OPHTHALMOLOGY • OCTOBER 1980 • VOLUME 87 • NUMBER 10

Botulinum Toxin Injection into Extraocular Muscles as an Alternative to Strabismus Surgery

ALAN B. SCOTT, MD

Abstract: Sixty-seven injections of botulinum A toxin were given to patients for correction of strabismus. No systemic complications of any kind have occurred. The maximum time of paralysis occurs four to five days following the injection, and then gradually diminishes, depending on the dose. The maximum correction of strabismus has been 40 prism diopters. The maximum follow-up following injection is six months. Injection of botulinum A toxin into extraocular muscle to weaken the muscle appears to be a practical adjunct or alternative to surgical correction. [Key words: acetylcholine release, botulinum toxin, extraocular muscles, strabismus surgery.] Ophthalmology 87:1044–1049, 1980

We report our experience with the injection of botulinum A toxin into individual extraocular muscles as a technique to alter eye alignment. The rationale for this treatment is to create temporary paralysis of sufficient depth and duration that the injected muscles become slightly atrophied and stretched; at the same time, the antagonist muscle shortens (so-called "contracture") taking up the slack created by agonist paralysis. We suppose this is what happens to create the concomitant esotropia sometimes seen after clinical human sixth nerve paralysis. Also in animal studies, after several weeks of paralysis, even though innervation returned to the injected muscle, and motion to the eye, alignment was altered and stayed so for two years.[1]

The release of acetylcholine from the nerve terminal requires an alteration in calcium ion concentration. Botulinum toxin acts to interfere with calcium metabolism in the nerve terminal. This effectively blocks release of acetylcholine, functionally denervating the muscle fiber for several weeks.[2] During this time, the myoneural junction and the muscle fibers undergo definite changes seen by electronmicroscopy.[3] Afterwards, the muscle regains its function. Even survivors of general botulinum intoxication with total paralysis typically return to normal skeletal muscle function.

From the Smith-Kettlewell Institute of Visual Sciences, San Francisco.

Presented at the Eighty-Fourth Annual Meeting of the American Academy of Ophthalmology, San Francisco, November 5–9, 1979.

Supported by grants 5P30 EY 01186 and 5R01 EY 02106 from the National Institutes of Health, and by the Smith-Kettlewell Eye Research Foundation.

Reprint requests to Alan B. Scott, MD, Smith-Kettlewell Institute of Visual Sciences, San Francisco, CA 94115.

MATERIALS AND METHODS

Purified botulinum A toxin is reduced into ampoules containing 0.05 μg (116 mouse LD/50

0161-6420/80/0100/1044/$00.80

Table 1. Definition of Toxin Effects

	Mild	Moderate	Marked	Extended
Alignment in primary position (change in Δ)	to 10Δ	to 20Δ	to 30Δ	Overcorrection beyond 60 days
Rotational amplitude (reduction of baseline amplitude)	−1 (0−20%)	−2, −3 (20−50%)	−3, −4 (50−100%)	Other muscles involved over 7 days
Velocity (Saccades into field of muscle) (% reduction)	to 20%	20−50%	50%	Decrease in ductions other than into full
Isometric Force (from opposite gaze into field of muscle) (reduction in %)	to 20%	20−50%	50−100%	Reduction other muscles over 7 days
Duration of Effects	to 7 days	to 30 days	to 60 days	Not applicable

units), freeze-dried, and the ampoules sealed and stored in a freezer. Individual ampoules are removed, diluted to the appropriate concentration, and injected in a volume of 0.1 ml using an electromyographic (EMG) needle. The starting dose is 6.25×10^{-5} or 3.12×10^{-4} micrograms, and this is repeated or increased according to the response (Table 1). From the tip of the EMG needle we record the muscle activity to determine if the injection is going into the muscle. The needle is inserted into the extraocular muscle region, the eye then turns into the field of action of that muscle to activate the motor units, and then the needle is advanced until it is in the area of the neuromuscular junction (about 2.5 cm posterior to the insertion) and the EMG response indicates it to be within the muscle itself. After dozens of electromyographic needle insertions, we find extraocular muscles still elusive, and believe it would be difficult to inject reliably without electromyographic guidance.

CASE REPORTS

Case 3. A 26-year-old man has esotropia from bilateral sixth nerve palsy together with lateral gaze palsy and optic nerve injury as a result of brain tumor in infancy. There have been four operations on the left eye for lateral rectus palsy, and this is the fixing eye. It has vision of 20/50 because of nystagmus and optic nerve injury. The right eye is 40 prism diopters esotropic, and has light perception from optic nerve injury (Fig 1).

