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Botulinum Toxin as a Treatment for Blepharospasm, Spasmodic Torticollis and Hemifacial Spasm

A. Albanese[a]
C. Colosimo[a]
D. Carretta[a]
A. Dickmann[b]
A.R. Bentivoglio[a]
P. Tonali[a]

[a] Istituto di Neurologia and
[b] Istituto di Clinica Oculistica, Università Cattolica del Sacro Cuore, Roma, Italy

Key Words
Blepharospasm
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Abstract
Fifty-two patients affected by focal dystonia or hemifacial spasm were treated with repeated injections of botulinum toxin. A clinical improvement was observed in all patients with blepharospasm; clinical benefit had a mean duration of 10 weeks. Clinical results were less inpressive, but also favorable in patients affected by spasmodic torticollis and by hemifacial spasm. In the latter, the incidence of drug-induced paresis was much higher than that observed in patients with blepharospasm, even though the doses of toxin injected were significantly lower.

Introduction

There is no global therapeutic approach for dystonia. Attempts to control dystonic postures and movements by means of the systemic administration of drugs acting on the central nervous system or with surgical procedures (either stereotactic lesions of the central nervous system or sections of peripheral nerves) have not been fully satisfactory [1]. Therefore, in recent years, researchers have directed a renewed interest to the search of new drugs acting upon different neurotransmitter systems in the brain [2].

In the early 1980s, Scott [3, 4] first introduced type A botulinum toxin as a symptomatic treatment for squint and blepharospasm. Type A botulinum toxin binds to a specific site on unmyelinated axon terminals where it blocks the reuptake of acetylcholine and promotes a reversible muscular paralysis [5, 6]. Following this pioneering work, many studies were published on the clinical efficacy of this therapeutic approach in patients affected by blepharospasm [7–15]. The possibility of treating other focal dystonias and other types of movement disorders was subsequently explored. Botulinum toxin is currently used for the management of spasmodic dysphonia, of focal dystonias affecting face, neck and arm and of hemifacial spasm [16–21].

Patients and Method

Fifty-two patients affected by focal dystonia or hemifacial spasm were selected in the outpatient clinic for movement disorders (table 1). Hospital ethical committee approval was obtained, and each patient signed an informed consent. Thirty-nine patients (23 women and 16 men) aged from 31 to 87 years (average 61.06) had blepharo-

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Dr. Alberto Albanese
Istituto di Neurologia, Università Cattolica
Largo A. Gemelli, 8
I-00168 Roma (Italy)

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Table 1. Clinical diagnosis of patients treated with butolinum toxin

Diagnosis	Patients n	M/F	Mean age years	Treatments[1] n
Idiopathic blepharospasm	23	7/16	61.91 ± 2.53	3.57 ± 0.58
Tardive blepharospasm	3	2/1	48.67 ± 1.86	4.67 ± 1.45
Meige's syndrome	7	6/1	63.71 ± 2.46	2.00 ± 0.69
Idiopathic torticollis	5	3/2	53.80 ± 7.88	2.40 ± 0.75
Segmental dystonia[2]	7	3/4	58.43 ± 3.87	3.00 ± 1.38
Tardive segmental dystonia[3]	1	0/1	44.00	2.00
Hemifacial spasm	6	5/1	67.00 ± 4.63	1.83 ± 0.65

[1] Mean number of repeated treatments.
[2] Three patients were treated for blepharospasm and for torticollis; 2 patients were treated only for blepharospasm; 2 patients were treated only for torticollis.
[3] Treated for blepharospasm and for torticollis.

spasm; of these, 23 patients (16 women and 7 men), aged from 31 to 87 years (average 61.91) suffered from an idiopathic form, 3 patients (1 woman and 2 men) aged from 45 to 51 years (average 48.67) had tardive blepharospasm, 7 patients (1 woman and 6 men) aged from 56 to 73 years (average 63.71) had upper and lower facial dystonia (Meige's syndrome); finally, 6 patients affected by different types of segmental dystonia were treated for blepharospasm. Eleven patients (6 women and 5 men) aged from 36 to 80 years (average 54.18) were treated for spasmodic torticollis; of these, 5 patients (2 women and 3 men) had isolated torticollis, 5 patients (3 women and 2 men) were affected by segmental dystonia; 1 patient, a 44-year-old woman affected by tardive multifocal dystonia, had severe torticollis, blepharospasm and trunk dystonia; she was treated for blepharospasm and torticollis. Six patients (4 women and 2 men), aged from 55 to 87 years (average 67) suffered from idiopathic hemifacial spasm.

