Sildenafil-associated Nonarteritic Anterior Ischemic Optic Neuropathy

Howard D. Pomeranz, MD, PhD,[1] Kyle H. Smith, MD,[2] William M. Hart, Jr., MD, PhD,[3] Robert A. Egan, MD[4]

Purpose: To describe the clinical features of five patients who developed nonarteritic anterior ischemic optic neuropathy (NAION) after ingestion of sildenafil citrate (Viagra; Pfizer Pharmaceuticals, New York, NY).

Design: Retrospective observational case series.

Participants: Five patients with NAION who reported the use of sildenafil citrate before the onset of ocular symptoms.

Main Outcome Measures: The symptoms presented, history, ophthalmic examination, and visual field examination of each patient.

Results: Nonarteritic anterior ischemic optic neuropathy developed in one eye within minutes to hours after ingestion of sildenafil. Four of the five patients had no vascular risk factors for ischemic optic neuropathy. The patients all developed unilateral blurry vision, altitudinal visual field defects, and optic disc edema. Each of the patients was noted to have a small cup-to-disc ratio in the unaffected optic nerve.

Conclusions: Sildenafil citrate may be associated with NAION. A small cup-to-disc ratio may be a risk factor for development of NAION in association with the use of sildenafil. *Ophthalmology 2002;109:584–587 © 2002 by the American Academy of Ophthalmology.*

Sildenafil citrate (Viagra, Pfizer Pharmaceuticals, New York, NY) is a selective phosphodiesterase 5 inhibitor and partial phosphodiesterase 6 inhibitor and is prescribed for erectile dysfunction. By enhancing the effect of nitric oxide and cyclic guanosine monophosphate pathway (GMP), sildenafil leads to smooth muscle relaxation in the corpus cavernosum, allowing inflow of blood during sexual stimulation. Sildenafil is rapidly absorbed after oral administration and has a half-life of 4 hours. Maximum plasma concentrations are reached within 30 to 120 minutes of oral ingestion in the fasted state with slower rates of absorption after high-fat meals.[1] Sildenafil is well tolerated. Headache and flushing are the most frequently reported adverse events and may potentiate hypotension in patients taking nitrates.[1]

Ocular side effects with sildenafil use that are listed in the package insert include mild and transient color tinge to vision, increased sensitivity to light, blurred vision, mydriasis, conjunctivitis, eye pain, eye hemorrhage, cataract, dry eyes, diplopia, temporary vision loss, decreased vision, ocular redness or bloodshot appearance, ocular burning, ocular swelling/pressure, increased intraocular pressure, retinal vascular disease or bleeding, vitreous detachment/traction, and paramacular edema.[1] There are few ocular side effects associated with this medication reported in the ophthalmic literature. These include transient changes in brightness or color perception,[2] third nerve palsy,[3] and two cases of NAION.[4,5] Donahue and Taylor[3] reported a pupil-sparing third nerve palsy associated with sildenafil. Sildenafil has also been noted to cause a reversible visual disturbance through its presumed action on phosphodiesterase type 6 in photoreceptor outer segments in the retina.[4] Transient changes in perception of color hue or brightness have been reported with sildenafil, although the exact mechanism for these changes is unclear.

Two cases of nonarteritic anterior ischemic optic neuropathy (NAION) associated with sildenafil use have been reported.[4,5] Because evidence is emerging of additional patients diagnosed with NAION associated with use of sildenafil, we reviewed well documented cases to date and report five patients who developed NAION after ingesting sildenafil. Included in this case report series are the cases previously published by Egan and Pomeranz[4] (patient 1), and by Cunningham and Smith[5] (patient 3).

Patients and Methods

Five patients who developed NAION subsequent to ingestion of sildenafil were identified from the medical records of four neu-

Originally received: March 14, 2001.
Accepted: July 17, 2001. Manuscript no. 210184.

[1] Department of Ophthalmology, University of Minnesota, Minneapolis, Minnesota.

[2] Scott and White Ophthalmology Clinic, Temple, Texas.

