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Effect of Viagra on the foveolar choroidal circulation of AMD patients

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Abstract

To investigate the effects of sildenafil citrate (Viagra) on foveolar choroidal circulation in patients with age related macular degeneration (AMD).

Double-blinded, randomized, placebo-controlled, crossover study. Fifteen male AMD patients received a dose of 100 mg of sildenafil or matching placebo on two separate days. Laser Doppler flowmetry was performed to assess relative choroidal blood velocity (ChB_{Vel}), volume (ChB_{Vol}) and flow (ChB_{Flow}) in the study eye prior to administration of the drug at baseline and 30, 90, 180, 300 min after dosing. Best corrected visual acuity (BCVA), contrast sensitivity (CS), mean arterial blood pressure (BPm), heart rate (HR), intraocular pressure (IOP) and ocular perfusion pressure (PP) were determined.

In comparison to placebo, sildenafil did not cause any statistically significant changes in mean ChB_{Vel} (ANOVA, $P=0{\cdot}12$), ChB_{Vol} (ANOVA, $P=0{\cdot}24$) or ChB_{Flow} (ANOVA, $P=0{\cdot}46$). There were no statistically significant changes in CS (ANOVA, $P=0{\cdot}59$), BCVA ($P=0{\cdot}58$), IOP ($P=0{\cdot}81$) or HR ($P=0{\cdot}07$) throughout the study. Significant decreases in BPm ($P=0{\cdot}006$) and PP ($P=0{\cdot}006$) were observed at 30 min after sildenafil.

Administration of sildenafil citrate didn't cause any statistically significant changes in the foveolar choroidal circulation of AMD patients.

Keywords: foveolar choroidal circulation; laser Doppler flowmetry; age-related macular degeneration; sildenafil citrate (Viagra)

1. Introduction

Sildenafil citrate (Viagra) is the first oral drug approved for the treatment of erectile dysfunction is a selective inhibitor of phosphodiesterase type 5 (PDE5), the predominant isozyme metabolizing cyclic GMP in the corpus cavernosum (Boolell et al., 1996). Endothelium-derived relaxing factors, such as nitric oxide (NO), (Ignarro et al., 1987; Furchgott and Vanhoutte, 1989) diffuse into the smooth muscle and increase levels of cGMP, producing smooth muscle relaxation and dilatation of blood vessels (Gruetter et al., 1981; Ignarro and Kadowitz, 1985; Furchgott and Vanhoutte, 1989). Sildenafil greatly enhances the dilating effects of NO by blocking PDE5 and because of this property it was initially designed to treat cardiac ischemic conditions (Jackson et al., 1999). As sildenafil has a direct effect on the blood vessels it is possible that it might affect ocular blood vessels.

Several investigators have studied the effects of sildenafil on ocular circulation in normal subjects (Dundar et al., 2001; Grunwald et al., 2001, 2002; Paris et al., 2001; Pache et al., 2002; Polak et al., 2003). The effect of sildenafil in disease, however, is less known. Because of previous reports suggesting that choroidal blood flow is decreased in age-related macular degeneration (AMD) (Sarks, 1976; Prunte and Niesel, 1988; Sarks et al., 1988; Friedman et al., 1989, 1995; Pauleikhoff et al., 1990; Chen et al., 1992; Boker et al., 1993; Holz et al., 1994; Grunwald et al., 1998), we investigated the effect of sildenafil on this vascular tissue.

Theoretically, because sildenfil has a strong systemic vasodilating effect that decreases systemic blood pressure, such effect could potentially result in decreased choroidal blood flow. On the other hand, since the choroid is a vascular tissue analogous in many respects to the corpus cavernosum (Paris et al., 2001), sildenafil could have a strong vasodilatory effect resulting in increased choroidal

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blood flow. Thus the purpose of this study was to evaluate the effects of sildenafil on the foveolar choroidal circulation of patients with age-related macular degeneration.

2. Design

We conducted a double-blinded, randomized, placebo-controlled, crossover study that included 15 male subjects with different stages of AMD.

