Botulinum Toxin in the Treatment of Tics

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Objective: To evaluate the safety and efficacy of botulinum toxin A (BTX) injections in the treatment of tics in patients with Tourette syndrome (TS).

Background: BTX is an effective treatment for an increasing number of conditions characterized by abnormal muscle contractions. BTX may improve not only the motor component of tics, but also premonitory sensations that precede tics.

Methods: Thirty-five patients (30 male, 5 female) were treated with BTX in the sites of their most problematic tics. Response to BTX was based on a 0 to 4 clinical rating scale (0, no improvement, to 4, marked improvement in both severity and function). Questionnaires were administered to evaluate patients’ impressions of overall efficacy and degree of benefit with premonitory sensations.

Results: Mean duration of tics prior to initial injection was 15.3 years (range, 1-62 years) and mean duration of follow-up was 21.2 months (range, 1.5-84 months). The mean peak effect response in 35 patients treated in 115 sessions was 2.8 (range, 0-4); the mean duration of benefit was 14.4 weeks (maximum, 45 weeks); and the mean latency to onset of benefit was 3.8 days (maximum, 10 days). Twenty-one (84%) of 25 patients with premonitory sensations derived marked relief of these symptoms (mean benefit, 70.6%). Total mean dose was 502.1 U (range, 15-3550 U); mean number of visits, 3.3 (range, 1-16); and mean dose per visit, 119.9 U (range, 15-273 U). Sites of injections were as follows: cervical or upper thoracic area (17), upper face (14), lower face (7), vocal cords (4), upper back and/or shoulder (3), scalp (1), forearm (1), leg (1) and rectus abdominis (1). Complications included neck weakness (4), dysphagia (2), ptosis (2), nausea (1), hypophonia (1), fatigue (1), and generalized weakness (1), which were all mild and transient.

Conclusions: Botulinum toxin A injections are an effective and well-tolerated treatment of tics. In addition to improving the motor component of tics, BTX also provides relief of premonitory sensations.

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Gilles de la Tourette syndrome (TS) is a complex, childhood-onset, neurobehavioral disorder characterized by chronic motor and phonic tics. The etiology of TS remains elusive, although the preponderance of the evidence suggests a genetically determined dysfunction of the basal ganglia and limbic structures with varying clinical expressions in individuals. Many patients with TS also experience premonitory sensations, described as a generalized urge or local feeling of discomfort, tingling, or tension that precedes the motor or phonic tic. While medications such as dopamine-receptor blocking agents or dopamine depleters have been used for many years to treat tics, these neuroleptics may have troublesome adverse effects such as tardive dyskinesia, hepatotoxicity, prolonged QT intervals, sedation, weight gain, school phobia, and depression.

Botulinum toxin (BTX) has been used effectively to treat a number of conditions characterized by excessive, abnormal, involuntary movements. In a pilot study, the therapeutic benefits of chemodenervation with local BTX injections were demonstrated in 10 patients with TS. A striking finding of this study was the amelioration of the premonitory sensory symptoms that often precede tics. We describe here the results of a longitudinal follow-up of additional patients with TS who underwent BTX treatment.

RESULTS

Thirty-five patients were included in this study, 30 male and 5 female, with a mean ± SD age of 23.3 ± 15.5 years (range,
PATIENTS AND METHODS

Thirty-five patients with a tic disorder were included in this study, 34 of whom fulfilled the criteria for TS according to the TS Classification Study Group criteria.19 The remaining patient fulfilled all the diagnostic criteria except for age at onset of tics, which was older than 21 years. Patients received intramuscular injections of BTX (Botox; Allergan Pharmaceuticals, Irvine, Calif) from 1992 to 1999 at the Parkinson’s Disease Center and Movement Disorders Clinic, Baylor College of Medicine, Houston, Tex. A written consent form, approved by the Institutional Review Board for Human Research for Baylor College of Medicine, was completed and signed by all patients or their legal guardians prior to the BTX treatment. All patients had at least one follow-up visit and/or a telephone interview within a 12-month period after treatment. Prospective data collected in a standardized form for each patient included (1) demographic data; (2) age at onset of tics; (3) duration of the tic(s) (in years); (4) disability secondary to the tic disorder or TS; (5) duration of treatment (in years); (6) duration of follow-up (in years); (7) total dose of BTX injected (in units); (8) total dose of BTX injected per site (in units); (9) site(s) of injection; (10) peak effect rating; (11) global response; (12) latency of onset of response (in days); (13) duration of total response (in weeks); (14) duration of maximum response (in weeks); (15) presence of disabling or non disabling complications; (16) presence of a premonitory sensory component; (17) percent improvement of the premonitory sensory component after BTX injection; and (18) global (overall) response to BTX (percentage).

