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The Diurnal and Nocturnal Effect of Travoprost with SofZia on Intraocular Pressure and Ocular Perfusion Pressure

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Abstract

Purpose—To determine the 24-hour effects of travoprost with sofZia on intraocular pressure (IOP) and ocular perfusion pressure as well as the endurance of IOP lowering after last dosing.

Design—Prospective, open-label study

Methods—Forty subjects with open angle glaucoma or ocular hypertension were admitted to our sleep laboratory for three 24-hour sessions monitoring IOP, blood pressure (BP), and heart rate. The first baseline session occurred after medication washout or immediately after enrollment for treatment naive patients. A second 24-hour monitoring session was performed after four weeks of once nightly treatment of travoprost with sofZia. The medication was then discontinued and a third 24-hour session was completed 60–84 hours after the last dose taken. IOP measurements were taken using a pneumotonometer every two hours in the sitting position during the 16-hour diurnal period and in the supine position during the 8-hour nocturnal period. Ocular perfusion pressure was defined as $2/3[\text{diastolic BP} + 1/3(\text{systolic BP} - \text{diastolic BP})] - \text{IOP}$.

Results—Treatment with travoprost with sofZia significantly lowered mean diurnal and nocturnal IOP levels from baseline (Diurnal 18.1 ± 3.9 to 15.3 ± 3.3 mm Hg; Nocturnal 20.6 ± 3.6 to 19.4 ± 3.4 mm Hg, $p < 0.01$ for both). Once treatment was discontinued, mean IOP remained at levels significantly less than baseline during both the diurnal (16.6 ± 3.8 mm Hg) and nocturnal periods (19.4 ± 3.5 mm Hg). Mean baseline ocular perfusion pressure was significantly increased during the diurnal but not the nocturnal period (Diurnal 73.7 ± 11.4 to 76.5 ± 10.3 mm Hg, $p = 0.01$; Nocturnal 64.4 ± 12.6 to 64.2 ± 11.1 mm Hg, $p = 0.67$).

Conclusion—Travoprost with sofZia significantly lowers IOP throughout the diurnal and nocturnal periods, and increases ocular perfusion pressure in the diurnal, but not the nocturnal period in open angle glaucoma and ocular hypertension. The treatment effect on IOP endures for at least 84 hours after the last dose.

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Introduction

Treatment of glaucoma centers on the reduction of intraocular pressure (IOP).^{1,2} While several laser and surgical therapies are available, topical medication continues to be a commonly utilized initial treatment option. Due to their once daily dosing, excellent efficacy, and favorable side effect profile, the prostaglandin analogues are frequently chosen as the first line medication for the reduction of IOP in most forms of glaucoma and ocular hypertension.³ It is believed that prostaglandin analogues lower IOP primarily by increasing aqueous outflow through the uveoscleral pathway.⁴ Based on more recent evidence, these medications may also augment the traditional outflow pathway through the trabecular meshwork and Schlemm's canal.^{5,6} There are currently several molecules within the prostaglandin analogue class that are commercially available with each having a distinct profile for pressure lowering and tolerability.

Travoprost (Travatan, Alcon, Fort Worth, TX) was first approved by the Food and Drug Administration (FDA) in 2001. The multi-dose bottle for travoprost available in the United States was originally preserved with the detergent preservative benzalkonium chloride (BAK). This formulation has been previously shown to significantly lower IOP during both the diurnal and nocturnal periods in patients with open angle glaucoma and ocular hypertension. A report by Sit et al has demonstrated a durable IOP lowering response of travoprost with BAK for 41 to 63 hours after last dose.⁷ Despite its efficacy and widespread use in ophthalmic medications, chronic use of BAK can have several negative effects on ocular tissues in specific patient populations.^{8,9} Prolonged BAK exposure in cell culture models results in arrest of cell growth, apoptosis, and even necrosis at very high doses.^{10,11} These detrimental effects are implicated in ocular surface disease that is frequently present in patients taking multiple BAK-preserved medications. In 2006, BAK was removed from travoprost and replaced with a novel ionic-buffered preservative system called sofZia (Travatan Z, Alcon). After application on the ocular surface, sofZia components break up into innate ingredients with the theoretical benefit of decreased hyperemia and improved tolerability, although results from published studies are conflicting.¹¹⁻¹³

