SCIENTIFIC CORRESPONDENCE

Sildenafil induces retinal vasodilatation in healthy subjects

Mona Pache, Peter Meyer, Christian Prünte, Selim Orgül, Ines Nuttli, Josef Flammer

Br J Ophthalmol 2002;**86**:156–158

Background: The cardiovascular effects of sildenafil (Viagra), a selective inhibitor of phosphodiesterase type 5 (PDE5), have been extensively studied. However, its effect on human retinal arteries and veins has not yet been investigated. The effect of a single dose administration of sildenafil on the retinal vessel diameters of healthy subjects was evaluated.
Methods: Sildenafil 50 mg was administered to 10 healthy subjects (male:female = 4:6; mean age 31 (SD 6) years). The diameters of retinal arteries and veins were measured by means of a retinal vessel analyser (RVA) immediately before and at 30, 60, 90, and 120 minutes after sildenafil uptake. Blood pressure, heart rate, and intraocular pressure were monitored in parallel.
Results: A significant increase of 5.8% ($p<0.001$) in both retinal arterial and venous diameters was found 30 minutes after sildenafil uptake. The diameters returned to baseline after 120 minutes. A mild systemic hypotensive response was seen. Changes in heart rate and intraocular pressure were not observed.
Conclusion: Sildenafil causes a significant dilatation of retinal arteries and veins in healthy subjects. A possible role for PDE5 in the regulation of retinal blood flow is implicated.

Sildenafil, a selective inhibitor of phosphodiesterase type 5 (PDE5), is the first licensed oral drug treatment for erectile dysfunction.[1] Inhibition of PDE5 is known to increase the level of cyclic guanosine monophosphate (cGMP), an intracellular messenger effecting vasodilation by relaxation of smooth muscle in arterioles.[2] Production of cGMP from guanosine triphosphate (GTP) is mediated through the nitric oxide (NO) signalling pathway. By inhibiting PDE5, sildenafil increases cGMP levels and thereby potentiates the NO elicited effect.[3]

The efficacy of sildenafil has been described not only for the corpus cavernosum,[1] but also for coronary arteries,[4] coronary resistance vessels,[5] pulmonary vessels,[6] and various other tissues.[7]

Recent ophthalmological studies of the retinal side effects of sildenafil mainly focused on transient blue/green tinge to vision, increased light sensitivity, and blurred vision, these being attributed to sildenafil's weak inhibition of PDE6, an enzyme involved in the phototransduction process.[8 9] Less attention has been paid to the possible inhibitory effects of PDE5 on ocular blood flow.

It has been demonstrated that NO functions as one of the most important modulators of vascular smooth muscle tone.[10] NO is continuously released by the endothelium of the ophthalmic artery and of the retinal arteries. Therefore, it can be hypothesised that sildenafil might increase the vasodilating effect of NO in the retinal circulation because of its inhibitory effect on PDE5. Indeed a sildenafil induced increase of blood velocity in the retinal microcirculation has recently been reported.[11] However, its effect on the smooth muscle containing retinal arteries and veins, important vascular determinants of retinal blood flow, has not yet been investigated. Therefore, using the newly developed retinal vessel analyser (RVA), we evaluated the diameter response of retinal vessels of healthy subjects to single dose administration of sildenafil.

SUBJECTS AND METHODS

Study population

Ten healthy subjects (male:female = 4:6; mean age 31 (SD 6) years) were included in this study. The subjects were screened for ocular and systemic diseases. A detailed medical and ophthalmological history was taken, and all subjects completed an ophthalmological examination. Exclusion criteria were pregnancy, a history of ocular or systemic disease, a history of alcohol or nicotine abuse, and any acute or chronic systemic or topical medication. All participants gave written informed consent for all procedures. The protocol was approved by the ethics committee of the department of internal medicine, University Hospital Basle, Switzerland and followed the tenets of the Helsinki declaration.

