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Fifteen-Year Experience in Treating Blepharospasm with Botox or Dysport: Same Toxin, Two Drugs

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Abstract *Objectives* To compare the clinical characteristics and the long-term outcome of a large series of patients with blepharospasm (BS) treated with the two most used brands of BoNT-A over the last 15 years. *Methods* We have reviewed the clinical charts of 128 patients with BS who received botulinum neurotoxin (BoNT) in 1341 treatments (Botox in 1009, Dysport in 332) over the last 15 years. *Results* Mean dose per session was 34U ± 15 for Botox and 152U ± 54 for Dysport. Mean latency of clinical effect was 4.5 ± 4.6 days for Botox and 5.0 ± 5.7 days for Dysport ($P > 0.05$). Mean duration of clinical improvement was higher for Dysport than Botox: 80.1 ± 36.3 and 66.2 ± 39.8 days, respectively ($P < 0.01$). In a six-point scale (0: no efficacy, 6: remission of BS), the mean efficacy of both treatments was 3.60 ± 1.3; 3.51 ± 1.4 (Botox) and 3.85 ± 1.2 (Dysport), $P < 0.01$. The doses of Botox ($\beta = 0.40$) and Dysport ($\beta = 0.16$) were significantly increased over time. Side effects occurred in 325 out of 1341 treatments (24.2%): 21.8% of the patients who had received Botox, and in 31.6% of those who had received Dysport ($P < 0.01$). *Conclusions* Both brands are effective and safe in treating blepharospasm; efficacy is long lasting. The differences in outcome and side effects suggest that, albeit the active drug is the same, Botox and Dysport should be considered as two different drugs.

Keywords Blepharospasm · Botulinum toxin · Botox · Dysport · Treatment

Abbreviations

BS	Blepharospasm
BoNT	Botulinum toxin
BoNT-A	Botulinum toxin type A
BoNT-B	Botulinum toxin type B
EDB	Extensor digitorum brevis

Introduction

Blepharospasm (BS) is a focal dystonia involving the orbicularis oculi muscle (and the periocular muscles), and (Jankovic and Orman 1984) when associated with oromandibular dystonia, it is referred to as "Meige's syndrome" (Meige 1910). Cranial dystonia may present within segmental or generalised dystonia. A recent systematic review conducted according to evidence-based medicine criteria concluded that botulinum neurotoxin (BoNT) "can be regarded as first line treatment for primary cranial dystonia" with a level A of recommendation (Albanese et al. 2006).

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BoNT is a potent neuromuscular toxin produced by *Clostridium botulinum* that induces a transient chemical denervation and atrophy of the injected muscles by irreversibly blocking the cholinergic transmission at the presynaptic nerve terminals. BoNT type A (BoNT-A) was first used to treat strabismus in humans in 1981 (Scott 1981). The efficacy on BS has been documented since 1984 (Frueh et al. 1984; Scott et al. 1985) and it was first demonstrated in a randomised double-blind clinical trial in 1987 (Jankovic and Orman 1987). Weakness of injected muscles is transient, since recovery occurs by ultraterminal sprouting of motor axons and formation of new neuromuscular junctions as well as reinnervation of denervated motor endplates (Duchen 1971). Two preparations of BoNT-A are widely used in Europe: Dysport and Botox. Botox is a lyophilised form, purified from the culture solution by acid preparations to a crystalline complex. Dysport is redissolved and purified by procedures involving ammonium sulphate precipitation and ion exchange chromatography, and it is then freeze-dried. These two BoNT-A preparations are different in terms of unit of weight, chemical properties, biological activities, and mouse LD_{50} units (Dressler and Hallet 2006). For these reasons, the clinical efficacy may be different and controversy remains about their respective potencies (Sampaio et al. 2004). Despite numerous reports confirming the efficacy of BoNT-A in the treatment of BS (Costa et al. 2005), very few studies have assessed the outcome of patients beyond the initial years (Mauriello et al. 1996; Silveira-Moriyama et al. 2005).

We analysed the clinical characteristics and the long-term outcome of a large series of patients with BS treated with BoNT over the last 15 years.

