BOTULINUM A TOXIN FOR THE TREATMENT OF SPASMODIC TORTICOLLIS: DYSPHAGIA AND REGIONAL TOXIN SPREAD

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Chemodenervation of cervical muscles with botulinum A toxin, although useful in treating spasmodic torticollis, has been associated with dysphagia. Retrospective analysis of dose and injection site (sternomastoid vs. posterior cervical muscle groups) in 26 patients (49 injections) suggested that dysphagia was related to the quantity of toxin injected into the sternomastoid muscle: dysphagia, median 150 IU (7 injections); and no dysphagia, median 100 IU (42 injections; \( p = 0.026 \) Wilcoxon test). In a prospective study (31 injections to 24 patients), limiting the dose administered to the sternomastoid to 100 IU, substantially reduced the incidence of dysphagia (0 of 31; \( p = 0.27 \), Fisher's exact test).

Denervation of human orbicularis muscle fibers, 5 weeks to 4 months after injection of botulinum A toxin for the treatment of blepharospasm, was successfully demonstrated by intense, diffuse acetylcholinesterase staining. A weight-adjusted dose similar to that given for torticollis was injected into longissimus dorsi muscle in 6 rabits. Using the acetylcholinesterase stain as a marker, a diffusion gradient was noted over a distance of 30 to 45 mm from the point of injection and in contralateral muscle 15 to 25 mm from this point. Thus, denervation was demonstrated to occur within a definable area which crossed anatomic barriers, such as fascia and bone. These clinical and laboratory data suggest that dysphagia following botulinum toxin therapy results from toxin spread to pharyngeal musculature from the sternocleidomastoid injection site. Limiting of the injection dose to 100 IU or less to the sternomastoid substantially decreases the incidence of this complication. HEAD & NECK 1990; 12: 392-398

Idiopathic adult onset spasmodic torticollis is a chronic disease of unknown origin, characterized by relentless involuntary contractions of various cervical muscle groups. The disease produces varying degrees of pain, posture deformity, involuntary head movements, limitations of spontaneous movements, and limitations of functional abilities due to involuntary contractions and increased tone and hypertrophy of the affected muscles. Prior attempts with neuroleptic and surgical therapies have not been associated with substantial success. More recently, injections of botulinum toxin have produced encouraging clinical responses,\(^1\)\(^-\)\(^3\) but substantial dysphagia has occurred with significant incidence.\(^1\)\(^-\)\(^3\) The cause of dysphagia occurring after treatment of spasmodic torticollis with botulinum A toxin is addressed herein.

The concept of directly injecting hypertrophied spasmodic cervical muscle groups with botulinum toxin\(^1\)\(^-\)\(^3\) emerged from the clinical suc-
cess achieved with the toxin in the management of various forms of involuntary facial spastic disease (essential blepharospasm, blepharospasm associated with Meige syndrome\textsuperscript{3-6}) and strabismus\textsuperscript{1}. Experimental applications for the treatment of occupational hand dystonias\textsuperscript{2} and spasmodic dysphonia\textsuperscript{3} have been effective. The physiologic basis of this investigational therapy is the creation of temporary, partial chemodenervation and muscular atrophy in involved cervical muscles. Relaxation of muscle tone, decrease in muscle size, and reduction in the amplitude of spontaneous contractions are the desired effects, which can relieve pain, increase active range of motion of the cervical spine, improve resting posture, and reduce the disfigurement of obviously hypertrophied cervical muscles. The unique pharmacologic feature of this drug is its long duration of action (2 to 5 months). This property allows for sustained benefit after the injection session.

