Effects of Acetazolamide on Infantile Nystagmus Syndrome Waveforms: Comparisons to Contact Lenses and Convergence in a Well-Studied Subject

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Abstract: *Aim:* To determine if acetazolamide, an effective treatment for certain inherited channelopathies, has therapeutic effects on infantile nystagmus syndrome (INS) in a well-studied subject, compare them to other therapies in the same subject and to tenotomy and reattachment (T&R) in other subjects.

Methods: Eye-movement data were taken using a high-speed digital video recording system. Nystagmus waveforms were analyzed by applying an eXpanded Nystagmus Acuity Function (NAFX) at different gaze angles and determining the Longest Foveation Domain (LFD).

Results: Acetazolamide improved foveation by both a 59.7% increase in the peak value of the NAFX function (from 0.395 to 0.580) and a 70% broadening of the NAFX *vs* Gaze Angle curve (the LFD increased from 20° to 34°). The resulting U-shaped improvement in the percent NAFX *vs* Gaze Angle curve, varied from ~60% near the NAFX peak to over 1000% laterally. The therapeutic improvements in NAFX from acetazolamide (similar to T&R) were intermediate between those of soft contact lenses and convergence, the latter was best; for LFD improvements, acetazolamide and contact lenses were equivalent and less effective than convergence. Computer simulations suggested that damping the central oscillation driving INS was insufficient to produce the foveation improvements and increased NAFX values.

Conclusion: Acetazolamide resulted in improved-foveation INS waveforms over a broadened range of gaze angles, probably acting at more than one site. This raises the question of whether hereditary INS involves an inherited channelopathy, and whether other agents with known effects on ion channels should be investigated as therapy for this condition.

Keywords: Infantile nystagmus syndrome, waveforms, foveation, drug.

INTRODUCTION

Infantile nystagmus syndrome (INS) [1] is an ocular motor oscillation with well-defined waveforms and characteristics [2]. The pathogenesis of INS is unknown, but in some it is an inherited disorder in which several modes of inheritance have been identified [3]. The oscillations may be present at birth but often develop during early childhood and persist to some degree, despite the best current therapy. Although adaptive strategies often develop, such as foveation periods [4], the basic oscillations persist. Therapeutically, several approaches have been successfully employed to improve INS waveforms and expand the range of gaze angles with higher acuity [5, 6]. They include surgical [7-9], optical [10], and pharmaceutical [11-13] therapies.

Several underlying functional mechanisms for INS have been postulated and subsequently eliminated by ocular motor studies except one, loss of smooth-pursuit damping [14, 15]. This has been hypothesized to be the direct, functional cause of INS in all patients, whether or not they have associated, and precipitating afferent visual or genetic deficits. The hypothesized loss of smooth-pursuit damping was supported when embodied in a behavioral ocular motor system model that exhibited many emergent properties (not designed into it) [15]. It was further strengthened when the model subsequently predicted both the different INS responses to the same stimulus (based on its timing with regard to the INS cycle) [16, 17] and the therapeutic results of the tenotomy and reattachment (T&R) procedure [8, 15, 18-20]. However, even if this functional hypothesis proves to be accurate, the pursuit-system instability itself could be the result of one or more abnormalities at the cellular or neuronal level in subsets of INS patients.

Following our fortuitous observation that acetazolamide, taken to prevent altitude sickness, improved the nystagmus

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in a subject with hereditary INS, we set out to compare this potential therapy with two other measures that had previously been reported to be effective in this subject—convergence (or wearing prism spectacles to induce convergence), and contact lenses. Since acetazolamide is known to be an effective treatment for certain inherited, P/Q calcium channel disorders, such as episodic ataxia type 2, our finding raises the question of whether hereditary INS also involves an inherited channelopathy.

MATERIALS AND METHODOLOGY

Recording

We used a digital video system (EyeLink II, SR Research, Mississauga, ON, Canada) for the eye-movement recordings. The system had a linear range of $\pm 30°$ horizontally and $\pm 20°$ 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. For the contact-lens experiment, calibration was done immediately after the subject's prescribed contact lenses were inserted.

Subject and Protocol

This study was approved by the local IRB and written consent was obtained from the subject before the testing. The subject was a calm 68-year-old male with INS. His nystagmus waveforms were well documented previously and their characteristics representative of others with INS. Because subjects have no voluntary control of their INS waveform characteristics, the data are not affected by subsequent testing. The subject had a convergence "null" and wore either 7 PD base-out prisms added to his refraction (OD: +3.00 S -2.50 C ax 150 and OS: +3.50 S -2.75 C ax 20) or contact lenses with no added prism. His best-corrected distance visual acuities were 20/25 with prisms and 20/40+ with contact lenses. For fixation targets, we use small LED's and reflected laser spots, which are not acuity limiting and 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. The contact-lens experiment consisted of five trials performed by the subject while wearing contact lenses; we allowed time between trials for the subject to rest. Each trial tested fixation of horizontal targets from 30° left gaze to 30° right gaze, in 5° steps. We used our standard patient paradigm to test the effects of acetazolamide on this subject. It consists of two trials, one in each direction (as described above), with the target remaining at each gaze angle for 5 sec during both the stepping out laterally and returning to primary position. Subtracting the required target acquisition times, this allows approximately 2-3 sec of steady fixation during each interval. NAFX values are calculated during steady fixations and averaged. This results in a small number of NAFX values at each gaze angle that we have found to be historically very close to each other in value, usually differing in the third decimal place in several studies of many patients. Our paradigm for taking and analyzing such data is based on real-life acquisition and identification of new targets in one's visual field.

