Nonarteritic Ischemic Optic Neuropathy Developing Soon After Use of Sildenafil (Viagra): A Report of Seven New Cases

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Abstract: Seven patients, aged between 50 and 69 years, had typical features of nonarteritic anterior ischemic optic neuropathy (NAION) within 36 hours after ingestion of sildenafil citrate (Viagra) for erectile dysfunction. Six patients had vision loss within 24 hours after use of the agent. Final visual acuity in the affected eye ranged from 20/20 to light perception. Both eyes were affected in one individual. All affected individuals had pre-existing hypertension, diabetes, elevated cholesterol, or hyperlipidemia. Seven similar cases have been previously reported. Sildenafil may provoke NAION in individuals with an arteriosclerotic risk profile.

(*J Neuro-Ophthalmol* 2005;25: 9–13)

Sildenafil citrate (Viagra; Pfizer Pharmaceuticals, New York, NY) is a selective phosphodiesterase 5 inhibitor and partial phosphodiesterase 6 inhibitor prescribed for erectile dysfunction. Use of sildenafil leads to smooth muscle relaxation in the corpus cavernosum, allowing inflow of blood to the penis during sexual stimulation. Headache and flushing are the most frequently reported adverse events associated with use of this drug. Sildenafil use is contraindicated in patients taking nitrates (1).

Sildenafil has been reported to cause transient changes in perception of color hue or brightness through a presumed action on phosphodiesterase type 6 in retinal photoreceptor outer segments (2). Seven cases of nonarteritic anterior ischemic optic neuropathy (NAION) associated with sildenafil use have been previously reported (3–7). This report adds an additional seven cases.

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Supported in part by an unrestricted grant from Research to Prevent Blindness Inc, New York, New York to the Department of Ophthalmology at the University of Minnesota Medical School.

METHODS

The medical records of seven patients in whom NAION developed subsequent to ingestion of sildenafil were identified between 1999 and 2003 and reviewed in a nonmasked manner at the University of Minnesota. All seven patients received complete ophthalmic examinations including visual field testing. Medications, medical history, the time of development of ocular symptoms after ingestion of sildenafil, visual acuity, pupil examination, visual field testing, and optic disc appearance at the time of presentation and on follow-up examination were recorded. Inclusion in this study was not dependent on a required length of follow-up.

RESULTS

The characteristics of the seven patients are summarized in Table 1 together with those of the seven previously described patients (3,6,7). All patients presented with blurred vision and loss of visual field. In some cases, the loss of visual acuity and visual field was progressive over days or weeks. The patients ranged in age from 50 to 69 years. All had at least one arteriosclerotic risk factor, including hypertension, diabetes, hypercholesterolemia, or hyperlipidemia. The dose of sildenafil was either 25 mg, 50 mg, or 100 mg. Some of the patients had been using the agent intermittently for months or years for treatment of erectile dysfunction before the occurrence of acute visual loss. Other individuals had only recently been prescribed sildenafil and had used one or a few doses before visual loss developed. In six patients, visual loss occurred within 24 hours after the use of sildenafil, most commonly on awakening the next morning. An ophthalmologist examined each patient soon after the acute visual loss. In affected eyes, visual acuity varied between 20/20 and light perception (median 20/180). Visual field loss was present in all patients, as was optic disc edema in the affected eye, often with associated nerve fiber layer hemorrhages. All patients had small cup-to-disk ratios in the fellow eye. Giant cell arteritis was ruled out by history, laboratory testing, or, in some cases, by temporal artery biopsy.

