Effects of Sildenafil on Retinal Blood Flow and Flicker-Induced Retinal Vasodilatation in Healthy Subjects

Kaija Polak,1,2 Barbara Wimpissinger,1 Fatmire Berisha,1 Michael Georgopoulos,1,2 and Leopold Schmetterer1,3

PURPOSE. Sildenafil is a specific inhibitor of phosphodiesterase V, which is widely used for the treatment of erectile dysfunction. Sildenafil has been shown to induce vasodilatation in several vascular beds by inhibiting the cGMP breakdown. The present study was conducted to investigate whether sildenafil increases blood flow in the human retina.

METHODS. In a randomized, double-masked, placebo-controlled, two-way crossover study in 12 healthy male volunteers the effects of a single dose of 100 mg sildenafil were studied. Subjects received sildenafil or placebo on two different study days. After administration, retinal hemodynamic parameters were measured every 20 minutes. Retinal vessel diameters and retinal blood velocity were assessed with the retinal vessel analyzer and bidirectional laser Doppler flowmetry, respectively. In addition, the response of retinal vessel diameters to stimulation with diffuse flicker light was studied. Blood pressure and intraocular pressure were measured with noninvasive techniques.

RESULTS. Sildenafil had no effect on mean arterial pressure, pulse rate, intraocular pressure, retinal blood velocity, or retinal arterial diameter. However, a significant increase in retinal venous diameters (4.7% ± 3.2%; P = 0.0028 versus placebo) and retinal blood flow 15.7% ± 18.0%; P = 0.029 versus placebo) was observed. Sildenafil had no effect on flicker-induced vasodilation in retinal arteries or veins.

CONCLUSIONS. The data indicate that sildenafil increases retinal venous diameters and retinal blood flow in healthy subjects. By contrast, it does not affect intraocular pressure and flicker-induced retinal vasodilation. Further studies are needed to elucidate whether this drug may be therapeutically used in retinal ischemic disease. (Invest Ophthalmol Vis Sci. 2003;44:4872–4876) DOI:10.1167/iovs.03-0177

Recently, sildenafil (Viagra; Pfizer, Inc., New York, NY), a specific inhibitor of phosphodiesterase V (PDE-V) has attracted much attention for the treatment of erectile dysfunction. It has been approved for use in the United States for this indication and has been shown to be effective in a wide range of patients with various causes of the dysfunction.1 The most frequently reported side effects were transient headache, flushing, dyspepsia, rhinitis, and visual disturbances. These side effects reflect the pharmacology of this PDE-V inhibitor, which elevates the intracellular second-messenger cyclic guanosine monophosphate (cGMP). Increase in intracellular cGMP is well known to cause vasodilation,2 acting as a second messenger for NO and vasoactive peptides. The concentrations of cAMP and cGMP are on the one hand controlled by the cyclases, which regulate synthesis, and on the other hand by the PDEs, which catalyze hydrolysis.

Although there is evidence that PDE-V inhibition has vaso-dilative effects in coronary arteries, no effect on IOP and optic nerve head blood flow has been observed in previous trials.3,4 Findings concerning the effects of sildenafil citrate on choroidal blood flow have been contradictory. Sildenafil has been shown to increase pulsatile choroidal blood flow,5 whereas foveolar choroidal blood flow, as assessed with laser Doppler flowmetry (LDF), was not affected.6 In the human retina, sildenafil has been shown to induce vasodilation in some7 but not in all8 studies. A study investigating the effect of sildenafil on retinal blood flow, however, had not been conducted.

In phototransduction, illumination activates the G-protein transducin that triggers activation of PDE-V and -VI. The rapid decline in cGMP levels, catalyzed by activation of PDE-V and -VI, closes cGMP-gated cationic channels in the membranes of photoreceptor cells. Photostimulation with diffuse luminance flicker has been shown to increase retinal vessel diameter.9 Hence, one may hypothesize that inhibition of PDE-V and -VI, both induced by sildenafil, may reduce flicker-induced vasodilatation by influencing signal transduction or by increasing cGMP levels in endothelial or smooth muscle cells.

We performed a study investigating the effect of sildenafil on retinal blood flow and flicker-induced retinal vasodilatation in healthy subjects. Retinal vessel diameters and retinal blood velocities were measured with a retinal vessel analyzer (RVA; Carl Zeiss Meditec, Jena, Germany) and bidirectional laser Doppler velocimetry (LDV), respectively.