The subject took 500mg of acetazolamide twice a day for three days prior to the study. This dose of drug was chosen because it is the conventional dose for treating glaucoma and idiopathic intracranial hypertension and is usually tolerated with minimal side effects (500 mg to 1000 mg daily, in divided doses). The side effects consisted of transient paraesthesia of the hands (once on day two and once on day three), some abdominal discomfort on day two, and "general, mild discomfort" during days two and three. For comparisons of therapeutic effectiveness, we retrieved data from previous studies using the same subject [5, 10], who performed the same trials without any refractive correction at far and at near with a convergence angle of 60 PD.

Analysis

All the analysis was performed in the MATLAB environment (The MathWorks, Natick, MA) using OMLAB software (OMtools, downloadable from http://www.om lab.org). Eye position was sampled directly; it was pre-filtered 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 five 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 eXpanded Nystagmus Acuity Function (NAFX) [21]. It is an extension of the previous Nystagmus Acuity Function (NAF) that consists of a mathematical function containing the following waveform parameters: foveation-period duration, 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) [22]. 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 [21]. In the absence of afferent deficits, the NAFX is highly correlated with measured acuity. We averaged the NAFX values if several were obtained at each gaze angle.

The longest foveation domain (LFD) [5, 8] is defined as the range of gaze angles in which the subject's NAFX stays above 90% of the NAFX *vs* Gaze Angle curve's peak value. LFD is a measure of the broadness of the NAFX *vs* Gaze Angle curve, i.e., the INS subject's high-foveation-quality field.

Computer Simulations

Ocular motor simulations of the effects of acetazolamide on INS were performed in the MATLAB Simulink (The

MathWorks, Natick, MA) environment. The most recent version of our behavioral ocular motor system (OMS) model (version 1.4) is also available from http://www.omlab.org. Details of the model can be found elsewhere [15, 17, 20, 23]. To simulate the subject's data, the NAFX peak was set to -2° and the breadth of the NAFX *vs* Gaze Angle curve was set to be moderate and symmetrical. To simulate the effects of acetazolamide, it was hypothesized to act centrally by

reducing the oscillation, originating in the damping control of smooth pursuit, which underlies most INS waveforms.

RESULTS

Subject Data

During fixation of a distant target, the subject had a peak NAFX of 0.385 at 2° left gaze. As Fig. (**1a**) shows, the
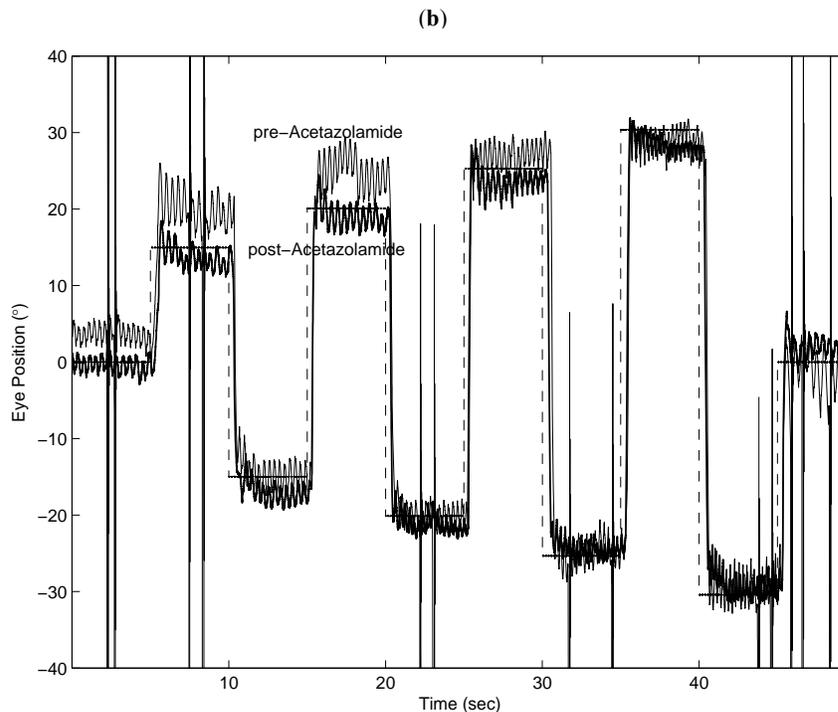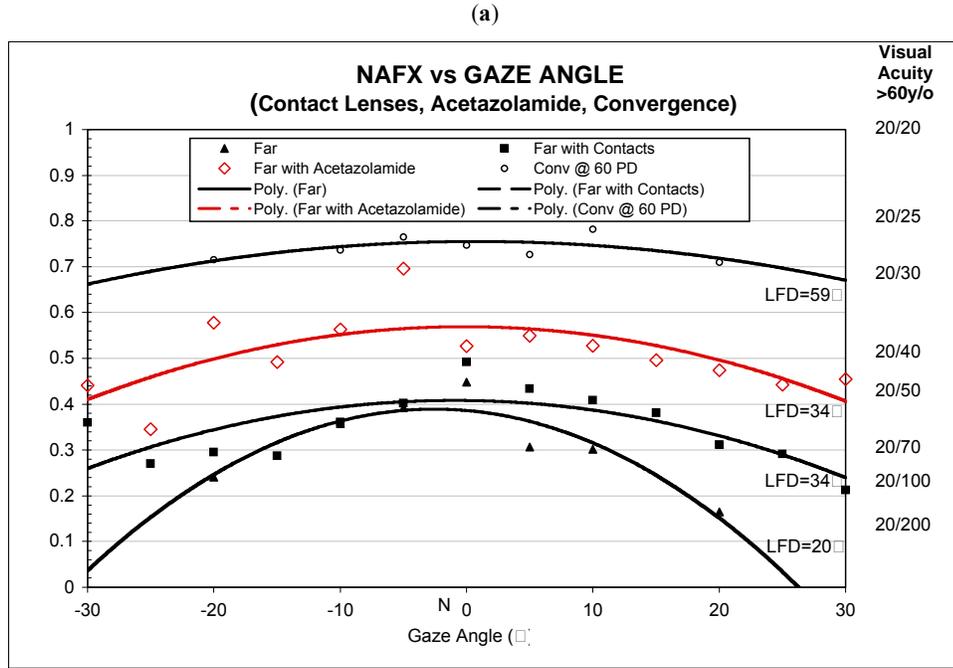
(a)

