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Original Article

Ocular Side Effects of Sildenafil: A Prospective Study

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Abstract

Background: Sildenafil citrate (Viagra) is a drug commonly used for the treatment of impotence and pulmonary hypertension. There have been reports of adverse ocular side effects on the administration of these drugs. However, the reports are not consistent, and also very few studies have been done in India and practically none from Eastern India.

Materials and Methods: Standard equipment for visual acuity, visual field, tonometry, Vitreal study, retina and fundus, ocular computerized tomography, electroretinogram, visually evoked potential, fundus fluorescent angiography was used. 100 patients to be put on sildenafil for their medical problem were studied for ocular status and then again after 6 months' sildenafil therapy. 100 healthy persons were also studied before and after giving placebo. The results of the two groups were compared, analyzed, and inference drawn.

Results: About 7 out of test subjects receiving sildenafil had errors in refraction, compared to 5 in controls. Obviously, this was not clinically significant. Only two of those receiving sildenafil reported bluish visual flush that also only those receiving sildenafil in high doses, that is, 100 mg or above. Only one in the test population reported diplopia. 7 of the test subjects showed conjunctival redness. Cataract was noted in none, either in controls or test subjects. Vitreal pathology in the form of vitreal detachment or traction was observed in 3 test subjects. In 4 of the test subjects, intraocular pressure was raised. Paramacular edema was found in two test subjects. Retinal ischemic features were detected in 11 test subjects who received sildenafil for more than 6 months in any dose. Our findings tallied well with studies from abroad, and the main side effects we encountered were conjunctival injection and ischemic ocular retinopathy.

Conclusion: Mentionable acute side effect of sildenafil is bluish visual flash. Some clinically significant patterns of effects, following long-term administration, are also recognized, of which retinal ischemic blockade is the most prominent one.

Key words: Ischemic optic neuropathy, Ocular side effects of sildenafil, Sildenafil

INTRODUCTION

Trobe, MD, the noted neuro-ophthalmologist of the University of Michigan, aptly commented: "Patients who take erectile dysfunction drugs also have other reasons to get ischemic optic neuropathy. But patients who use these drugs-especially those who have vision in only one eye-are entitled to know that they may be at risk for this condition."[1] Two commonly used drugs prescribed for the treatment of men with erectile dysfunction are: Sildenafil citrate (Viagra) and tadalafil. Having diverted blood flow from the head these two drugs cause two problems, *viz.*, blue vision by interfering with neurotransmission within the retina which is by the way just a temporary side effect and the second one is ischemic optic neuropathy which is of course a permanent one. However, it is difficult to establish a cause-effect relationship in this case because like as we find in case of amiodarone therapy, patients who take this drug might also get ischemic optic neuropathy due to other reasons. However, patients who use these drugs are definitely at risk for ocular side effects.[2]

According to Dr. Fraunfelder, in addition to vision having a blue hue, patients can also see shimmering around objects.[3]

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These drugs can cause central serous retinopathy, which is a collection of fluid in the macular and paramacular areas of the retina, and can also cause subconjunctival hemorrhages.[4] However, a recent study found that there is "lack of conclusive evidence to indicate a direct cause-effect relationship between phosphodiesterase enzyme type 5 (PDE5) inhibitor use and vision-threatening ocular events. Men who use PDE5 inhibitors appear to suffer vision-threatening complications at the same frequency as the general population."[5] The study found that minor visual adverse effects occur in 3-11% of users and that they are reversible.

At present, there are several drugs available for oral treatment of erectile dysfunction, but Viagra (sildenafil citrate) is the very first of this kind. Its main function is to inhibit cGMP-specific PDE5. This enzyme is found in high concentrations in the vascular smooth muscle cell as well as in the smooth muscle cells of corpus cavernosum. Other than the latter, it is also found, though in lesser concentrations in blood vessels of the systemic circulation.[6] In as much as sildenafil acts as a mild vasodilator, it was at one time envisaged as could have been a potential antianginal agent but that study totally fell flat.[7] Sildenafil is also a weak inhibitor of PDE6.[7] PDE6 is an enzyme present in high concentrations in the retina, particularly in the light receptor cells cones and rods.[8] The plasma half-life of sildenafil is about 4 h and reaches a peak plasma concentration in about 1 h.[8] In flexible-dose studies, visual abnormality in the form of a blue vision or flush was found to occur in 3% of patients treated with sildenafil where subjects received a high but fixed dose of sildenafil from the beginning of the study in the range 100-200 mg.[9] It is assumed that the effects of sildenafil on vision are probably due to concomitant inhibition of the retinal PDE6 enzyme by sildenafil.[10]

Under the above-noted background, we ventured to study the morbidity pattern of side effects of sildenafil on the ocular system in our medical college in Kishanganj, Bihar, India.

