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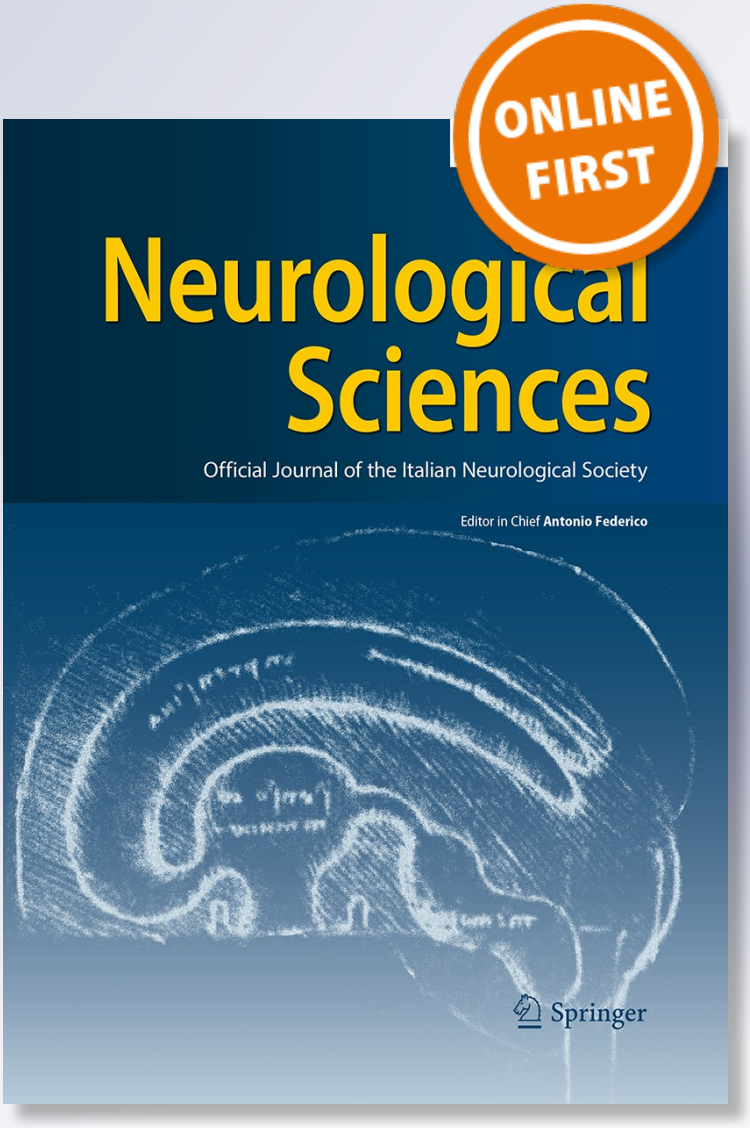

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REVIEW ARTICLE

Conversion ratio between Dysport and Botox in clinical practice: an overview of available evidence

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Abstract The optimal conversion ratio between Dysport and Botox—the two botulinum neurotoxin type A products (BoNT-As) supported by the larger bulk of evidence—has been extensively debated, because of its broad medical and economic implications. The article discusses the available evidence on the conversion ratio between Dysport and Botox in adults affected by spasticity, cervical dystonia, blepharospasm and hemifacial spasm, with a focus on clinical trials that specifically addressed this issue. In addition, some suggestions on the conversion ratio between Dysport and Xeomin can be extrapolated, since Xeomin has the same efficacy and safety profile as Botox and is exchangeable with Botox with a 1:1 conversion ratio. Taken together, the findings retrieved from this literature research suggest that a conversion ratio of 3:1 (Dysport:Botox)—or even lower—can be considered appropriate for the treatment of the above-mentioned conditions. Higher conversion ratios may lead to an overdosing of Dysport, with a potential increased incidence of adverse events. Therefore, we recommend that physicians using both products consider using a lower conversion factor as a guide, adjusting it upwards as required based on the specific characteristics and response to treatment of each patient.

Keywords Blepharospasm · Botulinum toxin · Cervical dystonia · Conversion ratio · Hemifacial spasm · Spasticity

Introduction

Botulinum neurotoxins (BoNTs) have shown considerable clinical efficacy in the treatment of a large range of disorders resulting from increased muscular tone, such as cervical dystonia, hemifacial spasm and blepharospasm, thanks to their mechanism of action [1, 2].

