포스포디에스테라아제-5 억제제 사용과 관련된 시신경병증

Optic Neuropathy Associated with the Use of Phosphodiesterase-5 Inhibitors

문인희, 강현승, 이성철, 김민

Inhee Moon, Hyun Seung Kang, Sung Chul Lee, Min Kim

연세대학교 의과대학 안과학교실 시기능개발 연구소

The Institute of Vision Research, Department of Ophthalmology, Yonsei University College of Medicine, Seoul, Korea

Purpose: To report a case of optic neuropathy associated with the use of phosphodiesterase-5 inhibitors.

Case summary: A 60-year-old male with no significant medical history presented with a headache and blurry vision in his left eye that had persisted for 3 days. He had been diagnosed with headaches, which was likely due to the use of phosphodiesterase-5 inhibitors (PDE-5i). His blood pressure was normal, and his best-corrected visual acuity was 16/20 in both eyes. His color vision, pupil light reflex, and relative afferent pupillary defect tests were normal. The right-eye visual field examination showed no signs of abnormality, but the left-eye visual field showed an inferior horizontal scotoma. Fundus examination showed disc edema in both eyes and disc hemorrhage in the left eye, while optical coherence tomography showed subretinal fluid at the nasal side of the fovea in the left eye and disc edema in both eyes. PDE-5i were discontinued, and a steroid was prescribed. The edema resolved after 8 weeks of tapering. Based on this study, discontinuation of PDE-5i and low dose steroid use may be helpful for optic neuropathy recovery.

Keywords: Optic disc hemorrhage; Optic neuropathy; Phosphodiesterase-5 inhibitor; Sildenafil; Viagra

Introduction

Phosphodiesterase-5 (PDE-5) inhibitors (PDE-5i) (Sildenafil, or Viagra®), the first-line oral pharmacotherapy for male erectile dysfunction, selectively inhibit PDE-5 in the corpus callosum [1]. These medications are known to cause transient visual disruptions by inhibiting phosphodiesterase type 6 (PDE-6), which mediates the phototransduction cascade of retinal photoreceptors [2]. Various ocular symptoms, such as transient visual loss, a change in color perception, a blue tinge to vision, an increase of photosensitivity, and visual disruptions, are also potential side effects of PDE-5i [2]. In addition, sildenafil can cause retinal hemorrhage, retinal vein

occlusion, and anterior ischemic optic neuropathy because of hemodynamic changes caused by changes in the cardiovascular system [2]. Cases of retinal hemorrhage, acute angle closure glaucoma attack, and hypertrophy of the inferior rectus muscle have been previously reported in Korea [3-5]. In this study, we report a case of optic neuropathy associated with the use of PDE-5i.

Case Report

A 60-year-old male with no previous significant medical history presented with headache and blurry vision in his left eye

Address reprint requests to Min Kim, MD, PhD

Department of Ophthalmology, Gangnam Severance Hospital, Yonsei University College of Medicine, #211 Eonju-ro, Gangnam-gu, Seoul 06273, Korea
Tel: 82-2-2019-3440, Fax: 82-2-3463-1049
E-mail: minkim76@gmail.com

Received: 2017. 7. 20

Revised: 2017. 10. 9

Accepted: 2017. 10. 16

Figure 1. Fundus photography, optical coherence tomography, fluorescence angiography, and visual field examination of the patient at first visit. (A, B) Optic disc swelling and disc hemorrhage were noted. (C, D) Fluorescence dye leakage around the disc was noted in both eyes. (E) Optic disc swelling was noted in both eyes. (F) Peripapillary subretinal fluid was noted in the left eye. (G, H) The right-eye visual field examination showed no specific signs, but examination of the left eye showed inferior horizontal scotoma. ONH = optic nerve head; RNFL = retinal nerve fiber layer; OU = oculus unitas; OD = oculus dexter; OS = oculus sinister; C/D ratio = cup/disc ratio; TEMP = temporal; SUP = superior; NAS = nasal; INF = inferior; S = superior; N = nasal; I = inferior; T = temporal; NA = normal arrange; GHT = glaucoma hemifield test; VFI = visual field index; MD = mean deviation; PSD = pattern standard deviation.

that had persisted for 3 days. He had no previous ophthalmological history, but had been diagnosed with headaches, possibly due to the use of PDE-5i. At initial presentation, his best-corrected visual acuity (BCVA), using a Snellen chart, was 16/20 in both eyes, with an intraocular pressure of 16 mmHg in his right eye and 18 mmHg in his left eye. Slit-lamp examinations showed no specific findings in the anterior segment, except for a mild cortical opacity in both lenses. His color vision test, pupil light reflex, and relative afferent pupillary defect (RAPD) tests were all normal. Fundus examination showed optic disc edema in both eyes and optic disc hemorrhage in his left eye (Fig. 1A, B), while optical coherence tomography showed subretinal fluid at the nasal side of the fovea in the left eye, and optic disc edema in both eyes (Fig. 1E, F). Fluorescein angiography showed fluorescent dye leakage around both optic discs (Fig. 1C, D). A visual field examination of the right eye showed no specific signs, but the left eye showed inferior horizontal scotoma (Fig. 1G, H). His blood pressure was 114/74 mmHg and his blood test

was normal, including a normal bleeding tendency.

