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Daytime and Nighttime Effects of Brimonidine on IOP and Aqueous Humor Dynamics in Participants With Ocular Hypertension

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Abstract

Purpose—The effects of brimonidine on daytime and nighttime intraocular pressure (IOP) and aqueous humor dynamics were evaluated in volunteers with ocular hypertension (OHT).

Patients and Methods—Thirty participants with OHT (58.6 ± 1.7 years old, mean $\pm$ SEM) were enrolled into this randomized, double-masked, cross-over study. For 6 weeks, participants self-administered 0.2% brimonidine or placebo 3 times daily. During daytime and nighttime visits, measurements included aqueous flow (F_a) by fluorophotometry, outflow facility (C) by tonography, episcleral venous pressure (P_{ev}) by venomanometry, and seated and supine IOP by pneumatonometry. Uveoscleral outflow (U) was calculated mathematically.

Results—When treated with placebo, nighttime supine P_{ev} (11.2 ± 0.25 mm Hg) was higher ($P < 0.05$) compared with daytime seated P_{ev} (10.2 ± 0.25 mm Hg), and F_a and U were significantly reduced at night. Brimonidine significantly lowered seated IOP at 9:00 AM and 11:00 AM, 9:00 PM and 11:00 PM and supine IOP at 9:00 AM and 11:00 AM. Brimonidine increased U at 9 AM and 11 AM ($P < 0.01$) and had no effect on daytime and nighttime F_a , C , or P_{ev} .

Conclusions—In subjects with OHT, brimonidine treatment for 6 weeks significantly reduces seated IOP during the day by increasing uveoscleral outflow. The lack of IOP effect at night can be explained by failure to overcome a normal nighttime reduction of uveoscleral outflow.

Keywords

brimonidine; aqueous humor dynamics; intraocular pressure; ocular hypertension

Visual impairment and blindness due to chronic progressive optic neuropathy developing from glaucoma are major health problems worldwide. Current treatments that reduce the risk and progression of glaucoma are limited to therapies that lower the intraocular pressure (IOP),^{1,2} thereby attenuating neuronal injury and minimizing visual field loss. Some

glaucomas may progress because nighttime IOPs are outside a healthy range.^{3,4} Monitoring nighttime IOPs may help to evaluate progression of glaucoma and fully assess the quality of IOP-lowering therapies.^{3–6}

Several classes of drugs are currently available for glaucoma therapy, including prostaglandin analogs, β -adrenergic antagonists, carbonic anhydrase inhibitors, α_2 -adrenergic agonists, and cholinergic agonists. Drugs that substantially decrease aqueous flow (F_a) (β -adrenergic antagonists, carbonic anhydrase inhibitors) and IOP during the day may be ineffective at night because they do not decrease F_a more than the normally slow nighttime rate.⁷ Conversely, drugs that increase uveoscleral outflow, like prostaglandin analogs, appear to reduce nocturnal IOP because they may stimulate the normally slow nighttime uveoscleral drainage rate.^{8–10}

Brimonidine, a selective α_2 -adrenergic agonist, is used topically to treat open-angle glaucoma and ocular hypertension (OHT).¹¹ Its daytime effects on aqueous humor dynamics have been described previously. Acutely, brimonidine reduces the aqueous humor flow,¹² possibly by causing vasoconstriction of the vasculature in the anterior segment.¹³ With prolonged use, the F_a effect fades but brimonidine continues to lower IOP because it increases uveoscleral outflow.^{12,14} This effect may be caused by relaxation of the ciliary muscle.¹⁵ At present, there is conflicting evidence on the nighttime efficacy of brimonidine on lowering IOP.^{6,16,17} Although effects of brimonidine on nocturnal aqueous humor dynamics have not been evaluated, theoretically brimonidine should reduce IOP at night because of its effects on uveoscleral outflow, similar to prostaglandin analogs. To test this idea, this study evaluated IOP and aqueous humor dynamics during the day and night in volunteers with OHT who were being treated with brimonidine or vehicle to uncover if or how brimonidine lowers IOP at night.

