Comparison of the Efficacy of Apraclonidine and Brimonidine as Aqueous Suppressants in Humans

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Objective: To measure and compare the effect of apraclonidine hydrochloride and brimonidine tartrate on the rate of aqueous humor flow in human subjects.

Subjects and Methods: Forty normal human subjects were given apraclonidine or brimonidine by topical instillation. Aqueous humor flow was measured by the rate of disappearance of topically applied fluorescein. Intraocular pressure was measured by applanation tonometry.

Results: Apraclonidine suppressed aqueous humor flow between 39% and 44% and lowered intraocular pressure between 20% and 23%. Brimonidine suppressed aqueous humor flow between 44% and 48% and lowered intraocular pressure between 19% and 22%.

Conclusion: No statistically significant differences were found between the effects of the 2 drugs on aqueous humor dynamics in normal subjects.


Animal and human studies have shown that α2-selective adrenergic agonists suppress aqueous humor formation and are efficacious for lowering intraocular pressure. Two drugs in this class are available in topical formulations for the treatment of glaucoma: 0.5% apraclonidine hydrochloride1-6 (Iopidine, Alcon Laboratories, Fort Worth, Tex) and 0.2% brimonidine tartrate7-12 (Alphagan, Allergan, Irvine, Calif).

Studies of apraclonidine have shown that the ocular hypotensive effect is principally caused by the suppression of aqueous humor flow.13-15 Studies of brimonidine have also shown that its ocular hypotensive effect is primarily caused by aqueous suppression.16-19 However, there is evidence from comparative studies in animals that the 2 drugs are not identical in their effects.17,19,20 Also, there is evidence in humans that brimonidine has significant outflow effects that contribute to its ocular hypotensive efficacy.18

It would be helpful to clinicians, who must make therapeutic decisions on behalf of their glaucoma patients, to know the relative efficacy of these 2 drugs as aqueous suppressors. This study is a quantification and direct comparison of the acute aqueous suppressing effects of apraclonidine and brimonidine in normal human subjects.

RESULTS

AQUEOUS HUMOR FLOW

In group 1, the flow of aqueous humor was measured in the drug-treated eye and the placebo-treated fellow eye at the same time. In half of these subjects, apraclonidine was studied first; in the other half, brimonidine was studied first. There was no statistically significant difference in the results for each drug between the subjects who were treated with the drug first and subjects who were treated with the placebo first (apraclonidine, \( P = .08 \); brimonidine, \( P = .36 \)), so these groups of 10 were combined into a single group of 20 for additional analysis.

The rate of aqueous humor flow in the apraclonidine-treated eyes of the 20 subjects was 1.39 ± 0.37 μL/min (mean ± SD), and in the fellow placebo-treated eyes, 1.94 ± 0.49 μL/min. Thus, the rate of flow was 28% lower in the treated eyes than in the placebo eyes (\( P < .001 \)). The rate of aqueous humor flow in the brimonidine-treated eyes was 1.33 ± 0.47 μL/min, and in the fellow placebo-treated eyes, 1.93 ± 0.46 μL/min.
SUBJECTS AND METHODS

Two groups of 20 normal subjects were studied, totaling 40 subjects. Group 1 (mean age, 28.7 years; 11 women and 9 men) was studied to permit the simultaneous measurement of aqueous flow when 1 eye was treated with 1 of the 2 \( \alpha_2 \)-adrenergic agonists and the other eye was treated with a placebo. Group 2 (mean age, 27.0 years; 9 women and 11 men) was studied to permit comparison of the effect of the 2 drugs on flow when the measurements were made simultaneously. This design has the greatest power to detect differences between the drugs.

Each group underwent 2 days of tests so that each subject would be treated with each drug. In addition, 16 members of group 1 underwent a third day of testing in which placebo was used in both eyes.

