Effect of Dual Endothelin Receptor Blockade on Ocular Blood Flow in Patients with Glaucoma and Healthy Subjects

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PURPOSE. Several lines of evidence indicate that altered blood flow regulation may contribute to the pathogenesis of glaucomatous optic neuropathy. Recent data support the hypothesis that the endothelin system is involved in the processes that lead to vascular dysregulation in glaucoma. This study was conducted to test the hypothesis that bosentan, a dual endothelin receptor antagonist, increases ocular blood flow in patients with glaucoma.

METHODS. Fourteen patients with primary open-angle glaucoma and 14 sex- and age-matched healthy volunteers were included. Both groups received bosentan 500 mg daily for 8 days. Ocular hemodynamics were assessed at baseline and on the last study day. Retinal vessel diameters and retinal red blood cell velocity were recorded with a retinal vessel analyser and laser Doppler velocimetry, respectively. Choroidal and optic nerve head blood flow were measured with laser Doppler flowmetry.

RESULTS. Retinal arteries and veins showed a significant dilatation after administration of bosentan in both groups (+5%–8%). Retinal blood velocity and retinal blood flow increased up to +45% after administration of bosentan in both patients and healthy subjects. Administration of bosentan increased choroidal (+12%–17%) and optic nerve head blood flow (+11%–24%) in both groups. The effect of bosentan on ocular blood flow parameters was comparable between the two groups.

CONCLUSIONS. The data from the present study indicate that dual inhibition of endothelin receptors increases ocular blood flow in patients with glaucoma and healthy subjects. Further studies are needed to study the dose-response relationship of this effect and to characterize the role of endothelin receptor subtypes. (Invest Ophthalmol Vis Sci. 2009;50:358–363) DOI: 10.1167/iovs.08-2460

Glaucoma is one of the most important causes of legal blindness in the industrialized nations. The pathogenesis of this disease, however, is not fully understood. Although increased intraocular pressure (IOP) is known to be a major risk factor for the progression of the disease, a large proportion of patients progress despite therapeutic IOP reduction.1 There is increasing evidence that ocular blood flow abnormalities are involved in the pathogenesis of the disease.2 In particular, several lines of evidence indicate that reduced optic nerve head blood flow and vascular dysregulation contribute to the progression of the disease.3

Because of its potent vasoconstrictor effects, endothelin (ET)-1 has been hypothesized to play a role in the ocular vascular dysregulation in glaucoma. This is based on several experiments providing a potential link between glaucomatous optic neuropathy and the endothelin system. Intravenous administration of ET-1 reduces choroidal, retinal, and optic nerve head blood flow in healthy subjects.4,5 In the animal, chronic local administration of ET-1 to the optic nerve head via an osmotically driven minipump induced a reduction in optic nerve head blood flow and an associated loss of retinal ganglion cells.6–9 Elevated levels of ET-1 were observed in plasma and aqueous humor indicating increased endothelin production.10,11 Thus, one may hypothesize that in patients with glaucoma, increased endothelin levels lead to a predominance of vasoconstricting factors associated with a decrease in ocular blood flow and vascular dysregulation.

Based on these data, endothelin receptor antagonists may offer a new option for the treatment of glaucoma. This class of drugs may be particularly suitable to normalize ocular blood flow in patients with glaucoma. In the present study the hypothesis that endothelin receptor antagonism increases ocular blood flow was tested. For this purpose, 500 mg bosentan (Tracleer, Actelion, Allschwil, Switzerland), a mixed ETA and ETB receptor antagonist, was administered once daily for 8 days in patients with glaucoma and in a healthy age- and sex-matched control group.

