

TREATING STRABISMUS BY INJECTING THE AGONIST MUSCLE WITH BUPIVACAINE AND THE ANTAGONIST WITH BOTULINUM TOXIN

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ABSTRACT

Purpose: We report the results of injection of bupivacaine (BUP) and botulinum toxin (BT) into agonist and antagonist muscles, respectively, to treat horizontal strabismus.

Methods: We treated both horizontal muscles of 7 patients with comitant horizontal strabismus, 2 patients with partial lateral rectus (LR) paralysis, and one elderly myopic patient with acquired esotropia, injecting the agonist muscle with BUP in concentrations of 0.75% to 3.0% and volumes of 3.0 to 5.0 mL, and the antagonist with BT in about half the usual therapeutic dose to prevent it from stretching the BUP-treated muscle during its regeneration following BUP myotoxicity. We reinjected BT in one patient who had an inadequate response from the initial BT dose.

Results: The 7 comitant patients were corrected (on average) 19.7 prism diopters (Δ), from 28.3 Δ to 8.6 Δ , at 193 days after injection. Muscle volume increase after BUP injection was 5.8% at 158 days. One LR palsy patient without LR atrophy was changed 55 Δ ; the other, with LR atrophy, was corrected 4 Δ . Two patients had transient vertical deviations from the BT injection. The myopic patient with esotropia was unchanged.

Conclusions: Injections of BUP and BT corrected 7 patients with comitant horizontal strabismus an average of 19.7 Δ , about double the correction reported from BUP injection alone. BUP-injected muscles increased size by 5.8%. Of 2 patients with LR weakness, one without LR atrophy was changed by 55 Δ , but another with LR atrophy was corrected only 4 Δ .

Trans Am Ophthalmol Soc 2009;107:104-111

INTRODUCTION

In addition to having an anesthetic effect, injection of the aminoamide anesthetic bupivacaine (BUP) into the fast muscle fibers, such as those of the extraocular muscles, damages the muscle fibers within minutes, probably by allowing excess Ca^{2+} ions to enter the cytoplasm from the sarcoplasmic reticulum. This results in separation of the muscle fiber sarcomeres at the Z band.¹ The damaged fibers and myocytes are then removed by macrophages, leaving the cell membranes, nerves, and blood vessels intact.² Within a few hours of exposure to BUP, autocrine growth factor molecules such as insulin-like growth factor 1 and mechano growth factor are released from the damaged area. These molecules activate satellite cells that proliferate over the next 10 to 20 days to form new muscle fibers and myocytes to replace the damaged muscle.^{3,4} In extraocular muscles, proliferation continues on to build a muscle having greater contractile strength, intrinsic elastic stiffness, and size than before, with consequent effects on eye alignment.⁵ These biomechanical alterations are not achievable with strabismus surgery. When this muscle response occurs inadvertently after retrobulbar anesthetic injection for eye surgery, misalignment or strabismus is produced.^{6,7} We are successfully harnessing this muscle response to improve eye alignment and correct strabismus.^{8,9}

We believe that yet another property of extraocular muscles can be manipulated with BUP: the BUP-injected muscle will regenerate to the length at which it is held during the process of regeneration. In the present study, to further increase strabismus correction, we sought to shorten the agonist muscle during regeneration by paralyzing its antagonist with a small dose of botulinum toxin (BT). That induces the BUP-injected muscle to regenerate to a shorter length than if the antagonist were allowed to stretch it out during the time of regeneration.

METHODS

Under a protocol approved by the Smith-Kettlewell Institutional Review Board, we treated 10 patients with injections of both BUP and BT. Seven of these patients had large comitant horizontal deviations or were previously unresponsive to injection of a single drug, either BUP or BT. We also injected the muscles of 2 patients with lateral rectus (LR) paresis in a similar fashion and those of one patient with esotropia from high myopia and a displaced LR muscle who asked to be treated in an attempt to avoid surgery. The averages reported are for the 7 comitant patients and do not include the data from these 3 patients. Using needles insulated except at their tips to record the EMG signal and thus determine the position of the needle tip, we injected BUP in concentrations of 0.75% to 3.0% and volumes of 3.0 to 5.0 mL into the medial rectus in exotropia or the LR in esotropia. Earlier magnetic resonance imaging (MRI) studies showed that BUP diffuses poorly along the muscle,⁶ so we attempted to fill the whole muscle by injecting most of the BUP in the posterior third and the remainder in the middle of the muscle, allowing some BUP to move anteriorly along the needle track. Simultaneously, we injected the antagonist muscle with BT, using small doses to create mild paresis lasting under a month. Patient 6 had little paralytic effect from the initial BT injection and received a second injection. Examination by standard clinical methods and by MR imaging of the eye muscles was done before injection, immediately afterwards to determine the site of injection, and at intervals thereafter to determine eye alignment, comitance, and eye muscle size changes, as described earlier.⁵

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Bold type indicates AOS member.

