PAPER

Respective potencies of Botox and Dysport: a double blind, randomised, crossover study in cervical dystonia

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Objectives: Botulinum toxin type A is a potent neuromuscular paralyzing agent used in various disorders including cervical dystonia. Two preparations of botulinum toxin are now commercially available (Dysport and Botox), but much controversy remains about their respective potencies. The aim of the study was to compare the efficacy of Botox with two different ratios of Dysport.

Methods: A double blind, randomised, three period cross over study involving 54 patients with cervical dystonia was performed. The patients received the following treatments in a randomised order: Botox at the usually effective dose, Dysport at a dose of 1:3 (conversion factor of 3 between Botox and Dysport units—that is, one Botox unit=three Dysport units) and at a dose of 1:4 (conversion factor of four). The improvement of the Tsui (primary outcome criteria) and of the TWSTRS pain scales between baseline and a control visit 1 month after each of the three injections, as well as the incidence of adverse events, were assessed.

Results: Comparison of the Tsui scores and of the TWSTRS pain scores showed a better effect on impairment and pain with Dysport 1:3 (p=0.02 and 0.04, respectively) and 1:4 (p=0.01 and 0.02, respectively) than with Botox. The number of adverse events was higher with both Dysport treatments. The most frequent adverse event was dysphagia, found in 3%, 15.6%, and 17.3% (Botox, Dysport 1:3 and 1:4, respectively) of the patients. No adverse event required withdrawal of therapy or specific management.

Conclusions: Dysport 1:3 (and Dysport 1:4 to a greater extent) is more efficient than Botox for both impairment and pain in cervical dystonia although with a somewhat higher incidence of minor adverse effects. This strongly suggests that the most appropriate conversion factor between Botox and Dysport units is less than 3 in cervical dystonia.

Botulinum toxin is a potent neuromuscular paralyzing agent that induces a temporary functional denervation and atrophy of the injected muscle. In the past decade, this property has been used therapeutically in various disorders characterised by inappropriate muscle contraction, including dystonia. Two preparations of botulinum toxin type A are now commercially available in Europe: Dysport (Ipsen) and Botox (Allergan). The efficacy and safety of both have been well established in various disorders,[1] but a strong controversy remains about their respective potencies.[2] Unlike studies conducted in animals or healthy volunteers,[3] clinical studies devoted to dystonic patients found that one unit of Botox is not bioequivalent to one unit of Dysport. Different experimental paradigms have been used to find an appropriate conversion factor in dystonic patients, but the results are conflicting, the ratio Botox:Dysport found being between 1:3 and 1:6.[4–8] Determining a more precise conversion factor is of paramount importance as an error when changing one preparation to the other may account either for an overdose or to an apparent non-response, both with severe clinical consequences.[9] It also has important economic implications, because botulinum toxin is an expensive treatment.

The objective of this study was to evaluate, in patients with cervical dystonia and usually good responders to a clinically established dose of Botox, the efficacy and tolerability of this treatment compared with two different doses of Dysport—that is, a dose of 1:3 (corresponding to a conversion factor of 3 between Botox units and Dysport units) and a dose of 1:4 (conversion factor of 4). The study was conducted in a double blind, cross over design, each patient receiving the three different treatments in a randomised order during the three periods of the protocol.

METHODS

Patients

The patients were consecutively recruited among the patients followed up in our movement disorders clinic. Patients with cervical dystonia were eligible for study if they obtained a satisfying improvement to the two last consecutive preprotocol Botox injections, made at the same dose and in the same muscles. The response was judged by the patient and confirmed by the investigator. Other inclusion criteria were age over 18 years; delay between the last preprotocol injection and the first protocol injection of 16 or more weeks; constancy in the protocol injections with regard to the muscles, the injection sites, and the dose at each injection site. Patients with any kind of contraindication to one of the botulinum toxin formulations were excluded. All patients gave informed consent to participate, and the study was approved by the local ethics committee.