METHODS

Subjects

The study protocol was approved by the Ethics Committee of the Medical University of Vienna and followed the guidelines of Good Clinical Practice and the Declaration of Helsinki. Fourteen patients with open-angle glaucoma and 14 healthy age- and sex-matched non-smoking subjects were included. All subjects signed a written informed consent and passed a screening examination that included medical history and physical examination, 12-lead electrocardiogram, complete blood count, activated partial thromboplastin time, thrombin time, fibrinogen, clinical chemistry (sodium, potassium, creatinine, uric acid, glucose, cholesterol, triglycerides, alanine aminotransferase, aspartate aminotransferase, γ-glutamyltransferase, alkaline phosphatase, total bilirubin, total protein), hepatitis A, B, C and HIV serology, and urine analysis. Subjects were excluded if any clinically relevant abnormality was found as part of the blood testing or physical examination. An ophthalmic examination was performed in each subject before the study day. In patients with open-angle glaucoma, a visual field test was performed.
Inclusion and Exclusion Criteria

Patients with Glaucoma. Inclusion criteria were open-angle glaucoma, defined as pathologic optic disc appearance and characteristic visual field loss, ametropia of less than 3 D, and anisometropia of less than 1 D. All patients were experienced in visual field testing, having performed at least three tests in total, one within 3 months of the beginning of the study. An abnormal visual field was defined as a glaucoma hemifield test result outside normal limits and/or a corrected pattern standard deviation with \( P < 0.05 \). Any of the following excluded a patient with glaucoma from participation in the trial: exfoliation glaucoma, pigmentary glaucoma, history of acute angle closure, mean deviation (MD) of visual field testing (30-2 program; Humphrey Visual Field Analyzer; Carl Zeiss Meditec, Oberkochen, Germany) of \(-12\) dB or worse, intraocular surgery, or argon laser trabeculoplasty within the past 6 months, ocular inflammation or infection within the past 3 months, and pregnancy. Further exclusion criteria were oculomotor disease that might interfere with the purposes of the study other than glaucoma, ametropia of more than 3 D, anisometropia of more than 1 D, blood donation during the previous 3 weeks, systemic treatment with oral anticoagulants, glibenclamide or vasoactive drugs, and a history of untreated IOP \( > 30 \) mm Hg (untreated).

Healthy Subjects. Included were healthy, nonsmoking subjects, who were of age and sex matched to the patients in the glaucoma group. Subjects were excluded if the pre-study screening revealed the presence of any clinically relevant illness. Further exclusion criteria were blood donation during the previous 3 weeks, regular intake of any drugs, or pregnancy.

Experimental Paradigm

Two trial days were scheduled for each subject. Dilation of the pupil was obtained with tropicamide (Mydriaticum Agepha-Augentropfen; Agepha, Vienna, Austria).

On the first study day baseline measurements were recorded in the subjects, after a resting period of at least 20 minutes in a sitting position. Thereafter, the first dose of the study medication (500 mg bosentan) was administered. The dose of bosentan was selected based on previously published results.13 Subjects were then instructed to ingest four 125 mg tablets bosentan (Tracleer, Actelion) every morning at 9.00 AM for the next 6 days at home. The last dose of the study medication was again administered at the Department of Clinical Pharmacology on the second study day. Subjects were asked to return empty blister packaging and compliance was tested by drug counting.

On the second study day subjects arrived at 8.00 AM. Before drug intake measurements of systemic and ocular hemodynamics and intraocular pressure were performed, followed by the administration of the last dosage of bosentan. Measurements were then repeated 120, 180, and 240 minutes after drug administration. Data analysis was performed by a person not aware of the diagnosis (masked analysis of the data).

Retinal Vessel Analyzer (RVA)

The RVA (Imedos, Weimar, Germany) is a commercially available system which comprises a fundus camera (model FF 450; Carl Zeiss Meditec), a video camera, a high-resolution video recorder, a real-time monitor and a personal computer with vessel diameter-analysis software. The RVA allows the precise determination of retinal vessel diameter with a time resolution of 25 readings/s. The fundus was illuminated with light in the range of wavelengths between 567 and 587 nm. In this spectral range, the contrast between retinal vessels and the surrounding tissue is optimal. Retinal irradiance was approximately 220 \( \mu W \cdot cm^{-2} \), which is approximately 50 times lower than the maximum level allowed for constant illumination of the retina at these wavelengths. The system provides excellent reproducibility and sensitivity.14 In the present study, major temporal arteries and veins were studied. Measurements of retinal vessel diameters were taken between 1 and 2 disc diameters from the margin of the optic disc.

