Original Article

Topical lambda-cyhalothrin in reducing eye oscillations in a canine model of infantile nystagmus syndrome

Richard W Hertle[1,2,3], Louis F Dell'Osso[4], Jonathan B Jacobs[4], Dongsheng Yang[1,3], Jeffery Dumire[2,3], Michelle Evano-Chapman[1,3]

Purpose: To determine the ocular and systemic safety of using topical Lambda-Cyhalothrin (LCL) in a canine model of infantile nystagmus syndrome (INS). The rationale for this proposal is based on a case study of a patient whose INS improved after inadvertent ocular exposure to a pyrethroid pesticide containing LCL. **Methods:** After *in-vitro* safety testing and IUCAC approval, we studied increasing concentrations of topical LCL drops (0.002% to 0.07%) in canines with a purposely bred defect in the *RPE65* gene resulting in both retinal degeneration and INS. We collected data on ocular and systemic effects and performed eye-movement recordings (EMR). **Results**: At the 0.07% concentration dose of LCL, there was minimal, reversible, conjunctival hyperemia. There was no other ocular or systemic toxicity. At the 0.06% dose, there was a visible decrease in the INS and EMR showed a 153%–240% increase in the nystagmus acuity function and a 30%–70% decrease in amplitude across gaze. There was also a 40%–60% decrease in intraocular pressure while on the drop in both eyes. **Conclusion**: This animal study suggests this new pharmacological agent has potential for topical treatment of both INS and diseases with raised intraocular pressure. Further, this new treatment approach confirms the importance of extraocular muscle proprioception in ocular motor diseases and their treatment.

Key words: Canine nystagmus, eye-drop treatment, infantile nystagmus

Videos Available on: www.ijo.in

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Website: www.ijo.in

DOI: 10.4103/ijo.IJO_586_20

Quick Response Code:

The most common form of nystagmus in infants and children is infantile nystagmus syndrome (INS).[1,2] Clinical characteristics, with variable association, include: associated afferent-system disease up to 85% (e.g., albinism, foveal dysplasia, achromatopsia, aniridia, and optic nerve dysplasia).[3-7] The oscillation affects visual functions separately from the associated afferent-system deficits mentioned above and includes additional deficits: high spatial acuity, contrast sensitivity, motion processing, visual recognition time, and gaze dependent vision.[3,4,6-8] Treatments of the eye oscillation have demonstrated improvement in all these visual functions.[7,9-12]

A previous adult patient with familial INS accidently sprayed the industrial pesticide Warrior[R] in the right eye while farming in Montana, USA. There was initial discomfort, relieved by copious water irrigation within minutes. Within 1 h after irrigation, better sight was reported out of the right compared to left eye and the "nystagmus was gone." An immediate consultation with a local ophthalmologist confirmed no serious damage from the contact of the pesticide with the eye and that indeed the vision was better and the nystagmus improved to "barely visible" in the right eye. Our evaluation months later revealed no toxicity and a persistent, significant improvement in nystagmus and monocular vision. We hypothesized that the use of the topical, active ingredient in Warrior[R] as an eye drop in an animal model with INS would result in improvements in the nystagmus in the animal model, thus the premise of this study.

Lambda cyhalothrin (LCL)

The active ingredient in the commercially available pesticide Warrior[R] is a 0.06% concentration of Lambda-cyhalothrin (LCL). LCL is also known by its chemical name (R)-cyano (3-phenoxyphenyl) methyl (1S, 3S)-rel-3-[(1Z)-2-chloro-3 ,3,3-trifluoro-1-propenyl]-2,2-dimethyl cyclopropane carboxylate [Fig. 1].

