Effects of Topical Brinzolamide on Infantile Nystagmus Syndrome Waveforms: Eyedrops for Nystagmus

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Background: Recent advances in infantile nystagmus syndrome (INS) surgery have uncovered the therapeutic importance of proprioception. In this report, we test the hypothesis that the topical carbonic anhydrase inhibitor (CAI) brinzolamide (Azopt) has beneficial effects on measures of nystagmus foveation quality in a subject with INS.
Methods: Eye movement data were taken, using a high-speed digital video recording system, before and after 3 days of the application of topical brinzolamide 3 times daily in each eye. Nystagmus waveforms were analyzed by applying the eXpanded Nystagmus Acuity Function (NAFX) at different gaze angles and determining the longest foveation domain (LFD) and compared to previously published data from the same subject after the use of a systemic CAI, contact lenses, and convergence and to other subjects before and after eye muscle surgery for INS.
Results: Topical brinzolamide improved foveation by both a 51.9% increase in the peak value of the NAFX function (from 0.395 to 0.600) and a 50% broadening of the NAFX vs Gaze Angle curve (the LFD increased from 20° to 30°). The improvements in NAFX after topical brinzolamide were equivalent to systemic acetazolamide or eye muscle surgery and were intermediate between those of soft contact lenses or convergence. Topical brinzolamide and contact lenses had equivalent LFD improvements and were less effective than convergence.
Conclusions: In this subject with INS, topical brinzolamide resulted in improved-foveation INS waveforms over a broadened range of gaze angles. Its therapeutic effects were equivalent to systemic CAI. Although a prospective clinical trial is needed to prove efficacy or effectiveness in other subjects, an eyedrops-based therapy for INS may emerge as a viable addition to optical, surgical, behavioral, and systemic drug therapies.

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Infantile nystagmus syndrome (INS) is an ocular motor oscillation with well-defined clinical characteristics and eye movement waveforms (1,2). In some individuals, it is inherited (2), but its pathogenesis remains unknown. Current therapy may damp INS oscillations and result in improved foveation, but the nystagmus persists despite the ocular motor system's best efforts to improve foveation periods (3). Surgical (4–6), optical (7), and pharmaceutical (8–10) therapeutic approaches have been successfully employed to improve INS waveforms and expand the range of gaze angles with higher visual acuity (11,12). We have recently studied the beneficial effects of systemic acetazolamide on INS simulated in a behavioral ocular motor system model, which suggested that the drug may have also had peripheral effects (13). The present report documents the results of applying topical brinzolamide eyedrops to the same INS subject that showed improvements with systemic acetazolamide and provides evidence for the hypothesis that an eyedrops-based therapy for INS is possible.

METHODS

Recording

We used a digital video system (EyeLink II; SR Research, Mississauga, Ontario, Canada) for the eye movement

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recordings. The system had a linear range of ±30° horizontally and ±20° vertically. System sampling frequency was 500 Hz, and gaze position accuracy error was 0.5°–1° on average. The data from this system were digitized at 500 Hz with 16-bit resolution. The EyeLink signal from each eye was calibrated with the other eye behind cover to obtain accurate position information; the foveation periods were used for calibration.