Laser Doppler Velocimetry (LDV)

The principle of red blood cell velocity measurement by LDV is based on the optical Doppler effect. Laser light, scattered by moving erythrocytes, is shifted in frequency. This frequency shift is proportional to the blood flow velocity in the retinal vessel. The maximum Doppler shift corresponds to the centerline erythrocyte velocity \( V_{max} \). With bidirectional laser Doppler velocimetry, the absolute velocity in the retinal vessels can be obtained.15,16 In the present study, we used a fundus camera-based system with a single-mode laser diode at a center wavelength of 670 nm (model 4000; Oculix Sarl, Arbaz, Switzerland). The Doppler shift power spectra were recorded simultaneously for two directions of the scattered light. The scattered light was detected in the image plane of the fundus camera. This scattering plane can be rotated and adjusted in alignment with the direction of \( V_{max} \) which enables absolute velocity measurements. Red blood cell velocity was measured at the same locations as retinal vessel diameters by using bidirectional laser Doppler velocimetry.

Calculation of Retinal Blood Flow

Retinal blood flow in single retinal veins was calculated based on the measurements of maximum erythrocyte velocity \( V_{max} \) assessed with LDV and retinal vessel diameter \( D \) obtained with the RVA. From \( V_{max} \), mean blood velocity in retinal vessels \( V_{mean} \) can be calculated as \( V_{mean} = V_{max}/2 \). With the use of this relation, mean velocities in retinal veins can be obtained. Blood flow \( (Q) \) through a specific retinal vessel was then calculated as

\[
Q = \left( V_{max}/2 \right) \cdot (\pi \cdot D^2/4).
\]

Laser Doppler Flowmetry

Choroidal blood flow (CBF) was assessed with a fundus camera-based laser Doppler flowmeter (model 4000; Oculix Sarl) introduced by Riva et al.17,18 The principles of laser Doppler flowmetry have been described in detail elsewhere.19 Briefly, the vascularized tissue is illuminated by coherent laser light. Light-scattering on moving blood cells (RBCs) leads to a frequency shift in the backscattered light. In contrast, static scattering in tissue does not change light frequency but leads to a randomization of light directions impinging on the RBCs and consequently a broadening of the spectrum of scattered light (Doppler shift power spectrum, DSPS). From the DSPS the mean RBC velocity, the blood volume and the blood flow can be calculated in relative units. The laser beam was directed to the fovea to assess blood flow in the submacular fovea. For measurement of optic nerve head blood flow, the laser beam was directed to the temporal neuroretinal rim. Care was taken that the location of measurement did not include any visible vessels.

Blood Pressure Measurement

Systolic, diastolic, and mean blood pressures were measured on the upper arm by an automated oscillometric device (HP-CMS patient monitor; Hewlett Packard, Palo Alto, CA). Pulse rate was automatically recorded from a finger pulse oximeter. Measurements were performed before, during, and after flicker stimulation.

Calculation of Ocular Perfusion Pressure (OPP)

OPP was calculated as \( \frac{1}{2} \) mean arterial pressure – IOP.

Statistics

Data are presented as the mean ± SD. Baseline differences between groups were assessed using one-way ANOVA. Time and treatment effects were assessed using repeated-measures ANOVA. Planned comparisons were used for post hoc analysis. \( P < 0.05 \) was considered as the level of significance. For all statistical analyses absolute data were used. For data description relative data were used. In the results section the maximum percent change over baseline is presented.
Calculations were performed with commercial software (Statistica; Statsoft, Tulsa, OK).

RESULTS

Patient Characteristics and Glaucoma Medication

Baseline characteristics of patients and healthy subjects are given in Table 1. All patients with glaucoma were receiving IOP-lowering therapy. Details of glaucoma medication are given in Table 2.

Systemic Hemodynamics and IOP

As shown in Table 1, baseline data of MAP and pulse rate were comparable between the two groups. Administration of bosentan significantly reduced MAP (−8% ± 14%, ANOVA time effect, P < 0.05) in both groups. This effect, however, was not different in the glaucoma group compared with healthy volunteers (ANOVA effect between groups, P = 0.5). Calculated OPP decreased by −9% ± 19% (ANOVA, time effect, P < 0.05).

Again, no difference was observed between the two experimental groups (ANVOA effect between groups P = 0.5). Absolute values of MAP, IOP, and OPP are given in Table 3. In the glaucoma group, baseline IOP was significantly higher than in the age-matched control group (17 ± 3 mm Hg glaucoma group; 14 ± 2 mm Hg healthy group, P < 0.01). Administration of bosentan had no effect on IOP (ANOVA, effect between groups, P = 0.95).