[3] Department of Ophthalmology and Visual Sciences, Washington University, St. Louis, Missouri.

[4] Casey Eye Institute, Portland, Oregon.

Presented in part as a poster at the annual meeting of the American Academy of Ophthalmology, Dallas, Texas, October 2000, and as a poster at the annual meeting of the North American Neuro-Ophthalmology Society, Mt. Tremblant, Quebec, Canada, March 2000.

None of the authors have any financial interest in sildenafil citrate or Pfizer.

Supported in part by Research to Prevent Blindness, Inc., New York, New York.

Address correspondence to Howard Pomeranz, MD, Department of Ophthalmology, University of Minnesota Medical School, MMC 493, 420 Delaware Street SE, Minneapolis, MN 55455-0501.

ISSN 0161-6420/02/$–see front matter
PII S0161-6420(01)00976-9

roophthalmologists. They all received complete neuroophthalmic examinations, including visual field testing. Follow-up examination was documented for four of the five patients. Attention was given to the time of development of ocular symptoms after ingestion of sildenafil, visual acuity, pupillary examination, visual field testing, and optic disc appearance at the time of presentation, as well as at follow-up examination. The records of these five patients were retrospectively reviewed in a nonmasked manner. Inclusion in this study was not dependent on a required length of follow-up.

Patient 1

A 52-year-old man had erectile dysfunction after transurethral resection of prostate cancer. He had Crohn's disease and took methylphenidate hydrochloride twice a day for attention deficit disorder. He took 50 mg of sildenafil for the first time in the evening. Within one hour he had a severe generalized headache and sweating develop. He saw blue "lightning bolts" and reported blurry vision in both eyes that lasted 30 minutes, but with persistence of the visual symptoms in the inferior field of the left eye. No erection occurred, and he did not have intercourse. He tried the medication again the next night and experienced a recurrence of the same symptoms. The blurry vision in the left eye persisted. Neuroophthalmic examination 5 days later showed corrected visual acuities of 20/20 in both eyes and normal color vision. Goldmann perimetry revealed an inferior altitudinal visual field defect in the right eye. Dilated fundus examination showed superior swelling of the left optic disc. The right optic nerve was normal and had a 0.1 cup-to-disc ratio. The remainder of the ophthalmic examination was normal. A follow-up neuroophthalmic examination 9 months later revealed superior pallor of the left optic nerve and persistence of the visual field defect.

Patient 2

A 69-year-old man developed painless vision loss in the right eye and visual field loss in the right inferonasal visual field, 45 minutes after ingestion of sildenafil. He did not know whether he used 50 or 100 mg of the drug. It is not known how long he had been using Viagra or whether sexual intercourse took place after ingestion of sildenafil. His past medical history was significant only for elevated cholesterol that was treated with atorvastatin. He also used daily aspirin. Neuroophthalmic examination 3 weeks after the onset of symptoms revealed visual acuities of 20/80 in the right eye and 20/20 in the left eye, with a right relative afferent pupillary defect. There was an inferonasal field defect in the right eye and diffuse edema of the right optic disc with associated disc hemorrhages. The remainder of his ophthalmic examination was normal. Two months later, his visual acuity was unchanged, superotemporal pallor of the right optic disc was noted, and the visual field defect persisted.

Patient 3

A 42-year-old man developed retro-orbital right eye pain, and pain on eye movement of the right eye 12 hours after taking the prescribed amount of Viagra for the second time. He had used Viagra 1 week prior for the first time without any adverse effects. When he took the prescribed amount of Viagra for the third time (the next night after the second time), he did not participate in sexual intercourse. The next morning he noted blurry vision in the right eye and dimness in the inferior visual field. Because the visual problem persisted, he was examined by a neuroophthalmologist 2 days later. His history was significant only for color blindness and depression which was treated with sertraline. His visual acuity was 20/20 in the right eye and 20/20 in the left eye, with the presence of a right relative afferent pupillary defect. On automated perimetry an inferior altitudinal defect, as well as a superior arcuate defect with sparing of central vision, was noted in the right eye, with a normal visual field present in the left eye. On fundus examination there was right optic disc edema predominantly at the superior aspect of the disc. Optic disc hemorrhages were also present. The left optic disc had a 0.1 cup-to-disc ratio. Visual acuity declined to 20/200 over the next 2 weeks without further changes in visual field or fundus appearance. Further workup, including magnetic resonance scanning, was normal. Two months later the visual acuity remained at 20/200 in the right eye. The right optic nerve appeared diffusely pale and the right visual field defect persisted.

