Short-term Oral Pentoxifylline Use Increases Choroidal Blood Flow in Patients With Age-related Macular Degeneration

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Objective: To study the ocular hemodynamic effects of a 3-month oral treatment with pentoxifylline in patients with nonexudative age-related macular degeneration.

Design: Double-blind, placebo-controlled, randomized, parallel group study.

Setting: Outpatient clinic of the Department of Ophthalmology, Vienna University, Vienna, Austria, that specializes in age-related macular degeneration.

Methods: Forty patients with age-related macular degeneration received pentoxifylline (400 mg 3 times a day orally, n=20) or placebo (n=20) for 3 months. Retinal blood flow was assessed by scanning laser Doppler flowmetry and pulsatile choroidal blood flow was assessed by laser interferometric measurement of fundus pulsation amplitude.

Main Outcome Measures: Changes in retinal blood flow and fundus pulsation amplitude.

Results: Four patients receiving pentoxifylline and 3 patients receiving placebo discontinued medication because of nausea. In the remaining subjects, the use of pentoxifylline increased ocular fundus pulsation amplitude (P<.001 vs placebo and baseline). The maximum increase was 28% after 3 months. In contrast, retinal blood flow was not changed by the use of pentoxifylline.

Conclusions: A 3-month course of oral pentoxifylline treatment increases choroidal but not retinal blood flow in patients with age-related macular degeneration. These data strongly support the concept that pentoxifylline might be useful in the treatment of age-related macular degeneration. Long-term clinical outcome trials are now warranted to test this hypothesis.


Although age-related macular degeneration (AMD) is the most common cause of blindness in Western countries, the pathogenesis of the disease is less well understood.¹ To date, the only treatment of this disease is the application of laser photocoagulation, which is effective for only a few patients. Even in successfully treated eyes, the development of central visual impairment often cannot be prevented. For patients with nonneovascular AMD, there exists no proven prophylactic treatment.

Recent studies indicate that blood flow in the choroid is impaired in patients with AMD. A prolonged choroidal filling phase demonstrated by fluorescein angiography has been ascribed to thickening of the Bruch membrane.² ³ The use of color Doppler imaging has shown increased pulsatility indexes in ocular vessels, which argues for an increased vascular resistance.⁴

Pentoxifylline is a synthetic xanthine derivative, the use of which has been proposed for the treatment of several eye diseases. The possible therapeutic value of the drug is based mainly on the increase in ocular blood flow that has been observed in healthy subjects,⁶ in patients with diabetes mellitus,⁷ ⁸ and in patients with branch vein or central retinal vein occlusion.⁹ The ability of pentoxifylline to increase blood flow results from its direct vasodilator action¹⁰ and improved deformability of erythrocytes¹¹ and leukocytes.¹²

Based on these findings, we hypothesized that pentoxifylline treatment may improve ocular blood flow in patients with AMD. We therefore studied its short-term effects over 3 months in a placebo-controlled, double-blind trial. Drug-induced changes in choroidal circulation were assessed with laser interferometric measurement of fundus pulsation¹³ ¹⁴ and the effect on retinal blood flow was assessed with scanning laser Doppler flowmetry.¹⁵ ¹⁷

Of the 40 patients, 33 finished the clinical trial. Three subjects stopped during the
SUBJECTS AND METHODS

SUBJECTS

After approval from the Ethics Committee of Vienna University School of Medicine and written informed consent were obtained, 40 subjects with AMD were studied. The diagnosis and staging of AMD were based on the results of indirect funduscopy, fundus photography, and scanning laser ophthalmoscopic videangiography. Visual acuity was determined with Snellen tables. Inclusion criteria were soft or hard drusen of more than 63 µm, hyperpigmentation and/or hypopigmentation of the retinal pigment epithelium, geographic atrophic atrophy of the retinal pigment epithelium, or (peri)retinal fibrous scarring. Patients with the exudative form of the disease (retinal pigment epithelial detachments or choroidal neovascular membranes, disciform scarring, or subretinal blood or lipid) were not included in the study. Exclusion criteria were evidence of any other retinal, choroidal, or optic nerve vascular disease; the regular use of pentoxifylline in the past month before the trial; a limited view of the fundus because of cataract or vitreous hemorrhage; active ocular inflammatory disease; and diabetes mellitus. Only 1 eye of each patient was included according to these criteria. Age-related macular degeneration was classified according to the grading system of Bressler et al. The main subject characteristics are summarized in Table 1.