RESULTS

The Table summarizes the patient details and the results. On average, the comitant patients were corrected 19.7Δ at 193 days after injection. Figures 1 through 3 show the data for eye muscle sizes and eye alignment after injection. Figure 4 shows the stages of events after injection for patient 3. In patient 8, whose LR had 30 gm of active force before injection (normal, 70 gm on the fellow LR) and whose LR was not atrophic, the treatment altered alignment by 55Δ, resulting in an overcorrection requiring surgical recession of the LR at 4 months after injection. At that surgery, the LR active force measured 35 gm and showed stiffness of passive rotation to adduction about twice that of the LR on the normal eye. This small increase in active force is well below that required to change alignment by 45Δ and implies that a reduction in length or increased stiffness of the LR, or both, were responsible for much of the alignment change. Treatment was ineffective for patient 9, who had a severely atrophic LR muscle, and for patient 10, who had high myopia, esotropia, and a displaced LR. Two patients developed a transient hypertropia from medial rectus injection of BT, and two patients developed significant swelling and discomfort for a few days after BUP injections that had a strong weakening effect on the injected muscle.

TABLE. SUMMARY OF PATIENT DATA*							
PATIENT NO.	BUP		BT	DEVIATION			
	CONC (%)	VOL (ML)	UNITS	FOLLOW-UP (days)	INITIAL DEV (Δ)	FINAL DEV (Δ)	CHANGE (Δ)
1	0.75	4.5	1	146	18	10	8
2	3.0	4	1.5	88	14	2	12
3	3.0	3	3	355	16	0	16
4	0.75	4	2	286	20	0	20
5	0.75	4	5	247	40	18	22
6	3.0	4.5	7.5	160	40	0	40
7	0.75	4.5	4	70	50	30	20
8	1.5	3.0	2.5	56	10	-45	55
9	0.75	5	1	44	10	6	4
10	0.75	4.5	3	110	30	30	0

BT, botulinum toxin; BUP, bupivacaine.

*Patients 1 through 7 had comitant horizontal strabismus. Patients 8 and 9 had lateral rectus paresis, and patient 10 had high myopia and a displaced lateral rectus muscle.

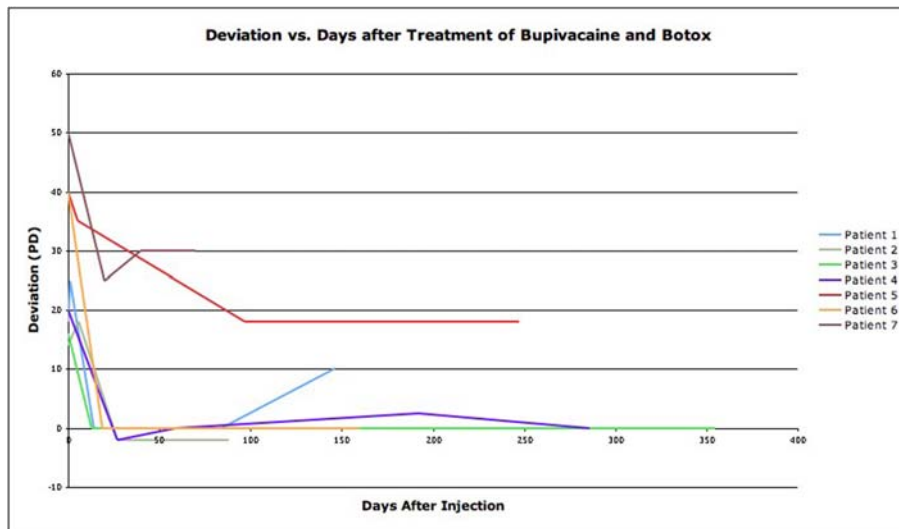


FIGURE 1

Changes in deviation over time in 7 patients injected with bupivacaine and botulinum toxin. PD, prism diopters.

