Comparison of the Early Effects of Brimonidine and Apraclonidine as Topical Ocular Hypotensive Agents

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Objective: To compare the mechanism of action of short-term administration of brimonidine tartrate and apraclonidine hydrochloride as topical ocular hypotensive agents.

Subjects and Methods: Two randomized, double-masked, placebo-controlled studies of 19 normal human subjects were carried out. The first study compared brimonidine with apraclonidine in timolol maleate–treated eyes, and the second study compared latanoprost with placebo in timolol-treated eyes. The rate of aqueous flow and intraocular pressure were measured in both studies. The topical drug combinations were instilled the night before and repeated the morning before the measurements. Aqueous humor flow was measured by the rate of disappearance of topically applied fluorescein. Intraocular pressure was measured by pneumatonometry every 2 hours from 8:15 AM to 4:15 PM.

Results: Both brimonidine and apraclonidine further reduced aqueous flow in timolol-treated eyes from 1.23 ± 0.21 µL/min to 0.96 ± 0.16 µL/min and 0.98 ± 0.17 µL/min, respectively. Consistent reductions were observed in intraocular pressure, with average reductions of 19% with brimonidine and 17% with apraclonidine. Latanoprost had no effect on aqueous flow in timolol-treated eyes ($P = .15$), but showed an average reduction in intraocular pressure of 13%.

Conclusions: Brimonidine and apraclonidine are similar in their effects on the aqueous system. Both reduce intraocular pressure in the timolol-treated eye, primarily, if not exclusively, by further suppressing aqueous flow. In contrast, latanoprost reduces intraocular pressure in the timolol-treated eye without affecting aqueous flow.

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BRIMONIDINE TARTRATE, 0.2% ophthalmic solution (Alphagan; Allergan, Irvine, Calif), is a highly selective α_2-adrenergic agonist that has recently become available for the treatment of chronic glaucoma. Its efficacy as an ocular hypotensive agent is well documented.[1-4] Whereas most studies attribute its hypotensive action to aqueous suppression, some studies suggest it enhances aqueous outflow as well.[5,6] This suggestion is included in the package insert that accompanies the drug.[7] No such evidence exists for a similarly classified ocular hypotension agent, 0.5% apraclonidine hydrochloride (Iopidine; Alcon Laboratories, Fort Worth, Tex), although it has undergone similar studies.[3,8] In contrast to brimonidine, the Food and Drug Administration approved information that accompanies apraclonidine that attributes its efficacy to reduction of aqueous flow.[9]

The idea that a fundamental difference exists between the mechanisms of action of these 2 drugs comes from evidence in rabbits and in humans. Serle and coworkers[5] measured uveoscleral flow in rabbits by observing the rate of appearance of fluorescein-labeled dextran in the tissues surrounding the

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supraciliary space after perfusion of the tracer in the anterior chamber. Apraclonidine had no effect on the rate of appearance of the tracer in these tissues, but brimonidine increased the rate by nearly 50%. In humans, the aqueous dynamics of apraclonidine were studied by Toris and coworkers,[8] and later the aqueous dynamics of brimonidine were studied.[6] In the study of apraclonidine, uveoscleral flow in the treated eye compared with baseline was *reduced* in the treated eye from 0.58 µL/min to 0.11 µL/min ($P < .03$); in the study of bri-

SUBJECTS AND METHODS

Twenty normal human volunteers were recruited, of whom 19 met all entry criteria and participated in 2 randomized, double-masked, placebo-controlled studies. The first study was a direct comparison of apraclonidine treatment in one eye vs brimonidine treatment in the other eye when both eyes were concurrently treated with timolol. The second study was a comparison of latanoprost treatment in one eye vs placebo treatment in the other eye when both eyes were concurrently treated with timolol. All subjects completed both studies; for each subject, the second study was carried out 2 weeks or longer after the first.

