Effects of topical nipradilol, a β blocking agent with α blocking and nitroglycerin-like activities, on intraocular pressure and aqueous dynamics in humans

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Abstract

Aims—To study the effects of topical nipradilol, a non-selective β blocker with α blocking and nitroglycerin-like activities, on intraocular pressure (IOP) and aqueous humour dynamics in normal humans and in patients with ocular hypertension.

Methods—Nipradilol (0.06%, 0.125%, 0.25%, 0.5%) was applied to normal volunteers (n = 12) to test for IOP lowering effects. In a second group of normal volunteers (n = 11), nipradilol (0.125% and 0.25%) and timolol (0.5%) were compared for IOP lowering effects. After a single administration of 0.25% nipradilol, IOP, flare intensity in the anterior chamber, aqueous flow, uveoscleral outflow, tonographic outflow facility, and episcleral venous pressure were either directly measured or mathematically calculated. Topical nipradilol (0.25%) was administered to 24 patients with ocular hypertension twice daily for 8 weeks.

Results—Administration of 0.25% nipradilol decreased IOP with a maximum reduction of 4.2 mm Hg lasting 12 hours. A single instillation of both 0.25% nipradilol and 0.5% timolol reduced the IOP in normotensive human subjects to the same degree. A single instillation of 0.25% nipradilol decreased the aqueous flow rate in the treated eye by 20%. Nipradilol produced no significant effect in tonographic outflow facility or episcleral venous pressure, but uveoscleral outflow was increased. In patients with ocular hypertension, twice daily instillation of 0.25% nipradilol decreased IOP without tachyphylaxis for the 8 week test period.

Conclusion—Topical nipradilol (0.25%) reduced IOP by decreasing the aqueous flow rate and probably also by increasing uveoscleral outflow. Nipradilol should be further investigated as a new antiglaucoma drug.

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Nipradilol is a non-selective β blocker with α_1 blocking and nitroglycerin-like vasodilating activities that are attributed to its nitroxyl moiety.[1–3] It has been registered as a systemic hypotensive drug.[4] The in vitro β blocking activity of nipradilol is approximately twice that of propranolol,[1] the α_1 blocking activity about one fifth that of phentolamine,[2] and the nitroglycerin-like vasodilating activity is approximately one fifth that of nitroglycerin.[2] Some α_1 blockers and nitroglycerin are reported to reduce intraocular pressure (IOP) in experimental animals or normal humans by increasing uveoscleral outflow or tonographic outflow for at least a short period of time.[5–13] A highly selective α_1 blocker, bunazosin, reduced IOP in glaucoma patients by about 4 mm Hg for 1 year without producing tachyphylaxis.[14]

The α_1 blocking and nitroglycerin-like activities of nipradilol might further enhance the ocular hypotensive effect owing to its β blocking activity, which is expected to reduce aqueous production. Further, the α_1 blocking and nitroglycerin-like vasodilating activities of nipradilol might provide an advantage over other β blockers that do not have such effects on ocular circulation. In a previous study, we found that the hypotensive effect of a single instillation of 0.25% nipradilol was significantly greater than that of 0.5% timolol in rabbit eyes. In rabbit eyes, the IOP lowering effect is attributed to both a decrease in aqueous humour production and an increase in uveoscleral outflow, and 2 weeks twice daily administration of 0.25% nipradilol might have beneficial effects on optic nerve head tissue circulation.[15]

To further evaluate the potential of topical nipradilol as a new antiglaucoma drug, we examined the effect of topical nipradilol on IOP and aqueous humour dynamics in normal human eyes. We also performed a preliminary clinical study in a group of patients with ocular hypertension to examine the clinical potential of nipradilol.

Material and methods

NORMAL HUMAN VOLUNTEERS

The study population consisted of a total of 23 normal volunteers ranging in age from 31 to 49 years without a history of ocular disease. Before admission into the study, written consent was obtained from each subject after the nature of the study was fully explained. Before treatment, a medical history was taken and a complete ophthalmological examination was performed on each patient. Inclusion criteria included IOP measurements in one eye within 2 mm Hg of the other eye, IOP in both eyes less than 21 mm Hg, gonioscopy demonstrating an open angle of grades 3–4, normal indirect ophthalmoscopic findings, and a normal appearance of the optic nerve head.