Lambda-cyhalothrin is an Environmental Protection Agency (EPA)-registered agent that is similar to the pyrethroid cyhalothrin and disrupts the nervous system by prolonging the deactivation of voltage-gated sodium channels, which results in prolonged excitation of nerve fibers.[13,14]

[1]Akron Children's Hospital, Akron, OH, Primary Place Work Completed, [2]SUMMA Medical Center, [3]Akron, OH, Northeast Ohio Medical College, Rootstown, OH, [4]The Daroff-Dell'Osso Ocular Motility Lab, LSC VA Medical Center and Departments of Neurology and Biomedical Engineering, Case Western Reserve University, Cleveland, OH, USA

Correspondence to: Dr. Richard W Hertle, 300 Locust Street, Suite 490, Akron OH 44302, USA. E-mail: rhertle@akronchildrens.org

Received: 19-Mar-2020 Revision: 10-Apr-2020
Accepted: 06-May-2020 Published: 23-Sep-2020

Cite this article as: Hertle RW, Dell'Osso LF, Jacobs JB, Yang D, Dumire J, Evano-Chapman M. Topical lambda-cyhalothrin in reducing eye oscillations in a canine model of infantile nystagmus syndrome. Indian J Ophthalmol 2020;68:2190-5.

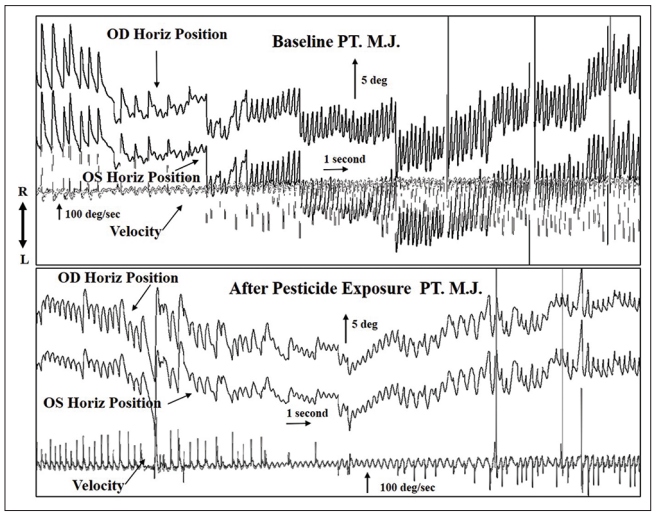

Figure 1: Eye movement recordings at baseline (top, above) and 4 weeks after (bottom, below) accidental exposure of pesticide on patient MJ. It is clear from this figure the decreased overall intensity (amplitude × frequency) of the patient's nystagmus. (PT = patient, Horiz = horizontal, OD = right eye, OS = left eye, R = rightward movements, L = leftward movements, deg = degrees, sec = second)

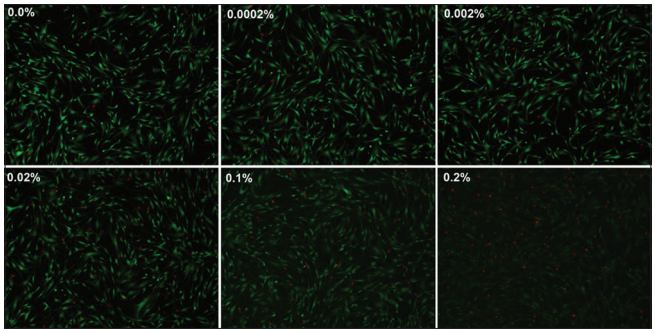

Figure 2: Effect of LCL on human fibroblasts measured by LIVE/DEAD assay using fluorescence microscopy. Green fluorescence indicates metabolically active (live) cells and red fluorescence indicates cells where the plasma membrane has been compromised (dead). Concentration of LCL is indicated for each panel and all assays used the same vehicle (0.4% DMSO + 0.6% PG in BSS)