Each subject underwent a baseline history and ocular examination to gather data and to determine eligibility. Exclusion criteria included pregnancy or breastfeeding, long-term use of eye medications, allergy to ocular medications, history of a major illness or notable eye disease, use of systemic medications known to affect aqueous humor dynamics, and recent participation as a volunteer in another medical study. Subjects were also excluded specifically for any of the following: intraocular pressure in either eye outside the inclusive range of 10 to 20 mm Hg, asymmetry of intraocular pressures greater than 3 mm Hg, obvious asymmetry of eyes, pigment dispersion, pseudoexfoliation, ametropia greater than 5 diopters, narrow angles, or any feature of the eyelids, cornea, or anterior chamber that would interfere with the accuracy of tonometry or fluorophotometry. All eligible subjects underwent the written informed consent procedure monitored by the institutional review board of the Mayo Foundation, Rochester, Minn.

The 4 drugs used in the study were obtained from commercial suppliers: 0.5% apraclonidine hydrochloride (Iopidine; Alcon Laboratories), 0.2% brimonidine tartrate (Alphagan; Allergan), 0.005% latanoprost (Xalatan; Pharmacia, Kalamazoo, Mich), and 0.5% timolol maleate (Timoptic; Merck & Co, West Point, Pa). The placebo was an artificial tear solution (Hypotears; IOLab, Claremont, Calif). All products except timolol were repackaged and relabeled by a pharmacist. All repackaged containers were identical and were labeled according to study number (1 or 2), according to eye (left or right), and according to subject number (1-19). The right and left eyes of all subjects for study 1 were randomized between brimonidine and apraclonidine. The right and left eyes of all subjects for study 2 were randomized between latanoprost and placebo.

All drug instillations were carried out by one of us (C.N.). For each study, 1 drop of timolol was instilled into each eye at 5 PM the day before the measurement of aqueous flow and intraocular pressure. Five minutes after instillation of timolol, the assigned drug from the masked container for each eye was instilled according to the labeled instructions. Subjects were allowed to blot each eye with separate tissues and then asked to close their eyes for 2 minutes after drug instillation and warned not to touch either eye so as not to transfer drug from one eye to the other.

At 2 AM during the night before the measurement of aqueous flow and intraocular pressure, each subject awakened and instilled 2% fluorescein sodium (Alcon Laboratories) into each eye several times to produce a depot of fluorescein in the cornea for measurement of aqueous humor flow the following day.

At 7:30 AM on the day of the measurements, timolol was instilled again into each eye. At 8 AM, the assigned drugs from the masked containers were instilled once again.

Beginning at 8:15 AM, and every 2 hours thereafter until 4:15 PM, the fluorescence in the cornea and anterior chamber was measured in each eye by fluorophotometry. Immediately after each measurement of fluorescence, 0.5% proparacaine hydrochloride (Alcaine; Alcon Laboratories) was instilled into each eye and intraocular pressures were measured with a pneumatonometer (Mentor O&O, Norwell, Mass). Three measurements were taken of the right eye followed by 3 measurements of the left eye. The intraocular pressure was recorded as the mean of the 3 measurements. The pneumatonometer tip was cleaned with an alcohol swab and allowed to dry between right and left eye measurements.

Aqueous humor flow was calculated from the fluorescence measurements and from measurements of the volume of the anterior chamber as described previously.[12] The variable apparent resistance to outflow (R)[13] was calculated for each eye from the relation R = intraocular pressure/aqueous flow. After completion of the study and tabulation of all data, the code was broken and the data were stratified by drug. The statistical analysis was carried out by making comparisons with a paired Student *t* test. A 2-sided test was used. A *P* value of less than .05 was considered significant.

monidine, uveoscleral flow in the treated eye compared with baseline was *increased* from 0.12 µL/min to 0.65 µL/min ($P = .04$).

It is important to know whether there is a clinically significant difference in the mechanism of action of these 2 drugs. For example, there is evidence from studies of aqueous humor flow that apraclonidine has much less efficacy when administered to subjects who are currently being treated with the aqueous-suppressing drug timolol maleate[10] as compared with subjects who are not being treated with aqueous suppressants.[11] If brimonidine has a dual mechanism of action and apraclonidine does not, it would be logical to assume that brimonidine might be more efficacious than apraclonidine when administered concurrently to persons already being treated with a β-adrenergic antagonist such as timolol.