3. Methods

Fifteen male patients (14 Caucasians and 1 African-American) with AMD features similar to those of AMD category 3 or worse of the AREDS study and visual acuity of 20/40 or better in the study eye were included in this study. We chose subjects with relatively good vision in the study eye because good fixation is important when laser Doppler flowmetry is used to measure choroidal blood flow in the center of the foveola. Mean age of study subjects was 75 ± 7 years (± 1 SD). All 15 patients had non-exudative macular degeneration with no evidence of choroidal neovascularisation (CNV) in the study eye. Two of these patients had exudative AMD with a disciform scar in the fellow eye. All subjects had bilateral large drusen in both eyes. Retinal pigment epithelium hyperpigmentary changes were present in 8 out of 15 study eyes. Five patients had small areas of extrafoveal geographic atrophy in the study eye or the fellow eye.

External and slit lamp exams were unremarkable except for the presence of mild nuclear sclerosis changes in 9 eyes and intraocular lens implants in 3 eyes. All subjects had a steady fixation and intraocular pressure (IOP) of 21 mmHg or less. None of the study eyes had any intraocular eye disease other than AMD.

Nine patients who had a history of well-controlled systemic hypertension were on antihypertensive medications: calcium channels blockers (5), β blockers (3), ACE inhibitors (2), diuretics (2), and angiotensin receptor blockers (3) patients. Among these 9 patients, 7 received a combination of 2 drugs and 2 patients were on a single medication. None of the 15 subjects was receiving nitrates nor had a history of systemic hypotension or serious heart condition. All study subjects took the same medications throughout the length of the study.

The study was carried out with approval from University of Pennsylvania Institutional Review Board. Detailed explanations of the study procedures were provided to all study participants. All subjects signed an appropriate IRB approved consent form. Those subjects who were enrolled in the study after 04/14/2003, signed a HIPPA consent form. The tenets of the Declaration of Helsinki were followed.

All patients were randomized to receive a single oral dose of either 100 mg of sildenafil citrate (Viagra; Pfizer Inc, New York, New York) or matching placebo on the first study visit day. The alternative drug was administered on a second study day. Both study days were separated by a washing out period of three or more days. Placebo pills were identical to the sildenafil ones, but they didn't contain the active component. Both patients and investigators were blinded to the treatment modality to prevent bias. The same protocol was performed on both study visits, with all tests done prior administration of the drug, and then 30, 90, 180 and 300 min thereafter. These times were chosen to coincide with the maximal serum levels of sildenafil, which are reached in 30–60 min; plasma half-life of sildenafil is about 4 hr (Marmor and Kessler, 1999). None of the study participants was under fasting conditions. All measurements were performed in one eye of each patient (study eye); right eye was chosen in ten patients and left eye in five patients.

Pupils were dilated with 1% Mydriacyl (Alcon, Ft Worth, TX) and 10% Neo-Synephrine (Sanofil-Synthelabo, NY, NY). Following pupillary dilatation, best-corrected visual acuity (BCVA) was measured using ETDRS charts at $3 \cdot 2$ m and contrast sensitivity (CS) testing was performed using Pelli-Robson contrast sensitivity charts at 1 m.

Laser Doppler flowmetry (Oculix, Inc, Berwyn, Pennsylvania) was used to assess the foveolar choroidal circulation. This noninvasive technique provides measurements of relative choroidal blood velocity (ChB_{Vel}), volume (ChB_{Vol}) and flow (ChB_{Flow}) in the center of the foveola. Once the pupils were dilated, a diode laser beam (670 nm) with a 20 mW intensity and diameter of 200 μm was delivered to the eye through a fundus camera (model TRC; Topcon, Tokyo, Japan). Subjects were asked to fixate on the probing laser beam. Proper fixation was monitored by observation thorough the fundus camera. The light scattered back was electronically analyzed. The same trained investigator performed LDF measurements throughout the study. A detailed description of the technique has been previously reported (Riva et al., 1992, 1994, 1996; Petrig and Riva, 1996).

