A Randomized, Double-Blind, Placebo-Controlled, Dose-Ranging Study to Compare the Efficacy and Safety of Three Doses of Botulinum Toxin Type A (Dysport) With Placebo in Upper Limb Spasticity After Stroke

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Background and Purpose—We sought to define an effective and safe dose of botulinum toxin type A (Dysport) for the treatment of upper limb muscle spasticity due to stroke.

Methods—This was a prospective, randomized, double-blind, placebo-controlled, dose-ranging study. Patients received either a placebo or 1 of 3 doses of Dysport (500, 1000, 1500 U) into 5 muscles of the affected arm. Efficacy was assessed periodically by the Modified Ashworth Scale and a battery of functional outcome measures.

Results—Eighty-three patients were recruited, and 82 completed the study. The 4 study groups were comparable at baseline with respect to their demographic characteristics and severity of spasticity. All doses of Dysport studied showed a significant reduction from baseline of muscle tone compared with placebo. However, the effect on functional disability was not statistically significant and was best at a dose of 1000 U. There were no statistically significant differences between the groups in the incidence of adverse events.

Conclusions—The present study suggests that treatment with Dysport reduces muscle tone in patients with poststroke upper limb spasticity. Treatment was effective at doses of Dysport of 500, 1000, and 1500 U. The optimal dose for treatment of patients with residual voluntary movements in the upper limb appears to be 1000 U. Dysport is safe in the doses used in this study. (Stroke. 2000;31:2402-2406.)

Key Words: botulinum toxins ■ muscle spasticity ■ stroke

Severe hypertonia of upper limb muscles is a common complication in patients with stroke. Only a very small minority (approximately 5%) of these patients regain useful function of the paralyzed arm, and the prospects of recovery after the first 3 months of the stroke are usually negligible. Although muscle weakness and loss of dexterity are important factors in the motor functional disability in these patients, the contribution of muscle spasticity is often quite significant. Spasticity may interfere with voluntary motor function in patients with residual muscle power. In addition, it frequently causes difficulties with activities of daily living, such as dressing and cleaning the palm of the clenched hand. In some patients the spasticity causes muscle pain or discomfort.

The current methods of treatment for muscle spasticity are unsatisfactory. Systemic antispasticity drugs are nonselective in their action and may cause functional loss, eg, inability to maintain sitting posture because of weakening of the trunk muscles. Paradoxically, in some patients these drugs reduce force in the normal muscles without having an effect on muscle spasticity. Furthermore, the value of the oral antispasticity drugs diminishes with prolonged use. Tolerance develops after a few months of treatment, and incremental increases in dosage are often required to maintain the initial clinical response. The high doses required often increase the incidence and severity of the adverse effects of these drugs.

An alternative strategy in the management of muscle spasticity is chemical neurolysis with alcohol or phenol. However, nerve blocks and motor point injections in the upper limbs often cause skin sensory loss and dysesthesia, and their effect often diminishes with repeated treatment.

In recent years, botulinum toxin type A (BtxA) has been shown to be an effective antispasticity agent. The use of BtxA for the relief of upper limb spasticity has several advantages. It is simple and can be performed as an outpatient procedure without anesthesia, and the toxin does not cause skin sensory loss or dysesthesia. However, the optimal dose...
Subjects and Methods

Study Design
This was an international, multicenter, prospective, randomized, double-blind, placebo-controlled study comparing the effect of 3 doses of Dysport (500, 1000, and 1500 U) with placebo. The study evaluated the efficacy and safety of Dysport in patients with upper limb spasticity who had suffered a stroke.

Patient Recruitment
Patients with hemiplegic stroke and severe or moderately severe muscle spasticity were recruited at least 3 months after the onset of the cerebrovascular event. They were included in the study if they had a muscle tone score of ≥2 on the Modified Ashworth Scale (MAS) in the wrist, elbow, and finger flexors. Those with muscle contractures of the upper limb joints were excluded (muscle contracture in this study was defined as severe restriction of the joint range of motion [ROM] on passive stretch). Other exclusion criteria were previous treatment with botulinum toxin, phenol or alcohol nerve blocks, or motor point injections for upper limb spasticity. De novo treatment with antispasticity drugs was not allowed. Stroke was defined according to the World Health Organization criteria. The possible effects of the etiology and site of the stroke, eg, thalamic versus cortical infarct, were not specifically addressed in this study.

