Botulinum toxin (Dysport®) treatment of hip adductor spasticity in multiple sclerosis: a prospective, randomised, double blind, placebo controlled, dose ranging study

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Abstract

***Objective*—To define a safe and effective dose of Dysport for treating hip adductor spasticity.**

***Methods*—Patients with definite or probable multiple sclerosis, and disabling spasticity affecting the hip adductor muscles of both legs, were randomised to one of four treatment groups. Dysport (500, 1000, or 1500 Units), or placebo was administered by intramuscular injection to these muscles. Patients were assessed at entry, and 2, 4 (primary analysis timepoint), 8, and 12 weeks post-treatment.**

***Results*—A total of 74 patients were recruited. Treatment groups were generally well matched at entry. The primary efficacy variables—passive hip abduction and distance between the knees—improved for all groups. The improvement in distance between the knees for the 1500 Unit group was significantly greater than placebo (p=0.02). Spasm frequency was reduced in all groups, but muscle tone was reduced in the Dysport groups only. Pain was reduced in all groups, but improvements in hygiene scores were evident only in the 1000 Unit and 1500 Unit groups. Duration of benefit was significantly longer than placebo for all Dysport groups (p<0.05). Adverse events were reported by 32/58 (55%) Dysport patients, and by 10/16 (63%) placebo patients. Compared with the two lower dose groups, twice as many adverse events were reported by the 1500 Unit group (2.7/patient). The incidence of muscle weakness was higher for the 1500 Unit group (36%) than for placebo (6%). The response to treatment was considered positive by two thirds of the patients in the 500 Unit group, and by about half the patients in the other groups.**

***Conclusion*—Dysport reduced the degree of hip adductor spasticity associated with multiple sclerosis, and this benefit was evident despite the concomitant use of oral antispasticity medication and analgesics. Although evidence for a dose response effect was not statistically significant, there was a clear trend towards greater efficacy and duration of effect with higher doses of Dysport. Dysport treatment was well tolerated, with no major side effects seen at doses up to 1500 Units. The optimal dose for hip adductor spasticity seems to be 500–1000 Units, divided between both legs.**

(*J Neurol Neurosurg Psychiatry* 2000;**68**:707–712)

Keywords: botulinum toxin; dose range; multiple sclerosis; spasticity

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Received 19 March 1999 and in revised form 3 November 1999
Accepted 3 December 1999

Spasticity is a state of hypertonicity with exaggeration of the tendon reflexes mediated by a loss of inhibitory control of upper neurons. The result is a resistance to passive movement. It is often associated with pain, spasms, and functional disability. Conventional treatment for spasticity includes systemic drug therapy, local nerve blocks, physiotherapy, orthoses, orthopaedic surgery, and neurosurgery. It is recognised, however, that no single treatment, or combination of treatments, is completely satisfactory. Surgical procedures and commonly used drugs, such as dantrolene, diazepam, and baclofen, also have potentially serious side effects.

Botulinum toxin treatment offers a new targeted approach to managing spasticity. Botulinum toxin type A is a neurotoxin derived from the bacterium *Clostridium botulinum*. It prevents the release of acetylcholine at neuromuscular junctions, thereby inhibiting muscle contraction. In recent years it has become the treatment of choice for some focal dystonias, including blepharospasm[1] cervical dystonia,[2–4] and hemifacial spasm.[1] The side effect profile of the toxin depends on the dose administered and the site of injection. Most of the side effects are a consequence of the pharmacological effect of the toxin, causing weakening of muscles adjacent to the site of injection. In addition to local side effects, there is a possibility that systemic spread of the toxin may produce effects at more distant cholinergic nerve terminals. At therapeutic doses side effects are often transient and rarely severe.

Preliminary reports have suggested a role for botulinum toxin in the treatment of spasticity, as it can reduce the degree of spasticity in both upper and lower limbs.[5–8] These studies used doses of 400–1600 Units of Dysport, and no problems related to side effects were encountered. In a double blind, cross over study of nine wheelchair bound or bed bound patients with chronic multiple sclerosis, injection of botulinum toxin (Botox®) into the adductor muscles of the leg produced a significant reduction in the degree of spasticity and an improvement in the ease of nursing care.[9] A reduction in adductor spasticity facilitates the care of the perineum,

and minimises the risk of soft tissue necrosis resulting from increased pressure between the legs. This study used 400 Units Botox, which is equivalent to about 1200 Units Dysport,[10] and no adverse events were reported.

