

Comparison of different preparations of botulinumtoxin A in the treatment of cervical dystonia

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Abstract

Background and Objectives: Botulinum neurotoxin A (BoNT-A) is the first line treatment for cervical dystonia (CD). Three different preparations are available: abobotulinumtoxinA, onabotulinumtoxinA, and incobotulinumtoxinA. However, potencies between these preparations vary and the products are therefore not easily interchangeable. **Methods:** We retrospectively compared the treatment plans and outcome of 51 patients with CD who were treated either with abobotulinumtoxinA (n = 19), onabotulinumtoxinA (n = 20), or incobotulinumtoxinA (n = 12). **Results:** There were no differences between the three treatment groups in respect to time of first improvement of symptoms (TIS), duration of symptom relieve (DSR), or maximum benefit (MaxB). However, the total units used for treatment in the abobotulinumtoxinA group was significantly higher than in both other groups, thus resulting in a conversion ratio of 4:1 for abobotulinumtoxinA to onabotulinumtoxinA and a conversion ratio of 4.3:1 for abobotulinumtoxinA to incobotulinumtoxinA.

Conclusion: In clinical practice, the conversion ratio between abobotulinumtoxinA and onabotulinumtoxinA might be higher than previously indicated by prospective studies or in mouse assays. Consequently, larger studies are needed to determine the conversion ratio of the different preparations available as well as the optimization of doses and selection of preparation, therefore resulting in improved cost-effectiveness of different treatment options in clinical practice.

INTRODUCTION

Botulinum neurotoxin A (BoNT-A) is the first line treatment for cervical dystonia (CD).¹ BoNT-A is a natural protein derived from clostridium botulinum, of which different preparations, abobotulinumtoxinA (Dysport®), onabotulinumtoxinA (Botox®), and incobotulinumtoxinA (Xeomin®), are commercially available. These various preparations of BoNT-A are produced using different methods and processes ultimately resulting in different potencies of each product, meaning dosing recommendations for each product are not easily interchangeable.^{2,3} Even though potencies are usually determined in mouse LD50 units (U), defined as the median lethal dose in a specified mouse population, the potencies are not always comparable, as the assay methodology varies, e.g. with the assay diluents used.^{4,6} Nevertheless, LD50-tests with comparable methodology demonstrated a 1:1 potency ratio of incobotulinumtoxinA and onabotulinumtoxinA⁷

and a 2.3:1 potency ratio of abobotulinumtoxinA and onabotulinumtoxinA⁶ in saline.

In clinical practice, the efficacy of the different toxins also depends on the solution used as diluent (e.g. saline or gelatin-containing phosphate buffer), as well as the volume of the diluent.⁸ In a clinical study on patients with cervical dystonia a dosing ratio of 1:1 between incobotulinumtoxinA and onabotulinumtoxinA has been found to result in comparable efficacy.⁹ In contrast, between abobotulinumtoxinA and onabotulinumtoxinA, the conversion ratio has been disputed.^{2,3} While one double blinded study on patients with CD used a conversion ratio of 3:1¹⁰ with equivalent treatment effects, another study compared two different conversion ratios of 4:1 and 3:1 in a cross over design and subsequently found no superiority of a treatment ratio higher than 3:1¹¹ between abobotulinumtoxinA and onabotulinumtoxinA. These studies led to the conclusion that 3:1 was the most likely conversion rate between abobotulinumtoxinA and onabotulinumtoxinA.^{12,13} In order to further investigate the conversion

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ratio for all three preparations, the doses used for treatment in CD in clinical praxis were analyzed retrospectively.

METHODS

Patients

Clinical data and treatment plans of 51 CD patients from the dystonia out-patient clinic of the University of Tübingen treated with one of the three different preparations of BoNT-A were analyzed retrospectively. Of those, 19 were treated with abobotulinumtoxinA, 20 with onabotulinumtoxinA and 12 with incobotulinumtoxinA. The three patient groups were comparable with respect to age, sex or severity of symptoms (Table 1). All patients had been treated previously with the respective preparations of BoNT-A with time intervals of at least 12 weeks in which the treatment plans and doses had been adjusted and optimized to each patient.

Assessment of clinical data

Severity of symptoms were rated according to the Toronto Western Spasmodic Torticollis Rating Scale (TWSTERS 1) on the basis of the reports of the exams in the patient files performed by the treating physician using only the Subscale A (Maximal Excursion) on the day of injection. "Time to First Improvement of Symptoms" (TIS) in days was defined as the time between last treatment and first subjective improvement of dystonic symptoms. "Duration of Symptom Relieve" (DSR) in weeks was defined as time between last treatment and first subjective notice of reduction of benefit from the treatment. "Maximum Benefit" (MaxB) in % was defined as subjective maximal improvement of the dystonic symptoms by the patient. TIS, DSR and MaxB were rated according to the patient's history as reported in the patients file.