Treatments
Patients were randomized to 1 of 4 study groups and received 1 of 3 doses of Dysport or placebo. Dysport was presented in powder form and was reconstituted in 2 mL of 0.9% sodium chloride solution to give 500, 1000, or 1500 U of Dysport. The placebo was identical to the active drug. The following muscles were injected: the biceps brachii, flexor digitorum profundus, flexor digitorum superficialis, flexor carpi ulnaris, and flexor carpi radialis. The injections were placed in the motor endplate zone with the use of anatomic landmarks, as in routine electromyography. The dose of Dysport injected into each muscle is given in Table 1.

Assessments
Patients were assessed before the injections and 2, 4, 8, 12, and 16 weeks afterward. Assessment was performed blind to randomization and, when possible, by 1 investigator in each participating center.

Outcome Measures
The efficacy of treatment was evaluated with the MAS. The joint ROM on voluntary extension of the elbow and wrist and on passive muscle stretch was measured with the use of a hand-held goniometer. The joint ROM in the fingers is difficult to measure accurately with goniometry. It was therefore assessed according to the following scale: hand closed, one quarter open, one half open, three quarters open, or fully open with active movement or passive muscle stretch. In addition, the severity of muscle pain was assessed on a 4-point scale (0=no pain, 1=mild pain, 2=moderate pain, 3=severe pain) at the shoulder, wrist, and fingers. The patient’s functional abilities were assessed with the Rivermead Motor Assessment (arm section) scale and the Barthel Index of activities of daily living. Patients and caregivers were also asked to score the difficulties encountered in performing 3 functional activities that often result from upper limb spasticity. These were as follows: (1) being able to put the affected arm through the sleeve of a garment, (2) being able to open the hand of the affected limb for cleaning the palm, or (3) being able to open the hand of the affected limb for cutting the fingernails. The difficulty was graded as follows: no difficulty, little difficulty,

### Table 1. Units of Dysport Injected at Each Site

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Total Dose</th>
<th>BB</th>
<th>FDP</th>
<th>FDS</th>
<th>FCU</th>
<th>FCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>II</td>
<td>500</td>
<td>200</td>
<td>75</td>
<td>75</td>
<td>75</td>
<td>75</td>
</tr>
<tr>
<td>III</td>
<td>1000</td>
<td>400</td>
<td>150</td>
<td>150</td>
<td>150</td>
<td>150</td>
</tr>
<tr>
<td>IV</td>
<td>1500</td>
<td>600</td>
<td>225</td>
<td>225</td>
<td>225</td>
<td>225</td>
</tr>
</tbody>
</table>

BB indicates biceps brachii; FDP, flexor digitorum profundus; FDS, flexor digitorum superficialis; FCU, flexor carpi ulnaris; and FCR, flexor carpi radialis.

### Table 2. Demographic Characteristics and Details of Stroke at Baseline

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=19)</th>
<th>Dysport 500 U (n=22)</th>
<th>Dysport 1000 U (n=22)</th>
<th>Dysport 1500 U (n=19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>63.6 (14.1)</td>
<td>64.1 (14.7)</td>
<td>60.7 (9.1)</td>
<td>61.6 (14.9)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>12</td>
<td>15</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Female</td>
<td>7</td>
<td>7</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td>Body weight mean (SD), kg</td>
<td>78.1 (15.4)</td>
<td>75.7 (22.2)</td>
<td>74.2 (15.1)</td>
<td>73.5 (14.2)</td>
</tr>
<tr>
<td>Body weight, median, kg</td>
<td>71.6</td>
<td>71.5</td>
<td>70.8</td>
<td>73.7</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>8</td>
<td>12</td>
<td>13</td>
<td>11</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>3</td>
<td>6</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Cerebral embolism</td>
<td>4</td>
<td>2</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Hemiparetic arm</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dominant</td>
<td>9</td>
<td>13</td>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td>Nondominant</td>
<td>8</td>
<td>8</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>Not recorded</td>
<td>2</td>
<td>1</td>
<td>3</td>
<td>2</td>
</tr>
</tbody>
</table>
moderate difficulty, a great deal of difficulty, or inability to perform the activity. The magnitude of benefit over the 16-week study period was also analyzed, as described in Sample Size and Statistical Analysis. The safety of Dysport was assessed by recording the reported adverse events. In addition, the presence or absence of swallowing difficulties was confirmed with a timed swallowing test. Patients were asked to drink 150 mL of tap water as quickly as possible. A swallowing speed of <10 mL/s and symptoms of coughing or choking during the test were considered evidence of dysphagia. Inquiries about adverse events of treatment and examination for dysphagia were made at each assessment visit.