New avenues of research for the clinical use of BoNTs are currently under development, with the aim of extending the clinical indications for these molecules, which currently range from the treatment of overactive skeletal and smooth muscles to the management of hypersecretory and painful disorders such as migraine, trigeminal neuralgia, and the myofascial pain syndrome [3].

Several different types of BoNT type A (BoNT-A) are approved and available in the market: Botox® (Allergan, Inc., Irvine, California, USA), Dysport® (Ipsen Limited, Berkshire, UK), and Xeomin® (Merz Pharmaceuticals GmbH, Frankfurt am Main, Germany). The only approved BoNT type B formulation is Myobloc® (US)/Neurobloc® (outside US) (Eisai Limited, Hatfield, UK).[1]

Due to their biological nature, each preparation of BoNT-A is characterized by different properties; therefore, the units of each BoNT-A are not interchangeable and the number of units recommended for each indication is specific for each

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[1] The use of commercial names is for communication purposes only and does not imply endorsement.

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preparation [4]. This may have important medical and economic consequences, as patients often need to switch to a different BoNT-A and the cost of treatment would change according to the conversion factor applied [4]. Therefore, the establishment of a correct conversion ratio between BoNT-As is necessary to guarantee the safety of treatment and to reduce national healthcare costs [4].

Indeed some evidence is available regarding the conversion ratio for Botox versus Dysport and Botox versus Xeomin, while few studies—in most cases non-therapeutic indications—have addressed the conversion ratio for Dysport versus Xeomin.

Park and colleagues have recently published a review which reports "biological activity in relation to Botox" (see Table 1 [5]), citing a ratio of 1:1 for Xeomin:Botox and 3:1 for Dysport:Botox. This so called "dose equivalence ratio" is probably the most contentious issue about the use of BoNT-A products and, in our opinion, should be discussed more in detail since regulatory authorities often require an insertion, in all BoNT-A product literature, clearly stating that the units of each product are specific to that product and are not interchangeable. In particular, any "ratio" between Dysport and Botox units is likely to range from 2 to 2.5, differing from the paper by Park et al. [5, 6].

The aim of this short, non-systematic review is to discuss the available evidence on the conversion ratio between Dysport and Botox. Indirectly, some suggestions on the conversion ratio between Dysport and Xeomin can be extrapolated, since some studies have shown that Xeomin has the same efficacy and safety profile as Botox and is exchangeable with Botox with a 1:1 conversion ratio [5, 7, 8] in adults affected by the following conditions: spasticity, cervical dystonia, blepharospasm, and hemifacial spasm, as they appear to be the BoNT-A indications supported by the most robust clinical trial evidence. We will also briefly review some aspects of BoNT-A pharmacology.

Methodology

Key studies conducted in adults for inclusion in this review were identified by a MEDLINE search, based on several interrelated queries. Restrictions in terms of year of publication were not applied, but only studies published in English were considered. Due to the non-systematic approach of this review, resulting articles were chosen according to their relevance, as judged by the authors, with a focus on well-designed clinical trials addressing the conversion ratio between Dysport and Botox, when available. The search results were then supplemented by manually browsing the reference list of identified articles, and by including other documents suggested by authors' experience.

Botulinum neurotoxins—overview of pharmacology

Clostridium botulinum is a Gram-positive anaerobic bacterium that produces seven different, antigenically distinct

Table 1 Properties of approved botulinum-A toxin drugs (reproduced with permission from Park et al. [5], Table 1, p.727)

