport/Azzalure®	Neuronox®	BTXA®/Prosigne®	Xeomin®/Bocouture®
Manufacturer/ Distributor	Allergan Inc., Irvine, CA	Ipsen, LTD, UK Medicis, Scottsdale, AZ	Medy-Tox Inc., South Korea	Lanzhou Biologics, Lanzhou, China	Merz Pharmaceuticals, Germany
Composition	100 U BTX-A 0.5mg human serum albumin (HSA) 0.9 mg NaCl	300 U and 500 U/125 U BTX-A 0.125 mg HSA 2.5 mg lactose	100 U BTX-A 0.5 mg HSA 0.9 mg NaCl	100 U BTX-A 5 mg gelatin (bovine serum albumin) 25 mg dextran 25 mg sucrose	100 U BTX-A 1 mg HSA 5 mg Sucrose
pH, KD	6.8 ± 0.5, 900 kD	6.8 ± 0.5 900 kD†	6.8 ± 0.5 900 kD	6.0 ± 0.4 900 kD	Pure 150 kD Toxin
Appearance	White lyophilized powder	White lyophilized powder	White lyophilized powder	White lyophilized powder	White lyophilized powder
Clostridium Botulinum Bacterial Strain	Hall Strain	Hall strain (NCTC 2916)	Not available	Not available	Strain ATCC 3205
Approved uses*	A, B, C, D, E	A, C, D, E	A, C, D, E	A, C, D, E	A, C, D, E

*Approved uses: A- Glabellar Rhytides; B- Primary Hyperhidrosis; C- Cervical Dystonia; D- blepharospasm; E- Strabismus

†The Dysport complex is 500-900kD per manufacturer at time of review

All information contained herein was provided in product inserts or from communication with the manufacturers.

300 U (Ipsen, UK—distributed by Galderma and Medicis), BXTA /Prosigne (Lanzhou Biologics, Lanzhou, China), Xeomin (Merz Pharmaceuticals, Frankfurt, Germany), Neuronox (Medy-Tox Inc., South Korea). Several newer Type A toxins are in phase 3 clinical trials, including PurTox® (Mentor Corp., Santa Barbara, CA), which was just completed.

Topical type A toxins are also in development, including RT001®, a type A toxin gel (Revance Therapeutics, Inc., Newark, CA). Linurase® (Prolenium Technologies, Ontario, Canada) is a topical serum based on botulinum type A aimed at reducing rhytides. Available type B toxins include Myobloc®/NeuroBloc® (rimabotulinumtoxinB, Solstice Neurosciences).

Practical Applications and Common Uses for Neurotoxins in Aesthetic Dermatology

There are currently three FDA approved neurotoxins available in the U.S. (Botox, Dysport and Myobloc). While type A toxins are used most frequently for cosmetic purposes (Botox, Dysport), type B toxins are used almost exclusively in the context of neuromuscular disease, (i.e., cervical dystonia [Myobloc]). Myobloc is FDA-approved only for cervical dystonia and the short duration of action of the type B toxins (i.e., two months) have limited their cosmetic use.

The common usage of type A botulinum toxins includes both on and off-label use. FDA approved applications of the type A toxins include: cervical dystonia, focal forms of hyperhidrosis, strabismus, blepharospasm (Botox) and the temporary improvement in the appearance of moderate to severe glabellar lines in adult patients under 65 years of age (Botox Cosmetic); Cervical dystonia, and the temporary improvement in the appearance to moderate-to-severe glabellar lines in adult patients under 65 years of age (Dysport).

Most clinicians use botulinum neurotoxin type A in treating off-label sites including, but not limited to: lateral canthal lines ("crow's feet"), horizontal forehead lines, nasalis fanning rhytides ("bunny lines"), perioral rhytides, chin, jaw and neck reshaping, as well as in focal forms, including compensatory hyperhidrosis. Other cosmetic indications include asymmetric and gummy smile, raising the tip of the nose, treatment of depressor anguli oris muscles, platysmal bands, "Nefertiti" (jaw line) lifting and in chest applications (i.e., Decolleté rhytides).¹⁰ As Botox has been the only type A toxin available in the U.S. over the last 20 years, the use of Dysport by American clinicians will naturally be influenced by their previous experience with Botox. In the authors' experience, the clinical outcomes produced by the use of Botox or Dysport at a 1:2.5 U dose-conversion are equivalent.