Preparation and Injection

All botulinumtoxines were diluted in saline 0,9%; onabotulinumtoxinA and incobotulinumtoxinA with 100 U/ml and abobotulinumtoxinA with 500 U/ml and injected using a 27 G syringe. Location, number of muscles injected and dose of each injection were chosen according to clinical symptoms and consistent over several previous treatment cycles.

Statistics

Statistics were obtained using IBM SPSS Statistics 19. For comparison between all three groups One-way ANOVA was used. Post hoc comparisons between groups were done using Tukey. Level of significance was set to 0.05.

RESULTS

Patients' groups treated with abobotulinumtoxinA, onabotulinumtoxinA or incobotulinumtoxinA did not differ significantly with respect to age, sex or severity of symptoms (Table 1). The mean maximum treatment benefit of all 51 patients was reported to be 72 (\pm 17) % and did not differ significantly between the three treatment groups. The mean TIS was 7.7 (\pm 5.9) days and the mean DSR 10.8 (\pm 2.6) weeks (Table 2). There was no significant difference in TIS or in DSR between the three treatment groups. However, the amount of units used for treatment was significantly different ($p < 0.00$) between all three groups. Post-Hoc analysis revealed that the amount of units of abobotulinumtoxinA differed significantly ($p < 0.00$) from those of onabotulinumtoxinA, as well as of incobotulinumtoxinA, while the amounts of onabotulinumtoxinA and incobotulinumtoxinA showed no differences (Figure 1). Comparing the mean of 708 units of abobotulinumtoxinA to the mean of 175 units of onabotulinumtoxinA and 165 units of incobotulinumtoxinA, resulted in a dosing ratio of 4:1 for abobotulinumtoxinA to onabotulinumtoxinA and a dosing ratio of 4.3:1 for

Table 1: Demographical characteristics of patients by treatment group

	n	Age (years)	Severity of symptoms	Sex
AbobotulinumtoxinA	19	57.3 \pm 11.1	1.73 \pm 0.9	11 female
OnabotulinumtoxinA	20	58.9 \pm 12.1	1.35 \pm 0.5	14 female
IncobotulinumtoxinA	12	56.8 \pm 16.8	1.33 \pm 0.5	9 female
Total / mean	51	57.8 \pm 12.8	1.5 \pm 0.8	34 female

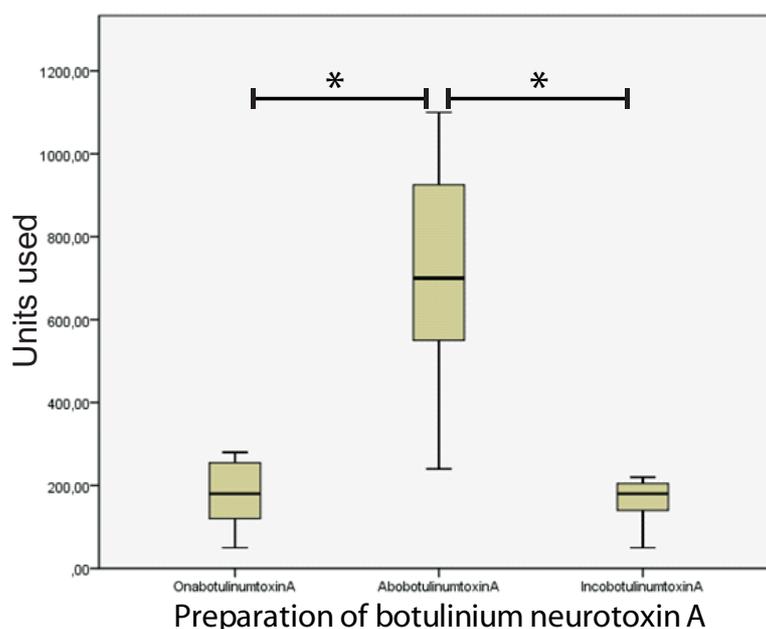


Figure 1. Differences between mouse LD50-units used of different preparations for the treatment of cervical dystonia (legend) * = significance, $p < 0.001$

