

Duration of Effect of Botulinum Toxin Type A in Adult Patients with Cervical Dystonia: A Retrospective Chart Review

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ABSTRACT

Background: Clinical trials have established the efficacy and safety of botulinum toxin type A (BTX-A) in patients with cervical dystonia. To maintain the clinical benefits of BTX-A, injections need to be repeated whenever patients' symptoms begin to recur.

Objective: The purpose of this study was to determine, in clinical practice settings, the mean duration of effect of BTX-A in the treatment of adult patients with cervical dystonia.

Methods: A retrospective chart review was undertaken at an academic center and a private neurology practice. At each site, ≥ 50 patients being treated for cervical dystonia were identified and randomized for chart review. Patients had to have received the first assessable injection of BTX-A between January 1, 1998, and March 31, 1998, to coincide with the clinical availability of the most current formulation of the neurotoxin. A chart was eligible for review if the patient was aged ≥ 18 years, had a documented diagnosis of idiopathic cervical dystonia, was being treated with BTX-A, and had been under the continuous care of investigators from January 1, 1998, to August 31, 1999. Of the 102 patients initially identified, the first 30 from each site who met the study inclusion criteria were assessed for (1) age and sex; (2) severity of dystonia; (3) years of BTX-A use; (4) dates of first, second, third, and fourth BTX-A injections; (5) drug dose; (6) use of electromyography; (7) use of other prescribed therapies; (8) laboratory tests; and (9) adverse events. The mean interval between each visit and mean per-patient duration of effect were calculated and stratified by patient characteristics.

Results: The mean age of the patients was 56.4 years. Two thirds of the patients were women. Forty-one of the 60 patients (68.3%) had either moderate or severe disease, and 48 (80.0%) had experienced cervical dystonia for >5 years. The mean per-patient duration of effect across the 4 visits was 15.5 weeks (range, 12.2–24.3 weeks). The duration of effect did not differ significantly between study sites despite the differences in disease severity, drug dose, and use of adjunctive therapy.

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Conclusion: BTX-A controls the symptoms of cervical dystonia for 12 to 24 weeks, with a mean duration of effect per patient of 15.5 weeks.

Key words: cervical dystonia, duration of effect, botulinum toxin type A, retrospective chart review. (*Clin Ther.* 2000; 22:1516–1524)

INTRODUCTION

The standard of care for patients with moderate or severe cervical dystonia includes intramuscular injections of botulinum toxin type A* (BTX-A), sometimes in concert with therapeutic adjuncts such as anxiolytic, anticholinergic, antiparkinsonian, or analgesic drugs, as well as physical therapy.^{1–19} BTX-A is 1 of 7 distinct botulinum neurotoxins (A–G), all of which are derived from the anaerobic bacillus *Clostridium botulinum*.^{1,2,7} Each is unique in its antigenicity, safety profile, and pharmacologic profile. Clinical trials have established the efficacy and safety of BTX-A in patients with cervical dystonia. To maintain the clinical benefits of BTX-A, injections need to be repeated whenever patients' symptoms begin to recur. A 3-month duration of action has been generally assumed or extrapolated from clinical trial data^{20–25}; however, observations made in clinical trials may not predict product effectiveness in clinical practice.²⁶ Therefore, a "real-world" assessment is required to estimate the duration of symptom control achieved with intramuscular injection of BTX-A in clinical practice.

The present study was undertaken to determine the duration of clinical response

to BTX-A (expressed as the time between injections) in patients who were treated in 2 large clinics for cervical dystonia. Additional goals of the study were to evaluate resources consumed during patient care, including the dosage and frequency of adjunctive therapies.

MATERIALS AND METHODS

A retrospective chart review was performed at 2 sites where BTX-A is used to treat patients with cervical dystonia. Criteria for site selection included (1) a sufficiently large patient population (150–600 patients under management for cervical dystonia); (2) recognized physician experience and expertise in the management of cervical dystonia; (3) accessible patient records; and (4) an expressed practice to allow patients to return for injections based on clinical need rather than a preset return-visit schedule. For diversity, an academic tertiary-care center and a private-practice neurology clinic in different areas of the country were identified and recruited.

