

## Localized Injections of Botulinum Toxin for the Treatment of Focal Dystonia and Hemifacial Spasm

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Dystonia is a neurologic disorder characterized by abnormal involuntary twisting movements that tend to be sustained and can result in abnormal postures. Symptoms usually begin as a focal dystonia involving a single region of the body. Spread to other body regions is commonly seen in childhood-onset dystonia, but the disorder tends to remain focal with adult-onset (1). Examples of focal dystonia are blepharospasm (involuntary eyelid closure), oromandibular dystonia (OMD) (involving facial, jaw, and tongue muscles), torticollis (neck muscles), writer's cramp (action-induced involvement of hand and arm muscles), and vocal cord adductor spasm (2,3). The etiology of dystonia is usually idiopathic but can be secondary to other disorders (4). Treatment with medications usually results in an incomplete response and is frequently unsuccessful. Peripheral surgical therapy is available for some focal dystonias and includes myectomy and facial nerve lesions for blepharospasm, cervical rhizotomies for torticollis, laryngeal nerve section for dystonic adductor dysphonia, and tendon transfers for limb dystonia. Often such procedures result in only temporary relief or have unacceptable complications.

Botulinum toxin (BOTOX) acts presy-

naptically at nerve terminals to prevent calcium-dependent release of acetylcholine (5). When injected locally, the effect is that of a chemical denervation. Injections of BOTOX locally into extraocular muscles for treatment of strabismus (6) and subcutaneously over orbicularis oculi for blepharospasm has proven to be effective in many cases (7-14). This strategy has been extended to treatment of hemifacial spasm (7,8,10,12,15,16) with similar encouraging results. We have extended this approach to additional regions and now report using local injections of BOTOX into the appropriate muscles for treatment of disabling focal or segmental dystonia and hemifacial spasm in 97 patients.

### MATERIALS AND METHODS

#### Patients

The study was approved by our Institutional Review Board, and all patients gave written informed consent. Patients underwent a comprehensive neurologic evaluation. In cases of dystonic adductor dysphonia, direct laryngoscopy and laryngeal electromyography (EMG) were performed.

Table 1. Patients treated with local injections of botox (6/14/84-2/9/86)

| Disorder  | N  |
|---|----|
| Blepharospasm: idiopathic   | 49 |
| with PSP  | 3  |
| Torticollis: idiopathic   | 29 |
| with palatal myoclonus  | 1  |
| Oromandibular dystonia  | 4  |
| Laryngeal dystonia  | 3  |
| Limb: EHL* spasm in parkinsonism  | 1  |
| stenographer's dystonia   | 1  |
| post-stroke hand dystonia   | 1  |
| Lingual dystonia  | 1  |
| Hemifacial spasm  | 4  |
| Total   | 97 |
| Lost to follow-up (4); unreliable (3)<br>(blepharospasm; torticollis 1) | 7  |
| Total for analysis  | 90 |

\* (EHL) Extensor hallucis longus.

Most patients had failed numerous pharmacologic trials.

Ninety-seven patients were treated between June 1984 and February 1986 (Table 1). There were 46 with idiopathic blepharospasm and three with blepharospasm associated with progressive supranuclear palsy (PSP). Thirty patients with torticollis were treated; 29 had idiopathic torticollis, and one had symptomatic torticollis with associated palatal myoclonus. Four patients had OMD, three had laryngeal dystonia (adductor dysphonia); three had limb muscles treated: one with extensor hallucis longus (EHL) spasm associated with parkinsonism, one with stenographer's dystonia, and one with a post-stroke hand dystonia; one had tongue dystonia; and four had hemifacial spasm. Excluding data on four patients who were lost to follow-up and three unreliable historians, there were 90 patients available for analysis.

#### Toxin

Lyophilized botulinum A toxin (Oculinum) was obtained from Dr. Alan Scott (San Francisco, CA) and stored frozen (-20°C) until reconstitution with sterile sa-

line (without preservative) at the time of injection. The quantity of toxin is expressed in units, where one unit (U) represents the mouse LD-50. For the typical injection, a dilution was performed to a final concentration of 2.5 U/0.1 ml.

#### Injection technique

Injections were individualized for each patient. In general, doses were divided into 2.5 to 7.5 U (0.1-0.3 ml) aliquots. Toxin was injected either subcutaneously or intramuscularly (Table 2). In all cases, a tuberculin syringe was used. In cases where precise localization of a particular muscle was required, a 25-gauge monopolar teflon-coated hollow recording EMG needle was used, and injections were performed under EMG control.