(b)

Fig. (1). a) Plots of NAFX *vs* Gaze Angle during fixation of far targets with no therapeutic aids, with contact lenses, with acetazolamide, and during convergence at 60 PD. The equivalent visual acuities shown are for subjects over 60 years of age. Curves are 2nd order polynomial fits to the data. N = "null" originally measured in 1963. **b**) Examples of the pre- and post-acetazolamide (heavy line) INS waveforms. Large spikes are blinks or video dropouts.

breadth of the NAFX *vs* Gaze Angle curve given by the LFD function was 20°. When using contact lenses, the NAFX peak was 0.405 with an LFD of 34°, and when converged at 60 PD, the NAFX peak was 0.755 with an LFD of 59°. During distant fixation while taking acetazolamide, the NAFX peak was 0.575 with an LFD of 34°. The NAFX values were slightly more variable for the acetazolamide data (mean standard deviation across gaze angles of 0.101) than for the other three conditions (0.095, 0.089, and 0.026 for distance, contact lenses, and convergence respectively). Fig. (**1b**) shows examples of the subject's waveforms pre- and post-acetazolamide.

The percent improvements in the NAFX at each gaze angle for the three therapies are shown in Fig. (**2**). Each therapy improved the NAFX values by roughly constant percentages within the central ±15° range of gaze angles, 15-40%, 50-100%, and 100-185% for the contact lenses, acetazolamide, and convergence therapies respectively. In addition, the three therapies produced much greater improvements in lateral gaze (600%, 1050%, and 1600%, respectively).

Comparisons to Contact Lenses, Convergence, and Tenotomy and Reattachment

In addition to comparing the therapeutic effects (on peak NAFX and the LFD) of acetazolamide to contact lenses and convergence therapies, we also compared each to the estimated effects of the T&R based on data from twenty-two patients [6]. Fig. (**3a**) demonstrates that acetazolamide raised the peak NAFX by an amount equivalent to that estimated for the T&R procedure, whereas contact lenses fell short

while convergence was better. The LFD improvements for both acetazolamide and contact lenses were the same as for the T&R procedure, but less than for convergence (Fig. **3b**). Fig. (**4**) compares the actual post-therapeutic NAFX and LFD values of each therapy relative to the estimated T&R values.

Computer Simulations

In order to investigate the possible mechanisms involved in these waveform improvements, we simulated the acetazolamide condition using a behavioral OMS model developed to investigate mechanistic ocular motor hypotheses ranging from normals to individuals with various ocular motor dysfunctions [8, 9, 14, 15, 19, 20, 23-32]. In an attempt to mimic the subject's INS characteristics, we used the OMS-model's built-in capabilities to set the NAFX peak to -2° with a symmetrical, medium Alexander's law variation of the INS amplitude with gaze angle. Fig. (**5**) shows the main components of the OMS model (Smooth Pursuit, Fixation, Saccadic Pulse Generator, Internal Monitor, Fast and Slow Neural Integrators, and Fast and Slow Plant pathways) and of the PMC+ Block (part of the Smooth Pursuit system responsible for its damping). There, we simulated the hypothesized central effect of acetazolamide by reducing the gain factor, "Central Therapy" from 1.3 (the value required to match this subject's pre-acetazolamide INS) to 0.6. As Fig. (**6a**) shows, the simulated INS amplitude increased at gaze angles lateral to -2° (as did the subject's) and the simulated effects of acetazolamide resulted in damped INS waveforms at all gaze angles. Calculating the NAFX values from the simulation
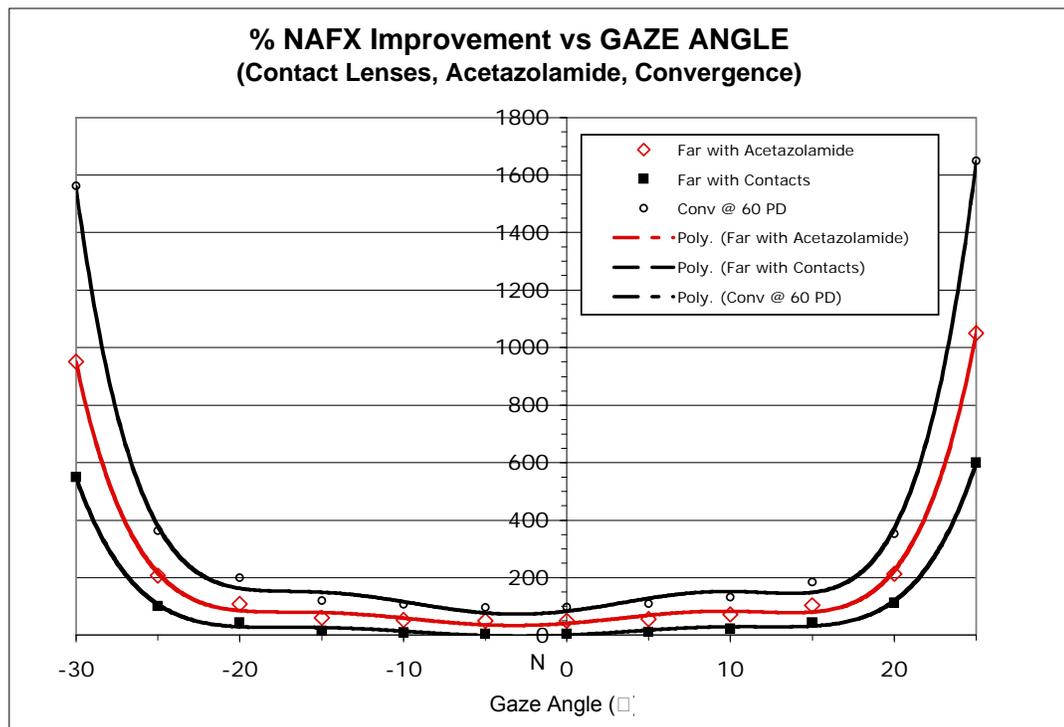

