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# Neurophysiological observations on the effects of botulinum toxin treatment in patients with dystonic blepharospasm

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**Abstract**

**Botulinum toxin treatment improves dystonic blepharospasm by inducing transient paresis of the orbicularis oculi muscle. It is not known if it also reduces the enhanced brainstem neuronal excitability found in this disorder. We have performed conventional electromyography (EMG) and blink reflex excitability studies on fifteen patients with blepharospasm before and after botulinum toxin treatment. Denervation signs were found with needle EMG in all treated muscles. Amplitude of the facial compound muscle action potential (CMAP) and R1 response was reduced after botulinum toxin injections. In blink reflex excitability studies, the recovery of R2 response was enhanced after treatment even when patients were tested at the time of maximal benefit from botulinum toxin injections. The results suggest that there is little influence of botulinum toxin treatment upon the enhanced excitability of brainstem interneurons in patients with blepharospasm.**

Local injections of botulinum toxin have been widely used as a symptomatic treatment for dystonic blepharospasm since 1985.[1] The administration of botulinum toxin causes a local blockage of neuromuscular transmission and a transient paresis of the orbicularis oculi muscle. The clinical result of this treatment is the reduction of the intensity and frequency of muscle spasms.[2–5]

Neurophysiological studies of patients with blepharospasm indicate an enhanced excitability of brainstem interneurons.[6 7] This enhancement is greater when the blepharospasm is more severe.[6] Until now, it is not known whether a modification of this neurophysiological abnormality takes place during treatment with botulinum toxin. The answer to such a question may afford a better understanding of the mechanism of action of botulinum toxin, and of the possible role that segmental afferents from cutaneous or muscular receptors may play in the genesis or the degree of disturbed excitability of brainstem interneurons in patients with blepharospasm.

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## Subjects and methods

Fifteen patients with cranial dystonia, five men and 10 women, were studied. Seven patients had isolated dystonic blepharospasm, seven patients had Meige's syndrome and one patient had blepharospasm plus spasmodic dysphonia. The mean duration of the disease was 4·2 years, ranging from two to 15 years. The patients' ages ranged between 44 and 74 years. Patients were chosen at random from a group of approximately 100 patients who have been treated with botulinum toxin in the neurology department at the Hospital Clinic, Barcelona, since 1986. None had evidence of basal ganglia or brainstem lesion on CT scan or NMR. All patients had been free of any medication for a period of at least one month before the onset of treatment with botulinum toxin. As a comparison, we used a group of 17 healthy subjects (six men and 11 women), with ages ranging from 22 to 68 years, whose results of the blink-reflex recovery curve have been already reported.[8]

Clinical assessment of patients included evaluation of spasm intensity and strength of the orbicularis oculi muscle. Spasm intensity was rated as follows: 0 = none; 1 = increased blinking caused by external stimuli; 2 = mild noticeable fluttering not incapacitating; 3 = very noticeable spasm, mildly incapacitating; 4 = severely incapacitating spasm (patient unable to drive, read, etc). Orbicularis oculi strength was rated according to the following scale: 0 = inability to close the eye; 1 = no resistance to lid opening; 2 = weak resistance to lid opening; 3 = moderate resistance to lid opening; 4 = strong resistance to lid opening.

Conventional electrophysiological examination included needle electromyography, cutaneous recording of the compound muscle action potential of the facial nerve at the orbicularis oculi (CMAP) and cutaneous recording of the blink-reflex to supraorbital electrical stimuli on both sides of the face.

The blink-reflex excitability curve was studied by using the paired shock technique suggested by Kimura.[9] A pair of cutaneous recording electrodes were placed on both orbicularis oculi, the active one on the middle part of the lower eyelid. The stimuli were applied to the supraorbital nerve at an intensity which produced a stable R2 response. Some responses to single stimuli were obtained first. Paired (conditioning and test) stimuli were then given at variable interstimuli interval that ranged between 100 and 1500 milliseconds. They were photographed on-line, by using a fibre optic system