Case 6. A 24-year-old woman has 20/20 vision in the right eye. The left eye has had three retinal detachment procedures because of sickle cell disease and is blind. There are 40 to 50 prism diopters of left exotropia (Fig 2).

Case 7. A 24-year-old woman has had three procedures for exotropia. During one of the procedures, the right medial rectus muscle

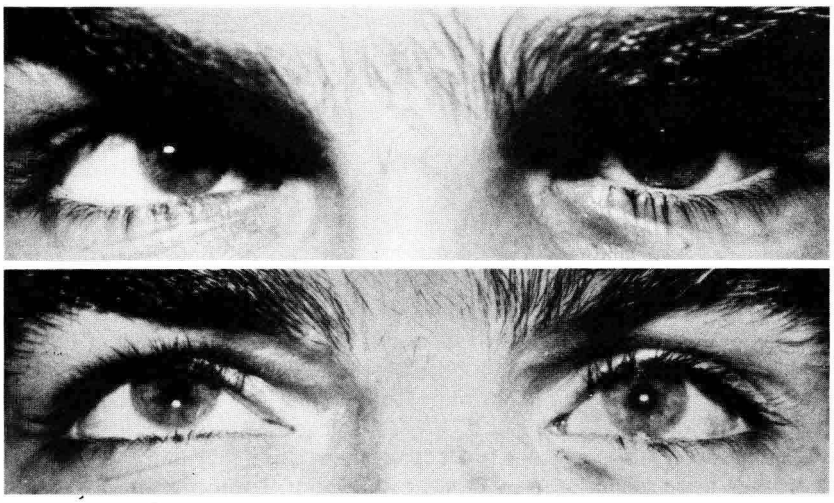
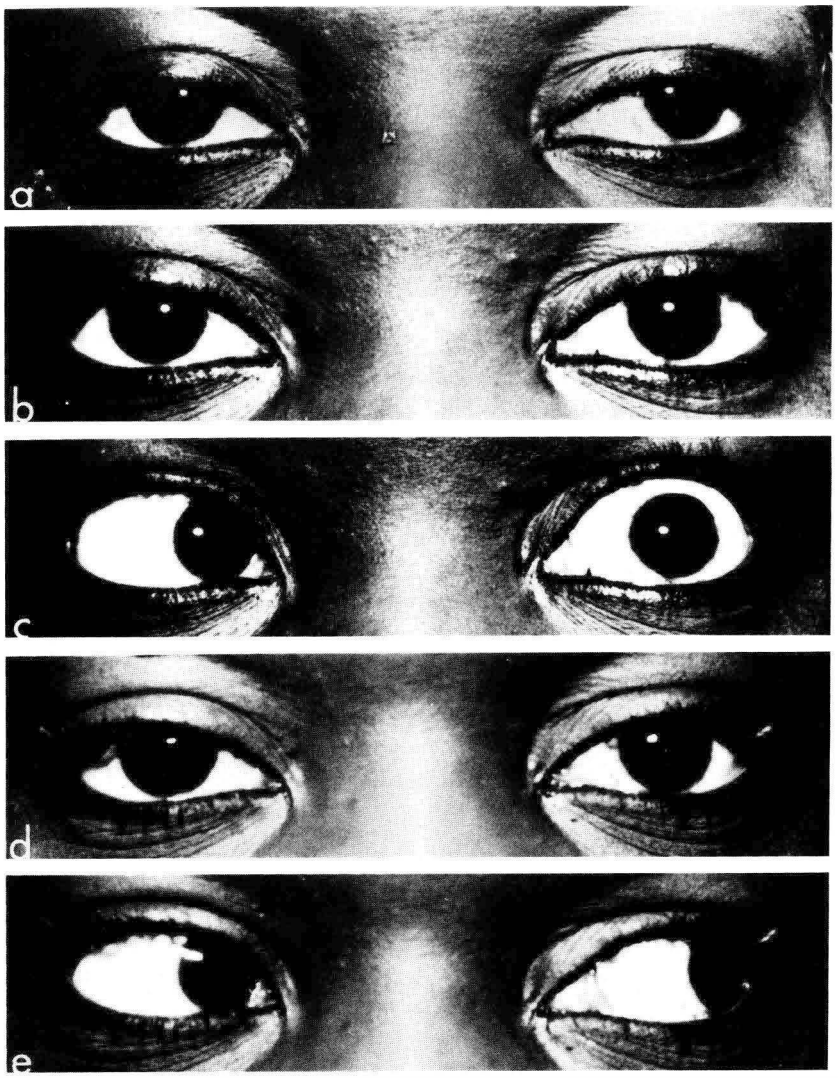


Fig 1. Case 3. *Top*, Prior to treatment. *Bottom*, 144 days after a dose of botulinum A toxin 3.12×10^{-4} micrograms. (This is 1.3 times a mouse LD-50 unit of toxin.)