Subjects wearing contact lenses were not included in the study.

PATIENTS WITH OCULAR HYPERTENSION

A preliminary study population consisted of a total of 24 subjects with ocular hypertension (14 women and 10 men; mean age 50.1 (SE 3.2) years) who had a documented IOP of 22 mm Hg or higher in at least one eye on two separate occasions during the follow up and had normal visual field (Humphrey Perimeter 30-2 program) and normal appearance of the optic disc. The study was approved by the ethics committee of the University of Tokyo School of Medicine. Exclusion criteria included any ocular disease except ocular hypertension.

DRUGS

Nipradilol ophthalmic solutions of 0.06%, 0.125%, 0.25%, 0.5%, and the vehicle solution were supplied by Kowa (Tokyo, Japan). Timolol maleate ophthalmic solution (0.5%) was purchased from Banyu Pharmaceutical (Tokyo, Japan).

INSTRUMENTS

The IOP was measured with either a Goldmann applanation tonometer or applanation pneumatonograph (Alcon, Fort Worth, TX, USA) under topical anaesthesia (0.4% oxybuprocaine hydrochloride). Fluorophotometric measurements were made with a scanning fluorophotometer (Fluotron Master, Coherent Radiation Inc, Palo Alto, CA, USA) aqueous flare intensity measurements with a laser flare cell meter (Kowa, Tokyo, Japan), tonographic measurements with an electronic tonometer (Handaya, Tokyo, Japan), episcleral venous pressure measurements with a Zeimer venomanometer (Eyetech, Skokie, IL, USA), and anterior chamber depth measurements with an anterior chamber depth meter (Haag Streit, Bern, Switzerland). All measurements were performed by investigators blind to the treatment.

EXPERIMENTAL PROCEDURES

Effect of topical nipradilol on IOP in normal volunteers

Dose response study—Twelve normal volunteers were randomly assigned to two six subject groups. In one group 0% (vehicle), 0.06%, or 0.25% nipradilol was applied and in another group 0% (vehicle), 0.125%, or 0.5% nipradilol was applied to test for the effects on IOP on 3 separate days, with a washout period of 2 weeks. Each solution was instilled in one randomly chosen eye and each subject received the test solution in the same eye during this series of experiments. Application of the three sets of solutions was randomly assigned in each subject.

At 0900 of each experimental day, the investigator blind to the treatments administered 50 µl of one of these drugs topically to the chosen eye. Intraocular pressure was measured with a Goldmann applanation tonometer and slit lamp examinations were performed immediately before and 0.5, 1, 2, 4, 6, 8, and 12 hours after drug administration. At the same time, blood pressure and heart rate were also measured. The results were analysed as the difference between the change from pretreatment values in the nipradilol treatment study and that in the vehicle treatment (control) study, because the baseline IOP was different among these subjects.

$$(IOP_{nipradilol,t} - IOP_{nipradilol,0}) - (IOP_{vehicle,t} - IOP_{vehicle,0}) \quad (1)$$

in which t represents the time of IOP measurements and 0 represents the pretreatment measurements. Subjects were questioned about specific ocular and systemic symptoms such as discomfort, burning on instillation, or blurred vision.

Comparison with 0.5% timolol ophthalmic solution—Normal volunteers (n = 11) were used. Vehicle of nipradilol ophthalmic solution (0%), 0.125% and 0.25% nipradilol, and 0.5% timolol were tested for their IOP lowering effects on 4 separate days, with a washout period of 2 weeks. The order of application of the four sets of solutions was randomly assigned in each subject.

At 0800 of each experimental day, an investigator blind to the treatments administered 50 µl of one of these drugs or the vehicle topically to one eye and vehicle to the other eye. Intraocular pressure was measured with a Goldmann applanation tonometer and slit lamp examinations were performed immediately before and 1, 2, 4, 6, 8, and 12 hours after drug administration. Before and after drug instillation, blood pressure and heart rate were measured in all subjects. The results were analysed as the difference between the change from pretreatment values in the nipradilol or timolol treatment study and that in the vehicle treatment study, using equation (1).