Uveoscleral outflow is difficult to measure in human subjects, and the precision and accuracy of the methods have not been established. Despite these difficulties, it is accepted that latanoprost's mechanism of action is to enhance outflow of aqueous humor. This acceptance is based on the observation that latanoprost lowers intraocular pressure in humans without producing any measurable change in tonographic facility of outflow or in the rate of aqueous humor flow. Whether brimonidine has uveoscleral outflow effects, however, is more difficult to demonstrate, since it has effects on flow and intraocular pressure that are comparable with those of apraclonidine and timolol, neither of which is thought to affect outflow.

The simplest way of determining if brimonidine but not apraclonidine has outflow effects would be to com-

pare them in eyes that have been pretreated with an aqueous suppressant, such as timolol. In this way, the aqueous-suppressing effects of both drugs would be blunted, and the stage would be set to observe any differences in their effects on intraocular pressure that could be attributed to outflow effects. To determine if the experimental procedure has sufficient sensitivity to measure such an outflow effect, one must simply test the experimental procedure with a known uveoscleral enhancer, such as latanoprost. This reasoning was the basis for the experiment described in this report.

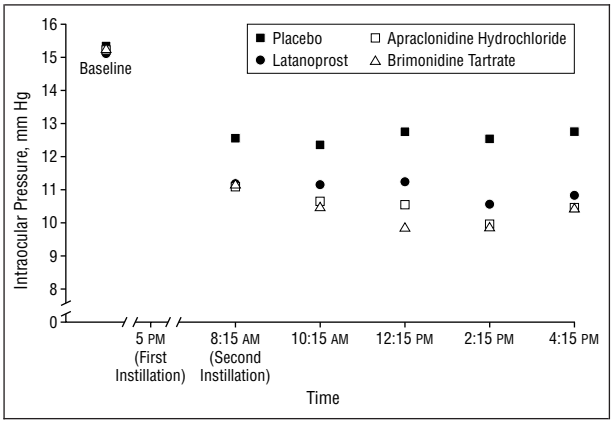
RESULTS

Timolol reduced the intraocular pressure, compared with the baseline examination, at all times that were tested. The pressure in the placebo-treated eyes before the administration of timolol was 15.4 ± 2.5 mm Hg (mean ± SD). After administration of timolol and artificial tears, the intraocular pressure was found to be lower at each measurement from 8:15 AM to 4:15 PM (all $P<.001$). Compared with the baseline examination, the intraocular pressure was reduced at all times in the eyes treated with timolol in combination with each of the 3 ocular hypotensive drugs (all $P<.001$) (**Figure**).

The flow of aqueous humor from 8:15 AM to 4:15 PM in the timolol- and placebo-treated eyes was 1.23 ± 0.21 µL/min, consistent with the well-known flow-suppressing effect of timolol. The addition of apraclonidine to timolol suppressed the aqueous flow an additional 20% to 0.98 ± 0.17 µL/min ($P = .001$). The addition of brimonidine to timolol suppressed the aqueous flow an additional 22% to 0.96 ± 0.16 µL/min ($P = .002$). The addition of latanoprost to timolol had no statistically significant effect on aqueous humor flow ($P = .15$) (**Table 1**). Both apraclonidine and brimonidine in combination with timolol suppressed aqueous flow more than latanoprost and timolol, but there was no difference between the aqueous flow in eyes treated with apraclonidine and timolol and that in eyes treated with brimonidine and timolol ($P = .60$).

The intraocular pressure was lowered by the addition of each drug to timolol at all times tested. Compared with timolol alone, latanoprost lowered intraocular pressure 13% from 10:15 AM to 4:15 PM ($P<.001$). Apraclonidine lowered intraocular pressure 17% ($P = .002$) and brimonidine lowered it 19% ($P = .001$) compared with timolol alone (**Table 2**). There was no difference in the timolol-treated eyes in the ocular hypotensive effect of apraclonidine compared with latanoprost ($P = .24$), of brimonidine compared with latanoprost ($P = .16$), or of brimonidine compared with apraclonidine ($P = .31$).