**MATERIALS AND METHODS**

**Analysis of Patient Data.** Patients with adult onset idiopathic spasmodic torticollis were given botulinum A toxin for a period of 2 to 38 months (average, 11.1 years) prior to this retrospective analysis of their records for the complication of dysphagia. Each patient was followed under the guidelines of the Massachusetts Eye and Ear Infirmary and Massachusetts General Hospital Guidelines for Human Studies and granted informed consent. The toxin was reconstituted in 1 mL normal saline without preservative and injected with a 25- or 27-gauge needle. Patients were evaluated biweekly or immediately if dysphagia occurred. A single treatment consisted of 1 or more injections to the sternomastoid muscle or to the posterior cervical muscles (splenius capitis, levator scapulae, splenius cervicis, scalene, and trapezius) or both. The muscles injected were determined to be dystonic based on palpation, hypertrophy, involuntary spasms, and posture deformity.

Each of the 49 injections to the cervical musculature was characterized with respect to dose and injection site. The injections that did not result in dysphagia were then compared to those that did (Table 1).

Once retrospective analysis of the data indicated a potential cause–effect relationship between dysphagia and sternomastoid dosage (see Results), the Human Studies Protocol was changed to limit the dose given to the sternomastoid muscle to \( \leq 100 \) IU, during any injection session. The 24 patients in this prospective study were specifically asked to contact one of the investigators should dysphagia occur. Each patient was also contacted within 4 weeks of the injection and specifically questioned to assess whether postinjection dysphagia had occurred. Thirty one injections were given with this dose limitation.

In addition, 8 injections were given to 6 patients who initially experienced dysphagia, yet benefited substantially from the injection. Patients within this group were injected after a period of at least 5 months and with the restriction of the sternocleidomastoid dose to \( \leq 100 \) IU (see Table 3).

**Acetylcholinesterase Staining of Human Muscle Clinically Affected by Botulinum A Toxin.** Muscle specimens were obtained from patients undergoing ptosis surgery who had been previously treated with botulinum A toxin for involuntary blepharospasm. Each patient demonstrated clinical findings strongly suggestive of levator aponeurotic disinsertion ptosis, such as an elevated upper eyelid crease and retracted preaponeurotic fat pads (deep superior orbital sulcus). During usual ptosis procedures, a 3- to 4-mm strip of orbicularis oculi muscle (measuring 20 to 25 mm in horizontal diameter) was removed to gain access to the levator aponeurosis. This muscle was the source of orbicularis oculi treated with botulinum toxin, in addition to 1 patient who underwent a myectomy for severe involuntary blepharospasm (Anderson procedure\textsuperscript{3}). Four control specimens of orbicularis oculi strips were from patients with involutional ptosis not injected with botulinum toxin.

The specimens of orbicularis were obtained 4 weeks to 4 months after the last botulinum toxin injection.

Each specimen was placed in Baker’s solution (10% formal calcium) and immediately refrigerated. After 24 hours, the muscle specimens were placed in 0.88 gum sucrose for 2 to 3 hours. The tissue was sectioned into 10-\( \mu \)m sections in a cryostat at \(-20\degr\text{C}\), and placed on gelatin-coated slides. Acetylcholinesterase activity was demonstrated by Karnovsky’s method. The slides were incubated for 90 minutes at 37\degr\text{C}, washed in distilled water, counterstained with fast green, dehydrated rapidly, and mounted with Permount.
Animal Model for Spread of Injected Botulinum Toxin. Botulinum toxin at a dose of 2 to 3 IU/kg was injected into longissimus dorsi muscle of 6 New Zealand white rabbits at 1 point in the region of the mid-dorsal spine. The toxin was reconstituted at a concentration of 1.25 IU/0.1 mL. The area of injection was marked with a circular tattoo. One animal received the nonperservative normal saline diluent for botulinum A toxin (control). Injections were at a depth of 5 to 8 mm to avoid subcutaneous diffusion. After 5 weeks, animals were killed by pentobarbital injection and paraspinal muscle specimens dissected. Muscle specimens were taken at 15, 30, and 45 mm from the site of injection. In order to assess toxin spread across natural anatomic barriers, such as fascial planes and bone, an additional muscle biopsy specimen was taken across the axial skeleton 15 to 25 mm from the injection site from contralateral longissimus dorsi muscle at the same vertebral level.

The acetylcholinesterase slide preparation was done in the same fashion as described above for human tissue.