The tic duration was defined as the time interval between the age at onset of tic(s) and the first BTX injection (in years). The injection sites included the upper eyelid, lower eyelid, eyebrow, and paranasal muscles for the upper face, masseters and the submental complex for the lower face, sternocleidomastoid, scalene, trapezius and splenius cervical muscles, and the vocal cords. The muscle sites designated as “other” included the deltoid, forearm, posterior tibialis, rectus abdominis, rhomboid, scalp, and upper back. To optimize the response to BTX, it is necessary to customize the treatment and tailor it to the needs of the individual patient. The injection sites and the doses were, therefore, adjusted at each visit depending on the location and description of the tics. The duration of follow-up was defined as the time interval between the first injection and the last BTX clinic visit or telephone interview (in months).

The response assessment methods for peak effect, global rating, latency, total duration, and total maximum duration have been previously described.20 Peak effect was defined as the maximum benefit in duration and frequency of the tic(s) after administration of the BTX injection and was rated on a 0- to 4-point scale (0, no effect; 1, mild effect but no functional improvement; 2, moderate improvement but no change in functional disability; 3, moderate change in both severity and function; and 4, marked improvement in both severity and function). Global rating was defined as the peak effect score minus 1 point if associated with the presence of mild or moderate complications, and minus 2 points for severe or disabling complications. Latency was defined as the interval (in days) between the first injection and the first sign of tic improvement. Duration of total response was defined as the number of weeks the patient noted improvement, and the duration of maximum response as the number of weeks that the patient experienced the peak effect. Patients who may have had spontaneous resolution of tics after the BTX injections were recorded to have duration of total and maximum responses of greater than 1 year. These individuals were not included in the data analysis of total and maximum duration of benefit (in weeks).

The premonitory sensory component was recorded using a percentage scale, with patients reporting an improvement of less than 25%, 25% to 49%, 50% to 74%, 75% to 99%, or 100% (complete resolution) following the BTX injections. Similar percentage assessment was performed for global (overall) response. Anti-tic medications were held constant during the observation period.

8.69 years. Mean age at tic onset was 7.9 ± 5.5 years (range, 2-17 years; for 1 patient, age 33 years), with mean tic duration of 15.3 ± 14.9 years (range, 1-62 years). Mean duration of follow-up was 21.2 ± 22.2 months (range 1.5-84 months). Total number of treatment sessions was 115, of which 102 had a global response rating. The most common muscles injected were cervical and those in the upper face, particularly the eyelids. The response data and dose information, averaged for all visits, are summarized in Table 1.

Twenty-nine patients experienced an improvement of tics following BTX injections, with 23 reporting a peak effect of 3 or higher (markedly improved function). Twenty-one (84%) of 25 patients with notable premonitory sensations derived marked relief of these symptoms from BTX. Seventeen patients who were able to specify their percent improvement with regard to premonitory symptoms rated their mean benefit at 70.6%. Three patients reported complete resolution of premonitory discomfort. Fourteen patients were injected on only 1 occasion; 4 of these had no response. Five patients had complete resolution of tics at the injected site, reporting a tic-free period of greater than 1 year; 3 of these patients were injected only 1 time.

No severe or disabling complications were reported. With the exception of neck weakness lasting an average of 23 days in 4 patients, ptosis lasting up to 28 days in 2 patients, generalized weakness lasting 7 days in 1 patient, nondisabling dysphagia lasting an average of 17.5 days in 2 patients, fatigue lasting 14 days in 1 patient, and nausea and/or vomiting lasting 1 day in 1 patient, no other adverse effects were noted.