PATIENTS AND METHODS

A total of 35 volunteers diagnosed with OHT were enrolled into this study. Before participant enrollment, the Institutional Review Board of the University of Nebraska Medical Center approved the study protocol. Individuals aged 19 years or older with a history of untreated, elevated IOPs (between 21 to 35 mm Hg on at least 2 measurements at least 3 months apart) were invited to participate in this study. After obtaining informed consent, a complete eye examination was conducted. This included a medical history, IOP measurement, visual acuity assessment, slit lamp biomicroscopy, dilated fundus examination, and gonioscopy.

The exclusion criteria included pregnancy or nursing, best-corrected visual acuity worse than 20/60 in either eye, chronic or recurrent severe ocular inflammatory disease, ocular infection or inflammation within 3 months of the screening visit, history of clinically significant or progressive retinal disease (eg, retinal degeneration, diabetic retinopathy, or retinal detachment), any abnormality of either eye preventing reliable tonometry, history of any severe ocular pathology or serious hypersensitivity to topical brimonidine or its placebo (artificial tears), either eye with cup-to-disc ratio >0.8 , history of intraocular or ocular laser surgery, history of severe, unstable, or uncontrolled cardiovascular, hepatic, or renal disease,

dosing changes within 1 month of the screening visit of any medication that affects IOP, gonioscopy angle less than Schaffer grade 2,¹⁸ inability to discontinue contact lens wear during the study visits, therapy with any investigational drug within 30 days of screening, use of any additional topical or systemic adjunctive ocular hypotensive medications during the study, or history of any form of glaucoma.

This prospective study was conducted in a double-masked, randomized, and cross-over manner. The active drug, 0.2% brimonidine tartrate (Bausch & Lomb, Tampa, FL), or the placebo, Artificial Tears (Alcon, Fort Worth, TX), were assigned in random order. The schedule of visits is outlined in Figure 1. If the treating physicians had any concerns about significant IOP elevation during the study (based on past history and current IOP targets), additional safety visits were added for IOP measurements, ranging from 1 to 3 weeks after the initiation of each study medication.

This study involved two 6-week washout periods of IOP-lowering drugs before administration of study drugs. This time frame allowed for washout of brimonidine, reported to occur after about 5 weeks,¹⁹ or any other glaucoma drug prescribed to the patient before study start. It also allowed for an evaluation of long-term effects of brimonidine, prominent after at least 4 weeks of administration. Each subject was instructed to self-administer the study drops 3 times daily for 6 weeks. Following the initial 6-week period, all procedures (Fig. 1) were performed initially at a daytime visit followed by a nighttime visit 2 days later. Between 6 and 10 hours before the start of each daytime visit, the participant self-administered 1 topical drop of 2% fluorescein at 5-minute intervals, until each eye received 6 to 8 drops.

During the daytime visit, at 8 AM, ultrasound pachymetry and A-scan (Pacscan Series 300; Lake Success, NY) were used to measure central corneal thickness and anterior chamber depth, respectively. Immediately following these measurements, an investigator administered to both eyes the morning dose of the study drug using the subject's assigned bottle. Every 2 hours, between 9 AM and 3 PM, a pneumatonometer (Model 30 Classic; Reichert Ophthalmic Instruments, Depew, NY) was used to measure seated and supine IOPs. Seated IOP was measured first followed by supine IOP 5 minutes after the patient reclined. A fluorophotometer (Fluorotron Master; OcuMetrics, Mountain View, CA) was used to measure fluorescence decay over time in the cornea and anterior chamber and enable calculation of F_a .²⁰ It was measured with the subject in the seated position. F_a has been reported to be unchanged by body position.²¹

At 1 PM, seated episcleral venous pressure (P_{ev}) was measured with an episcleral venomanometer (Eyetechn Ltd, Skokie, IL).²² Two readings were collected and a possible third if the first 2 differed by >2 mm Hg. The readings were averaged to obtain the reported value per eye.