Three weeks after his initial presentation, the symptoms persisted, and inferior horizontal scotoma in the left visual field exam was noted with RAPD 1+. Optic disc edema and hemorrhage were persistent (Fig. 2A, B). An oral steroid (60 mg) was prescribed while PDE-5i was discontinued. His symptoms improved with steroid therapy that was tapered over 1 month, and he did not experience changes in visual acuity. Optic disc edema and hemorrhage improved. The optic disc edema resolved (Fig. 2C, D) 8 weeks after the steroid treatment was stopped.

Discussion

The pharmacological action of sildenafil involves specific inhibition of PDE-5. This inhibition increases cyclic guanosine monophosphate (cGMP) levels, which causes smooth muscle relaxation of the corpora cavernosa and penile arteriolar

Figure 2. Fundus photography. (A, B) Optic disc swelling and disc hemorrhage after 3 weeks. (C, D) Reduced optic disc swelling and disc hemorrhage 8 weeks after steroid treatment was initiated.

smooth muscles. This relaxation leads to a drop in arterial resistance and increases blood flow into these tissues [6]. In the ocular system, PDE-5i inhibits PDE-5 which is expressed on retinal and choroid vessels and, to a lesser degree, on PDE-6, which is located on retinal rods and cones. PDE-6 is a unique isoenzyme with restricted localization to the retina, where it is located in the rod and cone outer segments, and plays a role in the conversion of light stimulation to electrical signals [7]. Serious ocular complications after treatment with PDE-5i have been previously reported. Previous reports include nonarteritic anterior ischemic optic neuropathy (NAION) with attendant visual loss, cilio-retinal artery occlusion, central retinal vein occlusion, and pupil sparing third nerve palsy [8,9].

PDE-5i can cause both optic nerve edema and disc hemorrhage. Sildenafil can affect choroidal blood flow and cause retinal hemorrhage, retinal vein occlusion, and NAION. Fraunfelder et al. [10] reported five cases of ischemic optic neuropathy after using PDE-5i. They suggested that ischemic changes of the optic nerve were related to an increase in blood flow due to nitric oxide increases after the use of sildenafil. There are two possible mechanisms that involve PDE-5i that have been proposed as a cause of optic neuropathy; PDE-5i can cause systemic hypotension or cause impaired local autoregulation at the optic nerve head in the

short posterior ciliary arteries [10]. However, neither of these possibilities has been conclusively proven or supported by animal models or human trials [10].

Our case showed different characteristics of optic neuropathy from previous cases of NAION, which involved optic disc edema and hemorrhage. These findings could be unique features of optic neuropathy that are associated with the use of PDE-5i. However, it is not clear whether the findings of this case are due to drug adherence alone or to other medical factors specific to the patient. The treatment approach included a natural discontinuation of PDE-5i to determine the relationship between the patient's symptoms and PDE-5i use. In addition, steroids were prescribed for ethical reasons. Neuro-ophthalmologists should be aware of this risk and should not prescribe PDE-5i in patients who have already experienced an episode of optic neuropathy in one eye.

In conclusion, PDE-5i may cause optic neuropathy. Discontinuing these inhibitors and prescribing low dose oral steroids may be helpful for effective treatment of this disorder.

Conflicts of interest

The authors have no conflicts to disclose.

References

1. Goldstein I, Lue TF, Padma-Nathan H, et al. Oral sildenafil in the treatment of erectile dysfunction. 1998. *J Urol* 2002;167(2 Pt 2):1197-203; discussion 1204.
2. Marmor MF, Kessler R. Sildenafil (Viagra) and ophthalmology. *Surv Ophthalmol* 1999;44:153-62.
3. Jang YS, Ahn GS, Kim SD. Retinal hemorrhage associated with viagra (sildenafil citrate). *J Korean Ophthalmol Soc* 2002;43:1340-4.
4. Lee WJ, Seong M. Bilateral simultaneous acute angle closure glaucoma following sexual intercourse aided by sildenafil citrate. *J Korean Ophthalmol Soc* 2011;52:1123-7.
5. Jung YH, Lee NY, Yim HB. A case of inferior rectus muscle enlargement after taking sildenafil citrate. *J Korean Ophthalmol Soc* 2013;54:382-6.
6. Jeon YH, Heo YS, Kim CM, et al. Phosphodiesterase: overview of protein structures, potential therapeutic applications and recent progress in drug development. *Cell Mol Life Sci* 2005;62:1198-220.
7. Lagnado L. The Wellcome Prize Lecture. Visual signals in the retina: from photons to synapses. *Exp physiol* 2000;85:1-16.
8. Brock GB, McMahon CG, Chen KK, et al. Efficacy and safety of tadalafil for the treatment of erectile dysfunction: results of integrated analyses. *J Urol* 2002;168(4 Pt 1):1332-6.
9. Bella AJ, Brant WO, Lue TF, Brock GB. Non-arteritic anterior ischemic optic neuropathy (NAION) and phosphodiesterase type-5 inhibitors. *Can J Urol* 2006;13:3233-8.
10. Fraunfelder FW, Pomeranz HD, Egan RA. Nonarteritic anterior ischemic optic neuropathy and sildenafil. *Arch ophthalmol* 2006;124:733-4.