*Table 1 Clinical evaluation of patients*

| Patients | Spasm intensity | | | O oculi strength | | |
|---|---|---|---|---|---|---|
| | BSLN | BoTox-1 | BoTox-2 | BSLN | BoTox-1 | BoTox-2 |
| 1 BSP | 4 | 0 | 3 | 4 | 1 | 2 |
| 2 BSP | 3 | 2 | 3 | 4 | 2 | 3 |
| 3 BSP | 4 | 1 | 3 | 4 | 1 | 4 |
| 4 BSP | 4 | 2 | 4 | 4 | 2 | 3 |
| 5 BSP | 4 | 3 | 3 | 4 | 1 | 3 |
| 6 BSP | 4 | 0 | 3 | 4 | 1 | 2 |
| 7 BSP | 4 | 2 | 3 | 4 | 2 | 4 |
| 8 Meige | 4 | 3 | 4 | 4 | 1 | 2 |
| 9 Meige | 3 | 2 | 3 | 4 | 2 | 3 |
| 10 Meige | 4 | 1 | 3 | 4 | 1 | 3 |
| 11 Meige | 4 | 3 | 3 | 4 | 2 | 4 |
| 12 Meige | 4 | 3 | 4 | 4 | 1 | 4 |
| 13 Meige | 4 | 2 | 3 | 4 | 3 | 3 |
| 14 Meige | 3 | 2 | 3 | 4 | 1 | 2 |
| 15 BSP (+) | 4 | 2 | 3 | 4 | 1 | 4 |

In this and next tables, BSLN = Baseline examination; BoTox-1 = 15 to 25 days after BoTox treatment; BoTox-2 = three to four months after BoTox treatment.
BSP: Isolated dystonic blepharospasm.
Meige: Meige's syndrome.
BSP (+): Blepharospasm plus spasmodic dysphonia.
Numbers represent the values of the rating scale scores, as outlined in the text.

(MEDELEC-FOR8), in a time scale of 200 mm/s. Responses which appeared artefactually altered by muscular spasms were discarded and the test repeated until a well defined response was obtained. The area of the R2 response that followed any stimulus was obtained by multiplying duration per peak to peak voltage (arbitrary units). For each inter-stimulus interval we measured the percentage of the area of the R2 response to the test stimulus with respect to that of the R2 response to the conditioning stimulus, which was considered to be 100%. Accordingly, the excitability curve of a single patient was built up by plotting the value of the percentage of R2 that was elicited by the test stimulus after each inter-stimulus interval. The blink reflex excitability curve of the group of patients was taken from the mean value of all single curves.

Clinical and electrophysiological examinations were systematically carried out at three pre-defined moments in relation to botulinum toxin treatment: a) baseline examination (BSLN), before the onset of treatment, b) between 15 and 25 days after botulinum toxin injections (BoTox–1), when patients reported maximum beneficial effects, and c) between three and four months after botulinum toxin injections (BoTox–2), when patients required new treatment. Baseline examination was carried out before the initial treatment with botulinum toxin in all patients. The examinations after the injections were made following the first treatment in five patients, whereas in the remaining 10 patients, these examinations were made after repeated treatments with botulinum toxin, usually applied every three to four months.

To compare the results, the two-tailed Student's *t* test was applied.

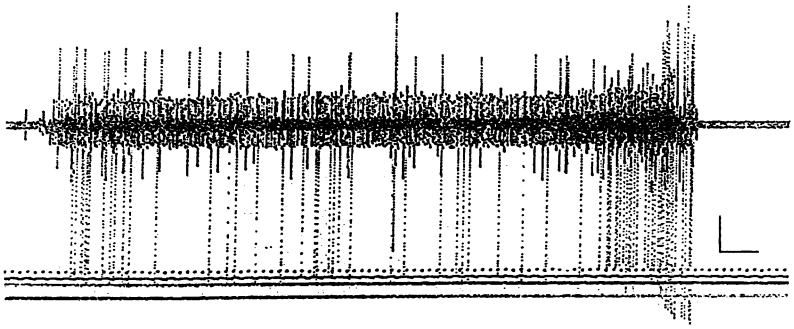

*Figure 1 Reduced interference pattern with increased temporal summation in needle EMG recording of orbicularis oculi muscle during voluntary contraction in a patient with blepharospasm 20 days after treatment with botulinum toxin. Calibration: 500 ms/ 100 microvolts.*

## Results

Results of the clinical examinations at the time of each of the three evaluations are shown in table 1. Both spasm intensity and strength scores ran almost parallel to each other, showing changes related to injections. At the time of BoTox-1, every patient had improved from their pre-treatment state as shown by the reduction in the intensity spasm score. Two out of the five patients that received botulinum toxin for the first time were almost completely free of spasms. At the time of BoTox-2 every patient deteriorated again reaching a degree of impairment which was not as high as the initial one. The analysis of the orbicularis oculi strength score shows that, at the time of BoTox-1, the power of the orbicularis oculi muscle diminished in every patient, but in no patient did the degree of weakness impede the occlusion of the eyelid and, at the time of BoTox-2, the power of the orbicularis oculi muscle increased in every patient again but in no patient did it reach the pre-treatment level.