Canine model

The *RPE65*-mutant strain of dog is an autosomal recessive model of Leber congenital amaurosis (LCA) but displays no other abnormalities.[15,16] Although initially termed a congenital stationary night blindness, affected dogs have variably severe abnormalities of cone-mediated vision as well, show slow progression of symptoms with age, and very slowly develop degenerative retinal morphologic changes.[17] This animal model has served as the basis for the development of a now-approved therapy consisting of the subretinal injection of adeno-associated virus (AAV) that has been modified to carry the genes necessary to produce RPE65 *in vivo* (AAV-*RPE65*).[18-20] As in most humans, the dogs' nystagmus was noted to appear shortly after eye opening and has dual-jerk waveform characteristics, all consistent with INS.[21]

Methods

After IUCAC approval, the study was performed in three stages: stage 1–*in-vitro* safety testing of LCL; stage 2–*in-vivo* safety testing combined with testing for treatment of nystagmus, i.e., increasing concentrations of topical LCL drops in two animals over 3 weeks; stage 3–continued study of effect on intraocular pressure of topical LCL.

Stage 1-In-vitro safety assessment of varied LCL concentrations

We used a LIVE/DEAD (Invitrogen^{R}) viability/cytotoxicity assay to test the effect of varying concentrations of LCL on mammalian fibroblast and epithelial cells [Fig. 2]. The two-color fluorescence assay allowed for simultaneous determination of both live and dead cells. We first tested LCL in its powder form, diluted with water, at concentrations ranging from 0.2% to 0.0002%. Cell viability was within the acceptable rate using LCL at concentrations of 0.0002% through the 0.07% concentrations. Due to its low water solubility (0.5 ng/ml) and highly lipophilic nature of LCL, we chose to initially dissolve pure LCL in dimethyl sulfoxide (DMSO) solvent followed by subsequent dilution with propylene glycol (PG) in balanced salt solution (BSS). We tested a range of LCL concentrations on the assay, including 0.1%, 0.07%, 0.06% (concentration present in the commercial pesticide product Warrior^{R}) 0.04%, 0.02%, 0.01%, 0.002%, and 0.0002%. All solutions had a final concentration of 0.4% DMSO and 0.6% PG in BSS.

Formulation of LCL-containing eye drops for in vivo (animal) safety study

Based on the information from our *in-vitro* studies, we assessed the safety of eye drops containing a range of LCL concentrations up to a maximum of 0.07% LCL. A 0.1% solution of Lambda-Cyhalothrin (LCL; Sigma) was first prepared by solubilization of LCL in sterile dimethyl sulfoxide (DMSO; Sigma) at 250 mg/ml. Sterile filtered propylene glycol (PG; Sigma^{R}) was then added to the solution to a final concentration of 60.0%. Subsequent 1:100 dilution with sterile balanced salt solution (BSS; Alcon^{R}) resulted in a formulation containing 0.1% LCL, 0.4% DMSO, and 0.6% PG in BSS. The LCL ophthalmic suspension was transferred to sterile 5-ml dispensers with controlled dispensing-tips. Further dilutions to achieve concentrations of 0.002%, 0.02%, 0.04%, 0.05%, 0.06%, 0.07%, and 0.1% LCL were made using a diluent of the sterile vehicle 0.4% DMSO and 0.6% PG in BSS. The desired composition was DMSO 4.0%, PG 3.0%, and LC 10 mg/ml (1% by weight), based upon the total composition. A maximum concentration of 1.0% (by weight) LC was prepared. The LCL ophthalmic suspension was transferred to sterile 5-ml dispensers with controlled dispensing-tips. Dilutions to achieve 0.002%, 0.02%, 0.04%, 0.06%, and 0.07% LCL were made using sterile vehicle (0.4% DMSO + 0.6% PG in BSS).

Stage 2-In-vivo safety testing combined with testing for treatment of nystagmus

All treatments were given continuously over a 3-week period and consisted of 1–2 drops of increasing concentrations of LCL instilled in the conjunctival fornix of both eyes TID for 3 days with a 1-day washout period as follows: 0.002%, days 1–3; 0.02%, days 5–7; 0.04%, days 9–11; 0.06%, days 13–15, 0.07%, days 17–19. Safety was assessed before and after each dose was administered and the concentration of the next dose was only increased if no adverse events were observed. The uppermost concentration of LCL formulation deemed safe by the preliminary *in-vitro* assay was 0.1%; thus, the highest dose used in the animals was 0.07%. Daily veterinarian physical examination, ophthalmic extraocular

and intraocular examinations, and hematological evaluations were completed (e.g., visual behavior, tonometry, external exam with photography, conjunctival and corneal fluorescein staining, slit-lamp exam of the anterior segment, indirect ophthalmoscopy, liver and kidney function testing, complete metabolic panel, and complete blood count).