Retinal Blood Flow

As shown in Figure 1, retinal arteries showed a significant dilation after administration of bosentan. This effect was 5.6% ± 5.6% in healthy volunteers and 7.6% ± 6.7% in the glaucoma group (ANOVA time effect, P < 0.01). In retinal veins, we also observed a vasodilatory effect of bosentan in both groups. In the glaucoma group, retinal venous diameters increased by 5.0% ± 5.4% and in the healthy group by 6.0 ± 3.7 (ANOVA, time effect, P < 0.01). There was no difference between the groups in terms of retinal vasodilatation (ANOVA, effect between groups, P = 0.72). After administration of bosentan, retinal blood velocity increased by 25% ± 32% in the glaucoma group and by 29% ± 44% in the control group (ANOVA, time effect, P < 0.01).

Calculated retinal blood flow increased by +45% ± 54% and 39% ± 41% in the control group and the glaucoma group, respectively (ANOVA, time effect, P < 0.01). No statistically significant difference in the blood flow or blood velocity increase was observed between the two study groups (ANOVA, effect between groups, blood flow: P = 0.72, blood velocity P = 0.96).

Choroidal Blood Flow

Administration of bosentan increased subfoveal choroidal blood flow by 17% ± 22% and 12% ± 29% in the healthy and the glaucoma group, respectively (ANOVA, time effect, P = 0.02). No significant difference was detected in the bosentan-induced increase in choroidal blood flow between the two study groups (ANOVA, effect between groups, P = 0.88).

Optic Nerve Head Blood Flow

Administration of bosentan significantly increased optic nerve head blood flow in the patients with glaucoma (11% ± 22%) and in the healthy subjects (24% ± 28%, ANOVA, time effect, P < 0.01). No significant difference was observed between the glaucoma group and the healthy group in terms of blood flow increase in the optic nerve head (ANOVA, effect between groups, P = 0.1).

DISCUSSION

The data of the present study provide first-time evidence that bosentan, a dual ETA and ETB receptor antagonist significantly increases retinal, choroidal, and optic nerve head blood flow, in patients with glaucoma and healthy subjects. In the retinal circulation, bosentan affected retinal arterial and venous diameters as well as retinal blood flow velocity, resulting in an increase of retinal blood flow up to 45%. Although not as pronounced as in the retina, administration of bosentan considerably increased subfoveal choroidal blood flow and optic nerve head blood flow ranging between 12% and 24%, respectively.

Data from recent experiments performed by our group, however, indicated that a specific ETA antagonist has no effect on ocular blood flow under physiological conditions. In particular, these studies revealed that intravenous administration of ET-1 induces a pronounced decrease in retinal and choroidal blood flow, which was fully antagonized by the selective ETA receptor antagonist BQ123, indicating that the ET-1 effects are mainly mediated via ETa receptors. However, when these previous data are compared to the data of the present study, several differences have to be considered.

First bosentan and BQ-123 differ in their mode of action. As stated, bosentan is available as an orally active, nonpeptide, dual ETa/ETb antagonist, whereas BQ-123 acts as a specific ETa receptor antagonist. The inhibition constant k for the ETa receptor is comparable for BQ123 and bosentan. However, given that at least three different endothelin receptors with a variety of biological functions exist, this hampers direct comparison of the data obtained with either BQ-123 or bosentan.

The three receptor subtypes that have been identified include the ETa receptor subtype, which is located in the vascular smooth muscle and plays the major role in the vasoconstrictor effects of ET-1, and the ETb1 and the ETb2 receptors. The ETb1-receptor subtype is present on endothelial cells and mediates vasodilatation by a process that includes the release of NO. The ETb2-receptor subtype mediates direct vasoconstriction. In addition to the vasoactive function of the ETb receptor, it has become clear that this receptor also plays an important role in the clearance of ET-1 in the plasma.