Design

The three treatments were the following: treatment 1: Botox at the usually effective dose; treatment 2: Dysport at a dose of 1:3 corresponding to a conversion factor of 3 between Botox units and Dysport units (one Botox unit=three Dysport units); treatment 3: Dysport at a dose of 1:4 (conversion factor of 4). Dysport was supplied in vials of 500 Dysport units, and Botox in vials of 100 Botox units. According to the manufacturer's recommendations, botulinum toxin was reconstituted in normal saline and used within 4 hours. Dilutions were prepared to obtain three indistinguishable solutions and to allow the

Abbreviations: TWSTRS, Toronto western spasmodic torticollis rating scale

Table 1 Baseline characteristics of the patients (n=54)

Male : female	14 : 40
Age (y (range))	56.09 (24–78)
Mean Tsui score at inclusion (SD)	8.98 (3.3)
Mean duration of disease (y (range))	13 (2–45)
Mean number of preprotocol injections (range)	17.5 (4–30)
Mean time between the last preprotocol injection and inclusion in days (range)	128.5 (91–210)
Mean total dose injected in the 2 last preprotocol injections in Botox units (range, SD)	104.44 (70–180, 20.6)
Concomitant treatments (number of patients):	
Benzodiazepines	22
Anticholinergics	29
Myorelaxants	30

injection of the same volume at each session for a given patient. Indeed, one volume of each solution contained respectively n Botox units (treatment 1), 3 n Dysport units (treatment 2), and 4 n Dysport units (treatment 3). The three treatments were prepared in the local hospital pharmacy.

Each patient received the three different treatments in a randomised order during the three periods of the protocol. Location, number of muscles injected, and doses of each injection were those used in the two preprotocol Botox treatments. All injections were performed by the same neurologist who was blind to the treatment and used the same technique: one single injection point per muscle, close to the motor point. The duration of each period varied according to the result of the treatment. To avoid a carry over effect, each treatment period was preplanned to last 16 weeks, as the benefit of an injection for cervical dystonia lasts generally 9 to 12 weeks.[10] However, two clinical situations could lead to a modification of this standardised treatment period: (1) It could be longer if the patient had not regained his or her baseline clinical state 16 weeks after the injection. In that case, the patient was reinjected only when he required retreatment. (2) It could be shorter for the patients without any sign of improvement at 8 weeks, or in cases of severe worsening. The last methodological point was decided on for ethical reasons and to avoid a severe worsening of cervical dystonia, which could introduce some bias in the evaluation (botulinum toxin is more efficient when the muscles are more hyperactive[11]).

Outcome measures

In each of the three periods, patients were clinically evaluated at baseline (day of the treatment) and 1 month (± 7 days) after the injection, when the patients were supposed to be at their best. The primary outcome measure was the change of the Tsui scale score[12] between the baseline and control visit. The Tsui scale is a clinical scale grading the amplitude and duration of both sustained and spasmodic movements and the presence of a shoulder elevation. The scale ranges from 0 to 25, 25 corresponding to the maximum disability. Secondary outcome measures included: (1)change in the Toronto western spasmodic torticollis rating scale (TWSTRS) pain scale score[13] between baseline and control visit (20 points=maximum pain). The TWSTRS pain score consists of a dimensional severity score for the patient's usual, best and worst pain as well as a duration component and an assessment of the contribution of pain to disability; (2) duration of action (defined as the interval between the day of treatment and the day the patient reported a waning of effect); (3) incidence of adverse events. The patients were systematically questioned about dysphagia, dysphonia, cervical hypotonia, and asthenia and were free to report any other adverse event; (4) assessment of pain during injections, which was rated on a six point scale (from 0=none to 5=extreme).

Statistical analysis

The sample size calculation was based on an equivalence between treatments defined by a difference in the post-treatment Tsui score of 1.5 points or less. It was estimated that the minimal sample size required was 43, with $\alpha=0.05$ and $\beta=0.1$ and an intraclass correlation coefficient of 0.5. To allow for a 20% drop out rate, at least 51 patients had to be enrolled.

For Tsui and TWSTRS pain scores, the data were analyzed by paired *t* test. Variables such as injection pain and duration of effect were compared by a non-parametric paired test (Wilcoxon), and the number of adverse events by χ^2 test. An order effect was evaluated by applying Fisher's PLSD test. Analysis of variance (ANOVA) was used to examine for a carry over effect. Data were analyzed on an intention to treat basis.

RESULTS

A total of 54 patients were randomised to treatment. The characteristics of the patients are summarised in table 1. Fifty two patients received oral drugs for the treatment of dystonia and the drug regimen was kept constant for the duration of the study. Out of the 54 patients, six received only one or two of the three planned injections for the reasons of non-compliance with the protocol (n=4) or long remission (n=2). All 54 patients were included in the intention to treat analysis.