METHODS

Subjects

The present study was performed in accordance with the Declaration of Helsinki and the Good Clinical Practice (GCP) guidelines. After approval of the study protocol by the Ethics Committee of the Vienna University School of Medicine and after written informed consent was obtained, 12 healthy nonsmoking male subjects were studied (mean age, 42 ± 6 years; range, 36–59). All subjects were drug free for at least 3 weeks before inclusion and passed a prestudy screening during the 4 weeks before the first study day that included medical history and physical examination; 12-lead electrocardiogram; complete blood count; activated partial thromboplastin time; thrombin time; clinical chemistry; hepatitis-A, -B, and -C and HIV serology; urinalysis; and an ophthalmic examination. Subjects were excluded if any abnormality was found as part of the pretreatment screening, unless the investigators considered the abnormality to be clinically irrelevant. In addition, subjects with anemia of more than 3 D, anisometropia more than 1 D, or any evidence of eye disease that might interfere with the purpose of this study were excluded.

Disclosure: K. Polak, Pfizer (F); B. Wimpissinger, Pfizer (F); F. Berisha, Pfizer (F); M. Georgopoulos, Pfizer (F); L. Schmetterer, Pfizer (F)

The publication costs of this article were defrayed in part by page charge payment. This article must therefore be marked "advertisement" in accordance with 18 U.S.C. §1734 solely to indicate this fact.

Corresponding author: Leopold Schmetterer, Department of Clinical Pharmacology, Währinger Gürtel 18-20, A-1090 Vienna, Austria; leopoldschmetterer@univie.ac.at
of the trial were excluded. All subjects had several training sessions with the LDV system before inclusion in the study. Only subjects with excellent target fixation and highly reproducible blood flow results were considered for inclusion.

**Study Design**

Subjects were asked to refrain from alcohol and caffeine for at least 12 hours before trial days and were studied after an overnight fast. The study followed a randomized double masked, placebo-controlled two-way crossover design with sildenafl (100 mg oral sildenafl; Viagra, Pfizer) or matching placebo. To allow for double-masked conditions placebo tablets were identical in appearance, weight and taste with the sildenafl tablets. The washout period between the two study days was at least 4 days.

**Description of Study Days**

Dilation of the pupil was obtained with tropicamide (Mydriatikum Roche; Hoffmann-La Roche, Vienna, Austria). After a resting period of at least 20 minutes baseline measurements of ocular and systemic hemodynamics were performed. In addition, a 60-second flicker period with an 8-Hz flicker stimulus was scheduled and retinal vessel diameters were measured continuously. Thereafter, subjects received a single dose of 100 mg sildenafl or placebo. Ocular and systemic hemodynamic parameters were measured every 20 minutes over 3 hours and finally after 6 hours. Intraocular pressure (IOP) was measured in the fellow eye with applanation tonometry at baseline, every 60 minutes. Hemodynamics were performed. In addition, a 60-second baseline measurement of ocular and systemic hemodynamics was performed. The principle of blood flow velocity measurement by LDV is based on the optical Doppler effect. Laser light, which is scattered by moving particles (e.g., 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 center line erythrocyte velocity. With bidirectional LDV the absolute velocity in the retinal vessels can be obtained. Measurements of retinal blood velocity were performed in retinal veins only at the same locations as were used for assessment of diameter with the RVA. During the measurements, care was taken that the DC value representing the total reemitted light from the fundus remained within ±15%. Evaluation of the LDV data was performed on computer (NeXT Computer, Redwood, CA), as described previously, using a time constant of 0.073. The full period of 60 seconds was taken for evaluation removing periods of eye blinks and saccades, as identified from unstable DC signals. Retinal blood flow was calculated based on these measurements of maximum erythrocyte velocity (Vel_max). Mean blood velocity (Vel) in retinal veins was calculated as (Vel_max/1.6). In the present study, only one vein was studied, to allow for the time schedule described earlier. Blood flow through a specific retinal vein can then be obtained as

\[ Q = \left( \frac{\text{Vel}_{\text{Max}}}{1.6} \right) \cdot \left( \pi \cdot \text{VD}^2/4 \right) \]

where VD is the diameter of the vein.

**Flicker Stimulation.** The flicker light was delivered through the illumination pathway of the fundus camera. The maximum luminance of the full-field flicker was approximately 2.5 \( \times \) 10 to 5 \( \mu \text{J}/(\text{cm}^2 \cdot \text{ms}) \). The flash duration was 30 \( \mu \text{s} \). Diffuse luminance flicker was applied for 60 seconds at a frequency of 8 Hz during RVA measurements. Each flicker period was preceded by 60 seconds of baseline recording. To avoid having the flicker light itself interfere with the diameter measurement procedure, the light of the fundus camera and that of the flicker stimulation had to be separated. For this purpose, the followed wavelength separation technique was adopted: One interference filter with a center wavelength of 590 nm and a bandwidth of 10 nm was introduced in the illumination pathway of the fundus camera. Hence, the eye was illuminated with light containing wavelengths between 580 and 600 nm. This window was chosen, because in this wavelength range the contrast between blood vessels and the surrounding tissue is optimal. A second matching interference filter was placed in front of the video camera. In addition, a 550-nm low-pass cutoff filter was placed in front of the flicker light source. With this technique the flicker stimulus is clearly perceived by the subject under study, but is not detected with the video camera. This ensures constant contrast in the fundus image throughout the flicker experiments.