Subject and Protocol

This study was approved by our institutional review board, and written consent was obtained from the subject. The patient was a 68-year-old man with INS. His nystagmus waveforms have been well documented over a period of approximately 50 years, and their characteristics have remained constant and proved to be representative of others with INS. Because subjects have no voluntary control of their INS waveform characteristics (i.e., they cannot change their INS waveforms or improve their foveation qualities), subsequent testing or knowledge of the experiment does not affect the data. Stress can only worsen INS, and our stress-free testing environment (requiring merely looking at light-emitting diodes (LEDs) or laser spots) allows for accurate intra- and intersubject comparisons. Our subject had a convergence ''null'' and normally wore either 7 prism diopters (PD) base-out prisms added to his spectacles (right eye: +3.00 −2.50 × 150° and left eye: +3.50 −2.75 × 20°) or contact lenses with no added prism. Best-corrected distance visual acuities were 20/25 with prisms and 20/40 with contact lenses. For fixation targets, we used small LEDs and reflected laser spots that yield the same ocular motor data with or without refraction. The subject was seated in a chair with a headrest and a chin stabilizer, far enough (>5 feet) from the stimulus screen to prevent convergence effects. At this distance, the target subtended less than 0.1° of visual angle. The room light was turned off during the recording. Each trial tested fixation of horizontal targets from 30° left gaze to 30° right gaze, in 5° steps. Our standard testing paradigm consisted of 2 trials, one in each horizontal direction, with the target remaining at each gaze angle for 5 seconds during both stepping out laterally and returning to primary position. Subtracting the required target acquisition times allowed approximately 2–3 seconds of steady fixation during each interval. eXpanded Nystagmus Acuity Function (NAFX) values (see below) were calculated during steady fixations and averaged. This resulted in a small number of NAFX values at each gaze angle that we have found to be historically close to each other in value. Gathering and analyzing such data are based on real-life acquisition and identification of new targets in the visual field.

The subject was given 1 drop of topical brinzolamide (Azopt) 3 times daily in each eye on days 1–3, after which the eyedrops were discontinued. The subject had eye movement recordings twice on day 1 (1 hour and 5 hours after the first administration of brinzolamide) and once on days 2–5 and 12. Ocular and systemic evaluations were performed during the 17-day study period [intraocular pressure (IOP) was first recorded 5 days prior to administration of brinzolamide] to check for adverse events. For comparisons of therapeutic effectiveness, we retrieved data from a previous study of the effects of systemic acetazolamide on the same subject (14).

Analysis

All the analyses were performed in the MATLAB environment (The MathWorks, Inc, Natick, MA) using OMLAB software (OMtools, downloadable from http://www.omlab.org). Eye position was sampled directly; it was prefiltered using a low-pass filter with a cutoff frequency of 20 Hz to reduce the noise while minimally affecting the foveation periods. The 20-Hz value is 5 times the maximum frequency present in foveation periods (0–2 Hz) and still allows separation of foveating and braking saccades from those periods. Analysis was always done on the fixating eye. Segments with inattention or blinking were discarded.

We analyzed the data using the NAFX (15). The NAFX is a mathematical function containing the following waveform parameters: duration of foveation period, standard deviations of main foveation periods and velocities, and number of cycles in a fixation interval. In the OMtools software, we use the NAFX's graphical user interface for data selection and analysis (details can be obtained from http://www.omlab.org/OMLAB_page/Teaching/Using_NAFX.html) (16). The NAFX provides an objective and repeatable measure of nystagmus foveation quality that accurately predicts the best-corrected visual acuity possible for subjects without afferent visual system defects, regardless of the eye movement recording system, the nystagmus type, and waveforms (15). We averaged the NAFX values obtained at each gaze angle.

The longest foveation domain (LFD) (5,11) is the range of gaze angles in which the subject's NAFX stays above 90% of the NAFX vs Gaze Angle curve's peak value. Thus, the LFD is a measure of the *broadness* of the NAFX vs Gaze Angle curve, i.e., the INS subject's high–foveation quality field.

RESULTS

Subject Data

During fixation of a distant target prior to the administration of topical brinzolamide, the subject's peak NAFX was 0.385 at 2° left gaze and the breadth of the NAFX vs Gaze Angle curve given by the LFD function was 20° (Fig. 1). Also shown for comparison are the data for contact lenses and when converged at 60 PD. During the 3 days of topical brinzolamide, the NAFX peaks were 0.440, 0.553, 0.540, and 0.680, respectively, for days 2, 3, 4, and 5, with LFDs of 46°, 35°, 30°, and 26°, respectively. All treatments (contact lenses, topical brinzolamide, and convergence)

