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ORIGINAL COMMUNICATION

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Efficacy and safety of a standardised 500 unit dose of Dysport® (Clostridium botulinum toxin type A haemaglutinin complex) in a heterogeneous cervical dystonia population: results of a prospective, multicentre, randomised, double-blind, placebo-controlled, parallel group study

Abstract Results from a dose-ranging study in a selected group of de novo patients with rotational cervical dystonia (CD) suggest that 500 units of Dysport *(Clostridium botulinum* toxin type A haemaglutinin complex) is the optimal starting dose. The present study aimed to confirm the efficacy and safety profile of this dose in a population of CD patients more representative of those seen in a typical dystonia clinic.

A total of 68 patients with moderate to severe CD (Tsui score ≥ 9) were randomly assigned to receive placebo or Dysport 500 units. Treatment was administered according to the clinical pattern of head deviation, using a standardised injection protocol. A total of 21 patients (11 Dysport, 10 placebo) had not previously received botulinum toxin type A (BtxA) injections, and 47 patients (24 Dysport, 23 placebo) had received BtxA more than 12 weeks previously. Assessments were performed at baseline and weeks 4, 8 and 16. Patients defined as non-responders at week 4 were re-treated in an open phase with 500 units of Dysport at week 6, and were followed up at week 10.

Significant between-group differences in Tsui scores were present at weeks 4 (p=0.001) and 8 (p=0.002). Similarly, there were significant between-group differences ($p < 0.001$) in patient and investigator assessments of response in favour of Dysport at weeks 4 and 8. Also, more Dysport (49 %) than placebo (33 %) patients were pain-free at week 4 (p=0.02). Overall, 30/35 (86 %) Dysport patients and 14/33 (42 %) placebo patients were classified as responders at week 4. Adverse events were reported by 15/35 Dysport patients and 9/33 placebo patients. Open phase treatment produced improvements in Tsui ($p < 0.001$) and pain scores (p=0.011), and 23/24 patients were classified as responders.

Although individual dose titration and muscle selection is desirable, this study demonstrated that a dose of 500 units of Dysport injected into clinically identified neck muscles without electromyographic guidance is safe and effective in the treatment of patients with the major clinical types of cervical dystonia.

Key words Botulinum toxin A · Cervical dystonia · Dose recommendation

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Introduction

Over the past ten years local injections of botulinum toxin type A (BtxA) have become a first line treatment for cervical dystonia. Published series now cover more than a thousand patients; however, most of the treatment recommendations are based on open-label trials [2, 6, 7, 13]. Results from a double-blind, randomised, placebo-controlled, dose-ranging study in a homogeneous group of previously untreated (de novo) patients with pure rotational cervical dystonia suggest that 500 units of Dysport® (Clostridium botulinum toxin type A haemagglutinin complex) divided between the splenius capitis muscle ipsilateral, and the sternocleidomastoid muscle contralateral to the direction of head deviation is the optimal starting dose [11]. The present multicentre, randomised, double-blind, placebo-controlled, parallel-group trial was performed to assess the efficacy and safety of 500 units of Dysport in the treatment of a less selected group of patients with moderate to severe cervical dystonia as typically seen in routine dystonia clinics.

Patients and methods

Patients

All participating centres obtained the approval of their local ethics committee, and all patients gave written informed consent. Patients with all major types of head deviation (except pure anterocollis) were eligible, regardless of whether they had previously received BtxA or not. Previously treated patients were eligible if the most recent treatment was not within 12 weeks of entry. The severity of cervical dystonia was measured according to the Tsui scale [12] and only moderately to severely affected patients (score ≥9) were eligible. Previously treated patients were excluded if their most recent dose of Dysport® was < 250 units or > 750 units, or comparable dose of Botox® (ratio of 3:1 between Dysport and Botox [9]). To exclude potential secondary non-responders, patients with a lack of response to one or more of their last three BtxA injections were not included. In addition, patients with a complex pattern of dystonic head deviation which would require electromyographic guidance and/or injection of more than three muscles were excluded.