Some of the patients took concomitant vasoactive medication because of other diseases. In the pentoxifylline-treated group, 1 patient received a β-adrenoceptor antagonist; 3 patients, calcium channel blockers; 3 patients, angiotensin-converting enzyme inhibitors, and 2 patients, norfenefrine. In the placebo-treated group, 2 patients received β-adrenoceptor antagonists; 4 patients, calcium channel blockers; 5 patients, angiotensin-converting enzyme inhibitors; 1 patient, a β2-adrenoceptor agonist; and 1 patient, theophylline monohydrate. None of these regular medications was discontinued throughout the study.

STUDY DESIGN

The study was performed in a double-blind, placebo-controlled, randomized, parallel group design. Subjects were randomly assigned (1:1) to pentoxifylline or placebo treatment. Pentoxifylline (Trental, Albert Roussel Pharma, Vienna, Austria) was administered as an oral dose of 400 mg 3 times a day. Placebo tablets were identical in appearance and taste to maintain the double-blind conditions. Subjects were instructed to take the medication 1 hour after breakfast, lunch, and dinner.

STUDY PROTOCOL

Baseline measurements of fundus pulsation, laser Doppler flowmetry, and systemic hemodynamics were performed on the first study day. In the morning of the next day, subjects started oral pentoxifylline or placebo treatment. Subjects were readmitted for measurements 1 week, 1 month, 2 months, and 3 months after the start of therapy. A difference of ±2 days was allowed for these follow-up investigations. The measurements were done in the morning before the drugs were taken. Patients’ compliance was assessed by tablet count.

STUDY METHODS

Systolic, diastolic, and mean blood pressures were measured on the upper arm by an automated oscillometric device. Pulse rate was automatically recorded from a finger-pulse oxymetric device (HP-CMS Patient Monitor, Hewlett Packard, Palo Alto, Calif).

Pulse synchronous pulsations of the ocular fundus were assessed by laser interferometry. The method is described in detail by Schmetterer et al. Briefly, the eye is illuminated by the beam of a single-mode laser diode with a wavelength (λ) of 783 nm. The light is reflected at both the front side of the cornea and the retina. The reflection from the retina most likely occurs from the Bruch membrane. The 2 remitted waves produce interference fringes from which the distance changes between the cornea and the retina during a cardiac cycle can be calculated. Distance changes between the cornea and the retina lead to a corresponding variation of the interference order (∆N(t)). This change in interference order can be evaluated by counting the fringes moving inward and outward during the cardiac cycle. Changes in optical distance (∆L(t)), corresponding to the distance changes between the cornea and the retina, can then be calculated by ∆L(t) = |∆N(t) × λ|/2. The maximum distance change, called fundus pulsation amplitude, estimates the local pulsatile blood flow. The short-term and day-to-day variability of the method is small, which allows even small drug-induced changes in local pulsatile blood flows to be detected. In contrast to systems that record the ocular pressure pulse, information on the ocular circulation can be obtained with high topographic resolution. To obtain information on the choroidal blood flow, the macula, where the retina lacks vasculature, was chosen for the measurements.

Retinal microcirculation was assessed with a commercially available scanning laser Doppler flowmeter (Heidelberg Retina Flowmeter, Heidelberg Engineering, Heidelberg, Germany). This system combines laser Doppler flowmetry with laser scanning tomography. Briefly, the vascularized tissue is illuminated by coherent laser light. Scattering on moving red blood cells leads to a frequency shift in the scattered light. In contrast, static scatterers in tissue do not change light frequency, but lead to a randomization of light directions impinging on red blood cells. This light diffusing in vascularized tissue leads to a broadening of the spectrum of scattered light, from which mean red blood cell velocity, the blood volume, and the blood flow can be calculated. These variables are calculated from the backscattered light for each point during the scanning process, and a 2-dimensional map of retinal perfusion is created. These variables can thus be quantified in relative units for any image point. In this study, a 20×20 pixel area was chosen for calculating retinal hemodynamics (200×200 µm). The area was located about 5° nasal to the center of the macula.

