

Distant Effects of Locally Injected Botulinum Toxin: Incidence and Course

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Small amounts of botulinum toxin (BOTOX) injected directly into skeletal muscle has been reported to ameliorate a variety of focal dystonic conditions (1-8). Despite the potency of BOTOX, only one patient has experienced generalized weakness and this patient received an overdose of toxin (2). Using single fiber techniques, abnormalities of neuromuscular transmission have been found in muscles distant to those injected (9,10). An inverse relationship between jitter and firing rate was noted in these muscles suggesting a presynaptic basis for the jitter (11), most likely reflecting spread of toxin. This report, reported in part previously (10), further delineates the incidence and course of the distant effects induced by local injection of BOTOX.

METHODS

We studied six patients, four women and two men, aged 28 to 68 years. All patients had a diagnosis of focal dystonia, four with torticollis, one with oromandibular dystonia, and one with painful dystonia attributed to levodopa therapy for parkinsonism (Table 1).

All patients received injections of BOTOX into the affected muscles. The toxin used was lyophilized BOTOX A (courtesy of Dr. Alan Scott, San Francisco) reconstituted with normal saline at the time of injection to achieve the desired concen-

tration). BOTOX concentration was calculated in mouse units (U) (1 Unit = Mouse LD50; 1 ng = 2.5 Units). The cumulative doses used in individual patients are listed in Table 1. Injections were administered in small doses (<50 ng per visit) at intervals of 2 to 3 weeks.

Electrophysiologic studies performed on all patients included median motor and sensory nerve conduction velocity, repetitive stimulation in the median/thenar system, and single fiber electromyography (SFEMG). Repetitive stimulation was performed with a supramaximal stimulus of the median nerve at the wrist with surface recording electrodes over the abductor pollicis brevis muscle. Stimulation rate was 3 Hz delivering a series of six stimuli. Studies were performed at rest, immediately after 15 sec of exercise and at 1, 2, 3, and 4 min after 1 min of exercise. Amplitude comparisons were made between the first evoked response before and after exercise (post activation facilitation) and between first and fourth responses from each series to detect decrement.

SFEMG and fiber density determinations were obtained using standard techniques (12) in the extensor digitorum communis (EDC), a muscle remote from the site of injection in all patients. Only fibers whose amplitude exceeded 200 μ V with rise time greater than 300 μ sec were included in measurements. Results were expressed as the

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Table 1. Study of six patients who received injections of botulinum toxin (BOTOX)

Patient (Sex) Age Diagnosis	Dose of BOTOX (Mouse Units) (Muscles Injected)	Time Interval between last injection and SFEMG study	SFEMG Results*		
			MCD (μ sec)	(no. fibers with excess jitter/blocking)	(fiber density)
1 (female) 51 years Torticollis	0 285 450 (SCM ^a & trapezius)	0 2 weeks 4 months 9 months	28 49.2 41.0 52.0	(0/0) (4/0) (4/0) (4/1)	(1.3) (1.3) (2.25) (2.0)
2 (female) 58 years Torticollis	372 687 (SCM & trapezius)	6 weeks 3 weeks	37.0 36.0	(0/0) (2/0)	(1.4) (2.05)
3 (female) 42 years Oromandibular dystonia	100 (temporalis & masseter)	2 weeks	27.1	(0/0)	(1.4)
4 (female) 49 years Torticollis	302.5 (SCM & trapezius)	3 weeks	54.2	(7/0)	(1.3)
5 (male) 62 years Painful dystonia of parkinsonism	245	6 weeks	65.2	(8/2)	(1.6)
6 (male) 28 years Torticollis	570 810	6 months 2 weeks	27.9 70.4	(0/0) (8/6)	(1.3) (1.6)

* Muscle: Extensor digitorum communis; 20 fibers studied.

^a (SCM) sternocleidomastoid.

mean consecutive difference (MCD), obtained by measuring jitter for 20 fiber pairs and comparing to normals (normal MCD < 34 μ sec). The number of fibers with absolutely increased jitter (>55 μ sec) and the number of blocked fibers were noted. Fiber density measurements were obtained by counting the number of fibers from one motor unit (i.e., time locked) within the uptake area of the electrode from 20 different sites and expressed as mean fiber density. Laboratory controls for this age range are 1.57 ± 0.17 . When possible, the results were compared to pre-injection control values.