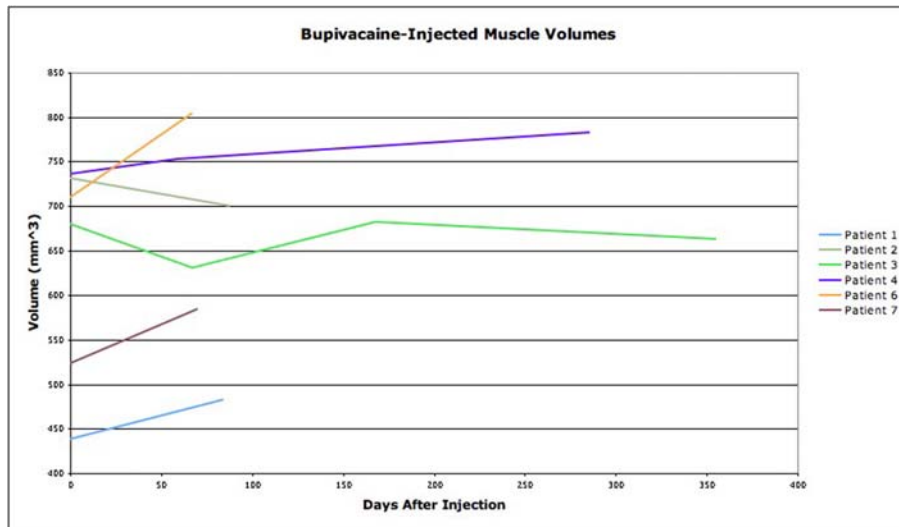


FIGURE 2

Changes in the size of the muscles injected with bupivacaine.

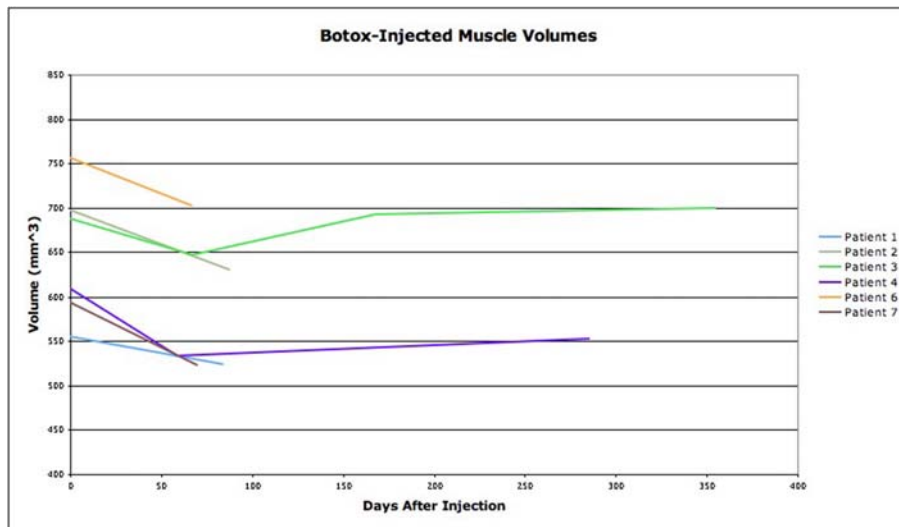


FIGURE 3

Changes in the size of the muscles injected with botulinum toxin.



FIGURE 4

Case 3. Top row, Preinjection, 16 Δ exotropia. Second row, 30 minutes after injection, with paralysis of the left medial rectus (LMR). Third row, 13 days after injection, 16 Δ exotropia, with paralysis of both the LMR and left lateral rectus. Bottom row, 355 days after injection, eyes are straight.

CASE REPORTS

Case 2

A 35-year-old man had diplopia and difficulty with binocular fusion from 14Δ residual esotropia following surgery for 30Δ esotropia. A first injection of BUP into the right lateral rectus (RLR) markedly weakened abduction and increased the esotropia to 25Δ. On day 76, abduction had fully recovered and the esotropia had returned to 14Δ in all gaze directions. Injection of BUP into the RLR was done again, adding 1.5 units of BT to the right medial rectus (RMR) (see Table). Twenty-one days after this second injection, the eye was straight. Both abduction and adduction were moderately reduced in amplitude, representing moderate paresis of both injected muscles. Thereafter, motility was gradually regained, and on day 88 the eye was 2Δ esotropic in the primary position. MRI scan showed the RLR muscle substantially enlarged in the posterior area. In gaze to the right, the strong RLR retracts the right eye 1 to 2 mm and causes 6Δ exotropia (Figures 5 and 6).