STATISTICAL ANALYSIS

The absolute values were chosen for data analysis. The effect of pentoxifylline on hemodynamic variables was assessed with repeated-measure analysis of variance vs baseline and vs placebo use. Data are presented as means±SD. A P value of less than .05 was considered the level of significance.
first week, 1 subject between the first week and the first month, and 3 subjects between the first and the second months. All 7 patients who discontinued treatment reported drug-related nausea. Of these patients, 4 were in the pentoxifylline group; 3 were in the placebo group.

The other 33 patients were included for statistical analysis. In 28 of these patients, the compliance was high, the tablet count being within 5% of the expected value. In 4 other patients, the deviation was 5% to 10%, and in 1 patient it was 12%.

During the study, a choroidal neovascular membrane developed in 2 patients, 1 of whom was in the pentoxifylline-treated group, the other in the placebo-treated group. In the other patients, no change was observed in the severity of the disease. Visual acuity was not altered during pentoxifylline or placebo treatment.

Baseline ocular hemodynamic values were comparable between the 2 study groups (Figure). In the pentoxifylline-treated group, a significant increase in the fundus pulsation amplitude was observed (P < .001 vs baseline and placebo). An increase in the fundus pulsation amplitude was already observed 1 week after the start of pentoxifylline treatment, although the maximum effect occurred at the end of the study (+28%). In contrast, the use of pentoxifylline did not change the retinal blood flow, as evidenced from scanning laser Doppler flowmetry.

Baseline systemic hemodynamic values were comparable between the 2 study groups (Table 2). Neither pentoxifylline nor placebo use had any effect on the mean arterial pressure or the pulse rate.

**COMMENT**

The results of this study show that a 3-month therapy with pentoxifylline increases the pulsatile choroidal blood flow in patients with AMD: the fundus pulsation amplitude in the macula increased by more than 25% following the administration of regular oral pentoxifylline, 400 mg 3 times a day. In contrast, we did not observe significant changes in retinal blood flow as evidenced from scanning laser Doppler flowmetry. This is in accordance with previous data in healthy subjects and suggests that pentoxifylline increases choroidal blood flow more than retinal blood flow.\(^5,6,8\)

Despite this increase in pulsatile choroidal blood flow, we observed no notable increase in visual acuity and no change in the severity of AMD. Given the small number of patients and the short follow-up, this is not surprising. Moreover, the exact role of choroidal perfusion abnormalities in the pathogenesis of AMD has not yet been established. A causal relationship may exist, however, between alterations in choroidal capillary blood flow and diffuse thickening of the Bruch membrane.\(^2\) Whether these changes are initiated by choroidal abnormalities or by the deposition of lipid in the sclera and the Bruch membrane is still a matter of controversy.

The use of pentoxifylline increased ocular fundus pulsations, although several of the patients received concomitant vasoactive drugs. The observed increase in pulsatile choroidal blood flow may, therefore, be partly caused by the effects of pentoxifylline on whole blood viscos-

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**Table 1. Characteristics of Subjects With Age-related Macular Degeneration (AMD)**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Pentoxifylline-Treated Group (n=20)</th>
<th>Placebo-Treated Group (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (±SD) age, y</td>
<td>79.6±8.1</td>
<td>77.3±8.9</td>
</tr>
<tr>
<td>Age range, y</td>
<td>61-92</td>
<td>61-94</td>
</tr>
<tr>
<td>Best-corrected visual acuity</td>
<td>20/25-20/200</td>
<td>20/25-20/200</td>
</tr>
<tr>
<td>Sex, No. F/M</td>
<td>16/4</td>
<td>13/7</td>
</tr>
<tr>
<td>AMD stage, No. of patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage 1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Stage 2</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Stage 3</td>
<td>13</td>
<td>11</td>
</tr>
<tr>
<td>Stage 4</td>
<td>2</td>
<td>5</td>
</tr>
</tbody>
</table>