Figs 2a–e. Case 6. (a) Prior to injection. (b) Two days following 1.56×10^{-3} micrograms of botulinum A toxin, primary position gaze. (c) Left gaze. Note the absence of abduction, due to complete paralysis of the lateral rectus. At this time, force tests show not more than 5–10 grams of lateral rectus force compared with the normal 80–90 grams for this patient. (d) Straight-ahead gaze three months following injection, primary position. Notice reduction of exotropia, but still some slight residual exotropia exists. (e) Note return of full abduction function.

slipped and was replaced. At the conclusion of this, she had a residual 12-prism-diopter right exotropia (Fig 3).

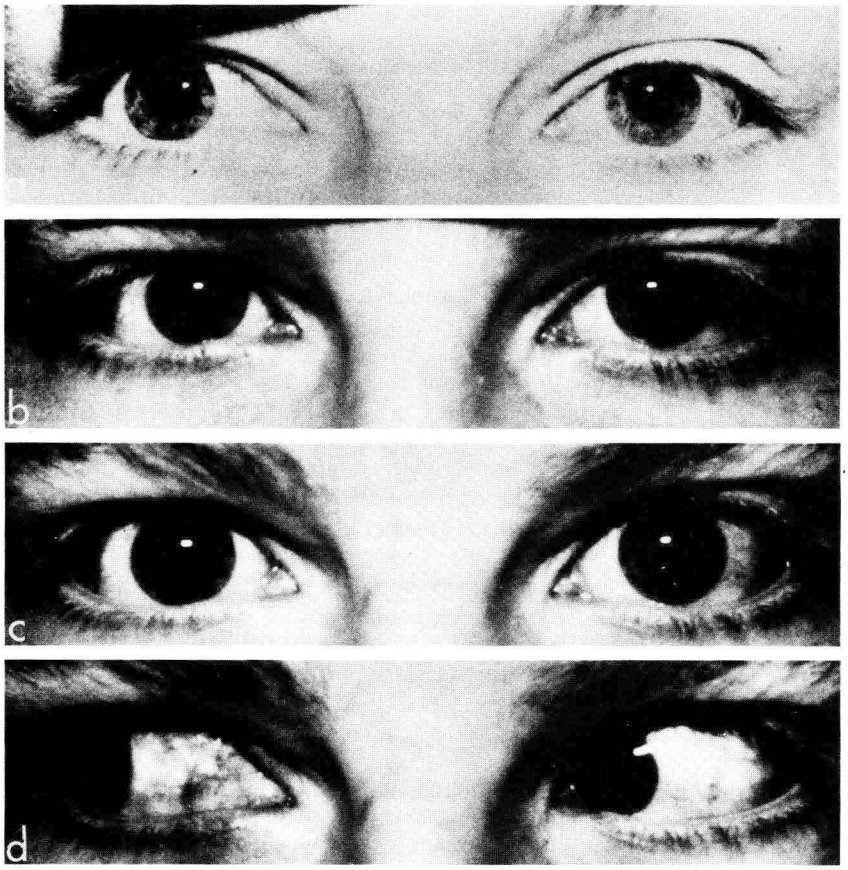
Case 17. A 59-year-old woman suffered head injury with bilateral total sixth nerve paralysis, confirmed two and a half months later by EMG and active force studies. Passive abduction was mildly and equally limited bilaterally. She had been alternatively patching her eyes. By the flip of a coin, the left eye was chosen for injection, done with 0.15 unit (8-30-79); 0.73 unit (9-11-79); and 3.6 unit (9-25-79). She continued to patch alternately, although she preferred using the straight, (injected) left eye (Fig 4).

RESULTS

As of this writing we have injected 67 doses of toxin into 19 patients. There have been no systemic effects of any kind. There has been no involvement of the pupil, influence on visual acuity, or change in retinal appearance. The paralytic effect on the injected muscle, and the effect on the strabismus, has been tightly correlated with the dose injected (Table 2). The dose is expressed in micrograms, or in multiples of the average LD/50 for mice (4.3×10^{-4} micrograms).