The aim of this placebo controlled, dose ranging study was to assess the effect of three different doses of Dysport (500, 1000, and 1500 Units), to define a safe and effective dose for the treatment of hip adductor spasticity in patients with definite or probable multiple sclerosis.

Methods

ETHICAL CONSIDERATIONS

This study was conducted in accordance with the Declaration of Helsinki and its amendments, as well as the guidelines for good clinical practice. It was approved by the appropriate national regulatory organisations and local research ethics committees. The study was explained fully to eligible patients, and written informed consent was obtained before any study specific assessments were performed.

PATIENT POPULATION

Adults (≥18 years) of either sex with definite or probable multiple sclerosis, and with disabling spasticity of the hip adductor muscles (Kurtzke EDS score ≥7), which had been stable for at least 6 months before entry, and which caused moderate pain or difficulty in nursing (hygiene score ≥2), were considered eligible. Patients were excluded if they had acute exacerbation of multiple sclerosis, established contracture of the hip, hypersensitivity to botulinum toxin, myasthenia gravis, or other neuromuscular junction diseases, or were pregnant or premenopausal and unwilling to use contraceptive measures. Patients were also excluded if they had received recent treatment with botulinum toxin (within 4 months), phenol injection (within 4 months), intrathecal baclofen (within 14 days), or any investigational new drug (within 3 months).

STUDY TREATMENT

Dysport (Ipsen Ltd, Maidenhead, UK) was supplied in clear glass vials as a freeze dried white pellet containing *Clostridium botulinum* type A toxin haemagglutinin complex together with 125 μg human albumin and 2.5 mg lactose. Each vial contained about 500 Dysport Units. Matching placebo supplies were presented in identical clear glass vials, containing 125 μg human albumin and 2.5 mg lactose. Patients were randomised to one of four treatment groups, and received a single treatment with either Dysport (500, 1000, or 1500 Units), or placebo. Study blinding was assured by supplying study medication as individual patient boxes with four identical vials, each containing either 500 Units Dysport or placebo. The contents of each vial were reconstituted with 1.0 ml sodium chloride injection BP (0.9%), to give a total injection volume of 4.0 ml, and patients were treated within 1 hour of reconstitution. Treatment was administered by intramuscular injection to the hip adductor muscles of both legs. The adductor magnus of each leg received a single injection of 1.0 ml, and the adductor longus and adductor brevis each received a single injection of 0.5 ml. Muscles were located by palpation, and were injected at the standard site used for EMG.[11] No further botulinum toxin treatment was given until the end of the study.

Oral antispastic and analgesic medication being taken by the patient at the time of entry was permitted at a constant dose throughout the study. Regular physiotherapy was also permitted to continue unchanged throughout the study. Other concomitant medication was permitted at the discretion of the investigator.

ASSESSMENTS

At entry patient demography, multiple sclerosis history, and any other concomitant medical conditions and medication were documented. Angles of active and passive hip abduction for both legs were assessed using a protractor goniometer with the patient in the supine position. Both arms of the goniometer were placed over the line from the anterior superior iliac spine (ASIS) to the midpatella, with the fulcrum on the ASIS. While holding one arm of the goniometer in place, the leg was abducted with the other arm of the goniometer still positioned on the ASIS/midpatella line, and the angle through which the leg moved was recorded. Passive abduction was performed smoothly and slowly, either until resistance was met, or as far as was comfortable for the patient. Active abduction was performed by asking the patients to move their legs sideways as far as they could. The maximum distance between the knees was measured during passive abduction.

