Central Retinal Vein Occlusion Associated With Sildenafil (Viagra)

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Abstract

Objectives
To report the occurrence of a severe, blinding and irreversible adverse effect following use of the drug sildenafil citrate (Viagra).

Methods
This is a case report of a 60 year old man who presented with unilateral, sudden-onset, painless, visual loss following the use of sildenafil citrate 100mg twice weekly, prescribed for his erectile dysfunction. Examination revealed a visual acuity of 6/6 in the right eye and counting fingers left eye. His left fundus showed marked, diffuse disc edema, extensive retinal hemorrhages in all quadrants, engorged retinal veins and cotton wool spots on the macula. His intraocular pressures were 27mmHg right eye and 25mmHg left eye.

Results
Fundus fluoresceine angiography confirmed left ischemic central retinal vein occlusion.

Conclusion
Central retinal vein occlusion is a possible adverse effect of sildenafil use. Physicians should be vigilant while prescribing this medication and avoid its use in patients with elevated intraocular pressure.

Key Words: Sildenafil, Central retinal vein occlusion, Adverse effects, Erectile dysfunction

Introduction

Sildenafil citrate is an oral medication widely used for the treatment of erectile dysfunction. It is a selective phosphodiesterase inhibitor which enhances smooth muscle relaxation in the blood vessels and lacunar spaces and allows inflow of blood in the corpus carvenosum. Because of its vascular and visceral smooth muscle effects the use of sildenafil has been extended to other conditions including idiopathic pulmonary arterial hypertension and pulmonary hypertension secondary to underlying lung disease.[1,2]

However, its use has been associated with several systemic and ocular adverse effects. Systemic adverse effects observed with the drug include headache, flushing, dyspepsia and nasal congestion.[3] The most common severe ocular adverse effects reported have been cases of non-arteritic anterior ischemic optic neuropathy (NAAION). At least 14 sildenafil-associated cases of this blinding disease have been reported in the literature.[4]

Sildenafil use has also been associated with alterations in color hue and brightness.[5] Two cases of sildenafil-associated central retinal vein occlusion (CRVO) have been reported in the literature.[6,7] We report a case of CRVO in a patient using sildenafil for erectile dysfunction and advise physicians to be aware of this possible complication.

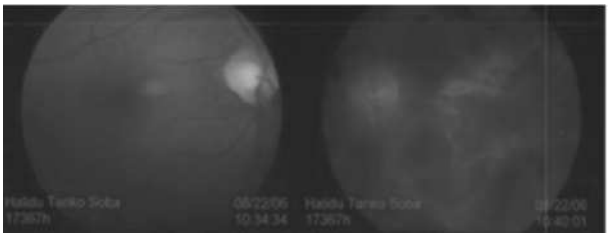
Case Report

A 60 year old man presented to the out-patient clinic with a history of sudden, painless, loss of vision in the left eye on waking from sleep in the morning. He reported having severe headache early that morning. He had experienced similar episodes of early morning headache in the past whenever he used the drug sildenafil citrate (Viagra; Pfizer Pharmaceutical Group, New York, US) prescribed for his erectile dysfunction. He had been on Viagra 100mg twice a week for three months prior to presentation. In spite of the headache he continued to use the drug because he found it very helpful. The night before presentation, he had taken 100mg of the drug around 10pm. Past ocular history was uneventful except for presbyopia. Past medical history was significant for erectile dysfunction and low sperm count. He was neither hypertensive nor diabetic. There was no

history of similar or other ocular disease in his family. None of his family members had hypertension or diabetes mellitus.

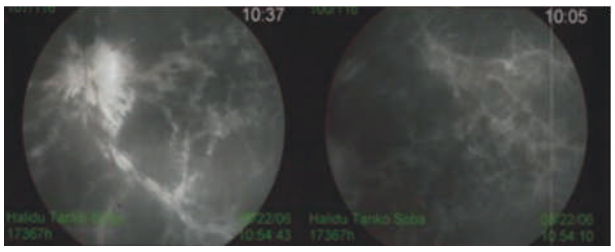
His general systemic examination was normal with pulse rate 86 beats per minute and blood pressure 100/70 mmHg sitting up. Ocular examination revealed visual acuity of 6/6 in his right eye and counting fingers (CF) in the left eye. The anterior segment of the right eye was normal with pupil size 2mm and brisk pupillary reflex. The right fundus was normal with a vertical cup-to-disc ratio of 0.4. The anterior segment of the left eye was normal except that the pupil was 3mm with reduced pupillary light reflex but no relative afferent pupillary defect. The left fundus showed marked diffuse disc edema, extensive retinal hemorrhages involving all retinal quadrants, engorged retinal veins and cotton wool spots on the macula (Picture 1).

Picture 1: Fundus Picture of Right and Left Eyes.



The intraocular pressures were 27mmHg right eye and 25mmHg left eye (Perkins). Gonioscopy showed normal and open angles in both eyes while perimetry was normal in the right eye with global central visual field depression in the left eye. Clinical diagnoses of left CRVO secondary to sildenafil use and ocular hypertension were made. Fundus fluoresceine angiography confirmed left ischemic CRVO (Picture 2).

