Sensitivity of the extensor digitorum brevis and Minor's starch-iodine tests at detecting dose-effects of Dysport® in male healthy volunteers

Laurent Pons [a], Jane Baxendale [b], Magali Volteau [a], Isabelle Paty [a]

[a] *Ipsen Innovation, Les Ulis, France*
[b] *Mac Research Clinical, Manchester, United Kingdom*

Introduction

The study rationale was to evaluate literature-referenced pharmacodynamic models, the extensor digitorum brevis (EDB) and Minor's starch-iodine tests, and assess their sensitivity at detecting a dose-effect using abobotulinumtoxinA (aboBoNT-A; Dysport®).

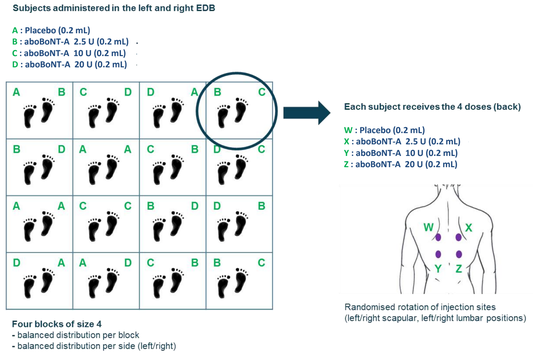
Methods

Subjects

- Male adult (aged ≥ 18 years) healthy volunteers.

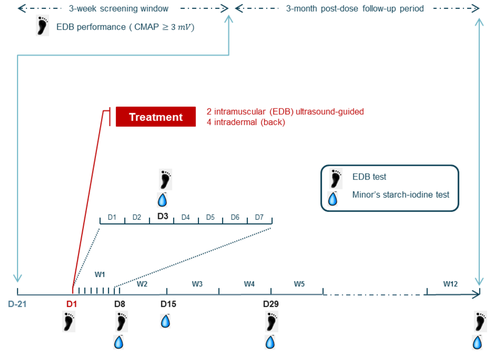
Design and treatment

- Single centre double-blind placebo-controlled randomised study.
- Sixteen eligible subjects randomised.



- Eligible subjects randomised (1:1:1:1; stratified per left/right foot) to receive one of the four treatments in each foot: aboBoNT-A 2.5 U, 10 U, 20 U or placebo.
- Subjects received one i.m. administration of study drug in their left and right EDB muscles under ultrasound guidance.
- Depending on the randomisation, the study treatment and dose in each EDB could be the same or different.
- Each subject also received the three doses of aboBoNT-A (2.5 U, 10 U and 20 U) plus placebo i.d. at four distinct sites on their back.
- Position in the back of each of the four treatments was allocated by randomisation.

Study flowchart



Extensor digitorum brevis test

- Electrophysiological evaluation of the compound muscle action potential (CMAP) amplitude (mV), elicited by supramaximal electrical stimulation of the peroneal nerve at the ankle.
- Use of surface electrodes as recording electrodes (placed over the muscle belly) and reference electrodes (placed over the tendon of the corresponding muscle).
- Point of maximum response of both EDB, as assessed during the screening period marked with indelible ink to allow recording from the same site at each visit.
- Three CMAP measurements at each visit.
- Visit values calculated by averaging the two highest CMAP values fro each visit (from the three measurements).

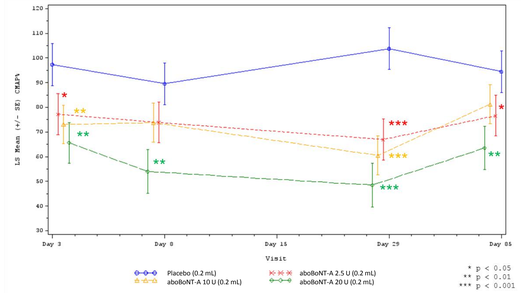
Minor's starch-iodine test

- Iodine solution (2% iodine in ethanol) painted on to the area of the back surrounding each injection site.
- Corn-starch solution (50 mg starch in 100 mL castor oil) painted onto each test site on top of the iodine solution.
- Volunteers subjected to a period of exercise (stationary bike pedalling for up to 45 minutes) in order to trigger persperation.
- Borders of anhidrotic areas lacking dark blue coloration (interaction between sweat and starch-iodine) traced onto sheets of acetate.
- Anhidrotic areas measured (cm²) using digital planimetry (Planix 10S planimeter, Tamaya Technics Inc. Tokyo, Japan).

Results

Extensor digitorum brevis test

- Statistical significant early reductions of the CMAP amplitude measured from Day 3 in all aboBoNT-A groups versus placebo (20 to 32% inhibition).
- Maximum effect (up to 55% inhibition at 20 U) reached by Day 29 in all aboBoNT-A groups.
- Linear dose-effect observed from Day 3 to Day 29.
- Persistence of a statistical significant difference versus placebo in some aboBoNT-A dose groups at Day 85.



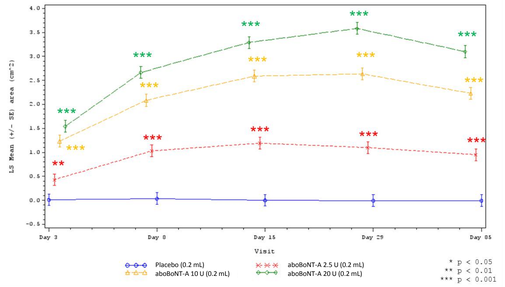
Significance testing

Generalised linear model with treatment as a fixed effect, baseline as covariate and subject as a random effect.
Based on a hierarchical procedure:

- aboBoNT-A 20 U compared to placebo (one tailed test, significance level 0.05).
- If significant result for aboBoNT-A 20 U, aboBoNT-A 10 U compared to placebo (one tailed test, significance level 0.05).
- If significant result for aboBoNT-A 10 U, aboBoNT-A 2.5 U compared to placebo (one tailed test, significance level 0.05).
- 90% Confidence Intervals presented for the differences between aboBoNT-A 20 U, 10 U and 2.5 U and placebo.

Minor starch-iodine test

- Early statistically significant increase of anhidrosis areas observed from Day 3 in all aboBoNT-A groups versus placebo (from 0.4 to 1.5 cm²).
- Maximum effect reached by Day 15 in the 2.5 U aboBoNT-A dose group (1.2 cm²).
- Maximum effect reached by Day 29 in the other aboBoNT-A dose groups (2.7 and 3.6 cm² at 10 and 20 U respectively).
- Linear dose-response from Day 3 to Day 29.
- Persistence of a statistically significant difference versus placebo in all aboBoNT-A dose groups at Day 85.



Conclusions

- aboBoNT-A injected in the EDB and the skin of the subjects was well-tolerated.
- Despite inter-subject variability, the EDB test was shown to be sensitive to demonstrate a dose-effect of aboBoNT-A on the CMAP total amplitude of the EDB striated muscle.
- The Minor's starch-iodine test also showed a clear dose-response with low inter-subject variability. This human pharmacology model also demonstrated a dose-effect of aboBoNT-A.

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