Fig. (2). Plots of Percent Improvement in NAFX *vs* Gaze Angle during fixation of far targets with contact lenses, with acetazolamide, and during convergence at 60 PD. Curves are 6th order polynomial fits to the data. N = "null" originally measured in 1963.
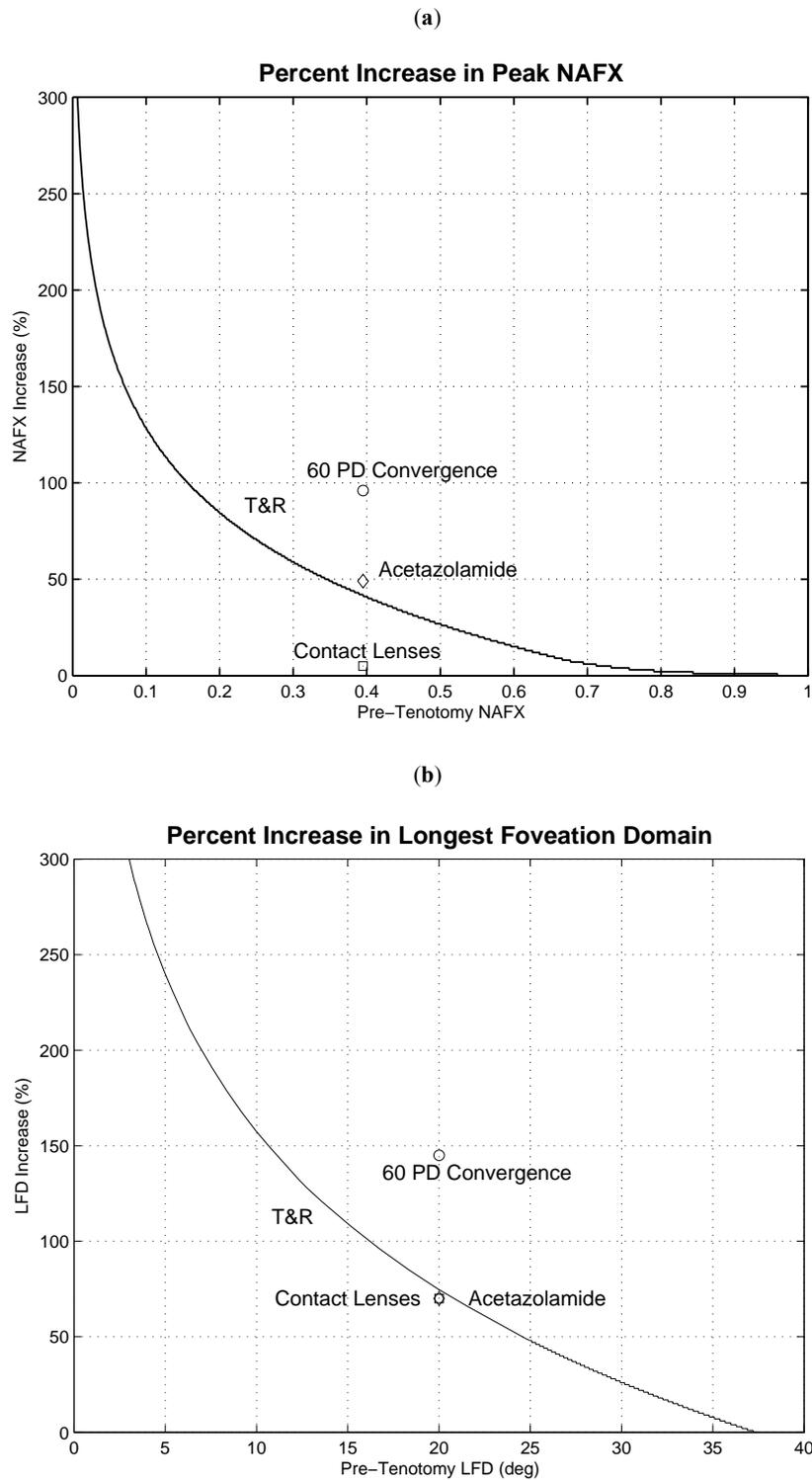
(**a**)

Percent Increase in Peak NAFX

(**b**)

Percent Increase in Longest Foveation Domain

Fig. (3). Comparative plots of **a**) percent increases in peak NAFX *vs* Pre-therapy NAFX and **b**) percent increases in LFD *vs* pre-therapy LFD during fixation of far targets with contact lenses, with acetazolamide, and during convergence at 60 PD. Curves shown are the estimated percent increases in peak NAFX and LFD for the tenotomy and reattachment (T&R) procedure.

data at those gaze angles resulted in a match to the subject's far-fixation data and an improved but *not* broadened NAFX *vs* Gaze Angle curve (i.e., the LFD values remained the same) for the simulated effects of acetazolamide (Fig. **6b**).