Results for the three formulations pooled over the three periods are presented in table 2. Fischer's PLSD test and

Table 2 Results (paired *t* test and Wilcoxon test)

	Before injection		Difference before injection/one month after injection		Duration of action	
Treatment (n injections*)	Tsui score (mean (SD))	TWSTRS-pain score (mean (SD))	Tsui score (mean (SD))	TWSTRS-pain score (mean (SD))	Injections† (n)	Mean in days (SD, range)
Botox (n=51)	8.65 (3.34)	5.65 (5.27)	3.25 (2.96)	2.59 (5.43)	42	89.3 (39, 0–235)
Dysport 1 :3 (n=51)	8.65 (3.39)	6.51 (5.29)	4.27 (2.91)‡	4.41 (5.76)‡	43	96.9 (39.3, 0–172)‡
Dysport 1 :4 (n=52)	9.02 (3.32)	6.81 (6.01)	4.92 (2.86)§¶	5.37 (6.49)§¶	46	114 (69.3, 46–491)§¶

*Six patients only received one or two protocol injections instead of three (see text for reasons). Consequently, 51, 51 and 52 injections were performed with Botox, Dysport 1:3 and Dysport 1:4, respectively; †duration of action calculated for patients able to identify dates of beginning and waning of efficacy. Comparisons for Tsui score, TWSTRS-pain score, and duration of action, respectively: ‡Dysport 1:3 versus Botox : p=0.02, p=0.04 and p=0.58, respectively; §Dysport 1 :4 versus Botox : p=0.01, p=0.02 and p=0.02, respectively; ¶Dysport 1:4 versus 1:3 : p=0.28, p=0.58 and p=0.09, respectively.

Table 3 Adverse events (χ^2 test)

	Botox	Dysport 1:3	Dysport 1:4
Number of injections*	n=51	n=51	n=52
Number of patients with adverse events	9 (17.6%)	17† (33%)	19‡ (36%)
Number of adverse events	10	22§	27¶
Type of adverse events:			
Dysphagia	2 (3%)	8 (15.6%)	9 (17.3%)
Dysphonia	0	3	3
Asthenia	2	2	7
Neck weakness	2	3	2
Prolonged pain at injection point	2	3	3
Dry mouth	0	2	1
Others	2	1	2

*See table 2 for explanation; †Dysport 1:3 *v* Botox, p=0.06; ‡Dysport 1:4 *v* Botox, p=0.03; §Dysport 1:3 *v* Botox, p=0.01; ¶Dysport 1:4 v Botox,p<0.01.

ANOVA showed that there was no significant difference in baseline Tsui and TWSTRS scores according to the order and types of injections. The mean improvement of the Tsui score was 3.22 for Botox, 4.32 for Dysport 1:3, and 4.89 for Dysport 1:4, showing that the three treatments were effective.[14] Comparison of the mean improvement of the Tsui score (1 month from injection) showed a difference between the three treatments (p=0.006, two factor ANOVA). Both Dysport 1:3 and 1:4 were significantly more effective than Botox (p=0.02 and 0.01, respectively). By contrast, there was no significant difference between the efficacy of Dysport 1:3 and Dysport 1:4 (p=0.28). Improvement of the TWSTRS pain score was significantly more important with both Dysport 1:3 and Dysport 1:4 treatments compared with Botox (p=0.04 and p=0.02, respectively). No difference was found between Dysport 1:3 and 1:4 (p=0.58). The duration of action could be determined only when the patient was able to identify the date of beginning and waning of efficacy. This was achieved for 42, 43, and 46 injections of Botox, Dysport 1:3, and Dysport 1:4, respectively. The mean duration of action was 7 days longer for Dysport 1:3 than for Botox (p=0.58), and 25 days longer for Dysport 1:4 than for Botox (p=0.02). The difference between Dysport 1:3 and 1:4 tended towards significance (p=0.09). We found four responses of more than 6 months with Dysport 1:4, two with Dysport 1:3 (one is still ongoing after 2 years), and one with Botox.