Protocol

Subjects were studied after pupil dilatation with tropicamide (Mydriaticum Dispersa, CibaVision, Switzerland). After a 20 minute resting period in the seated position, baseline measurement of the retinal vessels with the RVA was performed. The diameter of a segment of the superior temporal artery and the corresponding vein of the left eye was recorded for 30 seconds in each subject. The segment was located within two disc diameters of the optic nerve head. Blood pressure (BP) and heart rate were simultaneously monitored by automatic sphygmomanometry (Vitagnost 600, MARS, Taiwan). Additionally, intraocular pressure (IOP) of the right eye was measured by means of Goldmann tonometry. After establishment of baseline values a single dose of sildenafil 50 mg (Viagra, Pfizer, Zurich) was then administered to each subject. All parameters were measured again at 30, 60, 90, and 120 minutes after sildenafil uptake.

Method

Retinal vessel diameters were evaluated using a retinal vessel analyser (RVA, Imedos, Weimar, Germany). Technical details have been described extensively elsewhere.[12 13] In brief, the RVA consists of a charge coupled device (CCD) camera fitted to a fundus camera (Zeiss FF 450 IR, Carl Zeiss, Jena, Germany), a real time monitor, and a personal computer with analysing software. Fundus images are digitised using a frame grabber. Retinal vessel diameters are analysed in real time with a maximum frequency of 50 Hz, while the fundus image can be inspected on the real time monitor and stored on a video recorder. The region of interest is defined as a rectangle on the screen of the real time monitor, with the window including a retinal artery or a retinal vein or both. Retinal vessel diameters

Table 1 Venous and arterial diameters at baseline and at 30, 60, 90, and 120 minutes after sildenafil administration. Data are presented as mean (SD) (n=10)

Time after sildenafil administration (minutes)	Venous diameter (arbitrary units)	p Value	Arterial diameter (arbitrary units)	p Value
Baseline	137 (23)		111 (11)	
30	145 (25)	<0.001	117 (12)	<0.001
60	145 (25)	<0.001	116 (12)	<0.001
90	142 (24)	0.001	114 (11)	0.013
120	141 (23)	0.025	111 (10)	0.750

One way ANOVA for repeated measures for venous diameter: F(4.36) = 10.9, p<0.0001; for arterial diameter: F(4.36) = 12.0, p<0.0001. p Values indicate significance of difference between values at baseline and sildenafil administration (*p<0.005).

are then calculated along the arterial or venous segment within the rectangle. Providing the vessel segment under study remain within the selected rectangle, the system automatically corrects for eye movements. The retinal vessel diameters are presented in arbitrary units. We tested short term reproducibility of retinal vessel diameter in a similar setting. The coefficient of variation (CV) was 2–3%. This was in accordance with data provided by the manufacturer (CV of 2.2%).

Statistical analysis

To test for potential differences in retinal vessel diameter, BP, and heart rate over the time course (baseline, 30, 60, 90, and 120 minutes) we performed one way ANOVAs for repeated measures with Huynh-Feldt correction to adjust sphericity in the covariance matrix. Post hoc comparisons were performed with the Bonferroni-Dunn procedure for alpha adjustments of the multiple comparisons. Data are expressed as mean (SD).

RESULTS

Administration of 50 mg sildenafil resulted in a significant increase (p<0.001) of both retinal arterial and venous diameter. Arterial diameter increased by 5.8% above baseline 30 minutes after sildenafil administration. At 60 minutes after drug uptake, arterial diameter was 5.1% above baseline levels. At 90 and 120 minutes after sildenafil uptake, arterial diameter values no longer differed significantly from baseline (Table 1 and Fig 1). Venous diameter increased by 5.8% above baseline 30 minutes after drug uptake. This increase in venous diameter was maintained after 60 minutes, but decreased to 3.7% after 90 minutes and then normalised to baseline after 120 minutes (Table 1 and Fig 2). Absolute values of arterial and venous diameter are presented in Table 1.

