

# Botulinum toxin treatment in spasmodic torticollis

J D Blackie, A J Lees

## Abstract

**Botulinum toxin A was administered to 19 patients in a double-blind placebo controlled trial. Toxin was more effective than placebo for improving both head position and pain which was measured by an objective rating scale and videofilm assessments. Following the controlled trial, treatment with botulinum toxin was continued in an open fashion. A total of 60 patients with torticollis received toxin in a total of 117 treatment periods. The mean follow up period was 8.4 months. In 39 patients with pain there was benefit in 77% of treatment periods. Some improvement in neck posture occurred in 83% of the treatment periods with a mean duration of 12 weeks. Side effects were frequent with dysphagia being the most common (28% of treatment periods). Botulinum toxin is an effective treatment for torticollis but treatment should be initiated with doses at the lower end of the range used in this study (400-600 mouse units).**

The treatment of torticollis by local injection of botulinum toxin A was first reported in 1985.<sup>1</sup> Other reports have also indicated the usefulness of botulinum toxin in this condition.<sup>2-6</sup> However, the dose used and the method of administration has varied considerably in these studies. This report details our experience in treating 50 torticollis patients with botulinum toxin.

Botulinum toxin consists of seven antigenic types of which only type A has been used clinically. Its potent neurotoxicity is attributable to irreversible inhibition of presynaptic release of acetylcholine.<sup>7</sup> Botulinum toxin preparations vary in potency depending on the site and method of manufacture. It is therefore preferable to refer to the dose in terms of mouse units rather than nanograms. A mouse unit is the LD50 of a group of 18-20 gram female Swiss-Webster mice. There are still problems in using this unit because despite equivalent mouse toxicity there may be a variation in human neurotoxicity depending on the source of the toxin.<sup>8</sup>

## Patients

Initially 19 patients were enrolled in a double-blind placebo controlled crossover study. Hospital ethical committee approval was obtained and each patient signed an informed

consent. There were 11 females and eight males aged between 19 and 73 years (mean 49 years). Disease duration ranged from 0.75-25 years (mean 7.2 years). All patients had isolated torticollis, without evidence of a more widespread dystonia.

## Method

Botulinum toxin was supplied by the Vaccine and Research Laboratory, Porton Down, Salisbury, United Kingdom as a freeze dried toxin-haemagglutinin preparation. A vial contained 50 nanograms of the toxin-haemagglutinin which was equivalent to 2000 mouse units. The dose of toxin per muscle was determined by multiplying the amount of Porton Down toxin currently being used for injection into an orbicularis oculus muscle<sup>9</sup> by a factor of 4. This ratio of neck to eye muscle dose is comparable with other reports.<sup>1,2</sup> A pilot study in three patients using this dose did not result in side effects.

Each patient was randomly allocated to receive either botulinum toxin or normal saline placebo injection with the cross-over injection three months later. The two most active muscles of the sternomastoid, splenius capitis and trapezius pairs were injected. The muscles to be injected were determined by clinical assessment,<sup>10</sup> and supplemented in each patient by concentric needle EMG assessment. EMG also assisted in determining the depth of injection particularly for the splenius capitis muscle. Fifty nanograms were diluted in 2.5 mls of normal saline and 0.6 ml was injected into each of two muscles. Each muscle was injected at two sites, with an 0.3 ml aliquot per site. The total dose per muscle was 12 nanograms or 480 mouse units. The placebo injection consisted of an equivalent volume of normal saline. The injections were all administered "blind" by one of the authors (JB).

Video recording was performed before the injection and four weeks after. When the trial was completed the recordings were edited into random order and independently scored, blindly. A clinical rating scale devised and outlined by Tsui<sup>2</sup> was used to score the video recordings. In addition patients were asked to rate change in motor symptoms (nil, mild, moderate or marked) and to score their pain associated with the torticollis on a visual analogue scale of 0-10. Onset and duration of both benefit and side effects were recorded.

After completion of the double blind study, open administration of botulinum toxin to

**The National Hospital  
for Nervous Diseases,  
London**

J D Blackie  
A J Lees

Correspondence to: Dr A J  
Lees, The National Hospital  
for Nervous Diseases, Queen  
Square, London WC1N  
3BG, United Kingdom.

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patients with torticollis was continued. Toxin was administered to a total of 50 patients, which included the initial 19 patients, in a total of 117 treatment periods. A treatment period was the interval between subsequent injections. In this group there were three patients with oromandibular dystonia, one had a combination of blepharospasm and writer's cramp, the second patient had generalised torsion dystonia and the third writer's cramp. There were 28 females and 22 males. The follow up period ranged from three to 19 months with a mean of 8.3 months. The muscles injected were determined clinically and EMG was used only in complex cases or where there had been a poor response to toxin previously. A maximum of three muscles were injected during any one treatment period. Most injections were into the sternomastoid, trapezius or splenius capitis but additional muscles injected included the levator scapulae, semispinalis capitis and platysma muscles. The dose ranged from 120–480 mouse units per muscle with a mean of 396 mouse units. The mean total dose per treatment of toxin was equivalent to that used in the control study but a single aliquot only was injected into each muscle. The subjects were asked to rate their response to injections for both pain and motor symptoms as nil, mild, moderate or marked.