* Stages according to Bressler et al.\(^1^9\)

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**Table 2. Effect of 3 Months of Pentoxifylline or Placebo Use on Mean Arterial Pressure (MAP) and Pulse Rate (Pulse)**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Study Period</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
</tr>
<tr>
<td>Pentoxifylline (n=16)</td>
<td></td>
</tr>
<tr>
<td>MAP, mm Hg</td>
<td>100±12</td>
</tr>
<tr>
<td>Pulse, 1/min</td>
<td>82±14</td>
</tr>
<tr>
<td>Placebo (n=17)</td>
<td></td>
</tr>
<tr>
<td>MAP, mm Hg</td>
<td>103±13</td>
</tr>
<tr>
<td>Pulse, 1/min</td>
<td>80±10</td>
</tr>
</tbody>
</table>

* Data are presented as mean±SD.

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The effect of 3 months of pentoxifylline treatment (n=16, solid triangles) or placebo (n=17, open triangles) on retinal blood flow (top) and fundus pulsation amplitude (FPA; bottom). Data are presented as means±SD.
ity, which would be compatible with previous results in healthy subjects.\textsuperscript{5,6} Patients with AMD have been shown not to have altered rheological flow properties.\textsuperscript{7,8} Although we have not assessed variables of blood viscosity in our study, these effects of pentoxifylline may have substantially contributed to our results.

Ocular fundus pulsation measurements obviously estimate only the pulsatile component of choroidal blood flow. This does not limit our findings, however, because in this study measurements of the fundus pulsation amplitude rather underestimate the effect of pentoxifylline on total choroidal blood flow. Friedman et al\textsuperscript{8} observed an increased flow pulsatility, as shown by an increased pulsatility index, in the posterior ciliary arteries of patients with AMD. An increase of choroidal blood flow, caused by a reduction in peripheral vascular resistance or a reduction in whole blood viscosity, should lead to a reduction in flow pulsatility. Therefore, the increase in a nonpulsatile choroidal blood flow component might be even larger than that of a pulsatile flow component.

The reproducibility of scanning laser Doppler flowmetry is not yet satisfactory. This limits the power of the method to detect drug-induced blood flow changes.\textsuperscript{20} Moreover, it has been shown that the relationship between “flow” as obtained with this method and retinal blood flow may not be linear.\textsuperscript{21,22} Nevertheless, results of our previous study indicate that changes of at least 15% over baseline should have been detectable in the present study.\textsuperscript{9}

Of the 40 subjects, 4 receiving pentoxifylline and 3 receiving placebo discontinued prematurely. This drop-out rate is acceptable considering the age of the participants. All 7 subjects who did not finish the trial described nausea after drug administration. This is in agreement with previous reports that gastrointestinal symptoms are the most common adverse effects of the use of pentoxifylline (about 3%), although these and other adverse effects have not occurred to a significantly greater extent than with placebo.\textsuperscript{27}

A limitation of our results is that we did not measure pentoxifylline plasma levels in the patients with AMD. Subjects’ compliance was tested by drug counting, and in all subjects completing the 3-month trial, the tablet count was within 12% of the expected value. This does not ensure that all patients took the medications at regular intervals and that the scheduled times. All measurements, however, were performed in the morning before administering the drug. According to the pharmacokinetics of pentoxifylline,\textsuperscript{28,29} steady-state conditions should have been present at these times. Moreover, a low drug compliance would have resulted in false-negative findings of pentoxifylline’s effects.

In conclusion, our results indicate that a 3-month treatment with oral pentoxifylline, 400 mg 3 times a day, increases choroidal but not retinal blood flow in patients with AMD. Considering the evidence that choroidal blood flow is impaired in patients with AMD, this result strongly supports the concept that pentoxifylline might be useful in the treatment of this disease. A long-term clinical outcome trial is now warranted to test this hypothesis.

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REFERENCES