At the inception of the study, there were no published standard guidelines for the treatment of focal dystonias or hemifacial spasm. In general, our approach was empiric, beginning with small doses, titrating to the needs of the patient, and drawing upon previous experience. In the early phase of the study, we hospitalized patients with involvement of limb, tongue, and neck because toxin was injected directly into vascular muscles, and we were concerned about excessive systemic absorption. Injections into the tongue were initially diluted in a solution of epinephrine/xylocaine in order to minimize systemic spread. Subsequently, all injections for regions discussed in this report were performed in the outpatient setting of the Dystonia Clinical Research Center or of the EMG laboratory. Injections were performed by a neurologist except for laryngeal and lingual injections when the otolaryngologist performed the procedure.

#### Blepharospasm

Injections were performed with the patient supine. The eyelids and eyebrows

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Table 2. Disorders treated with botulinum toxin injections<sup>a</sup>

| Disorder         | Muscles injected                | Injection type | Injection needle | EMG monitoring         |
|------------------|---------------------------------|----------------|------------------|------------------------|
| Blepharospasm    | orbicularis oculi               | S.C.           | 27 gauge         | no                     |
| Torticollis      | SCM, trapezius, levator scapuli | I.M.           | 27 gauge         | no                     |
| Oromandibular    | temporalis, masseter            | I.M.           | 27 gauge         | initially <sup>b</sup> |
| Laryngeal        | vocalis                         | I.M.           | 25 gauge         | yes                    |
| Limb             | see text                        | I.M.           | 25 gauge         | yes                    |
| Lingual          | genioglossus, hyoglossus        | I.M.           | 27 gauge         | initially <sup>b</sup> |
| Hemifacial spasm | orbicularis ocula, buccinator   | I.M.           | 27 gauge         | no                     |

<sup>a</sup> (SCM) sternocleidomastoid; (S.C.) subcutaneous; (I.M.) intramuscular; (EMG) electromyogram.  
<sup>b</sup> First patient initially injected with EMG control; this was deemed unnecessary on follow-up injections

were cleansed with alcohol. Injections were subcutaneous, typically into the upper and lower lids, lateral canthus, and medial brow. Injections were modified on follow-up if additional muscles (such as corrugators) were involved. For instance, some patients had prominent medial and lateral brow contractions, and these were injected with 2.5 to 5.0 U. Some patients had a strong residual tarsal component, and the tarsal orbicularis was injected after placing a metal shield (Berke-Jaeger; Storz Instruments, St. Louis) between the eyelid and anesthetized cornea.

**Torticollis**

Injections were performed with the patient sitting. Muscles chosen for injection varied according to the degree of rotation, tilt or hyperextension present, and always included the obviously contracting, symptomatic muscles. Total dose injected was proportional to size and apparent mass of muscle present. For instance, in cases of head rotation, the sternocleidomastoid contralateral and trapezius ipsilateral to the direction of chin movement were injected with 45 U and 67.5 U, respectively, in divided doses of 7.5 U each. Typically, on follow-up, if additional muscles were detected to be actively contracting, causing

displacement of the head, these were injected.

**Oromandibular Dystonia**

Patients with forced jaw closure were treated. With the patient sitting, masseters and temporalis were injected. Typically, each masseter and temporalis muscle was injected with 40 U toxin in divided doses up to 7.5 U each.

**Laryngeal Adductor Dystonia**

Only patients with adductor spasm dystonia were treated. Patients were initially examined with the EMG/injection needle by the otolaryngologist. The vocalis muscle was identified (3) and injected. Small doses (2.5-7.5 U/cord) bilaterally were typically sufficient to produce a therapeutic effect. The cords were examined with direct laryngoscopy on each follow-up visit, and lower doses (2.5 U/cord) were used for subsequent injections.

**Limb Dystonia**

Focal dystonias of fingers or toes were treated. The dystonic muscle was identified with the EMG/injection needle and injected in divided doses.

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### Lingual Dystonia

In this case, the toxin was initially diluted in epinephrine/xylocaine solution instead of normal saline because we were concerned about spread of toxin through the vascular system. Subsequently, however, the toxin was diluted in normal saline. With the patient reclined, the genioglossus and hyoglossus muscles were injected by the otolaryngologist in divided doses.