Brand name Generic name	Botox® Onabotulinumtoxin A	Dysport® Abobotulinumtoxin A	Xeomin® Incobotulinumtoxin A
Manufacturer	Allergan Inc (USA)	Ipsen Ltd (UK)	Merz Pharmaceuticals GmbH (Germany)
Target SNARE	SNAP-25	SNAP-25	SNAP-25
Packaging (units/vial)	100	500	50, 100
Pharmaceutical preparations	Powder	Powder	Powder
Stabilization	Vacuum drying	Freeze drying	Vacuum drying
Complex size (kDa)	900	300–900	150
Complexing proteins	O	O	X
Excipients per vial	HAS 500 μg	HAS 125 μg	HAS 1,000 μg
	NaCl 900 μg	Lactose 2,500 μg	Sucrose 4,700 μg
Biological activity in relation to Botox®	1	1/3	1
Specific activity (units/ng)	20	40	167
Storage of packaged product	2–8 °C	2–8 °C	Room temperature
Shelf life (months)	36	24	36–48
pH of reconstituted preparation	7.4	7.4	7.4
Storage once reconstituted	2–8 °C for 24 h	2–8 °C for several hours (4 h if stored at room temperature)	2–8 °C for 24 h

neurotoxins [1]. These neurotoxins vary in terms of molecular size, ranging from 300 to 900 kDa, and contain a binding domain (heavy chain: 100 kDa), a catalytic domain (light chain: 50 kDa) and a translocation domain [1].

The mechanism of action of BoNT-A is based on the inhibition of the release of acetylcholine from the presynaptic nerve terminal: this causes local chemo-denervation [1]. In addition, BoNT-A also inhibits the release of other neurotransmitters, such as noradrenaline, dopamine, serotonin, gamma-amino-butyrate, glycine and the methionine-encephalin peptide [1].

Due to their biological nature, the different commercial preparations of BoNT-A have different characteristics, summarized by Park et al. (although with the limitations described above) (Table 1) [5], and therefore, should not be considered as generics or interchangeable with each other on an equivalent-dose basis [9]. Of note, the laboratory tests used to assess the clinical potency of Dysport and Botox are different, with that used to measure Dysport potency being more sensitive and that of the latter drug being less sensitive, so that the potency of Botox is underestimated relative to Dysport [10]. Translating specific potency into the quantity of toxin complex protein per vial determines the toxin protein load per clinical dose; with a higher specific potency, the quantity of toxin protein per dose reduces proportionally [11].

The molecular mass of the complexes is as follows: Botox (900 kDa), Dysport (300–900 kDa), Myobloc (700 kDa) and Xeomin (150 kDa). The amount of neurotoxin per vial also varies: Botox (~5 ng), Dysport (4.35 ng), Myobloc (25 ng) and Xeomin (0.6 ng) [1, 11]. In particular, the difference in sizes could account for the other differences observed among the preparations, with lower molecular masses potentially associated with a longer diffusion distance. Toxin diffusion is a key factor in clinical practice, as excessive diffusion can result in the onset of side effects due to toxin activity [4]. It is widely accepted that different complexing proteins used in the formulations of BoNT-As have no role in diffusion, since they dissociate from the toxin rapidly after the injection [4]. On the other hand, the injection of a specific dose of BoNT-A in a larger volume of diluent increases the area into which it initially spreads, thus increasing the risk of excessive diffusion [4]. In a double-blind, randomized study conducted in healthy volunteers, higher dilutions of both Dysport and Botox—injected in the extensor digitorum brevis (EBD) muscle in the foot—increased the contraction of neighbouring muscles, thus, suggesting a greater diffusion distance from the injection site [12]. In the same study, no differences in the dilution effect between the two preparations at the same dilution were reported, showing the lack of difference in diffusion characteristics [12]. Similar conclusions were reached in another study [13].

Another key element which regulates diffusion is the toxin dose, with higher doses associated potentially with broader diffusion [4]. Therefore, an optimal conversion ratio should be applied when switching from one BoNT-A to another, to avoid the risk of overdosing and, at the same time, maintain the clinical efficacy.

Dysport:Botox conversion ratio in the treatment of spasticity

To our knowledge, no study has addressed the optimal Dysport:Botox conversion ratio in adult patients with post-stroke spasticity directly, and the ratio is usually decided in an empirical, case-by-case fashion. Due to the lack of comparative studies, we decided to consider the results of available clinical trials collectively. In total, nine key studies with a robust design, although with different sample sizes and follow-up periods, have been used to investigate the optimal dose of either Dysport or Botox in this indication [14–22], and one article provided clinical recommendations [23]. For communication purposes, the details of each study are not reported here in extenso; however, the key findings of each study are summarized in Table 2. The optimal dosages of either Dysport or Botox required to exert the clinical effect in different muscles reported in the studies summarized in Table 2 suggest that a conversion ratio of 3:1 seems appropriate in the majority of cases, although this ratio can be only tentatively suggested on the basis of available findings, and proper ad hoc studies should be conducted to either confirm or discard this hypothesis.