At each study site, ≥50 patients who were treated with BTX-A between January 1, 1998, and August 31, 1999, were considered for enrollment. Patients had to have received their first assessable injection of BTX-A between January 1, 1998, and March 31, 1998, to coincide with the clinical availability of the most current formulation of the neurotoxin. To ensure patient confidentiality and anonymity, we coded the charts with unique random site-specific numeric identifiers. To ensure randomization, we then ordered the charts alphanumerically. The numeric order was then permuted as 1 block, and the new order served as the sequence in which charts were reviewed for inclusion and exclusion criteria. Once 30 patients per site qualified

*Trademark: Botox® (Allergan, Inc, Irvine, California).

for inclusion or the sample was exhausted, the review process was concluded.

Eligibility Criteria

A chart was deemed eligible for review if the patient was aged ≥ 18 years, had a documented diagnosis of idiopathic cervical dystonia, was being treated with BTX-A, and had been under the continuous care of the investigators from January 1, 1998, to August 31, 1999. Only patients who had received ≥ 4 sequential intramuscular injections of BTX-A during the study entry period were included.

We excluded the charts of any patients who had been treated with BTX-A for any reason other than cervical dystonia, had undergone therapy with other locally injected medications that affect neuromuscular-junction transmission, were involved in another investigational drug study, or had received a booster injection between January 1, 1998, and August 31, 1999. Restrictions in the therapeutic use of BTX-A for any reason during the assessment period also resulted in exclusion. All exclusions were documented on case-report forms.

Because information was collected retrospectively from charts and the patients were not treated in the study, a waiver of informed consent was obtained from the institutional review board at each site.

Data Extraction

Chart reviews were conducted at each participating site according to the study protocol. The primary study end point for each patient was the duration (length of time in weeks) between visits 1 and 2, visits 2 and 3, and visits 3 and 4. Demographic data were also collected, in-

cluding each patient's sex and date of birth as well as disease characteristics. Patient names were not disclosed to Health Economics Research or governing health authorities.

Duration of illness was categorized as < 1 year, 1 to 5 years, and > 5 years. Because no patients had disease for < 1 year, the classifications were dichotomized, as were years of BTX-A use (< 1 year vs ≥ 1 year). Disease was classified at each investigational site as mild (easily tolerated), moderate (interfering with common daily activity), or severe (incapacitating). Health insurance coverage (payer mix) and reason for each office visit were also recorded. Any untoward medical occurrence, including exacerbation of illness outside normal variation, was noted along with all adverse events, irrespective of their relation to BTX-A administration. Other data collected included the dates of each injection, the BTX-A dose at each visit, the use of electromyography (EMG) to guide injections, laboratory test results, and the use of adjunctive therapies.

Statistical Methods

A sample size of 60 charts was selected to allow a minimum detectable difference of ± 5.8 days (< 1 week) given an 80% level of power and 0.05 significance level (using a Student *t* test approximation for normal distribution). For data on the duration of clinical effect and the dose of BTX-A injected at each visit, we calculated the sample size, mean, and range, as well as 2-sided 95% CIs, stratified by patient characteristics. Numbers, percentages, and 95% CIs were calculated for the frequencies of adverse events.

RESULTS

Of the 102 charts identified and reviewed between September and October 1999, 30 charts from the private-practice clinic and 30 charts from the academic tertiary-care center were analyzed. All study participants (N = 60) had been in the care of clinicians specializing in movement disorders and had been treated for cervical dystonia with BTX-A for ≥ 1 year. The mean age of the patients was 56.4 years (range, 19–83 years); two thirds of the patients were women. Forty-one of the 60 patients (68.3%) had either moderate or severe disease, based on the data abstractor's appraisal, and 48 (80.0%) had experienced cervical dystonia for >5 years (Table I).

The mean (\pm SD) duration of clinical response for all 60 patients assessed was 15.6 (\pm 4.2) weeks, as measured by the interval between visits 3 and 4 (Table II). The per-patient average duration of effect ranged from 12.2 weeks to 24.3 weeks; the mean (\pm SD) per-patient average duration of response across 4 visits was 15.5 (\pm 3.4) weeks (figure). No significant difference in the mean duration of clinical response was noted between the sites (15.1 \pm 3.4 weeks and 16.2 \pm 4.9 weeks at the private clinic and academic clinic, respectively; $P = 0.30$). However, patients at the private clinic received higher doses of BTX-A than did patients at the academic center (287 U vs 244 U; $P = 0.02$). This observation may reflect the need for higher dosing among patients with more advanced disease. Significant differences ($P < 0.05$) in treatment doses at the 4 visits were observed across all disease severities (ie, mild, moderate, and severe) at both sites. Moreover, the mean dose administered to men was significantly higher

Table I. Demographic characteristics of the study population (N = 60).