Recent studies have shown that travoprost with sofZia lowers IOP with a profile similar to the original formulation, however the effects throughout a 24-hour cycle including the nocturnal period are poorly characterized.¹⁴⁻¹⁶ In a report by Gross et al, travoprost with sofZia was shown to have a prolonged duration of action up to 60 hours.¹⁵ The effect of travoprost with sofZia on IOP beyond this time remains unknown. In this study, we seek to further evaluate the IOP lowering effect of travoprost with sofZia in patients with open angle glaucoma and ocular hypertension and assess the durability of effect up to 84 hours after last dose taken. Furthermore, we aim to characterize the medication's effect on ocular perfusion pressure across the diurnal and nocturnal period.

Methods

Approval for this prospective, open-label study was obtained from the Colorado Multiple Institutional Review Board prior to initiation of the study and the tenets of the Declaration of Helsinki were followed. Informed consent was obtained from all subjects prior to enrollment in the study. A total of forty patients with open angle glaucoma (OAG) or ocular hypertension (OHTN) were recruited during regularly scheduled examinations at the Rocky Mountain Lions Eye Institute, University of Colorado Denver. Inclusion criteria included patients of any gender or ethnicity with an existing or new diagnosis of ocular hypertension or open angle glaucoma. Patients with ocular hypertension had untreated IOP reading >21 mm Hg on 2 or more office visits with otherwise normal optic nerve appearance and visual field testing. Patients with open angle glaucoma possessed abnormal visual field testing

(Zeiss Humphrey Field Analyzer, Dublin, CA) and/or optic nerve findings consistent with glaucomatous damage including increased cup to disc ratio, notching, rim defects, hemorrhage, nerve fiber layer defects, or a combination of these. Office IOP readings were not considered in the inclusion or exclusion criteria. Exclusion criteria included females who were pregnant or planning to become pregnant, angle closure glaucoma, narrow anterior chamber angle by gonioscopy (Schaffer grade <2), current smokers, irregular sleep patterns, inability to safely discontinue ocular glaucoma medications for four weeks, and history of cystoid macular edema, inflammatory eye disease or Herpes Simplex viral infection.

After enrollment, subjects already taking topical glaucoma medications underwent a wash out period of four weeks regardless of drug class before starting the study. Subjects not taking any glaucoma medications were allowed to proceed immediately to the first 24-hour study session. For each of three study sessions, subjects were admitted to a private bedroom at the University of Colorado Hospital Clinical and Translational Research Center for a 24-hour period. The first baseline session was performed off all glaucoma medications. A supply of travoprost with sofZia was then dispensed to the subject with instructions to place one drop nightly at approximately 9:00 pm in both eyes. After four weeks of therapy, subjects returned for their second 24-hour session. During this visit, the study medication was self-administered under supervision at the usual dosing time of 9:00 pm. After completion of the second study session, subjects were asked to discontinue the study medication and return for a third 24-hour session three days after the last dose was taken.

Subjects were not restricted in their activity during daytime hours of 6:00 am to 10:00 pm, but were required to remain supine in bed during nighttime hours of 10:00 pm to 6:00 am. Food and drink were provided to the subject at their leisure. Measurements of IOP, blood pressure (BP), and heart rate were recorded every two hours by a trained ophthalmic technician or clinical nurse on each study session. All measurements were performed with the subject in the habitual position for that time. Readings taken during the diurnal period of 6:00 am to 10:00 pm were done in the sitting position and those taken during the nocturnal period from 10:00 pm to 6:00 am were done in the supine position. A total of eight readings were performed during the diurnal period (7:00, 9:00, 11:00, 13:00, 15:00, 17:00, 19:00 and 21:00) and four readings in the nocturnal period (23:00, 1:00, 3:00, and 5:00) for each study session. A Model 30 pneumotonometer (Reichert Inc., Depew, NY) was used for all IOP measurements. Topical proparacaine 0.5% was used for anesthesia before each reading. Measurements with standard deviations greater than 1.0 were discarded and retaken. All measurements were performed on both eyes as long as the eye met inclusion criteria. A standard automated sphygmomanometer was used to measure blood pressure and pulse at the time of each IOP measurement.