Thirty minutes after drug uptake, sildenafil induced a mild but significant (p<0.0015) reduction of mean arterial BP, combined with a significant increase in heart rate (p<0.0004). Details of these parameters are given in Table 2.

Baseline IOP was 13 (SD 2) mm Hg. IOP did not vary significantly throughout the study.

DISCUSSION

In this study we examined the effect of sildenafil on the retinal vessel diameter of healthy subjects by means of the RVA. Single dose administration of 50 mg sildenafil resulted in a significant increase in both arterial and venous retinal diameters within 30 minutes. This was followed by a gradual decline towards baseline values during the succeeding 90 minutes.

The time course of the vasodilatory effect of sildenafil on retinal arteries and veins shows the same pattern as found in the corpus cavernosum[1] and various other human tissues.[4 5 7]

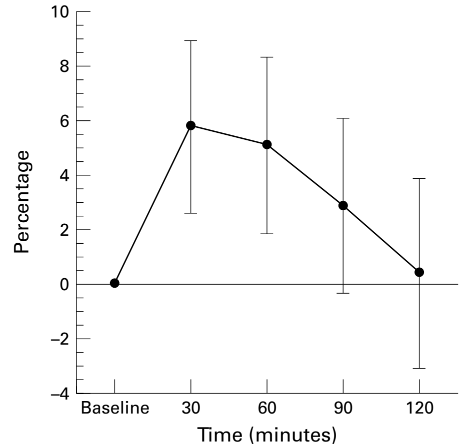

Figure 1 Percentage change (mean (SD), n = 10) of retinal arterial diameter 30, 60, 90, and 120 minutes after sildenafil administration in comparison with untreated baseline.

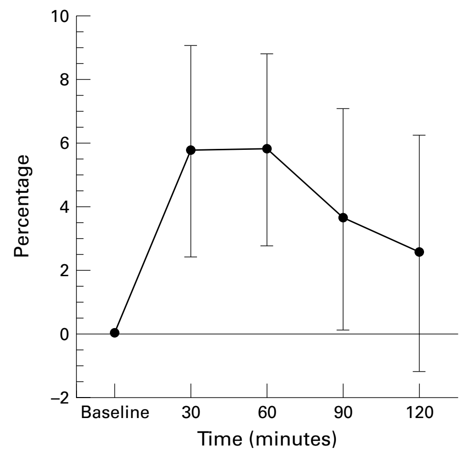

Figure 2 Percentage change (mean (SD), n = 10) of retinal venous diameter 30, 60, 90, and 120 minutes after sildenafil administration in comparison with untreated baseline.

Therefore, the same mechanism of action might be presumed. In the corpus cavernosum, the cavernous nerves release NO, which induces cGMP formation and thereby smooth muscle relaxation during sexual stimulation. Sildenafil facilitates the erectile process by inhibiting PDE5 and therefore the breakdown of cGMP.[2 14]

It has been shown that the retinal vessel endothelium continuously produces NO that maintains the retinal vessels in a constantly dilated state.[10] Assuming the existence of PDE5 in the retinal vasculature, it can be hypothesised that sildenafil administration might augment the vasodilatory effect of NO by blocking the breakdown of cGMP as it does in the corpus cavernosum.

Functionally, retinal arteries and veins act as arterioles and venules. As vascular resistance is inversely correlated with the fourth power of the radius of a blood vessel, small changes in diameter have a substantial influence on the blood flow through the vessel.[15] Therefore the increase in retinal vessel diameter by 5.8% observed in this study should lead to a considerable increase of retinal blood flow, if blood velocity is assumed constant.