Patient 4

A 62-year-old man with history of NAION in the left eye that occurred in June 1997 with a negative temporal artery biopsy was otherwise healthy. He had no history of hypertension or diabetes. He was taking a daily aspirin. He was well until June 1999 when he began to have difficulties with the inferior field of vision in the right eye. He had been using 50 mg of Viagra weekly for 15 months. His vision continued to worsen. It is unclear when his visual symptoms began, with respect to the use of sildenafil, or whether or not he participated in sexual intercourse. When he was examined by a neuroophthalmologist in August 1999, his visual acuity was 20/50 in the right eye and 20/80 in the left eye. Humphrey 30-2 visual fields (Zeiss; Dublin CA) revealed a prior documented superior altitudinal defect in the left eye and a new inferior altitudinal defect in the right eye. Fundus examination in the right eye revealed superior disc pallor, mild nerve fiber layer swelling temporally with a few small peripapillary hemorrhages, and a large hemorrhage at the nasal aspect of the disc. The left optic disc was pale inferiorly. Three months later, superior pallor of the right optic disc was present. The visual field defects persisted. Visual acuities remained unchanged.

Patient 5

A 59-year-old man with a past medical history of coronary artery disease and noninsulin-dependent diabetes for 10 years and insulin-dependent diabetes for 3 months underwent stent placement in the coronary artery 2 years prior. He smoked one to two packs of cigarettes per day for 45 years. His medications were insulin, metformin, and bisoprolol. The patient noted darkness over the inferior visual field in the right eye several hours after using 50 mg of Viagra. He had achieved an erection and had intercourse. He had been sporadically using Viagra for 2 years. On neuroophthalmic examination 1 week after the onset of visual symptoms, visual acuity was 20/25 in both eyes. A right afferent pupillary defect was present. An inferior visual field defect was present in the right eye. The left optic nerve was normal with a 0.1 cup-to-disc ratio. The right optic nerve revealed superior sectorial edema with disc hemorrhages. There was no evidence of diabetic retinopathy. He did not return for follow-up examinations.

Results

All of the patients were prescribed sildenafil citrate for treatment of erectile dysfunction. Four of the five patients reported loss of vision in the affected eye within a short period of time (minutes to several hours) after oral ingestion of the sildenafil, consistent with the absorption and half-life of the medication. One of the patients (patient 4) had been using sildenafil for more than a year on a

weekly basis, and because he experienced progressive loss of vision, could not recall a specific time of vision loss after using the medication. One of the patients (patient 1) also noted headache in conjunction with his visual symptoms, whereas another (patient 3) had eye pain, suggesting an acute effect of the drug.

The ages of the patients ranged from 42 to 69. Four of the five patients had no documented vascular risk factors such as hypertension, diabetes, or coagulopathy. One of the five cases (patient 5) had diabetes and coronary artery disease and was a smoker. Another case (patient 4) had a previous episode of NAION in the other eye before ever using sildenafil, putting him at higher risk for development of NAION in the contralateral eye. Documented visual acuity at presentation was variable. Three patients had acuities in the range of 20/20 to 20/25, whereas the remaining cases varied from 20/50 to 20/80. The patients demonstrated the characteristic findings of NAION, including altitudinal visual field loss, an afferent pupillary defect, and optic disc edema, with associated optic disc and/or peripapillary hemorrhages. All of the patients had optic discs with small cup-to-disc ratios. The affected optic discs progressed to optic disc pallor. The visual field defects remained permanent and vision did not improve in the two patients who had 20/50 and 20/80 visual acuities.