Three measurements of choroidal circulation of approximately 30 sec were obtained while patients were seated in the darkened room. Immediately after ocular circulatory measurements, brachial artery systemic blood pressure and heart rate (HR) were assessed by an automated sphygmomanometer (Accutorr 1A, Datascope, Paramus, NJ) and intraocular pressure (IOP) was measured by Tonopen. The mean brachial artery pressure (BPm) was calculated according to the following formula: $BPm = BPd + 1/3(BPs\text{-}BPd)$, where BPs and BPd are the systolic and the diastolic blood pressures. Perfusion pressure (PP) was estimated through the following formula: $PP = 2/3BPm\text{-}IOP$. An individual masked to treatment information performed analysis of the blood flow measurements using a NEXT computer.

Statistical analysis of the data comparing the changes from baseline after administration of sildenafil to the changes from baseline after administration of placebo was performed

Table 1
Mean foveolar choroidal blood velocity (ChB_{Vel}), volume (ChB_{Vol}), and flow (ChB_{Flow}) at baseline and change from baseline at 30, 90, 180 and 300 min after placebo and sildenafil citrate (Viagra) treatment, in arbitrary units (±1 SD)

	Baseline		Change from baseline							
			30 min		90 min		180 min		300 min	
	Placebo	Sildenafil	Placebo	Sildenafil	Placebo	Sildenafil	Placebo	Sildenafil	Placebo	Sildenafil
ChB_{Vel}	0·39±0·08	0·37±0·07	−0·01±0·03	0·00±0·03	−0·02±0·03	0·01±0·04	−0·01±0·03	0·01±0·05	−0·01±0·04	0·02±0·05
ChB_{Vol}	0·18±0·06	0·19±0·06	0·01±0·03	0·01±0·03	0·02±0·03	0·00±0·04	0·02±0·03	0·01±0·05	0·02±0·03	−0·02±0·04
ChB_{Flow}	5·9±2·2	6·0±2·1	0·3±0·8	0·2±0·5	0·2±0·8	0·2±0·9	0·3±0·9	0·2±0·7	0·3±0·6	−0·3±0·8

using analysis of variance (ANOVA) for repeated measures. To compare the differences between these two groups at each time point (30, 90, 180 and 300 min), alpha level adjustments for multiple comparisons by means of Bonferroni test were also carried out. Because we had 4 comparisons in time, we considered $P=0·0125$ ($0·05/4=0·0125$) as statistically significant. Regression analysis was also performed and results with a probability of 0·05 were considered to be statistically significant. Statview software (Cary, NC, USA) was used for the analysis of the data. All circulatory measurements are shown in arbitrary units (AU).

4. Results

Mean values of ChB_{Vel}, ChB_{Vol} and ChB_{Flow} at baseline, 30, 90, 180 and 300 min are shown in Table 1. In comparison to placebo, administration of 100 mg of sildenafil citrate did not cause any statistically significant changes in mean ChB_{Vel} (ANOVA, $P=0·12$), mean ChB_{Vol} (ANOVA, $P=0·24$) or mean ChB_{Flow} (ANOVA, $P=0·46$, Fig. 1) at any time points. Since no statistically significant changes in ChB_{Flow} were found, we estimated that we have 95% power to detect a 12% difference in the change ChB_{Flow} from baseline between the two groups (type I error of 0·05).

Comparison of blood flow parameters between AMD patients with and without hypertension showed no statistically significant difference in any of the circulatory parameters. However, the number of patients in each group is rather small and this precludes us from making any strong conclusions.

Mean values of best corrected visual acuity (BCVA) and contrast sensitivity testing (CS), IOP, PP, BPm and HR are shown in Table 2. In comparison to placebo, no statistically significant differences in the changes from baseline for BCVA (ANOVA, $P=0·58$), CS (ANOVA, $P=0·59$), IOP (ANOVA, $P=0·81$) or HR (ANOVA, $P=0·07$) were observed after treatment with sildenafil or placebo.