Mechanism of IOP reduction

Effects of a single application of 0.25% nipradilol on aqueous humour dynamics was investigated. Subjects included 12 normal volunteers. Those who participated in the former experiments were not included in this study.

A drug-placebo pair was allocated to each subject as a right/left eye pair and the subject's right or left eye always received the same solution of the paired solutions. Studies were performed on four separate occasions, with 1 week intervals. In the first experiment, IOP, aqueous protein flare intensity, and pupillary diameter were measured hourly from 0900 to 1100. Immediately after the 1100 measurement, 50 µl of one of the paired solutions (0.25% nipradilol or placebo) was applied to the right eye and 50 µl of the other of the paired solutions to the left eye. Thereafter, measurements of IOP using a Goldmann applanation tonometer and aqueous flare intensity were performed hourly till 1700. Pupillary diameter measured under constant lighting hourly from 1200 to 1400 and at 1700. Readings of the laser flare cell meter were converted into the equivalent of human serum albumin concentrations.[16]

In the second experiment, anterior chamber depth, IOP, and aqueous flow rate were measured. The same 12 subjects received drug placebo treatments with the same time schedule in the same eyes as on the first experimental day. One day before the study, autofluorescence of the subject's eyes was measured with a fluorophotometer equipped with an anterior chamber adapter. Thereafter, a fluorescein solution (5%) was instilled into each eye five times at 1 minute intervals after application of topical anaesthesia. Ten hours later (0900 on the day of the study), concentrations of fluorescein in the cornea and anterior chamber were measured with the fluorophotometer hourly until 1700. A test solution (50 μl of 0.25%) was instilled as described above at the same time of the day. The anterior chamber depth and IOP were measured at 1000 and 1300 using an anterior chamber depthometer and an applanation pneumatonograph, respectively. The anterior chamber volume was calculated according to the following equation.[17]

That is:

$$V_a = 6.5^2 \times D_a \times 1.51 \qquad (2)$$

where V_a is the anterior chamber volume, D_a is the anterior chamber depth, and posterior corneal curvature was assumed to be 6.5 mm.[18]

Aqueous flow rate was determined with a modification of Jones and Maurice method.[19][20] Averaged aqueous flow rate was calculated as follows:

$$f = |0.9[(\overline{F_c/F_a}) \times V_c A_c + V_a \times A_a]| \qquad (3)$$

in which V_a indicates anterior chamber volume, $\overline{F_c/F_a}$ are the average of the ratio of fluorescein concentrations of the cornea and anterior chamber, which was corrected according to the results of Mori and Araie.[21] The terms A_c and A_a refer to the slope of the line fitted to the logarithm of dye concentrations in the cornea and anterior chamber respectively. The corneal volume, V_c, was assumed to be 7 0 μl.[22]

In the third experiment, the test solution was instilled at 1100 as above and at 1000 and 1300, tonographic measurements were performed under topical anaesthesia using an electronic tonometer. Outflow facility was calculated from the result of a 4 minute tonographic measurement. Intraocular pressure was determined at 1000 and 1300 immediately before tonographic measurement with a Goldmann applanation tonometer.

In the fourth experiment, the test solution was instilled as above at 1100, and episcleral venous pressure was measured at 1000 and 1300 with a venomanometer mounted on a slit lamp microscope under topical anaesthesia. The pressure required to half blanch the selected episcleral vein was recorded. Three rapid measurements were taken half a minute apart and averaged for episcleral venous pressure values. Intraocular pressure was measured with a Goldmann applanation tonometer immediately after venomanometer measurements.

