ELSEVIER

Effect of Topical Carteolol on Tissue Circulation in the Optic Nerve Head

Yasuhiro Tamaki,* Makoto Araie,† Ken Tomita‡ and Atsuo Tomidokoro§

*Eye Clinic, Tokyo Metropolitan Geriatric Hospital, Tokyo, Japan; †Department of Ophthalmology, University of Tokyo School of Medicine, Tokyo, Japan; ‡Eye Clinic, Tokyo Kosei Nenkin Hospital, Tokyo, Japan; §Eye Clinic, Omiya Red Cross Hospital, Omiya, Japan

Abstract: The effect of topical 2% carteolol on tissue circulation in the albino rabbit optic nerve head (ONH) was investigated using a laser speckle tissue circulation analyzer. In the first experiment, the normalized blur (NB) value, a quantitative index of tissue blood flow velocity in the ONH, intraocular pressure (IOP), blood pressure (BP), and pulse rate were measured under general anesthesia before as well as 30, 60, 90, and 120 minutes after a 20-μL instillation of carteolol in one eye and the vehicle in the other eye in a masked, randomized manner. In the second experiment, one eye of a rabbit received carteolol twice daily for 20 days and the fellow eye received the vehicle in a masked, randomized manner. The IOP was measured every 5 days, and the NB in the ONH and IOP were measured before treatment and 2 hours after the last instillation on the 20th day. After a single instillation of carteolol, pulse rate showed a maximum reduction of 15%, and IOP in the carteolol-treated eyes showed a maximum decrease of 22%. The NB in the ONH and BP did not show any significant change during the experiment. After 20-day treatment with carteolol, IOP showed a maximum decrease of 25% in the carteolol-treated eyes and 21% in the vehicle-treated eyes. The NB showed a significant increase of 15% ($P < 0.01$) in the carteolol-treated eyes and 11% ($P < 0.01$) in the vehicle-treated eyes. It was indicated that long-term topical carteolol increased the blood velocity in the ONH tissue both in the carteolol- and vehicle-treated contralateral eyes in albino rabbits. **Jpn J Ophthalmol 1998;42:27–32** © 1998 Japanese Ophthalmological Society

Key Words: Carteolol, laser speckle phenomenon, optic nerve head, rabbit eye, tissue circulation.

Introduction

Previous studies have indicated that compromise of the tissue circulation in the optic nerve head (ONH) may play a causal role in glaucomatous injury in the ONH, although intraocular pressure (IOP) has been consistently found to be one of the most important risk factors in the development of open-angle glaucoma.[1–3] Therefore, the possible effects of antiglaucoma agents on ONH tissue circulation are of great clinical importance.

Beta-2 receptors generally mediate relaxation of vascular smooth muscle, and it is known that systemic beta-antagonists induce vasoconstriction in various tissues.[4,5] Carteolol hydrochloride, a nonselective beta-adrenergic antagonist, might have a different effect on tissue blood flow from other beta-antagonists such as timolol, since it has several vasodilative activities—intrinsic sympathomimetic activity (ISA) and weak endothelium dependent vasodilative activity.[6–9] Using laser Doppler velocimetry, Grunwald and Delehanty[10] reported that a single instillation of 1% carteolol in human eyes showed no significant effect on the centerline blood velocity in the large retinal veins. To the best of our knowledge, however, there are no reports on the effect of topical carteolol on the tissue circulation in the ONH.

We have recently developed an apparatus equipped with a diode laser for noncontact and two-dimensional estimation of ocular fundus tissue circulation utilizing the laser speckle phenomenon with which a quantitative index of the tissue blood flow velocity in an area of 0.42 × 0.42 mm of the ONH, normalized

Received: June 19, 1997

Address correspondence and reprint requests to: Yasuhiro TAMAKI, MD, 3-2-1-303, Nishigahara, Kita-ku, Tokyo 114, Japan

Published by Elsevier Science Inc.