MATERIALS AND METHODS

Case Selection

A total of 100 persons, between 18 and 70 years of age, all males, attending the Medicine OPD of MGM Medical College and LSK Hospital, Kishanganj, Bihar, and were getting sildenafil for the treatment of impotence, pulmonary hypertension, or for any other reason were randomly selected as subjects in the present study. They were thoroughly checked for ocular health before the commencement of sildenafil therapy. In our study, only errors of refraction were allowed, but persons with other initial ocular defects were rejected from the study. The same was also applied for controls. 100 male healthy persons were selected as controls, and they were given a placebo instead of sildenafil for 6 months. Thus, necessary data from 200 eyes were obtained.

Exclusion Criteria

A. All females of any age to keep uniformity of study
B. Males of <18 years age and more than 70 years were excluded from the study
C. Persons suffering from systemic illnesses such as diabetes mellitus, essential hypertension which themselves can have adverse effects on eyes
D. Persons getting drugs other than sildenafil, which can affect eyes
E. Persons already suffering from diseases of the eye before starting sildenafil, except minor errors of refraction
F. Individuals with history or signs of surgical and/or laser interference upon eye
G. Subjects who did not agree to give written consent.

Before commencement of the study permission of the college authorities, IEC, and written consent from participants were obtained.

Equipment Used

1. Snellen's chart
2. Jaeger's chart
3. Humphrey's visual field analyzer
4. Streak retinoscope
5. Ophthalmoscope: Direct and indirect
6. Fundus lens
7. Fundus fluorescent angiography (FFA) instruments
8. Ocular computerized tomography (OCT) apparatus
9. Visual evoked potential recorder
10. Ocular tonometer.

Clinical Study

All subjects and controls were first subjected to standard clinical examination in the MOPD preceded by usual history-taking, and followed by common laboratory tests. Being assured that these were within normal limits they were then officially registered as either subjects or controls.

These registered persons were then brought to ophthalmology OPD for ocular examinations. After a simple naked eye examination with torch and eye loop, they were then tested for acuity of vision regarding both near and distant vision with Snellen's and Jaeger's chart. Now, they were examined by direct and indirect ophthalmoscopy before and after pupillary dilatation. A streak retinoscopy was also done as also ocular tonometry.

The retina was then examined with fundus lens, FFA, and electroretinography. Subsequently, visual evoked potentials and OCT were also performed.

Data obtained from each eye by the above methods were corroborated.

Data Analysis

Data obtained from the clinical study were analyzed using Microsoft Excel. The findings of the controls were compared with those of the subjects receiving sildenafil.

RESULTS

The results of this study are given in Table 1 and Figure 1.

DISCUSSION

Our results show that 7 out of test subjects receiving sildenafil had errors in refraction, compared to 5 in controls. Obviously, this was not clinically significant. Only two of those receiving sildenafil reported bluish visual flush that also only those receiving sildenafil in high doses, that is, 100 mg or above. Only one in the test population reported diplopia. 7 out of 60 test subjects showed conjunctival redness. Cataract was noted in none, neither in controls nor test subjects. Vitreal pathology in the form of Vitreal detachment or traction was observed in 3 test subjects. In 4 of the test subjects, intraocular pressure (IOP) was raised. Paramacular edema was found in two test subjects. Retinal ischemic features were detected in 11 test subjects who received sildenafil for more than 6 months in any dose.