Statistical analysis by ANOVA showed that the changes in BPm and PP from baseline were different after

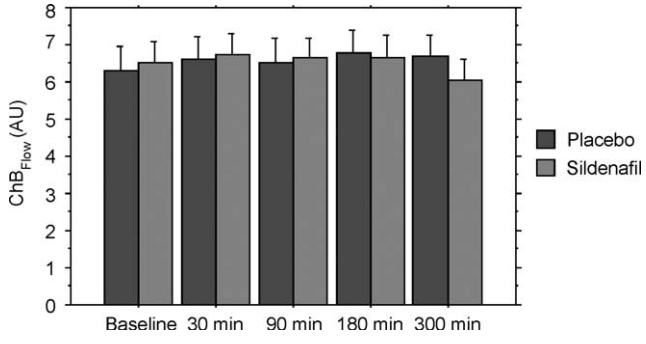

Fig. 1. Average choroidal blood flow (ChB_{Flow}) in arbitrary units (AU) at baseline, 30, 90, 180 and 300 min after treatment with placebo and sildenafil citrate (Viagra). Error bars correspond to ±1 standard error (SE).

Table 2
Mean number of letters correctly identified on best corrected visual acuity (BCVA) and contrast sensitivity (CS) testing, intraocular pressure (IOP), perfusion pressure (PP), mean blood pressure (BPm) and heart rate (HR) at baseline and change from baseline at 30, 90, 180 and 300 min after placebo and sildenafil citrate (Viagra) treatment, in arbitrary units (±1 SD)

	Baseline		Change from baseline							
			30 min		90 min		180 min		300 min	
	Placebo	Sildenafil	Placebo	Sildenafil	Placebo	Sildenafil	Placebo	Sildenafil	Placebo	Sildenafil
BCVA	53±9·1	54±7·2	0·3±4·0	−1·1±4·0	−1·5±3·4	−0·4±4·2	−0·6±4·9	−1·3±5·1	−0·4±4·4	−2·9±9·1
CS	33±2·1	34±2·1	−0·2±1·4	−0·1±1·4	−0·5±2·4	−0·5±1·5	−0·1±1·5	−0·2±2·0	−0·2±1·9	−0·9±1·8
IOP (mmHg)	13±2·8	13±2·3	0·2±2·3	1·4±1·7	0·7±1·9	0·5±1·9	−0·6±2·4	−0·9±2·5	−0·5±2·3	−0·5±1·3
PP (mmHg)	50±6·2	50±7·5	4·9±8·4	−6·1±6·6	1·6±7·7	−4·4±7·9	3·0±5·9	−1·3±6·9	5·1±4·9	0·4±5·6
BPm (mmHg)	95±10	95±11	7·5±11	−7·0±9·1	3·4±11	−5·9±11	3·6±9·1	−3·2±10	6·8±8·7	−0·1±8·7
HR (beats min^{-1})	70±14	68±12	−2·7±5·5	−0·7±3·9	−3·1±7·4	−2·3±4·6	−5·2±6·8	1·0±7·0	−2·7±7·5	−0·2±5·9

administration of sildenafil and placebo ($P=0·03$, for both parameters). After adjustments for multiple comparisons by Bonferoni test, statistically significant decreases in BPm and PP were found at 30 min after administration of sildenafil. ($P=0·006$, for both parameters).

We found significant inverse correlations between ChB_{Vel} and both BPm and PP at 180 min after administration of sildenafil (Pearson correlation coefficient $=-0·56$, $P=0·03$, Fig. 2; and Pearson correlation coefficient $=-0·59$, $P=0·02$, Fig. 3, respectively). Similar correlations were present at 300 min after administration of sildenafil between ChB_{Vel} and BPm (Pearson correlation coefficient $=-0·53$, $P=0·04$), and between ChB_{Vel} and PP (Pearson correlation coefficient $=-0·55$, $P=0·03$). No such correlations were found after administration of placebo. No other significant correlations were observed at any of the time points after administration of sildenafil or placebo.