The last measurement of the day was a 2-minute tonography using the tonography setting on the pneumatonometer. This measurement was made while the subject was supine. For each tonographic measurement of outflow facility, real-time IOP measurements were imported into a spreadsheet for data analysis. A regression line was generated using all

(approximately 4000) IOP data points and the initial and final IOP measurements were calculated at times 0 and 2 minutes. C was calculated using these values and the formulas reported previously.²³

Uveoscleral outflow (U) was calculated at 4 separate times by the modified Goldmann equation:

$$U = F_a - C(IOP - P_{ev}), \quad (1)$$

where IOP is the habitual (seated) intraocular pressure measured at 9 AM, 11 AM, 1 PM, and 3 PM, respectively. C is the tonographic outflow facility, F_a is the aqueous flow rate, and P_{ev} is the episcleral venous pressure measured at 1 PM.

Two days later, the nighttime measurements were performed in a hospital-based 2-room hotel suite. At 5 PM, an investigator instilled one drop of 0.5% proparacaine and 3 to 4 drops of 2% fluorescein in each eye of the participant. At 8 PM, an investigator administered the masked study drug into both of the subject's eyes. Using the same methods described for the daytime measurements, nighttime measurements were performed and included central corneal thickness and anterior chamber depth at 8 PM and outflow facility at 3:30 AM. At 9 PM, 11 PM, 1 AM, and 3 AM, supine IOPs were measured followed 5 minutes later by seated IOPs. Fluorophotometric scans were performed after each IOP measurement. Using a modified slit lamp, supine P_{ev} was measured at 1 AM. Between measurements, participants were instructed to return to sleep. Two-minute tonography, as described earlier, was the last measurement of the night.

Equation 1 was used to calculate 4 nighttime uveoscleral outflow values. Nighttime measurements of F_a , C , and P_{ev} and supine IOPs collected at 9 PM, 11 PM, 1 AM, and 3 AM, respectively, were used in the equation.

Statistical Analysis

Individual parameters were averaged for both eyes and if reliable measurements were available for 1 eye only, that eye was included in the analysis. The data are presented as mean $\pm$ SEM, unless otherwise indicated. A power analysis with a power of 0.80 determined that a minimum of 26 volunteers were needed to detect a 0.8 $\mu\text{L}/\text{min}$ change in uveoscleral outflow with an SD of a difference of 1.40 and α of 0.05. The Student 2-tailed paired t tests were used to compare all day versus night measurements and brimonidine versus placebo values for IOP. For all other reported comparisons, one-way repeated measures analysis of variance followed by post hoc Tukey or the Bonferroni test were performed. A P -value of ≤ 0.05 was considered statistically significant.

RESULTS

Of the 35 enrolled subjects, 29 completed all study visits. Two subjects voluntarily withdrew after initially consenting to participate in the study. One subject had an IOP of 35 mm Hg during a safety visit while on placebo. An additional 3 subjects were excluded because of occurrence of acute anterior uveitis during the placebo treatment phase, nonadherence to the study drug schedule, move to a different state, and development of symptoms necessitating

brimonidine discontinuation (nausea, dizziness, and light sensitivity). A total of 29 subjects (58.6 ± 1.7 y), comprised of 19 women, 21 whites, 6 African Americans, 1 Hispanic, and 1 Native American, completed all visits. Eleven subjects were on IOP-lowering therapy before enrollment that included latanoprost ($n = 4$), travoprost ($n = 2$), timolol ($n = 2$), bimatoprost ($n = 2$), and brimonidine ($n = 1$). Outflow facility measurements and subsequent uveoscleral outflow calculations were successful in 27 subjects. Tonography data was of poor quality for one subject and tonography was not attempted in a second subject because of the development of corneal epitheliopathy during the day.

Compared with placebo treatment, brimonidine significantly ($P < 0.05$) lowered seated daytime IOP at 9 AM (placebo, 20.3 ± 0.7 mm Hg; brimonidine, 18.1 ± 0.7 mm Hg) and 11 AM (placebo, 19.9 ± 0.8 mm Hg; brimonidine, 18.0 ± 0.7 mm Hg). Similarly, brimonidine lowered supine daytime IOP at 9 AM (placebo, 25.4 ± 0.7 mm Hg; brimonidine, 23.1 ± 0.7 mm Hg) and 11 AM (placebo, 24.7 ± 0.8 mm Hg; brimonidine, 23.1 ± 0.7 mm Hg). Compared with placebo, brimonidine lowered the nighttime seated IOP at 9 PM (placebo, 18.0 ± 0.7 mm Hg; brimonidine, 16.0 ± 0.6 mm Hg) and 11 PM (placebo, 18.4 ± 0.7 mm Hg; brimonidine, 16.7 ± 0.7 mm Hg) (Fig. 2).