TABLE 1. ***Characteristics of 14 reported cases of nonarteritic ischemic optic neuropathy occurring shortly after sildenafil use***

Reference	Case	Age	Eye	Latency Between Sildenafil Use and NAION	Final Visual Acuity	Cup/Disc Ratio	Risk Factors
Present study	1	59	OD + OS	Next AM	LP OD, HM OS	NK	HTN, elevated lipids
	2	58	OD	1 hr	HM	0.1	HTN, elevated lipids
	3	67	OD	Next AM	20/200	NK	HTN
	4	50	OS	Next AM	20/160	small	HTN, hypoplastic ON
	5	69	OS	24 hr	20/125	NK	HTN, RD OS
	6	66	OD	24–36 hr	20/25	small	HTN, DM, elevated lipids, RD OS
	7	60	OD	Next AM	20/20	0.2	HTN, elevated lipids
Dheer et al[6]		48	OS	90 min	20/20	NK	None
Boshier et al[7]		61	OD	NK	CF	NK	HTN, elevated lipids, smoking, CAD, MI, none
Pomeranz et al[3]		52	OS	30 min	20/20	0.1	Elevated lipids
		69	OD	45 min	20/80	NK	none
		42	OD	Next AM	20/200	0.1	NAION OS
		62	OD	NK	20/50	NK	DM, smoking, CAD
		59	OD	Several hours	20/25	0.1	

AM = morning; CAD = coronary artery disease; HTN = hypertension; DM = diabetes mellitus; MI = myocardial infarction; RD = retinal detachment; NK = not known.

The visual loss was disabling for several patients. One patient (Case 1) had bilateral sequential NAION with final visual acuities of hand movements in one eye and light perception in the other eye, despite treatment with intravenous corticosteroids. Another patient (Case 4) had a final visual acuity of 20/160 in the affected eye and dense amblyopia secondary to optic nerve hypoplasia in the fellow eye, reducing visual acuity to hand movements.

Several patients attributed the visual loss to sildenafil and subsequently stopped using it. Other individuals continued to use sildenafil after the occurrence of NAION. One of these individuals had bilateral sequential NAION (Case 1).

Case 1

A 59-year-old man was prescribed 50 mg sildenafil 18 months before presentation. Because this dose caused severe headaches, the dose was lowered to 25 mg 15 months before presentation. The patient used sildenafil sporadically. Medical history was significant for erectile dysfunction, headaches, depression, gastric reflux, and skin cancer. Medications were sertraline and omeprazole. One day before presentation, he took one 25 mg sildenafil tablet before intercourse after not having used the medication for several months. A few hours later after intercourse, he saw bright colors, followed by loss of vision in the OD and soreness around the eye.

The next day, examination disclosed visual acuities of 20/20 OU. A right afferent pupillary defect was present. Humphrey 30-2 visual field testing revealed an inferior altitudinal defect OD. The visual field OS was normal. Diffuse optic disc edema was present OD. The optic disc OS was normal. The sedimentation rate was 72 mm/h. ANA was negative. Cholesterol and triglycerides were elevated at 246 and 226 mg/dL, respectively. One week later, visual field testing revealed extension of the inferior altitudinal visual field deficit to the superior half of the visual field.

A temporal artery biopsy result was negative, but he was treated for 3 days with methylprednisolone 1 g/d intravenously, followed by prednisone 80 mg/d. One week later, visual acuity was 20/70 OD. An MRI scan of the brain and orbits was normal. The patient continued to experience a decline in vision OD. Six days later, visual acuity was light perception OD and 20/60 OS. Humphrey 30-2 visual field testing revealed an inferior altitudinal defect OS. A fluorescein angiogram showed late leakage in the optic disc OS.

The prednisone dose was tapered over several months. A repeat sedimentation rate a few months later was 3 mm/h. Four months after initial presentation, the patient noted progressive visual loss OS. Visual acuities were light perception OD and 20/70 OS. Fundus examination revealed optic disc pallor OD and optic disc edema OS. Two weeks later, visual acuity had decreased to 20/100 OS. A repeat

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MRI scan of the brain and orbits was negative. Complete blood count, antinuclear antibody, angiotensin-converting enzyme, and syphilis serology were negative. The sedimentation rate was 7 mm/h. Three weeks later, the patient took another 25-mg dose of sildenafil and subsequently engaged in sexual intercourse. A few hours later, he noted color changes with the OS, followed by loss of vision. A few days later, visual acuity was counting fingers OS, the optic disc OS was diffusely edematous, and the visual field OS was severely constricted. He was retreated with intravenous methylprednisolone. The sedimentation rate was 6 mm/h. Three months later, visual acuity was hand movements OS and the optic disc was pale. Final visual acuities 1 year later were light perception OD and hand movements OS.

