



## ***Scientific Advisory and Review Committee (SARC) Protocol***

**COMIRB # 15-1972**

**Protocol Title: The Diurnal and Nocturnal Effect of Pilocarpine on Intraocular Pressure and Ocular Perfusion Pressure**

**Version Date: 06Jan2017**

**Principal Investigator: Leonard K. Seibold, MD**

### **I. Hypothesis and Specific Aims**

We hypothesize that pilocarpine will achieve a decrease in intraocular pressure and increase in ocular perfusion pressure throughout the diurnal and nocturnal periods. The aim of this study will be to determine the effects of pilocarpine as an adjunct medication to ophthalmic prostaglandin analogue (PGA) monotherapy at multiple intervals throughout a 24-hour period and compare these effects to ophthalmic prostaglandin analogue alone.

### **II. Background and Significance**

Intraocular pressure (IOP) is a major risk factor for the development of glaucoma. In addition, it remains the only modifiable factor in the prevention and subsequent treatment of glaucomatous optic neuropathy.<sup>1</sup> Most clinicians only take a single IOP measurement during a patient visit that will typically occur once every four months. These snapshots in time are likely inadequate for the optimal management of glaucoma and may miss actual peak values. Diurnal IOP curves, consisting of serial IOP measurements, can provide a better estimate of each patient's individual IOP variation throughout the day. However diurnal curves fail to determine IOP values during another crucial time, the nocturnal period. Glaucomatous eyes have been shown to have different IOP curves during the nocturnal period compared to healthy controls.<sup>2</sup> In addition, different classes of glaucoma drugs have variable IOP lowering effects during the nocturnal hours compared to the diurnal/wake period.<sup>3</sup> Therefore it is crucial to determine an accurate IOP curve for each medication throughout a 24 hour time period.

Pilocarpine hydrochloride ophthalmic 2% is a commercially available, topical anti-cholinergic, FDA approved for treatment of glaucoma and ocular hypertension. Pilocarpine has a long history of use after FDA approval in 1974, but there is a paucity of data detailing its efficacy over a 24 hour period. One early study found average IOP lowering efficacy to be on the order of 20% from baseline over the diurnal period only.<sup>4</sup> The nocturnal effects of pilocarpine are poorly defined with only one study evaluating the 24 hour effects on IOP.<sup>5</sup> This study found a significant IOP lowering effect from pilocarpine throughout a 24 hour period, but this was in exfoliation glaucoma patients only. Pilocarpine's relatively short duration of action requires frequent daily dosing of 3 to 4 times per day making it a seldom chosen option for first line therapy compared to once daily dosed medications. However it is often considered as an adjunct to more easily administered medications such as the prostaglandin analogues (ie. Latanoprost, bimatoprost, travoprost, or tafluprost). It is in this real world clinical scenario that we wish to study this medication's effects.

In this study, we seek to better characterize the knowledge base of the IOP lowering effects of pilocarpine. We plan to determine the IOP lowering effects in patients with open angle glaucoma or ocular hypertension who are currently taking PGA monotherapy. Our goal is to define the potential additive effect of pilocarpine throughout a 24-hour period, not only for IOP, but for ocular perfusion pressure as well. Ocular perfusion pressure was defined as  $\frac{2}{3}[\text{diastolicBP} + \frac{1}{3}(\text{systolicBP} - \text{diastolicBP})] - \text{IOP}$ . These data will allow us to expand current knowledge of the effects of pilocarpine and help determine if this medication has a useful role as an adjunctive treatment in glaucoma

### III. Preliminary Studies

Our group has completed similar studies of the 24-hour effects of other glaucoma medications, including Travatan Z and Simbrinza. These protocols were reviewed and approved by SARC and COMIRB in 2012 and 2014 respectively and completed less than a year after approval. The results from the Travatan Z study were published in the American Journal of Ophthalmology, PMID 24182742. The results from the second trial are being analyzed and prepared for manuscript submission (COMIRB # 14-0362).