### Hemifacial Spasm

The orbicularis oculi and buccinator muscles were injected. The orbicularis muscle was treated with doses similar to those in blepharospasm; an additional 2.5 to 5.0 U was injected in divided doses in the involved lower facial muscles.

### Follow-up

A physician-patient contact was made within 2 weeks of the injection to report the effect of injections and side effects. A questionnaire was administered to all patients following treatment. The treatment period (TP) was defined as the interval during which dose of toxin injected was titrated to achieve maximum effect plus the following period of benefit. Treatment periods in which active improvement was still present were excluded from the present analysis. We asked about improvement in motor function and pain. Two scales were employed: a qualitative scale of none (0), mild (1+), moderate (2+), and marked (3+) improvement; and a quantitative scale asking the percent improvement for any treatment period. We analyzed the relationship between the two scales in our population and found a significantly linear relationship ( $R = 0.925$ ,  $p < 0.001$ ). Therefore, we relied on the qualitative scale for subsequent analyses. We determined the days to onset of relief of symptoms, days to peak relief of symptoms, and weeks duration of benefit.

Side effects were tabulated. For a global assessment, we asked the question: "during this assessment period, is BOTOX better, same, or worse than the medicines you have taken to treat your dystonia?"

Data were entered into a dBase II database on our Compupro computer and subsequently transferred and analyzed on the General Clinical Research Center VAX-11/750 computer using CLINFO software.

## RESULTS

### Case Reports

The following four case reports illustrate technique and complications:

**Case 1: 63-year-old man with dystonic adductor dysphonia.** At age 50, this salesman developed blepharospasm with associated involuntary contraction of lower facial muscles. At age 54, he developed noisy breathing which progressed to chronic hoarseness. Examination at 63 years revealed a strained, tense, squeezed, occasionally hoarse voice with intermittent breaks and pauses. He stated that this type of voice has interfered with his functioning as a salesman. There was lower facial muscle grimacing accompanying phonation. On indirect and fiberoptic direct laryngoscopy, no lesions were visualized, and the vocal cords abducted and adducted normally. No tremor or other movement disorder was seen. Bilateral laryngeal electromyography of the cricothyroid and vocalis muscles (3) was normal. Using the hollow recording/injection electrode and EMG guidance, the patient underwent a series of botulinum toxin injections into the vocal cords. On September 11, 1984, the right vocalis was injected with 2.5 U (0.1 ml); there was no significant clinical improvement, and indirect examination was unchanged. On September 25, 1984, 20 U BOTOX (0.4 ml) were injected into the left vocalis. Improvement in speech was noted within 2 days; indirect laryngoscopy revealed paralysis of the left

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vocal cord. On October 30, 1984 there was fluency of speech without breaks or pauses. On November 27, 1984, the voice remained improved but strain was returning; indirect examination revealed cord function returning but still weak. The right vocalis was injected with 18.75 U BOTOX in 0.3 ml. Benefit was noted within 2 days and lasted until January 10, 1985 when symptoms began to return. Indirect examination on January 22, 1985 revealed full cord function. EMG of the right vocalis revealed decreased numbers and polyphasic with decreased amplitude, whereas the left vocalis was normal. Right and left vocal cords were each injected with 7.5 U BOTOX (in 0.3 ml). There was slight choking on January 23 to January 24; he had breathy hypophonia January 26 and January 27. Speech returned on January 28 and examination on February 5, 1985 revealed speech was fluent, somewhat gravely, but fatigued easily. Speech continued to improve and he was fluent for 4 months. Fluency gradually deteriorated and on June 25, 1985, the right vocalis was again injected with 7.5 U BOTOX; improvement persisted for 6 months and gradually wore off. He did not deteriorate to his original level of disability, and on January 28, 1986, each cord was reinjected with 3.75 U toxin. Benefit persisted through June 1986.