The findings of this study of 35 patients support the use of BTX injections as a safe and effective treatment for tics. Of the 102 treatment sessions, 78 (76.5%) resulted in a global rating of 3 (n=23) or 4 (n=35) indicating marked benefit. In addition, the tics decreased in frequency, duration, and intensity, and 5 patients had a complete resolution of tics at the injected site for longer than 1 year. It
is possible that these patients achieved spontaneous remission, and they were therefore not included in the calculation of the mean duration of improvement. Reduction in tic frequency and severity is well recognized as a natural course of the disease. Some patients reported the spontaneous remission or near disappearance of tics by “late adolescence or early adulthood.” Bruun and Budman also found that at least two thirds of children with TS have a marked reduction or even near complete remission of tics, yet they believe that “complete, life-long remissions are rare.” It is not known whether the sustained remission observed in 5 of our patients was related to the treatment with BTX or was merely coincidental and would have occurred even without the treatment.

Twenty-five patients experienced premonitory sensations (“discomfort,” “pressure,” or “tingling”) in the location of the tics, and 21 (84%) derived marked relief of these symptoms from BTX (mean benefit, 70.6%). Premonitory sensations are not well understood, but sensory feedback mechanisms have been implicated not only in these premonitory sensations, but also in the generation of tics in TS. A patient with a long-standing history of TS, provided a vivid description of the premonitory sensations which accompanied his tics. Kurlan et al defined the sensations as “focal, localized uncomfortable sensations for which patients attempt to obtain relief by producing movements involving the affected body region.” Several other studies have noted the relatively high frequency of premonitory sensations in TS. One study of 60 patients with tic disorders showed that 93% perceived the tics to be “irresistibly but purposefully executed,” suggesting a voluntary motor response to an involuntary inner sensation or compulsion. In our study, 21 of 25 patients experienced relief of premonitory discomfort, 3 of whom reported complete resolution following the BTX injections. Although Obeso et al found no premovement potential (Bereitschaftspotential) prior to a spontaneous tic, Karp et al documented these premotor potentials in 2 of 5 patients with simple motor tics resembling the premotor potential pattern of self-initiated movements, which suggests a voluntary component to the tic. Thus, some benefit of BTX may be due to the relief of muscle contractions by BTX with disruption of the voluntary motor component of the sensory feedback mechanism.

A pilot study reported the results of BTX injections in 10 patients, 5 with disabling blinking and 5 with painful dystonic tics involving the neck musculature. All patients noted moderate to marked improvement in the intensity of tics and reduction of premonitory tension. Subsequent reports have confirmed the beneficial effects of BTX injections in the treatment of motor and phonic tics, including severe coprolalia. In an ongoing placebo-controlled study of 15 patients with simple motor tics, Marras et al have found a 42% reduction in the number of tics per minute in patients treated with BTX compared with an 8% increase in the placebo group. In addition, there was a 0.57 reduction in “urge scores” with BTX compared with a 0.4 increase in the

### Table 1. Results of Botulinum Toxin Injections*

<table>
<thead>
<tr>
<th>Clinical Variable</th>
<th>Results</th>
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<tbody>
<tr>
<td>Global response rating, 0-4 scale</td>
<td>2.7 ± 1.5 (0-4)</td>
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<tr>
<td>Peak effect, 0-4 scale</td>
<td>2.8 ± 1.5 (0-4)</td>
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<tr>
<td>Duration of maximum benefit, wk</td>
<td>12.3 ± 10.7 (0.3-45)</td>
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<tr>
<td>Total duration of benefit, wk</td>
<td>14.4 ± 10.3 (0.3-45)</td>
</tr>
<tr>
<td>Latency to onset of benefit, d</td>
<td>3.8 ± 2.9 (1-10)</td>
</tr>
<tr>
<td>Total dose, U</td>
<td>502.1 ± 779.4 (15-3550)</td>
</tr>
<tr>
<td>No. of visits</td>
<td>3.3 ± 3.6 (1-16)</td>
</tr>
<tr>
<td>Dose per visit, U</td>
<td>119.9 ± 70.1 (15-273)</td>
</tr>
<tr>
<td>Dose by injection site per visit, U</td>
<td>Cervical, 149.6 ± 49.1 (50-209); upper face, 57.4 ± 18.4 (30.0-91.7); lower face, 79.3 ± 52.5 (10-160); vocal cords, 17.8 ± 6.5 (10-23.8); other, 121.7 ± 92.4 (50-273.1)</td>
</tr>
<tr>
<td>Complications (No.)</td>
<td>Neck weakness (mild, transient) (4), ptosis (2), dysphagia (mild, transient) (2), nausea (1) (1), generalized weakness (7 d) (1), fatigue (1), hypophonia (1)</td>
</tr>
</tbody>
</table>