Although only recently available in the U.S., Dysport has been in use in 73 countries since 1990. The authors have drawn on this experience in their discussion comparing these products. In the authors' opinion it is initially acceptable to use the same

injection sites and technique for Botox and Dysport if appropriate dose-equivalence is being applied. However, Dysport has distinct properties, including toxin potency per unit, which may define product-specific field effects, the rate of onset and the duration of action. It is the authors' consensus that an initial "rule of 10's" be used, wherein 10 U of Dysport be injected at sites where 4–5 U of Botox would be used. This characterizes the suggested dose-equivalences of 1:2.5 or 1:2 U between Botox and Dysport, and produces safe and efficacious results.

Practical Techniques to Achieve Optimal Results and Minimize Complications

Reconstitution

Due to the lability of botulinum type A toxins when exposed to heat, the lyophilized (freeze-dried) products are stored at 4°C (2–8°C) both before and after reconstitution. It is recommended that both Botox and Dysport be reconstituted in 0.9% physiologic saline. Many clinicians use a 3 cc syringe to introduce the diluent using a large bore needle (16- to 25-gauge), while minimizing bubbling and agitation by gentle rotation of the vial. Most practitioners choose to inject using an insulin syringe (B-D Ultrafine II 0.3 cc) with a short 30-gauge needle to minimize dead-space. There is some discussion about the benefits of using preserved versus non-preserved 0.9% saline for reconstitution, as preserved saline is thought to reduce pain on injection.¹¹ Among the authors it is thought that either diluent is acceptable for use in reconstituting Botox or Dysport.

Volumes

Botox Cosmetic is supplied as 100 U of onabotulinumtoxinA per vial,¹² and commonly used dilution volumes are 1 mL to 2.5 mL, yielding final concentrations of 100 U/mL to 40 U/mL. Dysport is supplied in the U.S. as 300 U of abobotulinumtoxinA per vial and it is suggested by the manufacturer that 1.5 mL of 0.9% saline be used for reconstitution yielding 10 U/0.05 mL.¹³ Most clinical trials of Dysport have used a 1.5 mL dilution, yielding a final concentration of 10 U/0.05 mL.¹⁴ Studies examining the effect of di-

FIGURE 2. Field effects on sweat glands resulted from isovolumetric injections of 2 U of Botox and 5 U of Dysport (1:2.5 U equivalence between products) show no clinical difference in the size of the halos.



luent volume on efficacy and safety did not show any difference between reconstituting 30 U of Botox in 1 mL versus 10 mL of 0.9% saline.¹⁵ Similar studies have been performed for Dysport. Since the volume to reconstitute the products is a physician's choice, practitioners may continue to use the same volumes they use currently. When switching products, we suggest adding 20% more volume for Dysport 300 U than is used to dilute Botox 100 U in order to preserve an appropriate 1:2.5 unit-equivalence. For example, 3 mL of saline should be used for reconstitution to achieve 10 U/0.1 mL of Dysport. This allows physicians to inject familiar volumes and to use the same techniques for cosmetic applications while maintaining safety and efficacy. It is our opinion that the dose of toxin is more important than the volume of toxin injected in determining the field-effect of Botox or Dysport on muscular and sweat gland activity.

Storage

The manufacturers of Botox and Dysport recommend that prolonged storage of reconstituted toxins be avoided to maintain optimal potency. Although it is suggested by the manufacturer that Botox be used within 24 hours of reconstitution,¹⁶ Hessel and colleagues have demonstrated that it may be stored for up to six consecutive weeks at 4°C without losing clinical efficacy.¹⁷ Similar stability assays have shown that Dysport is stable for up to 15 days after reconstitution.¹⁸