Characteristic	
Mean age \pm SD, y	56.4 \pm 13.9
Sex, no. (%)	
Male	20 (33.3)
Female	40 (66.7)
Onset of disease, no. (%)	
1–5 y	12 (20.0)
>5 y	48 (80.0)
Disease severity, no. (%)	
Mild	19 (31.7)
Moderate	26 (43.3)
Severe	15 (25.0)
Insurance coverage, no. (%) [*]	
HMO/PPO/POS	24 (40.7)
Medicare	19 (32.2)
Private	11 (18.6)
Medicaid	3 (5.1)
Other	2 (3.3)

HMO = health maintenance organization; PPO = preferred-provider organization; POS = point of service.

^{*}n = 59.

than that administered to women (293.6 U vs 250.8 U; $P = 0.03$).

Although the duration of clinical effect of BTX-A did not vary according to study site or onset of illness, patients with moderate disease experienced a significantly longer clinical effect than did patients with either mild or severe illness (17.2 weeks compared with 14.9 and 13.9 weeks, respectively; $P = 0.03$). However, patients with moderate disease received a mean BTX-A dose (256.5 U) that was intermediate between those administered to patients with mild (238.4 U) or severe (316.3 U) cervical dystonia.

In general, BTX-A injections were well tolerated and did not lead to adverse events that required clinical management or the consumption of health care re-

Table II. Duration of clinical effect: Between-visit intervals.

Interval	Mean wk \pm SD	Range, wk	95% CI
1 (visits 1 and 2)	14.9 \pm 3.5	10.0–25.1	14.0–15.8
2 (visits 2 and 3)	16.0 \pm 4.2	11.7–29.6	14.9–17.1
3 (visits 3 and 4)	15.6 \pm 4.2	10.9–27.9	14.6–16.7
Per-patient average	15.5 \pm 3.4	12.2–24.3	14.7–16.4

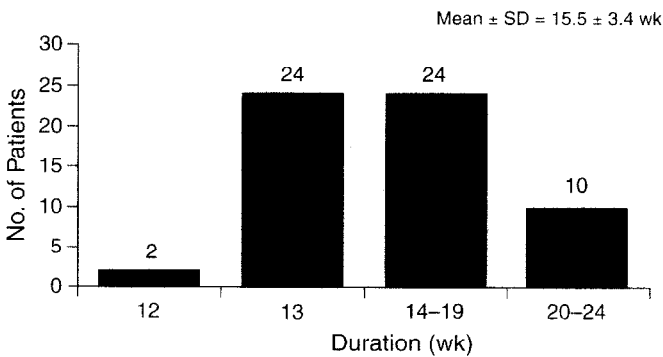


Figure. Per-patient average duration of effect (N = 60).

sources. Seven patients (11.7%) experienced ≥ 1 adverse event (Table III). Dysphagia was most common (8.3%); 1.7% of patients experienced weakness in the neck muscles and 1.7% reported pain in the shoulders or hands.

Across all visits, 40.0% (24/60) of patients received ≥ 1 adjunctive pharmacotherapy (Table IV). The 2 most commonly used prescription drugs were clonazepam (23.3%) and trihexyphenidyl (10.0%). Although nearly 4 times as many patients at the private-practice site were treated with adjunctive therapy compared with patients at the academic center (63.3% vs 16.7%; $P < 0.001$), no significant difference ($P = 0.24$) in duration of response was found between patients receiving adjunctive therapy

and those not receiving adjunctive therapy. The combined mean duration (\pm SD) of response was 14.7 (± 3.2) weeks in patients receiving adjunctive therapy and 16.1 (± 4.6) weeks in patients not receiving adjunctive treatment, as measured by the interval between visits 3 and 4. Similarly, no significant difference ($P = 0.31$) was observed in the mean per-patient average duration of response for patients receiving any adjunctive pharmacotherapy over the 4 clinical visits. Patients receiving any adjunctive treatment ($n = 24$) in the course of 4 visits exhibited a mean (\pm SD) per-patient average duration of response of 15.0 (± 3.0) weeks, whereas the other 36 patients experienced a mean (\pm SD) per-patient average duration of response of 15.9 (± 3.7) weeks.

