SHORT REPORT

Optimisation of botulinum treatment for cervical and axial dystonias: experience with a Japanese type A toxin

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Abstract

Twenty two patients with cervical and axial dystonias were treated with Japanese type A botulinum toxin. Injections were given repeatedly at intervals of 28-30 days to carefully chosen muscles with increased activities, with a maximum dose per session of 300 units. The maximum improvements in subjective and objective ratings were obtained only after repeated injections. No anti-toxin antibodies were detected; nor did any muscle fail to respond to the toxin. During the treatment, previously "silent" muscles were activated to reproduce the original abnormal posture, as if driven by a central motor programme. This resistance to treatment was overcome by injecting the toxin into newly activated muscles. Repeated injections are thus required to override central mechanisms in dystonias or to maximise drug delivery to large muscles. Antibody development may be controlled by the use of a less immunogenic toxin.

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Although botulinum toxin has been efficacious in the treatment of cervical dystonia,^{1,2} some patients do not respond sufficiently to this treatment. These poor responders show little clinical improvement from the beginning of treatment (primary failure) or become resistant to the toxin after repeated injections (secondary failure).

To optimise the technique of treatment and possibly overcome the treatment failure for cervical dystonia, we analysed changes in muscle activity and head position during repeated injections of a new crystalline preparation of botulinum toxin A. We also treated patients with axial dystonia involving larger muscles, for which little has been published on botulinum toxin injections.

Methods

PATIENTS

Patients were treated at Kyoto University Hospital or Takeda General Hospital (Kyoto, Japan). This clinical trial was approved by the institutional review boards of both hospitals

and informed consent was obtained from all the patients. Twenty two patients (17 men and five women) aged 18 to 80 (mean 40.6) years comprised 20 patients with spasmodic torticollis and two with axial dystonia. The mean duration of illness was 3.8 years. Eleven subjects had durations of less than one year, and the rest of more than one year. None of them showed evidence of contracture. Any medication being taken was continued during the study period.

BOTULINUM TOXIN

We used a crystallised type A botulinum toxin preparation (CS-BOT; Chiba Serum Institute, Chiba, Japan) with a specific biological activity of 15.2 mouse LD₅₀ units/ng. A solution of toxin with a concentration of 100 units/ml was injected intramuscularly.

INJECTION SCHEDULE

We made repeated injections at intervals of 28-30 days. Muscles with increased activity were carefully chosen from sternocleidomastoid, trapezius, scalene complex, levator scapulae, splenius capitis, and paravertebral muscles with the aid of surface EMG or inspection and palpation. The maximal dose was 150 units/muscle and 300 units/session. After reaching the clinical plateau at which an additional monthly injection gave no more improvement, booster injections were given at intervals of two to nine months. The cumulative dose before analysis ranged from 380 to 5550 (mean 1478) units.

CLINICAL EVALUATION

We evaluated muscle activities and clinical symptoms before and two weeks after each injection. Clinical improvement was assessed by subjective and objective scores. The subjective scores ranged from 0 (no improvement) to 100 (complete recovery), as rated arbitrarily by the patient. A neurologist (TH) blinded as to the injection schedule rated the objective score with the aid of a videotape from a scale modified from that of Tsui *et al* (table).³

ANTIBODY TESTING

Antitoxin antibody titre from 18 patients was tested by bioassay.⁴ The total dose of toxin given to these patients at the time of testing was between 300 and 5550 (mean 1178)

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Objective scores for the evaluation of the clinical effect of botulinum A injections on head position (modified from Tsui *et al*^B)

	Degrees	Objective score
Rotation of the head	0	0
	0-15	1
	15-30	2
	30-45	3
	>45	4
Anteroposterior flexion	0	0
	0-15	1
	15-30	2
	30-45	3
	>45	4
Lateral tilt	0	0
	0-15	1
	15-30	2
	>30	3
Shoulder elevation	0	0
	0-7	1
	7-15	2
	>15	3
Scoliosis	0	0
	0-15	1
	15-30	2
	>30	3

units given over periods that ranged from one to 21 (mean 9.2) months.

Results

CLINICAL IMPROVEMENT AND TREATMENT FAILURE

The objective scores for the patients before treatment ranged from 1 to 12 (mean 5.0). During treatment, no muscles failed to respond to injection. Onset latencies of the response were one to 14 (mean 5.2) days. After a single injection, 17 of the 22 patients improved in the objective score, and in the other five, clinical symptoms did not change (primary failure). In these patients, however, repeated injections improved the subjective and objective ratings. None showed secondary failure.

The plateau of clinical improvement was never reached after a single injection. The number of injections to obtain the clinical peak was three in nine patients (most frequent) and 4.0 in mean value (cumulative dose 150-4050 (mean 925) units). Overall, objective scores improved significantly both after a single injection (Wilcoxon signed rank test, $p = 0.004$) and after three injections ($p < 0.001$), but the scores after three injections were significantly better than those after a single injection ($p = 0.008$). At the peak of objective improvement, scores ranged from 0 to 4 (mean 1.0); 16 of the 22 patients had subjective scores of more than 50 points, seven patients scoring more than 80 points. All these patients required booster injections once in several months to maintain the clinical effect, and none showed spontaneous remission.

TREATMENT OF AXIAL DYSTONIA

We treated two patients with axial dystonia by injecting into paravertebral muscles. One was a 31 year old man with tardive generalised dystonia for 12 years. He had repeated injections into cervical and thoracic paravertebral muscles as well as cervical musculature

without EMG guidance. Although bedridden before treatment, he could walk after eight injections (cumulative dose 2100 units; figure). The other was a 59 year old man who had had idiopathic axial dystonia for five years. Injections (cumulative dose 700 units) mainly into cervical paravertebral muscles corrected his abnormal posture.