**Data Analysis**

All statistical analyses were performed on computer (Statistica, ver. 4.5; StatSoft Inc., Tulsa, OK). All outcome variables were calculated for each subject individually and then averaged. The effects of sildenafl on the outcome parameters was assessed with repeated measures ANOVA versus placebo. The interaction between time and treatment was taken as the level of significance to characterize treatment effects. The relative change in hemodynamic parameters induced by sildenafl was calculated. Data are presented as means ± SD. A two-tailed \( P < 0.05 \) was considered to indicate significance.
RESULTS

All outcome parameters were comparable on the two study days at baseline (Table 1). Sildenafil had no effect on MAP or pulse rate (Fig. 1). In addition, neither sildenafil nor placebo altered IOP, and consequently ocular perfusion pressure remained unchanged (Table 2).

Sildenafil induced a significant increase in retinal venous diameters, as shown in Figure 2 ($P = 0.0028$ versus placebo). The maximum increase in retinal venous diameters with sildenafil occurred 80 minutes after administration (4.7% ± 3.2%; range, −0.4% to +10.9%). A tendency toward an increase was also seen for retinal arterial diameters after administration of sildenafil. This effect, however, did not reach the level of significance ($P = 0.18$). The maximum increase in retinal arterial diameters occurred 60 minutes after administration of sildenafil (3.7% ± 7.0%; range, −6.9% to +15.7%). The drug had no effect on flicker-induced vasodilation in retinal arteries or veins (Fig. 3).

Sildenafil had no significant effect on retinal blood velocity (Fig. 4) although there was a tendency toward an increase ($P = 0.09$). The maximum increase in red blood velocity was observed 40 minutes after administration of sildenafil (8.9% ± 10.1%; range, −11.6% to +31.5%). By contrast, sildenafil induced a significant increase in retinal blood flow ($P = 0.029$).

### Table 1. Baseline Data

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo Day</th>
<th>Sildenafil Day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>125 ± 7</td>
<td>127 ± 8</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>68 ± 5</td>
<td>69 ± 4</td>
</tr>
<tr>
<td>Pulse rate (beats/min)</td>
<td>73 ± 8</td>
<td>74 ± 8</td>
</tr>
<tr>
<td>Intraocular pressure (mm Hg)</td>
<td>12 ± 2</td>
<td>12 ± 2</td>
</tr>
<tr>
<td>Retinal venous diameter (µm)</td>
<td>147 ± 17</td>
<td>148 ± 17</td>
</tr>
<tr>
<td>Retinal arterial diameter (µm)</td>
<td>125 ± 12</td>
<td>125 ± 13</td>
</tr>
<tr>
<td>Retinal blood velocity (cm/s)</td>
<td>1.58 ± 0.42</td>
<td>1.42 ± 0.50</td>
</tr>
<tr>
<td>Retinal blood flow (µL/min)*</td>
<td>14.0 ± 5.9</td>
<td>14.8 ± 6.9</td>
</tr>
</tbody>
</table>

Data are the mean ± SD.

* Blood flow through a specific vein and not total retinal blood flow.

### Table 2. Intraocular and Ocular Perfusion Pressures During Sildenafil or Placebo

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>0</th>
<th>60</th>
<th>120</th>
<th>180</th>
<th>360</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo Day</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intraocular pressure</td>
<td>12 ± 2</td>
<td>12 ± 3</td>
<td>12 ± 2</td>
<td>11 ± 2</td>
<td>11 ± 3</td>
</tr>
<tr>
<td>Ocular perfusion pressure</td>
<td>45 ± 5</td>
<td>46 ± 6</td>
<td>44 ± 4</td>
<td>46 ± 5</td>
<td>47 ± 4</td>
</tr>
<tr>
<td>Sildenafil Day</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intraocular pressure</td>
<td>12 ± 2</td>
<td>12 ± 2</td>
<td>12 ± 3</td>
<td>11 ± 3</td>
<td>11 ± 2</td>
</tr>
<tr>
<td>Ocular perfusion pressure</td>
<td>44 ± 5</td>
<td>43 ± 5</td>
<td>46 ± 6</td>
<td>46 ± 6</td>
<td>46 ± 5</td>
</tr>
</tbody>
</table>

Data are mean mm Hg ± SD.
This effect was at its maximum 80 minutes after administration of sildenafil (15.7% ± 18.0%; range, -17.2% to +39.4%).