Subjects were recruited from the students and employees of the Mayo Clinic, Rochester, Minn, and informed consent was obtained. Persons of either sex between the ages of 21 and 60 years were eligible. Exclusion criteria included the following: pregnancy or lactation, use of systemic medications, long-term use of eye medications, history of allergy to ocular medications, history of a major systemic illness, history of notable eye disease, and concurrent or recent participation in any other study. In addition, subjects were excluded on a preliminary examination for any of the following reasons: intraocular pressures outside the inclusive range of 10 to 20 mm Hg; intraocular pressures of the 2 eyes differing by more than 3 mm Hg; obvious asymmetry of lids, globes, or pupils; pigment dispersion or pseudoexfoliation; myopia or hyperopia of more than 5 diopters; narrow angles; and any condition of lids, cornea, or anterior chambers that would not permit accurate fluorometry and tonometry.

Commercial supplies of apraclonidine hydrochloride, 0.5%, and brimonidine tartrate, 0.2%, and an artificial tears preparation (Hypotears, IOLab, Claremont, Calif) were obtained. These products were repackaged and relabeled by a Mayo pharmacist. The new containers for all 3 products were identical. The containers were filled according to the randomization scheme and identified only by group number, subject number, experiment number, and right or left eye. In group 1, 1 eye was randomly assigned to receive placebo on both days of testing, and the fellow eye was assigned to receive the drugs. In half of the subjects, apraclonidine was given on the first day, and brimonidine on the second day. In the other half of the subjects, brimonidine was given on the first day, and apraclonidine on the second day. In addition, 16 members of group 1 underwent a third run; both eyes of each subject received placebo.

In group 2, half of the subjects received placebo in both eyes on the first day, and half, on the second day. On the day when the drugs were given, apraclonidine and brimonidine were randomly assigned to the left or right eye.

The code identifying the content of each container remained sealed until all subjects had completed the study and all data had been recorded in their final form in a statistical database. An exception was the study of the 16 subjects of subgroup 1. These subjects, all the members of group 1 who were still available, were called back after the completion of their 2 experiments for a third experiment in which placebo drops (Hypotears) were instilled into both eyes. This third experiment was done because comparison of the results of groups 1 and 2 suggested that each of the \( \alpha_2 \)-adrenergic agonists had a significant crossover effect in the fellow eye.

Three weeks or more was allowed between experiments to eliminate any lingering effects of the previous experiment.

The day before the measurement of aqueous flow and intraocular pressure, a technician (C.B.N.) administered the coded labeled drugs to each subject at 8 AM, noon, and 4 PM. The day of the measurement, each subject received these eyedrops at 8:15 AM and 12:15 PM. After instillation of each drop, the subjects were asked to close their eye for 2 minutes. A separate blotting tissue was used for each eye to reduce the chance of transfer of the drug from one eye to the other, and subjects were asked not to touch either eye after the instillation, closure, and blotting procedure had been completed.

At 2 AM the night before the measurement, each subject instilled 2% fluorescein sodium (IOLab) into each eye several times to produce a depot of fluorescein in the cornea for measurement of aqueous humor flow the following morning. At 8 AM on the day of the experiment, each subject underwent measurement of fluorescence in the cornea and anterior chamber with a scanning ocular fluorophotometer. This procedure was repeated every 2 hours through 4 PM. These data were used to calculate the rate of flow of aqueous humor through the anterior chamber.

Immediately after the 4 PM measurement, the intraocular pressure was measured with a Goldmann applanation tonometer. The right eye was measured first; the left eye, second; and these measurements were repeated for a total of 3 measurements per eye. The intraocular pressure was recorded as the mean of the 3 measurements.

The data within each of the 2 groups were analyzed for statistical significance with a 2-sided Student t test for paired samples. A \( P \) value of .05 or less was considered statistically significant.

The coefficient of variation of measurements of aqueous humor flow under the conditions of this experiment is approximately 16%.\(^2\)

For a paired test, a sample size of 20 subjects has the power to detect a 16% difference in flow between drug and placebo (\( \alpha = .05, \beta = .95 \)).