However, it is completely unclear whether the observed vasodilatation of the large retinal arteries and veins leads to an increase of flow and whether it interferes with retinal autoregulation. An increase of blood velocity after sildenafil treatment has, however, been documented by other authors.[11]

Table 2 Systolic BP, diastolic BP, and pulse rate at baseline and at 30, 60, 90, and 120 minutes after sildenafil administration. Data are presented as mean (SD) (n=10)

Time after sildenafil administration (minutes)	Systolic blood pressure (mm Hg)	p Value	Diastolic blood pressure (mm Hg)	p Value	Pulse rate (beats/min)	p Value
Baseline	115.8 (7.7)		72.8 (4.3)		67 (9)	
30	109.4 (6.0)	<0.001	67.2 (3.9)	0.027	75 (8)	<0.001
60	112.1 (9.5)	0.039	70.7 (9.3)	0.393	68 (9)	0.562
90	109.8 (8.0)	0.001	69.9 (5.6)	0.241	69 (7)	0.400
120	110.2 (10.6)	0.003	71.6 (6.3)	0.625	66 (5)	0.400

One way ANOVA for systolic BP: F(4.36) = 4.7, p<0.004; for diastolic BP: F(4.36) = 1.51, p<0.22; for pulse rate: F(4.36) = 6.6, p<0.0004. p Values indicate significance of difference between values at baseline and sildenafil administration (*p<0.005).

NO donors such as sodium nitroprusside and isosorbide mononitrate, which also increase cGMP levels, have been reported to increase retinal and optic nerve head blood flow.[13 16–18] Given this fact, sildenafil might have the potential to influence ocular perfusion in a similar manner. On the other hand, there are reports of retinal vascular occlusions,[19] anterior ischaemic optic neuropathy[20] and exacerbation of proliferative diabetic retinopathy[21] after sildenafil uptake. These might be coincidental events, but should not be neglected. They could be possible hints to a sildenafil induced disturbance of retinal autoregulation (for example, in the case of elderly patients with additional cardiovascular diseases).

Therefore, our study has some limitations that deserve comment: firstly, we examined only healthy young subjects with a presumed intact retinal autoregulation. Whether sildenafil exerts a comparable effect on retinal vessels of elderly patients with concomitant cardiovascular diseases is not yet clear. Owing to a pre-existing disturbance of the retinal autoregulation, patients with cardiovascular risk factors such as arterial hypertension and diabetes, or young subjects suffering from a vascular dysregulation, might present a different reaction to sildenafil administration.

Furthermore, the observed effect of sildenafil on retinal vessels was accompanied by a mild drop in systemic blood pressure and a slight increase in heart rate. As human retinal vessels are autoregulated, a mild vasodilatation can be expected if a drop of systemic blood pressure occurs.[15] It is, however, unlikely that this mild decrease of blood pressure explains the observed 5.8% extent of retinal vasodilatation on its own.

Whether PDE5 is indeed present and functionally important in retinal vessels will be evaluated in future studies. Furthermore, the influence of sildenafil in patients with vascular diseases is clinically significant and as yet unknown.

ACKNOWLEDGMENTS

The authors thank Walthard Vilser and Kurt Kräuchi for helpful scientific discussions, and Thomas Riemer for his competent introduction to the operation of the RVA. Furthermore we would like to thank all volunteers who kindly participated in this study.

Authors' affiliations

M Pache, P Meyer, C Prünte, S Orgül, I Nuttli, J Flammer, University Eye Clinic Basel, Switzerland

Correspondence to: Josef Flammer, MD, University Eye Clinic Basel, Mittlere Strasse 91, PO Box, CH-4012 Basel, Switzerland; josef.flammer@uhbs.ch