### IV. Research Design and Methods

#### A. Study Design Details

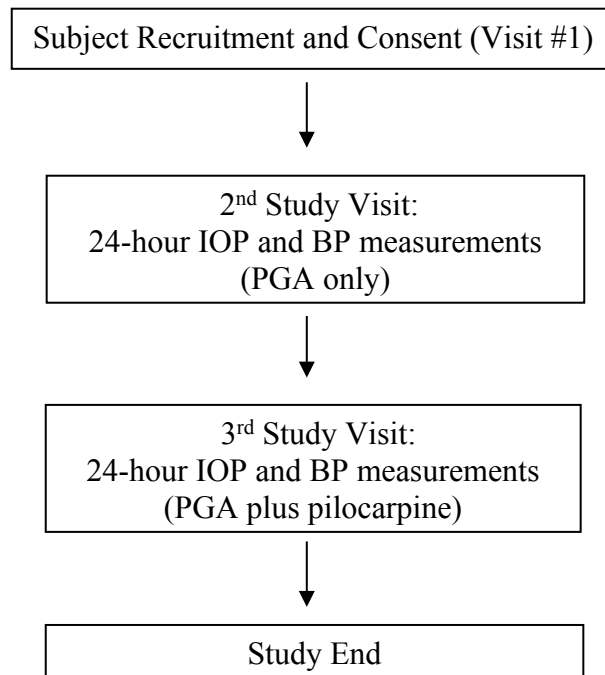
This is a single site, investigator-initiated, prospective, clinical, open-label study of the 24-hour IOP lowering effects of pilocarpine. Patients with open angle glaucoma (including pigment dispersion glaucoma and pseudoexfoliation glaucoma) or ocular hypertension who are currently on monotherapy with a prostaglandin analogue (PGA: latanoprost, bimatoprost, travoprost, or tafluprost) will be recruited at their regularly scheduled ophthalmology exam visits. A study coordinator will discuss study details and commitments and obtain informed consent from subjects on the same day or later date during visit 1.

The CTRC nurses will be trained by an ophthalmic technician (lead technician in our study group with experience in training others) with previous expertise with the pneumotonometer. This will include a 30 minute hands-on demonstration with the instrument and accompanying written instructions. The nurse must then demonstrate proficiency at obtaining an accurate and reproducible IOP measurement as determined by a performance evaluation from the training technician. In addition, the instrument records IOP waveforms and standard deviation values that will be reviewed during the study to ensure accuracy of measurements. The use of this device is very simple and straightforward and new technicians are frequently proficient with its use after a brief 30 minute introduction as outlined above.

Subjects will be asked to participate in three separate study visits. The first study visit will involve enrollment of subjects into the study after meeting inclusion criteria and reviewing the risks and requirements of the study. Informed consent will be obtained and urine pregnancy test performed where applicable. On the second study visit, baseline IOP measurements will be taken while on PGA monotherapy. The purpose of this 24-hour visit will be to establish individual baseline IOP and OPP while on PGA therapy before pilocarpine is administered at visit 3. Patients will check in at the inpatient Clinical Translational Research Center (CTRC) on the 12<sup>th</sup> floor of Anschutz Inpatient Pavilion at 09:30. Intraocular pressure of both eyes and blood pressure measurements will then be taken every 2 hours for a 24-hour period. Measurements during the diurnal period of 0600 to 2200 will be in the normal upright position (total of 8 measurements: 0700, 0900, 1100, 1300, 1500, 1700, 1900, 2100). Starting with the measurements after 2200, patients will be measured in the supine position during the nocturnal period (total of 4 measurements: 2300, 0100, 0300, 0500). Patients will self-dose with their current prescribed PGA at 2000. This dose will be observed by study staff. After the last measurement in a 24-hour period, subjects will be free to leave the CTRC. Meals will be provided to subjects through the CTRC inpatient food services during their stay. Visit 1 and 2 may be combined with consent being obtained prior to any study procedures taking place.

A second 24-hour visit (visit #3) will be performed at any point over the next 4 weeks. This time period was chosen to allow convenient scheduling for the patient and CTRC unit. Visit 3 will proceed as Visit 2 with IOP, BP and pulse measured every 2 hours for a 24 hour period. In addition, a dose of pilocarpine

2% will be administered by nursing staff at 0600, 1000, 1600, and 2200. Due to the relative lack of additional efficacy with extended use, no period of prolonged use of pilocarpine is needed prior to this visit. Patients will self-dose with current prescribed PGA at their usual dosing time similar to visit #2. At the conclusion of study visit #3, the subjects participation will be complete, and they will return to their prior treatment regimen and follow up with their treating ophthalmologist for further recommendations.