Case 2

A 58-year-old man used 50 mg of sildenafil, engaged in sexual activity with his wife and headache developed almost immediately. He noted that his face was "beet red" and that he could not see out of his OD. He had a history of amblyopia OS, lowering visual acuity to 20/40. He had remote epistaxis caused by dehydrational mucositis, hypercholesterolemia, and erectile dysfunction. Medications included aspirin and pravastatin.

Nine days after acute visual loss OD, visual acuity was hand movements OD and 20/40 OS. There was a right afferent pupillary defect and optic disc swelling with hemorrhages OD. He denied symptoms of temporal arteritis. The erythrocyte sedimentation rate was 43 mm/h. A temporal artery biopsy sample and carotid and vertebral artery ultrasound studies were normal. Two months later, visual acuity was unchanged and the optic disc OD was pale.

Case 3

A 67-year-old man awakened with decreased vision OD 1 day after he had used 50 mg sildenafil. He had been using the drug intermittently for 5 weeks. His medical history was significant for hypertension and a seizure disorder. Medications included metoprolol, enalapril, sertraline, bisoprolol, nifedipine, nortryptiline, doxazosin, phenobarbital, and diclofenac.

One week after acute visual loss OD, best-corrected visual acuities were 20/200 OD and 20/25 OS. The right pupil was poorly reactive to light. The optic disc OD was edematous and the optic disc OS was normal. Visual field testing revealed a depression in the superior aspect of the visual field OD. Two and one-half years later, the visual field OD was still abnormal.

Case 4

A 50-year-old man took one 50-mg tablet of sildenafil in the evening for 2 consecutive days without side effects. On the third day, at approximately 11:00 pm, he took two 50-mg tablets of sildenafil. The next day, he sensed "a flashbulb go off in my eyes" with persistent glare. During the early hours of the next morning, 30 hours after his last ingestion of sildenafil, he noted sudden worsening of vision OS.

Nine years earlier, visual acuity had been 20/20 OS with a normal Goldmann visual field but he had finger counting visual acuity OD from optic nerve hypoplasia. Past medical history was significant for renal stones, benign prostatic hypertrophy, and arthritis. Medications were terazosin, gabapentin, and metaxalone.

Examination on the day of visual loss OS showed visual acuities of finger counting OD and 20/70 OS. An afferent pupillary defect was present OS. The optic nerve OD was hypoplastic and the optic disc OS was swollen. Three days later, visual acuity had decreased to 20/160 OS. Humphrey visual field testing revealed inferior altitudinal and central defects OS. There were no symptoms of giant cell arteritis.

An erythrocyte sedimentation rate was 1 mm/h. Lipid profile, rheumatoid factor, antinuclear antibody, glucose levels, blood pressure, carotid and vertebral ultrasound studies, echocardiograms (transthoracic and transesophageal), magnetic resonance angiogram, and magnetic resonance imaging of the brain and orbits were normal. He was treated with anticoagulation and oral prednisone without improvement in vision. One week later, visual acuity had declined to finger counting OS. Goldmann visual field testing revealed a small island of visual field temporal to fixation OS. Four months later, pallor of the left optic disc was noted. Several years later, visual acuities and fields were unchanged.

Case 5

A 69-year-old man used a single 50-mg sildenafil tablet and reported acute visual loss OS the next day. He had used 50 mg sildenafil once per week for 3 months. He had undergone retinal buckle surgery 3 months earlier OS with postoperative visual acuities of 20/32 OD and 20/100 OS. His medical history was significant for hypertension, atrial flutter, prostate cancer treated with radioactive plaque, and occasional erectile dysfunction. Medications included chlorthalidone, warfarin, digoxin, and diltiazem.