Sample Size and Statistical Analysis
The best change from baseline in the MAS at week 4 in either the elbow, wrist, or finger joints was chosen as the primary efficacy outcome measure. The sample size was calculated to give 80% to 90% power (α=0.05, 2-tailed test) to detect a difference between the groups in posttreatment MAS scores of ≥1, assuming the SD of the posttreatment scores was ≤1. This gives a total sample size of 80 patients (20 patients per group).

The data of the intention-to-treat population were analyzed by logistic regression analysis, with the study center and baseline of MAS included as terms in the model. Comparisons were made between each dose of Dysport and placebo. When appropriate in the secondary efficacy analysis, changes from baseline at week 4 were analyzed with logistic regression, while the magnitude of benefit was examined with an area under the curve analysis. The area under the curve was derived by the trapezoidal method. ANOVA was used on the values obtained under the curve, and a model consisting of treatment, adjusted for center effects, was fitted to the data.

Results
Nine principal investigators in 11 West European centers took part in the study. A total of 83 patients were recruited and randomized into the following groups: placebo, n=20; Dysport 500, n=22; Dysport 1000, n=22; Dysport 1500, n=19. One patient in the placebo group withdrew from the study, leaving data on 82 patients for the final analysis. The demographic data and disease characteristics of all the study groups were similar at baseline (Table 2). The study groups were also well matched with respect to treatment with antispasticity drugs at study entry and during the trial.

Efficacy
All 3 doses of Dysport resulted in statistically significant reduction in the MAS score in any joint at week 4 compared with placebo (Table 3). Analysis of the magnitude of benefit

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Magnitude of Benefit, mean (SE)</th>
<th>Comparisons With Placebo, mean (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elbow Placebo</td>
<td>−3.2 (3.1)</td>
<td>−13.0 (−21.3, −4.7)</td>
<td>0.002</td>
</tr>
<tr>
<td>500U</td>
<td>−16.2 (2.8)</td>
<td>−11.8 (−20.1, −3.5)</td>
<td>0.006</td>
</tr>
<tr>
<td>1000U</td>
<td>−15.0 (2.8)</td>
<td>−10.9 (−19.5, −2.4)</td>
<td>0.013</td>
</tr>
<tr>
<td>1500U</td>
<td>−14.2 (3.0)</td>
<td>−10.8 (−19.3, −2.0)</td>
<td>0.013</td>
</tr>
<tr>
<td>Wrist Placebo</td>
<td>−6.3 (3.6)</td>
<td>−10.8 (−20.3, −1.2)</td>
<td>0.028</td>
</tr>
<tr>
<td>500U</td>
<td>−17.1 (3.3)</td>
<td>−14.4 (−24.0, −4.8)</td>
<td>0.004</td>
</tr>
<tr>
<td>1000U</td>
<td>−20.7 (3.3)</td>
<td>−12.2 (−22.1, −2.2)</td>
<td>0.017</td>
</tr>
<tr>
<td>1500U</td>
<td>−18.5 (3.5)</td>
<td>−6.3 (3.6)</td>
<td>0.163</td>
</tr>
<tr>
<td>Fingers Placebo</td>
<td>−11.8 (3.3)</td>
<td>−5.5 (−15.2, 4.2)</td>
<td>0.262</td>
</tr>
<tr>
<td>500U</td>
<td>−16.3 (3.3)</td>
<td>−10.0 (−19.8, −0.3)</td>
<td>0.044</td>
</tr>
<tr>
<td>1000U</td>
<td>−13.4 (3.5)</td>
<td>−7.1 (−17.2, 3.0)</td>
<td>0.163</td>
</tr>
</tbody>
</table>
The number (%) of patients in each change category are given. A negative number, and an increase was recorded as a positive number. The Barthel Index 0.7 (1.2) 0.1 (2.5) 0.8 (2.6)