abobotulinumtoxinA to incobotulinumtoxinA. The proportions of patients in each treatment group who received injections in cervical muscles were similar: sternocleidomastoid (AbobotulinumtoxinA, 17 of 19, 89%; OnabotulinumtoxinA, 19 of 20, 95%; IncobotulinumtoxinA 12 of 12, 100%), splenius capitis (AbobotulinumtoxinA, 16 of 19, 89%; OnabotulinumtoxinA, 19 of 20, 95%; IncobotulinumtoxinA 12 of 12, 100%), trapezius (AbobotulinumtoxinA, 16 of 19, 89%; OnabotulinumtoxinA, 11 of 20, 55%; IncobotulinumtoxinA 8 of 12, 67%), levator scapulae (AbobotulinumtoxinA, 11 of 19, 58%; OnabotulinumtoxinA, 9 of 20, 45%; IncobotulinumtoxinA 5 of 12, 42%), semispinalis capitis (AbobotulinumtoxinA, 11 of 19, 58%; OnabotulinumtoxinA, 10 of 20, 50%; IncobotulinumtoxinA 5 of 12, 42%), and scalenii (AbobotulinumtoxinA, 14 of 19, 74%; OnabotulinumtoxinA, 14 of 20, 70%; IncobotulinumtoxinA 5 of 12, 42%).

DISCUSSION

In this study, the treatment of three different preparations of botulinumtoxinA in a group of 51 patients was compared retrospectively. Patients treated with abobotulinumtoxinA, onabotulinumtoxinA or incobotulinumtoxinA did not differ significantly with respect to age

or severity of symptoms. Patients reported a mean time to first improvement of symptoms of 7.7 days after treatment and a mean duration of symptoms relieve of 10.8 weeks after treatment. The mean maximum benefit of treatment was reported to be 72%. There was no difference between the groups treated with the different preparations of BoNT-A regarding onset, duration or efficiency of the treatment. Efficacy of treatment in these three parameters, also only surveyed retrospectively and using subjective ratings by the patients, was comparable to previous studies examining the effect of BoNT-A in the treatment of CD.^{9,10,12} As expected, there was a significant difference in the amount of units used for comparable treatment benefits in the three groups treated with the three different preparations of BoNT-A. Units of abobotulinumtoxinA were significantly higher than those of both other preparations, onabotulinumtoxinA as well as incobotulinumtoxinA, resulting in a ratio of 4:1 for abobotulinumtoxinA to onabotulinumtoxinA and a ratio of 4.3:1 for abobotulinumtoxinA to incobotulinumtoxinA. These ratios are higher than those suggested in two prospective studies on BoNT-A treatment for CD comparing abobotulinumtoxinA to onabotulinumtoxinA, which suggested a conversion rate of 3:1 to be sufficient and no extra beneficial effect of a higher dose of abobotulinumtoxinA. The doses of each

Table 2: Effect of different preparations of botulinumtoxin A

	TIS (day)	DSR (weeks)	MaxB (%)	U used
AbobotulinumtoxinA	7.5 ± 6.3	11.4 ± 3.6	70 ± 16	708 ± 278
OnabotulinumtoxinA	6.2 ± 4.2	10.7 ± 1.9	76 ± 14	175 ± 76
IncobotulinumtoxinA	10.4 ± 5.4	9.9 ± 1.6	67 ± 22	165 ± 52
Total / mean	7.7 ± 5.9	10.8 ± 2.6	72 ± 17	

TIS = Time to First Improvement of Symptoms in days, DSR = Duration of Symptom Relieve in weeks, MaxB = Maximum benefit in %, U used = mouse LD50 units used;

preparation of BoNT-A used in our treatment plan had been adjusted and optimized in clinical practice over several treatment circles, suggesting that a lower dose of abobotulinumtoxinA would probably have had a lesser effect. Furthermore, it is noteworthy that onabotulinumtoxinA and incobotulinumtoxinA were diluted in saline 0.9% with 100 U/ml while abobotulinumtoxinA was diluted in saline 0.9% with 500 U/ml. The lower dilution might account for a poorer distribution and, therefore, a higher conversion ratio between abobotulinumtoxinA and both other preparations. In addition, dystonic symptoms in the group of patients treated with abobotulinumtoxinA were on average more severe (Table 1) and the mean duration of symptoms relieve lasted longer (Table 2) in the group of patients treated with abobotulinumtoxinA. Even though these differences did not reach significance this might partly explain, why doses in these patients were on average higher than expected.

In conclusion, the conversion ratios found in our clinical practice between abobotulinumtoxinA and onabotulinumtoxinA as well as incobotulinumtoxinA where 4:1 and 4.3:1 respectively and, therefore, higher than expected from previous prospective studies. Different dilutions of the BoNT-A preparations or variations in patients' groups treated with the abovementioned preparations might partly account for these discrepancies. Larger studies are needed to verify whether the conversion ratio in clinical practice differs from the conversion ratio determined from prospective studies. These data might contribute to optimizing doses and selection of preparations and consequently result in improved cost-effectiveness of treatment in clinical practice.

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