Ocular motor evaluation and eye-movement recording (EMR)

We performed EMR of 2 littermates, one male (Scout) and one female (Ginger) starting at 8 weeks of age (post-weaning) and continuing until 14 months of age; since Scout did not have canine INS, the ocular motor analysis of the effects of LCL drops was performed on Ginger's data. Nystagmus was roughly characterized for amplitude, frequency, and plane (s), and ocular alignment was noted. The external ocular anatomy, fundus, nystagmus, and visual behavior were photographed and videotaped. Eye-movement recordings were made using high-speed video systems (EyeLink II® and EyeLink 1000®, SR Research Ltd., Osgoode, ON, Canada) capable of measuring horizontal and vertical movement simultaneously at a sampling frequency of 500 Hz with 16-bit resolution [Fig. 3].[22] The dogs' eye movements were calibrated against known targets in the horizontal and vertical planes [Fig. 3]. To insure accuracy over the course of an experiment, the calibration presentation was repeated at the beginning of each trial.

All EMR were performed in accordance with the IACUC guidelines regarding animal experimentation. An experiment consisted of between two and seven trials. Each trial lasted from 30 to 120 s. One examiner stood 57 inches from the dog's eyes and alternated the fixation target between wall-marked points of 0°, ±15° horizontally and ± 10° vertically, holding the target for approximately 5 s at each point. The data-acquisition operator monitored the dog's performance using a live feed from the video camera and the EyeLink®.

Eye-movement analysis

Eye-movement records by the EyeLink® system were exported using the "edf2asc" routine provided by SR Research® into ASCII format that could be read into MATLAB® and analyzed, using the OMtools software. Only position data were measured directly; velocity was calculated by means of a two-point central differentiator algorithm that also acted as a low-order low-pass filter whose cutoff frequency decreased as the separation between the difference points increased. More information on this algorithm and its consequences can be read elsewhere.[23] The nystagmus acuity function (NAFX) calculates this value based on the duration and repeatability (i.e., standard deviation of fixation periods). Details for application of the NAFX have been described previously.[24] In the case of the dogs, we used ±3.0° horizontally and ±1.5° vertically to reflect the extent of the foveation window in canines, e.g., the *area centralis*. The velocity limits were set between ± 4 and ± 10°/s, as is done for humans. We limited our analyses to data segments that were no longer than 10 s and that showed no changes (or loss) in fixation during that time. Records where the dogs made head movements, or failed to attend to the targets were not analyzed.

Results

Stage 1–*In-vitro* safety

Solutions containing up to 0.1% LCL had no significant effect on cell viability [Fig. 2]. The 0.1% LCL solution started to display decreased cell viability but not at statistical significance.

Stage 2–Safety and effect on nystagmus

Safety

After 3 weeks of increasing concentrations of topical LCL applied TID OU (0.002%, 0.02%, 0.04%, 0.06%, and 0.07%), there was no evidence of clinical or laboratory toxicity until 3 days after administration of the 0.07% concentration at which time there was mild inferior conjunctival forniceal hyperemia and chemosis [Fig. 4a and b]. Both disappeared spontaneously without treatment over the next 24–48 h. There were no other veterinary or hematological abnormalities at any time before, during or since administration of the drops. Both animals are now almost 7 years old and completely healthy except for nycloptia and constricted visual fields.