RESULTS

Analysis of Clinical Data. Retrospective analysis revealed that dysphagia occurred after 7 of 49 cervical injections of botulinum toxin for the treatment of spasmodic torticollis (14%). Each patient, who experienced dysphagia, noted the onset of symptoms within 20 days of the injection; the reported duration of symptoms varied from 6 days to 4 weeks. One of these patients related a distinct episode of choking (shortness of breath and the inability to talk) while eating, suggesting upper airway obstruction. Her daughter performed a Heimlich Maneuver,10 which resulted in a forceful oral expulsion of a piece of meat with complete and immediate relief of symptoms.

Retrospective analysis of total dose received by each of the 26 patients at each treatment session revealed no significant difference between total dosages given patients who experienced dysphagia and those who did not (dysphagia: 160 IU (median), interquartile range = 10 IU; no dysphagia: 150 IU median, interquartile range = 100 IU, p = 0.45). However, if the dose given to individual muscles was evaluated, a significant difference in the dose administered to the sternomastoid muscle was apparent [sternocleidomastoid dose in dysphagia group: 150 IU (median), interquartile range = 10; sternocleidomastoid dose in group without dysphagia: 100 IU, interquartile range = 150, p < 0.05 Wilcoxon test]. Every patient who experienced dysphagia had 150 IU to 175 IU injected into the sternomastoid muscle (see Table 1). In addition to numeric analysis of dose, every patient who experienced dysphagia had their sternomastoid muscle injected, and the complication did not occur if only the posterior cervical muscle group was injected alone.

Based on these observations, we altered the treatment protocol limiting the maximum sternomastoid dose to 100 IU, administered at 2 sites which were 30 mm apart at any injection session. None of the next 31 injections in 24 patients were followed by dysphagia. The difference in incidence (0 of 31 patients vs. 7 of 49 patients) was significant (p < 0.05, Fisher’s exact test, 1-tailed). Table 2 outlines the statistical evaluation.

Six of 7 patients initially experiencing dysphagia received 8 injections under this new treatment protocol. After a minimum of 20 weeks follow-up, none had suffered recurrence of dysphagia (see Table 3).

Acetylcholinesterase as a Marker for Botulinum Toxin Effect on Orbicularis Oculi Muscle. The strips of orbicularis oculi muscle from patients who had received botulinum toxin demonstrated

<table>
<thead>
<tr>
<th>Sternocleidomastoid dose</th>
<th>No dysphagia</th>
<th>Dysphagia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median dose</td>
<td>100</td>
<td>150</td>
</tr>
<tr>
<td>Interquartile range</td>
<td>25</td>
<td>10</td>
</tr>
<tr>
<td>Wilcoxon test</td>
<td>p = 0.028</td>
<td>Z = 2.22</td>
</tr>
</tbody>
</table>

Table 1. Comparison of botulinum toxin dose and injection strategies in patients who later experienced dysphagia and those who did not.

<table>
<thead>
<tr>
<th>Dose not limited</th>
<th>Dose limited</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dysphagia</td>
<td>7</td>
</tr>
<tr>
<td>No dysphagia</td>
<td>42</td>
</tr>
<tr>
<td>Total</td>
<td>49</td>
</tr>
</tbody>
</table>

Numbers refer to injections. Fisher’s exact test (1-tailed), p = 0.027.

Table 2. Influence of changing the injection protocol limiting the dose to the sternocleidomastoid muscle to 100 IU or less per injection: Prospective analysis.
### Table 3. Additional treatments given to patients who previously suffered dysphagia. Dysphagia did not recur.

