Effect of sildenafil on ocular haemodynamics

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CLINICAL STUDY

Abstract

Purpose **To study the effect of sildenafil, which is an effective agent for the treatment of erectile dysfunction, on ocular haemodynamics.**

Methods **In this prospective study we examined the effect of a single oral dose of 50 mg sildenafil (Viagra) in a group of healthy young male volunteers, by using colour Doppler ultrasound imaging to measure haemodynamic variables in the central retinal artery (CRA), short temporal posterior ciliary artery (STPCA) and ophthalmic artery (OA). The following examinations were performed on both eyes immediately before and 1 h after a single oral dose of 50 mg sildenafil: visual acuity, intraocular pressure (IOP), colour vision, anterior segment, fundus appearance, resting heart rate, blood pressure and colour Doppler measurements.**

Results **After sildenafil administration, peak systolic velocity, mean velocity and end-diastolic velocity significantly increased in the OA of both eyes. All Dopper indices remained non-significant for the CRA and STPCA of both eyes. Sildenafil did not cause any significant change in IOP, colour vision, visual acuity, systolic blood pressure or diastolic blood pressure. However, heart rate measurements increased significantly after sildenafil administration compared with baseline ($p = 0.003$).**

Conclusion **The increased flow velocity in the ophthalmic artery seems to be due to a vasodilator effect of sildenafil.**

Key words Central retinal artery, Colour Doppler ultrasound, Ophthalmic artery, Sildenafil

Sildenafil (Viagra, Pfizer), an oral agent which has proven effective for the treatment of erectile dysfunction, is a novel inhibitor of the human cGMP-specific phosphodiesterase type 5 enzyme (PDE 5) found in human corpus cavernosum. This agent enables a natural erectile response to sexual stimulation by enhancing the relaxant effect of nitric oxide (NO) on the corpus cavernosum.[1–4] Although the role of sildenafil in erectile dysfunction is well understood and has been described in detail, ocular effects of sildenafil are still lacking. There are some reports in the literature on the retinal side-effects of sildenafil.[5,6] However, to our knowledge, no data are available on the ocular haemodynamic effects of sildenafil.

Colour Doppler imaging (CDI) is a non-invasive method for measuring blood flow velocity of the retrobulbar circulation *in vivo*. This is an ultrasound technique that combines B-scan grey-scale imaging of tissue structure, coloured representation of blood flow based on Doppler shifted frequencies and pulsed Doppler measurement of blood flow velocities.[7–12]

This study was designed to analyse the effect of a single oral dose of 50 mg sildenafil on the retrobulbar circulation in a group of healthy young male volunteers by means of CDI.

Materials and methods

Subjects

Fourteen healthy sexually active male volunteers between 20 and 38 years of age (average 27.01 years) were studied. Informed consent was obtained from all participants. The subjects showed no evidence of any clinically significant disease, or clinically significant abnormality following review of laboratory data and full physical examination, and none were taking medications. All had a normal eye examination with a best-corrected visual acuity of 20/20 or better. The intraocular pressure (IOP) was 19 mmHg or less and the anterior segment and fundus examinations within the normal range.

Study design

A single oral dose of 50 mg sildenafil was administered to 14 healthy male volunteers. The following tests were performed on both eyes immediately before and 1 h after sildenafil administration: visual acuity, IOP (Goldmann applanation tonometry), colour vision, anterior segment, fundus appearance, resting heart rate, blood pressure and colour Doppler measurements. The maximum effect of single dose administration has been reported to be at 1 h for sildenafil.[13] Therefore, 1 h after sildenafil administration, we repeated the tests.

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Table 1. *Heart rate, intraocular pressure, systolic blood pressure and diastolic blood pressure before and after sildenafil administration*

	Baseline	Sildenafil	*p* value
Heart rate (beats/min)	80.14 ± 8.16	92.28 ± 14.6	0.003
BP, systolic (mmHg)	128.2 ± 18.7	124.6 ± 17.7	0.061
BP, diastolic (mmHg)	79.6 ± 10.1	79.6 ± 10.8	0.85
IOP, right eye (mmHg)	15.46 ± 3.31	15.7 ± 3.2	0.32
IOP, left eye (mmHg)	15.07 ± 3.15	15.3 ± 2.8	0.52

Values are the mean ± SD.
BP, blood pressure; IOP, intraocular pressure.

Colour Doppler imaging

CDI was carried out using a colour Doppler ultrasound machine (Hitachi EUB 555). A linear-array high-resolution 7.5 MHz probe was used for imaging of the globe. All measurements were performed by one experienced sonographer (Y.D.). With the subject in supine position sterile ophthalmic gel was applied as a couplant to the closed eyelid, and the probe was positioned gently with minimal pressure. Peak systolic velocity (PSV), end-diastolic velocity (EDV) and mean velocity (MV) of the ophthalmic artery (OA), central retinal artery (CRA) and short temporal posterior ciliary arteries (STPCA) were measured in both orbits. After measurement of the flow velocities, the resistance index (RI) and pulsatility index (PI) were subsequently calculated by computer for each vessel measured. RI and PI are calculated as follows:

RI = PSV–EDV/PSV
PI = PSV–EDV/MV

Statistical analysis included a Wilcoxon rank-sum test. A *p* value of less than 0.05 was considered statistically significant.