Methods

Patients were randomly assigned to receive either placebo or 500 units of Dysport. Randomisation was stratified for patients previously treated with BtxA and de novo patients. According to the treatment protocol, the selection of muscles for injection was restricted to two or three muscles out of the following: sternocleidomastoid muscle (SM), splenius capitis muscle (SP), trapezoid muscle (TP), and levator scapulae muscle (LS) from either side. Muscle selection for injection was based on clinical assessment taking into account direction of head deviation and/or shoulder elevation, visible hypertrophy, and palpable stiffness as well as localisation of pain.

Blinded study medication was supplied by Ipsen Ltd. (Maidenhead, UK) as identical vials containing either Dysport (500 units of *Clostridium botulinum* type A haemagglutinin complex together with 125µg of human albumin and 2.5 mg of lactose) or placebo (125µg of human albumin and 2.5 mg of lactose). Immediately prior to injection the contents of the vial were reconstituted with 1.0 ml normal (0.9 %) saline. The total volume of 1.0 ml (500 units Dysport or placebo) was divided between the pre-defined muscles (two injection sites/muscle), within the following volume (dose) ranges for each muscle: SM 0.2–0.4 ml (100–200 units), SP 0.5–0.7 ml (250–350 units), TP 0.2–0.4 ml (100–200 units), LS 0.2–0.4 ml (100–200 units). The exact dose per muscle was determined within these guidelines according to the clinical judgement of the treating physician.

Prior to treatment the severity of cervical dystonia was assessed using the Tsui-scale [12] under standardised conditions (at least one minute assessment with the patient sitting in a comfortable chair, eyes open, making a subjective effort to relax the head and neck, and refraining from sensory manoeuvres during the assessment). In addition, the pain associated with cervical dystonia was assessed using a four point scale (none, mild, moderate, severe).

Patients returned four weeks after treatment, and Tsui scores and pain assessments were repeated. In addition, both the investigator and the patient assessed the change in their condition according to a five-point scale (symptom free, improvement ≥50 %, improvement < 50 %, no improvement, worse). According to prospective criteria, patients for whom both assessments were rated as either no improvement or worse were classified as non-responders, and were withdrawn from the blinded phase of the study. Patients for whom at least one assessment indicated improvement were classified as responders, and they continued in the blinded phase of the study.

Responders returned eight weeks after treatment, and Tsui scores, pain assessments, and the investigator/patient assessments of change from baseline were repeated. According to the same response criteria, any patient who had lost their response was withdrawn from the study. These patients did not enter the open phase. Patients with an ongoing response continued until the final clinic visit at 16 weeks post-treatment or retreatment was required.

Non-responders at week 4 entered an open phase and were retreated six weeks after the initial blinded treatment with 500 units of Dysport, in accordance with the same treatment protocol as used for the blinded phase. Tsui scores, pain scores, and investigator/patient assessments of change were then repeated at week 10.

Adverse events were assessed at each clinic visit using a combination of open questioning, and a checklist of ten conditions (dysphagia, dry mouth, voice changes, neck muscle weakness, tiredness, respiratory difficulties, discomfort at injection site, visual difficulties, jaw weakness and limb weakness) commonly considered to be related to BtxA use. The severity of each adverse event was assessed as mild, moderate or severe.

On completion of the study the investigator made a global assessment of efficacy and safety for each patient. Efficacy was assessed on a six-point scale (excellent, good, moderate, slight improvement, no change, or worse), and safety according to the adverse event profile was assessed on a five-point scale (none, mild, moderate, severe, or extreme). Treatment success was defined as an efficacy assessment of at least moderate improvement with a safety assessment of no worse than moderate. Patients defined as non-responders at week 4 were automatically considered treatment failures.