Materials and Methods

Patients

Among those patients attending the movement disorders clinic of Gemelli Hospital in Rome from 1986 to 2003, we studied retrospectively all the subjects with BS treated with BoNT. Inclusion criteria were: primary BS (focal or in the context of segmental, multifocal or generalised dystonia), two or more consecutive treatments with BoNT-A. Exclusion criteria were: secondary dystonia, unavailability of complete clinical data, treatment with neuroleptics or other drugs interfering with eyelids function.

Treatments

At the first visit, the patients were interviewed on their past and present medical history and underwent a full neurological evaluation. All the treatments were performed by one of the authors (TI, ARB and AA). Two preparations of BoNT-A were injected: Dysport (Ipsen, Ltd., Slough, Berkshire, UK); Botox (Allergan Inc, Irvine, CA, USA). The manufacturer's instructions were followed. Both toxins were reconstituted into sterile, preservative-free 0.9% saline solution and injected within 4 h from reconstitution. A dose of 500 U Dysport were diluted in 2.5 or 5 ml of saline solution to yield toxin in a concentration of 20 or 10 units per 0.1 ml, respectively. A dose of 100 U Botox was diluted in 2 or 4 ml of saline solution to yield toxin in a concentration of five units or 2.5 units per 0.1 ml, respectively. Higher dilutions were preferred to enhance the effect of the BoNT with lower doses while a higher concentration was used in order to avoid side effects due to the diffusion of the BoNT (Borodic et al. 1994). Occasionally, different dilutions were used, especially at the beginning of our experience and in a few cases after repeated failures to conventional treatments. In the analysis of our data, we have considered only treatment with standard dilutions (Table 1).

Injections were performed subcutaneously according to standardised procedures; the dose varied according to the severity of patient's spasm. The orbicularis oculi muscle was injected (in orbital or pre-tarsal portion) in three or four points (medial and lateral side of upper and lower eyelids close to palpebral rim) (Albanese et al. 1992). If hyperactive, the extra-orbicular muscles (e.g. frontalis, procerus) were also injected. The starting dose varied among the patients and was successively adjusted according to the severity of dystonia, the response to previous treatments and the occurrence and side effects. Patients were asked to annotate latency, size, duration of efficacy and the occurrence of adverse events (latency, duration, and severity).

Design and Outcome Measures

This research was designed as a longitudinal retrospective study. All the patients who satisfied the inclusion criteria were studied; the following data were retrieved and entered

Table 1 The most common dilutions used were 2 or 4 ml for Botox, and 2.5 or 5 ml for Dysport

BoNT	Nos. of treatment (n°)	Dilution (ml of saline solution)	Nos. of treatment (N°)	%
Botox	1009	4	908	90.0
		2	92	9.1
		1	9	0.9
Dysport	332	2.5	192	57.8
		5	140	42.2

into a standardised form: demographic data (gender, age at onset, follow-up, disease duration); number of treatments. For each treatment, the following data were recorded: date of treatment; brand used (Botox or Dysport); total dose and dilution; sites injected (orbicular/extra-orbicular muscles); number of BoNT injections. The severity of BS was assessed according to Fahn & Burke dystonia scale (Burke et al. 1985), the score ranging from 0 to 4 (0 = no dystonic signs, 1 = increased blink rate, 2 = sustained non-forceful closure of the eyelids, 3 = sustained and forceful spasms, 4 = functional blindness). Response to BoNT was inferred on the basis of the patient's interview considering the perception of response (expressed as 0−100%), interview of spouses or next-of-kin. Response was assessed by global rating from 0 to 6 (0 = no effect, 1 = effect less than 20%, 2 = effect ranging between 20 and 40%, 3 = effect ranging between 40% and 60%, 4 = effect ranging between 60 and 80%, 5 = effect ranging between 80% and 90%, 6 = complete resolution of BS). Besides the global rating, two further variables were: latency, defined as the interval (days) between injection and the first sign of improvement and total duration of improvement, defined as the interval (days) between the first report of improvement (latency) and the last day of reported benefit.