<table>
<thead>
<tr>
<th>Patient</th>
<th>SCM (IU)</th>
<th>Posterior cervical muscle (IU)</th>
<th>Total (IU)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CB</td>
<td>100</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>MC</td>
<td>100</td>
<td>100</td>
<td>200</td>
</tr>
<tr>
<td>MC</td>
<td>0</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>RM</td>
<td>0</td>
<td>150</td>
<td>150</td>
</tr>
<tr>
<td>AM</td>
<td>0</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>PM</td>
<td>50</td>
<td>0</td>
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</tr>
<tr>
<td>DN</td>
<td>0</td>
<td>150</td>
<td>150</td>
</tr>
<tr>
<td>DN</td>
<td>80</td>
<td>100</td>
<td>180</td>
</tr>
</tbody>
</table>

Diffuse, extensive spread of acetylcholinesterase activity over the individual muscle fibers (Figure 1A). The diffuse staining pattern, which was associated with muscle fiber atrophy, made identification of discrete neuromuscular junctions difficult. In contrast, each of the 4 specimens from untreated patients with involutional ptosis showed discrete areas of staining on the muscle fiber surface, corresponding to acetylcholinesterase activity and position of neuromuscular junctions of the muscle fibers (Figure 1B).

**Animal Model for the Spread of the Toxin.** Longissimus dorsi muscle from 6 rabbits was studied to assess differences in acetylcholinesterase staining activity at varying distances from the botulinum toxin injection site. There was a gradient effect of botulinum A toxin with respect to morphologic changes in muscle fiber size and degree of enzyme activity demonstrated. At the sites of the injection, diffuse acetylcholinesterase staining was seen over most muscle fibers (Figure 2A); similar findings were present 15 mm away from the injection sites but to a lesser degree (Figure 2B). At 30 mm from the injection site, there was substantially decreased staining and far less fiber atrophy (Figure 2C). At 45 mm (Figure 2D), there was little or no acetylcholinesterase staining and muscle fiber size was uniform.

This diffusion gradient, with the most marked decrease in stain between 30 to 45 mm away from the injection site, was apparent in each of the 6 animals studied. The saline control injection failed to produce any increase in acetylcholinesterase staining at the injection site or at 15, 30, and 45 mm away from it.

All contralateral longissimus dorsi biopsy specimens taken at 15 to 25 mm from the injection site revealed acetylcholinesterase staining intensities similar to those observed in specimens taken at a similar distance from the injection site but on the same side (Figure 2E).

**DISCUSSION**

Our data suggest that the size of the field of action of therapeutic injections of botulinum toxin may be dose-dependent and that specific complications may be correlated with the anatomic injection sites and dose. Because the clinical applications of botulinum A toxin involve...
FIGURE 2. Diffusion of botulinum toxin in longissimus dorsi muscle of rabbits with acetylcholinesterase staining. At the injection site (A) and at a 15-mm distance from the site (B), diffuse acetylcholinesterase staining is associated with muscle fiber atrophy. (C) Diffuse staining and muscle fiber atrophy begins to substantially diminish 30 mm from the injection site. (D) Markedly decreased acetylcholinesterase staining activity and muscle fiber atrophy are noted 45 mm from the injection site. (E) Acetylcholinesterase staining of muscle fibers from contralateral longissimus dorsi within 25 mm of the injection site. Diffuse muscle fiber atrophy and spread of acetylcholinesterase enzyme staining indicates the point injection of the toxin diffused across skeletal and facial barriers to other muscle groups.
limiting its effect to a specific area, an understanding of the toxin’s diffusion properties would be useful.

In this study, the spread of acetylcholinesterase on the orbicularis oculi muscle fibers, from patients whose blepharospasm had been treated with the toxin, reflected the denervation–reperfusion cycle noted by Duchen in mice. We demonstrated the spread of enzyme 4 weeks to 4 months after the last therapeutic toxin injection. The degree of tissue reaction was clearly distinguished from that of control specimens. Duchen found that the spread of acetylcholinesterase activity began 2 to 3 weeks after the injection to mouse soleus muscle and that the intensity of staining was temporarily associated with the formation of new myoneural junctions from collateral axonal sprouting. Collateral axonal sprouting in human orbicularis oculi has been recently demonstrated by Holt and Anderson.