**Case 2: 56-year-old woman with oromandibular dystonia with mid-facial collapse.** At the age of 50, her loose upper teeth-caps were replaced with a denture. At age 52, her jaw began to move involuntarily resulting in sustained clenching. Symptoms progressed and her upper gums were lacerated by the bottom teeth. At age 53, she had difficulty breathing through her nose and her facial appearance had changed. Facial x-rays showed pressure resorption of the alveolus bone and palate with midfacial collapse. At age 54 there was severe clenching caused by forceful and sustained contractions of the temporalis and masseter muscles. She could open her mouth partially but could not sustain mouth opening for greater

than 1 sec; tongue protrusion was limited because of jaw clenching. Attempting to talk increased clenching with spread of contractions to zygomatic muscles. Oromandibular dystonia interfered markedly with eating and speaking, and she lost 30 lb. Pharmacologic treatments with multiple agents resulted in modest benefit and distressing side effects including depression and sedation. Maximum improvement was achieved with a combination of ethopropazine 450 mg/day and lithium carbonate 450 mg/day. On this regimen there was forgetfulness; lower doses of ethopropazine were met with increased dystonia, and higher doses resulted in diarrhea.

At age 56, on December 11, 1984, each masseter was injected with 12.5 U BOTOX divided into five separate sites. Although the masseters weakened, there was only slight clinical improvement. The following week, we injected the anterior segment of each temporalis muscle with 12.5 U BOTOX divided into five separate sites. Within 1 week there was marked improvement in speech and eating; duration of mouth opening was prolonged. She subsequently regained 30 lb and has been able to discontinue all medicines; memory became normal. Reconstructive facial surgery, previously not possible because of involuntary jaw movements, was initiated.

Mild symptoms returned, and on April 16, 1985, we reinjected each masseter (45 U) and temporalis (20 U) muscle with excellent relief of symptoms. In an effort to provide maximum relief during reconstructive surgery, masseters and temporalis were reinjected on June 14, 1985, July 25, 1985, August 1, 1985, and October 24, 1985. Reconstructive surgery continued; muscles were injected on February 6, 1986. Benefit continued through June 1986. Whereas she estimated about 70% disability prior to treatment, she is now functioning with only an estimated 25% disability.

**Case 3: 57-year-old man with stenographer's dystonia (an occupational cramp).**

This court stenographer developed difficulty with stenotyping at age 49. His hands were normal at rest. As he began to type, the middle finger of the left hand extended at the metacarpo-phalangeal (MP) joint with the fourth and fifth fingers flexing at the MP joints. Usually, if he stopped typing for a few seconds, the sustained spasm disappeared but sometimes he had to force the middle finger down. He had no problem playing piano or writing. Biofeedback relaxation therapy and drug trials with anticholinergics, carbamazepine, clonazepam, baclofen, and valproate were of no benefit. He had been disabled as a stenographer for 7 years. On November 1, 1984 (age 57), under EMG guidance, the extensor digitorum communis (EDC) of the left middle finger was identified and 2.5 U BOTOX was injected into each of 10 sites along the length of the muscle (total, 25 U). There was weakness of middle finger extension within 12 hours after injection; maximum weakness occurred in 2 days. By November 16, 1984, he was able to slowly raise the finger, but it remained below the horizontal plane. Strength gradually improved; by January 14, 1985, he could stenotype with only rare mistakes. Whereas prior to injections, there were 85% typing errors, his post-injection status revealed only 5% to 10% errors. Examination on February 7, 1985 showed middle finger extension was easily overcome but functional. Ethopropazine was added to his regimen. Follow-up 11 months after the injection revealed that on ethopropazine 200 mg/day he was able to work in his occupation; he was previously unresponsive to this medication. Disability returned in early November 1985 and on November 24, 1985, we injected 2.5 U BOTOX into three sites (total, 7.5 U) along the EDC. Two days later, his finger became weak, and it remained at 45° below the horizontal. All medications were discontinued, and he continued to work in the courtroom. Within 6 weeks, he could bring the finger to the horizontal. By January 1986, dystonic hyper-

extension began to interfere although not to the preinjection severity. On January 30, 1986, we injected 2.5 U into the EDC. The finger weakened; strength gradually returned over 8 weeks. Clinical benefit persisted through June 1986.

**Case 4: 50-year-old woman with painful torticollis.** This woman developed torticollis at age 45; pain has been a prominent complaint. At age 53, she had a spontaneous remission for 8 months. Trihexyphenidyl and (Sinemet) resulted in only modest benefit. She developed severe pain at the muscle insertion at the left mastoid process. On December 3, 1985, we injected 82.5 U BOTOX into the left sternocleidomastoid muscle; there was 85% pain relief within 2 days. On January 7, 1986, an additional 180 U were injected into the left and right trapezi resulting in additional benefit. Benefit persisted until April 1986 when pain gradually began to return.