The assessment of spasticity involved separate assessment of the muscle tone and spasm frequency of both legs, in accordance with the modified Ashworth score.[9] Passive movement of the hip was made with the patient in the supine position, and muscle tone and spasm frequency were assessed for each leg according to the five point scales presented in table 1. The modified Ashworth score, calculated for both legs, was the product of muscle tone and spasm frequency. In addition, patients were asked to assess the pain associated with hip adductor spasticity for both legs on a four point scale (absent, mild, moderate, severe), and the investigator recorded a clinical global rating of hip adductor spasticity symptoms according to a four point scale (symptom free, mild, moderate, severe).

An assessment of perineal hygiene was made by grading the ease of cleaning and/or catheterising the patient, according to a six point scale

Table 1 Components of the modified Ashworth score

Muscle tone	*Score*	*Spasm frequency*
No increase in muscle tone	0	No spasms
Increased tone: hips easily abducted to 45° by one person	1	One or fewer spasms/day
Hips abducted to 45° by one person with mild effort	2	One to five spasms/day
Hips abducted to 45° by one person with major effort	3	Six to nine spasms/day
One person unable to abduct hips to 45°	4	≥10 spasms/day, or continuous contractions

(0=independent with self care; 1=one person able to clean and/or catheterise with ease; 2=one person able to clean and/or catheterise with effort; 3=one person able to clean and/or catheterise with major difficulty; 4=two people required, but able to clean and/or catheterise easily; 5=two people clean and/or catheterise with difficulty).

At each subsequent clinic visit (2, 4, 8, and 12 weeks after treatment) assessments of joint range of motion, muscle tone, spasm frequency, upper leg pain, perineal hygiene, and the clinical global rating of upper leg spasticity were repeated. Whenever possible, for each assessment, the assessor at entry was also the assessor at each subsequent visit. In addition, adverse events either seen by the investigator or reported by the patient, and any changes in concomitant medication, were assessed and recorded.

ASSESSMENTS ON COMPLETION OF THE STUDY

Whenever possible, patients continued until the week 12 assessment, although the protocol allowed patients to be re-treated at any time during the study. On completion of the study, patients and investigators were asked to rate the response to treatment on a five point scale (excellent, good, fair, poor, no benefit). Patients who were not re-treated on completion of the study were followed up until re-treatment was required, or until it was decided that the patient would not be re-treated.

STATISTICAL ANALYSIS

The sample size calculation was based on the assumption of a 5% response rate in the placebo group and 49% in any of the active treatment groups, so that a study with 80 patients (20/group) would have 90% power to detect a difference at the 5% level of significance. The study was brought to a close once all available patients had been recruited from participating centres. As only 74 patients were entered the power of the study to detect the expected difference in response rate was reduced to 80%. Plans for the statistical analysis of the study were summarised in the protocol, refined during the course of the study, and finalised in a prospective analysis plan before unblinding the study. All randomised patients received study medication, and were included in the efficacy and safety analyses. The sum of the angles of passive hip abduction for both legs, and the maximum distance between the knees, were the primary efficacy variables.

The angles of active and passive hip abduction for both legs were combined to give a total angle. As most of the patients were unable to actively abduct their hips, data for this variable were treated as binary, and presented as the proportions that could and could not achieve abduction. Modified Ashworth score, muscle tone, spasm frequency, and upper leg pain were recorded as categorical data for each leg. Patients' and investigators' overall opinions were further categorised into binary data sets, such that a positive opinion of the response to treatment was defined as excellent, good, or fair. Duration of effect was defined as the time between week 0 and retreatment with botulinum toxin.

The primary statistical comparison for all variables was between the Dysport 1500 Unit group and placebo. Secondary comparisons were made between the Dysport 500 Unit group and placebo, and the Dysport 1000 Unit group and placebo. The primary analysis was performed on the change from baseline at week 4. Passive hip abduction data were analysed using the Wilcoxon rank sum test for non-parametric data, and changes in the maximum distance between the knees were analysed using analysis of variance (ANOVA) for parametric data. Between group comparisons of the proportion of patients able to actively abduct their hips were performed using the χ^2 test, or Fisher's exact test when frequencies were small. Modified Ashworth scores were compared by ANOVA. Between group comparisons of muscle tone, spasm frequency, clinical global spasticity rating, upper leg pain, hygiene scores, and patients' and investigators' overall opinions were performed using the Cochran Mantel-Haenzel test. Duration of effect data were analysed using the Wilcoxon rank sum test. Where applicable ($p<0.05$) the level of statistical significance is indicated,

