

SHORT REPORT

Botulinum toxin therapy: distant effects on neuromuscular transmission and autonomic nervous system

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Abstract

To evaluate distant effects of botulinum toxin, single fibre electromyography on the extensor digitorum communis muscle and six tests of cardiovascular reflexes were performed in five patients injected with *BoTox* (Oculinum[®]) 20–130 units for craniocervical dystonia and hemifacial spasm. Patients underwent two sessions of treatment and the second time the dosage was doubled. Botulinum toxin injection induced an increase of mean jitter value above normal limits in all cases. An increase of fibre density was recorded six weeks after the treatment. Cardiovascular reflexes showed mild abnormalities in four patients. The data confirm distant effects of botulinum toxin on neuromuscular transmission and on autonomic function.

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Local injection of botulinum A toxin (BoTox) is widely used in the treatment of focal dystonias such as blepharospasm and spasmodic torticollis as well as in strabismus. Single fibre electromyography (SFEMG) is very sensitive in revealing neuromuscular transmission defects and in detecting reinnervation phenomena.¹ SFEMG abnormalities in muscles distant from the site of the BoTox injection have been reported and ascribed to presynaptic blockade^{2,3} or to stimulation of terminal sprouting.⁴ Accurate and extensive follow up studies, however, are not available. Moreover, the possible effects of BoTox therapy on the autonomic nervous system (ANS) have never been investigated, although autonomic disturbances are the rule in botulism.⁵

Methods

Five patients aged 25 to 64 years participated in the study. They received a local injection of BoTox (Oculinum); three patients with blepharospasm and one patient with hemifacial spasm received 20 units each, and to the fifth patient with spasmodic torticollis 65 units were administered. Patients underwent two sessions of treatment and the second time the dosage was doubled.

The protocol included a SFEMG and a number of cardiovascular autonomic reflex

tests which were performed before the toxin was administered and repeated 1, 4, 7, 14, 30 and 45 days after the first injection and 1, 4, 7, 14, 30, 45, 60 and 90 days following the second BoTox injection.

SFEMG was carried out on voluntarily activated extensor digitorum communis muscle and in each examination 20 potential pairs were recorded. In each of 20 pairs, the mean value of consecutive differences (MCD) was determined and subsequently the mean MCD was calculated. Fibre density was also measured.¹

The ANS investigation consisted of six tests: (R-R) interval variation test, deep breathing, Valsalva manoeuvre, heart rate and blood pressure responses to standing, and a sustained handgrip test. Elsewhere we have detailed the methodology of the tests.⁵ The results obtained were evaluated according to age by Bayesian analysis, a pattern recognition method,⁶ and statistics included a Student's *t* test for paired observations and the ANOVA one way test.

Results

All five patients experienced moderate to marked improvement of their disturbances without complaints related to local side effects.

The BoTox injection induced, in all subjects, an increase of jitter which exceeded normal limits. Compared to the baseline, a statistically significant increase in MCD was already present 14 days after the first injection. The difference reached its maximum 14 and 30 days after the second injection maintaining a statistically significant level until 60 days (fig A). In some recordings, the jitter was inversely related to the firing rate. Moreover, statistical analysis revealed a significant difference ($p < 0.005$) between the mean (SD) jitter value recorded one to 45 days after the first BoTox injection [32.6 (6) μ s] and that obtained in the analogous time points after the second injection [40 (11.5) μ s]. Fibre density showed a mild increase that became statistically significant at the more delayed time points following the second injection of BoTox (fig B).

Four patients showed mild abnormalities in cardiovascular reflexes. The patients were asymptomatic but one, aged 53 years, experienced, 24 hours after the first BoTox injection, borderline postural hypotension which was indicated by a 20 mm Hg fall in systolic blood