Assessment

Rivermead Motor

Pain scores

Active ROM, °

Wrist

Increase of 4 1.4 (7.2) −6.3 (35.8) 0.1 (25.3) 2.4 (14.0)

Increase of 3 1 (5.3) 1 (4.6) 1 (4.6) 0

Increase of 2 0 0 2 (9.1) 1 (5.3)

Increase of 1 5 (26.3) 7 (31.8) 1 (4.6) 4 (21.1)

No change 11 (57.9) 14 (63.3) 17 (77.3) 14 (73.7)

Elbow

Increase of 3 1 (5.3) 1 (4.6) 1 (4.6) 0

Increase of 2 0 0 2 (9.1) 1 (5.3)

Increase of 1 5 (26.3) 7 (31.8) 1 (4.6) 4 (21.1)

No change 11 (57.9) 14 (63.3) 17 (77.3) 14 (73.7)

Passive ROM in fingers*

Decrease of 1 2 (10.5) 0 1 (4.6) 0

Decrease of 3 0 1 (4.6) 0 0

No change 11 (57.9) 13 (59.1) 7 (35.0) 10 (52.6)

Increase of 1 5 (26.3) 6 (27.3) 11 (55.0) 1 (5.3)

Increase of 2 1 (5.3) 1 (4.6) 1 (5.0) 4 (21.1)

Increase of 3 0 1 (4.6) 1 (5.0) 0

Increase of 4 0 0 0 1 (5.3)

Active ROM in fingers*

Decrease of 1 2 (10.5) 0 0 3 (15.8)

Decrease of 3 0 1 (4.6) 0 0

No change 11 (57.9) 13 (59.1) 7 (35.0) 10 (52.6)

Increase of 1 5 (26.3) 6 (27.3) 11 (55.0) 1 (5.3)

Increase of 2 1 (5.3) 1 (4.6) 1 (5.0) 4 (21.1)

Increase of 3 0 1 (4.6) 1 (5.0) 0

Increase of 4 0 0 0 1 (5.3)

Passive ROM in fingers*

Decrease of 1 2 (10.5) 0 0 3 (15.8)

Decrease of 3 0 1 (4.6) 0 0

No change 11 (57.9) 13 (59.1) 7 (35.0) 10 (52.6)

Increase of 1 5 (26.3) 6 (27.3) 11 (55.0) 1 (5.3)

Increase of 2 1 (5.3) 1 (4.6) 1 (5.0) 4 (21.1)

Increase of 3 0 1 (4.6) 1 (5.0) 0

Increase of 4 0 0 0 1 (5.3)

Pain scores −1.3 (2.7) −1.4 (1.7) −0.9 (1.8) −1.2 (1.4)

Rivermead Motor Assessment

0.2 (0.7) 0.2 (1.0) 0.3 (0.7) 0.1 (0.5)

Barthel Index

0.7 (1.2) 0.1 (1.4) 0.1 (2.5) 0.8 (2.6)

*Fingers ROM: a decrease in the ability to open the fingers was recorded as a negative number, and an increase was recorded as a positive number. The number (%) of patients in each change category are given.

also showed that the MAS was significantly reduced in the hemiparetic arm for all Dysport doses over the 16-week follow-up period in the elbow and wrist areas and also for the fingers in the 1000 U Dysport group (Table 4). Similar results were observed in patients with complete weakness of the affected limb (data not shown). The number of patients who had an improvement of the MAS in all 3 joints was significantly higher in the Dysport groups than in the placebo group (P<0.02).