Electrophysiologic studies were performed 2 to 6 weeks after injection in most patients. Patient 1 was studied serially: pre-injection, 2 weeks after receiving 285 U, 4 months and 9 months after receiving 450 U. Patient 6 was studied 7 months after receiving 570 U and 4 weeks after an additional 240 U were given.

All patients were evaluated for serum antibodies to BOTOX with serial determinations using an *in vivo* mouse assay (Dr. Chas Hathaway, Center for Disease Control, Atlanta).

RESULTS

No patient developed clinically evident weakness and routine nerve conduction, and repetitive stimulation studies were normal. The overall results of single fiber studies in muscles distant from the injection site are given in Table 1. Patient 1 was studied serially and found to have normal neuromuscular transmission in the EDC as measured by SFEMG prior to BOTOX injection. Injections into the trapezius and sternocleidomastoid (SCM) muscles for torticollis occurred until a dose of 285 U was administered. Two weeks later, SFEMG in the EDC was abnormal (Fig. 1). After a total dose of 450 U was given, injections were

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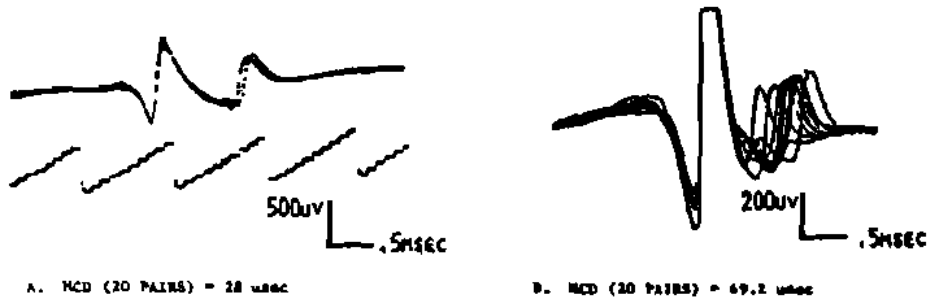


FIG. 1. Sample single fiber electromyography (SFEMG) tracings before (A) and 2 weeks after (B) receiving 285 U of botulinum toxin (BOTOX) injected into neck muscles for torticollis (Patient 1; Muscle: extensor digitorum communis). (Ref. 10.)

stopped. Repeat SFEMG studies revealed increased jitter which was inversely related to firing rate at 4 months and 9 months after receiving her last injection (Fig. 2). Another patient (No. 6) received a total dose of 570 U but none thereafter for 6 months. SFEMG at that time was normal, but 2 weeks after an additional series totaling 240 U was given, jitter was found to be markedly abnormal with blocking in six of the 20 pairs studied. Only one other patient (No. 5) exhibited blocking.

All patients receiving BOTOX in cumulative doses greater than 245 U were found to have excess jitter when studied soon after injection (2-6 weeks). Patient 2 received the second largest cumulative dose of BOTOX in our series yet had the smallest increase in jitter. This patient was found to have antibodies to BOTOX in her serum. She was the only person in our series with detectable antibodies to BOTOX.

Fiber density was increased in two of three patients who received the largest cumulative dose. In all other patients, fiber density was normal.

DISCUSSION

Using SFEMG techniques, abnormalities in neuromuscular transmission in muscles distant to those injected with BOTOX are

present. An inverse relationship between firing rate and jitter suggests that the basis for the jitter is presynaptic (11). These findings therefore support previous findings that locally injected BOTOX spreads to and affects neuromuscular transmission in distant muscles (9,10). The mechanism of spread is unknown but presumed to be vascular.

The abnormalities induced by BOTOX may be long lasting. Patient 1 was found to have normal jitter before injections began. After 285 U was injected into neck muscles for torticollis, jitter became abnormal in the EDC. A total of 485 U was administered. Jitter remained abnormal 4 months and 9 months after cessation of injections. Persistent abnormalities after sublethal injections of BOTOX have been found in mice (13). Pathological examination of injected muscles revealed persistent muscle fiber atrophy and excessive nerve sprouting 9 months after injection (13). Our findings therefore suggest that a similar process occurs in muscles distant to the BOTOX injection in humans. Others, however, have found that jitter in distant muscles requires about 3 months to resolve. The exact length of time required before these abnormalities disappear is therefore unresolved at present.