DISCUSSION AND CONCLUSIONS

Acetazolamide

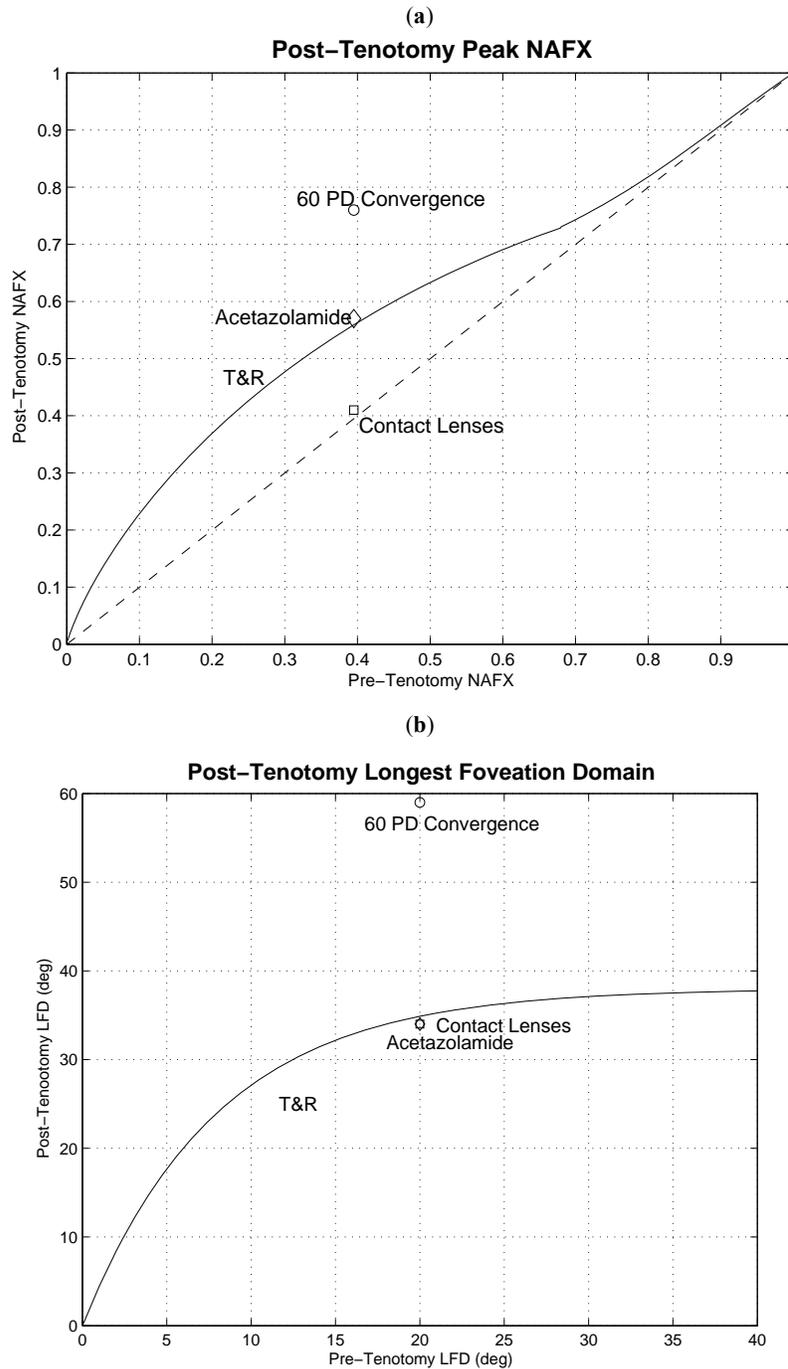Acetazolamide, a potent carbonic anhydrase inhibitor is the most common and best-studied agent for the amelioration

(a)
Post–Tenotomy Peak NAFX

(b)

Post–Tenotomy Longest Foveation Domain

Fig. (4). Comparative plots of **a**) post-therapy peak NAFX *vs* pre-therapy peak NAFX and **b**) post-therapy LFD *vs* pre-therapy LFD during fixation of far targets with contact lenses, with acetazolamide, and during convergence at 60 PD. Curves shown are the estimated peak NAFX and LFD for the tenotomy and reattachment (T&R) procedure.

of acute mountain sickness; it also is used in the treatment of idiopathic intracranial hypertension and as adjunctive treatment for primary open angle glaucoma. The aim of our study is to evaluate if this subject with INS, who took 1000mg/day of acetazolamide for three days to prevent altitude sickness, showed changes in his nystagmus waveforms. However, this subject's INS waveforms at each gaze angle were unchanged by acetazolamide, as they have been since his first eye-movement recording in the mid 1960's (compare also the original "null" position shown in