Not all of the patients were initially forthcoming in admitting to the use of sildenafil. Frequently, the patients withheld this information while their partners were present in the examination room, and relayed information about the use of sildenafil at a later time. Three of the patients developed NAION after using sildenafil for the first time, either once or twice, or after using the medication for a few days. The other two patients had been using the medication periodically for 1 to 2 years.

Discussion

Nonarteritic anterior ischemic optic neuropathy is not an uncommon disorder with an annual incidence of 2.3 to 10.2 per 100,000 persons over 50 years of age, and 0.54 per 100,000 for all ages.[6,7] In the Ischemic Optic Neuropathy Decompression Trial, 60% of patients with NAION had conditions associated with small-vessel occlusive cerebrovascular disease, including hypertension, diabetes, and cigarette use.[8] The first visual symptoms noticed by patients with NAION are typically blurred vision, loss of part of the visual field, or both. Altitudinal defects are the most common pattern of visual field loss. A diffuse or focally swollen optic disc is observed and multiple flame-shaped hemorrhages are usually present.

Nonarteritic anterior ischemic optic neuropathy is thought to be associated with vascular insufficiency at the optic nerve head, leading to ischemia. Alteration in perfusion of branches of the posterior ciliary artery that supply the optic nerve head has been implicated in NAION. Structural factors have also been implicated in the pathogenesis of NAION. It is believed that optic discs with small physiologic cups are more common in patients with NAION.[9,10] Crowding of the nerve fibers through a small scleral canal may make these optic nerves more susceptible to damage from ischemia. Burde[11] labeled the typical disc seen in NAION as a "disc at risk," which he characterized as one having a small physiologic cup, elevation of the disc margins by a thick nerve fiber layer, anomalies of blood vessel branching, and the appearance of a crowded and small optic nerve head.

The role sildenafil may play in causing injury to the optic nerve is not known. Sildenafil citrate is a selective phosphodiesterase 5 inhibitor, and its mechanism of action works through the nitric oxide-cyclic GMP pathway. Nitric oxide has been implicated as a possible toxic agent to the optic nerve and to retinal ganglion cells, and has been implicated in the pathogenesis of glaucoma, a more common form of optic neuropathy than NAION. Inhibition of nitric oxide synthetase in an animal model for glaucoma rescued retinal ganglion cells from damage[12] and has been suggested as a means of neuroprotection for the optic nerve. Sildenafil may alter the perfusion of the optic nerve head by way of its influence over the level of nitric oxide. Nitric oxide is a potent vasodilator and it physiologically regulates blood pressure. This compound may cause vasodilation of blood vessels on the optic nerve head and influence optic nerve perfusion. Nitric oxide might interfere with autoregulation of blood flow to the optic nerve head. Sildenafil has been shown to increase pulsatile ocular blood flow, a result of filling of the choroidal circulation, in 12 normal adults.[13] Although nitric oxide may play a role in intraocular pressure regulation, sildenafil did not cause an increase in intraocular pressure in healthy male volunteers.[14]

One healthy, young female subject in another study[15] developed severe flushing and headache, plus bilateral superior visual field depression with a 17.8 dB decrease in mean deviation on blue-on-yellow, and bilateral inferonasal depression with a 4.7 dB decrease in mean deviation on white-on-white Humphrey visual field testing after ingestion of 200 mg of sildenafil. This suggests that the effect on the optic nerve is acutely and temporally related to ingestion of this medication.

None of these studies were exclusively performed with subjects with known small physiologic optic cups. The cup-to-disc ratio was not documented in any of the subjects of the studies. Therefore, these reports do not refute the hypothesis that sildenafil may increase the risk of NAION in individuals with the optic "disc at risk."

The rapid onset of ocular symptoms in 4 of 5 subjects is supportive of an association between use of sildenafil and NAION. Because of the large number of prescriptions for sildenafil that have been written, the overlap in the populations that are at risk for NAION and likely to be prescribed sildenafil, and the small number of cases reported in this article, a definite causal relationship between sildenafil and NAION cannot be established here. Development of an animal model for NAION would provide an experimental paradigm in which to test a relationship between the two. The association may become more convincing as new cases of NAION after sildenafil use are documented.