Type A botulinum toxin was obtained from the Smith Kettlewell Eye Research Institute (San Francisco, USA; Oculinum) or from the Vaccine and Research Laboratory (Porton Down, Salisbury, UK; Dysport). The first was graded in mouse units, while the latter was measured as weight of the toxin-hemagglutinin complex. Vials of Oculinum were stored frozed; vials of Dysport were stored at 4 °C. Both types of toxin were reconstituted with 0.9% sterile saline solution at the time of injection. Most patients were treated with Dysport; Oculinum was used in a limited number of patients with blepharospasm and with hemifacial spasm.

In patients with blepharospasm, the toxin was injected intradermically, because the orbicularis oculi is a very superficial muscle, which can be easily reached by a local diffusion of the toxin. Four injections were placed around each eye, two in the superior eyelid and two in the inferior one. The mean dose of each injection was 2.5 U of Oculinum, and 0.7 ng of Dysport (usually slightly higher doses in the lateral quadrants and lower doses in the medial ones). In patients with hemifacial spasm, the toxin was always injected in the eyelids of the affected side (four injections; average total dose: 7 ± 3 U of Oculinum or 1.89 ± 0.20 ng of Dysport) and in three occasions also in the orbicularis oris (two to three injections; average total dose: 1.25 ng of Dysport; table 2).

In spasmodic torticollis, the toxin was administered intramuscularly. The hyperactive muscles to be injected were determined only by inspection and palpation. Patients with simple rotational torticollis usually required three or four injections into the sternocleidomastoid muscle (SCM), and two injections in the contralateral splenius and trapezius. The total amount of toxin injected averaged 11.20 ± 0.74 ng (table 2); but 1 patient, who was affected by a severe segmental axial dystonia, was treated with much higher doses than the remainder of cases. This patient had torticollis: he received 3.0 ng in the right SCM, 6.0 ng in the left SCM, 2.5 ng in the left splenius, 4.0 ng in the right splenius and 1.25 ng in each trapezius.

Before and after each treatment, all patients were evaluated with a rating scale for dystonia [22]. Clinical evaluations were performed before each new treatment and at least once in each interval between two consecutive treatments. The patients were asked to fill up a questionnaire concerning the duration of therapeutic efficacy and the occurrence of side effects. Data were analyzed by means of two sample Student's t test.

Table 2. Botulinum toxin: summary statistics for treatments

	Total dose (mean ± SEM)	Injections n
Blepharospasm		
Dysport (39 patients)	5.60 ± 0.69	8
Oculinum (2 patients)	20 ± 0	8
Torticollis		
Dysport (11 patients)	11.20 ± 0.74	5.86
Hemifacial spasm		
Dysport (6 patients)[1]	1.89 ± 0.20	4
Oculinum (1 patient)	7 ± 3	4

The mean number of injections per treatment is given. Dysport is given in nanograms and Oculinum in units.
[1] Figures refer only to periocular injections. Three patients also received perioral injections.

Results

Botulinum toxin was effective in all cases of blepharospasm. Improvements were observed in all 39 patients (table 3). The mean duration of effect was 69.0 ± 6.03 days with a mean latency of 5.89 ± 1.69 days after injection. The maximal clinical efficacy was usually observed 1 week after the treatment; therapeutic effects lasted in all cases for at least 1 month. The mean baseline pretreatment score was 2.63 ± 0.13; it dropped to 0.32 ± 0.10 at the time of the peak effect. We did not observe any significant variation in the duration of the effect of repeated treatments.

In addition to the improvement of motor symptoms, we also observed the recovery of ophthalmologic abnormalities (e.g. conjunctivitis, keratitis), which are usually associated with blepharospasm. All patients regained a good visual function and, with repeated treatments, they were able to have a normal life for years.