0021-5155/98/$19.00
PII S0021-5155(97)00099-3

Jpn J Ophthalmol
Vol 42: 27–32, 1998

blur (NB) value, was measured with reproducibility of about ±10%.[11] Further, we have already reported that, using this apparatus, twice daily 20-day instillation of 0.5% timolol[12] or 0.5% betaxolol[13] caused a significant increase in ipsilateral ONH tissue blood velocity in albino rabbits. The rabbit ONH vasculature has some similar features with that of humans or primates; the principle blood supply of the rabbit ONH is derived from the short posterior ciliary arteries by the arterial circle.[14] In the present study, we studied the effects of a single- or twice-daily 20-day instillation of carteolol on ONH tissue circulation in rabbit eyes using the same apparatus. The NB in the ONH was found to correlate well with the blood flow rate in the ONH, as determined by using the hydrogen gas clearance method in albino rabbits.[15]

Materials and Methods

Laser Speckle Tissue Circulation Analyzer

The ONH tissue circulation was evaluated with a laser speckle tissue circulation analyzer, details of which have been described elsewhere.[11,16] The apparatus consists of a fundus camera (TRC-WT3®, Topcon, Tokyo) equipped with a diode laser (wavelength = 808 nm) and an image sensor (100 × 100 pixels, BASIS type, Canon, Tokyo). A halogen lamp illuminated the fundus where the laser beam was focused. The scattered laser light was imaged onto the image sensor, which corresponds to a field of 0.62 × 0.62 mm in the rabbit ONH, where a speckle pattern appeared. The difference between the average of the speckle intensity (I_{mean}) and the speckle intensity for successive scannings of the image speckles at the pixels on the sensor plane was calculated, and the ratio of I_{mean} to this difference was defined as NB. The NB is nearly equivalent to the reciprocal of speckle contrast described by Fercher and Briers[17,18] and is thought to be indicative of tissue blood velocity. The results are displayed in a color graphic showing the two-dimensional variation of the NB level over the field of interest. The average of NB levels in the measured field in the ONH was expressed as NB_{av}. The coefficient of reproducibility of 5-minute or 24-hour interval in vivo measurements of NB_{av} in 70 × 70 pixels, which corresponds to 0.42 × 0.42 mm in the rabbit ONH, was approximately 10% for both time intervals.[11]

Drug

Carteolol hydrochloride 2% ophthalmic solution was purchased from Otsuka Pharmaceutical Company (Tokyo). The vehicle was kindly supplied by the same company.

NB_{av} Measurement in the ONH

Albino rabbits weighing 2.5–3.0 kg were used and handled in accordance with the ARVO Resolution of the Use of Animals in Research. The animals were entrained to a light schedule of alternating 12-hour periods of light and dark (12L:12D, light on at 4:00 AM) for at least 3 weeks prior to use. After dilating the pupil with one drop of Mydrin M® (0.4% tropicamide, Santen Pharmaceutical, Osaka), the image speckles from the largest square field in the ONH free of visible surface vessels were recorded to measure the NB_{av} value in the ONH tissue ($NB_{av(ONH)}$) (Figure 1). Color fundus photographs were taken to record the site of NB measurement referring to visible surface vessels near the measurement field as markers to identify tissue sites.

Experimental Protocol

Effect of a single instillation. General anesthesia was induced by intravenous injection of 30 mg/kg pentobarbital sodium and maintained carefully with additional small doses. The femoral artery was cannulated with a polyethylene catheter and connected to a pressure transducer (DTX®, Spectramed, CA, USA) for measurements of the femoral arterial blood pressure and pulse rate. The mean femoral arterial blood pressure (BP_m) was calculated according to the formula:

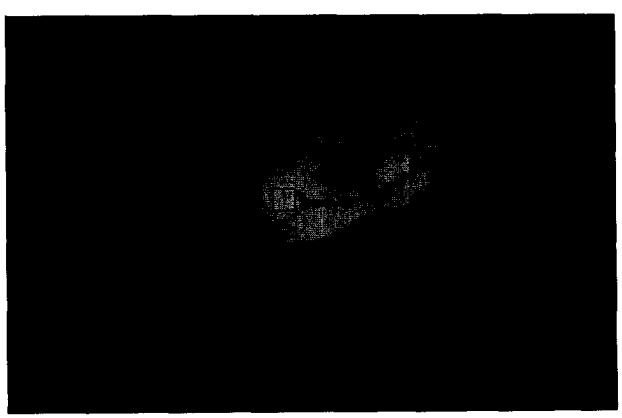

Figure 1. Measurement field of normalized blur in the optic nerve head (ONH) tissue. The image speckles from the inferior field of ONH where no discrete vessels were visible (0.42 × 0.42 mm, □) were recorded to measure the normalized blur in the ONH tissue.

$$BP_m = BP_d + 1/3(BP_s - BP_d),$$

where BP_d and BP_s are diastolic and systolic femoral arterial blood pressures, respectively. After dilating the pupil with one drop of Mydrin M®, the $NB_{av(ONH)}$ was measured as described above. The average of six measurements obtained at intervals of 1 minute was adopted as the initial value.