Primary resistance was considered when inconsistent improvement (<20%) was achieved in all (at least two) consecutive injections of increasing amounts of BoNT-A. Secondary resistance was considered when an improvement of at least 40% in two or more consecutive treatments was followed by an inconsistent improvement (<20%) after two or more subsequent treatments. The extensor digitorum brevis (EDB) test was performed to disclose indirectly anti-BoNT-A antibodies in patients with secondary resistance (Kessler and Benecke 1997).

Patients were instructed to report the occurrence of side effects: type, duration and severity. Global severity of side effects was measured considering a score ranging from 1 to 3 (1 = mild, duration less than 1 week without medical intervention; 2 = moderate, duration less than 1 week with medical intervention; 3 = severe, duration more than 1 week with medical intervention or duration more than 1 month with or without medical intervention.

Statistical Analysis

Demographic data were expressed as mean ± standard deviation (range). The analysis of the severity and treatment response scores was performed by means of ANOVA and *t*-test to compare the mean of continuous variables of sample in exam (age at onset, age at last evaluation, years of disease duration and follow up) and between the different treatments, (dose and occurrence of side effects, dilution and occurrence of side effects). Fisher's exact test was used to compare the categorised variables (male to female ratio, occurrence of side effects, and occurrence of treatment failure). The Pearson test was used to correlate the continuous variables (dose and dilution versus duration and efficacy of treatment). The linear regression analysis and the repeated measure ANOVA were used to assess the time course of dose, efficacy, and duration of clinical benefit. In this computing, the first 10 treatments were considered suitable. The test was considered significant when the P value was <0.05.

Results

Out of the 259 patients, 128 (98 females, 76.6%) were eligible. Mean age at onset was 57.7 ± 10.3 years (6–81). Mean BS severity at the first evaluation, according to Fahn & Burke dystonia scale, was 2.6 ± 0.7 (1–4). Mean disease duration was 13.5 ± 7.4 years (2–44); mean age at onset and disease duration were overlapping in males and females.

A total number of 1341 treatments were performed. Each patient received 10.6 ± 8.9 (2–48) injections. Botox was injected in 1009 treatments, Dysport in 332. Most patients (113/128) were first injected with Botox at the first treatment. At the preceding visit, the ongoing treatment was Dysport in 44 subjects, Botox in 81. Three patients, unresponsive to either preparation, were shifted to BoNT-B (Neurobloc, Elan Pharma International Ltd.). Fifty-six patients (44%) shifted from one brand to the other, due to different reasons: (1) unsatisfactory clinical response to the treatment (47%), (2) occurrence of side effects (22%), (3) unavailability of either of the two preparations in the remaining cases (31%).

The mean dose injected per session was 34U ± 15 (7.5–140) of Botox and 152U ± 54 (40–400) of Dysport, resulting in a mean dose ratio between toxins of 4.5. In most patients, 20U Botox or 80U Dysport were injected in the first treatment. Both the dose of Botox ($\beta = 0.40$, $P = 0.0046$) and Dysport ($\beta = 0.16$, $P < 0.00001$) were significantly increased over time (Fig. 1). Eight out of 128 (6.2%) patients were unresponsive to the commonly used doses and failed to have a sustained benefit until a dose as high as 100U Botox or 400U Dysport was reached.

No correlation between dose and benefit duration was found. Dose injected and benefit magnitude were positively correlated only in treatments with Botox ($r = 0.9$, $P < 0.05$).

No correlation was observed between BoNTs dilution (Table 1) and efficacy of each treatment with the exception of a correlation between dilutions and duration of clinical effects of Botox: a higher dilution (25 U/ml) was associated with a longer duration of clinical benefit when

