Biological activity of two botulinum toxin type A complexes (Dysport® and Botox®) in volunteers

A double-blind, randomized, dose-ranging study

Introduction

Despite the manifold uses of and large body of literature regarding botulinum toxin [9, 20], there are still questions regarding the clinical substitution of one formulation for another, and comparisons of their efficacies, side-effects and cost-effectiveness. The clinical literature on dose-equivalence ratios is inconsistent, and often marred by small sample sizes and preconceived assumptions. As a result, for example, dose-equivalence ratios for Dysport®:Botox® ranging from 1:1 to 6:1 are advocated; this is clearly an unacceptable margin of error. Sampaio et al. [16] applied Cochrane criteria to head-to-head studies investigating dose-equivalence ratios for these two formulations in patients with a single focal dystonia. They found only four randomized controlled trials, which tested only two fixed conversion factors (3:1 and/or 4:1 for Dysport:Botox), that met their criteria for evidence-based medicine. The data from
these trials strongly suggested that 4:1 'is not the ratio that guarantees bioequivalence in terms of clinical efficacy, duration of effect, or frequency of adverse reactions'. At a dose ratio of 3:1, Dysport had a stronger clinical effect than Botox (greater response, longer duration of effect and increased risk of side-effects). The authors of one of these trials [14] and the author of a commentary relating to it [13] both noted that the data seem to suggest a conversion factor lower than 3:1 would be more appropriate. Clearly, further investigation is warranted, especially as ratios of 3:1, and sometimes more, are employed in clinical practice [11].

This dose-ranging, electroneurographic (ENG) study was designed to investigate the dose equivalence, diffusion characteristics (spread) and safety of Dysport and Botox in healthy volunteers. The target muscle in this study, the extensor digitorum brevis (EDB), was chosen for its accessibility and because weakening this muscle has no impact on the daily life of participants. The model also generates more precise comparative data than clinical studies do. This is because a clinical effect (nearly complete paralysis of a target muscle) requires toxin doses in the range where dose–response curves reach a plateau (i.e. where large variations in dose produce little difference in effect), whereas this model allows investigators to measure dose effects in the steep section of a dose–response curve, where the effect changes rapidly with dose. ENG methods are well suited to the detection of such subtle, and potentially subclinical, changes in the muscle studied.

Materials and methods

Study population

Male and female volunteers aged 18–60 years were included in the study. Individuals were excluded if they had a history of alcohol or drug abuse, or if they had associated serious diseases, particularly of the heart, liver, kidneys, or systemic diseases, malignant diseases or serious infections. Volunteers with immune or coagulation disorders were also excluded from the study. Women who were pregnant, lactating or of childbearing age without adequate contraceptive protection were not eligible for inclusion. Other exclusion criteria included: ingestion of prohibited or undocumented concomitant medication; artificial heart valves or prior damage to heart valves; ongoing or recent (during the past 3 months) participation in a clinical study; simultaneous participation in another clinical trial; pretreatment with botulinum toxin type A; known allergy or antibodies to botulinum toxin type A.

Study design

This was a randomized, double-blind, prospective, dose-ranging study of Dysport and Botox. The study was of 12 weeks’ duration and was conducted in two university hospitals in Germany. Volunteers were randomly assigned to one of 18 treatment groups that differed in terms of dose (number of units per injection; five doses in total) and concentration (high or low) of toxin received (see Study treatments and Fig.1), and into which foot Dysport and Botox were injected. A randomization list of permuted blocks was used to ensure balance among treatment groups and prepare numbered sealed envelopes containing treatment instructions. One individual in each centre, who was not otherwise involved in performing the study, prepared the injection solutions and assigned volunteers to treatment by consecutively drawing the envelopes.

The study was conducted according to the principles of the Declaration of Helsinki (1996 amendment), Good Clinical Practice and German Drug Law (AMG). The protocol was approved by the local independent ethics committees and all volunteers were required to provide written informed consent before inclusion in the study.

Study treatments

Vials of Dysport (500 Dysport U; Ipsen Biopharm, Wrexham, UK) and Botox (100 Botox U; Allergan, Irvine, CA, USA) were reconstituted and diluted in 0.9 % saline to provide solutions of two concentrations: 50 and 100 units/mL. All volunteers received an injection, administered under electromyographic control using a 27 G needle, of Dysport into the EDB of one foot and an injection of Botox into the EDB of the other foot according to the randomization schedule. Five doses (four doses at two different concentrations and one dose at one concentration for each product) were given as described in Table 1. Doses and concentrations were chosen based on previous trials in the same setting [21, 22]. The doses used were expected to cause a weakening of the target muscle (EDB), but no functional impairment of either it or the neighbouring muscles. Because the effect of a unit of Botox was expected to be greater than that of a unit of Dysport, the highest dose (20 units) was given only for Dysport and the lowest dose (1.25 units) given only for Botox (Table 1). As the solutions for injection did not differ in appearance or odour, the investigator administering treatment was blinded to concentration and toxin formulation but not, however, to injection volume.

Assessments and outcome measures

ENG examinations, performed according to standard methodology [10], were used to assess the effects of dose and concentration on the target (EDB) and two neighbouring muscles (abductor hallucis [AH] and abductor digiti minimi [ADM]). Examinations were performed (using surface electrodes) during the screening period before the day of the injection, immediately preceding treatment on the day of the injection (baseline), and then 2 and 12 weeks (± 3 days) after treatment. At each time point, the peroneal (for the EDB) and tibial nerves (for the AH and ADM) were supramaximally stimulated at the level of the ankle joint; recordings were then taken from the EDB, AH and ADM. The stimulation distance depended on the size of the foot, but it was kept constant for each volunteer for the duration of the study. Base-to-peak compound muscle action potential (CMAP) amplitude, the primary efficacy parameter, was measured at each time point and for each muscle.

Other parameters measured were the duration and area of the CMAP and the distal motor latency (DML; the conduction time between the differential stimulating and recording electrodes). The results for these parameters are not shown as they were either similar to those for CMAP amplitude, albeit with more ‘noise’ (CMAP duration and area), or they showed no meaningful or consistent changes (DML). Sural and peroneal neurography was carried out at screening to exclude polyneuropathy; these examinations showed that nerve conduction velocities were normal in all volunteers.

Any adverse events were classified according to the guidelines of Good Clinical Practice, graded for severity and recorded by the investigators at each of the last three visits.