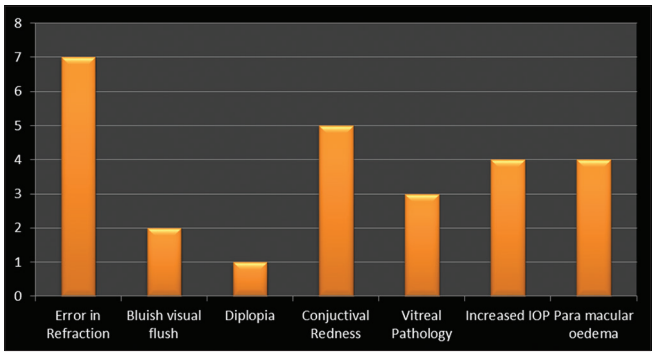

Figure 1: The ocular effects of sildenafil in column diagram

Studies done by previous workers showed that sildenafil did not have any noticeable ocular effect during short-term use except bluish visual flashes that also when suddenly put on a high dose (>100 mg).[11] However, when given for a long period, sildenafil does produce ocular side effects. These are discussed hereunder.

- According to reports by Pfizer[12] ocular side effects occur in:
  - About 3% of men taking doses of 25-50 mg
  - About 11% taking 100 mg doses
  - About 50% of men taking 200 mg
  - Nearly all men taking 600-800 mg.

In one report of the FDA Office of Post marketing drug risk assessment, it is mentioned that there have been a few cases of signs and symptoms suggesting conjunctival vasodilatation following sildenafil therapy.[13] The commonly occurring presentations of this type are: Conjunctival injection, ocular redness, bloodshot appearance, and ocular burning. Two instances of extraocular muscle paresis have also been documented. One case reported that in the American Journal of Ophthalmology[14] mentioned that an oculomotor nerve paresis but not affecting pupil was found to occur in a 56-year-old man with the pre-existing microvascular disease 36 h after he took a 50 mg dose of sildenafil. Again an abducent nerve palsy in a 76-year-old man with diabetes was found in another case. Other commonly reported complaints within the eye observed with sildenafil therapy are: Posterior vitreous detachment, retinal hemorrhage, and vascular occlusion. However, they were more common in individuals with preexisting diabetes mellitus, and these reports were not very frequent either.[15]

In early animal studies with sildenafil, it was found that sildenafil inhibits retinal PDE6 enzymes with an IC50 of 27-58 nM.[16] This was substantially less than its effect on the intended target, PDE5 (IC50 3.9 nM), and therefore, from this it could be presumed that sildenafil is safe for eye in its standard dose therapy. Yet, the evaluation of the safety of high doses of sildenafil on retinal histopathology was undertaken in rats and dogs as also on electroretinograms (ERGs) in the dog.[17] As the plasma

Table 1: Comparison of ocular abnormalities between healthy controls and persons getting sildenafil

Population type	Error in refraction	Bluish visual flush	Diplopia	Conjunctival redness	Cataract	Vitreal pathology (detachment/traction)	Increased IOP	Paramacular edema	Retinal hemorrhage
Healthy controls	05	Nil	Nil	Nil	Nil	Nil	Nil	Nil	Nil
Subjects getting sildenafil for 6 months	07	02	01	05	Nil	03	04	04	Nil

IOP: Intraocular pressure

levels of sildenafil decreases, the ocular side effects also decrease pari passu.[17]

Subsequent to the animal studies, studies were done to investigate the visual effects of sildenafil in human clinical studies also. These studies were done in three phases, *viz.*, Phase I, Phase II, and Phase III studies, that is, short-term, intermediate-term, and long-term studies.

In both Phase I and Phase II studies, sildenafil did not produce clinically significant changes in visual acuity, ERGs, IOP, contrast sensitivity, or pupillometry measurements compared with placebo. If however, a single oral dose of 100 and 200 mg was applied, a transient impairment of color discrimination in the blue/green range was detected using the Farnsworth-Munsell Hue test. However, these effects were fully reversible, dose related. Further study also failed to demonstrate any side effect on visual performance in any of the subjects.[18] Overall, sildenafil was generally well tolerated in this limited sample of patients.[19] In more than 50 countries, extensive use of sildenafil almost confirms well-toleration of the drug in general population.[20]

Another point that we need to distinguish actual drug effect for attribution of vascular events to sildenafil is from too much exertion during sexual arousal which obviously happens after sildenafil therapy.

CONCLUSIONS

Overall, current clinical data suggest that treatment with sildenafil can cause short-term, transient, reversible effects on color discrimination in the blue-green range with few if any clinically significant effects on other acute visual function tests. Some clinically significant patterns of effects, following long-term administration, are presently recognized. Of these, the retinal ischemic blockade is the most prominent one.

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