Many patients do not disclose to their eye doctors information regarding impotence and sildenafil usage. Therefore, physicians should directly ask about the possible use of this medication when obtaining patient history. Several of our patients were relatively young, so inquiring about sildenafil usage should not be deferred in a young, healthy man presenting with NAION. It is probably premature to advocate screening for the optic "disc at risk" in patients who request sildenafil for treatment of erectile dysfunction. Nonetheless, patients should be counseled about the poten-

tial ocular side effects of this medication. In an editorial about sildenafil and ophthalmology, Marmor[16] advocates that ophthalmologists should make sure that their patients are informed about the potential risks of sildenafil. We also recommend that patients with a prior history of monocular NAION should not be prescribed sildenafil because it may increase the risk of NAION in the fellow eye.

References

1. Physicians Desk Reference, 55th ed. Montvale, NJ: Medical Economics, 2001. Viagra®;2534–7.
2. 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. In: Viagra (Sildenafil): Joint Clinical Review for NDA-20-895. Washington, DC: Center for Drug Evaluation and Research, FDA, 1998;160–1.
3. Donahue SP, Taylor RJ. Pupil-sparing third nerve palsy associated with sildenafil citrate (Viagra). Am J Ophthalmol 1998; 126:476–7.
4. Egan RA, Pomeranz HD. Sildenafil (Viagra) associated anterior ischemic optic neuropathy. Arch Ophthalmol 2000;118: 291–2.
5. Cunningham AV, Smith KH. Anterior ischemic optic neuropathy associated with Viagra. J Neuroophthalmol 2001;21: 22–5.
6. Hattenhauer MG, Leavitt JA, Hodge DO, et al. Incidence of nonarteritic anterior ischemic optic neuropathy. Am J Ophthalmol 1997;123:103–7.
7. Johnson LN, Arnold AC. Incidence of nonarteritic and arteritic anterior ischemic optic neuropathy. Population-based study in the state of Missouri and Los Angeles County, California. J Neuroophthalmol 1994;14:38–44.
8. Characteristics of patients with nonarteritic anterior ischemic optic neuropathy eligible for the Ischemic Optic Neuropathy Decompression Trial. Ischemic Optic Neuropathy Decompression Trial Study Group. Arch Ophthalmol 1996;114: 1366–74.
9. Beck RW, Servais GE, Hayreh SS. Anterior ischemic optic neuropathy. IX. Cup-to-disc ratio and its role in pathogenesis. Ophthalmology 1987;94:1503–8.
10. Doro S, Lessell S. Cup-disc ratio and ischemic optic neuropathy. Arch Ophthalmol 1985;103:1143–4.
11. Burde RM. Optic disc risk factors for nonarteritic anterior ischemic optic neuropathy. Am J Ophthalmol 1993;116:759–64.
12. Neufeld AH, Sawada A, Becker B. Inhibition of nitric oxide synthase 2 by aminoguanidine provides neuroprotection of retinal ganglion cells in a rat model of chronic glaucoma. Proc Natl Acad Sci USA 1999;96:9944–8.
13. Sponsel WE, Paris G, Sandoval SS, et al. Sildenafil and ocular perfusion [letter]. New Engl J Med 2000;342:1680.
14. Yajima T, Yajima Y, Koppiker N, et al. No clinically important effects on intraocular pressure after short-term administration of sildenafil citrate (Viagra). Am J Ophthalmol 2000; 129:675–6.
15. McCulley TJ, Lam BL, Marmor MF, et al. Acute effects of sildenafil (Viagra) on blue-on-yellow and white-on-white Humphrey perimetry. J Neuroophthalmol 2000;20:227–8.
16. Marmor MF. Sildenafil (Viagra) and ophthalmology [editorial]. Arch Ophthalmol 1999;117:518–9.