Dysport:Botox conversion ratio in the treatment of cervical dystonia

Cervical dystonia is the most common type of segmental dystonia; treatment of this condition usually requires high doses of BoNT-A. To our knowledge, two trials have addressed the conversion ratio between Dysport and Botox in patients with cervical dystonia [24, 25].

Ranoux et al. [24] compared Dysport and Botox in a double-blind, randomized, three period cross-over study in 54 patients with cervical dystonia. Patients received the following treatments: Botox at the usual effective dose or Dysport at a conversion factor of 3:1 and 4:1. Overall, Dysport doses at both conversion factors provided a significant improvement in the Tsui score and the TWSTRS-pain score, and a longer duration of action compared with Botox (Table 3) [24]. The differences between the two Dysport doses in terms of these parameters were not statistically significant. However,

Table 2 Overview of the key studies on Dysport or Botox in the treatment of post-stroke adult spasticity considered in this article

First author and year of publication	Patients	Treatment	Weeks of follow-up	Key findings
Hesse, 1994 [14]	12 chronic hemiparetic outpatients with pronounced lower limb extensor spasticity	Dysport 400 U	8	Dysport safely improved muscle tone, gait ability, and other motor functions in all patients
Bhakta, 1996 [15]	17 Patients with severe spasticity and a non-functioning arm	Dysport 400–1,000 U Botox 100–200 U	2	BoNT-As were safe and effective for reducing disability in patients with severe upper limb spasticity
Simpson, 1996 [16]	39 Patients with chronic upper limb spasticity after stroke	Botox 75 U Botox 150 U Botox 300 U Placebo	12	Botox safely reduced upper extremity muscle tone in patients with chronic spasticity after stroke, with a more evident effect for the 300 U dose
Bhakta, 2000 [17]	40 Patients with stroke and spasticity in a functionally useless arm	Dysport 1,000 U Placebo	12	Dysport reduced carer burden and forearm flexor spasticity
Bakheit, 2000 [18]	82 Patients with upper limb spasticity	Dysport 500 U Dysport 1,000 U Dysport 1,500 U Placebo	16	All doses of Dysport were safe and effective, with the most evident benefit with the 1,000 U dose
Hyman, 2000 [19]	74 Patients with multiple sclerosis, and disabling spasticity affecting the hip adductor muscles of both legs	Dysport 500 U Dysport 1,000 U Dysport 1,500 U Placebo	12	Dysport safely reduced the degree of hip adductor spasticity. The optimal dose for hip adductor spasticity appears 500–1,000 U, divided between both legs.
Pittock, 2003 [20]	234 Patients with post-stroke calf spasticity	Dysport 500 U Dysport 1,000 U Dysport 1,500 U Placebo	12	Dysport reduced muscle tone, limb pain and dependence on walking aids The greatest benefits were observed with Dysport 1,500 U Few adverse events were reported
Woldag, 2003 [21]	10 Patients with post-stroke spasticity of an upper limb	Dysport 480 U	12	Dysport increased the functional capacity of the entire arm, and the range of motion of fingers and wrist
Childers, 2004 [22]	91 Patients with post-stroke spasticity of upper limbs	Botox 90 U Botox 180 U Botox 360 U Placebo	24	Botox reduced muscle tone of upped limbs in a dose-dependent manner, but did not improve global quality of life or disability

Studies are listed in chronological order

Dysport treatment was associated with a slightly higher incidence of mild adverse events than Botox, albeit not requiring withdrawal of therapy or specific management. These results show that Dysport 4:1 and 3:1 are more efficient than Botox in the treatment of cervical Dystonia. The higher incidence of adverse events reported with Dysport could lend support to the hypothesis of a conversion factor lower than 3 in patients with cervical dystonia (or requiring injection in other large muscles with inappropriate contraction).