A variable amount of fibrillation potentials was found on the needled EMG examination of the orbicularis oculi muscle at the time of BoTox-1, whereas they were not observed or were present in much less quantity at the time of BoTox-2. When the patient was asked for a voluntary contraction, a high degree of functional loss of motor units was observed at the time of BoTox-1. In most patients, only very few motor units were activated giving rise to a clear pattern of temporal summation (fig 1). In two patients (numbers 6 and 10), there were no active motor units in the needle recording sites. In the examination at the time of BoTox-2, an interference pattern was usually observed during contraction to maximal effort, with abundant low amplitude polyphasic motor unit action potentials, indicating, probably, a certain degree of reinnervation.

Results from conventional neurographic studies are shown in table 2. The amplitude of the facial CMAP decreased after treatment. On average, the amplitude of the CMAP observed in the examination at the time of BoTox-1 was around 45% and the one observed in the examination at the time of BoTox-2 was around 70% of the CMAP amplitude observed in the baseline examination. The amplitude of the blink reflex responses also decreased after the treatment. On average, the amplitude of R1 response was of around 15% at the time of BoTox-1 and around 55% at the time of BoTox-2, when compared with the amplitude of the R1 observed in the baseline examination. In some patients, we were not able to obtain blink-reflex responses at the time of BoTox-1 and they were excluded from the calculation.

*Table 2 Results of neurographic studies*

| | | BSLN | BoTox-1 | BoTox-2 |
|---|---|---|---|---|
| Facial CMAP | amplitude (mV) | 1·5 (0·57) | 0·67 (0·25)* | 0·95 (0·26)** |
| | latency (ms) | 3·2 (0·34) | 3·9 (0·62)* | 3·8 (0·55)* |
| R1 response | amplitude (mV) | 0·33 (0·16) | 0·07 (0·03)* | 0·18 (0·08)** |
| | latency (ms) | 11·6 (1·1) | 13·8 (1·6)* | 12·1 (1·05)** |
| R2 response | area (a units) | 4·6 (1·8) | 1·2 (0·9)* | 2·1 (1·5)* |
| | latency (ms) | 32·5 (7·2) | 35·8 (7·5) | 35·3 (6·8) |

Numbers represent the mean (SD) value.
(*) $p < 0.01$ when compared with BSLN.
(**) $p < 0.01$ when compared with each of the other groups.

When testing the excitability cycle, blink-reflex responses were sometimes masked by background EMG activity. In some patients, the contralateral recording helped in assessing the onset latency and size of the R2 response, but an accurate measuring was not possible in others, in spite of several attempts. Thus the presence of abundant spasms and of activity coming from mouth muscles prevented us from obtaining measurable responses in one patient with Meige's syndrome (number 11). The excitability curve of patients in the baseline examination was built-up by using the results from 14 patients. As expected, the degree of recovery of R2 was found to be significantly enhanced ($p < 0.05$) in patients when compared with control subjects in any of the inter-stimulus intervals studied except the one of 1500 milliseconds. Recordings at the time of BoTox-1 examination had to be discarded in three patients (number 1, 6 and 10) in which the background activity appeared even enhanced with respect to the pre-treatment observation. So, the R2 recovery curve at the time of BoTox-1 was obtained by using the results from 11 patients. We found no statistically significant difference between that curve and the one obtained in the examination before the treatment. Examples of the results in some patients of paired stimuli at 200 milliseconds inter-stimuli interval before and after the treatment are given in fig 2. In the BoTox-2 examination, the results of nine patients were available. The mean values of the percentage recovery of R2 found in that examination were not statistically different from the previous ones. Figure 3 shows the R2 excitability curves of the control subjects together with those of patients at the three selected times of their follow up. The mean values and one standard error of the mean for all inter-stimuli intervals are reported in table 3.