TREATMENT OF ACTIVATED MUSCLES

In 20 of the patients treated, one muscle after another was activated as if to restore the original abnormal head position. Secondly activated muscles were the synergists of the originally active muscles. We repeated injections to these newly activated synergists. The patients regained normal or near normal head position only after repeated injections into all the synergists.

DISEASE DURATION AND CLINICAL IMPROVEMENT

We examined the relation between the duration of disease and the efficacy of botulinum injections. Eleven patients had durations of less than one year (group A); the others exceeded one year (group B). There was no significant difference in severity before treatment between the groups ($p = 0.48$; Mann-Whitney U test). The mean objective scores after the treatment were 0.46 in group A and 1.55 in group B, significantly better ($p = 0.047$; Wilcoxon signed rank test) in group A.

A 31 year old man with generalised tardive dystonia before (A) and after (B) injections of botulinum A.

SIDE EFFECTS

Unfavourable effects found transiently after 16 of the 139 injections (nine patients) were mild dysphagia (eight injections), local pain around the site of injection (four injections), and excessive weakness of the injected muscles (seven injections). All these occurred after repeated injections, except in two patients, who developed excessive weakness or dysphagia after the first session. Dysphagia, which needs special attention because of its potential hazard for aspiration pneumonia, developed after treatment of neck muscles with 100–300 (mean 238) units of the toxin.

ANTITOXIN ANTIBODIES

No antibody was detected in blood samples from 18 patients (mean cumulative dose and treatment period 1178 units and 9.2 months). Samples were not taken from the other four patients.

Discussion

Previous studies have shown the beneficial effect of botulinum toxin injection for patients with cervical dystonia, but not all those showed objective improvement.^{1,2} In our study with a new Japanese type A toxin, however, all the patients, including two with axial dystonia, showed objective improvement.

There are two commercially available preparations of type A toxin, Dysport (Porton, England) and Botox (Allergan, USA). Although the potency of our CS-BOT (15.2 units/ng) is different from that of Dysport (40 units/ng) or Botox (4 units/ng),⁵ the effective dose was equivalent to those reported with Botox. The exact comparison remains to be done, because the technique for measurement of biological activity might be different among manufacturers. CS-BOT is now on the phase-II clinical trial for hemifacial spasm and focal dystonias, and is expected to be commercially available in the near future.

All our patients showed maximum improvement only after repeated injections. In 20 of them the pattern of muscle activities changed after injections into muscles with increased activities, as if to maintain the original posture (primary failure). Most often, the anterior margin of the trapezius muscle was activated after an injection into the sternocleidomastoid muscle on the same side. Gelb *et al.*⁶ described a similar phenomenon and hypothesised that the underlying abnormality in torticollis involves a general motor programme. Our results support their hypothesis. To overcome the abnormal motor

programme, we gave repeated botulinum injections into newly activated synergists.

The patients with durations less than one year had better outcomes than those with longer durations. This was not due to spontaneous remission, because these patients needed repeated injections to maintain the clinical effect. We speculate that the normal motor programme is not retrievable once dystonia is protracted.

Secondary failure is mostly ascribed to the development of antitoxin antibodies,^{7,8} which is the major concern when repeated injections are given. We did not detect antibodies to the toxin, or any failure of response during treatment. The cumulative dose we used (mean 1178 units) was larger than, or at least comparable with, doses used in previous studies. The previous studies reported antibody development in three of 31 patients given an average dose of 208 (maximum 413) units⁷ and in five out of 115 given an average dose of 1200 (SD 300) units,⁸ which is comparable with our study. The discrepancy remains unsolved, but possible factors include different immunogenicity and the non-equivalence of units among products from different manufacturers; also, some of our patients may eventually develop antibodies.

In conclusion, repeated injection of our Japanese toxin successfully treated both cervical and axial dystonias. There was no measurable antitoxin antibody production. Earlier treatment is preferred, because the abnormal motor programme may be fixed once dystonia is protracted.

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- 1 Tsui JKC, Eisen A, Stoessl AJ, *et al.* Double-blind study of botulinum toxin in spasmodic torticollis. *Lancet* 1986;ii:245–6.
- 2 Greene P, Kang U, Fahn S, *et al.* Double-blind, placebo-controlled trial of botulinum toxin injections for the treatment of spasmodic torticollis. *Neurology* 1990;40:1213–8.
- 3 Tsui JKC, Eisen A, Mak E, Carruthers J, Scott A, Calne DB. A pilot study on the use of botulinum toxin in spasmodic torticollis. *Can J Neurol Sci* 1985;12:314–6.
- 4 Hatheway CH, Snyder JD, Seals JE, Edell TA, Lewis Jr GE. Antitoxin levels in botulism patients treated with trivalent equine botulism antitoxin to toxin A, B and E. *J Infect Dis* 1984;150:407–12.
- 5 Schantz EJ, Johnson EA. Preparation and characterization of botulinum toxin type A for human treatment. In: Jankovic J, Hallett M, eds. *Therapy with botulinum toxin*. New York: Marcel Dekker, 1994: 41–9.
- 6 Gelb DJ, Yoshimura DM, Olney RK, Lowenstein DH, Aminoff MJ. Change in pattern of muscle activity following botulinum toxin injections for torticollis. *Ann Neurol* 1991;29:370–6.
- 7 Greene P, Shale H, Fahn S, Brin M, Friedman A. Treatment of torticollis with injections of botulinum toxin. *Neurology* 1987;37 (suppl 1): 123.
- 8 Jankovic J, Schwartz KS. Longitudinal experience with botulinum toxin injections for treatment of blepharospasm and cervical dystonia. *Neurology* 1993;43:834–6.