Preliminary clinical study in subjects with ocular hypertension
If a patient received pilocarpine or adrenaline (epinephrine), there was a washout period of 2 weeks or more before entry into the study and if a patient received a β adrenergic blocker, there was a washout period of 4 weeks or more. IOP measurement with a Goldmann applanation tonometer, routine ophthalmological examinations, and blood pressure and heart rate measurements were performed immediately before and 1, 2, 4, 6, and 8 weeks after beginning the therapy about 3 hours after the morning dosing. Measurements during study periods were performed at approximately the same time of day. The patients were instructed to self administer the drops twice daily in both eyes at 0800 and 2000 during the study period. At each visit, subjects were questioned about compliance, specific ocular, and systemic symptoms, (for example, discomfort, burning on instillation, or blurred vision). The IOP of one eye, which was randomly chosen, was used for analysis.

Results

EFFECT OF TOPICAL NIPRADILOL ON IOP IN NORMAL VOLUNTEERS

Dose-response study
The average mean pretreatment IOP level was 13.6 (SE 0.8) mm Hg (n=12). A single application of nipradilol induced a significant reduction in IOP. An ophthalmic solution of 0.25% nipradilol significantly decreased IOP from 0.5 through 12 hours and the maximum IOP reduction calculated using equation (1) was 4.2 (0.9) mm Hg at 1 hour, whereas the maximum mean IOP reduction was 1.5 (0.8) mm Hg 1 hour after administration of 0.06% nipradilol, 3.3 (0.8) mm Hg 2 hours after administration of 0.125% nipradilol, and 2.7 (0.9) mm Hg 2 hours after administration of 0.5% nipradilol. Mean percentage IOP reduction between 0 and 12 hours after instillation was calculated to compare IOP reducing effect among these concentrations. It was the ratio of the mean IOP reduction during 12 hours after drug instillation calculating equation (1) to the mean IOP during 12 hours after vehicle instillation. Difference in the measurement interval was corrected in calculating the mean. The mean percentage IOP reduction after instillation of 0.06%, 0.125%, 0.25%, and 0.5% nipradilol were 2.7 (4.0), 7.7 (4.1), 25.4 (6.9), and 6.3 (4.2), respectively. There were significant difference between 0.06% nipradilol and 0.25% nipradilol with unpaired *t* test (p=0.0006), (p=0.0036 with Bonferroni's correction) and between 0.5% nipradilol and 0.25% nipradilol with unpaired *t* test (p=0.03). The ophthalmic solution of 0.25% nipradilol was the most effective among these concentrations. Nipradilol ophthalmic solutions of 0.06%, 0.125%, and 0.25% caused slight to mild conjunctival hyperaemia lasting for less than 2 hours after instillation, but no subjects complained of pain or irritative sensation at any concentrations. On the other hand, after instillation of 0.5% nipradilol, four of six subjects complained of some irritative sensa-
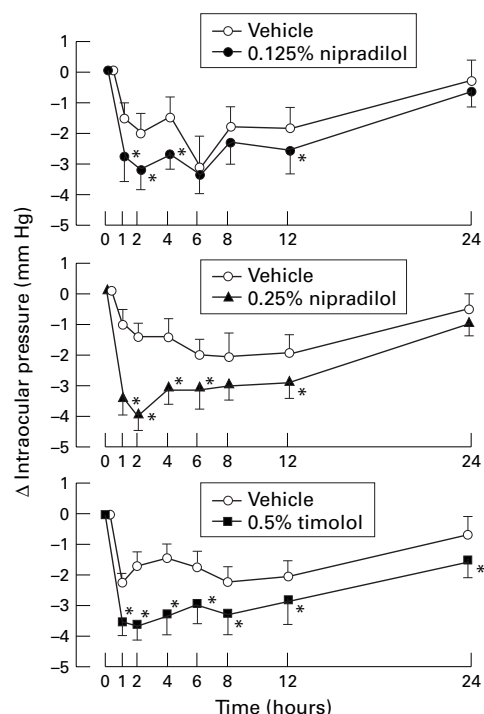
Figure 1   Reduction in the intraocular pressure after 0.125%, 0.25% nipradilol, or 0.5% timolol instillation in drug treated eye and vehicle treated eye. Δ Intraocular pressure = difference between the change from pretreatment values in the drug treated experiment (0.125% or 0.25% nipradilol or 0.5% timolol solution instilled in one eye and vehicle in fellow eye) and that in the control experiment (vehicle solutions instilled in both eyes). Figures are significantly negative, *p<0.05. Bars represent mean (SE) (mm Hg) in 11 eyes of 11 subjects.

tion and one of six subjects reported mild ocular pain, although there was no apparent evidence of ocular surface toxicity. There were no significant changes in blood pressure or heart rate from pretreatment measurements.