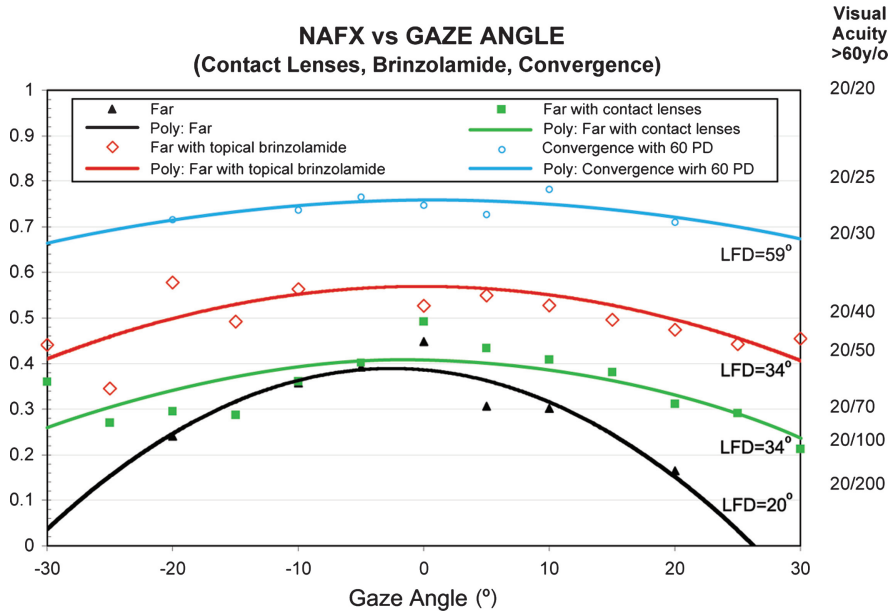

FIG. 1. NAFX vs Gaze Angle plots before administration of topical brinzolamide, with contact lenses, during convergence, and on day 4 with topical brinzolamide. Measured visual acuity values are those determined clinically via a Snellen chart to correlate with NAFX values. Data of convergence and contact lenses are from prior studies (7,11) of the same subject. Poly, polynomial fit curve; positive gaze angle, gaze right; negative gaze angle, gaze left.

broadened the pretreatment curve. In addition, topical brinzolamide and convergence also raised its peak value.

Figure 2 shows the damping of the subject's waveforms after topical brinzolamide. It should be noted that although the post-brinzolamide INS waveforms have noticeably lower amplitudes at 0° and ±15°, they do not at the other gaze angles shown. This finding and the lack of correspondence of INS amplitude to visual acuity reinforce the need for functions like the NAFX and LFD to identify and quantify meaningful therapeutic improvements. For example, the percentage increases in the NAFX at 0° (where there is an amplitude difference) and 20° (where there is a minimal amplitude difference) are 36.7% and 184%, respectively.

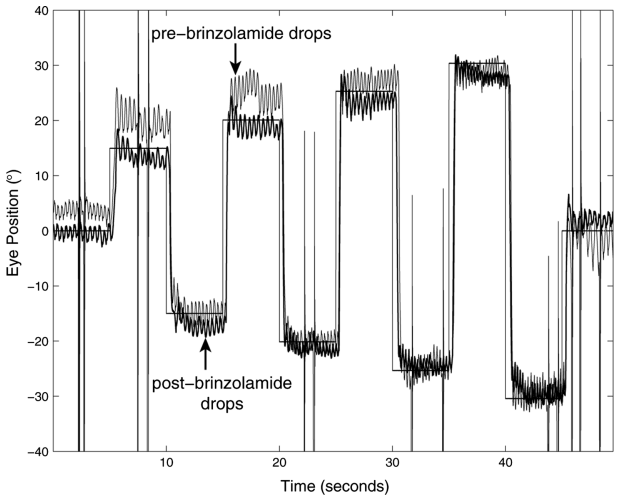

FIG. 2. Example of INS waveforms prior to (*gray line*) and following (*black line*) the use of brinzolamide eyedrops.