Accepted for publication 18 July 2001

REFERENCES

1 **Goldstein I**, Lue TF, Padma-Nathan H, *et al*. Oral sildenafil in the treatment of erectile dysfunction. Sildenafil Study Group. *N Engl J Med* 1998;**338**:1397–404.
2 **Corbin JD**, Francis SH. Cyclic GMP phosphodiesterase-5: target of sildenafil. *J Biol Chem* 1999;**274**:13729–32.
3 Sildenafil for erectile dysfunction. *Drug Ther Bull* 1998;**36**:81–4.
4 **Saeki T**, Adachi H, Takase Y, *et al*. A selective type V phosphodiesterase inhibitor, E4021, dilates porcine large coronary artery. *J Pharmacol Exp Ther* 1995;**272**:825–31.
5 **Traverse JH**, Chen YJ, Du R, *et al*. Cyclic nucleotide phosphodiesterase type 5 activity limits blood flow to hypoperfused myocardium during exercise. *Circulation* 2000;**102**:2997–3002.
6 **Abrams D**, Schulze-Neick I, Magee AG. Sildenafil as a selective pulmonary vasodilator in childhood primary pulmonary hypertension. *Heart* 2000;**84**:E4.
7 **Wallis RM**, Corbin JD, Francis SH, *et al*. Tissue distribution of phosphodiesterase families and the effects of sildenafil on tissue cyclic nucleotides, platelet function, and the contractile responses of trabeculae carneae and aortic rings in vitro. *Am J Cardiol* 1999;**83**:3C–12C.
8 **Gonzalez CM**, Bervig T, Podlasek C, *et al*. Sildenafil causes a dose- and time-dependent downregulation of phosphodiesterase type 6 expression in the rat retina. *Int J Impot Res* 1999;**11 Suppl 1**:S9–14.
9 **Vobig MA**. Retinal side-effects of sildenafil. *Lancet* 1999;**353**:1442.
10 **Haefliger IO**, Flammer J, Luscher TF. Nitric oxide and endothelin-1 are important regulators of human ophthalmic artery. *Invest Ophthalmol Vis Sci* 1992;**33**:2340–3.
11 **Sponsel WE**, Paris G, Sandoval SS, *et al*. Sildenafil and ocular perfusion. *N Engl J Med* 2000;**342**:1680.
12 **Vilser W**, Riemer T, Bräucher-Burchardt C. Retinal vessel analyzer (RVA)—a new measuring system for examination of local and temporal vessel behaviour. *Invest Ophthalmol Vis Sci* 1997;**38**:S1050.
13 **Polak K**, Dorner G, Kiss B, *et al*. Evaluation of the zeiss retinal vessel analyser. *Br J Ophthalmol* 2000;**84**:1285–90.
14 **Corbin JD**, Francis SH, Osterloh IH. Effects of sildenafil on cAMP and cGMP levels in isolated human cavernous and cardiac tissue. *Urology* 2000;**56**:545.
15 **Delaey C**, Van De Voorde J. Regulatory mechanisms in the retinal and choroidal circulation. *Ophthalmic Res* 2000;**32**:249–56.
16 **Grunwald JE**, Iannaccone A, DuPont J. Effect of isosorbide mononitrate on the human optic nerve and choroidal circulations. *Br J Ophthalmol* 1999;**83**:162–7.
17 **Iannaccone AE**, DuPont J, Grunwald JE. Human retinal hemodynamics following administration of 5-isosorbide mononitrate. *Curr Eye Res* 2000;**20**:205–10.
18 **Donati G**, Pournaras CJ, Tsacopoulos M. Effect of nitroprusside on arteriolar constriction after retinal branch vein occlusion. *Invest Ophthalmol Vis Sci* 1998;**39**:1910–7.
19 **Tripathi A**, O'Donnell NP. Branch retinal artery occlusion; another complication of sildenafil. *Br J Ophthalmol* 2000;**84**:934–5.
20 **Egan R**, Pomeranz H. Sildenafil (Viagra) associated anterior ischemic optic neuropathy. *Arch Ophthalmol* 2000;**118**:291–2.
21 **Burton AJ**, Reynolds A, O'Neill D. Sildenafil (Viagra) a cause of proliferative diabetic retinopathy? *Eye* 2000;**14(Pt 5)**:785–6.

Sildenafil induces retinal vasodilatation in healthy subjects

Mona Pache, Peter Meyer, Christian Prünte, et al.

Br J Ophthalmol 2002 86: 156-158
doi: 10.1136/bjo.86.2.156