31% lower in the brimonidine-treated eyes than in the placebo eyes (\( P < .001 \)).

When the aqueous-suppressing effect of apraclonidine was compared with the effect of brimonidine, there was no statistically significant difference (\( P = .63 \)).

At a later time, 16 members of group 1 were restudied when placebo was instilled in both eyes and neither active drug was used in either eye. The rate of aqueous flow in the placebo-treated eyes when apraclonidine was given in the opposite eye was 1.92 \( \pm \) 0.46 \( \mu l/min \). The rate of aqueous flow in the placebo-treated eyes when placebo was given in the opposite eye was 2.30 \( \pm \) 0.46 \( \mu l/min \), a 16% difference. This difference was statistically significant (\( P = .004 \)), indicating that apraclonidine has a consensual effect on aqueous humor flow.

A similar consensual effect was observed for brimonidine. The rate of aqueous flow in the placebo-
treated eyes when brimonidine was given in the opposite eye was 1.90 ± 0.47 µL/min. When placebo was given in the opposite eye, the flow was 2.30 ± 0.46 µL/min, a difference of 17%. This difference was statistically significant (P = .007).

In group 2, in 1 session, apraclonidine was instilled into 1 eye and brimonidine was instilled into the other. In the other session, placebo was instilled into both eyes. In half of the subjects (n = 10), the placebos were studied first; in the other half, the drugs were studied first. There were no statistically significant differences between the results in one sequence or the other (apraclonidine, P = .22; brimonidine, P = .83), so the data were combined into a single group of 20 subjects for additional statistical analysis.

The rate of aqueous flow in the apraclonidine-treated eyes when the fellow eyes had been treated with brimonidine was 1.39 ± 0.34 µL/min. The rate of aqueous flow in the same eyes when placebo had been instilled in both eyes was 2.26 ± 0.49 µL/min, a difference of 39% (P < .001).

The rate of aqueous flow in the brimonidine-treated eyes when the fellow eyes had been treated with apraclonidine was 1.24 ± 0.28 µL/min. The rate of aqueous flow in the same eyes when placebo had been instilled in both eyes was 2.20 ± 0.38 µL/min, a difference of 44% (P < .001).

When apraclonidine’s effect on flow was compared with brimonidine’s effect on flow, there was a trend for brimonidine’s effect to be greater (39% vs 44%; P = .05).

INTRAOCULAR PRESSURE

In groups 1 and 2, the intraocular pressure was measured in each eye at 4 PM, after the completion of the last measurement of fluorescein. All the subsequent data in this section refer to these afternoon measurements, taken 4 hours after the last instillation of drug.

In group 1, the intraocular pressure in the apraclonidine-treated eyes of the 20 subjects was 10.2 ± 1.8 mm Hg (mean ± SD) and in the fellow placebo-treated eyes was 11.4 ± 1.8 mm Hg. Thus, the intraocular pressure was 11% lower in the treated eyes than in the control eyes (P = .005). The intraocular pressure in the brimonidine-treated eyes was 10.6 ± 2.0 mm Hg and in the fellow placebo-treated eyes was 11.8 ± 2.0 mm Hg, 11% lower in the brimonidine-treated eyes than in the placebo eyes (P = .005).

When the intraocular pressure-lowering effect of apraclonidine was compared with the effect of brimonidine, there was no statistically significant difference (P = .60).

At a later time, when the 16 members of group 1 were restudied by instillation of placebo into both eyes and neither active drug was used in either eye, the intraocular pressures were also measured at 4 PM. The intraocular pressure in the placebo-treated eyes when apraclonidine was given in the opposite eye was 11.3 ± 1.9 mm Hg. The intraocular pressure in the same placebo-treated eyes when placebo was given in the opposite eye was 12.9 ± 1.7 mm Hg, a 12% difference. This difference was statistically significant (P = .02), indicating that apraclonidine has a consensual effect on intraocular pressure that is consistent with its consensual effect on aqueous humor flow.