**DISCUSSION**

Since the introduction of sildenafil for the treatment of erectile dysfunction, there has been considerable interest in the ocular side effects of the drug. Whereas the overall ocular safety of sildenafil is good, dose-related effects on color vision and mild electrophysiological signs have been reported. These side effects may be related to either inhibition of PDE-V, resulting in vasodilation, or to inhibition of PDE-VI, modulating the retinal phototransduction pathway.

The present study indicates that sildenafil induces retinal vasodilation and increases retinal blood flow in vivo. After single dose administration of 100 mg sildenafil to healthy volunteers we observed a 4.7% increase in retinal venous diameters and a 15.7% increase in retinal blood flow. Results of studies investigating ocular hemodynamic effects of sildenafil are contradictory. In a randomized placebo-controlled crossover study in 15 healthy volunteers, no changes in retinal vessel diameters were observed 1 and 5 hours after administration of sildenafil. In this study, digitized monochromatic fundus images were used to measure retinal vessel size. The power in this study to detect a change in retinal vessel diameters of 6.5% was 80%. Considering that the changes in retinal vessel diameters observed in the present study were considerably smaller, these data are compatible. Our data are in keeping with the results from another study, in which an increase in retinal venous diameter was observed after 50 mg sildenafil (5.8%) in an open, uncontrolled study in which the same RVA was used as in the present trial. This study also reported a significant increase in retinal arterial diameter (5.8%) that was not observed in the present study. One possible explanation for this discrepancy is that younger subjects were used in the previous study (average age, 31 years). Our study is the first, however, to quantify changes in retinal blood flow after administration of sildenafil and thus the first to show that the increase in venous retinal diameters is accompanied by an increase in retinal perfusion. The lack of effect on red blood cell velocity, however, is compatible with a study using color Doppler imaging, in which no effect of sildenafil on blood velocities in the central retinal artery was observed. To speculate on the site of action of sildenafil in the present study is difficult, because we do not have data on the retinal microvasculature. However, our results are compatible with the idea that sildenafil induces vasodilation primarily on retinal microvessels with the observed venous dilation representing a passive secondary response. In this case, retinal venous velocity may well be unchanged, whereas retinal arterial velocity should be increased although not measured in the present study because of lower reproducibility.

Two different studies focused on the effect of sildenafil on choroidal blood flow, but the results were dependent on the methodology used. With LDF, no change in choroidal blood flow was observed in a randomized placebo-controlled study in

---

**FIGURE 3.** Effects of sildenafil (▲) and placebo (▼) on arterial (top) and venous (bottom) flicker responses. Data are presented as means ± SD (n = 12).

**FIGURE 4.** Effects of sildenafil (▲) and placebo (▼) on retinal blood flow (top) and retinal blood velocity (bottom). Data are presented as means ± SD (n = 12).
15 healthy subjects. This study had the power to detect a change of 20% in choroidal blood flow.6 By contrast, a significant increase in pulsatile ocular blood flow was reported after 50 mg of sildenafil using pneumotonometry.7–9 One may hypothesize that this is also the case in the retina, where nitrates increase retinal vessel diameters after acute and chronic administration.10,11 This is in keeping with the idea that NO plays a key role in ocular blood flow regulation, as shown in numerous animal and human experiments. The NO dependence of sildenafil-induced vasodilation in the human retina, however, has not been shown.

In the present study, sildenafil did not alter the response of retinal arteries or veins to diffuse luminance flicker. In the retina, as in the brain, there is a tight coupling between metabolism and activity.9,13,23,24 The increase in optic nerve head blood flow appears to be directly related to activity changes in neural retinal tissue.25 The mechanism underlying the increase in retinal blood flow and retinal vessel diameters during flicker stimulation is hitherto unknown. There is some evidence, however, that NO plays an important role in retinal neurovascular coupling.24,26 Hence, it is somewhat unexpected that sildenafil, which is assumed to act through the l-arginine/NO pathway, does not affect flicker-induced vasodilation. Preserved neurovascular coupling during sildenafil administration, however, may in part explain the mild ocular side-effect profile of the drug.

Changes in blood pressure, pulse rate, and IOP in the present study were small, in keeping with results in several published trials.3,4,27,28 Hence, our results indicate that ocular perfusion pressure remained constant throughout the study period and that the increase in retinal blood flow resulted from direct vasodilation, rather than from changes in systemic hemodynamic parameters.

In conclusion, in our study, sildenafil increased retinal venous diameters and retinal blood flow in healthy subjects. By contrast, it did not affect IOP and flicker-induced retinal vasodilation. Further studies are needed to elucidate whether this drug may be used therapeutically in retinal ischemic disease.

References