Specific Cosmetic Applications

Upper Face Applications

It is currently accepted that the standard dose of Botox for the treatment of glabellar lines in women is 20–25 U.¹⁹ Randomized, double-blind, placebo-controlled trials have shown that 50 U of Dysport is the optimal dose for treating glabellar lines,²⁰ reinforcing the 1:2.5 U equivalence between the products. Doses up to 70 U can, however, be used. Interestingly, the dosing study by Kane et al. did not demonstrate more adverse events with increasing doses of Dysport (up to 80 U).¹⁴ The most common injection-related side effects were similar to those seen with Botox, namely headache, injection site pain or bruising, and nasopharyngitis. Importantly, the glabellar injection points used for Dysport in this study, as well as in most others, mirrors those used for Botox.²¹

It is a common belief that Dysport has a greater “diffusion” potential than does Botox at equivalent doses. A head-to-head pilot study by Hessel and colleagues examining the use of Botox vs. Dysport for forehead hyperhidrosis at 1:2.5 U equivalent dose showed that the size of the action halos (or field effects) on sweat glands and frontalis muscles induced by 5 U of Dysport was not clinically different from that induced by 2 U of Botox (Figure 2) injected on the contralateral side.²² This suggests that the differences in the field of muscular and sweat gland effects—often misnamed “diffusion”—of Botox and Dysport are not clinically relevant at a dose of 1:2.5 U. Additional studies of toxin diffusion in forehead hyperhidrosis suggest that Dysport diffuses more than does Botox.³⁶ The authors agree that this disparity is likely due to study methods rather than actual diffusion characteristics.

Commonly used dosing of Botox for periorbital rhytides are 8–16 U for women and higher doses of 12–16 U in men due to greater muscle mass.²³ Injections are typically placed lateral to the orbital rim at three sites overlying the lateral fibers of the orbicularis oculi, and doses should be customized to the patient's needs. The present authors have had good results using Dysport (20–40 U, average 30 U on each side) for this application (Figure 3). Further, similar to the combined use of Botox and fillers, excellent clinical results can be obtained using the combination of Dysport and fillers, like Restylane® (Medicis, Scottsdale, AZ) as shown in Figure 4. This applies not only to the lower face, but to all facial applications where combining toxins and fillers is desired.

Pointers on Lower Face Applications

Lower face injection of botulinum type A neurotoxin is thought to require more skill than upper face injection, largely because potential side effects involving the mouth can be frustrating for patients. Since the lower face musculature is very responsive to toxin and connects directly or indirectly to the mouth, low doses of toxin are recommended to avoid side effects, such as muscle or lip laxity and asymmetric smile. In the experience of the authors, it is advisable to reduce the effective dose when using

FIGURE 3. Before and after results of periorbital rhytides treated with 30 U of Dysport per side (total 60 U).



FIGURE 4. Combined procedure using hyaluronic acid (Restylane™) and botulinum toxin (Dysport) for the treatment of periorbital rhytides. This has been published in *Surgery of the Skin*, Second Edition (Elsevier, 2010).



Dysport in the lower face to 1:2 U from 1:2.5 U. Figure 5 demonstrates the use of Dysport in correcting an asymmetric, gummy smile. Injection of 5–10 U of Botox into the mentalis is often used to correct “peau d’orange” chin. In the authors’ experience, and as referred to in the consensus, it is usually 10 U divided into two injection points that produces cosmetically pleasing results.²⁴

Hyperhidrosis

At present there are no published data to suggest that patient selection or injection technique should differ when using Botox or Dysport. Research on the off-label use of Dysport in hyperhidrosis has shed light on important dose-response data that aids us in comparing the relative “field effects” of Botox and Dysport. Studies by Hexsel et al. determining the action halos of both toxins on muscular and sweat gland activity at euvoletic doses (0.02 mL) and a unit ratio of 2.5:1 U, produced similar action halos ($P=0.897$ and 0.557). This supports the assumption that the unit equivalence is approximately 2.5:1 U, and shows a trend toward a slightly larger but not clinically different action halo for Dysport. Additionally, Heckmann and Plewig demonstrated that 100 U was as effective as 200 U of Dysport in treating primary axillary hyperhidrosis (100 U per axilla, a 1:2 equivalence per published data using 50 U of Botox per axilla), with a mean duration of effect of 48 weeks.²⁵