No visual complaints were reported following sildenafil citrate or placebo. The following side effects were noted following sildenafil ingestion: headache (2), puffiness of the face and lips (1), dizziness (1), facial flushing (1), and perspiration (1). No complaints were reported after placebo.

5. Discussion

Because of sildenafil's strong vasodilatory qualities we investigated whether this compound may have an effect on the ocular circulation. We were particularly interested in the possibility that sildenafil may have an effect on the choroidal circulation of patients with AMD, because our previous study and several other reports had suggested that the choroidal blood flow is decreased in AMD patients (Sarks, 1976; Friedman et al., 1989, 1995; Prunte and Niesel, 1988; Sarks et al., 1988; Pauleikhoff et al., 1990; Chen et al., 1992; Boker et al., 1993; Holz et al., 1994; Grunwald et al., 1998). A decreased choroidal circulation could have a role in the etiology of AMD since the vascular bed supplies nutrients and removes metabolic waste products from the outer retina.

Our results, however, did not show any statistically significant effects of sildenafil on ChB_{Vel}, ChB_{Vol} or ChB_{Flow} in our patients. The lack of significant change in the choroidal circulation is a reassuring finding. Sildenafil citrate is known to decrease systemic blood pressure and this could potentially lead to a decrease in choroidal circulation. Such a potential effect would be deleterious in patients that may have a compromised choroidal circulation

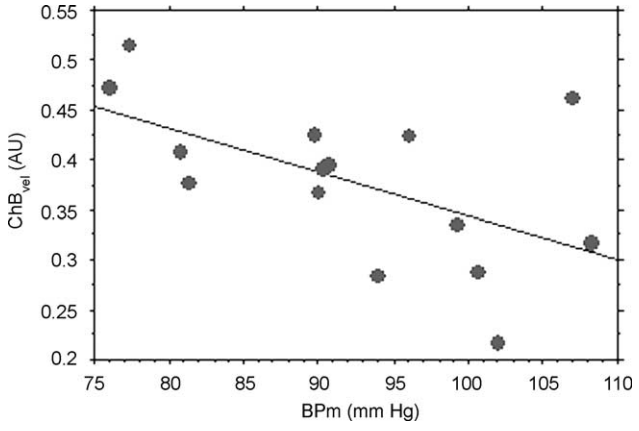

Fig. 2. Choroidal blood velocity (ChB_{Vel}) 180 min after sildenafil citrate (Viagra) treatment versus mean blood pressure (BPm). (Pearson correlation coefficient $=-0·56$, $P=0·03$). The solid line represents a regression line, $ChB_{Vel}=0·784-0·004$ BPm.

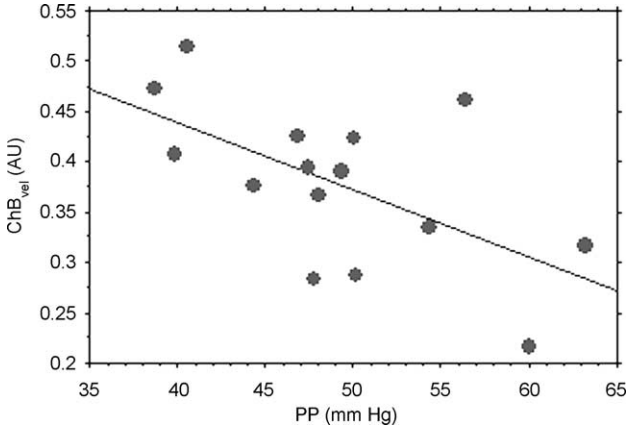

Fig. 3. Choroidal blood velocity (ChB_{Vel}) 180 min after sildenafil citrate (Viagra) treatment versus perfusion pressure (PP). (Pearson correlation coefficient $=-0·59$, $P=0·02$). The solid line represents a regression line, $ChB_{Vel}=0·707–0·007$ PP.

or may be at risk of ocular ischemic conditions. Indeed several cases of anterior ischemic optic neuropathy have been reported in patients receiving sildenafil (Egan and Pomeranz, 2000; Cunningham and Smith, 2001; Boshier et al., 2002; Pomeranz et al., 2002), although a casual relationship to the drug is rather uncertain, given that most of these patients had a variety of other risk factors for developing this condition.