Table 3 shows the adverse events found during the study. A higher percentage of patients reported adverse events with Dysport than with Botox, but the difference was significant only for Dysport 1: 4 (p=0.03). When the number of adverse events was considered, the difference became significant between the Botox and both Dysport groups (p=0.01 and <0.01, respectively). The most frequent adverse event was dysphagia, found in 3% (Botox) to 15.6% and 17.3% (Dysport 1:3 and 1:4, respectively) of the patients. Dysphagia was clinically significant for one patient in each of the two Dysport groups. The muscles injected in these two patients were the splenius capitis and the contralateral sternocleidomastoid and the doses were respectively 280 and 120 Dysport units for one patient, and 300 and 120 Dysport units for the other patient. None of these patients required withdrawal of therapy or specific management. The other adverse events were mild in intensity and were not responsible for any functional impairment. The mean score of pain at injection was 1.20 (range=0 to 5, SD=1.61) for Botox, 1.06 (range=0 to 4, SD=1.33) for Dysport 1:3, and 1.04 (range=0 to 4; SD=1.37) for Dysport 1:4 (non-significant).

DISCUSSION

In this double blind randomised cross over study, we found that Dysport provides a better result than Botox on impairment and pain in cervical dystonia with a conversion factor of 3 (and of 4 to a greater extent). We chose the Tsui scale as the primary outcome measure as this scale has been widely used in the previous literature and substantially contributed to many of the assessments of efficacy for botulinum toxin. The Tsui and the TWSTRS pain scales used together are considered to adequately assess improvement of cervical dystonia after treatment with botulinum toxin.[15] In addition to a higher mean improvement of these two scales, we found that Dysport 1:4 and 1:3 provided a more prolonged effectiveness compared with Botox. The difference reached 7 days with Dysport 1:3 (p=0.58) and 25 days with Dysport 1:4 (p=0.02). This tendency towards a positive relation between the dose of Dysport injected and the duration of clinical benefit was previously reported in a dose ranging study in cervical dystonia.[16]

Our study is difficult to compare with others adressing the same issue, because most were conducted in patients with blepharospasm or hemifacial spasm[4 5 7] or spasmodic dysphonia.[6] In these conditions, the results were conflicting, with a ratio Botox:Dysport being found between 1:3 and 1:6, probably because of methodological differences. The two largest studies[5 7] found a conversion factor of 3 and 4, respectively. However, the results obtained in diseases involving small muscles cannot be simply applied to cervical dystonia, as the doses of treatment definitely differ and the spreading pattern of the botulinum toxin may vary according to the size of the muscles involved.[10]

Only one previous study considered the question of the conversion factor between Botox and Dysport units in cervical dystonia,[8] and an equivalence between one Botox unit and three Dysport units was found. The design of this study (two parallel groups) was different from ours. Because of the tremendous individual variability of cervical dystonia, we preferred a cross over design in which each patient acts as his own control, a relevant design considering the absence of order effect or carry over effect. It was also decided to control for variables that could induce misinterpretations. Firstly, a standardised protocol for injections was used. Predefining the number of injection sites is important as it has been reported that multiple and single injection sites can provide different results with regard to efficacy and adverse events.[17] Secondly, the same volume was injected for each of the three treatments. It has been previously found that an increase in the volume injected can enhance diffusion of the toxin and consequently increase the incidence of adverse events.[18]

The adverse events found in our study were those usually reported after botulinum toxin injection. These treatment related adverse events were more frequent with Dysport, either 1:3 (33%) or 1:4 (36%), than with Botox (17.6%). The most frequent was dysphagia. Our results are somewhat different from those obtained by Odergren *et al*[8] who found treatment related adverse events in about one third of the patients treated either with Dysport or Botox, but are in

accordance with other reports.[19] Moreover, we assume that a cross over design gives an optimal profile of the adverse events, because adverse events due to botulinum toxin may be related to uncontrolled individual characteristics such as a thin neck. The reason why we found a greater incidence of adverse events with Dysport remains to be explained. This could be some direct consequence of the treatment efficacy but also of a higher tendency of Dysport to diffuse within the tissues, in relation to still undefined pharmacological parameters.[18]

In conclusion, our results show that Dysport 1:4 and even Dysport 1:3 are more efficient than Botox for both impairment and pain in cervical dystonia although with a somewhat higher incidence of adverse effects. This strongly suggests that the most appropriate conversion factor between Botox and Dysport units is inferior to 3 in cervical dystonia. These results could have significant clinical implications for the treatment of other large muscle diseases with inappropriate contraction such as spasticity, a growing indication of botulinum toxin. Because botulinum toxin is an expensive treatment, our findings are also of interest from the economic point of view.

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