Table 5 summarizes the results of the secondary outcome measures. All study groups had an increase in the ROM at the elbow, wrist, and fingers. However, the differences between the groups were not statistically significant. Similarly, there were no statistically significant differences between the study groups in the scores of pain, the Rivermead Motor Assessment Scale, or the Barthel Index for activities of daily living. Not surprisingly, 15.8% of patients who received 1500 U of Dysport and had residual muscle strength in the affected limb lost their ability to extend their fingers voluntarily.

Patients and their caregivers made a subjective evaluation of the effects of treatment on the ease (or difficulty) of extending the elbow to put the affected arm into a garment sleeve or to open the hand for cleaning the palm or for cutting the fingernails. However, formal statistical analysis was not performed on the data because of the small sample size. As shown in Table 6, more patients in the Dysport study groups showed improvement at 4 weeks compared with the placebo group, and this seemed to correlate with the dose of Dysport given.

Safety

Adverse events were reported by 33 patients in the 4 treatment groups, ie, 40.2% of the study population. No fatal, life-threatening, or incapacitating adverse events relating to the study medication were reported or observed. Overall, 8 of 19 patients (42.1%) reported adverse events in the placebo group, compared with 13 of 22 (59.1%), 4 of 22 (18.2%), and 8 of 19 (42.1%) in each of the 500, 1000, and 1500 U Dysport groups, respectively. The most frequently reported adverse events during the study were epileptic seizures (n=5), accidental injury (n=5), and urinary and respiratory tract infections (n=6), but these were not considered related to the study medication. Other common adverse events that were probably due to the study medication were skin rashes and flu-like symptoms. These occurred in 6 and 3 patients, respectively. There were no statistically significant differences in the incidence of any of the adverse events between the study groups. The results of the timed swallow test were also similar.

Discussion

The present study demonstrated that treatment with Dysport reduces muscle tone in patients with poststroke upper limb spasticity and confirmed the findings of previously reported open-label studies.6,15,16 Treatment was effective and safe at doses of 500, 1000, and 1500 U. The optimal dose of Dysport for the treatment of patients with residual voluntary movement in the upper limb appears to be 1000 U. At a dose of 1500 U, the range of active movement was sometimes reduced, probably because of excessive weakening of these muscles. The findings of a previous study using Botox (Allergan Inc) in doses of 75, 150, and 300 U were similar to...
the present study, assuming a Dysport/Botox dose conversion ratio of 3:1. In this dose ratio, the 2 products appear to have the same therapeutic equivalence.\textsuperscript{17}

Although the 3 doses of Dysport that were evaluated in this study resulted in significant reduction in muscle spasticity, their overall effect on the global disability scores was minimal. This is hardly surprising because the global assessment scales used have a low level of sensitivity. The Rivermead Motor Assessment is a hierarchical scale, and once a patient has reached a level at which he/she cannot perform the test activity, the assessment is discontinued. The Barthel Index includes mobility and continence items that are unlikely to be affected by localized treatment of upper limb muscle spasticity. In a similar study,\textsuperscript{8} other investigators did not observe a measurable improvement on global functional outcome measures, such as the Functional Independence Measure. This suggests that individualized goal-attainment scales, eg, ability to put the spastic arm through a garment sleeve, are more relevant outcome measures in studies of this nature. On further analysis of the effects of Dysport, we found that patients with the greatest difficulties or who were unable to put their arm through a sleeve or open their clenched hand for cleaning or cutting fingernails showed the greatest improvement. This suggests that individualized goal-attainment scales are more sensitive measures of functional change in this patient population. Another explanation for the poor functional improvement would be the choice of muscles injected. In this study we used a standard protocol for all patients. An individualized approach based on the distribution of spasticity in the individual patient would have given a more accurate indication of the effects of treatment on functional disability.

Although spasticity is frequently associated with muscle pain, this symptom was not a prominent feature in our study population. It is therefore not possible to make conclusions from the findings of this study regarding the effects of BtxA on muscle pain or painful muscle spasms.

Acknowledgments

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References