Eight out of 11 patients with spasmodic torticollis had a clear clinical improvement, which lasted for 29.35 ± 5.11 days. The mean baseline pretreatment score for neck dystonia was 3.07 ± 0.28; it was 1.92 ± 0.45 at the time of the maximal clinical efficacy (table 3). The patients also reported a relief from pain, which is commonly associated with spasmodic neck movements. Three patients, who were affected by severe forms of dystonia, did not have any benefit from the treatment; 2 of them were treated only once, the other was treated three times with increasing doses of the toxin.

Due to the occurrence of side effects, the 6 patients with hemifacial spasm only received a limited number of repeated treatments. Three patients were treated only with injections around the eye on the affected side; they had a moderate improvement of the spasm, but no complete relief. The remaining 3 patients experienced important side effects. (1) One woman aged 60 years was treated three times. In the first two treatments Oculinum was injected around the affected eye (average total dose: 6 U); facial jerks were consistently reduced, although they did not disappear completely. The clinical improvement lasted for approximately 3 months. In the third injection, Dysport was injected around the eye (2.5 ng) and in the orbicularis oris (2.0 ng); few days later, facial weakness and diplopia occurred, the latter recovered 10 days after the injection, while facial weakness lasted for approximately 3 months. (2) Another woman (aged 70) was treated only once with Dysport (2.5 ng around the eye, 1.0 ng in the orbicularis oris); 2 days after the treatment, it was observed the onset of a severe facial weakness affecting all muscles innervated by the facial nerve but the frontalis. An EMG study performed 5 weeks later showed signs of a marked axonal loss without any impairment of neuromuscular transmission. Three months after the treatment, when hemifacial spasm reappeared, EMG analysis revealed that nerve regeneration was in progress. (3) A third woman (aged 69) was treated only once with Dysport (2.5 ng around the eye, 0.75 ng in the orbicularis oris); hemifacial spasm was relieved, but ptosis and diplopia occurred on the 3rd day after treatment. Three months after treatment diplopia and ptosis were mild, but still evident.

Table 3. Clinical efficacy of botulinum toxin (mean ± SEM)

Blepharospasm	
Latency of clinical effect, days	5.89 ± 1.69
Mean duration of the clinical effect, days	69 ± 6.03
Mean baseline score	2.63 ± 0.13[1]
Mean score (at peak efficacy)	0.32 ± 0.10[1]
Torticollis	
Latency of clinical effect, days	4.82 ± 0.96
Mean duration of clinical effect, days	29.35 ± 5.11
Mean baseline score	3.07 ± 0.28[2]
Mean score (at peak efficacy)	1.92 ± 0.45[2]

[1] $t < 1 \cdot 10^{-9}$.
[2] $t < 0.05$.

Side effects were also observed in patients treated for blepharospasm (table 4). 19 patients had ptosis, which usually appeared 2 days after treatment and lasted for 4 weeks. 5 patients had xerophthalmia, which was controlled by the administration of artificial tears. Six patients had eyelid edema, and 5 had hyperemia of the conjunctiva. A local hematoma, which resorbed in few days, occurred in 2 patients. Side effects occurred also in patients treated for torticollis. One patient, who received quite large amounts of the toxin (18 ng total), had transient dysphonia and difficulty in swallowing, which gradually recovered within 1 week. Another patient had transient local pain and stiffness following the injections in neck muscles. No systemic side effects were ever observed in patients treated for either blepharospasm and torticollis.

Discussion

The present data show that botulinum toxin is a safe and effective treatment for cranial dystonias. Our results in patients affected by blepharospasm are in keeping with

Table 4. Side effects

Side effects	Patients n	Incidence %	Mean duration days
Blepharospasm			
Ptosis	19	48.72	26.4
Edema	6	15.38	13.0
Xerophthalmia	5	12.82	15.0
Conjunctival hyperemia	5	12.82	21.0
Blurred vision	4	10.26	12.5
Diplopia	3	7.69	10.0
Local pain	3	7.69	16.0
Eye closure weakness	2	5.13	10.0
Tearing	2	5.13	17.0
Local hematoma	2	5.13	7.0
Eye burning	2	5.13	8.0
Torticollis			
Dysphagia	2	18.18	23.5
Excessive weakness	2	18.18	12.0
Dysphonia	1	9.09	11.0
Local pain	1	9.09	7.0