In a masked manner, one eye of each animal received 20 μL of 2% carteolol, and the fellow eye received the vehicle at 6:00 PM (carteolol group, n = 8). To serve as a control, both eyes received the vehicle of carteolol at 6:00 PM in another group of rabbits that were anesthetized and treated in the same way as in the carteolol group (control group, n = 8). During the experiment, $NB_{av(ONH)}$ and IOP in both eyes of the carteolol group and one randomly chosen eye of the control group as well as BP_m and pulse rate were monitored prior to instillation and at 30, 60, 90, and 120 minutes after instillation. The IOP was monitored with a calibrated applanation pneumotonometer. Arterial P_{O2}, P_{CO2}, and pH were checked before instillation and 60 and 120 minutes after instillation using the pH/Blood Gas Analyzer, Model 170 (Corning Glass, Corning, NY, USA). Body temperature was monitored with a rectal thermometer.

Effect of a 20-day topical treatment. The IOP was measured in both eyes with a calibrated applanation pneumotonometer after instillation of topical anesthesia (0.4% oxbuprocaine hydrochloride) at 8:00 PM under dim light. General anesthesia was induced by intravenous injection of 15 mg/kg pentobarbital sodium. The pupil was dilated as described above. Fifteen minutes after induction of general anesthesia, the $NB_{av(ONH)}$ in both eyes was measured as described above, and the average of six measurements obtained at intervals of 1 minute was adopted as the initial value. Color fundus photographs were taken to record the site of NB measurement.

From the next day on, one eye of each animal received 20 μL of 2% carteolol, and the fellow eye received the vehicle twice daily (6:00 AM and 6:00 PM) for 20 days in a masked manner (carteolol group, n = 27). To serve as a control, both eyes of another group of rabbits, which were treated in the same way as the carteolol group, received the vehicle twice daily (6:00 AM and 6:00 PM) for 20 days (control group, n = 16). During the treatment period, the light schedule was the same as described above, and the IOP was measured under topical anesthesia in both eyes of the carteolol group and one randomly chosen eye of the control group at 8:00 PM on the 5th, 10th, 15th, and 20th day under dim light. On the 20th day, after measuring the IOP under topical anesthesia, general anesthesia was induced. The $NB_{av(ONH)}$ at the same site of ONH tissue was measured again as described above in both eyes of the carteolol group and a chosen eye of the control group. All measurements were carried out by investigators unaware of the treatment given the animals.

Calculations and Statistical Analysis

The results were presented as mean ± SEM. Paired Student's *t*-tests or unpaired *t*-tests were applied to evaluate statistical significance. For multiple comparisons, Bonferroni's correction was used to calculate *P* values. Significance levels of $P < 0.05$ were considered statistically significant.

Results

Effect of a Single Instillation

Only those rabbits whose systemic condition parameters, except for the pulse rate, showed little change during the experiments and were within the normal range of healthy rabbits[19,20] were accepted; systemic parameters obtained in these rabbits are summarized in Table 1. Figure 2 summarizes the time course of NB_{av}, IOP, and pulse rate after instillation of carteolol or vehicle. The IOP and pulse rate showed no significant change in the control group. The IOP in the carteolol-treated eyes was significantly lower at 30, 60, 90, and 120 minutes compared with that of the control group ($P < 0.05$–0.01 with Bonferroni's correction), while the IOP in the vehicle-treated eyes of the carteolol group showed no significant difference from that in the control group. The pulse rate in the carteolol group was significantly lower between 30 and 120 minutes compared with that of the control group ($P < 0.05$–0.01). The NB_{av} showed no significant change throughout the experimental period in the carteolol-treated and vehicle-treated eyes of the carteolol group and in those of the control group.