**B. Sample size justification and analytical plan**

A statistical consultation was made with the Colorado Biostatistics Consortium. Their recommendations are as follows: The sample size calculations were based on the assumption that the mean difference in IOP will be 1.9 mmHg. The sample sizes required to detect this difference using a paired t test with 80% or 90% power using two assumed standard deviations are:

	SD = 3.0	SD = 4.0
80% power	22	37
90% power	29	49

Based on these power calculations, we have decided to use a sample size of 30. Due to the repeated measures of IOP and BP over each study visit, mixed models will be utilized to compare IOP and OPP across all time points.

**C. Primary Outcome Measure(s)**

The primary outcome measure will be the change in intraocular pressure and ocular perfusion pressure after the addition of pilocarpine to PGA monotherapy at multiple time points throughout a 24-hour period.

## **V. Human Subjects**

### **A. Inclusion Criteria**

- Current confirmed diagnosis of open angle glaucoma or ocular hypertension including pigment dispersion glaucoma and pseudoexfoliation glaucoma.
- Current use of topical PGA (latanoprost, bimatoprost, travoprost, or tafluprost) once a day in both eyes for at least 6 weeks
- Age  $\geq$  18 years, of either gender, or any race/ethnicity

### **B. Exclusion Criteria**

- Females who are currently pregnant or planning to become pregnant during the study period
- Diagnosis of any other form of glaucoma other than open-angle
- Intraocular pressure readings of  $<14$ mmHg in either eye when measured during routine office visit in the past 12 months.
- Schaffer angle grade  $< 2$  in either eye by gonioscopy
- Intraocular surgery within 6 months or laser within 3 months
- History of retinal tear or detachment in either eye
- Active iritis in either eye as determined by most recent eye examination
- Patients who smoke or have irregular daily sleep patterns
- Patients who have started or changed glucocorticoids therapy in the last 3 months
- Patients who are currently using medical or recreational marijuana
- Any use of a non-FDA approved medication for glaucoma in the last 3 months
- History of allergy to pilocarpine
- History of allergy to proparacaine ophthalmic solution

### **C. Anticipated risks**

Intraocular pressure: Measurement will be performed using an FDA approved pneumotonometer device. This measurement requires the use of a topical anesthetic drop (proparacaine 0.5%) before measurement. The pressure is obtained by placing a probe onto the corneal surface for approximately 5-10 seconds per eye and requires the subject's cooperation in remaining motionless. All measurements will be performed by trained CTRC nursing staff. During awake hours (0600 – 2200), the measurements will be taken in the upright position. During sleep hours (2200 - 0600), subjects will be awakened gently and measurements taken in the resting, supine position to more closely approximate typical sleeping posture and IOP.

The pneumotonometer and associated topical anesthesia are both used routinely in everyday ophthalmologic examinations for IOP measurement. Risks associated with these measurements include ocular surface irritation and minor corneal abrasion. There is also a small risk of hypersensitivity with topical anesthesia (proparacaine). Patients may experience a mild stinging or blurring of vision that is brief and self-limited. Rare risk of allergic reaction may occur causing diffuse epithelial keratitis. The risk of corneal abrasion during intraocular pressure measurement using a Pneumotonometer is small and estimated at 1/3,000. This risk is no greater than that encountered in every day ocular exams as part of routine work-ups. Any persistent or significant pain or discomfort sustained during or after IOP measurements will be assessed by slit lamp examination and will be addressed as per clinical standards. Any antibiotics eye drops and lubricating eye drops needed to treat a corneal abrasion will be provided at no cost to the subject. Clinical follow up until resolution of the corneal abrasion will also be done by the eye clinic at no cost to the subject. Subjects will also be at risk for sleep loss due to the frequency of IOP checks during the nighttime hours. This cannot be avoided due to the nature of the study. However, sleep disturbance will be minimized by very brief testing measurements that can be performed in dim lighting with accuracy.

Blood pressure: Measurement will be performed using an automated, electronic FDA approved sphygmomanometer. There are no significant risks associated with the use of this device.

Pregnancy Test: All women of childbearing potential (who are not postmenopausal for at least 1 year or surgically sterile) will undergo a urine pregnancy test prior to the start of study medication. Any positive results will result in exclusion from the study. [Quidel Corp QuickVue hCG urine test]

Study Medication: All subjects will receive 4 doses of pilocarpine 2% in both eyes during the third study visit. The study medications have been FDA approved for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension. The inclusion criteria were designed to include only this population. Therefore, the medication will be used in a manner that is in complete accordance with the labeled indications and dosing recommendations.