| Table 1. Main Patients’ Characteristics, Including IOP, MAP, PR, and Visual Field MD |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
| Glaucoma Group                  | Healthy Subjects |
| Sex (male/female)              | 8/6             | 8/6             |                 |
| Age (y)                        | 69              | 65              |                 |
| IOP (mm Hg)                    | 17 ± 3          | 14 ± 3          |                 |
| MAP (mm Hg)                    | 88 ± 11         | 91 ± 8          |                 |
| PR (bpm)                       | 72 ± 10         | 71 ± 8          |                 |
| MD (dB)                        | -3.0 ± 3.0      | —               |                 |

Table 2. Antiglaucoma Treatments

<table>
<thead>
<tr>
<th>Glaucoma Medication</th>
<th>Patients (n)</th>
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<tbody>
<tr>
<td>Latanoprost</td>
<td>4</td>
</tr>
<tr>
<td>Brinzolamide</td>
<td>3</td>
</tr>
<tr>
<td>Timolol</td>
<td>2</td>
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<tr>
<td>Timolol + dorzolamide</td>
<td>2</td>
</tr>
<tr>
<td>Travoprost</td>
<td>1</td>
</tr>
<tr>
<td>Travoprost + timolol</td>
<td>1</td>
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<tr>
<td>Bimatoprost</td>
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Could ETB receptor blockade in the present study induce vasodilatation? Several previous studies indicate that this is unlikely. The ratio between ETA and ETB receptor expression is approximately 35:65 in the rat retina.24 Experimental data on isolated ophthalmic vessels obtained by using pharmacologic stimulation of ETB receptors indicate a net vasodilatation mediated via this receptor subtype,25 which is in keeping with most other vascular beds.22 This finding is in agreement with rabbit data showing a vasoconstrictor response in the choroid with a specific ETB receptor subtype blockade.26 Hence, it is unlikely that the difference between our previous results using BQ-123 and the results of the present study using bosentan are related to ETB receptor blockade. Further human studies with specific ET receptor agonists are needed to clarify the role of the different receptor subtypes in the ocular circulation.

More likely, the observed difference is related to the different time regimen used in the studies. In all our previous studies, BQ-123 was intravenously applied as a short-term infusion, whereas in the current experiments 500 mg of bosentan was given orally over 8 days. In a previous short-term experiment, ETA receptor blockade did not affect choroidal blood flow in the rabbit choroid,26 whereas the ETB receptor blockade induced vasoconstriction. The author of the latter study speculated that this behavior may be related to the localization of the ETA and ETB receptors. More specifically, endothelin concentration may be higher at ETB receptors located at the endothelial cells than at ETA receptors located at smooth muscle cells. In line with this idea, it may well be that concentrations of BQ-123 at the level of the vascular smooth muscle cell after short-term infusion is much lower than that of bosentan after 8 days of treatment, where considerable tissue levels may have developed.

This interpretation is further supported by another observation. In our previous experiment, not exogenous ET-1, nor ET-1 plus BQ-123, nor BQ-123 alone affected retinal arterial or venous diameters.4 Nevertheless, we observed a pronounced fusion, whereas in the current experiments 500 mg of bosentan was given orally over 8 days. In a previous short-term experiment, ETA receptor blockade did not affect choroidal blood flow in the rabbit choroid,26 whereas the ETB receptor blockade induced vasoconstriction. The author of the latter study speculated that this behavior may be related to the localization of the ETA and ETB receptors. More specifically, endothelin concentration may be higher at ETA receptors located at the endothelial cells than at ETA receptors located at smooth muscle cells. In line with this idea, it may well be that concentrations of BQ-123 at the level of the vascular smooth muscle cell after short-term infusion is much lower than that of bosentan after 8 days of treatment, where considerable tissue levels may have developed.

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| Table 3. MAP, PR, IOP, and Calculated OPP in the Study Groups |
|----------------------|----------------------|----------------------|----------------------|
|                       | Glaucoma Group (n = 14) | Healthy Subjects (n = 14) |
|                       | Baseline | Day 8 Baseline | Day 8 240 min | Baseline | Day 8 Baseline | Day 8 240 min |
| MAP (mm Hg)           | 88 ± 11  | 80 ± 7         | 85 ± 6        | 91 ± 7   | 85 ± 8         | 81 ± 9        |
| PR (bpm)              | 72 ± 10  | 70 ± 7         | 70 ± 7        | 71 ± 8   | 72 ± 8         | 75 ± 10       |
| IOP (mm Hg)           | 17 ± 3   | 16 ± 3         | 16 ± 3        | 14 ± 3   | 14 ± 3         | 13 ± 3        |
| OPP (mm Hg)           | 42 ± 8   | 37 ± 5         | 39 ± 4        | 47 ± 4   | 42 ± 5         | 41 ± 6        |