Effect on nystagmus

Initial dosages of 0.002% of LCL did not produce improvements in either INS amplitudes or NAFX values. However, at a dosages of ≥0.04% TID OU, significant ($P < 0.05$) improvements in both were documented. Video 1 shows Ginger's biplanar INS before the administration of LCL drops. Video 2 shows the dramatic damping of Ginger's biplanar INS 3 days after the administration of 0.06% LCL drops. Figs. 4 show examples of the nature of the biplanar nystagmus. The elliptical trajectories were markedly diminished as the RE portion of Fig. 4 shows. The post-drops' eye-movement data also showed that, in addition to markedly damped nystagmus cycles, there were intervals of no nystagmus at all.

Figs. 4 and 5 also show examples of the baseline horizontal nystagmus and post-LCL-drop nystagmus. The waveform is predominantly pendular with an average frequency of ~10 Hz (for both pre- and post-drop data). The horizontal, pre-drop, peak-to-peak amplitude ranged from 2°–5°, whether the right or left eye was viewing. Post-drop, the amplitudes ranged from 0.2°–1.5°, a 90%–70% reduction.

Effect on intraocular pressure

During the first week of the trial with increasing concentrations of topical LCL to both eyes in both animals, it was noted that there was a reduction in intraocular pressure temporally related to administration of the eye drops. This observation was further studied with additional testing of the topical LCL over a 2–3 week period in both animals. Additional safety experiments were conducted. The results are shown in Fig. 6. Overall, the results show that topical LCL reduces IOP by 35%–40% using dosages ranging from 0.002% to 0.07%. There were no local or systemic adverse events (as measured by daily, complete ophthalmic examinations and toxicology studies of blood) except for minimal, reversible inferior conjunctival hyperemia at the 0.07% dose.

Discussion

In summary, this canine study of topical LCL showed that at the 0.07% concentration there was minimal, reversible, conjunctival hyperemia. There was no other ocular or systemic toxicity. At the 0.06% concentration used TID OU, there was a visible decrease in the INS and EMR showed a 153%–240% increase in NAFX and 30%–70% decrease ($P < 0.001$) in nystagmus amplitude across gaze; therefore, increases in the NAFX

translate directly into increases in visual acuity.[24,25] Based on the values of the right-eye NAFX, the primary position improvement of 0.060 to 0.330 is equivalent to an increase in canine acuity from 20/1200^{+} (0.017) to 20/200^{-} (0.094). For the left eye, the NAFX improvement of 0.150 to 0.380 is equivalent to an increase in canine acuity from 20/500^{+} (0.043) to 20/200^{+} (0.109). There was also a sustained (40%–60%) significant ($P < 0.05$) decrease in intraocular pressure from baseline.

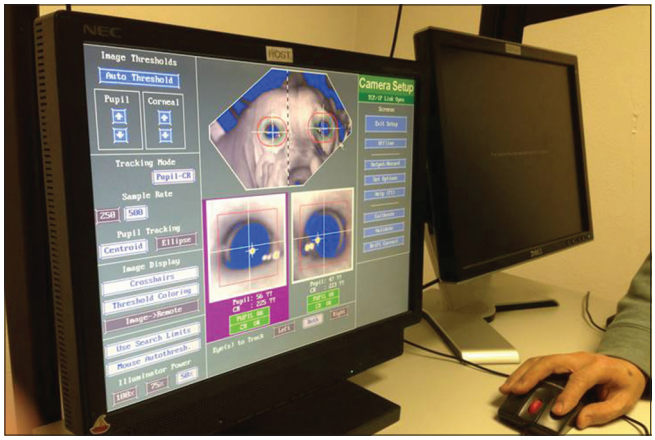

Figure 3: Computer showing Ginger being recorded using high-speed video system (EyeLink II and EyeLink 1000, SR Research Ltd., Osgoode, ON, Canada), capable of measuring horizontal and vertical movement simultaneously at a sampling frequency of 500 Hz and resolution of 16 bits