When treated with placebo, nighttime supine P_{ev} (11.2 ± 0.2 mm Hg) was higher ($P < 0.05$) than daytime seated P_{ev} (10.3 ± 0.2 mm Hg) (Fig. 3). Similarly, with brimonidine treatment, nighttime supine P_{ev} (11.3 ± 0.3 mm Hg) was higher ($P < 0.05$) than daytime seated P_{ev} (10.3 ± 0.2 mm Hg).

Eyes treated with placebo had lower ($P < 0.001$, Tukey post hoc test) F_a at night compared with day. With brimonidine treatment, a similar nighttime lowering was observed ($P < 0.001$). The effects of brimonidine on daytime and nighttime F_a rates were no different from placebo (Fig. 4).

Outflow facility did not change significantly at night compared with day or with brimonidine treatment compared with placebo treatment (Fig. 5).

Compared with vehicle, brimonidine had an effect on uveoscleral outflow during the day (RMANOVA, $P < 0.001$) but not at night (RMANOVA, $P = 0.90$). Post hoc analysis (Bonferroni post hoc test comparing time matched values of uveoscleral outflow) showed an increase in uveoscleral outflow with brimonidine use at 9 AM [increase of $0.84 \mu\text{L}/\text{min}$; 95% confidence interval (CI), 0.24 – 1.46 ; $P < 0.01$] and 11 AM (increase of $0.72 \mu\text{L}/\text{min}$; 95% CI, 0.11 – 1.34 ; $P < 0.05$) but not at 1 PM or 3 PM (Fig. 6).

DISCUSSION

Numerous clinical studies have reported that brimonidine treatment results in a decrease in IOP with the theoretic potential to delay the onset and progression of glaucomatous damage.^{16,17,24–26} Twice-daily administration of 0.2% brimonidine (at 8 AM and 8 PM) for 6 weeks reportedly maintained a lower IOP over a 24-hour period with no difference between daytime and nighttime values.¹⁷ However, thrice-daily administration of 0.1% brimonidine for 4 weeks decreased IOP during the daytime but not at night.¹⁶ Differing results may be

attributed to dosing schedule, concentration of brimonidine, time between treatment and measurement, intrinsic differences in patient populations, and tonometer used.

The current study found that the effect of brimonidine on IOP was partially dependent on both the body position of the subject during the measurement and on the time between measurement and last dose. The IOP-lowering effect was not statistically significant at 5 hours after the last administered dose possibly because the drug effect was short-lived.

Although the Goldmann tonometry is the “gold standard” for IOP measurements, a pneumatonometer was used in the current study for several reasons: (1) with this tonometer, fluorescein is not necessary for the measurement. Adding fluorescein while collecting fluorophotometric scans would invalidate the F_a assessment. (2) The data can be stored digitally. (3) IOP can be measured in the seated or supine position, as the orientation of the tonometer probe, whether in the vertical or horizontal position, does not contribute to any IOP change.⁸

The most plausible explanation for brimonidine’s effect on IOP is an increase in uveoscleral outflow. The IOP reduction during the day occurred within 1 hour of the previous dose, at a time when uveoscleral outflow was increased. The insignificant decrease in IOP at night in eyes dosed with brimonidine may be because the spontaneous nighttime reduction in uveoscleral outflow, seen in healthy subjects⁸ or patients with OHT,¹⁰ counteracts the mechanism of action of brimonidine. The hypothesis that brimonidine, like prostaglandin analogs, would reduce nighttime IOP because of its effects on uveoscleral was not proven true. A shorter duration of action of brimonidine as compared with prostaglandins may be a contributory factor. Had a dose been administered at 1 AM, a nighttime IOP reduction might have been detected.