Statistical analysis

In the double-blind phase the comparison of interest was Dysport versus placebo. All patients, including non-responders, were included in this analysis. Assumptions of homogeneity of variance and normality of distribution were satisfied. No treatment by centre, treatment by strata, or treatment by baseline interactions were observed. Between-group differences in Tsui score were tested by analysis of covariance. Tsui score data are also presented as percentage improvement from baseline. Logistic regression was used to test between-group differences in pain scores, patient and investigator assessments of change, and the global assessment of efficacy and safety. In order to remove the bias created by the withdrawal of the majority of placebo patients at week 4, a last observation carried forward tech-

nique was used for the week 8 analyses. In the open phase the comparison of interest was week 10 versus week 0. Only non-responders who left the double-blind phase at week 4 were included in this analysis. Change in Tsui score was assessed by paired t-test and change in pain scores was assessed using the McNemar test.

Results

Double-blind phase

A total of 68 patients with moderate to severe uncomplicated cervical dystonia were included in the study. Of these, 33 were randomised to receive placebo and 35 received 500 units of Dysport. Overall, the treatment groups were well matched with respect to age, sex, weight and height (Table 1). All patients were Caucasian. Twenty-one patients (11 Dysport, 10 placebo) were de novo, and 47 patients (24 Dysport, 23 placebo) had received previous treatment with BtxA. For those patients who had previously received treatment with BtxA, both groups were well matched with respect to the history of BtxA treatment. Table 2 presents the patient population according to the type of cervical dystonia at entry, and demonstrates that both groups were similarly heterogeneous.

Both groups were well matched with regard to Tsui score at baseline (Table 3). At week 4 following treatment, mean Tsui score had improved for both groups (Dysport 41 %, placebo 17 %), but the improvement in the Dysport® group was significantly greater than placebo (p=0.001). This between-group difference in Tsui scores remained significant at week 8 post-treatment (p=0.002). Fig. 1 demonstrates that in both treatment groups the de novo and previously treated patients had similar improvements in mean Tsui score.

The pain associated with cervical dystonia at baseline was also similar for both groups at entry into the study (Table 4), with 10/35 (29 %) Dysport patients and 10/33 (30 %) placebo patients being pain-free. At week 4 the Dysport group demonstrated a reduction in pain that was significantly better than the placebo group (p=0.02).

Table 1 Demographic characteristics for the placebo and Dysport group.

	Placebo	Dysport
Patients (n)	33	35
Age (years)[a]	49.7±9.6 (26–68)	45.8±13.2 (18–75)
Female:Male (n)	19:14	16:19
Weight (kg)[a]	77.0±15.6 (50–110)	71.7±11.5 (47–98)
Height (cm)[a]	172±9 (154–192)	172±7 (157–185)
Time since diagnosis (years)[a]	4.8±4.4 (0–14)	6.5±8.0 (0–31)
De novo:Previously treated (n)	10:23	11:24
Time since first BtxA treatment (years)[a]	2.2±2.1 (< 1–9)	2.5±2.2 (< 1–7)
BtxA treatments (n)[a]	8.1±5.8 (1–19)	10.3±7.0 (1–26)
Time since most recent BtxA treatment (days)[b]	97 (84–436)	98 (81–560)
Most recent BtxA dose (units)[a, c]		
Dysport	531±105 (250–700) [n=21]	531±124 (300–750) [n=22]
Botox	100±0 [n=2]	150±0 [n=2]

[a] Data presented as mean ± SD (range)
[b] Data presented as the median (range)
[c] Not recorded for one patient in the Dysport group
BtxA = Botulinum toxin type A

Table 2 Clinical classification of cervical dystonia according to the pattern of head deviation

	Placebo	Dysport
Pure rotational	4	4
Predominantly rotational (with laterocollis)	12	16
Predominantly rotational (with anterocollis)	3	1
Predominantly rotational (with retrocollis)	2	2
Predominantly laterocollis (with rotational)	0	3
Predominantly retrocollis (with rotational)	0	1
Predominantly retrocollis (with laterocollis)	1	0
Mixed rotational and laterocollis	0	1
Mixed rotational, laterocollis and anterocollis/retrocollis	11	7

Data presented as the number of patients classified according Tsui et al.

Table 3 Mean Tsui scores at baseline, week 4 and week 8 for the placebo and Dysport groups.