An increase in fiber density was observed

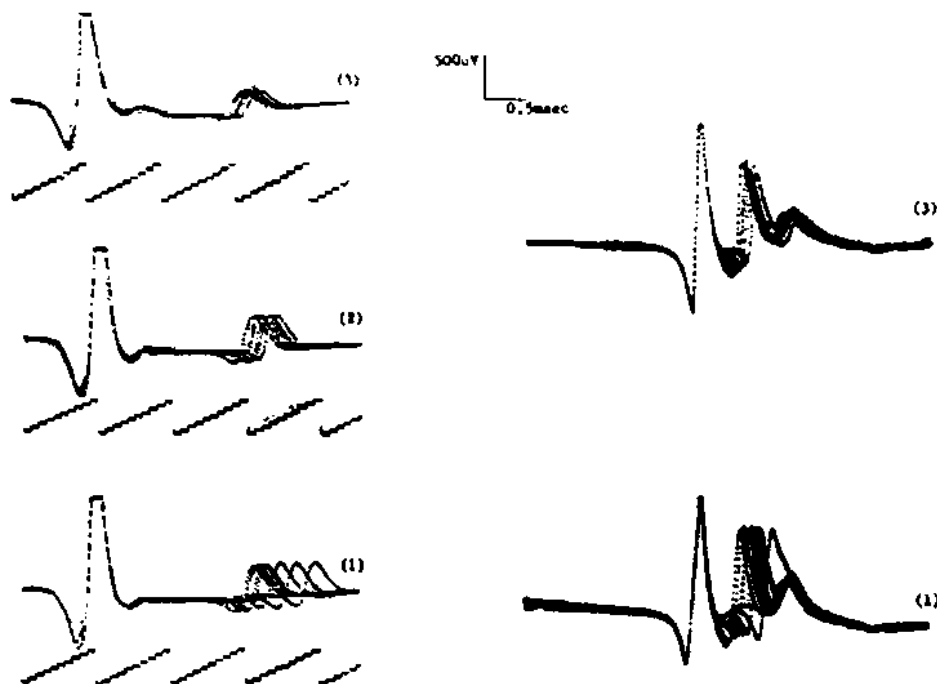


FIG. 2. Persistent effects on neuromuscular transmission. Sample single fiber electromyography (SFEMG) tracings 4 months (left) and 9 months (right) after botulinum toxin (BOTOX) injections totaling 450 U were stopped. In both, jitter is maximal at slow activation rates (1) and improves as activation increases to moderate (2) and fast rates (3). (Patient 1; Muscle extensor digitorum communis; Inset gives calibration for all). (Modified from ref. 10.)

in two of three patients who received the largest dose of BOTOX. Fiber density has been found to be closely correlated with methods used to estimate reinnervation, e.g., terminal innervation ratios (14). Thus, increased fiber density after BOTOX injection supports the observation that nerve sprouting is enhanced by substances which impair acetylcholine release, e.g., BOTOX (15). It also supports the finding in mice that excessive nerve sprouting occurs after sublethal injections of BOTOX in mice (13).

In the patient who received the highest dose of BOTOX, increased fiber density and persistent effects on jitter were not encountered. Jitter was, however, markedly

increased with six of 20 pairs blocked 2 weeks after injections were restarted. Why this patient did not manifest persistent changes in fiber density and jitter is not clear at present. One obvious factor separating this patient from others is age. Patient 6 is the youngest person in our series. Age has been found to be an important factor in determining normalcy in motor unit potential duration and fiber density (12,16) presumably because of motor unit rearrangement during aging. How this affects the response of the neuromuscular junction to BOTOX remains to be elucidated.

Jitter was only minimally increased in Patient 2 who received large doses of BOTOX.

Despite receiving the second largest dose of BOTOX, she was found to have the least abnormal jitter. This patient was found to have an antibody to BOTOX detected in her serum. It is possible that the antibody interfered with BOTOX's action at the neuromuscular junction.

No clinically significant weakness has been observed in our series. The abnormalities detected are, however, extremely important to be aware of for clinical reasons. Patients with already impaired neuromuscular transmission albeit subclinical may be supersensitive to the effects of other drugs which may further interfere with neuromuscular transmission, e.g., certain antibiotics and anesthetics (17).

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