FIGURE 5

Case 2. Eye rotations 88 days after injection. Bottom photo of patient during right gaze shows retraction and exotropia.

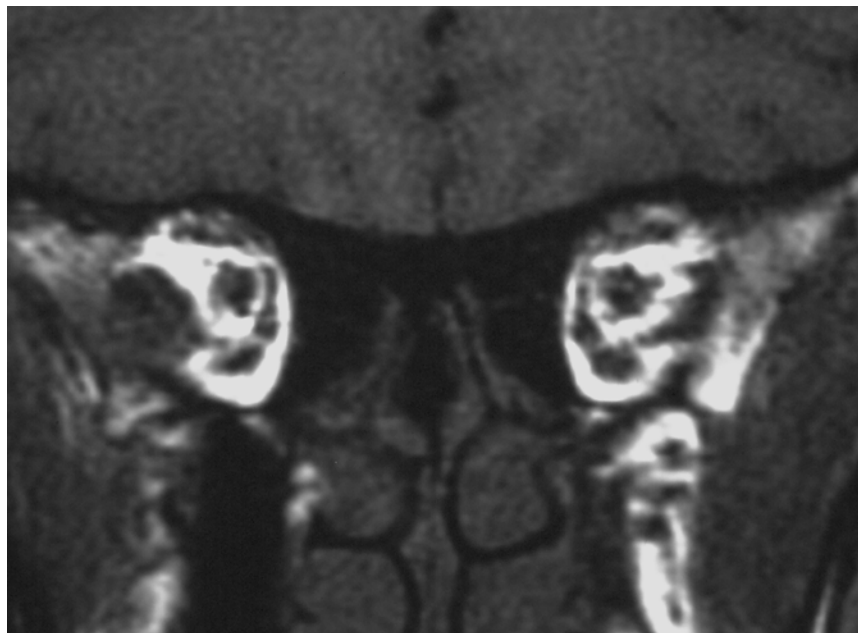


FIGURE 6

Case 2. Magnetic resonance coronal plane image 88 days after injection, showing local enlargement of right lateral rectus injected with bupivacaine..

Case 6

A 26-year-old man had been operated on for 90 Δ exotropia by 12-mm recession of each LR and 8-mm resection of the left medial rectus (LMR). A residual 40 Δ exotropia remained. The RMR was injected with BUP and the RLR with BT. Five days later adduction was fully paralyzed by the BUP injection and the eye was even further exotropic. The medial conjunctiva was swollen and red for several days. The RLR was only minimally paralyzed by the BT dose used; it was injected with additional BT on day 5, paralyzing the muscle and reducing the exotropia. On day 29, both RLR and RMR were regaining function and the eye was aligned. Full rotations and straight alignment were present on day 160, when the patient was last seen. The RMR is clearly larger than the LMR. Mild swelling of the right eye remains (Figure 7).



FIGURE 7

Case 6. Top, Before injection, the left eye is still healing from prior surgery. Bottom, 160 days after injection, the eyes are straight.

Case 8

A 62-year-old woman had a pontine hemorrhage in 1994, resulting in a partial RLR paresis. Three horizontal muscle procedures had been done, leaving her with 14 Δ esotropia, increasing to 25 Δ in right gaze due to abduction weakness. She declined surgical intervention on the left eye. Measured isometric RLR active force was 30 gm, but the RLR was not atrophic on MRI studies. Injection of the RLR with 3.0 mL of 1.5% BUP was done. Seventy days after this injection, the esotropia had improved only to 10 Δ esotropia, and eye rotations had returned to the preinjection level. A second injection of 3.0 mL of 1.5% BUP was then done to the RLR with the addition of 2.5 units of BT to the RMR. On day after the second injection, the eye was 10 Δ exotropic and there was -3 abduction and -3 adduction, representing moderate paresis of both injected muscles. On day 56, the eye had moved to a position of 45 Δ exotropia, where it remained until postinjection day 113. Adduction was limited, but adduction saccades appeared sharp and of normal speed. The patient asked then that the eye be straightened, and a 6.5-mm recession of the RLR was done. At that surgery, the measured RLR isometric active force was 35 gm, only a slight increase above the initial 30-gm force. The RLR stiffness by traction test, however, was estimated to be twice that of the normal left lateral rectus. The RMR isometric active force was 55 gm, within normal limits. The eye measured 5 Δ exophoria on postoperative day 7, with a further reduction to zero on postoperative day 138. There is single binocular vision over a useful area.