	Placebo	Dysport
Patients (n)	33	35
Baseline	11.5±1.8	11.1±1.7
Week 4	9.5±0.67	6.5±0.63 **
Week 8	10.1±0.62	7.7±0.58 *

Baseline data presented as the mean±SD. Post-treatment data presented as the mean±sem adjusted for the effects of centre, strata, baseline Tsui score, and treatment. Between-group statistical comparison (** p=0.001, * p=0.002).

Table 4 Pain scores at baseline, week 4 and week 8 for the placebo and Dysport groups.

		Placebo	Dysport
Baseline	None	10 (30.3)	10 (28.6)
	Mild	11 (33.3)	13 (37.1)
	Moderate	9 (27.3)	10 (28.6)
	Severe	3 (9.1)	2 (5.7)
Week 4	None	11 (33.3)	17 (48.6)
	Mild	11 (33.3)	14 (40.0)
	Moderate	10 (30.3)	3 (8.6)
	Severe	1 (3.0)	1 (2.9)
Odds ratio (95 % C. I.)		3.3 (1.2, 9.4), p=0.024	
Week 8	None	14 (42.4)	18 (51.4)
	Mild	8 (24.2)	11 (31.4)
	Moderate	9 (27.3)	5 (14.3)
	Severe	2 (6.1)	1 (2.9)
Odds ratio (95 % C. I.)		2.1 (0.8, 5.6), p=0.152	

Data presented as the number (%) patients in each category.

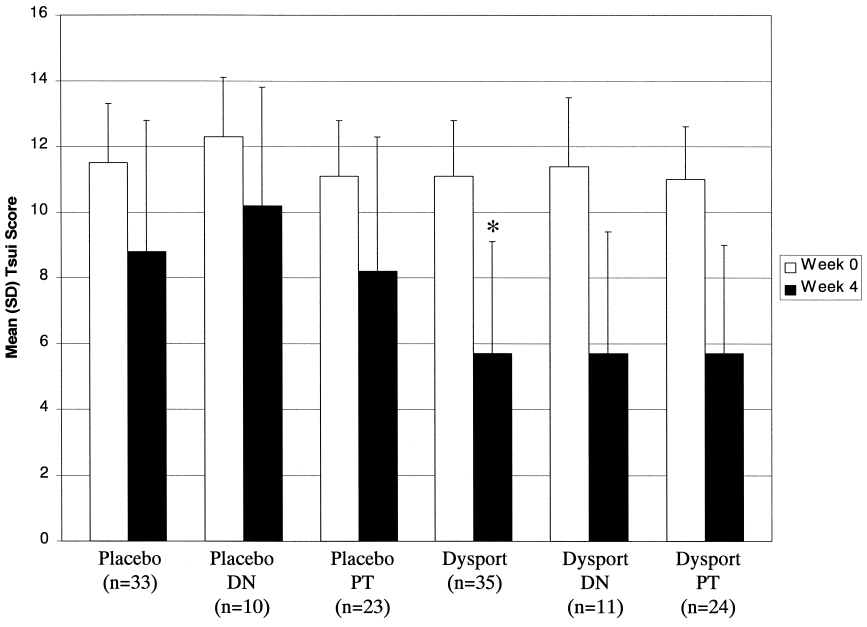

Fig. 1 Mean (SD) Tsui scores at baseline (week 0) and at week 4 for all patients and for the de novo (DN) and previously treated (PT) patients in the placebo and Dysport groups. Only the difference at week 4 between all placebo and all Dysport patients was tested statistically (*p=0.001).

Patient and investigator assessments of overall change (Table 5) both demonstrated significant between-group differences at weeks 4 and 8 following treatment (all $p < 0.001$). Using the prospective definition described earlier, 30/35 (86 %) Dysport patients and 14/33 (42 %) placebo patients were classified as responders at week 4. In the Dysport group 9/11 (82 %) de novo patients and 21/24 (88 %) previously treated patients were classified as responders, and in the placebo group 3/10 (30 %) de novo patients and 11/23 (48 %) previously treated patients were classified as responders. At week 8, 26/35 (74 %) Dysport patients and 11/33 (33 %) placebo patients were still classified as responders. At the end of the study at week 16 two Dysport patients and two placebo patients were not retreated as they were still considered to have an ongoing response. For all patients classified as responders the mean (±SD) time to retreatment was 88 (±18) days for Dysport patients (n=28), and 82 (±20) days for placebo patients (n=12).