The percent improvements in the NAFX peaks were 13%, 42%, 38%, and 74% for the effects of 4 days of topical brinzolamide. The corresponding percent improvements in the LFD were 130%, 75%, 50%, and 30%. As with all other therapies, topical brinzolamide produced much greater percent NAFX improvements in lateral gaze (550%, 713%, and 738%, respectively, at −30°). The steady-state values of posttherapy peak NAFX and LFD were approximately 0.6° and 30°, respectively, corresponding to increases in these measures of 51.9% and 50%.

Comparison to Contact Lenses, Convergence, and Tenotomy and Reattachment

In addition to comparing the therapeutic effects of topical brinzolamide on peak NAFX and LFD to contact lenses and convergence therapies, we also compared each to the estimated effects of tenotomy and reattachment (T&R) eye muscle surgery based on the data from 22 previously studied patients (12). Figure 3A demonstrates that brinzolamide raised the peak NAFX by an amount equivalent to that estimated for the T&R procedure and was superior to contact lenses but not as efficacious as convergence. The 50% LFD improvement for topical brinzolamide was slightly less than for systemic acetazolamide, contact lenses, and the estimate for surgery; all were less than for convergence (Fig. 3B). The curves in Figure 3 are the estimated percent increases in peak NAFX and LFD for the T&R procedure based on the results from INS patients who

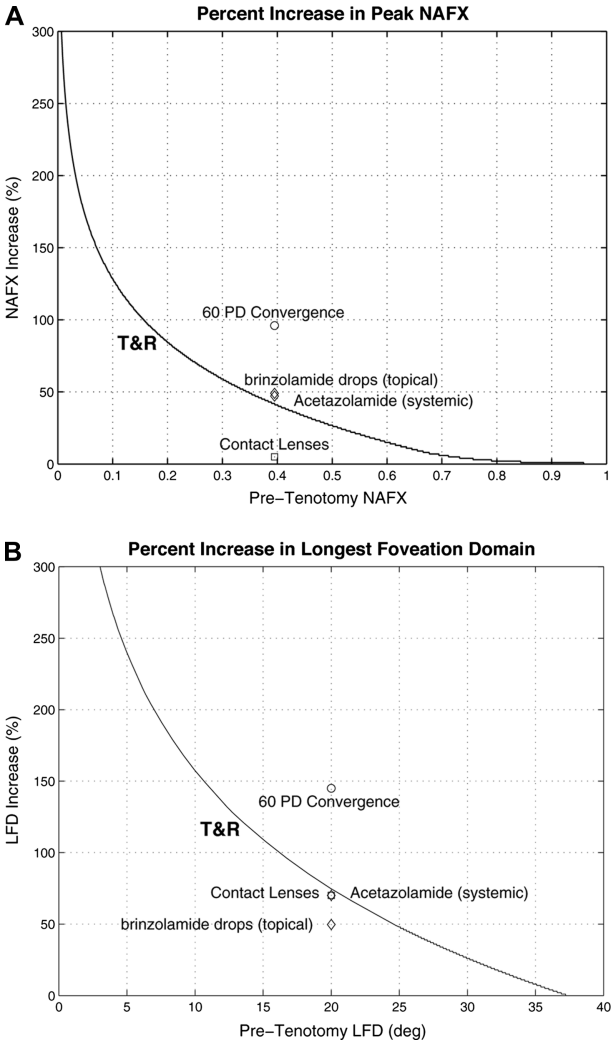

FIG. 3. Comparative plots of percent increases in peak NAFX vs pretherapy NAFX (**A**) and percent increases in LFD (**B**) vs pretherapy LFD during fixation of far targets with contact lenses, with topical brinzolamide, and during convergence at 60 PD. The estimated improvement curves were fitted to data from a study on the effects of T&R surgery (7), and data points from prior publications are taken from studies of convergence (11), contact lenses (7), and systemic acetazolamide (13).

underwent that procedure. Once the pre-T&R NAFX and LFD values are calculated, the curves allow estimation of the post-T&R improvements independent of the existence of any afferent sensory deficits or of the age of the patient. Given the pre-T&R measured visual acuity, we can estimate the post-T&R measured acuity. This cannot be done from clinical observations or tests.