Comparison with 0.5% timolol ophthalmic solution

A single application of 0.125% or 0.25% nipradilol, and 0.5% timolol significantly reduced the IOP in the drug treated eye for 12 hours after instillation (Fig 1). The maximum reductions of IOP calculated from equation (1) were mean 3.2 (SE 0.7) mm Hg (n = 11) 6 hours after instillation of 0.125% nipradilol, 3.3 (0.4) mm Hg 4 hours after instillation of 0.25% nipradilol, and 3.1 (0.6) mm Hg 4 hours after instillation of 0.5% timolol. A small but significant effect of these drugs was also observed in the contralateral eye. There was no

significant difference among these treatments. Mean percentage IOP reduction between 0 and 12 hours was calculated as above to compare IOP reducing effect of these drugs. The mean percentage IOP reduction of 0.125%, 0.25% nipradilol, and 0.5% timolol (vehicle treated eye) were 21.0 (6.0) (11.7 (4.6)), 26.1 (2.9) (8.9 (4.9)), 23.7 (4.4) (11.9 (4.3)), respectively. There was no significant difference among the test solutions. Although two subjects treated with 0.125% nipradilol, three subjects treated with 0.25% nipradilol, and one subject treated with 0.5% timolol noted slight to mild conjunctival injection, it disappeared within 2 hours after the application. There was no other remarkable subjective or objective evidence of side effects from the treatment. There were no significant changes in blood pressure or heart rate from pretreatment measurements.

MECHANISM OF IOP REDUCTION

After instillation of drugs, the aqueous protein concentration of 0.25% nipradilol treated eyes was higher than in vehicle treated eyes, and the IOP of 0.25% nipradilol treated eyes were lower than in vehicle treated eyes (Table 1). The pupillary diameter did not change. The average aqueous flow rate over the time period from 0900 to 1100 (from 2 hours before instillation to the time of instillation) and that from 1200 to 1600 (from 1–5 hours after the instillation) were calculated. The aqueous flow rate was significantly reduced by an average of 20% in the nipradilol treated eyes but not in the vehicle treated eyes (Table 2). The IOP was significantly reduced by 3.3 (0.3) mm Hg from 13.6 (0.3) mm Hg (n=6) in the nipradilol treated eyes and by 1.2 (0.3) mm Hg from 13.8 (0.3) in the vehicle treated eyes 2 hours after instillation. The anterior chamber volume did not change significantly.

The coefficient of protein entry into the anterior chamber (k_{in}) averaged over the measurement period was calculated from the protein concentration of the anterior chamber (C_a), plasma protein concentration (C_p), anterior chamber volume (V_a), and aqueous flow rate (f) both of which were assumed to be the same as determined in the same eye in the second experiment. That is:

$$k_{in}=(A_p+f\times \overline{C_a}/V_a/(C_p-\overline{C_a}) \qquad (4)$$

in which A_p is the average of dC_a/dt, approximated by the difference of the equation during the measurement period, f is the averaged flow

Table 1   Time course of intraocular pressure (mm Hg) and aqueous protein concentration (mg/dl) before and after single instillation of 0.25% nipradilol

	Time after instillation (hours)								
	−2	−1	0	1	2	3	4	5	6
Intraocular pressure (mm Hg)									
vehicle treated eye	14.3 (0.7)	13.9 (0.7)	13.6 (0.7)	12.8 (0.7)	12.3 (0.7)	12.7 (0.7)	12.5 (0.7)	12.6 (0.7)	13.3 (0.7)
nipradilol treated eye	14.3 (0.8)	13.6 (0.7)	13.2 (0.7)	10.4 (0.8)	9.7 (0.6)	10.3 (0.7)	10.4 (0.8)	11.2 (0.8)	12.2 (0.7)
Aqueous protein concentration (mg/dl)									
vehicle treated eye	26.3 (2.1)	25.0 (2.1)	24.9 (1.7)	24.1 (1.7)	22.2 (1.4)	23.8 (1.3)	22.7 (4.3)	25.2 (1.8)	25.1 (1.1)
nipradilol treated eye	26.8 (2.2)	24.8 (1.6)	22.9 (1.3)	29.7 (2.1)	28.4 (1.7)	29.6 (1.6)	27.6 (1.2)	29.1 (1.3)	29.1 (1.3)

