Review

Effects of Erectile Dysfunction Drugs on Eyes

Hui Yang, Xinzu Gu, Xiulan Zhang, Changxian Yi
Zhongshan Ophthalmic Center, Sun Yat-sen University, Guangzhou 510060, China

Abstract

With the increasingly extensive application of erectile dysfunction (ED) drugs, it is of importance for an ophthalmologist to understand the association between ED drugs and human eyes. In this study, we retrospectively studied the effects of ED drugs on human eyes, including visual symptoms, ophthalmological electrophysiology, ocular blood flow, intraocular pressure, visual field, retina, cerebral hemodynamics and nervous system and retinal blood vessels, particularly focusing on the relationship between these agents and nonarteritic ischemic optic neuropathy (NAION), in order to highlight the ocular adverse effects induced by these agents thus contributing to preventive measures.

Introduction

Currently, the orally administered first-line drugs against erectile dysfunction (ED) included sildenafil (brand name: Viagra), vardenafi (brand name: Cialis) and tadalafil (brand name: Levitra). According to the statistical data from Pfizer, about 23 000 000 men from all over the world had used sildenafil since it was approved for clinical application in 1998. The elderly people who account for a large proportion in patients with eye conditions are at high risk both for developing intraocular vascular diseases and for experiencing ED that requires medication therapy. Therefore, these patients need useful advice from a professional ophthalmologist. More importantly, ED drugs have a direct influence on the retinal chemical metabolism, showing an unidentified long-term safety for eyes. In addition, a majority of patients administered with ED drugs are aged people with baseline retinal diseases, thus susceptible to the adverse effects and toxicity of the agents. Therefore, it is of importance to understand the association between ED drugs and eyes, for which, the recent development of the effect of ED drugs on human eyes was reviewed as follows in this article.

DOI: 10.3969/g.issn.1000-4432.2011.02.013
Corresponding author: Hui Yang, E-mail: yanghui9@hotmail.com

Mechanisms of ED drugs

ED drugs are selective inhibitor of cGMP-specific phosphodiesterase 5 (PDE 5), which is distributed in the smooth muscle, functioning to suppress the relaxation of smooth muscle triggered via nitric oxide (NO)-cGMP pathway. Through inhibiting PDE5, ED drugs strengthen this pathway, relaxing the smooth muscle at the cavernous body, thus enhancing the blood flow to penis and the erectile function. Moreover, ED drugs can also slightly inhibit cGMP-specific phosphodiesterase 6 (PDE 6), which is distributed in the retinal rod and cone cells, playing a role in visual transduction cascade reaction. The inhibitory effect of sildenafil on PDE 6 is one tenth of that on PDE 5.

Effects of ED drugs on eyes

Visual symptoms

It is a commonsense that ED drugs can lead to the occurrence of visual symptoms, most of which are mild and transient changes in color vision such as blue halo or enhanced sensitivity to light stimuli. It is well-known that these are related to the inhibition to PDE 6 in the rod and cone cells by ED drugs. The emergence of visual symptoms is roughly consistent with the changes in blood levels of ED drugs: appearing at 1 hour after administration and disappearing at 3 to 4 hours later. These symptoms were only observed in 3% of patients with low-dose medication (25 mg–50 mg), but increased to 11% and 50% after a 100 mg and 200 mg of exposure, respectively.

Even at a dose as high as 200 mg, ED drugs were not observed to have effects on visual acuity, con-

trast sensitivity, visual fields and/or papillary reaction[1]. However, at the maximal blood concentration after a single dosing of 200 mg, the subjects showed difficulties in distinguishing the slight color discrepancy, especially in the blue green color region.

Electrophysiological change

Animal studies and clinical trials showed that ED drugs are similar to other PDE inhibitors in directly inhibiting the photoreceptor. Although a large dose of sildenafil may inhibit ocular electrophysiological reaction, this inhibitory effect is illegible at the clinical standard dosage.

For the animal studies, as reported by FDA in 1998[2], electroretinography (ERG) demonstrated that sildenafil could directly inhibit the retina in a dose-dependent manner: At the similar blood levels to those in human after a routine medication, only slight wave amplitude reduction and conduction delay were recorded in the electroretinogram in dogs, but these changes would become more conspicuous with the increase of doses. After exposure to the drug with its blood level 10 folds than that in human, a moderate amplitude reduction and obvious conduction delay of a-wave and b-wave was observed in ERG.