Although the acetylcholinesterase stain may not be as sensitive an indicator of the botulinum toxin effect as single fiber electromyography, it may be a more accurate indicator of the focal denervation effects relevant to the therapeutic mechanism of the drug. Single-fiber electromyography has produced evidence of effects at muscle sites remote from injections. Although therapeutic injections of botulinum toxin may impair acetylcholine release at remote muscle sites, as reflected by single-fiber electromyography, systemic effects have not been observed clinically nor has histologic evidence of reinnervation at distant sites been reported. Perhaps denervation with collateral axonal sprouting after botulinum injection may be a local phenomenon,
whereas partial neuromuscular transmission blockage at remote locations, as detected by single-fiber electromyography, may occur without subsequent reinnervation.

Using increased acetylcholinesterase muscle fiber staining as a marker for botulinum toxin effect in our rabbit model, we were able to identify the area in which denervation occurred. The longissimus dorsi muscle was chosen because of its length and easy accessibility. The toxin dose at 2 to 3 IU/kg was comparable on a weight-adjusted basis to that given to patients for the treatment of idiopathic adult onset spasmotic torticollis.

Our finding of a clear diffusion gradient of acetylcholinesterase staining from the injection site is consistent with the clinical impression that therapeutic botulinum toxin injections produce localized muscle atrophy and weakening. It also suggests that this effect is contained within one portion of the muscle and diminishes with increasing distance from the injection site. However, the denervation can spread to regional muscles in close proximity to the injection site, regardless of fascial or skeletal barriers, as evidenced by our findings on contralateral longissimus dorsi.

The concept that injection of botulinum toxin creates denervation within a definite field (or, more accurately, a sphere) may prove useful in the treatment of focal and segmental dystonias. A precise knowledge of the histologic field of action of botulinum toxin might ultimately result in the development of injection strategies which could limit the effects of the toxin to specific muscles. This information could also be useful in establishing standard distances between injection sites, in order to produce a more homogeneous effect on larger muscles. Precise knowledge of the innervation zone of muscles (distribution pattern of neuromuscular junctions) would also be particularly useful, since an injection strategy which placed the toxin's field of action over the innervation zone would also achieve the greatest effect on the injected muscle at the lowest dose. Unfortunately, precise locations of innervation zones for most muscles are not well documented.

If injected toxin spreads to contiguous muscle groups, undesired complications from weakness of these muscles may occur. For instance, ptosis results when the injections are placed close to the lid crease in the midline of the upper lid which minimizes the distance to the muscular portion of the levator palpebrae superioris muscles when the orbicularis is the target muscle in treating blepharospasm. Our clinical study on the treatment of spasmodic torticollis indicates that a similar problem may be occurring, with dysphagia resulting from spread of the toxin to deeper muscle groups surrounding the pharynx. While the total dose given at an injection session did not appear to be correlated with this complication, the dose given to the sternomastoid was an important factor. The incidence of dysphagia was significantly reduced when we lowered the dose of the toxin administered to the sternomastoid. The absence of dysphagia in patients having only the posterior cervical muscles treated supports the concept that the sternomastoid injection method may be an important factor in the incidence of this complication. Figure 3, an artist's representation of the anatomic cross section of the human neck at the level of the vocal cords, shows that the pharynx is further from the posterior cervical muscle groups (line B) than from the sternomastoid (line A). This greater distance may be protective, since the toxin probably does not diffuse this distance at therapeutic doses. Our animal model lends support of this concept. A dose of 2 to 3 IU/kg given at a single point produced a field of action that extended 30 mm from the injection site. In humans, this distance would be sufficient to permit spread of the toxin from the sternomastoid to deeper pharyngeal muscles.

Dysphagia has been shown in our study group, as well as others, to be one of the most significant complications of botulinum administration for the treatment of spasmodic torticollis. In fact, one of our patients related an episode of choking which required a Heimlich maneuver. The retrospective and prospective clinical data presented herein support the concept that the risk of dysphagia can be reduced by limiting the sternomastoid dose to 100 IU or less. Recommending a soft diet for 3 weeks after the injection may also be prudent.
REFERENCES