### Results

In the controlled trial assessment the two scorers had a correlation coefficient of 0.64 between the objective clinical rating scores. As this was relatively poor, each scorer was assessed independently using a Mann-Whitney U test to see if the toxin had a larger effect than placebo. This was significant for both scorers (scorer 1  $p < 0.02$ , scorer 2  $p < 0.05$ ). Three patients had no objective response from the injections. The mean (SD) score before treat-

ment was 10.8 (3.2) compared with 8.5 (2.8) four weeks post injection. Subjective motor response was rated as marked in two patients, moderate in five, mild in seven and nil in five. Only one patient had improved motor symptoms following placebo and this was mild. In those patients that had a response the mean onset of effect was six days (range 1–21 days) with a peak effect at 14 days (range 7–28 days) and duration of effect 12 weeks (range 6–20 weeks). In view of the prolonged effect in some patients beyond the three month cross-over period each scorer was tested for any carry over effect in those patients that received the toxin initially. This was not found to be significant (Mann-Whitney U  $p > 0.05$ ).

Sixteen out of 19 patients had pain associated with their torticollis. Transient increase in local pain and stiffness was a common side effect after both toxin and placebo injections and this persisted for a few days. In one patient pain at the site of the injection persisted for 12 weeks following toxin injection. Sustained improvement in pain occurred in 12 patients following toxin injections compared with two patients in the control group. Mean pain scores in patients with pain fell from 6.1 to 3.3 four weeks after the botulinum toxin injection.

The side effects of the controlled trial are listed in table 1. The dysphagia in all three patients was mild, with sticking of solids at the post-cricoid level persisting for three to four weeks. ENT review of two of these patients revealed mild slowing of transit time on swallow cine-radiography in one patient but no other abnormality. There was wasting of neck muscles in 12 patients and this was commented on by the patients themselves in a few instances. This may have influenced the effectiveness of a blinded controlled assessment with the subjective ratings. However, muscle wasting was not apparent on the video recordings used for the objective clinical ratings.

There was no significant predictor of response to toxin injection when analysing sex, age, duration or severity of the torticollis or the pattern of muscle involvement (agonist or antagonist<sup>11</sup>) using Fisher's exact test.

In the group of 50 patients there was subjective improvement in motor symptoms in 83% of the 117 treatment periods. This was marked in 21 (18%), moderate in 48 (40%), mild in 28 (25%) and nil in 20 (17%). The mean duration of effect was from six to 30 weeks with a mean of 12 weeks. A diminished response to repeat injection was noted in three patients. In 39 of the 50 patients with pain there was a 77% response rate in 75 out of 97 treatment periods. This was marked in 12 (12%), moderate in 49 (51%), mild in 14 (14%) and nil in 22 (23%). In general, pain response paralleled the motor response in terms of degree and duration. A total of nine patients withdrew from further treatment with botulinum toxin. In six patients there was no response in two treatment periods. Two patients withdrew because of side effects (dysphagia). A single patient continued to improve spontaneously after a single dose of toxin. He has not required further injection over an 18 month follow up period.

Table 1 Side effects of controlled trial ( $n = 19$ )

Side effect	Placebo	Botulinum toxin
Local pain	9	7
Malaise/lethargy	1	4
Muscle atrophy	—	12
Dysphagia	—	3
Vertigo	—	2
Local weakness	—	2

Table 2 Side effects of botulinum toxin ( $n = 50$  patients)

Side-effect	Incidence			
	Treatment periods (%)	Patients (%)	Males ( $n = 22$ )	Females ( $n = 28$ )
Dysphagia	33/117 (28)	26/50 (52)	8	18
Lethargy	10/117 (9)	8/50 (16)	2	6
Local weakness	6/117 (5)	6/50 (12)	—	6
Vertigo	4/117 (3)	3/50 (6)	3	—
Dysphonia	2/117 (2)	2/50 (4)	—	2
Dry mouth	1/117 (1)	1/50 (2)	1	—
Excess saliva	1/117 (1)	1/50 (2)	1	—
Dyspnoea	1/117 (1)	1/50 (1)	—	—

Side effects are listed in Table 2. The most significant side effect was dysphagia which occurred in 28% of treatment periods and in 26 of the 50 patients treated. Generally this was mild in severity, with minor difficulty in swallowing solids persisting for two to three weeks. The mean dose per treatment period in those that developed dysphagia was 836 (184) units. This compared with a mean dose of 888 (156) units in those treatment periods not associated with this side effect. In five patients the dysphagia was moderately severe with an intolerance for solids persisting for up to six weeks. The most severely affected patient required intravenous fluids for one week and his chest radiograph showed aspiration changes. Side effects were more frequent in females. This was statistically significant (Chi-Square test) for total side effects ( $p < 0.02$ ) and for dysphagia ( $p < 0.05$ ). Despite this there was no significant difference (Chi-square test  $p > 0.5$ ) in the number of marked or moderate motor responses in females (40/66 treatment periods) compared with males (29/51). The mean dose in females per treatment period was 850 mouse units compared with the male dose of 905 mouse units.