For the clinical trials, Balacco Gabrieli reported in 2001[3] and 2003[4] that the statistical significance was found on V_{max} and K-value in healthy volunteers who were administered with 50 mg of sildenafil. In 2004, a randomized, double-blinded and placebo-controlled clinical trial was conducted by Jagle et al[5] in male volunteers aged between 20 and 40 years old to evaluate the changes in ERG after a single oral ly dosing of 100 mg sildenafil. They found a markedly enhanced sensitivity and conspicuous conduction time delay in a-wave in dark adaption, b-wave in light adaption and 3.3 Hz of flash waves a and b. In 1999, Vobig et al[6] evaluated the effect of 100 mg of sildenafil on ERG from 5 volunteers, revealing that the markedly reduced amplitude of a-wave and b-wave in dark adaption restored 6 hours later and no changes in ERG in the light adaption was observed during the study. In 2001, after evaluating the ERG findings in 14 healthy volunteers who were administered with 200 mg of sildenafil, Luu et al[7] found that the single flash wave in light adaption attenuated markedly, 30 Hz flash wave delayed significantly and the multifocal ERG at the overall posterior pole delayed for 5-9%, with the strength decreased for 14-22%.

In brief, sildenafil can induce a slight and transient change in ERG, but no reports with regard to the long-term changes in ERG induced by ED drugs are available.

Changes in ocular blood flow

Previous studied showed that sildenafil could increase the choroid blood flow and dilate ophthalmic artery, but its effect on the blood flow of central retinal arteries and veins still remains unclear.

For the effect of the drugs on choroid blood flow, Paris et al[8] revealed in 2001 that sildenafil could increase choroid blood flow, which was demonstrated by a fact that the dosed 50 mg of the drug could increase around 30 percent of the ocular blood flow. In 2005, a prospective, double-blinded and placebo-controlled clinical trial was conducted by Koksal et al[9] in patients with ED who underwent color ultrasonography at 1 hour after orally taking 100 mg of sildenafil, but no change in the blood flow of central retinal arteries were observed, except the significant increase of peak systolic flow velocity, mean flow velocity and end diastolic flow velocity was observed in ophthalmic and short posterior ciliary arteries (SPCA). They attributed this dilative effect of sildenafil on the choroid arteries to the presence of intraelastic layer and smooth muscle in these vessels (thus increasing the blood flow of the ophthalmic artery and SPCA). In 2001, Dundar et al[10] evaluated the change in ocular blood flow in 14 healthy volunteers using color ultrasonography at 1 hour after they were administered with 50 mg of sildenafil. They found, other than short temporal posterior ciliary artery (STPCA) and central retinal artery, sildenafil had a marked vasodilative effect on the ophthalmic artery, with significantly increased peak systolic flow velocity, mean flow velocity and end diastolic flow velocity. The similar findings were reported by Kustular et al[11] in 2004, who evaluated the changes in the blood flow of central retinal artery using color ultrasonography in 39 patients with ED who were administered with 100 mg of sildenafil. However, in 2002, Pache et al[12] reported that, as evaluated using

a retinal blood vessel analyzer, the diameter of retinal arteries and veins increased 5.8% and lasted for 60 min in 10 healthy volunteers at 30 min after they took 50 mg of sildenafil. However, whether this was caused by the increased blood flow or a regulatory self-dilation of the retinal blood vessels to response to the systemic hypotension was not clarified yet.

Effects on intraocular pressure

There is no current evidence available showing that ED drugs have effects on intraocular pressure. As reported by Yjima et al[13] in 2000, sildenafil administered even as a high dose as 150 mg did not have effects on intraocular pressure. In 2001, Grunwald et al[14] reported that not any acute changes in intraocular pressure were observed in male patients with primary open angle glaucoma who were administered with 100 mg of sildenafil.

Effects on visual field

As reported by McCulley et al[15] in 2000, 4 of 5 volunteers administered with a high dose (200 mg) of sildenafil did not present with any changes in Humphrey field, but a remaining one person developed significant acute sensitivity impairment at the bilateral lower hemifields and the mean deviation decreased for 17.8 dB at the blue-yellow visual cursor (yellow background and blue stimulating cursor) and for 4.7 dB at the white-white visual cursor (white background and white cursor). Any positive conclusion was not made in that study due to the small sample size.

Effects on retina

In 2004, Alllibhai et al[16] reported a 37-year-old man who experienced a central serous retinopathy after six dosing of sildenafil (50 mg each). At 6 hours after the final administration, he developed an acute visual impairment, with the visual acuity decreased to 20/40, and continuously to 20/400 a week later. The impaired vision recovered spontaneously at 3 weeks after drug withdrawal. In 2005, Quiram et al[17] reported two cases of serous macular epithelial detachment after sildenafil medication (50–100 mg, twice to four times daily). The two patients either remitted completely or got improvement after drug withdrawal. Whether these phenomena are related to the increased choroid blood flow after exposure to sildenafil should be further evaluated.