Side Effects of Topical Carbonic Anhydrase Inhibitor

We monitored the effects of the eyedrops on IOP of our patient. The pretherapy IOP was 16 mm Hg, which was reduced to 12 mm Hg during the trial and had returned to 14.5 mm Hg by day 5 (2 days after the last eyedrops). There were no adverse systemic events as a result of the 3-day course of topical brinzolamide.

DISCUSSION

Rationale for the Use of Topical Carbonic Anhydrase Inhibitor in the Treatment of Infantile Nystagmus Syndrome

Dell'Osso et al (17) and Hertle et al (4,18) have demonstrated that eye muscle T&R alone had salutary effects on nystagmus amplitude and velocity in dogs with nystagmus and in 2 human trials in patients with INS. A hypothesis evolved that T&R altered proprioceptive structures in the eye muscle tendon at its insertion on the globe (enthesis) that favorably affected the nystagmus oscillation. Hertle et al (19) and Büttner-Ennever et al (20,21) have studied the anatomical and physiological properties of enthesial neurons. These neurons probably provide feedback that assists with ocular alignment and stabilization. Surgical disruption of enthesis in patients with INS results in long-standing beneficial effects on nystagmus and visual function (4,5,18,22). This may be due to a reduction of small signal gain of the ocular motor plant by interfering with enthesial proprioceptive tension control. Enthesial nerves are probably palisade-type non-twitch motoneurons and are likely involved in modulating the gain of sensory feedback from the eye muscles analogous to the gamma motoneurons, which control the gain of proprioceptive feedback in skeletal muscles.

Carbonic anhydrase (CA) may play an important role in the neurochemical functioning of the membrane potentials of enthesial nerve endings as it does in other sensory systems (23–27). Numerous CA-positive neurons have been found in the trigeminal and geniculate ganglia as well as in the mescencephalic trigeminal nucleus (28–30). There is evidence that CA participates in the response of sensory stretch receptors of the trigeminal nerve and its nerve endings. A functioning CA system may be involved in facilitating enthesial neuronal feedback to central ocular motor areas and continuing to enhance the developmentally disturbed circuit, thereby resulting in potentiating the ocular oscillation of INS. A carbonic anhydrase inhibitor (CAI) may interfere with the sodium–potassium ATPase membrane-bound system, thus interrupting enthesial neurophysiology (analogous to surgery) and creating a damped circuit, resulting in improvement in the ocular oscillation and enhanced visual function.

Underlying Mechanisms

Ocular motility studies have shown that INS has characteristic waveforms with typical variations depending on gaze and vergence angles. This is true regardless of associated

afferent visual abnormalities. INS instability is indistinguishable between the patient populations and has the *same* direct functional cause of loss of pursuit-system damping (31–33). Although the direct functional cause is the same in individual patients, the precipitating factors and other mechanisms (e.g., effects of vestibulo-ocular imbalance on the position and breadth of the null area, the thresholds at which pendular waveforms convert to jerk) probably differ. Therapies may be directed: 1) *afferently* to alleviate the visual condition that interfered with damping calibration (34–36), 2) *centrally* at the cells responsible for damping miscalibration (10–12), or 3) *peripherally* to reduce the effects of the underlying instability (e.g., vergence prisms, contact lenses, T&R procedure) (6,7,37).

Comparative Therapies

Topical brinzolamide had similar therapeutic effects on the INS waveforms compared to systemic acetazolamide. These benefits also mimicked the effects of the T&R surgical procedure. Increases of 50% in both the peak NAFX and the LFD occurred, and these increases were documented within 5 hours of administration of the eyedrops. The clinical implication of the improvements shown in Figure 1 is that the subject will have a higher posttreatment peak visual acuity (increase in the peak NAFX value) and that the improved acuity will be present over a larger range of gaze angles (increase in the LFD value) than pretreatment. Only convergence provided a larger improvement in peak visual acuity (peak NAFX value) in our patient.