### Conclusion

The results of this study indicate that botulinum toxin is an effective means of treatment for torticollis. The subjective motor response rate in the double-blind study was 74% and 88% of 50 patients in the larger group with an 83% response rate in the 117 treatment periods. These results are comparable to the response rates reported in other studies.<sup>1-6</sup> The objective rating scale was not employed following completion of the double-blind study. This was because of the poor correlation between the two scorers and also often with patient symptoms. Patients commented on improvement in such activities as reading or attending the theatre or with walking which would not necessarily be detected in a score based on observation in the sitting position over a short period. The mean duration of effect is also comparable with other studies, being 12 weeks in both patient groups.

There was a high incidence of side effects, the most prominent of which was dysphagia. In the initial controlled group dysphagia was less severe and less frequent (15%) than in the larger group (28% of treatment periods). The technique of injection changed from the controlled trial where two injection sites per muscle were used, to a single injection site with a 0.6 ml aliquot. The larger volume of toxin injected at a single site may have resulted in less toxin being bound at cholinergic nerve terminals with more diffusing into the blood-stream.<sup>12</sup> In addition EMG localisation was not employed after the initial trial, and toxin was possibly more likely to have been injected outside the muscle particularly with the splenius capitis. These factors may have contributed to the higher incidence of dysphagia in the larger group. It is possible that with recurrent injections there was an accumulation of toxin effect.

A progressive neuromuscular transmission abnormality in muscles distant from the injection site has been reported with repeated injections.<sup>13</sup> However, in three out of the five patients with severe dysphagia this was the result of the initial injection with botulinum toxin.

There was evidence that the dysphagia was dose related. In those patients that developed dysphagia subsequent injection with a reduced dose usually resulted in diminution of this side effect. Interestingly, four out of five patients with severe dysphagia requested repeat injection because they considered the benefit outweighed the discomfort of the dysphagia. There was a higher incidence of dysphagia and side effects in general in females compared with males. Local haematogenous spread of toxin, unbound to the neuromuscular junctions in the injected muscles, to pharyngeal muscles may have occurred. Oesophageal dysfunction may represent an early manifestation of systemic botulism.<sup>14</sup> This may be related to increased susceptibility of oesophageal endplates to botulinum toxin. Single fibre studies indicate that local injections of toxin do have an effect on distant muscles even when low doses are employed.<sup>15-16</sup> Single fibre studies were not measured in our patient group. Other mechanisms that have been invoked are the retrograde spread of toxin with transynaptic spread into the spinal cord.<sup>6</sup>

The incidence of dysphagia is higher in this study than in other reported series with one exception. In the group of 10 patients described by Stell nine developed dysphagia.<sup>6</sup> The source of botulinum toxin was the same as used in this study and the dose somewhat higher. It was suggested in that study that because of the incidence of side effects the dose be lowered to 25 ng (1000 mouse units) for males and 20 ng (800 mouse units) for females. Our experience indicated that doses of this level are associated with a relatively high incidence of side effects. It is difficult to compare relative doses of toxin which is produced at different sites for the reasons previously mentioned. However, the dose of toxin in studies conducted in Canada and USA<sup>1-5</sup> in terms of mouse units was lower than our dose. The current starting dose in our patients for initial injection is 10 ng (400 mouse units) per treatment period. A number of the patients treated have tolerated repeat injections at the upper end of the dose range without side effects and without diminution in effect. It is possible, therefore, that the dose may need to be titrated to this level (24 ng = 960 mouse units) in individual patients depending on benefits and side effects.

The comparative higher doses used in this study may have theoretically been expected to result in a higher incidence of antibody formation due to a larger amount of unbound toxin. Antibody formation has been found to correlate with refractoriness to subsequent injections of the toxin.<sup>4</sup> In our study antibody levels were not measured but three patients noted a diminution of effect in subsequent treatment periods.

In the six patients who did not respond to

any injection of toxin other neck muscles inaccessible to toxin injection may have been responsible for the torticollis. It was of interest that some patients required injection of different muscle groups with subsequent injections. These were the patients with the more complex patterns of muscle involvement. It has been suggested that a new pattern of muscle activity may result in persistence of abnormal neck posture without apparent clinical change.<sup>17</sup>

We conclude that botulinum toxin is an effective treatment for the majority of patients with torticollis, but it should be used with caution. In the dose range used in this study there was a relatively high incidence of side effects and it is recommended that treatment be initiated at a dose at the lower end of the spectrum and titrated up depending on response. The longer term efficacy and safety have yet to be proven.

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