Different formulations of botulinum toxin type A have different migration characteristics

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Background: Different formulations of botulinum toxin type A (BoNTA) are not identical. As a result, their clinical behavior is different and results obtained with one formulation cannot be extrapolated to another.
Methods: In this single-center, double-blind, randomized, placebo-controlled study, 12 healthy volunteers received a single intradermal injection of each of two formulations of BoNTA ($BoNTA^1$ and $BoNTA^2$). Subjects received a single 4U injection of $BoNTA^1$ on one side of their forehead and a single 12U injection of $BoNTA^2$ on the other side of their forehead. Both injections were 0.1 mL and made into the mid-forehead above the pupillary line. Each subject also received an intradermal injection of placebo (normal saline) in the centre of the forehead. Two weeks later a Minor's Iodine test was performed to assess the areas of anhidrosis and the foreheads were photographed using Canfield photography.
Results: $BoNTA^1$ was associated with a significantly smaller area of anhidrosis than $BoNTA^2$.
Conclusion: After injection into the forehead, $BoNTA^1$ results in a smaller area of migration than $BoNTA^2$ even with identical injection volumes. Minimizing the area of migration is important for accurate localization of clinical effects so that the potential for adverse events is minimized.

$BoNTA^1$ is the formulation from Allergan, Inc. $BoNTA^2$ is the formulation from Ipsen, Ltd. Dosing and results reported in this study are specific to each formulation. Botulinum toxin products are not interchangeable and cannot be converted by using a dose ratio.

Note: Full version of poster presented at meeting follows abstract.

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Different Formulations of Botulinum Toxin Type A Have Different Migration Characteristics

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INTRODUCTION

Although only one formulation of botulinum toxin type A (BoNTA) is available in the US, two formulations are available in the United Kingdom and several other countries.[1,2] Different formulations of BoNTA are not identical—they behave differently electrophysiologically[3] and clinically[4,5] and therefore results obtained with one formulation cannot be extrapolated to another.

The migration of BoNTA post-injection appears to be influenced not only by the dose and volume of injection[6-8] but also by the formulation itself—with migration reported to be greater with BoNTA[2] than BoNTA[1].[5,9] A greater degree of migration may increase the potential for adverse effects and reports confirm that BoNTA[2] has been associated with a significantly higher incidence of adverse events than BoNTA[1] in a variety of clinical applications (the treatment of facial wrinkles,[10] essential blepharospasm,[11] cervical and other dystonias,[12,13] and hemifacial spasm.[13])

A double-blind, randomized pilot study has been performed to further evaluate the extent of migration of BoNTA from these two formulations after their injection into the forehead of healthy volunteers.

METHODS

Study design

- Single-center, double-blind, randomized, placebo-controlled study

Inclusion criteria

- Healthy volunteers aged 18-40 years old
- Females of childbearing potential were required to have a negative pregnancy test at the screening and baseline visits and to use a reliable method of contraception

Exclusion criteria

- Marked asymmetry in the forehead region
- History of facial palsy, bleeding disorders, or allergy to iodine
- Any medical condition that could increase the risks of exposure to botulinum toxin or interfere with neuromuscular function
- Any known defect of cholinesterase activity
- Profound atrophy or excessive weakness of the muscles in the target areas of injection
- Systemic infection or infection at the injection site
- Tattoo in the injection area
- Non-uniform sweat duct activity evident with Minor's iodine starch test
- Breastfeeding, pregnancy, planning to become pregnant, or not using a reliable form of contraception
- Current use of an aminoglycoside antibiotic, curare-like agent, or agent that might interfere with neuromuscular (skeletal) function or neuromuscular nerve impulse transmission
- Receipt of a prescription drug in the preceding 14 days that may affect sweating (anti-inflammatory agent, muscarinic agonist, etc.)
- Participation in an investigational drug study in the previous 30 days
- Laser resurfacing, soft tissue augmentation, or significant dermabrasion of the forehead in the previous 12 months
- Planning a non-study facial cosmetic procedure other than standard facial skin care during the study period

Concomitant drugs

- Prescription drugs that may affect sweating were not allowed

Study procedures

- Before the injections subjects rested comfortably for approximately 30 minutes without exercise or hot drinks.
- Three injection sites approximately 2 cm above the orbital rim were marked using a template and treated with an antimicrobial solution (Figure 1).