The percent increase curves shown in Figure 3 are used to estimate, prior to 4-muscle surgery, the percent improvement and final values for both the NAFX and the LFD and allows estimation of the improvement in *measured* (not just potential) visual acuity of INS patients with or without afferent visual deficits (12).

Given the positive therapeutic effects of brinzolamide eyedrops on INS, it would be preferable to an oral preparation of CAI because it has no systemic side effects and acts faster. Thus, the patient could use it on an as-needed basis.

Testing the efficacy and/or effectiveness of topical brinzolamide as a therapy for others with INS requires prospective clinical trials. The results of this preliminary study provide data to support the hypothesis that CAI eyedrops may be used as an intervention in the treatment of the nystagmus waveforms associated with INS in future randomized trials (8,9).

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Addendum

Figures 1 and 2 of the attached paper were published in error; they should be replaced by the correct Figures below.

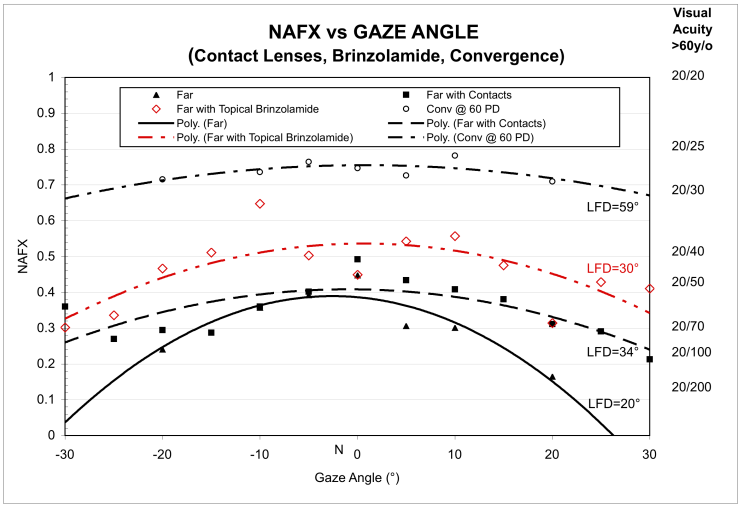

Figure 1.

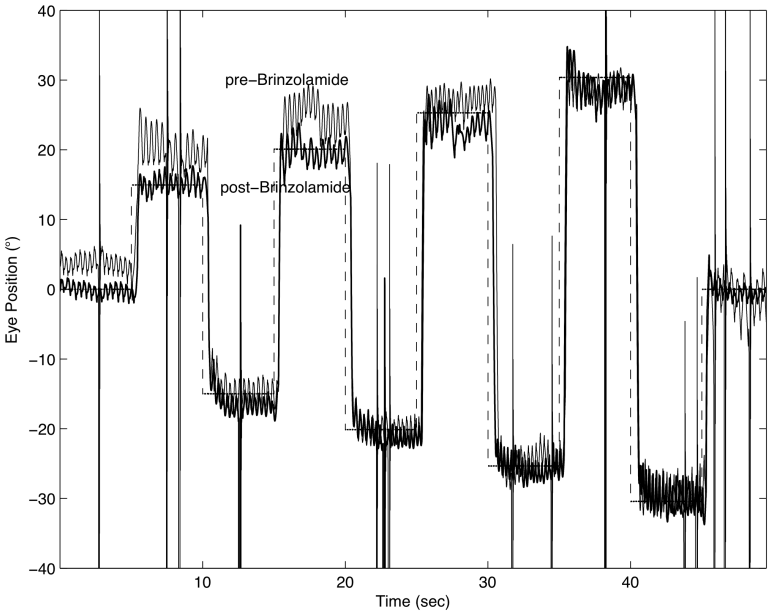

Figure 2.