Apparent resistance to outflow was lowered by latanoprost from 10.6 ± 2.3 mm Hg · min · µL^{-1} to 9.0 ± 2.3 mm Hg · min · µL^{-1} ($P<.001$), as expected from its known action as an outflow-enhancing drug (**Table 3**). Neither apraclonidine nor brimonidine changed the apparent resistance compared with placebo but had higher apparent resistance compared with latanoprost, the demonstration drug for an outflow effect. No difference in apparent resistance was observed between apraclonidine and brimonidine.



Mean intraocular pressures of all subjects at each measurement for each drug.

COMMENT

Initial studies of the acute effect of timolol demonstrated its flow-suppressing effect.[14,15] In a recent study, Schadlu et al[16] found the rate of aqueous flow in a group of untreated normal volunteers under conditions identical to those of the current study to be 2.26 ± 0.49 µL/min. In that same study, apraclonidine reduced the flow to 1.39 ± 0.34 µL/min and brimonidine reduced the flow to 1.24 ± 0.28 µL/min. In the current study, the rate of aqueous humor flow when timolol only was administered was 1.23 ± 0.21 µL/min. Thus, timolol, apraclonidine, and brimonidine each acting alone produce suppressions of flow of 1.03 µL/min, 0.87 µL/min, and 1.02 µL/min, respectively, and appear to be equally efficacious in this effect. These findings are similar to what was found by Koskela and Brubaker,[10] where apraclonidine suppressed aqueous flow by 0.84 ± 0.61 µL/min and where

Table 1. Aqueous Humor Flow, 8 AM to 4 PM*

	Flow, Mean ± SD, µL/min	% Difference (Probability)		
		vs Placebo	vs Latanoprost	vs Apraclonidine
Placebo	1.23 ± 0.21	. . .†	. . .	. . .
Latanoprost	1.28 ± 0.27	4 (.15)	. . .	. . .
Apraclonidine hydrochloride	0.98 ± 0.17	–20 (.001)	–23 (.002)	. . .
Brimonidine tartrate	0.96 ± 0.16	–22 (.002)	–25 (.002)	–2 (.60)

**All eyes treated with timolol maleate.*
†Ellipses indicate not applicable.

Table 2. Intraocular Pressure, Average, 10:15 AM to 4:15 PM*

	Intraocular Pressure, Mean ± SD, mm Hg	% Difference (Probability)		
		vs Placebo	vs Latanoprost	vs Apraclonidine
Placebo	12.6 ± 1.8	. . .†	. . .	. . .
Latanoprost	11.0 ± 1.3	−13 (<.001)	. . .	. . .
Apraclonidine hydrochloride	10.4 ± 1.5	−17 (.002)	−5 (.24)	. . .
Brimonidine tartrate	10.2 ± 1.8	−19 (.001)	−7 (.16)	−2 (.31)

*All eyes treated with timolol maleate.
†Ellipses indicate not applicable.

Table 3. Apparent Resistance (Intraocular Pressure/Flow)*

	Apparent Resistance, Mean ± SD, mm Hg · min · μL^{-1}	% Difference (Probability)		
		vs Placebo	vs Latanoprost	vs Apraclonidine
Placebo	10.6 ± 2.3	. . .†	. . .	. . .
Latanoprost	9.0 ± 2.3	−15 (<.001)	. . .	. . .
Apraclonidine hydrochloride	11.1 ± 2.9	5 (.52)	23 (.005)	. . .
Brimonidine tartrate	11.0 ± 3.2	4 (.55)	22 (.005)	−1 (.92)

*All eyes treated with timolol maleate.
†Ellipses indicate not applicable.

the effects of timolol and apraclonidine on flow were not significantly different.

The addition of either apraclonidine or brimonidine to timolol caused further suppression of aqueous humor flow. Apraclonidine caused an additional 0.25-μL/min suppression and brimonidine caused an additional 0.27-μL/min suppression. Thus, neither drug appears to be superior to the other as a suppressor of aqueous humor flow either in untreated eyes or in timolol-treated eyes.