DISCUSSION

The alignment correction achieved using BUP plus BT was twice what was reported with BUP injection alone.⁶ Since BT alone has been found ineffective in changing eye alignment in the low doses used, we believe that it acted through the mechanism of temporary paresis of the antagonist, preventing stretch of the agonist as the latter was being rebuilt. The average muscle size increase of 5.8% was very similar to the 6.2% we found from use of BUP alone.⁵ The decrease in size of the muscles injected by BT is not unexpected but has not been reported for eye muscles. This must play some part in the alignment change, and both alignment and muscle sizes will be monitored further. Cases 2 and 8 show that eye position during regeneration greatly influences the outcome of BUP injection.

Each case received minimal effect after BUP alone, but much larger effect after injection of both BUP and BT. Case 6 shows that the BT paralysis must be sufficient to disable the antagonist RLR and prevent it from stretching the RMR muscle injected with BUP. While the total BT fully paralyzed the LR, a correction of 40Δ from a single injection of BT alone would be extraordinary, so we credit the enlargement of the medial rectus as the major factor correcting this deviation.

The specific changes induced in these muscles by BUP are unclear. In treatment of strabismus, strengthening, shortening, and stiffening of the muscle would all be beneficial changes. An increase in myofibrils within the muscle cells would increase size, strength, and stiffness. Intercellular deposition of noncontracting molecules has been postulated to account for the increase in size and stiffness without concomitant increase in force production after BUP injection in rat muscles.^{10,11} This would likely apply to case 8, in which a large angular correction and increased stiffness of the BUP-injected LR without much increase in muscle strength, suggesting a role for this mechanism as part of the action of BUP injection. In our earlier reports on injecting BUP alone in horizontal strabismus, the stability of the alignment changes and the persistence of muscle enlargement up to 500 days were striking.^{8,9} Stability seems to be present in these patients, too, although follow-up time is shorter. Orbital inflammation from the muscle damage was the likely cause of the inflammation in case 6. While not a serious or limiting factor in these cases, swelling from injection of multiple muscles or of even one muscle in a compromised orbit with thyroid eye disease might compress the optic nerve.

Case 8 shows that a large correction can be obtained even in a muscle that is partly paralyzed, so long as it is not atrophic. Further, it shows that muscle shortening and stiffening, both desirable in stabilizing strabismus deviations, are major components of the muscle change in addition to muscle strengthening. Patient 9, who had LR paresis with atrophy, received little clinical benefit or change in size of the BUP-injected LR. Perhaps there is a relative absence of satellite cells as a part of the atrophy,¹² or perhaps there is a lack of muscle tissue to be injured and thus produce the signaling autocrine proteins. This leaves open the possibility that signaling molecules like mechano growth factor¹³ given directly, rather than indirectly through the effects of BUP on myofibers, might be useful for these patients. Both clinical and laboratory studies are under way to answer many of these questions.

ACKNOWLEDGMENTS

Funding Support: This study was supported by the Pacific Vision Foundation and by the S. T. Reeves Foundation.

Financial Disclosures: None.

Author Contributions: Design of the study (A.B.S., J.M.M.); Conduct of the study (A.B.S., J.M.M.); Data analysis (A.B.S., J.M.M., K.R.S.); Preparation, review, or approval of the manuscript (A.B.S., J.M.M., K.R.S.).

Conformity With Author Information: This study was approved by and carried out under the supervision of the Institutional Review Board of the Smith-Kettlewell Eye Research Institute.

Other Acknowledgments: Vanitha Sankaranarayanan, MS, provided important help in data analysis. The authors thank the patients for their willing participation in this study. We thank InSight Health Corporation for their cooperation in supporting this study.

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PEER DISCUSSION

Dr. SEAN P. DONAHUE: I consider it an honor to be asked to discuss this paper by Dr. Alan Scott, whose career has been defined by his work investigating the role of botulinum toxin in medicine. While botulinum toxin has not gained much traction as primary treatment for patients with strabismus, this medication has essentially revolutionized the management of many other chronic debilitating disorders of skeletal muscle, specifically some of the dystonias, torticollis, benign essential blepharospasm, and some types of chronic headache, the spasticity associated with cerebral palsy, and even axillary hyperhidrosis and incontinence. And, of course, let's not forget your wrinkles.