Table III. Incidence of adverse events across all visits, by study site.

Adverse Event	No. (%) of Patients		
	Private Clinic (n = 30)	Academic Clinic (n = 30)	Total (n = 60)
Shoulder and hand pain	0 (0.0)	1 (3.3)	1 (1.7)
Dysphagia	1 (3.3)	4 (13.3)	5 (8.3)
Cervical pain	1 (3.3)	0 (0.0)	1 (1.7)
Weakness in neck muscles	1 (3.3)	0 (0.0)	1 (1.7)
Any adverse event*	2 (6.7)	5 (16.7)	7 (11.7)

*One patient experienced >1 adverse event.

Table IV. Adjunctive treatments.

Drug	No. (%) of Patients		
	Private Clinic (n = 30)	Academic Clinic (n = 30)	Total (n = 60)
Clonazepam	12 (40.0)	2 (6.7)	14 (23.3)
Trihexyphenidyl	6 (20.0)	0 (0.0)	6 (10.0)
Lorazepam	3 (10.0)	0 (0.0)	3 (5.0)
Amitriptyline	1 (3.3)	1 (3.3)	2 (3.3)
Gabapentin	2 (6.7)	0 (0.0)	2 (3.3)
Hydrocodone	0 (0.0)	2 (6.7)	2 (3.3)
Baclofen	1 (3.3)	0 (0.0)	1 (1.7)
Propoxyphene/acetaminophen	0 (0.0)	1 (3.3)	1 (1.7)
Diazepam	1 (3.3)	0 (0.0)	1 (1.7)
Alprazolam	0 (0.0)	1 (3.3)	1 (1.7)
Any adjunctive treatment*	19 (63.3)	5 (16.7)	24 (40.0)

*Eight patients received >1 adjunctive pharmacotherapy.

DISCUSSION

This review of patient records from 2 sites demonstrated that intramuscular BTX-A was well tolerated among patients with cervical dystonia, with 11.7% of patients experiencing mild, self-limiting adverse events. The duration of clinical effect (15.6 weeks; range, 10.9–27.9 weeks) between

visits 3 and 4 was similar at the 2 independent study sites even though the populations treated and the clinical practices at each location varied slightly. For example, patients treated at the private-practice site tended to have more severe disease than did those treated at the academic institution. Patients at the private-practice site received significantly higher mean doses

($P = 0.02$) of BTX-A and were significantly more likely ($P < 0.001$) to receive adjunctive pharmacotherapy, consistent with the fact that they had more severe disease. BTX-A injections were guided with EMG at the academic center but not at the private-practice site. According to the site investigator, patients at each study site returned for their next injection based on clinical need; however, potentially confounding factors such as reimbursement restrictions and transportation or other travel-related issues could have exerted some influence on the timing of follow-up visits. (Data on the type of health insurance were not analyzed.) Although these factors would tend to offset each other, their relative influence cannot be assessed fully through a retrospective chart audit, and further study is warranted in randomized, controlled trials.

The information revealed in this study is timely because of the expected clinical availability of an alternative neuromuscular blocking agent, botulinum toxin type B. Although the type A and type B neurotoxins may be similar in action, they may differ in other respects, such as potency, antigenicity, tolerability, and possibly clinical effect among patients with cervical dystonia. To assess the health economics of competitive treatments, dedicated research is required, including the development of disease and interventional models, the establishment of meaningful outcomes, and the collection of comparable data to run appropriate analyses. These initiatives have begun with the abstraction of outcomes data from the records of patients with cervical dystonia who were treated with BTX-A. For control and comparative purposes, these data should be matched with comparable clinical practice data from similar patients who are

treated with botulinum toxin type B, and finally the costs associated with each intervention should be compared. Such comparisons can provide a greater understanding of the best use of health care resources as well as the clinical choices that offer the greatest efficacy and value.

CONCLUSION

BTX-A controls the symptoms of cervical dystonia for 12 to 24 weeks, with a mean duration of effect per patient of 15.5 weeks.

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