As previously described, ocular perfusion pressure was calculated as the difference between two thirds of the mean arterial blood pressure (MAP) and IOP (Ocular perfusion pressure = $2/3\text{MAP} - \text{IOP}$) where MAP was calculated as the diastolic blood pressure plus one third of the difference between systolic and diastolic blood pressures [$\text{MAP} = \text{DBP} + 1/3(\text{SBP} - \text{DBP})$].¹⁷ The means of IOP, ocular perfusion pressure, SBP, and DBP were calculated for each two hour time point as well as the diurnal period (eight readings in the upright position) and nocturnal period (four readings in the supine position). For comparison of study metrics during each study period, mixed models were fit to the data and various contrasts were reported through linear combinations of the models parameters. Mixed models were specifically designed to take correlation from repeated measurements into account. The Pearson correlation coefficient (PCC) was used to assess the relationship between baseline IOP and absolute IOP reduction during treatment. All statistical analyses were performed using SAS 9.3 software (SAS Institute Inc., Cary, NC, USA). Statistical significance was defined as $p < 0.05$.

Results

Of the 40 subjects enrolled, there were 28 females and 12 males with a mean age of 65 years (range: 43-84 years). There were 21 Caucasians, 13 African-Americans, 4 Hispanics, and 2 Asians. Diagnoses of subjects included primary open angle glaucoma (37), ocular hypertension (2), and pigmentary glaucoma (1). All subjects completed the three study visits. The medication was well tolerated by all subjects with no serious adverse events related to drug administration. Mean central corneal thickness was $541.0 \pm 34.0 \mu\text{m}$.

The 24-hour IOP profiles for each study visit are displayed in Figure 1. After four weeks of travoprost with sofZia therapy, the mean IOP was significantly reduced at all time points during both the diurnal period (upright positioning) and nocturnal period (supine positioning) ($p < 0.05$). The mean IOP for the entire diurnal period was significantly lowered from a baseline of 18.1 ± 3.9 to 15.3 ± 3.3 mm Hg during treatment ($p < 0.01$). Similarly, mean IOP during the nocturnal period was lowered from 20.6 ± 3.6 mm Hg at baseline to 19.4 ± 3.4 mm Hg on treatment ($p < 0.01$). Three days after the last dose taken, the mean IOP during the diurnal period remained significantly lower than baseline (16.6 ± 3.8 mm Hg, $p < 0.01$) for the entire period and at each individual timepoint. The magnitude of IOP lowering effect was less than during treatment ($p < 0.01$). For the nocturnal period, the IOP lowering effect was unchanged from active treatment even after three missed doses (19.4 ± 3.5 mm Hg, $p = 0.4$). The mean IOP for each study visit during the diurnal, nocturnal, and 24-hour period are listed in Table 1. The relationship between baseline IOP level and absolute IOP reduction during treatment is displayed in figure 2. A significant, negative correlation was found with a PCC of -0.80 (95% confidence interval: -0.84 to -0.76, $p < 0.01$).

Figure 3 displays the 24-hour ocular perfusion pressure profiles for each study visit. The mean ocular perfusion pressure was significantly increased during travoprost with sofZia therapy from a baseline of 73.7 ± 11.4 to 76.5 ± 10.3 mm Hg ($p = 0.01$) during the diurnal period, but was unchanged during the nocturnal period (64.4 ± 12.6 to 64.2 ± 11.1 mm Hg, $p = 0.67$). This effect was no longer seen after three missed doses. The mean ocular perfusion pressure for each study visit during the diurnal, nocturnal, and 24-hour period are listed in Table 2.

Mean systolic and diastolic blood pressures at baseline (124.7 ± 16.0 and 72.8 ± 10.9 mm Hg, respectively) were unchanged during active treatment (122.6 ± 15.4 , $p = 0.11$ and 72.4 ± 10.6 mm Hg, $p = 0.64$, respectively). However, during the third study visit after three missed doses, there was a statistically significant decrease in both systolic and diastolic BP compared to baseline (121.2 ± 14.8 and 70.8 ± 10.4 mm Hg, $p = 0.01$ for both).

Discussion

In this study, we further characterize the IOP lowering effects of travoprost with sofZia throughout a 24-hour period and define the effects of ocular perfusion pressure in a population of ocular hypertension and open angle glaucoma patients. At every time point during the circadian cycle, IOP was significantly reduced from baseline after four weeks of treatment. In addition, our results confirm the prolonged duration of action by travoprost with sofZia even up to 84 hours after the last dose taken. There was no difference in nocturnal IOP levels between the period on therapy compared to data collected up to 84 hours after discontinuation of therapy.