#### Analysis of Effect of Injections

The mean number of visits per treatment period (Table 3) varied from one in patients with PSP to 3.4 in patients with torticollis. Most patients with blepharospasm required one or two visits. The mean dose of toxin injected into each region per treatment period varied from 10.5 U for laryngeal dystonia to 276 U for torticollis.

Approximately two thirds of patients with blepharospasm and torticollis had improvement (Table 4). In the three patients with blepharospasm associated with PSP, there was no benefit from the toxin despite marked weakness of the orbicularis muscles. Toxin injections provided significant motor benefit in three of four patients with OMD, all patients with dystonic adductor dysphonia, two of three patients with limb dystonia, the patient with tongue dystonia, and all patients with hemifacial spasm. It is noteworthy that some torticollis patients with only minimal obvious objective motor benefit expressed meaningful subjective

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Table 3. Analysis of treatment periods (TP) with botulinum toxin

| Disorder                                     | No. visits/TP |        | Dose/TP |        |
|--|---------------|--------|---------|--------|
|  | mean          | median | mean U  | median |
| Blepharospasm: idiopathic                    | 1.6           | 1.3    | 47.3    | 45.6   |
| with PSP <sup>a</sup>                        | 1.0           | 1      | 40.3    | 43.3   |
| Torticollis: idiopathic                      | 3.4           | 3.0    | 276.2   | 247.5  |
| with palatal myoclonus                       | 2*            |        | 240.0*  |        |
| Oromandibular dystonia                       | 1.6           | 1.7    | 91.5    | 97.9   |
| Laryngeal dystonia                           | 1.2           | 1.3    | 10.5    | 9.6    |
| Limb: EHL <sup>a</sup> spasm in parkinsonism | 1.7*          | 2.0    | 81.7*   | 50     |
| stenographer's dystonia                      | 1.0*          |        | 16.1*   |        |
| post-stroke hand dystonia                    | 3.0*          |        | 50.0*   |        |
| Lingual dystonia                             | 2*            |        | 30.0*   |        |
| Hemifacial spasm                             | 1.5           | 1.5    | 27.5    | 26.1   |

(\*): one patient in each category, number of visits = 2.

<sup>a</sup> (PSP) progressive supranuclear palsy; (EHL) extensor hallucis longus.

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clinical improvement in daily living. For some, the greatest benefit was from relief of constant pain. In addition, the patient with a dystonic hand (an example of delayed-onset dystonia [17,18]) had only minor motor improvement but significant pain relief.

Of the patients with essential blepharospasm, 69% had meaningful benefit (Table 3). Among the torticollis patients, 64% derived meaningful benefit, and 73% of those with pain had relief. In both groups, about 75% stated that the toxin was preferable over medications previously used to treat their dystonia.

For further analysis, we segregated the patients with blepharospasm and torticollis into none/mild and moderate/marked benefit (Table 5). Among the patients with blepharospasm, days to peak response was between 5 and 7 days. However, whereas the whole group experienced about 11 weeks' benefit, the good responders were satisfied for nearly 13 weeks, and poor responders experienced benefit for an average of 7 weeks. Among the torticollis patients, onset of relief was slightly later by 1 day in the responders, and peak relief of symptoms was also slightly prolonged. In this group, duration of benefit was about the same.

Table 4. Number of patients showing benefit from injections with botulinum toxin<sup>a</sup>

| Disorder                                     | Motor |       | Pain  |       |
|--|-------|-------|-------|-------|
|  | 2+/3+ | (%)   | 2+/3+ | (%)   |
| Blepharospasm: idiopathic                    | 29/42 | (69%) |       |       |
| with PSP <sup>b</sup>                        | 0/3   |       |       |       |
| Torticollis: idiopathic                      | 16/25 | (64%) | 14/19 | (74%) |
| with palatal myoclonus                       | 0/1   |       |       |       |
| Oromandibular dystonia                       | 3/4   |       |       |       |
| Laryngeal dystonia                           | 3/3   |       |       |       |
| Limb: EHL <sup>a</sup> spasm in parkinsonism | 1/1   |       | 1/1   |       |
| stenographer's dystonia                      | 1/1   |       |       |       |
| post-stroke hand dystonia                    | 0/1   |       | 1/1   |       |
| Lingual dystonia                             | 1/1   |       |       |       |
| Hemifacial spasm                             | 3/3   |       |       |       |

<sup>a</sup> Benefit = mean of benefits for all treatment periods/patient; 2+ = moderate; 3+ = marked.