Effect of a 20-Day Topical Treatment

The IOP in the control group showed no significant change throughout the experimental period. The IOP both in the carteolol-treated eyes and the vehicle-treated eyes of the carteolol group was significantly lower between 5 and 20 days as compared with the control group ($P < 0.01$ with Bonferroni's correction) (Figure 3). The values of $NB_{av(ONH)}$ in the ONH tissue before and after 20 days of topical

Jpn J Ophthalmol
Vol 42: 27–32, 1998

Table 1. Values of Systemic Condition Parameters Before and After Single Topical Instillation of Carteolol or Vehicle

	0 Min	30 Min	60 Min	90 Min	120 Min
Carteolol Group					
BP_m (mm Hg)	90.9 ± 5.0	89.9 ± 4.7	90.6 ± 5.2	85.9 ± 4.2	85.9 ± 3.6
BT (°C)	38.8 ± 0.3	—	38.2 ± 0.3	—	38.4 ± 0.4
pH	7.35 ± 0.03	—	7.37 ± 0.01	—	7.36 ± 0.01
P_{CO2} (mm Hg)	33.8 ± 2.4	—	34.6 ± 1.4	—	35.2 ± 1.2
P_{O2} (mm Hg)	89.6 ± 1.2	—	92.5 ± 1.4	—	96.3 ± 1.4
Control Group					
BP_m (mm Hg)	96.3 ± 2.7	94.1 ± 2.8	94.5 ± 3.0	94.3 ± 2.7	94.0 ± 3.1
BT (°C)	38.5 ± 0.2	—	38.3 ± 0.3	—	38.2 ± 0.4
pH	7.38 ± 0.03	—	7.39 ± 0.02	—	7.39 ± 0.02
P_{CO2} (mm Hg)	32.2 ± 2.5	—	33.9 ± 2.8	—	33.1 ± 2.8
P_{O2} (mm Hg)	90.4 ± 1.8	—	92.1 ± 2.3	—	93.7 ± 2.5

BP_m and BT indicate mean femoral arterial blood pressure and body temperature, respectively. Figures are mean ± SEM (n = 8).

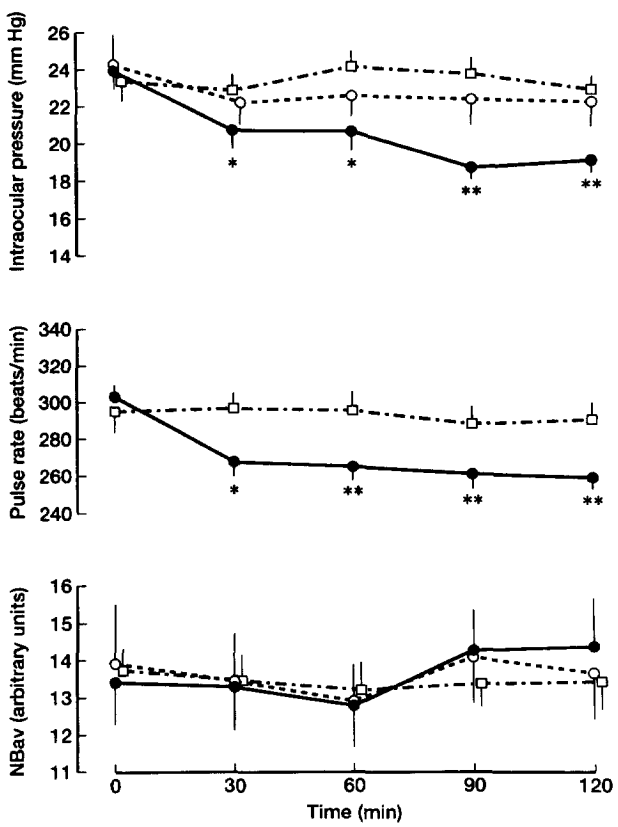

Figure 2. Time course (min) of the average normalized blur (NB_{av}) (70 × 70) obtained from the optic nerve head tissue, intraocular pressure, and pulse rate after a single instillation of carteolol (●) or vehicle (○) in the carteolol group and vehicle in the control group (□). Each plot represents the mean value of eight rabbits. Error bars represent SEM. Asterisk (*) indicates $P < 0.05$ by unpaired t-test for difference from control and double asterisks (**) indicate $P < 0.01$.

treatment are summarized in Table 2. Baseline values of $NB_{av(ONH)}$ in the ONH tissue were not significantly different among the carteolol- and vehicle-treated eyes of the carteolol group and eyes of the control group. After treatment, the average change from baseline in $NB_{av(ONH)}$ was not statistically significant in the control group. In the carteolol group, there was a significant increase in $NB_{av(ONH)}$ of 14.7% ($P < 0.01$) and of 11.1% ($P < 0.01$) as compared with baseline both in the carteolol- and vehicle-treated eyes, respectively. In comparison with the eyes of the control group, $NB_{av(ONH)}$ after treatment was significantly greater in the carteolol-treated eyes ($P < 0.01$ with Bonferroni's correction) and in the vehicle-treated eyes ($P < 0.05$ with Bonferroni's correction) of the carteolol group. The difference in the $NB_{av(ONH)}$ before and after treatment was significantly larger both in the carteolol-treated eyes ($P < 0.01$ with Bonferroni's correction) and vehicle-treated eyes ($P < 0.05$ with Bonferroni's correction) of the carteolol group than in the control group.