LCL Pyrethroids are a group of man-made (synthetic) pesticides designed to resemble the natural pesticide pyrethrum, which is produced by chrysanthemum flowers.[13] Pyrethroids disrupt the normal functioning of the nervous system in an organism or animal, including human, by prolonging the deactivation of voltage-gated sodium channels, which results in prolonged excitation of nerve fibers. In a study that investigated abnormalities in neurological signs and electrophysiological findings among individuals who had experienced paresthesias from contact exposure to synthetic pyrethroids, no significant differences were observed in comparison to unexposed (control) subjects.[14] There were no serious adverse events in the canines as a result of 3 weeks of continuous use of topical LCL in this animal model.[14]

Studies conducted on INS and its treatment have demonstrated that it is primarily a single motor disorder

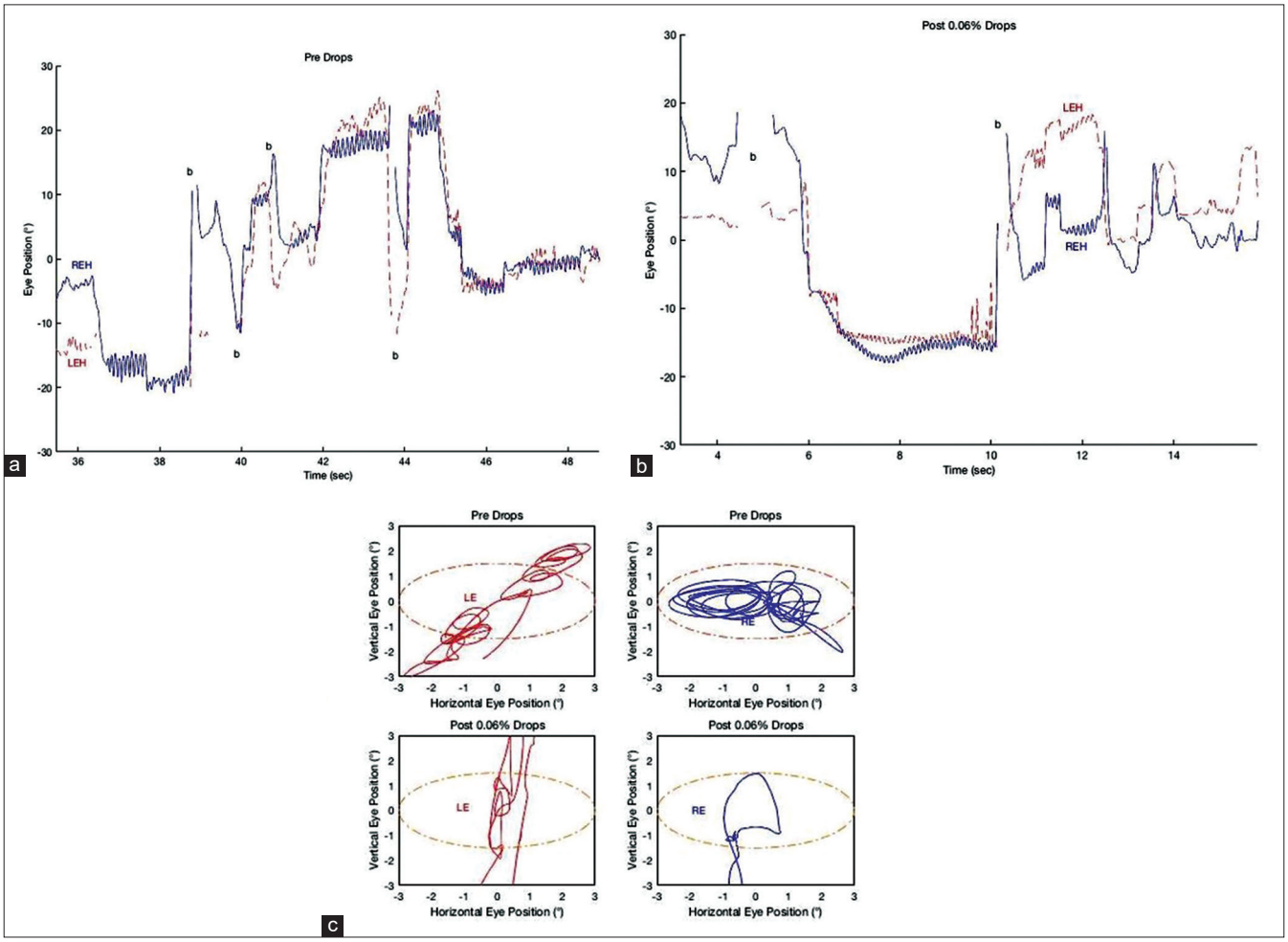

Figure 4: Right eye-horizontal and left-horizontal (LEH) data from the pre- (a) and post-0.06% (b) showing the marked decrease in INS amplitudes at all gaze angles. Areas centralis indicated by "b". Also shown in (c) are pre- and post-0.06% LCL eye movement data from each eye showing improved areas of target centralization ("foveation") and NAFX values. (RE = right eye, LE = left eye, REH = right eye horizontal, LEH = left eye horizontal, up is right and down is left, X-axis time in seconds, and Y-axis is eye position in degrees)

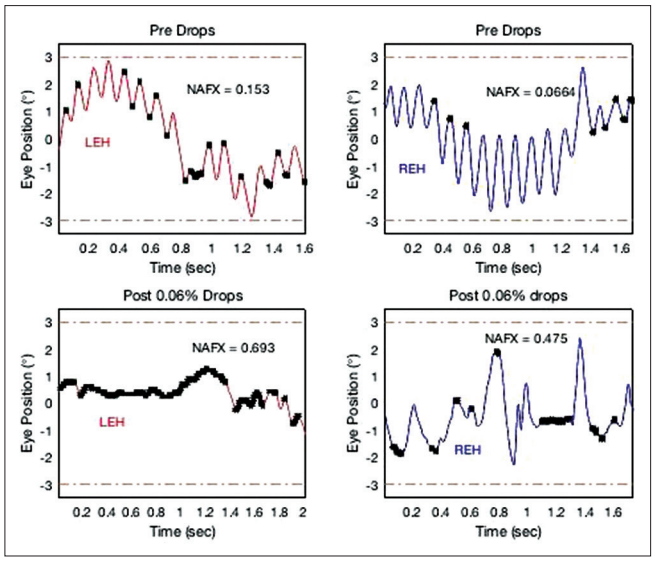

Figure 5: Plots of the pre- and post-0.06% LCL dosage in Ginger showing the 153%– 240% increases in horizontal NAFX values and 30%–70% decreases in nystagmus amplitudes in the right and left eye. (REH = right eye horizontal, LEH = left eye horizontal, sec = seconds, X-axis time in seconds, and Y-axis is eye position in degrees)