Results

PATIENT DISPOSITION

A total of 74 patients (Placebo, 16; 500 Units, 21; 1000 Units, 20; 1500 Units, 17) entered the study at eight centres (six UK, one German, one Austrian). Two patients, one in the placebo group, and one in the 1000 Unit group were withdrawn due to a need for re-treatment before the primary analysis time point at week 4. Overall, 14 patients (Placebo, 7/16, 44%; 500 Units, 2/21, 10%; 1000 Units, 3/20, 15%; 1500 Units, 2/17, 10%) were withdrawn before the scheduled end of the study at week 12. With the exception of one patient in the placebo group who withdrew consent, and one patient in the 1000 Unit group who was withdrawn after admission to hospital for a urinary tract infection, all other patients were withdrawn due to a need for retreatment.

DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Table 2 presents a summary of patient demographic data and concomitant medication at entry. The groups were well matched for age, height, weight, duration of multiple sclerosis, and Kurtzke EDS score. About half of the patients in the 1000 Unit and 1500 Unit groups were women, compared with about

Table 2 Baseline characteristics

	Placebo	*500 Units*	*1000 Units*	*1500 Units*
Demographic details:				
No of patients	16	21	20	17
Age (y (SD))	50.7 (10.9)	47.0 (12.2)	54.0 (9.9)	46.8 (10.3)
Females (n (%))	12 (75)	16 (76)	9 (45)	9 (53)
Height (cm (SD))	166 (13)	165 (10)	171 (9)	170 (9)
Weight (kg (SD))	60.3 (9.9)	60.5 (14.0)	68.2 (10.6)	67.9 (14.1)
Duration of MS (y (SD))	16.6 (6.4)	16.5 (7.3)	22.9 (10.6)	21.2 (10.6)
Kurtzke EDS score (median)	7.75	8.00	7.50	7.50
Concomitant medication:				
Skeletal muscle relaxant (n (%))	6 (38)	17 (81)	13 (65)	9 (53)
Analgesics (n (%))	2 (13)	7 (38)	7 (35)	3 (18)
Diazepam (n (%))	4 (25)	7 (33)	5 (25)	6 (35)

three quarters of the patients in the placebo and 500 Unit groups. Fewer patients in the placebo group were receiving concomitant skeletal muscle relaxants and analgesics.

Baseline efficacy assessments are summarised in table 3. The groups were well matched in terms of maximum distance between the knees, passive and active hip abduction, clinical global rating, and hygiene scores. Most patients had severe spasticity at baseline according to the clinical global rating, and this is emphasised by the fact that most patients recorded a maximum score for muscle tone and spasm frequency. The total spasticity score was slightly higher for the 1000 Unit group (mean 13.3) compared with the other groups (range of means 10.3–11.5) due to greater spasm frequency. The proportion of pain free patients was lowest in the placebo group (19%) compared with the Dysport groups (range 30–52%).

ASSESSMENT OF EFFICACY

Efficacy data are summarised in table 3. At week 4, the angle of passive hip abduction and the maximum distance between the knees were greater than at entry for all groups. For both of these primary efficacy variables the smallest improvement was seen in the placebo group, but only the improvement in the maximum distance between the knees for the Dysport 1500 Unit group was statistically better than placebo (p=0.02). The Modified Ashworth score improved to a similar extent for all groups at week 4 compared with entry, however, in the Dysport groups this improvement was due to both reduced spasm frequency and improved muscle tone, whereas for the placebo group only spasm frequency improved. Few patients in any group demonstrated improvement in active hip abduction at week 4. The median clinical global rating improved from severe at week 0 to moderate at week 4 for all groups. The proportion of pain free patients increased for all groups at week 4 compared with week 0, and although the greatest improvement was in the placebo group the proportions of pain free patients at week 4 were similar for all groups. Compared with week 0 the median hygiene score remained unchanged for the placebo and 500 Unit groups, and improved from 2 to 1 for the 1000 Unit and 1500 Unit groups. Investigator and patient overall opinions were similar, with a positive opinion for about two thirds of the patients in the 500 Unit group, and half the patients in the other groups. A higher proportion of placebo patients (88%) either requested re-treatment or had re-treatment indicated before week 12 compared with the Dysport groups (range 55%–62%). Time until re-treatment was significantly longer for all Dysport groups (1500 Units, p=0.015; 1000 Units, p=0.017; 500 Units, p=0.042) compared with placebo; however, the trend for increased duration of effect with increasing dose was not statistically significant.