In case 10, injection of 6.25×10^{-5} micrograms into the inferior rectus for a vertical strabismus was effective without influence on the nearby inferior oblique; in case 9, injection of 1.56×10^{-3} micrograms in the *levator palpebrae superioris* for lid retraction was effective without involvement of the underlying superior rectus. There was slight involvement of adjacent extraocular muscles on day two, but not thereafter, in the highest dose, 7.8×10^{-3} micrograms. At the 6.25×10^{-5} microgram dose, all injections required retreatment, or treatment was inadequate. At the 3.12×10^{-4} microgram dose, four

Note:
0.15 unit - 6.25×10^{-5} µg
0.73 unit = 3.12×10^{-4} µg
3.6 unit = 1.56×10^{-3} µg



Figs 3a–d. Case 7. (a) Prior to injection. (b) 84 days following injection of the right lateral rectus muscle with 3.12×10^{-4} micrograms of botulinum A toxin. Approximately 10 prism diopters of esotropia remain. (c) 156 days following injection. The eye is straight. (d) 156 days following injection. There is full return of abduction.

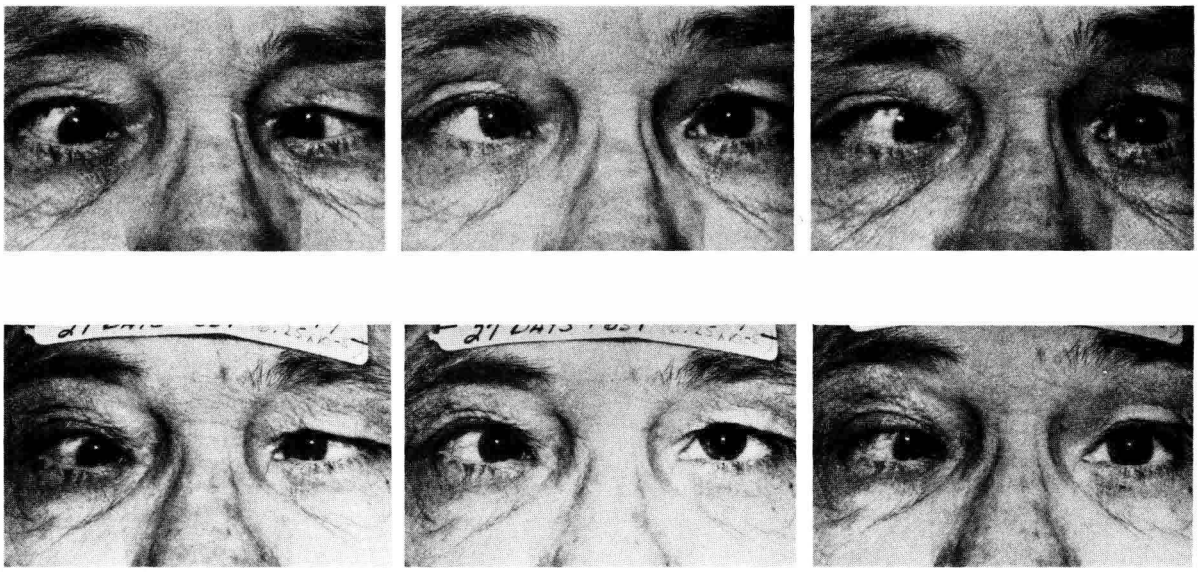


Fig 4. Case 17. Bilateral lateral rectus palsy. *Top*, Preinjection (right gaze, primary position, left gaze). *Bottom*, postinjection (right gaze, primary position, left gaze).

Table 2. Results of Injections*

Patient	Age (years)	Condition	1×10^{-7} μg	5×10^{-7} μg	2.5×10^{-6} μg	1.25×10^{-5} μg	6.25×10^{-5} μg	3.12×10^{-4} μg	1.56×10^{-3} μg	7.8×10^{-3} μg
1	26	20 LXT	None	None						
2	75	12 RET	None	None						
3	26	35 RET Sixth nerve paralysis	None	None	None	None	Mild	Moderate	Marked	
4	30	20 LXT		None	None	None	Mild	Moderate Moderate	Marked	
5	43	30 LXT		None	None	None	Mild	Moderate	Marked	Marked
6	24	45 LXT			None	None	Mild	Moderate	Marked	
7	24	16 RXT			None	None	Mild	Moderate		
8	41	40 LXT				None				
9	70	Lid Retraction					Mild	Moderate	Moderate	
10	27	6 LHT				None	Mild			
11	38	20 LET				None	Mild	Moderate Moderate Marked		
12	43	16 RET						Mild Moderate†		
13	48	25 RET						Marked		
14	33	40 LXT								
15	39	2 EP					Mild† Mild†	Moderate		
16	33	6 RXT					Mild	Moderate		
17	59	60 ET Bilateral Total Sixth nerve paralysis					Moderate	Moderate		
18	19	25 RXT						Moderate		

* The effect is graded according to Table 1. The toxin lot was number 10-14-74. The average mouse LD-50 was 4.36×10^{-4} micrograms. Two injections not listed were external to the muscle rather than into it—no effect resulted, even though the doses were at effective levels (0.145 units and 0.73 units) and LD-50 assay showed the vial contents as potent. Also not included are six injections done 4-27-79 that had almost no effect. The content of the vial was shown by assay to be of low potency (probably an improperly sealed vial allowed oxygen to contact the freeze-dried toxin).