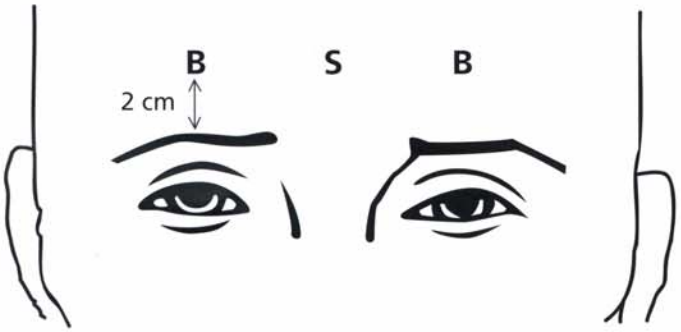


Figure 1. Injection sites in the forehead. B = BoNTA, S = saline.

- All subjects received 3 intradermal injections:
  - 1 injection of BoNTA[1] (4U) on one side of their forehead
  - 1 injection of BoNTA[2] (12U) on the other side of their forehead
  - 1 injection of preservative-free saline in the centre of the forehead.
- Forehead side was determined by random assignment.
- All injections were of identical volume (0.1 mL) and used 30 gauge needles.
- Preservative-free saline was used to reconstitute each product (2.5 mL for BoNTA[1], 4.16 mL for BoNTA[2]).
- Minor's iodine starch test was performed at the screening visit and at day 14. Each patient's forehead was dried and painted with 2% iodine in ethanol. Once this had dried, an oily paste made by mixing castor oil with dry starch powder (1mL castor oil to 1g dry starch powder) was applied in order to allow areas of sweating to be identified.
- The subjects were asked to walk around in a hot room (~ 32°C/90°F) until areas of anhidrosis around the injection sites were clearly delineated from the surrounding areas of sweating (areas of anhidrosis lack the blue/black coloration indicative of the interaction of sweat with the starch and iodine).

Outcome measures

- Canfield photography was used to document the appearance of the forehead.
- The anhidrotic halos were mapped onto an acetate sheet and their area calculated using graphical software.

Statistical analyses

- The areas of anhidrosis evident after injections of BoNTA[1] and BoNTA[2] were compared between groups using an ANOVA model (where treatment and sequence were treated as fixed effects and subject within sequence was treated as a random effect).
- A P value of <.05 was considered to be statistically significant.

RESULTS

Subjects

- 12 healthy volunteers were enrolled (7 female, 5 male) and all completed.
- Their mean age was 30 years (range, 19-39 years).

Efficacy

- Overall, the area of anhidrosis was significantly larger with BoNTA[2] than BoNTA[1] (P=.005) (Figure 2).
- The area of anhidrosis was greater with BoNTA[2] than BoNTA[1]:
  - In 11 of 12 (92%) patients
  - By a mean of 77%
  - By a median of 39%.
- The *mean* difference in area of anhidrosis between groups was substantially higher than the *median* difference because some patients exhibited particularly large differences.
- The area of anhidrosis ranged from:
  - 0.76-2.76 cm^2 with BoNTA[1]
  - 1.90-4.26 cm^2 with BoNTA[2].
- No anhidrosis was apparent as a result of the control injections with saline alone.

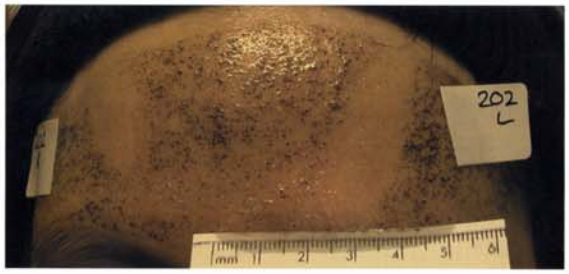
Tolerability

- There were 3 adverse events that were considered almost definitely or probably related to treatment (mild tenderness or tightness across the forehead). However, as the tenderness or tightness was felt across the whole forehead, they were not attributable to a single agent.

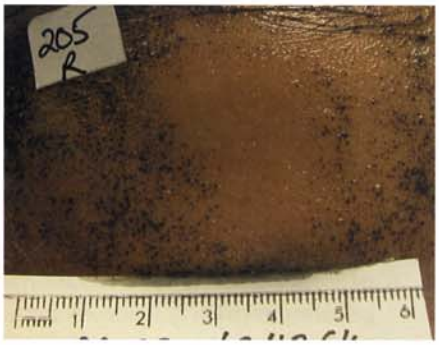
Figure 2. Larger area of anhidrosis evident after injection of BoNTA[2] than BoNTA[1].