Table 5. Open studies on the clinical efficacy of botulinum toxin for blepharospasm

Patients n	Dosage per eye U	Improvement % of patients	Duration of effect, days	Reference
22	12.5	89.5	70	[10]
43	12.5–25	93	81	[14]
39	21	100	70	[4]
22	12.5	100	56	[13]
34	12.5	82.4	70	[9]
50	12.5	90	84	[19]
28	12.5	96	84	[12]
77	5–10	98	83	[7]
46	23.6	69	80	[16]
16	16.4	100	91	[11]

other reports [23]. As shown in table 5, in earlier studies a clinical improvement was observed in 69–100% of patients treated for blepharospasm. The mean duration of clinical efficacy was between 8 and 13 weeks.

In keeping with data reported by others, we have observed that clinical results are less favorable in patients affected by spasmodic torticollis. Stell et al. [24] reported that treatment with botulinum toxin is highly effective in relieving the pain associated with muscle spasm, but produces inconstant effects on dyskinetic movements. Tsui et al. [21] claimed that the toxin is more effective on the slow component of movement than it is on the fast component. The main side effects they observed were hypophonia and local pain. The low incidence of side effects reported in our series is probably related to the low mean doses we have used, which is much lower than that used in other studies on patients affected by torticollis [21, 24]. The high degree of variability in the clinical response of patients with torticollis is probably related to the existence of a more complex pattern of activation among different neck muscles, as compared to facial muscles. Tsui et al. [21] also suggested that EMG analysis of muscle activity should be performed before and after injections of the toxin in order to unequivocally identify the muscles affected.

All the side effects observed in out patients have already been described in other series. Their incidence is also comparable to that reported in other series, with few

noticeable exceptions. First, our patients with blepharospasm had a significantly lower incidence of diplopia [15]. We believe that this may depend upon the fact that our patients were treated with intradermic, rather than subcutaneous, injections of the toxin into the eyelids. This may have not influenced a possible weakening of the levator palpebrae, since this muscle lies very close to the epidermis, but may have rather reduced the diffusion to external oculomotor muscles. Secondly, dysphagia occurred in 2 out of 11 patients treated for torticollis; both of them received relatively high doses of the toxin in the SCM. This muscle is very close to the pharynx; therefore it seems likely that the occurrence of this quite disabling side effect may be related to the amount of botulinum toxin delivered into the SCM. This may also explain why in some previous series the incidence of dysphagia occurred in 90% of patients treated for spasmodic torticollis [24].

Side effects observed in patients with hemifacial spasm are probably related to the amount of toxin injected. Jankovic et al. [25] recently claimed that the presence of a subclinical denervation may account for a lower than usual dose needed for the treatment of hemifacial spasm. To this respect, it must be considered that the EMG picture observed in 1 patient showed that axonal damage only affected facial nerve branches which innervate the perioral and periocular muscles. The finding that the facial nerve branch innervating the frontalis muscle was unaffected suggests that a dying-back phenomenon, rather than an immunomediated process [26, 27], may be responsible for the prolonged posttreatment paresis which occurred in this patient.

Some differences in the occurrence of side effects between patients affected by blepharospasm and by hemifacial spasm are probably related to a different pathophysiology of these movement disorders. Blepharospasm is a focal dystonia; hemifacial spasm, instead, is a focal myoclonus [25], which is possibly always caused by a compression of the facial nerve root [28]. Therefore, clinical experience appears to indicate that botulinum toxin is a rather specific treatment for focal dystonias. To this respect, however, many facets still need to be elucidated. First, it is not yet known in which way this drug, that mainly acts on the peripheral nervous system, may interfere with the pathophysiology of central nervous system disorders, such as dystonia. Second, the neurological and systemic long-term effects of the toxin have not been studied yet. This is a very crucial point for understanding the long-term expectations of botulinum toxin therapy, and it is a matter for future studies.

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