Discussion

Koelle et al[21] reported that the penetration depth of near-IR laser (wavelength = 811 nm) in the cat optic nerve exceeds 1 mm. Thus, in the present apparatus, the effective depth of sampling in the ONH tissue will be greater than 1 mm, and some contribution from the retroscleral region (retrolaminal region in human eyes) to the measured NB is expected in addition to that from the anterior ONH and

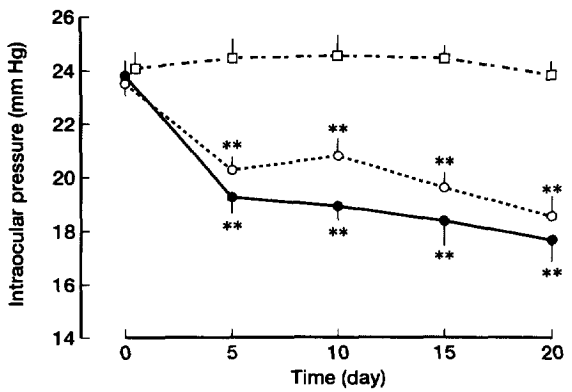

Figure 3. Time course (day) of intraocular pressure after topical instillation of carteolol (●) or vehicle (○) in the carteolol group and vehicle in the control group (□). Each plot represents the mean value of 27 or 16 rabbits. Error bars represent SEM. Double asterisks (**) indicate $P < 0.01$ by paired t-test for difference from control.

scleral region. Sugiyama et al[15] compared $NB_{av(ONH)}$ determined by the present method with the ONH tissue blood flow rate determined simultaneously by the hydrogen gas clearance method in the same rabbit eye before and after inhalation of 10% carbon dioxide (CO_2) or intravenous injection of a small amount (10^{-10} M/kg) of endothelin-1 (ET-1). Fifteen minutes after inhalation of 10% CO_2 $NB_{av(ONH)}$ increased by 16%, and the ONH tissue blood flow rate determined with the hydrogen gas clearance method increased by 14%. Fifteen minutes after intravenous injection of 10^{-10} M/kg ET-1, $NB_{av(ONH)}$ decreased by 22%, and the ONH tissue blood flow rate determined with the hydrogen gas clearance method decreased by 17%. Furthermore, a significant correlation ($r = 0.92$, $P < 0.01$) was found between a relative change in NB_{av} and in the ONH tissue blood flow rate determined with the hydrogen gas clearance method. These results suggest that $NB_{av(ONH)}$, which is a quantitative index of blood velocity in ONH tissue, also correlates with the ONH tissue blood flow rate.

Table 2. Average Normalized Blur (70 × 70) in Optic Nerve Head Tissue Before Treatment and After 20-Day Instillation of Carteolol

	n	Before	20 days	Δ[a]
Carteolol	27	12.9 ± 0.3	14.8 ± 0.5[b]	1.9 ± 0.5[c]
Vehicle	27	13.5 ± 0.5	15.0 ± 0.4[b]	1.5 ± 0.5[d]
Control	16	13.5 ± 0.3	13.2 ± 0.4	−0.3 ± 0.4

Carteolol indicates carteolol-treated eyes, while vehicle indicates vehicle-treated contralateral eyes and control indicates eyes in the control experiment. Figures are mean ± SEM.

[a] Δ indicates the difference between the values on the 20th day from those before treatment.

[b] $P < 0.01$ (paired t-test) as compared with the value before treatment.

[c] $P < 0.01$ (unpaired t-test with Bonferroni's correction) as compared with control.

[d] $P < 0.05$ (unpaired t-test with Bonferroni's correction) as compared with control.