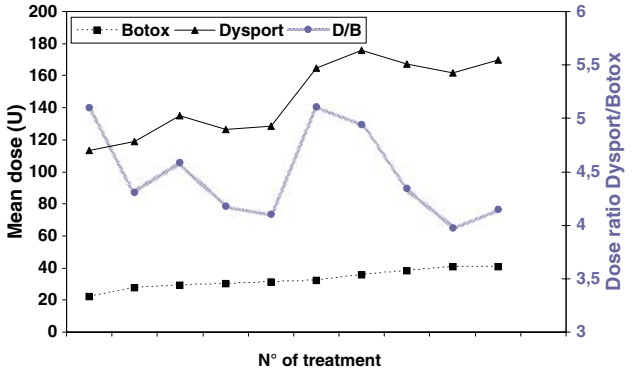

Fig. 1 Either the dose of Botox ($\beta = 0.40$, $P = 0.0046$) or Dysport ($\beta = 0.16$, $P < 0.00001$) was significantly increased over time. Different ratios between the mean doses used along time ranged from 4.0 and 5.1

compared to 50 U/ml ($r = 0.8$, $P < 0.05$). The difference between mean latencies (4.5 ± 4.6 days (0–60) for Botox and 5.0 ± 5.7 days (0–30) for Dysport), was statistically meaningless. Mean duration of clinical improvement was higher after the injection of Dysport than Botox: 80.1 ± 36.3 days (0–210) and 66.2 days ± 39.8 (0–520), respectively ($P = 0.000000024$). The longitudinal analysis of benefit revealed an increasing trend over time, independent from the dose injected for both brands (Fig. 2).

In a six-points scale, the mean efficacy of both treatments was 3.60 ± 1.3; 3.51 ± 1.4 for Botox and 3.85 ± 1.2 for Dysport ($P = 0.000076$); the magnitude of improvement produced by each treatment increased over time with both toxins ($\beta = 0.11$; $P < 0.00001$): the increase was more evident when considering Dysport ($\beta = 0.12$) than Botox ($\beta = 0.06$); however, the difference among BoNTs failed to reach statistical significance. As a consequence of the above mentioned observation, the

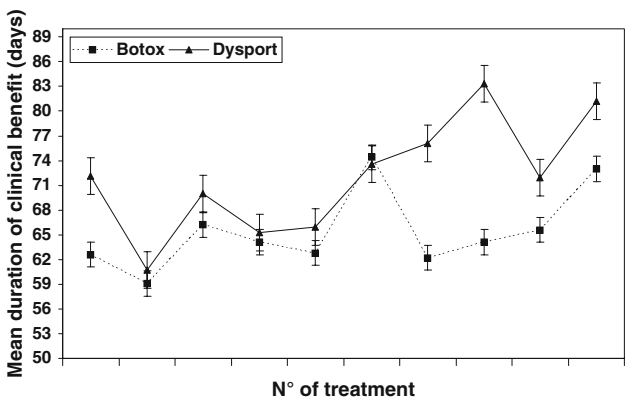

Fig. 2 The longitudinal analysis of the mean duration of clinical benefit showed a trend to increase along the time, independently from the dose injected for both BoNTs used

severity of BS improved along time ($\beta = -0.08$; $P < 0.00001$); men tended to improve more than women ($\beta = -0.13$ vs. $\beta = -0.06$, respectively; no statistically significant difference).

Treatment failure (less than 20% of amelioration) occurred in 94 out of 1353 (6.9%) sessions: 7.7% of Botox treatments and 3.6% of Dysport ($P = 0.0093$). Among the 128 patients treated with BoNT-A, three (2.3%) were secondary non-responders, probably due to the presence of antibodies anti-BoNT-A, as suggested by a lack of response at the EDB-test (Kessler and Benecke 1997).

Side effects (one or more) occurred in 325 out of 1341 sessions (24.2%): in 21.8% of the patients treated with Botox, and in 31.6% of patients treated with Dysport ($P = 0.00029$). The most common was palpebral ptosis (occurred with comparable frequency between Botox and Dysport); diplopia, blurred vision, conjunctival distress were uncommon, though more frequent after Dysport than after Botox. There were two episodes (0.1% of all the treatments) of distant side effects (allergic reactions), both following Dysport treatments. Other infrequent adverse reactions are listed in Table 2. When considering the severity, 28 treatments (2.1%) led to a severe side effect: this occurred in 3% and in 1.8% of the sessions performed with Dysport or Botox, respectively (P = ns). No correlation was found between dose and occurrence of side effects.

The most relevant features of treatments are summarised in Table 3.