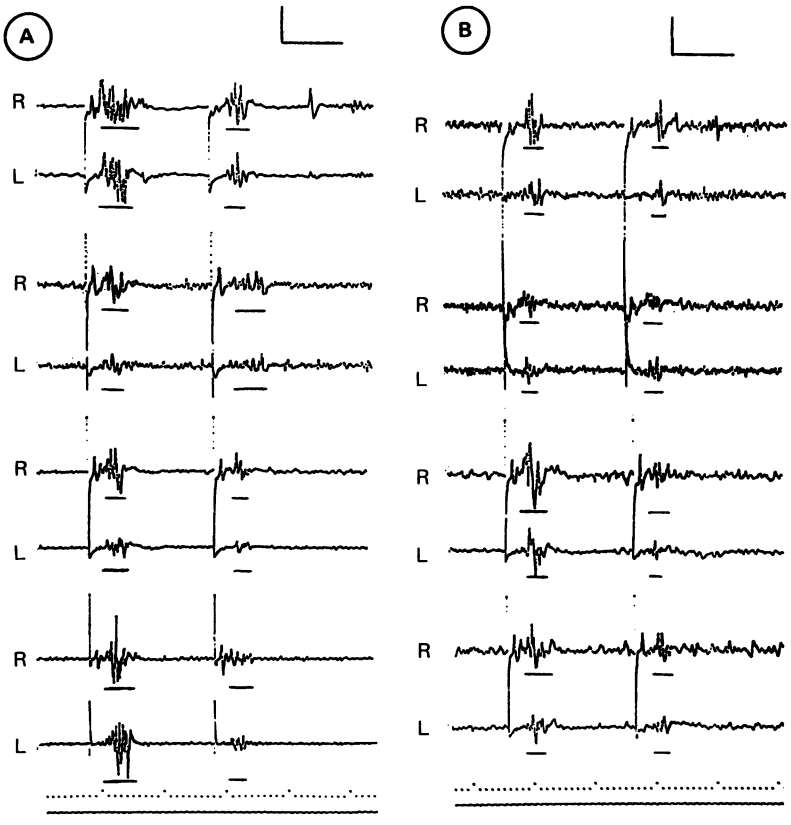


*Figure 2 Examples of the 200 ms inter-stimuli interval shots of the blink-reflex recovery curve in four patients with blepharospasm before (A) and 15 days after (B) the treatment with botulinum toxin. Stimuli are given at the right supraorbitrary nerve at the arrow position. R: right; L: left. Horizontal bars indicate duration of R2 responses.*

## Discussion

From our results we conclude that the blink reflex excitability cycle of patients with blepharospasm appears equally abnormal before and after local injections of botulinum toxin. The same conclusion has been already reached by Cohen *et al*[10] in a similar study with only a few cases. In our patients, blink reflex responses were poorly inhibited by a preceding stimulus before botulinum toxin and remained so afterwards, when clinical improvement in blepharospasm occurred. These observations suggest that the enhanced excitability of brainstem interneurons which is present in patients with blepharospasm is not modified by the toxin itself or by the presumed lack of peripheral sensory input from the paralysed muscle on trigeminal and brainstem neurons. The lack of modification of the underlying pathophysiological process by botulinum toxin is in line with the commonly observed recurrence of spasms in patients with blepharospasm once the paretic effect of the injected toxin disappears. Currently used treatment with botulinum toxin produces only a partial and transient improvement in blepharospasm,[2-5] and it remains possible that a more complete attentuation of muscle spasms could modify blink reflex excitability.

Berardelli *et al*[6] reported no significant difference in the R2 excitability cycle of normal

*Table 3 Percentage of recovery of R2 in the paired shock technique*

| Inter-stimuli interval | BSLN | BoTox-1 | BoTox-2 |
|---|---|---|---|
| 100 | 8·6 (3·3) | 13·2 (5·1) | 14·7 (8·1) |
| 200 | 18·4 (5·2) | 24·5 (6·0) | 14·1 (4·0) |
| 300 | 25·6 (5·6) | 41·1 (7·9) | 25·2 (6·3) |
| 400 | 41·0 (6·6) | 45·1 (6·3) | 40·3 (8·1) |
| 500 | 44·4 (6·2) | 47·3 (8·4) | 45·6 (3·3) |
| 600 | 56·9 (6·2) | 56·0 (5·3) | 56·1 (6·1) |
| 700 | 57·7 (3·8) | 61·2 (9·8) | 61·5 (6·1) |
| 800 | 79·3 (9·9) | 72·2 (5·8) | 71·5 (8·0) |
| 1000 | 95·6 (5·3) | 91·6 (5·1) | 88·4 (8·1) |
| 1500 | 105·6 (8·7) | 98·7 (5·5) | 95·0 (4·5) |

Numbers represent the mean value of the percentage of recovery of R2 test response related to the conditioning one, with one standard error in brackets. None of the possible comparisons attained the level of statistical significance.