A similar consensual effect was observed for brimonidine. The intraocular pressure in the placetreated eyes when brimonidine was given in the opposite eye was 11.9 ± 2.1 mm Hg. When placebo was given in the opposite eye, the intraocular pressure was 12.9 ± 1.7 mm Hg, a difference of 8%. However, this difference was not statistically significant (P = .12).

In group 2, the intraocular pressure in the apraclonidine-treated eyes when the fellow eyes had been treated with brimonidine was 10.2 ± 2.4 mm Hg. The intraocular pressure in the same eyes when placebo had been instilled in both eyes was 12.8 ± 2.5 mm Hg, a difference of 20% (P < .001).

The intraocular pressure in the brimonidine-treated eyes when the fellow eyes had been treated with apraclonidine was 9.6 ± 2.0 mm Hg. The intraocular pressure in the same eyes when placebo had been instilled in both eyes was 12.4 ± 2.3 mm Hg, a difference of 22% (P < .001).

When apraclonidine’s effect on pressure was compared with brimonidine’s effect on pressure, there was no statistically significant difference (P = .37).

The results of this study indicate that apraclonidine and brimonidine both suppress aqueous humor formation, an effect that is sufficient to account for their ability to lower intraocular pressure. Toris and coworkers18 studied patients with ocular hypertension whose baseline intraocular pressures were 21 mm Hg and who were treated for 8 days with brimonidine. In that study, brimonidine suppressed aqueous humor flow by 20% and increased uveoscleral outflow by more than 4 times. In this study, aqueous suppression was 44% to 48%. The effect on intraocular pressure could be attributed entirely to the drug’s effect on flow, but this notion cannot be proved from our data since outflow resistance or uveoscleral flow was not measured. However, we presume that if the short-term administration (1 day) of 1 drug had had a significant effect on outflow and the other drug had not, we would have seen a difference between the 2 drugs in their relative effects on pressure and flow. We do not know whether the differences in results of the 2 studies are caused by differences in the condition of the subjects, the length of treatment with brimonidine, or the techniques of measurement.

Apaclonidine and brimonidine, like timolol, have a consensual effect on aqueous humor flow in the fellow eye. The reason for this effect is not known, but could result from systemic absorption of the drugs.5,8 In this experiment, we made every effort to prevent direct transfer of the drug into the placebo-treated eye by having the technician, rather than the subject, instill the drops and by using different tissues for blotting after instillation. However, there remains the chance that the subject may not have followed directions and may have manually transferred some drug from one eye to the other.
The results of group 1 and group 2, taking into account the consensual effects of each drug, are very comparable. In group 1, the net effect of apraclonidine on aqueous humor flow (28% direct + 16% consensual) was a 44% suppression. The net effect in group 2 was 39%. In group 1, the net effect of brimonidine on aqueous humor flow (31% direct + 17% consensual) was 48%. The net effect in group 2 was 44%. In group 1, the net effect of apraclonidine on intraocular pressure (11% direct + 12% consensual) was a reduction of 23%. In group 2 the net effect was 20% lower. In group 1, the net effect of brimonidine on intraocular pressure (11% direct + 8% consensual) was a reduction of 19% lowering. The data on flow pertain to effects that might exist in the effects on aqueous humor dynamics. That aqueous flow has been found to be normal by these methods in many types of glaucoma. The study was designed to demonstrate any differences between the 2 drugs in terms of their short-term efficacy at reducing aqueous humor flow or intraocular pressure. The study was conducted, and has the greatest sensitivity at, uncovering differences, if any, in the short-term effects of the 2 drugs on aqueous humor flow. Normal subjects are satisfactory for flow studies, because aqueous flow has been found to be normal by these methods in many types of glaucoma. The study does not have good sensitivity to discover small differences that might exist in the flow on aqueous humor outflow. Studies of drug effects on outflow resistance are preferably conducted in subjects who have elevated intraocular pressure. Also, the data on flow pertain to the short-term effects of these drugs; effects may be greater than the sustained effects during long-term usage.

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