Figures indicate mean (SE) in 12 eyes of 12 subjects.
Difference between intraocular pressure in vehicle treated eye and nipradilol treated eye were significant (p=0.0001, analysis of variance of repeated measurement).
Difference between aqueous protein concentration in vehicle treated eye and nipradilol treated eye were significant(p=0.0002, analysis of variance of repeated measurement).

Table 2 Aqueous flow rate and coefficient of protein entry into the aqueous chamber (k_{in}) before and after single instillation of 0.25% nipradilol

	Before	After
Aqueous flow rate (µl/min)		
vehicle treated eye	2.53 (0.21)	2.54 (0.07)
nipradilol treated eye	2.80 (0.25)	2.25 (0.08)*†
Coefficient of protein entry; k_{in} ($\times 10^{-5}$/min)		
vehicle treated eye	4.77 (0.47)	4.73 (0.25)
nipradilol treated eye	4.87 (0.47)	4.92 (0.08)

Figures indicate mean (SE) in 12 eyes of 12 subjects. Before = average −2–0 hours; after = average 1–5 hours.
*Compared with before, p=0.0491 (paired *t* test).
†Compared with vehicle treated eye, p=0.0030 (paired *t* test).

Table 3 Outflow facility, episcleral venous pressure (P_{ev}) before and after single instillation of 0.25% nipradilol

	1 hour before	2 hours after
Outflow facility (µl/min/mm Hg)		
vehicle treated eye	0.40 (0.02)	0.37 (0.03)
nipradilol treated eye	0.38 (0.03)	0.38 (0.02)
P_{ev} (mm Hg)		
vehicle treated eye	8.7 (0.1)	8.6 (0.1)
nipradilol treated eye	8.7 (0.1)	8.6 (0.1)

Figure are mean (SE) in 12 eyes of 12 subjects.

rate during the measurement period, $\overline{C_a}$ is the average protein concentration during the measurement period, and ($C_p - \overline{C_a}$) is approximated by C_p with reasonable accuracy. The averaged k_{in} over the time period from 900 to 1100 and that from 1200 to 1600 was calculated. The calculated value, k_{in}, did not
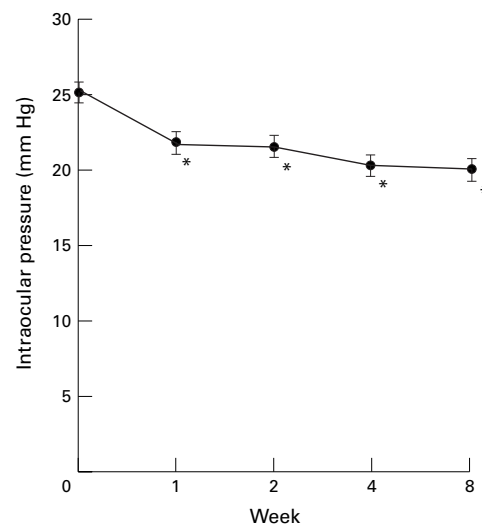

*Figure 2 Intraocular pressure after twice daily instillation of 0.25% nipradilol during 8 weeks. Bars represent mean (SE) (mm Hg) in 24 eyes of 24 subjects. *Compared with week 0, v week 1; p=0.0016, v week 2; p=0.0022, v week 3; p<0.0001, v week 4; p<0.0001 (paired t test with Bonferroni's correction).*

Table 4 Number of patients with ocular findings and symptoms reported during a 8-week treatment with 0.25% nipradilol (n=24)

Findings	No (%)
Irritation, eye	5 (21)
Pain, eye	1 (4)
Foreign body sensation	1 (4)
Blurred vision	1 (4)
Dry eye	1 (4)
Discharge	1 (4)
Conjunctival hyperaemia	1 (4)
Conjunctival chemosis	1 (4)

change significantly from pretreatment values (Table 2).