Figs. (**1**, **2**) with the more recent NAFX peaks and % NAFX-improvement troughs). Such intra-subject consistency is common, despite inter-subject variability, and has been documented in many patients who have had repeat studies in our laboratory years, or even decades, apart. Although acetazolamide did improve the average NAFX values over contact lenses, there was more variability at each gaze angle (possibly related to the subject's mild discomfort); this and the other the side effects might be contraindications to using acetazolamide (at the dosage used) as a therapy for INS.
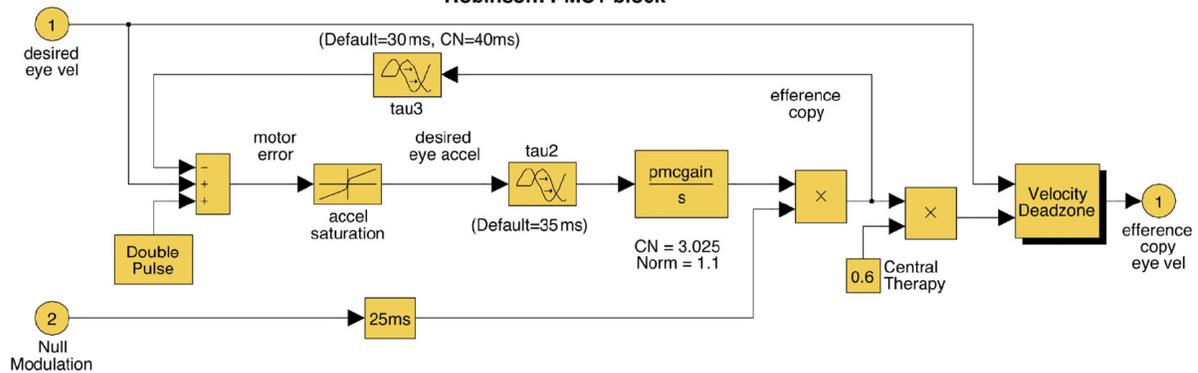
OMS Block Diagram
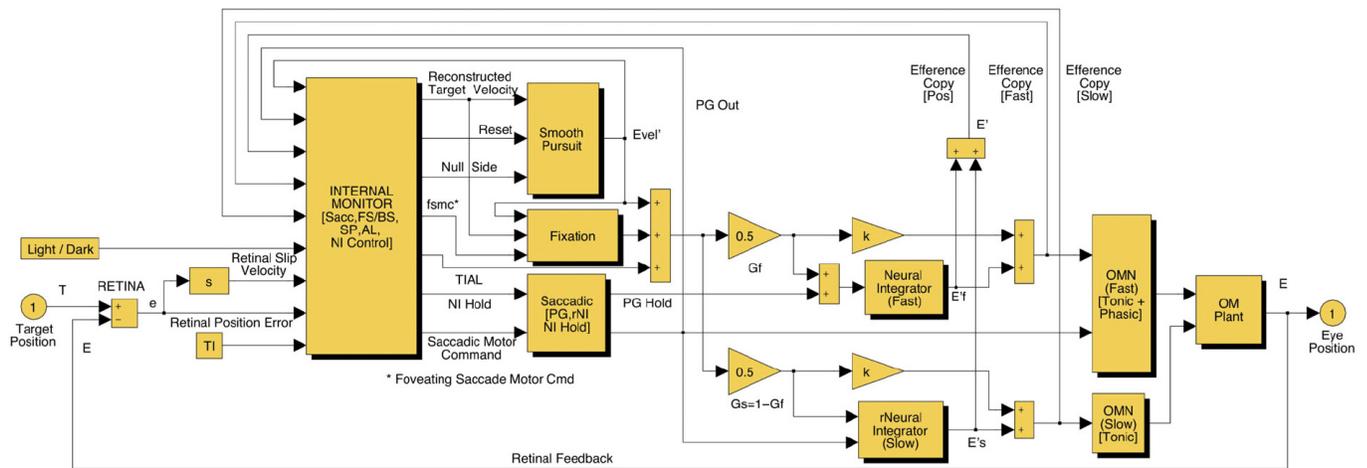
Fig. (5). Block diagrams of the behavioral ocular motor system model and the PMC+ block (controlling damping within the Smooth Pursuit system) where the hypothesized central effect of acetazolamide was simulated. The gain factor "Central Therapy" (lower input to the final multiplier) was adjusted downward from its pre-acetazolamide value of 1.3.

Underlying Mechanisms

Ocular motility studies of INS have demonstrated that, despite minor idiosyncrasies and whether or not there is an associated visual abnormality or it is hereditary, all INS is the same disorder (i.e., the *same* common waveforms and their characteristic variations with gaze and vergence angles). Thus, the ocular motor system instability is indistinguishable between patient subpopulations and has the *same* direct, functional cause (e.g., loss of pursuit-system damping). As is evident from the literature, the terminology used and the questions posed when discussing the "cause" of a disorder often reflect one's training or approach to the problem. The geneticist speaks of a genetic abnormality, the physiologist or anatomist, of the misbehavior of a group of cells, their absence, or misrouting of their connections, and the control-systems analysist, of an unstable feedback loop. However, such diverse putative "causes" of a condition may be neither contradictory nor repetitious. Rather, each is a meaningful description to those with the corresponding background, while the other descriptions may seem somehow lacking. Going from initial speculation to a realistic hypothesis for INS requires establishing a functional connection between the putative "cause" and the resulting

eye oscillation and ocular motor behavior. For example, in some with INS, a genetic abnormality or spontaneous occurrence could result in a channelopathy of the subset of cells that set the smooth-pursuit damping gain. Other INS patients might have calibration of that gain altered by lack of adequate visual input, still others by another physiological or anatomical disorder of the cells controlling pursuit damping. In all of these putative scenarios, the INS instability will be indistinguishable among patients, the direct, functional cause will be the same, but the precipitating factors and lower level mechanisms will differ.