Table 2 Side effects observed in 1009 treatments with Botox and 332 treatments with Dysport; they occurred in 325 out of 1341 sessions (24.2%): in 21.8%, the patients had received Botox, in 31.6% Dysport ($P = 0.00029$). Some patients reported more than one side effect

Side effect	Botox		Dysport	
	N°	(%)	N°	(%)
Ptosis	98	(9.71)	38	(11.45)
Hematoma	35	(3.47)	8	(2.41)
Irritation of conjunctiva	26*	(2.58)	16*	(4.82)
Lacrimation	25	(2.48)	15	(4.52)
Palpebral edema	23	(2.28)	6	(1.81)
Blurred vision	15**	(1.49)	13**	(3.92)
Diplopia	7***	(0.69)	18***	(5.42)
Dry eye	4	(0.4)	3	(0.9)
Lagophtalmos	2	(0.2)	3	(0.9)
Diffusion to other facial districts	2	(0.2)	3	(0.9)
Entropion	1	(0.1)	0	(0)
Systemic reactions	0	(0)	2	(0.6)
Other	11	(1.09)	1	(0.3)

* $P = 0.042$; ** $P = 0.0072$; *** $P = 0.000001$

Table 3 Features of treatments performed with Botox and Dysport

	Botox	Dysport	*P*=
No of treatments	1009	332	–
Patients treated in first session	113/128	12/128	–
Patients treated in last session	81/128*	44/128*	–
Mean dose used (U)	34 ± 15 (7.5–140)	152 ± 54 (40–400)	–
Mean latency (days)	4.5 ± 4.6 (0–60)	5.0 ± 5.7 (0–30)	NS
Mean duration of benefit (days)	66.2 ± 39.8 (0–520)	80.1 ± 36.3 (0–210)	0.000000024
% of treatment failure	7.7	3.6	0.0093
% of treatments with a side effect	21.8	31.6	0.00029

* = 3/128 patients were shifted to BoNT-B as occurred a secondary resistance

Discussion

So far, more than 50 open case–control studies encompassing about 2,500 BS patients have been published. Three double-blind studies (Jankovic and Orman 1987; Fahn et al. 1985; Park et al. 1993) and one single-blind study (Sampaio et al. 1997) have also focussed on this topic. A recent Cochrane meta-analysis (Costa et al. 2005) concluded that few studies have been published on a large population with a long follow-up (Mauriello et al. 1996; Silveira-Moriyama et al. 2005); moreover, longitudinal results of patients treated with two brands lack.

In our retrospective study, demographic and clinical data of the 128 patients with BS that we studied are comparable with previously reported data (Jankovic and Orman 1984; Grandas et al. 1988). In this series, the most used brand was Botox. Since for the majority of patients the first treatment was performed using Botox, most changes consisted in a shift from Botox to Dysport. This is mostly due to the fact that when we started BoNT injections, only Botox was available in our clinic. Later on, both toxins were available; however, patients were shifted to the other brand only when repeated treatment failures or side effects had occurred, or for temporary unavailability of the brand in use.

The overall incidence of primary resistance in our series was 2.3%, similar to other reports (Mauriello et al. 1996); moreover, no secondary resistance occurred; this is in keeping with other series, in which BS patients were reported to have the lowest incidence of secondary resistance (from 0 to 3%), when compared with other dystonias and hemifacial spasm (Van den Bergh et al. 1995; Mauriello et al. 1996; Hsiung et al. 2002; Echeverria Urabayen et al. 2004; Silveira-Moriyama et al. 2005).