Picture 2: Fundus Fluoresceine Angiography of the Left Eye.



The patient was advised to stop taking Viagra and placed on topical timolol 0.5% twice daily. Laboratory investigations revealed normal fasting blood glucose (4.2mmol/L), normal total cholesterol (2.57mmol/L) and elevated triglycerides (5.80mmol/L). His full blood count, erythrocyte sedimentation rate, platelet count and C-reactive protein were normal.

Four days after presentation, a relative afferent pupillary defect was detected in the left eye and the visual acuity remained CF. He was educated on his condition and oral acetylsalicylic acid 150mg daily added to his medication.

Discussion

Sildenafil is commonly prescribed for men with erectile dysfunction. Penile erection is dependent on sexual stimulation which leads to the release of nitrous oxide (NO) which in turn induces the formation of cyclic guanosine monophosphate (cGMP). cGMP signals the corpus cavenosum smooth muscle to relax, allowing inflow of blood, leading to erection of the penis. Sildenafil enhances the effect of NO on the smooth muscle relaxation by inhibiting phosphodiesterase 5 (PDE5) which is responsible for degrading cGMP, thereby increasing the level of cGMP and sustaining penile erection.[8]

Ocular adverse effects of erectile dysfunction agents can be categorized based on the World Health Organization Casualty Assessment Guide into those that are 'certainly' due to the drug; changes in color and light perception, blurred vision, conjunctival hyperemia, ocular pain, photophobia and those that are 'possibly' due to the drug; mydriasis, subconjunctival hemorrhage, ischemic optic neuropathy and retinal vascular accidents.[9] The altered color and brightness perception is thought to be caused by sildenafil's inhibitory action on phosphodiesterase 6 in the retinal photoreceptors.[5] Most of the other adverse effects are thought to be caused by the vasodilatory effect of sildenafil. The endothelium of the ophthalmic and retinal arteries are known to continuously release NO which is an important modulator of vascular smooth muscle tone. Indeed immunohistochemical analysis has demonstrated the localization of PDE5 in endothelial and smooth muscle cells of retinal and choroidal vessels.[10]

Sildenafil reaches peak plasma concentration within 2 hours of ingestion and elevated levels are present in blood for 8-12 hours.[11] Our patient had been taking sildenafil before sleeping at night sporadically for 3 months. He had episodes of early morning headache associated with the medication. On the eventful day, he had taken sildenafil before sleep and had severe headache and visual loss on awakening which was within the 8-12 hours of drug activity. It is our considered opinion that the CRVO was acutely and temporally related to the ingestion of sildenafil.

Headache and flushing are the most frequently reported acute adverse effects of sildenafil.[3]

They are thought to be related to the nocturnal hypotension caused by sildenafil's vasodilatory effect. Indeed some of the patients reported to have sildenafil associated NAAION had similar headaches and eye pain.[4] An open-label trial of sildenafil in Nigeria had reported headache as the most common adverse effect (6.9%), with transient, mild visual haziness in one patient (1.7%).[12] Another study had observed severe flushing and headache with bilateral superior visual field depression after ingesting 200mg of sildenafil.[13] The time course of drug ingestion, headache and visual loss in our patient supports the probability of sildenafil-induced CRVO.

CRVO is a blinding condition with no known cure. Its pathogenesis involves occlusion of the central retinal vein in the region of the lamina cribrosa where the central retinal vein and artery share a common adventitia. Current opinion is that arteriosclerosis leads to thickening of the central retinal artery which compresses the central retinal vein leading to secondary changes including stasis, endothelial cell loss and thrombus formation.[14] The known risk factors for CRVO include diabetes, systemic hypertension and glaucoma. The evidence for dyslipidemia, high body mass index and smoking are less consistent.[14] Our patient had no evidence of diabetes or systemic hypertension. Although he had elevated triglycerides, its association with CRVO is uncertain.

The patient had ocular hypertension and there is an association between CRVO and ocular hypertension. The prevalence of glaucoma and ocular hypertension are significantly higher in patients with CRVO than in the general population.[15] Although the pathogenesis is unclear and thought to be multifactoral, it is postulated that glaucoma and ocular hypertension by producing stasis in the central retinal vein may contribute to CRVO.

Sildenafil-related CRVO has been reported twice in the literature.[6,7] Its pathogenesis is not yet known. We postulate that in our patient, the sporadic use of sildenafil caused repeated cycles of vasodilation, leading to stasis and thrombus formation in the setting of elevated intraocular pressure. Further studies will be required to prove this association and the development of a model for testing the relationship between sildenafil and CRVO will be invaluable. Meanwhile physicians should be encouraged to be vigilant and report these adverse effects. Also all men presenting with CRVO should be questioned on the use of sildenafil since they may not volunteer this information spontaneously.

Conclusion

We conclude that sildenafil should be avoided in patients with elevated intraocular pressure and arteriosclerotic risk factors. The drug should not be prescribed in patients with unilateral CRVO because it may increase the risk of CRVO in the fellow eye

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