**FIGURE 1.** Effect of bosentan on ocular hemodynamic parameters in patients with glaucoma (○) and healthy volunteers (■). All ocular blood flow parameters were increased after bosentan therapy (P < 0.05 each). No differences were observed between groups. All data are presented as the mean ± SD.
reduction in retinal blood flow associated with a reduction in retinal blood flow. We assumed that this is the cause, because neither BQ-123 nor exogenous ET-1 was able to cross the blood–brain barrier. More likely, the decrease in retinal blood flow was due to an effect on the contractile pericyte, as observed previously in vitro.27 In the present study, however, bosentan increased retinal arterial and venous diameter, indicating that endogenous ET-1 contributes to retinal vascular tone even under physiological conditions. Again, this indicates that the concentration of bosentan as achieved at the level of the smooth muscle cell may be higher than that of BQ-123 in our previous studies.

Finally, one has to consider that the present study was not performed in young subjects as in previous studies,4,5,20 but in patients with glaucoma and age-matched volunteers. Given that endothelin plasma concentration increases with increasing age,28 we cannot exclude that the increase may result in a different effect of endothelin receptor antagonists. We deem this unlikely, however, because no difference in the ocular hemodynamic effects was observed between subjects with glaucoma and healthy control subjects.

Given that endothelin levels are known to be increased in glaucoma, the finding that no significant difference in the ocular hemodynamic response was detected between the two experimental groups is surprising. However, the data do not necessarily contradict the hypothesis that the endothelin system is involved in the pathogenesis of glaucoma. A dose–response relationship would be necessary to resolve this question. It may well be that the selected dose of bosentan is high enough to elicit full vasodilatation via the blockade of ET receptors in patients with glaucoma and healthy control subjects. Furthermore, it should be considered that because of the small sample size the power to detect differences between groups is limited. For our sample size calculation, we have chosen ONH blood flow as the main outcome variable. Based on previously published data on the methods in our laboratory,29 a minimum difference of 22% can be detected in 14 subjects between groups, based on the assumption of an alpha error of 0.05 (double sided) and a β error of 0.2.

Laser Doppler measurements in the optic nerve head and the choroid have limitations that require discussion.29,30 This is especially important in patients with glaucoma, because remodeling of the optic nerve head may alter the scattering properties of tissue, which in turn may affect optic nerve head measurements. In particular, the excavation and atrophy of the ONH may lead to an increased penetration depth of the laser beam and may alter the tissue measured. In the present study, however, the focus was directed toward bosentan-induced changes in blood flow and not on comparison of absolute laser Doppler flowmetry values. A limitation of this study is that we had no time control of the bosentan effect on the second study day. We have shown, however, that parameters of retinal, choroidal, and optic nerve head blood flow showed no significant diurnal fluctuation.29,30

It is worth noting that bosentan had no effect on IOP in the present study. It has previously been noted, however, that the endothelin system may play an important role in IOP homeostasis.31 The present data do not necessarily contradict this assumption. After systemic administration bosentan may have a variety of effects including an increase in ciliary body blood flow associated with enhanced aqueous humor production as well as effects on outflow facility.

In terms of glaucoma treatment, the increase in blood flow to the posterior pole of the eye may be beneficial. Considering that the ET₉ receptor mediates vasodilatation, it may well be that chronic treatment with a specific ET₉ receptor antagonist results in even larger blood flow changes. On the other hand, several ET-1 induced effects, which may be play roles in glaucoma pathogenesis, are at least partially ET₉ receptor dependent. These effects include activation of optic nerve head astrocytes,32 inhibition of components of anterograde axonal transport in the optic nerve,33 and changes in extracellular matrix collagen expression in cells of human lamina cribrosa.34

In conclusion, we present first-time evidence that oral administration of the nonselective endothelin receptor antagonist bosentan for 8 days increases ocular blood flow in patients with glaucoma and healthy persons.

References