The mean doses reported in previous series is wide, ranging from 8 U (Frueh and Musch 1986) to 100 Botox U (Levy et al. 2006), and from 55 U (Van den Bergh et al. 1995) to 120 Dysport U (Binari 2005). The mean dose that we used was slightly higher than previously reported. This is probably due to the long follow-up of our patients, since we observed that the dose was increased over time for both toxins in order to obtain a sustained benefit. This is in keeping with the reports of other authors (Frueh and Musch 1986; Carruthers and Stubbs 1987; Ainsworth and Kraft 1995) who found that the dose was increased to about 50% during the first six injections (but no further increase was required with later treatments); a dose decrease from the first to the fourth year was recently described as well as an increase after the fifth year (Hsiung et al. 2002; Echeverria Urabayen et al. 2004). In the "low dose" protocol using Dysport, a not statistically significant decrease in the amount of BoNT used was described (Van den Bergh et al. 1995). Dutton and Buckley reported the need to increase doses only in 9.1% of their patients (Dutton and Buckley 1988). Many authors failed to observe an association between dose and efficacy (Scott et al. 1985; Burns et al. 1986; Levy et al. 2006). However, we observed that a minority of patients who had failed to respond to standard treatment regimens improved with very high doses thus confirming a recent prospective, non-randomised, open-label interventional case series (Levy et al. 2006). In our series, we observed a constant, linear increase of mean dose over the time. This was related to the efficacy of each session for Botox only. No data about dilution of BoNT are available, and in several studies a wide range of dilution was considered (up to 10 ml of saline solution) (Elston and Russell 1985). In this series, we used different dilutions. Botox at higher dilution provided longer duration of clinical benefit whereas no further correlation was found between dilution and therapeutic outcome.

When comparing the therapeutic proprieties of the two brands we found no difference in latency which, in line with previous reports (from 1.9 (Cakmur et al. 2002), to 6.1 (Tsai et al. 2005)). In approximately 7% of the treatments, patients reported an immediate improvement after the injection, probably due to a mechanical effect of the liquid injected into the muscle or to placebo effect. Most treatments (55%) led to a clear benefit within 3 days. The rate of successful treatments ranged in previous series from 47.8% (Nussgens and Roggenkamper 1997) to 100% (Shorr et al. 1985; Albanese et al. 1992) whereas the rate in our series (93.3% of sessions), overlaps the most frequently reported rates, ranging from 90 to 96% (Dutton and

Buckley, 1988; Jankovic et al. 1990; Hsiung et al. 2002; Silveira-Moriyama et al. 2005). Duration of benefit in this series is comparable with the previously reported data (Frueh et al. 1984; Brin et al. 1987; Ruusuvaara and Setälä 1990; Mauriello and Aijian 1991; Ainsworth and Kraft 1995; Mauriello et al. 1996; Thussu et al. 1999; Cakmur et al. 2002): indeed, the mean duration of action in all the studies was estimated between 49 (Shorr et al. 1985) and 126 days (Van den Bergh et al. 1995). Exceptionally, a few patients reported a very long-lasting benefit. The cause of this "long-lasting" effect is unclear, and might be considered as a spontaneous remission similar to those described as uncommon yet possible (1.9% and 2.2% according to Grandas (Grandas et al. 1988) and Mauriello (Mauriello et al. 1996), respectively).

Long-term Results and Outcome Predictors

Data on benefit duration in repeated successive treatments are contradictory: it has been reported that duration increases (Elston and Russell 1985; Frueh and Musch 1986; Engstrom et al. 1987) decreases (Elston 1992; Ainsworth and Kraft 1995; Hsiung et al. 2002); or—as most authors observed—remains unchanged over time (Shorr et al. 1985; Cohen et al. 1986; Perman et al. 1986; Carruthers and Stubbs 1987; Dutton and Buckley 1988; Ruusuvaara and Setälä 1990; Taylor et al. 1991; Silveira-Moriyama et al. 2005). Others observed a variability of duration along time (Kraft and Lang 1988). It has been suggested that the change in duration of symptoms relief may reflect atrophy in the facial muscles, secondary to chemical denervation; however, histological studies failed to confirm this hypothesis (Wojno et al. 1986; Borodic and Ferrante 1992). Besides this, no apparent cumulative effect from consecutive injections nor evidence of permanent effect from the injections have been described (Frueh et al. 1984). Long-term results show that pre-treatment scores during subsequent treatments were slightly lower (approximately 15%) (Van den Bergh et al. 1995).

In this series, we observed that efficacy and duration of clinical benefit increased along time, and this is in keeping with a previous study on a long-term follow-up (Mejia et al. 2005); moreover, no correlation between the total dose injected and benefit duration was observed as previously described (Ainsworth and Kraft 1995) while BS severity decreased over time. Even if in our series males improved slightly more than females, gender probably has a marginal influence on the outcome: most authors failed to confirm gender-related difference (Thussu et al. 1999). According to previous studies, even other variables (such as age, age of onset and disease duration) were not correlated to the outcome (Scott et al. 1985).