ASSESSMENT OF SAFETY

Adverse events (table 4) were reported for 32/58 (55%) patients treated with Dysport, and by 10/16 (63%) patients treated with placebo. The most frequent adverse events in the patients treated with Dysport were hyper-

Table 3 Efficacy assessments

	Placebo	*500 Units*	*1000 Units*	*1500 Units*
Maximum distance between knees (cm):				
Week 0 (mean (SD))	28.2 (12.8)	29.8 (12.1)	24.9 (11.9)	28.5 (10.3)
Week 4 (mean (SD))	32.1 (12.3)	36.7 (12.8)	31.9 (9.2)	39.2 (10.4) (p=0.02)
Passive hip abduction (degrees):				
Week 0 (mean (SD))	42.6 (27.5)	39.4 (20.6)	39.4 (21.3)	48.2 (23.0)
Week 4 (mean (SD))	53.9 (19.7)	56.5 (24.8)	63.4 (24.3)	61.3 (25.4)
Active hip abduction:				
Abduction possible at week 4 (n (%))	4 (27)	5 (26)	5 (31)	7 (41)
Improved from week 0 (n (%))	2 (13)	1 (5)	1 (6)	2 (12)
Modified Ashworth score:				
Week 0 (median)	12.0	8.5	16.0	14.0
Week 4 (median)	8.0	4.0	12.0	8.0
Muscle tone:				
Patients with maximum score at week 0 (n (%))	14 (88)	17 (81)	18 (90)	15 (88)
Patients with maximum score at week 4 (n (%))	13 (87)	13 (68)	13 (76)	10 (59)
Spasm frequency:				
Patients with maximum score at week 0 (n (%))	7 (44)	9 (43)	13 (65)	8 (47)
Patients with maximum score at week 4 (n (%))	3 (20)	3 (16)	7 (41)	4 (24)
Clinical global rating:				
Week 0 (median)	3.0	3.0	3.0	3.0
Week 4 (median)	2.0	2.0	2.0	2.0
Upper leg pain:				
Pain free at week 0 (n (%))	3 (19)	11 (52)	6 (30)	7 (41)
Pain free at week 4 (n (%))	10 (67)	11 (61)	7 (41)	11 (65)
Hygiene assessment:				
Week 0 (median)	2.0	2.0	2.0	2.0
Week 4 (median)	2.0	2.0	1.0	1.0
Overall opinions:				
Investigator: positive*response (n (%))	7 (44)	14 (67)	9 (48)	6 (36)
Patient: positive*response (n (%))	7 (44)	13 (62)	10 (53)	8 (47)
Retreatment with botulinum toxin:				
Requested or indicated before week 12, (n (%))	14 (88)	13 (62)	11 (55)	10 (59)
Time to retreatment, days (median)	56 (n=7)	99 (n=8) (p=0.042)	111 (n=10) (p=0.017)	119 (n=9) (p=0.015)

*Positive response defined as excellent, good, or fair.
Statistical comparisons with placebo.

Table 4 Adverse event profile

Adverse event	*All Dysport patients*	*1500 Units*	*1000 Units*	*500 Units*	*Placebo*
Patients (n)	58	17	20	21	16
Total Adverse Events (n)	92	46	23	23	35
Hypertonia	22	35	20	14	25
Muscle weakness	14	35	0	10	6
Fatigue	7	18	5	0	13
Urinary tract infection	5	18	0	0	19
Headache	5	12	5	0	13
Micturition frequency	5	6	0	10	13
Back pain	5	6	0	10	0
Diarrhoea	5	0	0	14	0
Arthralgia	3	0	5	5	6
Gait abnormal	3	6	5	0	6
Abscess	3	6	5	0	0
Constipation	3	12	0	0	0
Infection	3	6	5	0	0
Influenza-like symptoms	3	6	0	5	0
Nausea	3	12	0	0	0
Skin disorder	3	0	5	5	0
Abdominal pain	2	6	0	0	6
Fever	2	6	0	0	6
URTI	2	6	0	0	6