whether or not there are associated afferent system abnormalities.[9] Eye-movement characteristics of the INS instability are the same across patient populations, e.g., loss of pursuit-system damping. Treatment of the visual system in patients with INS may be directed: (1) toward the many associated afferent system abnormalities (decreased acuity, amblyopia, ametropia, retinal and optic pathway disease, photophobia); (2) centrally at the neuronal level responsible for the oscillations (e.g., medications); or (3) peripherally to reduce the underlying oscillation (eye-muscle surgery, botulinum toxin, topical eye drops). Clinical and electrophysiologic data collected for more than 50 years supports the novel hypothesis that eye-muscle surgery alone improves visual functions (other than binocularity) in patients with INS.[8,9,18] This was elaborated in the electrophysiogic observations and reports by Dell'Osso *et al*. in the 1970s and 1980s and by animal work and National Eye Institute–supported clinical trials performed in the early 2000s.[19,20,22,26-28] These reports contain data showing improvements in visual acuity, head positioning, nystagmus waveforms, useful vision per unit of time and as a function of gaze, faster object recognition, less head oscillations, better motion and contrast sensitivity, improved eccentric null zone size, nystagmus periodicity and associated strabismus. These results suggest that neurovisual changes take place as a result of the surgical procedure. The current hypothesis is that surgical interference with peripheral extraocular enthesial proprioceptive nerve endings influences central ocular motor pathways, disturbance of which, results in an improved INS oscillation.[29]