Botulinum toxin works by binding to the presynaptic portion of the neuromuscular junction, preventing release of acetylcholine, and inducing a temporary paralysis of muscle function. In patients who have small to moderate angle comitant strabismus and good potential for stereopsis, restoration of fusion can occur following its use, and the changes that occur in vergence fusional amplitudes and muscle dynamics during the temporarily induced paralysis can impart a clinical cure. Patients who have subnormal fusion associated with early onset ocular misalignment tend not to do as well with a single injection.

In 1970, Benoit and Belt recognized that the sodium channel blocker bupivacaine caused muscle cell death, a temporary loss of function, and subsequent regeneration of skeletal muscle.¹ It took fifteen years for Bruce Carlson to begin studies of bupivacaine in extraocular muscle, and an additional decade before most of ophthalmology recognized that this was the mechanism by which the standard retrobulbar injection of bupivacaine prior to cataract surgery occasionally produced a restrictive strabismus.^{2,3}

Recently, Dr. Scott and his colleagues described the intentional injection of bupivacaine into a human rectus muscle to produce a restrictive strabismus and treat ocular misalignment.⁴ The current paper uses botulinum toxin to induce a temporary palsy of the antagonist muscle during which time a muscle injected with bupivacaine becomes fibrotic. Seven patients with comitant strabismus sustained from 10 to 30 prism-diopters of correction. In two patients with incomitant strabismus from sixth nerve palsy, the response appeared to depend upon the presence of active myocytes in the paretic lateral rectus muscle: although the sample size was limited to one patient with, and one without, global lateral rectus atrophies.

What might be the clinical usefulness of such a treatment? For the pediatric patient with a comitant horizontal strabismus, who is treatment-naïve and has reduced potential for binocular vision, the proposed treatment is probably less favorable than standard strabismus surgery, since both procedures require general anesthesia, and surgery has much less variability and more permanence.

On the other hand, adult patients who have incomitant strabismus, residual comitant strabismus after previous surgeries and excellent potential for post-operative binocularity may benefit from a variant of this technique, as it would be safer, and less traumatic than standard surgery. A specific example would be the adult patient with an acquired unilateral third nerve palsy, for whom surgical options are extremely limited, technically difficult, and prone to failure. I look forward to continuing to hear more in the future about the continued evolution of this exciting technique.

ACKNOWLEDGMENTS

Funding/Support: Research to Prevent Blindness

Financial Disclosures: None

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DR. IRENE H. LUDWIG: This is one of the most interesting strabismus papers that I have heard in years with potentially very important usefulness. As someone who specializes in extremely complex strabismus, one of the most difficult problems I encounter is restrictive strabismus that is not in up gaze, but in down gaze or lateral gaze where I need to produce a comitant restriction. In these patients, I find that the final outcome of the procedure is very unpredictable. Does this treatment produce a potentially significant restriction? Are you mainly creating a hypertrophy of the muscle or have you tested the compliance and ability of the muscles to stretch? Are you producing a graded fibrosis response? In certain situations that effect could be very useful.

DR. STEVEN E. FELDON: No conflicts. The most difficult patients I have are the CPEO patients, because it does not matter how much I operate on their muscles or lids, the response is minimal. Would injection into the extraocular muscles or levator muscle perhaps help some of these patients? Of course, if one needs to have normal muscles rather than muscles with mitochondrial disease, perhaps the role would be limited.

DR. ALAN B. SCOTT: I thank Dr. Donahue for his generous comments. Clearly this is something in the works and there is a lot of further study to be done. The long persistence of the effect is very encouraging. The relatively brief turn around time, about three weeks or a month for bupivacaine is much faster than it is for botulinum injection, thus making it a much easier procedure for patients to tolerate. As Dr. Ludwig pointed out, one aspect of this treatment is increasing the stiffness of the muscle, and that is a very

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valuable effect. Not only are the muscle fibers regenerated and increased in size, but there are probably some additional non-contractile proteins which act to hold the muscle and make it stiffer. In the case I showed you, a lateral rectus muscle was made at least twice as stiff. It is entirely possible that you can treat an eye that you wish to move over by creating a leash effect with this stronger and stiffer muscle. Dr. Feldon, I have done one case of CPEO. Unfortunately it did not work. It was in an individual who had marked irregular atrophy through the muscles and bupivacaine does not seem to work well in atrophic muscles. We have to try further in other cases without atrophy.