In addition to studying dose, Hexsel studied the effects of Dysport injection depth in compensatory hyperhidrosis.²⁶ Injection of 5 U of Dysport was performed into back skin at depths of 2 mm, 3 mm and 4 mm, diluted in three different volumes (0.02, 0.04 and 0.06 mL/5 U). The injection of Dysport at these three different depths and dilutions in regions with more intense sweating showed smaller fields of anhidrotic effects than in more lateral sites, suggesting lesser “diffusion.” These data demonstrate that several qualitative variables, including the intensity of local sweating and the type of skin injected, may be more important in determining the field effect of a toxin than the volume or depth of toxin injection. Based on the current data, injection of 100 U of Dysport can be used in each axilla, as one would use 50 U of Botox for primary axillary hyperhidrosis. The number of injection sites vary from 10–15 per axilla.

FIGURE 5. Before and after results of injections of 2.5 and 7.5 U of Dysport in each side of levator labii superioris muscle, to correct asymmetric gummy smile. The higher dose was injected at the left side. This has been published in *Surgery of the Skin*, Second Edition (Elsevier, 2010).



Review of Safety and Efficacy

At doses of 1:2.5 U Botox and Dysport have similar clinical efficacy in treating glabellar frown lines.^{27–29} The rate of onset of either toxin is between two to 10 days, and the duration of effect is three to six months. In the authors’ clinical experience, Dysport seems to have a more rapid onset of action compared to Botox (48 versus 72 hours). This observation has been substantiated by review of several phase 3 clinical trials demonstrating onset of action in as soon as 24 hours and a median time to onset of three to four days.³⁷ Contraindications to the use of Botox or Dysport, are similar, and include neuromuscular disorders (myasthenia gravis, amyotrophic lateral sclerosis [ALS], Lambert-Eaton Syndrome), pregnancy (both are category C), active local infection and the concomitant use of aminoglycoside antibiotics or muscle relaxants.³⁰ While there is a hypothetical risk of inducing an allergic reaction to Dysport in patients with milk allergies due to the lactose contained in the stabilizing complex, we have not found this to be clinically relevant. In the authors’ clinical use of Dysport over the past six years there have been no documented allergic reactions. Interestingly, this group included patients with known milk allergies.⁶

Complications related to botulinum toxin use are usually both dose and technique related.³¹ The most commonly observed side effects are headache, injection site pain or bruising, and nasopharyngitis. The incidence of ptosis, a common concern, ranges between 0.8 and 9%³² and it is encouraging to note that

the incidence of ptosis decreases with repeated treatments.³³ Published papers using Dysport at 3–5:1 U equivalence ratios have demonstrated a much higher incidence of complications. This is the result of an effective overdose of the toxin.²⁷

Botulinum toxin type A is an immunogenic peptide that can induce neutralizing or non-neutralizing antibodies. There appears to be no cross-reactivity between type A and B toxins, however. A subpopulation of patients being treated with high doses of toxin for dystonias developed neutralizing antibody to botulinum toxin. However it is thought that this was due to frequently administered, high doses of toxin.³⁴ Cosmetic studies to date following patients after multiple treatments have failed to detect neutralizing antibodies to either Dysport or Botox over 17–23 months,^{29,35} and long-term clinical use of both products suggests that this is an exceedingly rare event.

CONCLUSION

The introduction of a new botulinum type A toxin, Dysport, in April 2009 has broadened the therapeutic options available to clinicians. The safe and efficacious use of this new toxin requires an understanding of how it differs from the previously approved product, namely Botox. The authors have described multiple applications for Dysport using a dose-equivalence of 1:2.5 U in the upper face and 1:2 U in the lower face. In the authors' experience, Dysport can be injected at the same sites as Botox with equivalent, highly pleasing cosmetic outcomes. Complications can be minimized by avoiding overdosing Dysport and by tailoring injection patterns to the individual patient. Pharmacologic differences between Botox and Dysport do not appear to influence clinical use, and further head-to-head clinical trials are needed to explore these subtleties.

DISCLOSURES

Dr. Hexsel is a researcher, speaker and consultant for Galderma and Ipsen. She has received a research grant from Allergan, and she is a consultant for Revance.

Dr. Spencer is an investigator for Medicis.

Dr. Woolery-Lloyd is an investigator for the Medicis Dysport trial.

Dr. Gilbert has no conflicts of interest to disclose.

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