The additional effect on flow is approximately one fourth the effect that the 2 α_2-adrenergic agonists have when acting on the untreated eye. In a previous study, a single drop of apraclonidine was administered to normal human volunteers 4 hours after treatment with timolol, and the investigators were unable to demonstrate any additional effect of apraclonidine on aqueous humor flow.[10] However, in long-term timolol users, apraclonidine did have an additional suppressing effect similar to what was observed in this study.[17]

Apraclonidine and brimonidine each caused a small but significant lowering of intraocular pressure in the timolol-treated eye of approximately 2 mm Hg, representing 17% to 19% lowering. This is comparable with the results of Stewart and coworkers,[18] who found an additional 10% to 22% lowering of intraocular pressure when apraclonidine was added to the timolol-treated eye. The change in intraocular pressure in the current study was consistent with the additional suppression of aqueous humor flow without invoking an effect on any other measure of aqueous humor dynamics. Latanoprost also lowered intraocular pressure approximately 2 mm Hg, but without any additional suppression of aqueous flow. Latanoprost's effect therefore must be attributed to an effect on outflow, an effect that is consistent with previous studies of its mechanism of ocular hypotension.

The magnitude of this effect in our volunteers was somewhat lower than what has been observed when latanoprost has been added to the regimen of patients with glaucoma receiving long-term treatment with aqueous suppressors, including β-adrenergic antagonists and carbonic anhydrase inhibitors. Alm et al[19] found a 30% additional decrease, whereas Diestelhorst et al[20] found a 25% decrease, Khouri et al[21] found a greater than 15% increase in 13 of 18 patients, and Seong et al[22] found a 23% decrease. The effect that we measured, although smaller, was nonetheless consistent and easy to measure despite the fact that the intraocular pressure of these subjects was very low.

In 1972 Bárány et al[23] and later Reiss and Brubaker,[13] Brubaker,[24] and Lee et al[25] introduced the concept of apparent resistance to outflow to study the nonlinearity of outflow resistance. Apparent resistance is simply the intraocular pressure divided by the rate of aqueous outflow from the eye. This measure of aqueous dynamics can be calculated simply and reliably for any eye when the rate of aqueous humor flow through the anterior chamber and the intraocular pressure are known. Knowing the apparent resistance sheds no light on the pathway that aqueous humor might take on its way to the heart. However, the apparent resistance will change in predictable ways when the eye is acted on by an ocular hypotensive drug. If the drug suppresses aqueous humor flow, apparent resistance will increase; if the drug enhances outflow via any pathway, it will decrease. This relationship can be seen in **Table 4**, a compilation of calculations from previous studies in which flow and pressure were measured by the same techniques reported in this study.

In a recent study comparing apraclonidine and brimonidine in normal eyes receiving no concurrent treatment,[13] apraclonidine was found to increase apparent resistance from 5.9 ± 1.8 mm Hg · min · μL^{-1} to 7.9 ± 3.0 mm Hg · min · μL^{-1} (P = .01) and brimonidine increased it from 6.1 ± 2.6 mm Hg · min · μL^{-1} to 8.1 ± 2.5 mm Hg · min · μL^{-1} (P = .008) (Table 4). No difference in

Table 4. Effect of Ocular Hypotensive Drugs on Apparent Resistance: Results of Previous Studies