Our results do not show any statistically significant change in the choroidal circulation in spite of a significant decrease in BPm and PP at 30 min. In a passive vascular system, a decrease in a mean blood pressure and perfusion pressure would be accompanied by a parallel decrease in flow. The lack of significant change in blood flow may be due to the ability of the choroid to autoregulate in an attempt to maintain a constant choroidal blood flow in spite of changes in perfusion pressure. The inverse correlation between BPm, PP and ChB_{Vel} further supports this hypothesis. In other words, larger decreases in mean blood pressure and perfusion pressure were accompanied by larger increase in ChB_{Vel}, a response aimed at maintaining a constant choroidal perfusion.

Our data are in agreement with the findings of McCulley et al. (2002), who assessed chororidal thickness with ultrasonography in a group of 13 normal subjects. Their data did not show any consistent increase in choroidal thickness after ingestion of 200 mg of sildenafil, a dose that is twice the highest recommended dose for the treatment of erectile dysfunction.

The results of this investigation are also consistent with our previous study of the effects of sildenafil citrate on the ocular circulation in normal healthy male volunteers that showed no changes in choroidal blood flow and optic nerve blood flow parameters (Grunwald et al., 2001).

Several studies have focused on the effects of sildenafil on retinal blood flow and retinal vessel diameters in normal subjects. Polak et al. (2003) have shown after 100 mg of sildenafil citrate a significant 15·7% increase in retinal blood flow by means of bidirectional laser Doppler Flowmetry, and a significant 4·7% increase in retinal venous diameters, using the Retinal Vessel Analyzer (RVA). These data are in agreement with those of: (a) Pache et al. (2002), who reported a 5·8% increase in both retinal arterial and venous diameter measured by RVA after administration of 50 mg of sildenafil; (b) Dundar et al. (2001) who reported increase in flow velocity in ophthalmic artery after 50 mg of sildenafil using color Doppler ultrasound imaging; and (c) Paris et al. (2001), who reported a 29% increase in pulsatile ocular blood flow (POBF). These results, however, are in disagreement with our previous study in which we did not detect a significant change in retinal vascular diameters following 100 mg of sildenafil in normal males (Grunwald et al., 2002). Because the retinal and choroidal circulations are very different it is possible that the effects of sildenafil may be quite different in these two vascular beds. Furthermore there is controversy as to what exactly POBF measures in terms of blood flow.

In comparison to placebo, we did not detect any statistically or clinically significant differences in Visual Acuity or Contrast Sensitivity scores after administration of sildenafil at any of the time points. Birch et al. (2002) also reported no changes in VA in AMD patients at 3 and 7 hr after sildenafil treatment. In normal individuals, Dundar et al. (2001) reported similar VA results 1 hr after treatment with 50 mg of sildenafil. McCulley et al. (2002) also observed no changes in CS in a group of normal volunteers at 0, 90 and 180 min after treatment with 200 mg of sildenafil. Food and Drug Administration (FDA f) Joint Clinical Review (1998) also reported no changes in visual acuity and CS in healthy male volunteers taking 200 mg of sildenafil. However, Paris et al. (2001) reported 33·6% increase in 7·5 Hz temporally-modulated Contrast Sensitivity.

There were no visual adverse events noted during our study, a finding similar to the report of Birch et al. (2002) in a small group of age-related macular degeneration patients taking 100 mg of sildenafil citrate.

In summary, our results show no significant effect of sildenafil citrate on the circulation of the foveolar choroid in patients with AMD, a result that may be reassuring for AMD patients that may have decreased choroidal blood flow.

Competing interest statement: None of the authors had any commercial or proprietary interest in the product or company. None of the authors received payment as a consultant, reviewer, or evaluator.

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