There are some possible adverse effects and reactions with the study medication, pilocarpine 2%, as outlined in the drug information sheet. We anticipate a low occurrence of these, as the study participants will only be receiving a total of 4 doses of the study medication.

The most frequently reported adverse reactions occurring in  $\geq 5\%$  of patients in the pilocarpine 2% populations were: headache/browache, accommodative change, blurred vision, eye irritation, visual impairment (dim, dark, or "jumping" vision), and eye pain.

Precautions include:

- Night Driving
  - Caution is advised with night driving and when hazardous activities are undertaken in poor illumination.
- Accommodative Spasm
  - Pilocarpine Hydrochloride Ophthalmic Solution may cause problems when changing focus between near objects and distant objects. Do not drive or use machinery if vision is not clear.
- Contact Lens Wear
  - Contact lens should be removed prior to the instillation of Pilocarpine Hydrochloride Ophthalmic Solution. Wait 10 minutes after dosing before reinserting contact lenses.

Contraindications to the use of pilocarpine: None

Safety stopping rules will also be put into place to hold or stop the study until further review if either of the following occurs:

- >3 corneal abrasion related to the study protocol
- >2 episodes of bacterial keratitis related to the study protocol

Individual subject stopping will occur if a subjects becomes intolerant to study testing, intolerant to study eye drops, or develops a corneal abrasion during testing,

#### **D. Describe plan to minimize risk**

All patients will receive full disclosure of these possible adverse events and be monitored during the study for any occurrences. To minimize systemic absorption, patients will be instructed on proper eye drop administration including closing of the eyelids and punctual occlusion after administration. The exclusion criteria have been designed in a manner to eliminate subjects with a high risk of adverse events. All women of childbearing age will take a urine pregnancy test at visit 1 prior to starting the first overnight visit. Any significant adverse events or patient intolerance will be evaluated by the study coordinator and/or the PI and result in removal from the study. Subjects will be able to contact the study coordinator during business hours and have access to the Rocky Mountain Lions Eye Institute after hours call center and on call ophthalmologists for any concerns that arise after normal business hours. Any evaluation,

diagnosis, and treatment of adverse events related to the medication will be provided at no charge to the subject until the event is resolved. Subjects will be advised of potential for sleep deprivation after Visits 2 & 3 and suggested options of arranging transportation or staying at facility to sleep longer if needed to drive.

The PI will review all reported adverse events and stop individual subjects or the study as defined in risks section. As the ocular medications in this study are all FDA approved and being used on-label, a separate safety officer will not be utilized.

#### **E. Describe the potential benefits of the study**

This study is designed with the intention to further elucidate the 24-hour effects of pilocarpine on intraocular pressure and ocular perfusion pressure. Prior work regarding nocturnal effects of other medications (PGAs, CAIs, AAs) has been published. This will be the first known 24hr IOP study of pilocarpine as an adjunct to PGA therapy. A better understanding of the effects of this drug on intraocular and blood pressure will contribute to physician's ability to prescribe appropriate and effective therapy for glaucoma and ocular hypertension. The results of this study will help better determine the effect of this medication in the overnight hours.

#### **VI. References**

1. Coleman AL, Miglior S. Risk factors for glaucoma onset and progression. *Surv Ophthalmol.* 2008 Nov;53 Suppl1:S3-10.
2. Drance SM. Diurnal Variation of Intraocular Pressure in Treated Glaucoma. Significance in Patients with Chronic Simple Glaucoma. *Arch Ophthalmol.* 1963 Sep;70:302-11.
3. Liu JH, Kripke DF, Weinreb RN. Comparison of the nocturnal effects of once-daily timolol and latanoprost on intraocular pressure. *Am J Ophthalmol.* 2004 Sep;138:389-95.
4. Harris LS, Galin MA. Dose response analysis of pilocarpine induced ocular hypotension. *Arch Ophthalmol* 1970;84:605-8.
5. Konstas AG, Lake S, Maltezos AC, Holmes KT, Stewart WC. Twenty-four hour intraocular pressure reduction with latanoprost compared with pilocarpine as third-line therapy in exfoliation glaucoma. *Eye.* 2001 Feb;15(Pt 1):59-62.