Data presented as the proportion of patients reporting each adverse event. Adverse events occurring once in only one group have not been included in this table.

tonia (new or worsening spasticity) of injected and/or non-injected muscles (22%), weakness of non-injected muscles (14%), fatigue (7%), urinary tract infection (5%), headache (5%), micturition frequency (5%), back pain (5%), and diarrhoea (5%). The adverse event profile was very similar for the placebo group, with the exception of muscle weakness, which was reported by 1/16 (6%) patients. Twice as many adverse events were reported by the 1500 Unit group (mean 2.7/patient) compared with the 500 Unit group (mean 1.1/patient) and 1000 Unit group (mean 1.2/patient).

Six patients experienced serious adverse events. One patient was admitted to hospital with diarrhoea and a urinary tract infection, 36 days after receiving 1500 Units of Dysport. Another patient was admitted to hospital with a urinary tract infection, chest infection, and hypothermia 69 days after receiving 1000 Units of Dysport. These symptoms were considered by the investigator to be unrelated to study medication. Four placebo patients were also admitted to hospital. The reasons were bowel spasticity, gastroparesis, pulmonary embolism, and urinary retention/urinary tract infection due to a blocked catheter.

Discussion

This study confirms the previous report from Snow *et al*[9] that administration of botulinum toxin type A reduces the degree of hip adductor spasticity associated with multiple sclerosis. Importantly, this benefit was evident despite the extensive use of concomitant oral antispasticity medication and analgesics.

The multiple sclerosis population targeted by this study was deliberately homogenous, to minimise the number of patients that would be required to demonstrate statistical significance. Furthermore, the selection of patients with a Kurtzke score of at least 7 was considered prudent, due to the possibility that the higher doses may produce excessive muscle weakness and affect mobility. Patients' spasticity was required to have been stable for at least 6 months before study entry to exclude patients whose spasticity was known to be variable or deteriorating. It is recognised, however, that spontaneous changes in spasticity during the study cannot be excluded. The advantage of defining a homogenous patient population is a reduction in the variability of response to treatment. The disadvantage is that the number of eligible patients at one centre is reduced so that more than one centre is required to achieve the target recruitment. In this study eight centres in three European countries were involved. Thorough training can greatly assist in standardising assessment methods between centres; however, there will always be a degree of variability, especially with the more subjective assessments that can be influenced by differences in clinical judgement. Although this study only demonstrates efficacy and safety of Dysport in this select patient population, there is little evidence to suggest that the response to Dysport would be dependent on the aetiology of the spasticity.

The efficacy of Dysport was demonstrated by the objective assessment of the range of hip abduction and the maximum distance between the knees made during passive abduction of the hips. Consistently greater improvements were evident in the three Dysport groups compared with placebo. Theoretically, the sum of the angles achieved for left and right maximum passive hip abduction should correlate with the maximum distance between the knees. The decision to use both measures in this study reflected the difficulty in performing these assessments, and a lack of consensus as to which was more reliable. The fact that data for distance between the knees were normally distributed and data for passive hip abduction were not normally distributed confirms the problems foreseen at the start of the study and supports the use of both assessment methods. Analysis of the components of the modified Ashworth scale indicated that the improvement in hip adductor spasticity was due to reductions of both muscle tone and spasm frequency. However, as spasm frequency was also reduced in the placebo group, it can be concluded that the major effect of Dysport was on muscle tone. In addition, patients treated with Dysport demonstrated a significantly longer duration of effect, with a more prolonged effect associated with higher doses. Patients treated with Dysport also demonstrated improvements in the assessment of perineal hygiene, with a trend towards greater improvement with higher doses. In the absence of an objective and validated assessment of perineal hygiene the scale devised for this study was considered appropriate for investigating functional benefit in this area. Although all assessments demonstrated improvement after Dysport treatment, it should be noted that the placebo group also showed improvements, which for pain associated with spasticity and the clinical global rating of spasticity were at least as good as the Dysport groups, suggesting that the efficacy of Dysport is less clear.