<sup>b</sup> (PSP) progressive supranuclear palsy; (EHL) extensor hallucis longus.

Table 5. Relief of motor symptoms\*

| Dystonia                 | Days to onset |          | Days to peak |         | Weeks duration |
|--------------------------|---------------|----------|--------------|---------|----------------|
|                          | average       | (range)  | average      | (range) |                |
| Blepharospasm (all)      | 2.7           | (0-8)    | 7.4          | (1-42)  | 11.4 (0-34)    |
| moderate/marked response | 2.4           | (0-10)   | 7.6          | (1-42)  | 12.9 (2-34)    |
| poor response            | 2.9           | (0-7)    | 5.3          | (2-8)   | 7.2 (0-21)     |
| Torticollis              | 3.3           | (1-9)    | 5.7          | (1-34)  | 10.8 (1.5-30)  |
| moderate/marked response | 3.8           | (0.5-12) | 7.2          | (0.5-4) | 11.6 (1-10)    |
| poor response            | 2.8           | (1-7)    | 3.2          | (2-7)   | 9.7 (3-16)     |

\* Values expressed as means of mean time/treatment period/patient.

being 10.8 weeks on average, in all groups. Frequently, patients requested reinjection before their neurologic condition returned to baseline. Some patients, and in particular those with dystonic adductor dysphonia, experienced more persistent benefit and required reinjection at less frequent intervals.

Adverse effects (Table 6) were experienced in a small group of patients. Three patients with blepharospasm had conjunctivitis and all occurred during the early phase of the study. The conjunctivitis responded rapidly to ophthalmic antibiotics. Eight developed ptosis, likely related to diffusion of toxin into the levator palpebrae muscle; this resolved in all, and more rapidly than eventual decay of benefit. One patient had an entropion, which also resolved as muscle strength of the lower lid returned. Two patients with torticollis complained of an excessively weak or floppy neck. One torticollis patient experienced a clinical

worsening early in the TP caused by injection of antagonist muscles; this resolved with injection of the appropriate agonists. In two torticollis patients, antibodies were detected using an *in vivo* mouse assay (Dr. Charles Hathaway, Center for Disease Control, Atlanta, GA). These patients became refractory to subsequent injections. The patients with dystonic adductor dysphonia typically experienced 1 to 3 days of slight choking and aspiration; there were no pulmonary complications. One patient with limb dystonia, and one with hemifacial spasm complained of fatigue. The man with stenographer's dystonia initially had an excessively weak finger. One hemifacial spasm patient developed a transiently droopy lip.

#### DISCUSSION

Previous investigators (7-15, Table 7) have concentrated on using local injections of BOTOX for the treatment of blepharospasm and torticollis; in addition to these disorders, we also emphasize the value of this technique in treating other disabling focal dystonias. We have found local injections of botulinum toxin valuable in relieving disabling dystonic spasms when limited to one muscle or a small group of muscles. Although our results are similar to those published for blepharospasm, we found a smaller percentage of patients with significant benefit. This is likely because of our stringent criteria, grouping the "mild ben-

Table 6. Adverse effects with botulinum toxin injections

|  |
|--|
| Blepharospasm: conjunctivitis 3/43 (7%)                        |
| ptosis 8/43 (19%)  |
| entropion 1/43 (2%)  |
| Oromandibular: none  |
| Torticollis: weak neck muscles 2/28                            |
| antibody formation 2/28  |
| Laryngeal: transient (3 days) mild choking, and aspiration 3/3 |
| Limb: excessive local weakness 1/3                             |
| generalized fatigue 1/3  |
| Hemifacial spasm: fatigue 1/4                                  |
| droopy lip 1/4   |

Frueh et al  
Tsou et al  
Scott et al  
Schorr et al  
Elston & I  
Mauritello,  
Savino et al  
Fahn et al  
Teui et al  
Perman et al  
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Table 7. Reports on treatment with botulinum toxin\*