Odergren et al. [25] evaluated 73 patients with predominantly rotational cervical dystonia, and a minimum of four previous Botox treatments. Patients were randomly assigned, in a double-blind fashion, to receive either the clinically indicated dose of Botox or Dysport at a conversion factor of 3:1. BoNT-A was injected into one or more clinically indicated muscles, at one or more sites per muscle, and the volume of injection was strictly controlled. A substantial improvement in the Tsui score was reported in both groups by week 2, with no significant differences between Dysport and Botox. The two BoNT-As were also comparable in terms of duration of effect (assessed as time to retreatment) and a slightly higher percentage of patients achieved treatment success with Dysport (76 %) compared

Table 3 Key efficacy results reported in patients with cervical dystonia treated with either Botox or Dysport at two different conversion ratios [3:1 and 4:1] (Reproduced with permission from Ranoux et al. [24], Table 2, p.460)

Treatment (in injections)	Before injection		Difference before injection/1 month after injection		Duration of action	
	Tsui score (mean (SD))	TWSTRS-pain score (mean (SD))	Tsui score (mean (SD))	TWSTRS-pain score (mean (SD))	Injections	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, 0–23.5)
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)[§,#]

[§] Dysport 1:4 vs Botox: $p = 0.01$, $p = 0.02$ and $p = 0.02$, respectively

[#] Dysport 1:4 vs 1:3: $p = 0.28$, $p = 0.58$ and $p = 0.09$, respectively

with Botox (66 %), but this difference was not statistically significant. The safety profile was comparable.

Taken together, the above-mentioned findings, reported in studies with a rigorous design, indicate that a conversion ratio 3:1, or possibly lower, can be considered optimal in patients with cervical dystonia.

Dysport:Botox conversion ratio in the treatment of blepharospasm and hemifacial spasm

BoNT-As have been extensively evaluated in the treatment of blepharospasm and hemifacial spams. We report the key results of two clinical trials which have specifically addressed the conversion ratio between Dysport and Botox in this indication [26, 27].

Nüssgens and Roggenkämper [26] performed a double-blind study on 212 consecutive patients, who received one injection of Dysport and one injection of Botox in two consecutive treatment sessions. The conversion factor, determined empirically, was 1:4. In this trial, Botox and Dysport treatments were reported to be statistically similar, but a trend for a longer duration of effect was seen in the Dysport group. Local adverse reactions were more frequent with Dysport than with Botox.

Another double-blind study, conducted by Sampaio et al., on 91 patients with blepharospasm or hemifacial spasm led to overall similar results [27]. These findings suggest that a 4:1 conversion ratio between Dysport and Botox might be optimal in blepharospasm and hemifacial spasm. A large Italian study—which we have decided to include in this article despite its retrospective design, as we consider it of particular relevance—reached the same conclusion, but also suggested that the 4:1 ratio should not be considered an exact measure [28].

The clinical efficacy of a 4:1 conversion ratio was also challenged by a long-term study, which included 97 patients with hemifacial spasm, 44 of whom received Dysport and 53 Botox [28]. At a conversion ratio of 2.56:1, the two BoNTs-A showed therapeutic equivalence and were associated with a similar safety profile. However, the observational nature of this study should be taken into account to interpret these findings correctly. Taken together, the above-described evidence lends some support to a conversion ratio lower than 4:1 (e.g. 3:1) between Dysport and Botox in these indications.

Conclusions

The optimal conversion ratio between Dysport and Botox—the two BoNT-As whose use is supported by the larger bulk of evidence—has been extensively debated, because of its medical and economic implications. Historically, a conversion rate of 4:1 or higher has been adopted in clinical practice, likely originating from excessive unit differences that were proposed before quantitative data became available. In this article, we selected key clinical studies with robust design to investigate this issue further. Taken together, the findings retrieved from these studies could suggest that a conversion ratio of 3:1—or even lower—could be appropriate for the treatment of spasticity, cervical dystonia and blepharospasm or hemifacial spasm. Higher conversion ratios may lead to an overdosing of Dysport, with a potential for increased incidence of adverse events. However, available evidence is still too scant—in particular regarding the treatment of spasticity where trials specifically addressing the conversion factor between Dysport and Botox are lacking—to permit precise recommendations.

In line with previous suggestions, we suggest that physicians using both products consider the use of a lower conversion factor as a guide, and adjust it upwards as required, based on the specific characteristics and response to treatment of each patient.

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Conflict of interest Authors declare no conflicts of interest directly relevant to this study.

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