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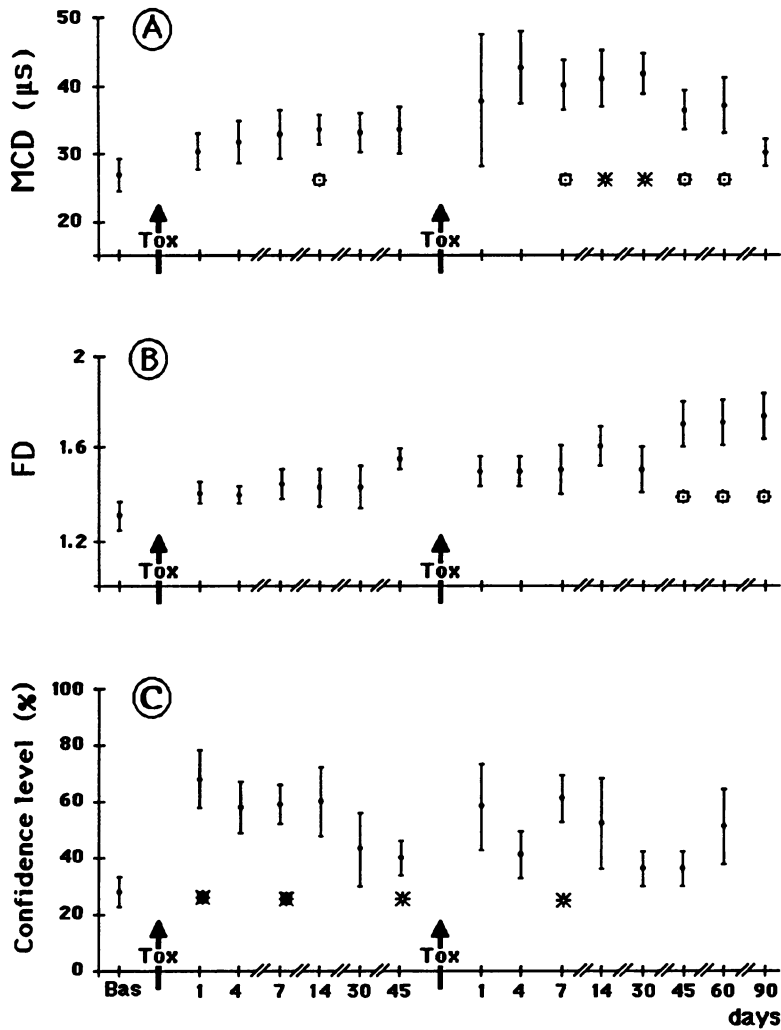


Figure Mean consecutive differences (A), fibre density (B) and confidence level in autonomic test evaluation by Bayesian analysis (C) at baseline and at different time points after BoTox injections. Statistically significant differences are indicated by asterisks.

■ = $p < 0.01$; * = $p < 0.02$; ⊕ = $p < 0.05$; MCD = mean consecutive differences; FD = fibre density; Bas = baseline; Tox = BoTox injections; the arrows = different time points after BoTox administered. Means are expressed standard error (SE).

pressure on standing. When Bayesian analysis was performed, the increase in confidence level from baseline appeared statistically significant at an early stage after both BoTox injections, reverting to normal in the following weeks (fig C).

Discussion

Botulinum toxin has a potent effect in blocking acetylcholine release at presynaptic level. Its prevalent action has been demonstrated in the skeletal neuromuscular junction, but in the ANS it blocks ganglionic nerve endings, postganglionic parasympathetic nerve endings, and those postganglionic sympathetic nerve endings at which acetylcholine is the transmitter. A partial antagonist action on motor response has been also demonstrated in some adrenergic and non-adrenergic atropine-resistant autonomic neuromuscular sites.⁷ When injected

into mammalian muscles, BoTox is transported to the spinal cord by retrograde axoplasmic flow.⁸ Moreover, BoTox probably circulates in blood after local administration and this is presumed to be the mechanism of spread to distant sites.³

The present study confirmed an effect of local BoTox injection for focal movement disorders in muscles distant from the site of inoculation and revealed an action also on cardiovascular autonomic pathways. Our data showed that, already in an early stage, BoTox has a dose dependent effect on neuromuscular transmission in distant muscles and in some cases, jitter was dependent on firing rate, confirming its presynaptic origin. The increase in fibre density provides evidence that, later on, nerve sprouting and reinnervation phenomena occur and induce a longlasting change of motor unit arrangement. An accurate follow up investigation therefore matches the apparently discordant data of previous reports.²⁻⁴

It is not surprising that the BoTox injection affects ANS, since an impaired control of heart rate and blood pressure responsiveness has been reported in botulism.⁵ Such an effect can be ascribed to a lesion in any part of the afferent or efferent pathway of the autonomic reflex arc. We found an increased confidence interval on Bayesian analysis, still significant at 45 days after BoTox injection (single abnormal value ≥ 95). This finding agrees with the known, slow recovery of autonomic function in botulism.⁵ The marked variability of the results in individual patients, as shown by a high standard error, may be explained by the different doses, ages and the factors concerning pharmacokinetics and pharmacodynamics which can affect drug response.

From a practical point of view, it appears advisable, therefore, to monitor patients undergoing such BoTox treatment, especially when a high cumulative dosage is used and when patients also take drugs impairing neuromuscular transmission or autonomic pathways, or suffer with diseases involving ANS.

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