Recent anatomic studies have clarified that each rectus extraocular muscle passes through a pulley located near the globe equator in Tenon's fascia and diverges into the global and orbital layers.[30,31] These anatomic differences suggest that the global layer acts to move the eye against the antagonist extraocular muscle while the orbital layer moves the pulley plane. The tendino-scleral junction (enthesis) is part of the

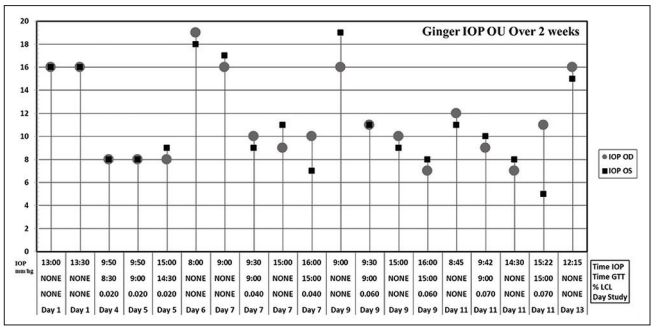

Figure 6: Graphical representation showing effect of topical LCL on intraocular pressure (IOP) in Ginger

global layer and probably has an additional role in ocular motor proprioception.[32] These results have led to the hypothesis that disruption of enthesial proprioceptive structures as a result of eye-muscle surgery or topical medications favorably affects the nystagmus oscillation. The enthesial endings could be therapeutically targeted by topical eye drops for similar reasons as eye-muscle surgery. The application a topical eye-drop medication to treat INS has been previously reported.[11,12]

The canines in this study had intervention immediately after weaning, which is theoretically during their "sensitive period" of visual and ocular motor development.[33] Early intervention in the treatment of eye movement disorders is not a new idea. The results obtained by Birch *et. al.* suggest that early surgical alignment is associated with better stereopsis and higher prevalence of fusion without adverse motor outcomes, because early surgery *minimizes the duration of* misalignment. The use of topical LCL in these animals may have taken advantage of treating them during their "sensitive" period of ocular motor development. This factor may also have contributed to the significant reduction in their nystagmus. Repeating the study in visually mature animals is needed to confirm or deny this hypothesis.

By monitoring the effects of the LCL on IOP, we observed a consistent reduction in IOP. We do not understand this apparent causal relationship. It is known that a functioning sodium/potassium ATPase pump system in the ciliary epithelium is involved in facilitating aqueous outflow.[34] It may be that after topical LCL administration, absorption into the eye results in interference with sodium-potassium-ATPase activity in nonpigmented ciliary epithelium inhibiting aqueous humor production, thus lowering IOP.

Limitations of this trial include that this is a proof of concept, safety study in a nonprimate model of nystagmus in two animals; thus, its effects in nonhuman primates or humans are unknown. We did not study long-term side effects on nystagmus or IOP or whether there was any benefit to topical LCL on other visual functions. Understanding the pharmacology and pharmacodynamics of LCL in the eye and its systemic effects requires further investigation. It will require phase1-2 human testing to determine LCL safety, formulation, efficacy and dosing regimens.

Conclusion

Our animal study suggests LCL has potential for topical treatment of both INS and diseases with raised intraocular pressure. Further, this new treatment approach confirms the

importance of extraocular muscle proprioception in ocular motor diseases and their treatment.

Financial support and sponsorship

This work was supported in part by the Akron Children's Hospital Considine Research Institute and Foundation and The Office of Research and Development, Medical Research Service, Department of Veterans Affairs, NIH Grant EY06855 and NIH Training Grant EY07157.

Conflicts of interest

There are no conflicts of interest.

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