*Unless otherwise indicated, data are mean ± SD (range).

### Table 2. Prior Series and Case Reports of Botulinum Toxin Injections for Tics

<table>
<thead>
<tr>
<th>Authors, y</th>
<th>No. of Patients</th>
<th>Site(s) of Injection (No.)</th>
<th>Duration of Response</th>
<th>Response of Premonitory Sensation</th>
<th>Complications (No.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jankovic,1994</td>
<td>10</td>
<td>Upper face (5) (blinking), cervical (5)</td>
<td>2-20 wk</td>
<td>Abolished or decreased markedly</td>
<td>Transient ptosis (2), weakness (3)</td>
</tr>
<tr>
<td>Scott et al,1996</td>
<td>1</td>
<td>Vocal cords</td>
<td>&gt;5 wk</td>
<td>Decreased markedly</td>
<td>Hypophonia</td>
</tr>
<tr>
<td>Salloway et al,1996</td>
<td>1</td>
<td>Vocal cords</td>
<td>9 wk</td>
<td>Not specified</td>
<td>Hypophonia</td>
</tr>
<tr>
<td>Trimble et al,1998</td>
<td>1</td>
<td>Vocal cords</td>
<td>12-24 wk</td>
<td>Not specified</td>
<td>Hypophonia</td>
</tr>
<tr>
<td>Present study, 1999</td>
<td>35</td>
<td>Cervical (17), upper face (14), lower face (7), vocal cords (4), other (3)</td>
<td>0.3 to &gt;1 y</td>
<td>Decreased markedly</td>
<td>Neck weakness (4); transient ptosis (2); mild dysphagia (2); nausea, fatigue, hypophonia, generalized weakness (1 each)</td>
</tr>
</tbody>
</table>
placebo group. This preliminary study, however, lacks the power to show significant differences in the measured variables. Additional patients and longer follow-up is needed to further evaluate the efficacy of BTX in the treatment of tics. These preliminary results seem to support our findings and suggest that BTX is a safe and effective treatment for selected focal tics. The most common adverse effect in our study was neck weakness, which lasted an average of 23 days in 4 patients. Although the study was not designed to compare the effects of BTX at different sites, our subjective impression was that the injection was most effective for eyelid tics and less so for cervical tics. Patients with vocal tics, however, also responded very well.

Our study has several shortcomings and, therefore, the results must be interpreted cautiously. This was an open-label evaluation and, as such, subject to biases. There is currently no universally accepted, validated rating scale for Tourette syndrome. A Unified Tourette Syndrome Rating Scale is in development, but it has not yet been validated. Although a video rating protocol has been suggested by some, this method also has limitations, and it would not assess the effects of botulinum toxin on premonitory sensations. Fourteen of the patients were injected only 1 time; 4 had no response to the first injection; and 3 had a sustained (>1 year) marked reduction or resolution of the tics, which may indicate a spontaneous remission. Those who failed to respond to the first injection may have benefited from a higher dose or alteration of injection site. Financial considerations might also have contributed to the lack of follow-up in these patients. One patient in particular had a dramatic response but declined further injections because of cost considerations.

Our study does provide evidence that BTX is both well tolerated and a highly effective treatment for tics and premonitory sensations in patients with TS. The results from this open trial, including the effects on premonitory sensations and the frequency of long-term remissions, can be used to design a double-blind, placebo-controlled trial.

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REFERENCES