| Duration | Authors (ref. no.)                | Type Study   | Bleph/Meige      | Tort | OMD | Vocal | Limb | Tongue | Hemifacial spasm |
|----------|-----------------------------------|--------------|------------------|------|-----|-------|------|--------|------------------|
| (0-54)   | Frush et al., 1984 (7)            | OL           | 19               | .    | .   | .     | .    | .      | 3                |
| (2-54)   | Tsoy et al., 1985 (8)             | OL           | 38               | .    | .   | .     | .    | .      | 5                |
| (0-21)   | Scott et al., 1985 (9)            | OL           | 39               | .    | .   | .     | .    | .      | .                |
| (1.5-30) | Schorr et al., 1985 (10)          | OL           | 17               | .    | .   | .     | .    | .      | 3                |
| (1-30)   | Eaton & Ross Russell, 1985 (11)   | OL           | 34               | .    | .   | .     | .    | .      | .                |
| (3-16)   | Maurello, 1985 (12)               | OL           | 39               | .    | .   | .     | .    | .      | 11               |
|          | Savino et al., 1985 (16)          | OL           | .                | .    | .   | .     | .    | .      | 15               |
|          | Fahn et al., 1985 (13)            | DB           | (5) <sup>a</sup> | .    | .   | .     | .    | .      | .                |
|          | Tsui et al., 1985 (15)            | DB           | .                | 12   | .   | .     | .    | .      | .                |
|          | Perman et al., 1986 (14)          | OL           | 28               | .    | .   | .     | .    | .      | .                |
|          | Brin et al., 1987 (present study) | OL           | 46               | 30   | 4   | 3     | 3    | 1      | 4                |
|          | Total                             | 2 DB<br>9 OL | 260              | 41   | 4   | 3     | 3    | 1      | 43               |

\* (OL) open label study; (DB) double-blind study; (Bleph) blepharospasm; (Tort) torticollis; (OMD) oromandibular dystonia.

<sup>a</sup> Included in present study.

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Table 7) injections lepharos- these dis- ue of this ling focal injections eving dis- ed to one cles. Al- iose pub- found a lb signifi- se of our mild ben-

efit" patients in the group without significant benefit. If these were included with the moderate/marked benefit group, the percentage of patients improved would be 83% for blepharospasm and 82% for torticollis.

In contrast to surgery, in which interruption of nerves to the involved muscles may result in complete and permanent weakness, the approach of chemically weakening sustained contractions has advantages. First, the injections are performed with the patient awake; the muscle can be identified and injected under EMG control, thereby lending precision to the procedure. Second, graded responses of weakening of the muscles can be obtained by using low dosages initially and then repeating the injections to achieve the desired result. After titrating the dose needed to obtain the optimum amount of weakness, one can use that determined dosage for future injections, as the toxin's effect dissipates. Third, if too much local weakness is induced (e.g., Cases 1 and 3), strength gradually returns and the weakness is not permanent. Fourth, drugs can be used simultaneously, as with Case 3, who was originally unresponsive to high dose anticholinergics (19), and later responded well (nevertheless, he preferred toxin to drugs).

Fifth, the procedure is simple and acceptable to the patients, and they were satisfied with the result. Sixth, it does not have the added risk of general anesthesia with surgery. And seventh, the procedure is less costly than surgery.

In contrast to systemic pharmacotherapy with cognitive and sedative side effects, local injections of BOTOX were without clinically significant systemic side effects in all patients except the one with limb dystonia who felt generalized fatigue after injections.

It is too soon to say how often injections need to be repeated or if there will be any long-term adverse effects. Experience with multiple injections of the orbicularis oculi muscles for blepharospasm suggests that injections are required approximately every 3 months (10), although this is quite variable in our experience. It appears that patients with laryngeal dystonia require subsequent injections at less frequent intervals.

Although no persistent side effects from BOTOX injections have occurred in our experience, we (20) and Sanders et al. (21) have reported a subclinical defect of neuromuscular transmission seen on single fiber electromyography of limb muscles dis-

tal to the site of injection. The patient with parkinsonism and toe dystonia developed fatigue after two series of injections. Defective distant neuromuscular transmission was seen after the first symptoms (second treatment period), but this defect was no more severe during the second episode of fatigue (third treatment period). The production of antibodies suggests that the toxin solution is immunogenic, and we caution that theoretically patients have a risk of developing additional immunologically mediated responses such as anaphylaxis.

Clinical experience with the toxin suggests many avenues for further research into the pathophysiology of the response. For instance, in blepharospasm, the decrease of the typically increased eyeblink rate seen is not fully explained by primary muscle weakening. It is not clear why some patients do not respond, even in the presence of marked local weakening of affected muscles. Finally, there are no long-term human or animal studies examining the effect of repeated exposure of toxin on muscle anatomy and physiology or on the neuromuscular junction.

#### ACKNOWLEDGMENTS

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