The results of tonographic outflow facility and episcleral venous pressure measurements are shown in Table 3. No significant difference was observed before and after the instillation either in the nipradilol treated or vehicle treated eyes. In these two experiments, the IOP in the nipradilol treated eyes was reduced similarly in both experiments.

During this series of experiments, no ocular or systemic side effects were encountered except for mild hyperaemia in five of 12 subjects.

PRELIMINARY CLINICAL STUDY IN SUBJECTS WITH OCULAR HYPERTENSION
During twice daily application of 0.25% nipradilol for 8 weeks, nipradilol significantly decreased the IOP 3 hours after the morning dose (Fig 2) by 3.4 mm Hg (week 1), 3.6 mm Hg (week 2), 4.8 mm Hg (week 4), and 5.0 mm Hg (week 8) from the baseline (25.2 (0.6) mm Hg, n=24). The systolic pressure, diastolic pressure, and heart rate did not change significantly during the study period and values at 0 and 8 weeks were 133.7 (20.7) and 134.9 (19.8) mm Hg, 77.9 (12.1) and 81.1 (11.3) mm Hg, and 74.8 (11.2) and 74.8 (11.3) per minute respectively. Some subjects noted slight to mild conjunctival injection. There was no other remarkable subjective or objective ocular evidence of side effects attributable to the treatment (Table 4).

Discussion

A single application of nipradilol ophthalmic solution reduced the IOP in normotensive human subjects in a dose dependent manner from 0.06% to 0.25% and the maximum effective concentration was 0.25%. The decrease in effect for the 0.5% solution is probably attributable to washout of the drug by excessive tearing caused by irritation. A single instillation of 0.25% nipradilol and 0.5% timolol reduced the IOP in normal subjects to the same degree. A small but significant contralateral effect was demonstrated after the drug instillation for both drugs. In the in vitro system, the β blocking activity of nipradilol is about twice that of propranolol,[1] while that of timolol is about seven times that of propranolol.[23] The maximum plasma concentration of 0.5% timolol was reportedly 1.28 ng/ml 1 hour after a single instillation of 0.5% timolol.[24] Although the maximum plasma concentration of nipradilol is not available, it is presumed to be similar to the value obtained for timolol. Thus, when the 0.25% concentration of nipradilol is used, systemic β blocking activity of nipradilol after its topical instillation is expected to be considerably less than that after topical 0.5% timolol. Topical 0.25% nipradilol, however, also produced contralateral IOP lowering effects probably attributable to systemically absorbed nipradilol. This result indicates that systemic β blocking effects in the cardiovascular, respiratory, or other organs are also possible when 0.25% topical nipradilol is applied in patients. Nipradilol has pharmacological effects other

than β blocking activity that timolol does not share—α_1 blocking activity and/or nitroglycerin-like activity. Several α_1 blockers are reported to reduce the IOP in both experimental animals and humans,[5–11] and previous studies suggest that nitroglycerin also has an ocular hypotensive effect in monkeys and rabbits.[12 13] These pharmacological effects of systemically absorbed nipradilol might be at least partly responsible for the contralateral effect of this drug.

The effects of a single instillation of 0.25% nipradilol on the aqueous dynamics were examined by measuring the aqueous protein concentration, tonographic outflow facility, episcleral venous pressure, and fluorophotometrically determined aqueous flow rate. If nipradilol caused significant dilatation of the iridial blood vessels by its α blocking and/or nitroglycerin-like activity, a subsequent increase in the transfer coefficient by diffusion would be expected. In the rabbit eye, we demonstrated that 0.25% nipradilol had no significant effect on iris permeability to fluorescein.[15] Further, the coefficient of protein entry into the anterior chamber (k_{in}) did not significantly change before and after topical nipradilol, suggesting that nipradilol did not affect the blood-aqueous barrier. Topical 0.25% nipradilol reduced the aqueous flow rate by 20% in the nipradilol treated eye, probably because of its β blocking activity. Calculations using equation (4) indicated that the increase in the aqueous protein concentration observed after topical nipradilol is almost exclusively attributable to a decrease in the aqueous flow rate—that is, a decrease in the washout of protein molecules from the anterior chamber, rather than an increase in their entry into the anterior chamber.