In the present study, $NB_{av(ONH)}$ showed little change after a single instillation of carteolol. On the other hand, after 20 days of twice-daily carteolol treatment, there was a significant increase in $NB_{av(ONH)}$ both in the carteolol- and the vehicle-treated contralateral eyes. It is quite likely that systemically absorbed carteolol reached a sufficient plasma concentration to act as a systemic beta-blocking agent in the present study since a significant reduction in pulse rate was encountered after a single instillation of carteolol and a significant reduction in the IOP in the vehicle-treated contralateral eyes was encountered after 20-day treatment. The vascular beta-2 receptor blocking effect itself generally induces vasoconstriction,[4,5,22] Under the condition that the total blood flow is not significantly changed, vasoconstriction may increase the blood velocity and consequently the NB. However, the above-cited result obtained after ET-1 injection speaks against this possibility: vasoconstriction induced by ET-1 reduced both NB and blood flow rate as determined with the hydrogen gas clearance method in the ONH.[15] Rather, the increase in the NB is thought to be indicative of not only the tissue blood velocity but also the blood flow rate through the ONH. Therefore, the beta-blocking effect itself is rather unlikely to be involved in the present finding.

Hester et al[23] reported that carteolol has weak vascular-relaxing properties similar to Ca^{2+} channel blockers in porcine long posterior ciliary artery at the concentration of 100 μM or higher. After 20-day instillation of carteolol in one eye of a pigmented rabbit, the concentration of the drug in the ONH was reportedly on the order of 5 μM,[24] which is probably too low for carteolol to exert its weak direct vascular-relaxing property.[23] Thus, the results of the long-term carteolol instillation may be attributed to effects other than a beta receptor blocking effect by systematically absorbed rather than those by locally penetrating carteolol.

Carteolol is characterized by the presence of ISA,[6] with which the agent can reduce peripheral vascular resistance.[7,8] Janczewski et al[9] reported that carteolol releases endothelium-derived relaxing factor (EDRF) or prostacyclin at a concentration of 10^{-8} M or higher, through which it exerts vasodilating ac-

Jpn J Ophthalmol
Vol 42: 27–32, 1998

tions. According to Fujio and Shimizu,[24] the concentration of carteolol in rabbit plasma after a 3-week instillation of 2% solution twice daily was 60 ng/mL or 2.05×10^{-7} M. Therefore, it seems possible that 20-day carteolol instillation given as in the present study increases ONH blood velocity through its ISA-, EDRF-, and/or prostacyclin-releasing effect. The discrepancy of the results between a single and 20-day instillation experiment may be explained by much lower carteolol concentration in the plasma after a single instillation as compared with that after 20-day instillation.[24–26] Further, induction of pentobarbital anesthesia generally caused vasodilation in various ocular tissues in albino rabbits including the optic nerve.[27] A total dose of pentobarbital used in the single-instillation experiment was twice more than that used in 20-day treatment. The discrepancy may be partly attributed to a higher dose of pentobarbital, resulting in a vasodilative effect that might have masked the $NB_{av(ONH)}$-increasing effect of carteolol in the single-instillation experiment.

In summary, the present study showed that long-term carteolol instillation caused a significant increase of the tissue blood velocity in the ONH both in the carteolol- and vehicle-treated contralateral eyes in albino rabbits. Although its precise mechanisms are still unknown and caution must be taken in speculating about the results of the effects of carteolol on ONH blood flow in humans, the finding here may have clinical relevance in the treatment of glaucoma.

This work was supported in part by a Grant-in-Aid for Developmental Scientific Research (B) No. 01870074 from the Ministry of Education, Science, Sports and Culture of Japan.