Effects on cerebral hemodynamics and nervous system

In 2005, a double-blinded, placebo-controlled study was conducted by Diomedi et al[18] in 28 patients with ED who were administered with 50 mg of sildenafil to evaluate the mean cerebral blood flow velocity and mesemcephalic arterial pulse index using transcranial color ultrasonography and monitor the cerebrovascular reactivity using breath-holding index. The study showed that 50 mg of sildenafil could significantly improve the cerebrovascular reactivity, but had no effect on other hemodynamic parameters. By now, there are a number of case reports available describing brain vascular accidents after sildenafil medication. In 1998, Donohue and Taylor[19] reported a patient who developed a unilateral mydriasis (without oculomotor paralysis) at 36 hours after 50 mg of sildenafil medication. In 2001, Morgan et al[20] reported a case of sildenafil-related transient ischemia attack and subsequent stroke. This 50-year-old male patient did not have erection or sexual activity after medicated with 50 mg of sildenafil. At 2 hours after medication, the patient experienced right facial weakness, asophia, dysphagia, right limb perceive changes and right hemiparesis, all of which subsided 4 hours later. Six days later, he also experienced the same symptoms at 2 hours after 100 mg of sildenafil medication which did not result in a successful erection and sexual activity. The symptoms did not subside spontaneously and MRI revealed acute and subacute brain infarcts. He had previously received three doses of sildenafil (50 mg–100 mg) before this episode and each of them would cause a "strange feeling". In 2001, Monastero et al[21] reported a case of sildenafil-related cerebral hemorrhage. The 66-year-old patient presented with homonymous hemianopsia in the next morning after 20 mg of tadalafil medication and subsequent intercourse 6 hours later. In 2004, Marti et al[22] reported a 62-year-old man experienced left limb spasm after taking 50 mg of sildenafil and having sex, and the symptom was resulted from a small hemorrhagic focus at the right hypothalamic-encephalic region as demonstrated by the subsequent examination.

Effects on retinal blood vessels

In 2000, Tripathi and O-Donnell[23] reported a case of branch retinal artery obstruction developed in a 69-year-old man absent of vascular risk factors at several hours after he was administered with 100 mg of sildenafil. In 2003, Bertolucci et al[24] reported a hypertensive man who was in verapamil medication experienced a unilateral branch retinal artery obstruction during a sexual activity at 4 hours after 100 mg of sildenafil administration.

Associations with nonarteritic ischemic optic neuropathy (NAION)

Currently, there are a number of case reports describing the occurrence of NAION after exposure to ED drugs. Twelve of the reports involve sildenafil and other three involve tadalafil. In 2000, Egan and Pomeranz[26] reported the first case of sildenafil-related NAION. The patient was a 50-year-old man who suffered ED after undergoing a surgery against prostate cancer. Within 1 hour after the first sildenafil exposure, he experienced hidrosis, severe extensive headache, visible blue sparkle points in front of eyes and blurred vision, all of which lasted for 30 min. In the next evening, after he received the second dose of sildenafil (50 mg), the same symptoms emerged again and did not subside at this time. The ophthalmological examination demonstrated the diagnosis of NAION by the findings including bilateral visual acuity 20/20, left horizontal lower hemi-field defects and left visual disc edema. In 2001, Cunningham and Smith[27] reported a case of horizontal lower hemi-field defects in a 42-year-old male patient occurred in the next morning after he received the third dose of sildenafil (50 mg), manifested as bilateral visual acuity 20/20, relative introduction retardation in right pupil and visual disc edema, and was identified as NAION. In 2002, Pomeranz et al[25] reported 5 cases of sildenafil-related NAION, including the above-mentioned 2 cases. Four of the 5 cases did not present with vascular risk factors and all of the 5 cases were in presence of a risk factor for NAION-a small cup-disc ratio for the visual disc. For the onset time, 4 of the 5 cases occurred at several hours after administration, three of which occurred during the first exposure and the two remainders occurred at 1 to 2 years after repeated administration. In 2005, Pomeranz and Bhavsar[28] reported another 7 cases of sildenafil-related NAION. Six of the 7 patients developed visual impairment only within 24 hours after the first dosing and all of them had a vascular disease history. So, they proposed that the ED drug use history should be traced in all the patients with NAION and those with NAION in a single eye should be recommended to quit ED drugs.