A total of 15/35 (43 %) Dysport patients reported 26 adverse events, and 9/33 (27 %) placebo patients reported 15 adverse events. Table 6 provides details of the adverse event profile. Only one adverse event (headache, placebo group) was considered severe, and no adverse events were considered serious. No statistically significant difference between the treatment groups was observed in the overall incidence of adverse events ($p > 0.05$). Previous treatment with BtxA appeared to reduce

Table 5 Patient/Investigator assessment of change from baseline at week 4 and week 8 for the placebo and Dysport groups.

		Investigator Assessment		Patient Assessment	
		Placebo	Dysport	Placebo	Dysport
Week 4	Symptom-free	1 (3.0)	1 (2.9)	1 (3.0)	2 (5.7)
	Improvement ≥ 50 %	7 (21.2)	18 (51.4)	4 (12.1)	16 (45.7)
	Improvement < 50 %	4 (12.1)	11 (31.4)	9 (27.3)	12 (34.3)
	No improvement	18 (54.5)	5 (14.3)	11 (33.3)	5 (14.3)
	Worse	3 (9.1)	0	8 (24.2)	0
Odds ratio (95 % C. I.)		6.5 (2.4, 17.5), p < 0.001		8.5 (3.1, 23.0), p < 0.001	
Week 8	Symptom-free	0	1 (2.9)	1 (3.0)	0
	Improvement ≥ 50 %	5 (15.2)	11 (31.4)	5 (15.2)	17 (48.6)
	Improvement < 50 %	6 (18.2)	14 (40.0)	6 (18.2)	9 (25.7)
	No improvement	19 (57.6)	9 (25.7)	13 (39.4)	9 (25.7)
	Worse	3 (9.1)	0	8 (24.2)	0
Odds ratio (95 % C. I.)		6.9 (2.4, 19.3), p < 0.001		6.8 (2.5, 18.3), p < 0.001	

Data presented as the number (%) of patients in each category

Table 6 Adverse event profile

	Placebo	Dysport
Patients reporting adverse events	9/33 (27.3 %)	15/35 (42.9 %)
Total number of adverse events	15	26
Dry mouth	2	5
Neck muscle weakness	0	4
Dysphagia	1	3
Cold	1	3
Injection site pain	2	2
Hypertension	2	0
Others[a]	7	9

[a] Adverse events reported once for either group.

the incidence of adverse events. In the Dysport group, 7/11 (64 %) de novo patients reported 15 adverse events, and 8/24 (33 %) previously treated patients reported 11 adverse events. In the placebo group 3/10 (30 %) de novo patients reported seven adverse events, and 7/23 (30 %) previously treated patients reported nine adverse events.

The global assessment of efficacy and safety demonstrated a significant between-group difference (p=0.001) with 30/35 (86 %) Dysport patients and 13/33 (39 %) placebo patients being classified as treatment successes.

Open phase

The 24 patients (5 Dysport, 19 placebo) classified as non-responders at week 4 were re-treated with 500 units of Dysport six weeks after the first treatment. Patients were assessed again four weeks later, by which time the mean (±SD) Tsui score was 6.0 ± 3.0, which was significantly better ($p < 0.001$) than at entry (11.4 ± 1.8). Similarly, pain associated with cervical dystonia had also improved significantly (p=0.01), with 16/24 (67 %) patients reporting no pain compared with 7/24 (29 %) at entry. One patient, previously treated with placebo, was still classified as a non-responder at week 10. A total of 19 adverse events were reported by 9/24 (38 %) patients, and comprised five reports each of dry mouth and dysphagia, three reports of neck muscle weakness, two reports of tiredness, and one report each of jaw weakness, itching at the injection sites, respiratory difficulties and voice changes. No adverse events were severe or serious.