References

1. Minckler DS, Sapeth GL. Optic nerve damage in glaucoma. Surv Ophthalmol 1981;26:128–48.
2. Anderson DR, Quigley HA. The optic nerve. In: Hart WM JR, ed. Adler's physiology of the eye. 9th ed. St. Louis: Mosby, 1992:616–40.
3. Flammer J. The vascular concept of glaucoma. Surv Ophthalmol 1994;38:S3–6.
4. Nies AS, Evans GH, Shand DG. Regional hemodynamic effects of beta-adrenergic blockade with propranolol in the unanesthetized primate. Am Heart J 1973;85:97–102.
5. Cruickshank JM. The clinical importance of cardioselectivity and lipophilicity in beta blockers. Am Heart J 1980;100:160–78.
6. Yabuuchi Y, Kinoshita D. Cardiovascular studies of 5-(3-tert-butylamino-2-hydroxy) propoxy-3,4-dyhydrocarbostyril hydrochloride (OPC-1085), a new potent beta-adrenergic blocking agent. Jpn J Pharmacol 1974;24:853–61.
7. Man In't Veld AJ, Schalekamp MADH. How intrinsic sympathomimetic activity modulates the haemodynamic responses to beta-adrenoreceptor antagonists: A clue to the nature of their antihypertensive mechanism. Br J Clin Pharmacol 1982;13:245S–57S.
8. Frishman W, Kostis J. The significance of intrinsic sympathomimetic activity in beta-adrenoceptor blocking agents. Cardiovas Review and Reports 1982;3:503–12.
9. Janczewski P, Boulanger C, Iqbal A, Vanhoutte PM. Endothelium-dependent effects of carteolol. J Pharmacol Exp Ther 1988;247:590–5.
10. Grunwald JE, Delehanty J. Effect of topical carteolol on the normal human retinal circulation. Invest Ophthalmol Vis Sci 1992;33:1853–6.
11. Tamaki Y, Araie M, Kawamoto E, et al. Non-contact two-dimensional measurement of microcirculation in choroid and optic nerve head using laser speckle phenomenon. Exp Eye Res 1995;60:373–84.
12. Tamaki Y, Araie M, Tomita K, Tomidokoro A. Effect of topical timolol on tissue circulation in the optic nerve head. Jpn J Ophthalmol 1997;41:297–304.
13. Araie M, Muta K. Effect of long-term topical betaxolol on tissue circulation in the iris and optic nerve head. Exp Eye Res 1996;64:67–72.
14. Sugiyama K, Bacon DR, Morrison JC, Van Buskirk M. Optic nerve head microvasculature of the rabbit eye. Invest Ophthalmol Vis Sci 1992;33:2251–61.
15. Sugiyama T, Utsumi T, Azuma I, Fujii H. Measurement of optic nerve head circulation: Comparison of laser speckle and a hydrogen clearance methods. Jpn J Ophthalmol 1996;40:339–43.
16. Tamaki Y, Araie M, Tomita K, et al. Real-time measurement of human optic nerve head and choroid circulation, using the laser speckle phenomenon. Jpn J Ophthalmol 1997;41:49–54.
17. Fercher AF, Briers JD. Flow visualization by means of single-exposure speckle photography. Opt Commun 1981;37:326–30.
18. Briers JD, Fercher AF. Retinal blood-flow visualization by means of laser speckle photography. Invest Ophthalmol Vis Sci 1982;22:255–9.
19. Kozuma C, Macklin W, Cumminus LM, Mauer R. Anatomy, physiology, and biochemistry of the rabbit. In: Weisbroth SH, Flatt RE, Kraus AL, eds. The biology of the laboratory rabbit. New York: Academic Press, 1974:50–72.
20. Neutze JM, Wyler F, Rudolph AM. Use of radioactive microspheres to assess distribution of cardiac output in rabbits. Am J Physiol 1968;215:486–95.
21. Koelle JS, Riva CE, Petrig BL, Cranstoun SD. Depth of tissue sampling in the optic nerve head using laser Doppler flowmetry. Lasers Med Sci 1993;8:49–54.
22. McSorley PD, Warren DJ. Effects of propranolol and metoprolol on the peripheral circulation. Br Med J 1978;2:1598–1600.
23. Hester RK, Chen Z, Becker EJ, et al. The direct vascular relaxing action of betaxolol, carteolol and timolol in porcine long posterior ciliary artery. Surv Ophthalmol 1994;38:S125–34.
24. Fujio N, Shimizu T. Distribution of radioactivity after repeat instillation of ^{14}C-carteolol to pigmented rabbits (Inhouse Report No. 1950). Tokyo: Otsuka Pharmaceutical Co. Ltd, 1984:1–5.
25. Fujio N, Kitazawa K. Intraocular penetration of ^{14}C-carteolol hydrochloride (β-blocker) in the albino rabbits. Acta Soc Ophthalmol Jpn 1984;88:236–41.
26. Fujio N, Odomi M, Kusumoto N. Ocular distribution of carteolol after single and repeated ocular instillation in pigmented rabbits. Acta Ophthalmol 1994;72:688–93.
27. Bill A, Stjernschantz J. Cholinergic vasoconstrictor effects in the rabbit eye: Vasomotor effects of pentobarbital anesthesia. Acta Physiol Scand 1980;108:419–24.