Although a "placebo effect" is often seen in clinical studies a notable aspect of this study was the unexpectedly good improvement dem-

onstrated by the placebo group, both for objective and subjective assessments. Consequently, for some of the assessments the sample size was not large enough to be able to show a statistically significant difference between Dysport and placebo. This seems to be especially true for the analysis of week 4 data; however, the clear difference between Dysport and placebo in terms of the duration of effect demonstrates that the benefits of placebo are transient. It is difficult to provide a clear explanation for this finding, and although the usual psychological factors associated with clinical trial participation may be contributory it is likely that other factors are also involved. Treatment groups were generally well balanced; however, the placebo group was receiving fewer concomitant antispasticity and analgesic medications, had fewer pain free patients at entry, and perhaps had a greater capacity to improve, at least in the short term. In addition, although it was the intention to ensure that concurrent physiotherapy remained unchanged during the study, this is difficult to control for, and so the possibility exists that changes in physiotherapy and/or carer assisted exercises contributed to this finding. Equally, it is possible that spontaneous changes in hip adductor spasticity may have occurred during the study.

In addition to being placebo controlled, another strength of the study was that treatment was administered in a double blind manner, thereby removing a major source of bias. As blinding was only possible if all patients received the same volume of injection, it was not possible to control for the concentration of the injection, which consequently varied threefold between the highest and lowest dose groups. Although there is a belief that there may be less spread outside the target muscles with increasing concentrations this has never been demonstrated, and so it is not possible to comment on how this variable affected safety and efficacy assessments. The selection of 1500 Units as the highest dose in this study reflected the experience gained from previous studies of the use of botulinum toxin in the treatment of spasticity. Snow *et al*[9] used a similar patient population and demonstrated the safety and efficacy of 400 Botox Units, which is equivalent to about 1200 Dysport Units.[10] In addition, upper limb spasticity had been successfully treated with a dose of 1600 Dysport Units.[5 7] Additional treatment groups receiving 1000 Units and 500 Units were considered appropriate for this dose ranging study to help define the minimum effective dose. Although this study did not show a statistically significant dose response for any assessment, there were clear trends suggesting that higher doses were more effective.

The most often reported adverse event was hypertonia, although this is unlikely to be related to Dysport treatment, as there was a similar incidence in the placebo group. It is more probable that the new and worsening muscle spasms reflect the normal variation of the disease state in this patient population. This study has shown that the main between treatment difference was the higher incidence of muscle weakness in patients treated with Dysport, especially in the 1500 Unit group, suggesting that this dose could be too high in a proportion of these patients. As most of these reports reflected weakness of the leg muscles, it suggests that there is a degree of spread to adjacent muscle groups. The few reports of muscle weakness of the hand and trunk, and the one report of generalised muscle weakness, indicates that Dysport may also affect more distant muscle groups. With administration of Dysport to the hip adductor muscles of the upper leg, there is also potential for spread to the muscles around the pelvic floor, and an expectation of an increased incidence of urinary and faecal incontinence. Although most patients in this study already had a degree of urinary dysfunction, there was no evidence that Dysport made the problem worse. Equally, there was no evidence of urinary incontinence developing in the patients with normal urinary function.

In conclusion, the administration of Dysport reduced the degree of hip adductor spasticity associated with multiple sclerosis. Despite patients receiving concomitant oral antispasticity and analgesic medication Dysport treatment produced an additional clinical benefit, with trends suggesting greater benefit with higher doses. Dysport treatment was well tolerated, with no major side effects found at doses up to 1500 Units. A risk-benefit assessment would suggest that the optimal starting dose for treating hip adductor spasticity would be 500–1000 Units, divided between both legs, with subsequent dose titration as required. Although this study confirms the efficacy and safety of Dysport there is clearly a need for further work in this area to clarify its role in the overall management of spasticity, especially in relation to other currently available treatments.

This study was supported and coordinated by Ipsen Limited.

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