† Three of the injections were simultaneous injections of both medial rectus muscles.

out of ten injections were adequate, at 1.56×10^{-3} microgram dose, two out of four injections were adequate.

DISCUSSION

For our purposes, botulinum toxin has the following appropriate characteristics.

1. No known effects apart from muscle paralysis.
2. No antigenic effects in the small doses that we use (although it is quite a good antigen in large doses). We have injected one patient eight times with increasing doses, another nine times. In no instance was a reduction in effect (or an enhancement) found that was attributable to prior injection.
3. Slow diffusion out of the injected muscle into adjacent muscles, probably because it is a large molecule. In addition, the high blood flow around the periphery of extraocular muscles probably acts to wash away toxin diffusing out of the injected muscles or into adjacent ones.
4. The toxin will act for several weeks.

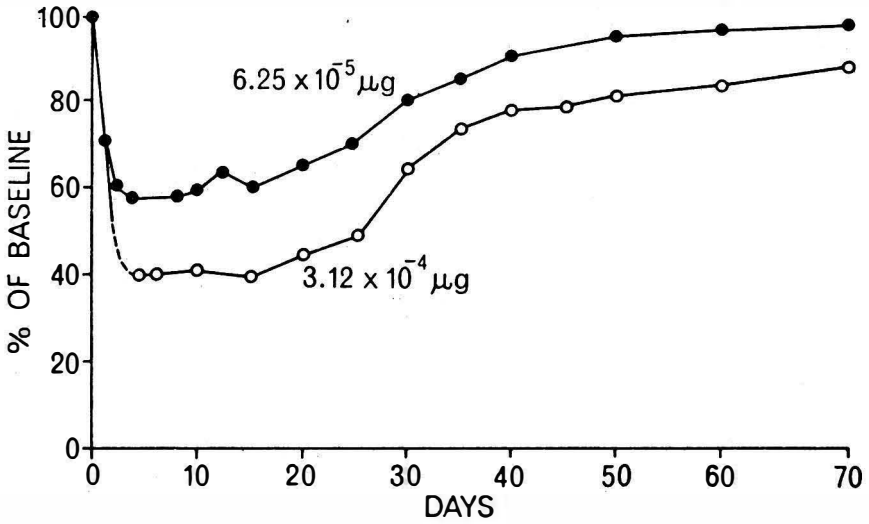


Fig 5. Rotation amplitude change following toxin injection.

5. The paralytic intensity is tightly correlated with the dose injected. From these initial data, we expect the adult therapeutic range for strabismus to be between 2×10^{-4} and 8×10^{-3} micrograms.

6. When injected into extraocular muscles in totally paralyzing doses, it has no systemic effect of any kind.

From this experience, we estimate that the alignment change is about 5° to 10° per month of total paralysis. This is quite variable, and reinjection is used to titrate the effect. There is a tendency following injection of the eye to return to the original strabismic position as the muscle paralysis diminishes, and even thereafter (Fig 5). This is more evident in long-standing, large deviations in which muscle contracture and supporting tissues have adapted to the constant angle and return the eye to the original position. Nonetheless, persistence for months of the correction obtained by toxin injection in humans, the persistence of years of strabismus created in animals by toxin injection, and the indefinite persistence of comitant strabismus following some recovered muscle paralysis in humans, provide a reasonable basis for hope that this will become a significant addition to the existing approaches for strabismus correction. Effects on lid retraction, on blepharospasm, and on the motor and sensory aspects of childhood strabismus are being explored.

ACKNOWLEDGMENTS

The author thanks Dr. Edward Schantz for the toxin supply and his good advice; the physicians who referred patients: James Carlyle, William Casteen, James Dowling, Scott Foster, Wayne Fung, Arthur Jampolsky, Arthur Rosenbaum, and Tamara Suslov; and the patient-volunteers.

REFERENCES

1. Scott AB, Rosenbaum A, Collins CC. Pharmacologic weakening of extraocular muscles. Invest Ophthalmol 1973; 12:924–7.
2. Kelly RB, Deutsch JW, Carlson SS, Wagner JA. Biochemistry of neurotransmitter release. Ann Rev Neurosci 1979; 2:399–446.
3. Mukuno K. Personal communication.