Comparative Therapies

As Figs. (**3**, **4**) shows, there are broad ranges of initial NAFX and LFD values within which the T&R procedure produces significant improvements (e.g., $0.05 \leq NAFX \leq 0.6$ and $2.5° \leq LFD \leq 25°$). This use of accurate eye-movement data to diagnose INS and determine the therapeutic approach with the maximal therapeutic efficacy has also resulted in an analysis procedure whereby we can estimate a priori the percent improvement and final values for both the NAFX and LFD; the former also allows estimation of the improvement in measured (not just potential) visual acuity of
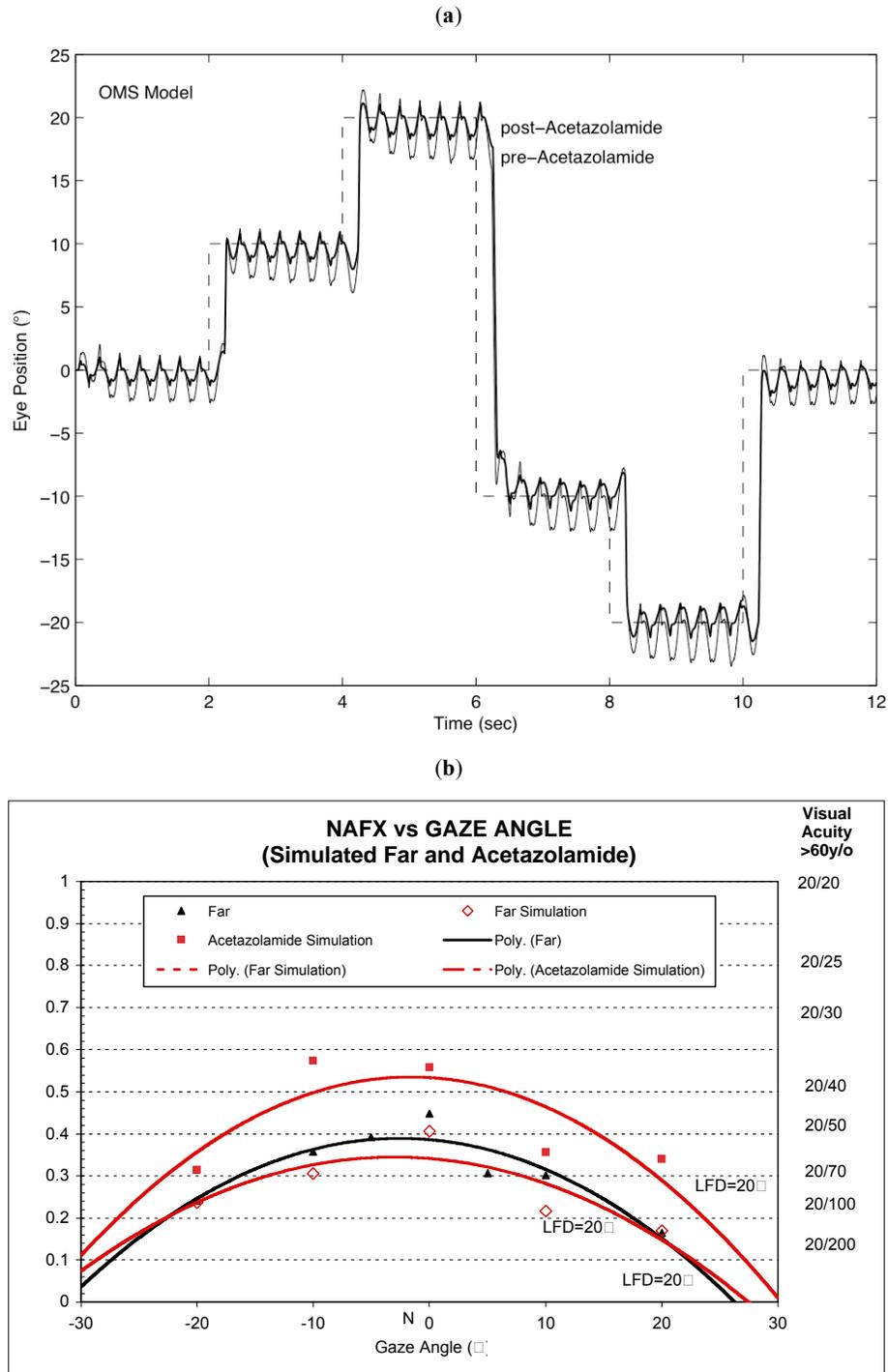
(a)

(b)

Fig. (6). (**a**) Plots of OMS model outputs simulating far fixation at 0°, ±10°, and ±20° for both the pre- and post-acetazolamide (heavy line) conditions. (**b**) Plots of NAFX *vs* Gaze Angle for the simulated data in (**a**). Shown for comparison is the Far curve from the subject's data.

INS patients with or without afferent visual deficits [6]. The present study demonstrates how, for an individual patient, we can determine the relative improvements of several different types of therapies and compare them to the estimated improvement from the T&R procedure. The effects of this drug are independent of, and act at different sites from, either convergence or gaze-angle nulls. Therefore, the presence or absence of convergence or gaze-angle nulls would not alter the effects of the drug on INS. Therapeutic effects of such diverse treatments have been

shown to be multiplicative, acting in different ways at different sites. This is the first time objective INS eye-movement data analyses have been used for these purposes.