BoNTA[1] injection
Area of anhidrosis = 2.54 cm[2]

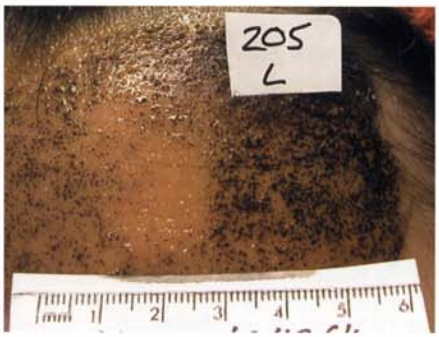
BoNTA[2] injection
Area of anhidrosis = 4.26 cm[2]



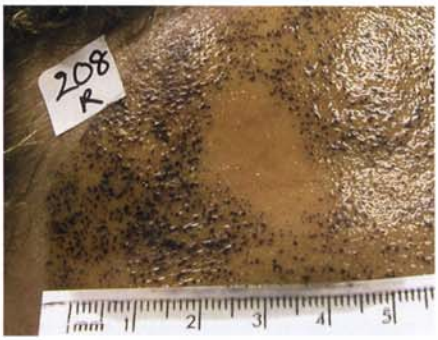
BoNTA[2] injection
Area of anhidrosis = 4.06 cm[2]



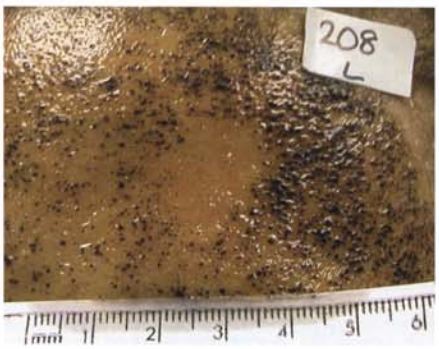
BoNTA[1] injection
Area of anhidrosis = 0.81 cm[2]



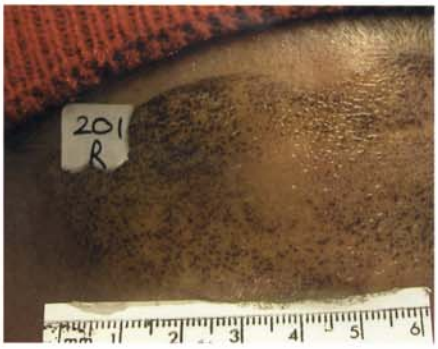
BoNTA[2] injection
Area of anhidrosis = 2.27 cm[2]



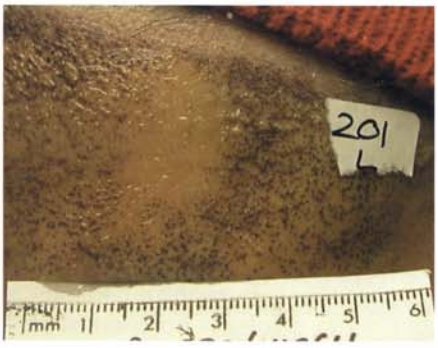
BoNTA[1] injection
Area of anhidrosis = 1.65 cm[2]



BoNTA[1] injection
Area of anhidrosis = 0.76 cm[2]



BoNTA[2] injection
Area of anhidrosis = 1.90 cm[2]



- There were no serious, severe, or other significant adverse events.

CONCLUSION

BoNTA[2] shows greater migration in the forehead than BoNTA[1] when using a BoNTA[1]:BoNTA[2] dose ratio of 1:3 and identical injection volumes. This may explain why some authors have noted a higher incidence of adverse effects after BoNTA[2] treatment than after BoNTA[1] treatment.[10-14]

In order to minimize the potential for adverse events, it is important to ensure that clinical effects are precise and localized. This is particularly important in the face and palms where other muscles lie close to the target muscles.

Using a reproducible test (the Minor's starch iodine test), the results from this study show that the migration of BoNTA[1] from its site of injection is less than that of BoNTA[2]—making BoNTA[1] the preferred product for many clinicians.

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DISCLOSURES

Poster supported by Allergan, Inc.

BoNTA[1] is the formulation from Allergan, Inc. and is not approved by the US Food and Drug Administration for the treatment of forehead hyperhidrosis.

BoNTA[2] is the formulation from Ipsen, Ltd. (United Kingdom) and is not approved by the US Food and Drug Administration.

Note

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