There have been 3 cases of tadalafil-related NAION reported previously (by Peter et al[29]. in 2005; Escaravage et al[30] in 2005; and Bollinger and Lee[31] in 2005). The first case involved a 59-year-old man who developed ED after undergoing radial prostatotomy. After administered with 20 mg of tadalafil for 7 days, he experienced headache and blurred vision and was diagnosed as NAION. The second patient was a 59-year-old man who developed ED after prostatotomy. At 15 hours after medicated with 20mg of tadalafil, he reported dizziness, developed a lower hemi-field defect in one eye 45 hours later and diagnosed as NAION. The third patient was a 67-year-old patient with cholesterolemia history, who had received 5 doses of tadalafil (20 mg each) within 1 month. At 2 hours after the first four administrations, he showed a temporal lower visual field defect in the right eye, which subsided within 24 hours. However, the fifth medication resulted in a permanent visual field defect and diagnosed as NAION.

In July 2005, a patient prosecuted Pfizer due to a NAION after sildenafil medication. FDA considered that although a definite causality between NAION and ED drugs could not be validated, the relationship between the two reflected by the above-mentioned case reports was adequate to launch a modification to the labeling of these products, and they separately issued a warning for the relationship between ED drugs and NAION.

To clarify the relationship between ED drugs and NAION, in 2006, McGwin et al[33] conducted a retrospective study in 38 patients with ED and 38 healthy male volunteers with matched age. They did not find a higher ED drug use rate in NAION population than that in the controls, but the development of NAION was significantly correlated to the use of ED drugs in those with myocardial infarction history. Therefore,

they concluded that the application of ED drugs to male patients with a history of hypertension or myocardial infarction may increase the risk of NAION.

Conclusion

In conclusion, ED drugs may have effects on the ocular electrophysiological and hemorrhage performance, particularly having a potential to induce ischemic optic neuropathy. However, ocular side effects and negative impacts on human eyes should be noted and prevented during the application.

References

1 Food and Drug Administration Joint Clinical Review. Study 148-004: Phase I investigator-blind, placebo-controlled, evalustion of safety, toleration, and pharmacokinetics of sildenafil following escalating single oral doses in healthy male volunteers, pp 96-98.

2 Food and Drug Administration Joint Clinical Review. Study 148-223: A double-blind, randomized, placebo-controlled, four period crossover study to assess the effect of orally administered sildenafil (50, 100 and 200 mg) on visual function in healthy male volunteers, pp 160-161.

3 Food and Drug Administration Review and Evaluation of Pharmacology and Toxicology Data. Section 1.2.3.6 Pharmacology: Activities related to mechanism of action: Functional effects on other tissues expressing PDE5 enzyme: Retinal effects, 1998, pp19-21.

4 Balacco Gabrieli C, Regine F, Vingolo EM, et al. Subjective visual halos after sildenafil administration. Ophthalmology 2001; 108: 877-881.

5 Balacco Gabrieli C, Regine F, Vingolo EM, et al. Acute electroretinographic changes during sildenafil treatment for erectile dysfunction. Documenta Ophthalmologica 2003; 107: 111-114

6 Jagle H, Jagle CZ, Serey L, et al. Visual short-term effects of Viagra: Double-Blind study in healthy young subjects. Am J Ophthalmol 2004; 137: 842-849.

7 Vobig MA, Klotz T, Staak M, et al: Retinal side-effects of sildenafil. Lancet 353: 375, 1442, 1999.

8 Luu JK, Chappelow AV, McCulley TJ, et al. Acute effects of sildenafil on the electrortinogram and multifocal electroretinogram. Am J Ohthalmo 2001: 132: 388-394.

9 Paris G, Sponsel WE, Sandoval SS, et al. Sildenafil induces retinal vasodilatation in healthy subjects. Br J Ophthalmol 2002; 23: 355-358.

10 Koksal M, Ozdemir H, Kargi S, et al. The effects of sildenafil on ocular blood flow. Acta Ophthalmol Scand 2005; 83: 355-359.

11 Dundar SO, Dundar M, Ak IK, et al. Effect of sildenafil on ocular haemodynamics. Eye 2001; 15: 507-510.

12 Kurtulan E, Gulcu A, Secil M et al. Effects of sildenafil on ocular perfusion demonstrated by color Doppler ultrasonography. Int J Impotence Res 2004; 63: 534.