Results

There was no significant effect of sildenafil on visual acuity and colour vision. None of the volunteers complained about visual disturbances after sildenafil. The examinations of anterior and posterior segments of the eye did not reveal any abnormality after drug administration. No statistically significant difference in IOP, systolic blood pressure or diastolic blood pressure was noted after sildenafil administration compared with baseline values ($p > 0.05$, Table 1). However, heart rate increased significantly after sildenafil administration compared with baseline ($p < 0.05$, Table 1).

Tables 2–4 show PSV, EDV, MV, RI and PI in the CRA, OA and STPCA calculated at baseline and after sildenafil administration. After sildenafil administration PSV, EDV and MV significantly increased in the OA of both eyes ($p < 0.05$, Table 2). All Doppler indices remained non-significant for CRA and STPCA of both eyes ($p > 0.05$, Tables 3, 4).

Discussion

Sildenafil is a highly selective inhibitor of PDE5, responsible for the breakdown of cGMP in the corpus cavernosum.[14–16] Inhibition of cGMP degradation allows for normal penile erection by the NO-cGMP-mediated relaxation pathway.[17,18] PDE5 is also found in platelets and vascular smooth muscle cells.[19]

Sildenafil has been proven to be an effective treatment in patients with impotence of no known organic or definable cause such as diabetes mellitus.[20,21] In addition, the drug is mostly used in elderly patients – an age group who may have age-related ocular diseases such as macular degeneration and numerous ocular vascular disorders. Many of the adverse affects of sildenafil may be related to the presence of PDE5 in tissues other than the corpus cavernosum or to the effects of the drug on PDE6.[4,22] *In vitro* studies have shown that PDE6, found in retinal photoreceptors, modulates the transduction cascade.[19,23,24] Sildenafil is mainly a specific PDE5 inhibitor and it is roughly 10% as effective in blocking PDE6.[6,14] Vobig and colleagues[5] reported a decrease in the a-wave and b-wave amplitudes in the electroretinogram after oral administration of 100 mg sildenafil and these changes completely disappeared 5 h later. Results of all other electrophysiological and clinical tests such as visual acuity, colour vision and IOP were normal. In our study, we did not observe any change in visual acuity, colour vision and IOP, similar to Vobig *et al.*[5]

A previous study by Jackson *et al.*[25] on the cardiovascular effects of sildenafil in healthy volunteers showed a significant reduction in systolic and diastolic blood pressure after intravenous administration and no significant change in heart rate. Webb *et al.*[26] also showed that sildenafil produced an average decrease of approximately 10 mmHg in blood pressure after a single oral dose of 100 mg. However, Sipsky *et al.*[27] reported modest increases in heart rate and mild decreases in blood pressure after sildenafil administration across all stimulation conditions in premenopausal women with

Table 2. *Colour Doppler ultrasound measurements at baseline and after sildenafil administration in the ophthalmic artery*

	Right eye			Left eye		
	Baseline	Sildenafil	*p* value	Baseline	Sildenafil	*p* value
PSV	42.12 ± 7.34	50.48 ± 15.1	0.048	40.85 ± 7.35	51.19 ± 13.74	0.035
EDV	13.61 ± 4.53	18.49 ± 5.64	0.019	13.75 ± 3.18	17.57 ± 5.22	0.047
MV	22.00 ± 5.82	27.80 ± 9.04	0.035	21.39 ± 4.30	27.93 ± 8.35	0.022
RI	0.67 ± 0.07	0.64 ± 0.07	NS	0.69 ± 0.07	0.65 ± 0.06	NS
PI	1.34 ± 0.35	1.20 ± 0.29	NS	1.29 ± 0.35	1.25 ± 0.27	NS

Values are the mean ± SD.
PSV, peak systolic velocity; EDV, end-diastolic velocity; MV, mean velocity; RI, resistance index; PI, pulsatility index.