Side effects complicated 24.2% of treatments; previous reported rates ranged from 10% (Hsiung et al. 2002) to 65% (Shorr et al. 1985). As described elsewhere, the most frequent side effect was ptosis, all the remaining side effects were mild, occurring in less than 4% of the treatments. Occurrence of side effects has not been associated to the number of sessions for each patient. After a patient experiences a side effect, the probability to suffer from another one does not increase, thus confirming the conclusions reported in recent meta-analysis regarding the safety profile of BoNT (Naumann and Jankovic 2004). This is in contrast with the observation by Dutton and Buckley who reported that risk increased as the number of treatments increases, and it is likely that patients undergoing 15 or more treatments should be expected to have at least one episode of ptosis (Dutton and Buckley 1988). Occurrence of side effects was not related to the amount of BoNT used in each treatment, as observed by other authors (Burns et al. 1986; Kraft and Lang 1988; Levy et al. 2006; Pang and O'day 2006).

Comparison Between Botox and Dysport

It is difficult to compare the two toxins used since the study was more powered for Botox, this being due to the high number of treatments performed with this BoNT compared to Dysport. However, some statistically significant differences emerged. When considering the benefit duration and the rate of treatment failure, Dysport provided a longer benefit duration than Botox (80 days versus 66); on the other hand, Dysport caused more numerous side effects; noteworthy, diplopia, blurred vision and irritation of conjunctiva were significantly associated with Dysport use. Both our study and other data support the view that Botox and Dysport are two different drugs. As a matter of fact, although Botox and Dysport namely contain the same chemical substance (confirmed by the observation that the two BoNTs have the same potency given the identical conditions both in vivo and in vitro studies (Wohlfarth et al. 1997)), they are different in terms of manufacturing (e.g. methods of extraction, diluents and stabilizers used, volume of injection recommended) (Mclellan et al. 1996). An interesting finding is that Dysport produces intrinsically more swallowing problems than Botox when injected into cervical muscles (Dressler 2002). According to our data, Dysport has a different spectrum of side effects as it causes more frequently diplopia, blurred vision and irritation of conjunctiva. This might be due to the fact that Dysport is more diffusible than Botox and when injected with an identical technique, it reaches more distant (and unwanted) targets. On the other hand, this may explain the better outcome observed with Dysport.

As a consequence, a real bioequivalence between Botox and Dysport might not exist due to the intrinsic difference in pharmacokinetic properties between these products. A

conversion factor must be considered only as a relationship of equivalence regarding the magnitude of clinical improvement. Recently, the comparison between Botox and Dysport was addressed in a single-arm, crossover-design study involving 27 patients with BS and using a 4:1 conversion ratio. Botox resulted more efficacious than Dysport although the design of the study was biased, due to the measurements based on a one-injection cycle. In addition, all cycles were characterised by the one-direction switching to Botox 12 weeks after Dysport was injected (Binari 2005). Thus, it is possible that at the time of Botox injection, a residual effect of Dysport was still ongoing and enhanced the clinical benefit due to the injection of the second drug (Botox).

A recent Cochrane review concluded that there are no high-quality randomised, controlled studies to support the use of BoNT-A for BS; however, as many studies suggest, it is highly effective and safe. As a consequence, it would be difficult and possibly unethical to design new placebo-controlled trials. The authors therefore concluded that "future trials should explore technical factors such as the optimum treatment intervals, different injection techniques, doses, BoNT types and formulations […] service delivery, quality of life, long-term efficacy, safety, and immunogenicity" (Costa et al. 2005).

In conclusion, we illustrated the natural history of a large group of patients who have received BoNT type A injections of the two most commonly used products (Botox or Dysport) over a long period; to our knowledge, this is the first long-term outcome study regarding this issue. The limitation of this study is at the same time the strength of an unbiased method: it is not a prospective blinded trial, which would be impossible, given such a long follow-up duration.

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