13 Pache M, Meyer, Prunte C, et al. Sildenafil induces retinal vasodilatation in healthy subjects. Br J Ophthalmol 2002; 86: 156-158.

14 Yajima T, Yajima Y, Koppiker N, et al. No clinically important effedts on intraocular pressure after short-term administration of sildenafil citrate (Viagra). Am J Ophthalmol 2000: 129: 675-676.

15 Grunwald JE, Jacob SS, Sui K, et al. Acute effects of sildenafil citrate (Viagra)on intraocular pressure in open-angle glaucoma. Am J Ophthalmol 2001; 132: 872-874.

16 McCulley Tj, Lam BL, Marmor MF, et al. Acute effects of sildenafil (Viagra) on blue-on-yellow and white-on-white Humphrey perimetry. J Neuro-Ophthalmol 2000, 20: 227-228.

17 Allibhai ZA, Gale JS, Sheidow TS. Central serous chorioretinopathy in a patient taking sildenafil citrate. Ophthalmic Surg Lasers Imaging 2004; 35: 165-167.

18 Quiran P, Dumars S, Parwar B Sarraf D. Viagra-associated serous macular detachment. Graefe's Arch Clin Exp Ophthalmol 2005; 243: 339-344.

19 Diomedi M, Sallustio F, Rizzato B, et al. Sildenafil increases cerebrovascular reactivity; A transcranial Doppler study. Neurology 2005; 65: 919-921.

20 Donahue SP and Taylor RJ. Pupil-sparing third nerve palsy associated with sildenafil citrate (Viagra). Am J Ophthalmol 1998; 126: 476-477.

21 Morgan JC, Alhatou M, Oberlies J, Johnston KC. Transient ischemic attack and stroke associated with sildenafil (Viagra) use. Neurology 2001; 57: 1730-1731.

22 Monastero R, Pipia C, Camarda LK.Transient ischemic attack and stroke associated with sildenafil (Viagra) use. Neurology 2001; 57: 1730-1731.

23 Marti I, Marti Masso JF. Hemiballism due to sildenafil use. Neurology 2004; 63: 534.

24 Tripathi A, O'donnaell NP. Branch retial artery occlusion; another complication of sildenafil. Br J Ophthalmol 2000; 84: 934-935.

25 Bertolucci A, Latkany RA, Gentile RC, et al. Hemirectial artery occlusion associated with sexual activity and sildenafil citrate (Viagra). Acta Ophthalmologica Scand 2003; 81: 198-200.

26 Egan R, Pomeranz H. Sildenafil (Viagra) associated

with anterior ischemic optic neuropathy. Arch Ophtalmol 2000;118:291-292.
27 Cunningham AV, Smith KH. Anterior ischemic optic neuropathy associated with Viagra. J Neuro-Ophthalmol 2001;21:22-25.
28 Pomeranz HD, Smith KH, Hart WM, et al. Sildenafil-associatted nonarteritic anterior ischemic optic neuropathy. Ophthalmology 2002; 109:584-587.
29 Pmeranz HD, Bhavsar AR, Nonarteritic ischemic optic neuropathy developing soon after use of sildenafil (Viagra):A report ofseven new cases. J Neuro-Ophtahalmol 2005; 25:9-13.
30 Peter NM, Singh MV, Fox PD. Tadalafill-associated anterior ischemic optic neuropathy. Eye 2005;19:715-717.
31 Escaravage GK, Wright JD, Givre SJ. Tadalafil associated with anterior ischemic optic neuropathy. Arch Ophthalmol 2005;123:399-400.
32 Bollinger K and Lee MS. Recurrent visual field defect and ischemic optic neuropathy associated with tadalafil rechallenge. Arch Ophthalmol 2005; 123:400-401.
33 McGwin G Jr, Vaphiades MS, Hall TA, et al. Non-arteritic anterior ischaemic optic neuropathy and the treatment of erectile dysfunction.Br J Ophthalmol. 2006 Feb;90 (2):154-157.

(from page 90)

V, et al. Detection of vascular endothelial growth factor messenger RNA and vascular endothelial growth factor-like activity in proliferative diabetic retinopathy. Arch Ophthalmol. 1994; 112(11):1476-1482.
24 Jo N, Wu GS, Rao NA. Upregulation of chemokine expression in the retinal vasculature in ischemia-reperfusion injury. Invest Ophthalmol Vis Sci.2003;44(9):4054-4060.
25 Yang Y, Zou L, Wang Y, et al. Axon guidance cue netrin-1 has dual function in angiogenesis. Cancer Biol Ther. 2007; 6(5):743-748.