Topical nipradilol reduced IOP in the contralateral vehicle treated eye also, but there was no significant change in aqueous flow rate in the contralateral eye. These findings suggest that the decrease in aqueous flow rate in the contralateral eye, due to systemic β blocking activity, was not large enough to be detected fluorophotometrically in the present subjects. It is possible that the decrease of IOP in the contralateral eye is partly due to effects of α blocking or nitroglycerin-like activities.

Topical nipradilol had little effect on the episcleral venous pressure and the tonographic outflow facility. In the present study, we did not use the fluorophotometric method to measure the uveoscleral outflow[25] because the IOP after topical nipradilol was approximately 10 mm Hg in the present subjects, too low for the fluorophotometric method[25] to determine the uveoscleral outflow with reasonable accuracy. The uveoscleral outflow (f_u) can be roughly calculated using the following equation.[26]

$$f_u = f - C_{conv} \times (IOP - P_{ev}) \quad (5)$$

where f_u is the uveoscleral outflow, f aqueous flow rate, C_{conv} is outflow facility via the conventional route, IOP intraocular pressure, and P_{ev} is the episcleral venous pressure. Topical nipradilol decreases IOP without significant changing C_{conv} and P_{ev}. Thus,

$$f_{u \cdot before} - f_{u \cdot after} = (f_{before} - f_{after}) - C_{conv} \times$$
$$(IOP_{before} - IOP_{after}) \quad (6)$$

where $f_{u \cdot before}$ and $f_{u \cdot after}$ are f_u before and after nipradilol instillation, f_{before} (IOP_{before}) and f_{after} (IOP_{after}) are f (IOP) before and after nipradilol instillation, respectively. Assuming the tonographic outflow facility obtained to be C_{conv} and using the values of P_{ev}, f, and IOP, f_u can be roughly estimated as follows.

$$f_{u \cdot before} - f_{u \cdot after} = (2.80 - 2.25) - 0.38$$
$$(13.77 - 10.40) = -0.73 < 0 \quad (7)$$

Thus, it is difficult to explain the decrease in IOP in the present experiment only by a reduction of the aqueous flow. Topical nipradilol increases uveoscleral outflow, estimated using the fluorophotometric and anterior chamber perfusion methods, in rabbit eyes.[15] These findings suggest that topical nipradilol also increases uveoscleral outflow in humans.

Previous studies demonstrated that bunazosin significantly reduced IOP by enhancing uveoscleral outflow both in rabbits and normal humans.[6 7] In vitro, the α_1 blocking activity of nipradilol is approximately 1/50 that of bunazosin.[1] The least effective concentrations of topical bunazosin, which reduces IOP in humans, is 0.001% or higher.[27] Therefore, the α_1 blocking activity of topical 0.25% nipradilol is sufficient to exert its pharmacological effects in human eyes, assuming a similar permeability of the cornea to the two drugs.

Twice daily instillation of 0.25% nipradilol significantly reduced IOP in patients with ocular hypertension by approximately 4 mm Hg and no evidence of drug tolerance was observed over 8 weeks. There were no significant changes in blood pressure and heart rate during the study periods. These results suggest the clinical potency of nipradilol.

In summary, topical 0.25% nipradilol decreased IOP in normal human eyes to a similar degree as 0.5% timolol, and the mechanism of action might involve a reduction in the aqueous flow and increase in the uveoscleral outflow. Twice daily instillation of 0.25% nipradilol for 8 weeks reduced the IOP in patients with ocular hypertension by approximately 4 mm Hg without affecting blood pressure and heart rate or producing any signs of tachyphylaxis. Topical nipradilol deserves further study as a new antiglaucoma agent.

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