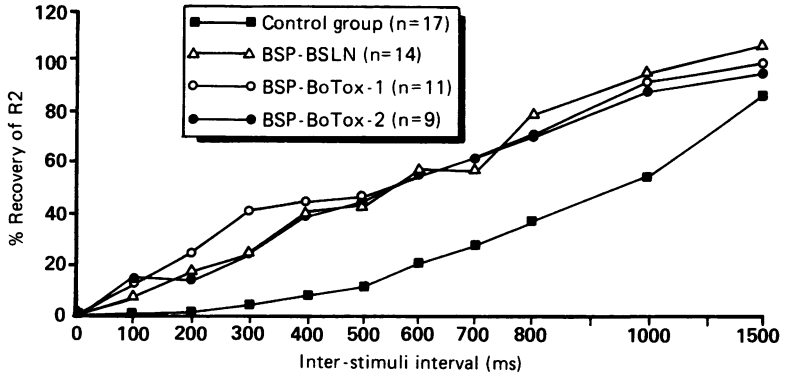


*Figure 3 Blink-reflex recovery curves to paired stimuli in control subjects and in patients with blepharospasm in BSLN, BoTox-1 and BoTox-2.*

subjects at rest or during a sustained voluntary contraction of orbicularis oculi. In this paper, we report no differences in the R2 excitability cycle of patients with blepharospasm when the muscles are abnormally hyperfunctioning or when they are paralysed. Both findings suggest that there is little influence of muscular afferents upon the excitability of brainstem interneurons.

After treatment with botulinum toxin, most patients claim that, besides a reduction of the spasm intensity, they also notice a reduction of the spasm frequency,[2 3 5] an effect that is difficult to explain on the basis of muscle paresis alone. Our findings suggest that this effect cannot be ascribed to a concomitant normalisation of brainstem interneuron excitability. Since there is evidence from animal experiments of a retrograde axonal transport after local muscular injection of botulinum toxin,[11] its action upon the motoneuron excitability has to be taken into account. Wiegand and Wellhoner[11] found a decrease in the inhibitory effect of the antidromic stimulation upon the monosynaptic reflex in cats after unilateral injection on the gastrocnemius muscle of 1 ug of botulinum toxin per kg of body weight. According to Hagenah *et al*[12] such an effect would be probably related to an estructural damage at the motor neuron cell body. An easier explanation of the reported decrease in the frequency of the orbicularis oculi spasms is that some of the previous strong contractions of the muscle become weak eyelid movements after treatment and they may not be considered as a spasm by the patients themselves.

Botulinum intoxication produces a presynaptic functional block at the neuromuscular junction which may be partially overcome by temporal summation resulting in a potentiation of muscle responses following electrical stimuli given at a high frequency.[13 14] It is unlikely, however, that a mechanism of this sort has interfered with our results, since the rate of stimulation applied with the paired shock technique in our study is far below the one necessary to produce temporal summation.

Some patients exhibited an increased background EMG activity in the cutaneous recording after botulinum toxin injections when compared with the recording before treatment. This may be due to an increased EMG activity in adjacent non-paralysed muscles. If such is the case, the question may be raised here of the need of applying the local injections of the toxin not only in the orbicularis oculi muscle but also in other periocular muscles that may be synergistic for eye closure. We also observed that in spite of the absence of motor unit action potentials recorded in the needle EMG recording of orbicularis oculi, a facial CMAP was obtained, although reduced in amplitude, by using cutaneous electrodes. It probably originated in adjacent facial muscles not affected by the toxin. After botulinum toxin treatment, the facial CMAP was less reduced in amplitude than the blink reflex R1 response recorded by cutaneous electrodes in orbicularis oculi. The reasons for this may be that fewer groups of muscle fibres contribute to the R1 response than to the facial CMAP.

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