The outcome data from vergence prisms also represents the results of performing a bimedial rectus recession procedure, since the resulting induced convergence to align the eyes has equivalent effects on INS in the two cases. Our research has shown that it is the act of convergence that damps INS in those patients who demonstrate this effect.

That act of convergence is the same whether or not it is induced by prisms or by a surgically induced divergence. The static concept of "weakening" a muscle is of little use in understanding the dynamic effects of most eye-muscle surgery or vergence on an oscillation like INS. Although the antagonist muscles of each eye receive different innervations for convergence, the resultant force is equal in each muscle. Rather, it is alteration of the proprioceptively controlled resting muscle tension that is responsible. In fact, we test for the efficacy of the bimedial rectus recession procedure in binocular patients with an INS convergence null by having them wear BO prisms. Also, due to the fact that the muscles wrap around the equator and attach closer to the cornea, small recessions do not substantially weaken the mechanical advantage of the muscle. The different innervations of the EOM during convergence result in equal and opposite forces in the two antagonist muscles of each eye and are not what reduces their small-signal gain. Prism-induced vergence produces the same broadening effects as the T&R procedure, implying the same mechanism of action and removing the requirement for the addition of bilateral rectus muscle T&R to the bimedial rectus recession procedure. Based on our analyses of hundreds of INS patients, where convergence nulls have always been greater than gaze-angle nulls, we concluded long ago that inducing convergence in binocular patients with convergence damping would have greater therapeutic improvement than any other known therapy— either base-out prisms or the bimedial rectus recession procedure should be the therapy of choice in these patients. Because the eye-movement data from this subject are representative of the INS population in general, if surgery were to be considered for the subject of this study, maximal therapeutic improvement would result from a bimedial rectus recession procedure. There is no evidence that inducing convergence by either method will cause strabismus in these binocular patients; both therapies have resulted in large, sustained improvements in visual function. Further neurophysiological study of convergence's effects on proprioception is needed to clarify the specific mechanism involved.

The past four decades of INS research suggests that the direct, functional cause of INS is the miscalibration of smooth-pursuit damping [14, 15, 28]. Therapies may either be directed: 1) *afferently* to alleviate the visual condition that interfered with damping calibration [33-35]; 2) *centrally* at the cells responsible for damping miscalibration (as some drugs may do, although they may also act elsewhere with possibly undesirable side effects) [11-13]; or 3) *peripherally* to reduce the effects of the underlying instability (e.g., vergence prisms, contact lenses, or the T&R procedure) [7, 8, 36]. It is unclear whether acetazolamide affected a channelopathy in a subset of central or peripheral neurons (i.e., whether it affected the "cause" or merely ameliorated the "effect"—as does the T&R procedure). Finally, to the extent that one particular type of therapy insufficiently improves the INS waveform, other types may be added that will multiply the therapeutic improvement [37].

Recent work on the pathogenesis of some hereditary forms of INS has focused on the FRMD7 gene, which is expressed in retina and cerebellum. Exactly how mutations of this gene could cause INS is debated, although the cerebellum plays an important role in smooth tracking eye movements and gaze

holding. Future studies aimed at investigating whether ion channels or specific neurotransmitters are affected by the FRMD7 gene may lead to identifying more specific drug therapies for hereditary INS [38].

Computer Simulations

We used computer simulations to explore a possible mechanism of action of acetazolamide in this subject's INS. After simulating the subject's INS waveform variation with gaze angle, we investigated the effects on INS of simply reducing the oscillatory signal in the smooth-pursuit damping circuitry (*no other changes to the model were made*). That is, we hypothesized that acetazolamide has the *single* ocular motor effect of centrally damping the causal INS oscillation. Analysis of the simulated results produced an NAFX *vs* Gaze Angle curve that was higher (i.e., allowing better visual acuity) but not wider (i.e., allowing high acuity over more gaze angles). This did not accurately simulate the subject's data, which showed both improvements. Thus, this single-site hypothesis for the effects of acetazolamide on this subject was disproven; i.e., the model suggested that acetazolamide's action was not limited to only that ocular motor site. This should not be surprising, given its systemic actions as evidenced by the unrelated side effects.

Our computer simulations demonstrated that a central reduction in the magnitude of the initial INS instability was insufficient to mimic the measured INS-waveform improvements and suggested that acetazolamide also acts centrally at another site to broaden the Alexander's law variation of INS amplitude. That combination could be simulated in the same way the pre-acetazolamide simulation was matched to the subject's far-fixation data. A third possibility is that acetazolamide acted peripherally and therefore, affected INS in a manner similar to that of the T&R procedure; we have already simulated and reported those peripheral therapeutic effects [20]. Finally, acetazolamide could have acted both centrally and peripherally.

The efficacy of acetazolamide as a therapy requires studies at a reduced dosage to determine if its therapeutic effects can be maintained without side effects. In addition, the repeatability of its effects over time and the number and type of patients (i.e., other than those with hereditary INS) in whom it is effective need to be determined. Other, similar drugs (e.g., methazolamide) should also be investigated. The results of this preliminary study provide a foundation for a randomized, double-blind, drug-efficacy study of these drugs in patients with INS and a comparison to the known effects of other drugs on INS [11, 12] and to the known surgical effects.

ACKNOWLEDGEMENT

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