In the current study, outflow facility in participants with OHT did not change when comparing daytime and nighttime measurements. This measurement necessarily had to be done while the volunteer was supine. However, an earlier study reported that tonography is independent of body position.²⁷ During the day, outflow facility is lower in OHT subjects compared with healthy subjects but at night the values between the 2 groups are comparable.^{8,10} Apparently, outflow facility normally increases during the day but in OHT eyes, something is preventing the outflow facility rise. One possibility is the 24-hour fluctuations in plasma corticoid levels, which have been shown to affect outflow facility in normal and glaucomatous eyes.²⁸ Brimonidine did not alter outflow facility during the day or night in the OHT subjects of the current study. Thus, changes in outflow facility do not explain the effects of brimonidine on IOP.

P_{ev} is an important factor in the determination of IOP, but it is often not measured because of the difficulty in obtaining accurate values, especially noninvasively in supine subjects. Animal²⁹ and human studies^{30,31} have shown that P_{ev} is markedly influenced by posture. P_{ev} is higher when supine compared with when seated.^{32–34} The effect of the increased P_{ev} in the supine position may be the increase in choroidal vascular volume^{29,30,35} that in turn may increase IOP. In agreement with other studies^{12,14} the current study found that > 1 week of brimonidine treatment had no effect on P_{ev} during the day. A new finding is that

brimonidine also did not affect P_{ev} at night. Acutely, brimonidine causes significant vasoconstriction and decrease in P_{ev} in rabbits when dosed within 10 minutes of the measurement.¹³ If a similar effect occurs in humans, it does not persist with 6 weeks of dosing and likely does not contribute to any change in IOP.

There are several limitations in this study, which are inherent to the currently available techniques for studying the aqueous humor dynamics. The precision of calculated uveoscleral outflow is limited by the intrinsic variability of each element of the equation used to determine uveoscleral outflow. The use of constant daytime and nighttime F_a , outflow facility, and P_{ev} values in our calculations for uveoscleral outflow will cause some error considering there may be diurnal changes in both variables.

In summary, in this study of individuals with OHT, F_a decreased from day to night, P_{ev} increased at night in the supine position when compared with during the day in the seated position, and outflow facility remained unchanged. Brimonidine did not affect F_a , P_{ev} , and outflow facility but it did increase uveoscleral outflow during the daytime concurrent with significant IOP lowering. The lack of IOP and uveoscleral outflow effect at night could be because the physiologic suppression of nocturnal uveoscleral outflow could not be overcome. In addition, brimonidine may be sufficiently short acting that the nighttime measurements were collected when no drug effect remained.

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FIGURE 1.

Study schedule of visits. Following screening, participants were randomized to either brimonidine or a placebo treatment for 6 weeks. Next, daytime and nighttime measurements were collected as described. Subsequently, the participants self-administered the alternate eye drop for 6 weeks and daytime and nighttime measurements were repeated.

FIGURE 2.

Brimonidine significantly decreased seated and supine intraocular pressure (IOP) at 9 AM and 11 AM, and seated IOP at 9 PM and 11 PM ($P < 0.05$, paired t test). Error bars represent SEM.

FIGURE 3.

Episcleral venous pressure was higher at nighttime when compared with daytime.

Brimonidine did not alter this pattern. *P*-values were obtained using the Tukey post hoc test.

Error bars represent SEM.

FIGURE 4.

Aqueous flow was lower at night compared with day in placebo-treated eyes. Brimonidine did not alter this pattern. *P*-values < 0.001 by the Tukey post hoc test. Error bars represent SEM.

FIGURE 5.

Outflow facility did not change at night compared with day in placebo-treated eyes or brimonidine-treated eyes. Statistical tests were repeated measures 1-way analysis of variance (ANOVA), with 5% confidence levels ($P = 0.98$). Error bars represent SEM.

FIGURE 6.

Changes in uveoscleral outflow with brimonidine treatment compared with placebo treatment. Increase in uveoscleral outflow with brimonidine was statistically significant at 9 AM ($P < 0.01$) and 11 AM ($P < 0.05$; Bonferroni post hoc test), but not at other times. Error bars represent SEM.