The findings of this study are in line with previous work reporting the circadian IOP effects of travoprost with BAK. In a similarly designed study of 20 patients, Sit et al found travoprost with BAK significantly lowered IOP throughout the diurnal and nocturnal periods

in the habitual positions (Diurnal: 20.2 mm Hg → 16.7 mm Hg, Nocturnal: 24.1 mm Hg → 22.4 mm Hg).⁷ In the same study, the 24-hour IOP levels remained significantly less than baseline after two missed doses with the nocturnal effect remaining unchanged from active treatment. Our results confirm a comparable effect of sofZia preserved travoprost compared to the BAK preserved solution. In addition, we demonstrate that the sustained effect of the medication on IOP is durable even up to 84 hours after last dose taken. Our findings demonstrate an unchanged persistence of the nocturnal effect and mitigation of the diurnal effect.

Several studies have confirmed the IOP lowering ability of travoprost during the diurnal period. In a report by Dubiner et al, results from seven different studies were pooled to confirm a 30% reduction in IOP with travoprost monotherapy.¹⁸ Each of these studies collected a mini-diurnal curve based on only three IOP measurements from 0800 to 1600 hours. A meta-analysis by Stewart et al compiled the 24-hour IOP treatment curves of patients on travoprost from three different studies.¹⁹ The mean 24-hour IOP reduction was 22.5 to 16.5 mm Hg (27%) however all readings were done in the upright position, with only one reading taken between 2200 and 0600. Our results show a more modest reduction of IOP at 16% during the diurnal period, 6% during the nocturnal period, and 12% for a 24-hour period in the habitual position.

We can suggest a few reasons for the discrepancy between our findings and prior studies of travoprost IOP lowering efficacy during the diurnal period only. It may in part be explained by the difference in protocol from prior work, particularly the difference in body positioning, tonometry methods and more frequent collection time periods. In fact, our results are more comparable to the 24-hour study of travoprost with BAK by Sit whose protocol was congruent with ours. In that study, the authors found an IOP lowering efficacy of 17% in the diurnal, 7% in the nocturnal, and 13% over a 24-hour period.⁷ Another important factor that differentiates our data from those of other diurnal studies is the lower baseline IOP of our enrolled population. Baseline IOP levels ranged 24.6-29.8 mm Hg in the Dubiner analysis, and 20.2-24.3 mm Hg in the meta-analysis by Stewart.^{18,19} The baseline IOP in our study only ranged 17.1-21.0 mm Hg. It has been shown that eyes with a higher baseline IOP level may have a greater IOP reduction with medication treatment.²⁰ Our findings also show a strong correlation between baseline IOP and absolute IOP reduction during travoprost with sofZia therapy. Therefore given the lower mean baseline IOP in our sample, it is not surprising to find a more moderate degree of IOP reduction compared to prior work.

Several population-based studies have identified ocular perfusion pressure as a risk factor for glaucoma in addition to IOP.²¹⁻²³ Ideal medications should not only decrease IOP but also increase ocular perfusion pressure to improve optic nerve perfusion. In this study, we show that ocular perfusion pressure was significantly increased (4%) by travoprost with sofZia throughout the diurnal period, however remained unchanged during the nocturnal period. Since systolic and diastolic BP readings were unchanged between baseline and treatment visits, the increase in ocular perfusion pressure can be attributed to the decrease in IOP levels. Despite the continued IOP lowering effect after three missed doses, the effect on ocular perfusion pressure was not significant for both time periods. This may in part be explained by the decline in blood pressure that occurred over each successive study visit, becoming significant on the third visit off medication. It is possible that subjects were increasingly more relaxed with study measurements causing a drop in blood pressure, but any medication effect cannot be determined without a control group.