Table 3. *Colour Doppler ultrasound measurements at baseline and after sildenafil administration in the central retinal artery*

	Right eye			Left eye		
	Baseline	Sildenafil	*p* value	Baseline	Sildenafil	*p* value
PSV	9.95 ± 2.28	9.69 ± 2.24	NS	9.89 ± 2.57	10.67 ± 1.30	NS
EDV	2.91 ± 0.80	3.22 ± 1.19	NS	3.21 ± 1.07	3.56 ± 0.92	NS
MV	5.47 ± 1.46	6.34 ± 1.79	NS	5.75 ± 1.34	6.70 ± 1.47	NS
RI	0.69 ± 0.07	0.66 ± 0.09	NS	0.67 ± 0.1	0.66 ± 0.07	NS
PI	1.28 ± 0.32	1.18 ± 0.35	NS	1.15 ± 0.19	1.18 ± 0.24	NS

Values are the mean ± SD.
PSV, peak systolic velocity; EDV, end-diastolic velocity; MV, mean velocity; RI, resistance index; PI, pulsatility index.

spinal cord injury. Our results confirmed no significant effect of sildenafil on systolic and diastolic pressure. However, a significant increase in heart rate was observed after sildenafil administration when compared with placebo, similar to Sipsky *et al.*[27] This finding is in accordance with the role of sildenafil as a mild vasodilator. Although the haemodynamic results of the present study showed some discrepancy with the literature, this may be related to the difference in dosage and administration of the drug. Shirasaki *et al.*[28] reported that the relaxation responses to the nitrovasodilators were reduced progressively with ageing in their experimental study on healthy rats. The alteration in heart rate may also be explained by the younger age of our study group.

In humans, the haemodynamic effects of sildenafil have been investigated in the forearm.[25] A modest vasodilatation of resistance arteries and a reversal of noradrenaline-induced preconstriction of forearm veins were observed after brachial artery infusion of sildenafil. Modest reductions in systemic vascular resistance were also observed with sildenafil administration. It was postulated that sildenafil is a modest vasodilator, producing a haemodynamic balance between decreased arterial resistance and increased venous compliance. The mechanism is likely to be due to a potentiation of the endogenous NO-cGMP pathway.

In the eye, to our knowledge, no data are available on the haemodynamic actions of sildenafil. Many different methods have been used to measure the dynamics of the ocular circulation *in vivo*. CDI was shown to offer reproducible measures in the ophthalmic and central retinal arteries. However, the reproducibility of velocities from the posterior ciliary vessels is variable and thus less reliable.[29]

The main result from the present study is that PSV, EDV and MV of the OA increased significantly. An increase in flow velocity in the OA during sildenafil administration does not necessarily indicate increased blood flow, as both vessel diameter and velocity are required for this determination. No technique is currently available to measure retrobulbar vessel diameter accurately and non-invasively. However, previous studies showed that changes in CDI velocity measures are highly predictive of changes in volumetric flow in cerebral vessels both *in vitro* and *in vivo*, and our data therefore may indicate an increase in ophthalmic artery blood flow.[30–32]

Sildenafil augments the effect of NO by preventing the degradation of cGMP. NO is a potent vasodilator and plays an important role in the regulation of vascular tone.[33,34] There is evidence that ocular blood vessels are innervated by NO-producing neurons.[35,36] It has also been reported that NO regulates the ocular circulation and is a very potent modulator of vascular tone in human ophthalmic arteries.[37] Schemetterer *et al.*[38] showed that L-arginine, an inhibitor of NO synthase, decreased mean flow velocity in the OA in healthy subjects. The results of our study confirm this finding. On the basis of these findings we propose that increased flow velocity may be due to the vasodilatory effect of sildenafil.

Limitations of this study include the relatively small number of subjects and the lack of a control group for comparison. Nevertheless, our study shows that oral sildenafil increased ophthalmic artery systolic, diastolic and mean blood flow velocity in healthy male volunteers. The significance of this remains to be determined. As more information becomes available about the effect of sildenafil on the retinal circulation we may need to consider situations in which the medicine may be beneficial or detrimental to the retinal and/or optic nerve head circulations. Conditions in which retinal ischaemia is present may benefit from the medication. The effect of increased flow on retinal oedema will also need to be

Table 4. *Colour Doppler ultrasound measurements at baseline and after sildenafil administration in the short temporal posterior ciliary artery*

	Right eye			Left eye		
	Baseline	Sildenafil	*p* value	Baseline	Sildenafil	*p* value
PSV	9.87 ± 3.32	9.79 ± 3.02	NS	10.32 ± 2.36	11.27 ± 3.12	NS
EDV	3.37 ± 1.28	3.22 ± 1.35	NS	3.49 ± 1.21	3.85 ± 1.32	NS
MV	5.82 ± 2.06	5.63 ± 1.81	NS	6.08 ± 1.51	6.44 ± 1.74	NS
RI	0.65 ± 0.06	0.66 ± 0.07	NS	0.66 ± 0.07	0.65 ± 0.05	NS
PI	1.11 ± 0.13	1.19 ± 0.28	NS	1.14 ± 0.22	1.59 ± 1.63	NS

Values are the mean ± SD.
PSV, peak systolic velocity; EDV, end-diastolic velocity; MV, mean velocity; RI, resistance index; PI, pulsatility index.

evaluated. The same considerations may need to be taken into account when using systemic medications which are known to be vasodilators.

More extensive and controlled studies are necessary to clarify the mode of action of sildenafil on retinal function and ocular circulation and to study the long-term effects of the drug in patients with retinal diseases.

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