Drug	Subjects	Apparent Resistance, mm Hg · min · μL^{-1}		Direction of Change	Source, y
		Placebo	Drug		
Aqueous Suppressors					
Timolol maleate	Normal	4.5	5.2	↑	Coakes and Brubaker,[15] 1978
Timolol	Normal	5.8	7.2	↑	Dailey et al,[26] 1982
Timolol	Normal	6.6	7.6	↑	Topper and Brubaker,[27] 1985
Timolol	Normal	3.9	5.7	↑	Wayman et al,[28] 1997
Betaxolol hydrochloride	Normal	4.5	5.5	↑	Reiss and Brubaker,[13] 1983
Clonidine hydrochloride	Normal	5.4	5.9	↑	Lee et al,[25] 1984
Acetazolamide	Normal	5.8	7.3	↑	Dailey et al,[26] 1982
Acetazolamide	Normal	4.2	5.3	↑	Topper and Brubaker,[27] 1985
Acetazolamide	Normal	3.9	4.5	↑	Maus et al,[29] 1997
Apraclonidine hydrochloride	Normal	4.0	5.0	↑	Gharagozloo et al,[11] 1988
Apraclonidine	Glaucoma (taking long-term timolol)	11.0	12.2	↑	Gharagozloo and Brubaker,[17] 1991
Dorzolamide hydrochloride	Normal	3.9	4.1	↑	Maus et al,[29] 1997
Dorzolamide	Normal	3.9	4.1	↑	Wayman et al,[28] 1997
Outflow Enhancers					
Epinephrine	Normal	4.9	3.4	↓	Townsend and Brubaker,[30] 1980
Epinephrine	Normal	4.8	3.9	↓	Higgins and Brubaker,[31] 1980
Epinephrine	Normal	4.7	4.1	↓	Nagataki and Brubaker,[32] 1981
Pilocarpine hydrochloride	Normal	5.0	4.2	↓	Nagataki and Brubaker,[33] 1982
Prostaglandin $F_{2\alpha}$-isopropylester	Normal	5.7	4.4	↓	Kerstetter et al,[34] 1988
Latanoprost	Normal	4.4	3.4	↓	Ziai et al,[35] 1993
Latanoprost	Ocular hypertension	7.6	6.1	↓	Ziai et al,[35] 1993
Latanoprost	Normal (taking timolol)	10.6	9.0	↓	Present study
Apraclonidine Compared With Brimonidine					
Apraclonidine	Normal	5.9	7.9	↑	Schadlu et al,[16] 1998
Brimonidine tartrate	Normal	6.1	8.1	↑	Schadlu et al,[16] 1998
Apraclonidine	Normal (taking timolol)	10.6	11.1	(↑)	Present study
Brimonidine	Normal (taking timolol)	10.6	11.0	(↑)	Present study

apparent resistance was observed between the 2 drugs ($P = .60$). The effect on resistance was similar to that of other drugs that are believed to be pure aqueous flow suppressors (Table 4). In the current study, the use of timolol reduced the aqueous-suppressing effects of these drugs, and the increase in apparent resistance was not significant. However, the use of timolol should have unmasked an outflow effect or differences in an outflow effect between the 2 drugs if one but not the other had such an effect. In contrast to latanoprost, no such effect was observed with either drug, and no difference between them was seen.

Toris and coworkers[6] demonstrated with their technique that uveoscleral outflow was increased by brimonidine from 0.12 to 0.65 μL/min, a change of 0.53 μL/min in ocular hypertensive volunteers, whereas uveoscleral flow was reduced from 0.58 to 0.11 μL/min by apraclonidine, a change in the opposite direction of 0.47 μL/min.[8] We were able to demonstrate changes in intraocular pressure corresponding to changes in inflow of 0.25 and 0.27 μL/min in our normotensive volunteers. It would appear logical that we could have observed a difference in the ocular hypotensive effects of these 2 drugs if either of them had caused the changes in uveoscleral flow reported previously. Thus, we cannot confirm the findings of the previous studies. It must be remembered, however, that we studied normal subjects (average intraocular pressure, 15 mm Hg), whereas patients with ocular hypertension were used in the previous study (average intraocular pressure, 22 mm Hg). There was also a difference in duration of drug exposure (1 day vs 8 days).

What remains to be done is to carry out a similar study in patients with ocular hypertension and glaucoma with longer exposure to the drugs. These additional studies should be done before the notion is accepted that brimonidine has clinically significant effects on aqueous humor outflow in contrast to apraclonidine.

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A look at the past. . .

BERNHEIMER, by experimental investigations on monkeys, confirmed his views, already published by Bergmann in monograph form, on the region of the oculo-motor nuclei in man. He demonstrated a series of preparations stained by Nissl's method, which show that the intrinsic muscles of the eye are supplied from what he has called the accessory nucleus of the oculomotor, the fibres crossing. The ciliary ganglion is not to be regarded as the primary centre for pupillay reaction.

Reference: *Arch Ophthalmol*. 1898;27:118.