We believe this is the first report on the 24-hour ocular perfusion pressure effects of travoprost as no similar analysis could be found in Pubmed indexed literature. Two studies

of OAG and OHTN patients found a significant increase in ocular perfusion pressure with travoprost with BAK, however the authors only tested a single time point (8:00-10:00 AM).^{24,25} For comparison, two studies by Quaranta et al have studied other prostaglandin analogue medications effects on circadian ocular perfusion pressure. In their first study of OAG patients, latanoprost did not have an effect on DBP or SBP, but increased ocular perfusion pressure by 11% in OAG patients.²⁶ In a second study of normal tension glaucoma (NTG) patients, latanoprost showed a small (3%) but significant increase in ocular perfusion pressure, while bimatoprost had no effect.²⁷ However in a later report by Ishibashi et al on NTG patients, latanoprost was found to have no effect on mean ocular perfusion pressure.²⁸

There are a few notable limitations of the present study. First, it should be noted that true ocular perfusion pressure requires measurement of the blood pressure within the ophthalmic artery, which is difficult to acquire. As a surrogate measure in this study, brachial blood pressure was used to calculate an estimate of the true ocular perfusion pressure. This method is frequently used throughout the literature but it should be noted that this is an estimation only of true ocular perfusion pressure.¹⁷ Furthermore, the increase in ocular perfusion pressure found in our study during the diurnal period may be largely due to a decrease in IOP given that BP was not significantly changed during treatment. A separate IOP independent mechanism of ocular perfusion pressure increase cannot be inferred from our calculations alone. Second, the non-comparative design of the study makes it difficult to make true inferences between the efficacy of travoprost with BAK and travoprost with sofZia. Our data can only be compared to similarly performed studies on travoprost with BAK in the literature.

In conclusion, travoprost with sofZia significantly lowers IOP at all time points throughout a 24-hour period in open angle glaucoma and ocular hypertensive patients. The IOP lowering effect endures for up to 84 hours after the last dose taken with no change in the nocturnal effect and a moderate decline in the diurnal effect. Ocular perfusion pressure is significantly improved during the diurnal period but did not change with treatment in the nocturnal period. The diurnal effect on ocular perfusion pressure did not persist after three missed doses.

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Figure 1.

Mean 24-hour intraocular pressure profiles in habitual body positions at baseline, during treatment with travoprost with sofZia, and after three missed doses. Circles represent baseline measurements off treatment, squares represent measurements during treatment with travoprost with sofZia, and triangles represent measurements after three missed doses of medication. Error bars represent the standard error of the mean.

Figure 2. Relationship of baseline intraocular pressure and absolute change of intraocular pressure with travoprost with sofZia. Pearson correlation coefficient = -0.80, $p < 0.01$.

Figure 3.

Mean 24-hour ocular perfusion pressure profiles in habitual body positions at baseline, during treatment with travoprost with sofZia, and after three missed doses. Circles represent baseline measurements off treatment, squares represent measurements during treatment with travoprost with sofZia, and triangles represent measurements after three missed doses of medication. Error bars represent the standard error of the mean.

Table 1

Intraocular pressure during the nocturnal and diurnal periods at baseline, during treatment with travoprost with sofZia, and after 3 missed doses.

Study Visit	Diurnal Period (Upright)	Difference from Baseline	p value	Nocturnal Period (Supine)	Difference from Baseline	p value	24 Hour (H)
Baseline	18.1 ± 3.9	-	-	20.6 ± 3.6	-	-	19.0 ±
On Treatment	15.3 ± 3.3	-2.9	<0.01	19.4 ± 3.4	-1.2	<0.01	16.6 ±
After 3 missed doses	16.6 ± 3.8	-1.5	<0.01	19.4 ± 3.5	-1.2	<0.01	17.5 ±

^aAll values are mean ± standard deviation in mm Hg.

Table 2

Ocular perfusion pressures during the nocturnal and diurnal periods at baseline, during treatment with travoprost with sofZia, and after 3 missed doses.

Study Visit	Diurnal Period (Upright)	Difference from Baseline	p value	Nocturnal Period (Supine)	Difference from Baseline	p value	24 Hour (H)
Baseline	73.7 ± 11.4	-	-	64.4 ± 12.6	-	-	70.6 ±
On Treatment	76.5 ± 10.3	2.8	0.01	64.2 ± 11.1	-0.2	0.67	72.4 ±
After 3 missed doses	73.2 ± 10.3	-0.5	0.51	63.4 ± 11.1	-1.1	0.27	69.9 ±

^aAll values are mean ± standard deviation in mm Hg.