Discussion

Although local BtxA injections are generally accepted as a first line treatment for cervical dystonia there is no consensus on dose standardisation owing to the lack of data from properly controlled trials. There is emerging agreement that the high doses used in the early series [1, 8] can be replaced by lower doses without decreased efficacy, and with a reduced incidence of side effects [2, 3, 6, 10]. Retrospective analysis of published large open series (including studies with more than 80 patients, with all degrees of severity, dystonic head deviations, and including de novo as well as previously BtxA treated patients) suggest that doses of about 700 units of Dysport and 200 units of Botox, injected without EMG-guidance, are effective without the risk of severe side effects or an increased incidence of BtxA antibody formation [4, 5, 6, 7, 13].

A recent double blind, placebo controlled study employing different doses of Dysport (250, 500, 1000 units) in a selected group of de novo patients with pure rotational cervical dystonia suggested that 500 units of Dysport was the starting dose with the optimal risk/benefit ratio [11]. The present prospective, randomised, double-blind, placebo-controlled study clearly demonstrated the efficacy and safety of a standard dose of 500 units of Dysport in the treatment of a heterogeneous group of patients with moderate to severe cervical dystonia. The group of patients studied in this trial was less selected than the population with pure rotational cervical dystonia in the dose-ranging study [11], and was more representative of the cervical dystonia population seen in routine dystonia clinics. In addition, this is the first prospective placebo-controlled trial to demonstrate that a dose of 500 units of Dysport is equally effective in de novo as well as previously treated patients.

All objective and subjective assessments demonstrated improvements from baseline that were significantly better than placebo, and overall 86 % of Dysport treatments were considered successful. Despite the high number of patients who were classified as responders, there were a number of patients who had a modest improvement, and it is probable that these patients may have responded better to an individualised treatment regime with EMG-guidance or a higher dose of Dysport® distributed to more than three muscles.

The results of this study also confirm the considerable placebo response in patients with cervical dystonia, and highlight the problems when interpreting results from uncontrolled studies. Although the majority of placebo group patients demonstrated no improvement in Tsui and pain scores, overall 42 % of them were classified as responders on the basis of their own and the treating physician's subjective opinion. The duration of this benefit was similar to that demonstrated by Dysport patients. Strong placebo responses are often seen in such studies, and so this observation was not unexpected, but perhaps it was also partly a reflection of the criteria used to define response. These criteria were defined primarily to minimise the potential for patients to receive two active doses in short succession, and so were more likely to result in high responder rates.

It is noteworthy that all five Dysport patients who

failed to respond to double-blind treatment were able to respond to a repeat dose of 500 units of Dysport six weeks later. Only one of these patients had exactly the same injection pattern on both occasions, so it is possible that the initial injections for these patients were misplaced, or that inappropriate muscles were identified for treatment. It is equally likely that the patients received a sub-therapeutic dose, and that the open phase re-treatment provided a sufficient cumulative dose to produce a beneficial response. Although it is possible to speculate as to why these patients failed to respond initially, it is clear that failure to respond to one treatment does not necessarily mean that a patient is unable to respond.

Randomisation was stratified to ensure an equal distribution of de novo patients between treatment groups, in the expectation that de novo patients would present with more severe symptoms that could demonstrate more dramatic improvements. Unexpectedly, de novo and previously treated patients demonstrated very similar baseline conditions, especially in the Dysport group, and it is clear that in terms of efficacy at least, prior treatment with BtxA does not affect the response. The situation is not quite as clear for the adverse event profile, however, as de novo patients reported twice as many adverse events, suggesting that patients who have previously received BtxA have developed some degree of tolerance.

The overall incidence of adverse events was low, especially considering that patients were specifically asked whether they had experienced any of the ten most common toxin-related side effects. It is probable that the incidence could be reduced further if those patients reporting toxin-related adverse events were given lower doses of Dysport. In addition to the low incidence, the majority of adverse events were considered mild and resolved quickly, and no patient refused re-treatment at the end of the study.

Although individual dose titration is desirable, this study demonstrated that 500 units of Dysport injected into clinically identified major neck muscles without EMG-guidance is safe and effective in the treatment of patients with the major clinical types of moderate to severe cervical dystonia.

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