Visual acuities 1 day after the acute visual loss OS were 20/32 OD and 2/200 OS. The optic disc OS was edematous with peripapillary nerve fiber layer hemorrhages. Six months later, visual acuities were 20/32 OD and in 20/125 OS. The optic disc OS was pale and the retina attached.

Case 6

A 66-year-old man experienced acute visual loss OD while exercising. He had used sildenafil 36 hours earlier and had noted flushing and headache the next day. He had a history of no light perception OS because of a traumatic retinal detachment. Medical history was significant for diabetes, hypertension, and hypercholesterolemia. Medications were glipizide, metformin, lisinopril, furosemide, amlodipine, and fluvastatin.

Four days after the acute visual loss OD, visual acuity was 20/25 OD and no light perception OS. The optic disc OD was swollen and the optic disc OS was flat and pale. Complete blood count, erythrocyte sedimentation rate, and serum protein electrophoresis were normal. Carotid ultrasound demonstrated no significant stenosis or plaque. Thirty months later, visual acuity was 20/30 OD and the optic disc OD was pale.

Case 7

A 60-year-old man reported a "shade coming down over the OD" on awakening the morning after using sildenafil (exact dose unknown). He had used sildenafil sporadically over the past year. Medical history was significant for obesity, cardiac dysrhythmia, and hypercholesterolemia. Medications were metoprolol, simvastatin, and aspirin.

Examination on the day of acute visual loss OD disclosed visual acuities of 20/20 OU. An afferent pupillary defect was present OD. The optic disc OD was swollen with nerve fiber layer hemorrhages; the optic disc OS was normal. Humphrey 24-2 visual field testing revealed a superior altitudinal defect OD and a normal field OS.

Complete blood count, erythrocyte sedimentation rate, thyroid stimulating hormone, and C-reactive protein were normal. Electrolytes were normal except for blood urea nitrogen of 21 mg/dL and a creatinine of 1.5 mg/dL. Cholesterol and triglyceride levels were 286 and 624 mg/dL, respectively. Two weeks later, Humphrey 24-2 visual field testing revealed a new inferior defect OD. Carotid ultrasound did not reveal any significant stenosis. A trial of levodopa did not result in visual improvement. Three months later, visual acuity was 20/20 OD through a small central island. Pallor of the optic nerve OD was apparent.

DISCUSSION

The onset of NAION within hours after ingestion of sildenafil in our seven patients supports an association between use of this agent and NAION. We recognize that patients with erectile dysfunction are more likely to have the microvascular risk factors typically associated with spontaneous NAION, as many of our patients did, but an ischemic effect of sildenafil on the optic nerve is plausible.

This drug is a selective phosphodiesterase 5 inhibitor causing vasomotor effects through its action on the nitric oxide-cyclic GMP pathway. In 12 normal adults, it increased pulsatile ocular blood flow, a result of filling the choroidal circulation (8). Grunwald et al. (9,10) did not find any significant change in optic nerve rim or foveolar choroidal blood flow (9) or retinal vessel caliber (10) after treatment with sildenafil, but Pache et al. (11) found that sildenafil caused significant dilation of retinal arteries and veins in healthy individuals. One healthy, young woman in another study (12) had severe flushing, headache, and visual field defects after ingestion of 200 mg of sildenafil, suggesting that the effect on the optic nerve is acutely and temporally related to ingestion of the medication.

Morgan et al. (13) reported the occurrence of a transient ischemic attack in a 50-year-old man 2 hours after ingesting 50 mg sildenafil. On re-challenging himself with 100 mg sildenafil 6 days later, permanent neurologic deficits from an ischemic stroke developed.

Studies by Pfizer (published in the *Physicians Desk Reference* and available through the Food and Drug Administration [FDA] web site) show that sildenafil reaches a peak plasma concentration within 2 hours (30–120 min) during fasting and over a longer period of time in the presence of lipid (2). Elevated levels of sildenafil and its active metabolite are present in the blood for 8 to 12 hours after ingestion. Therefore, if sildenafil is ingested at night, sufficient drug levels may be present during sleep or the next morning. Many of our patients recognized visual loss on awakening, implying that it took place during sleep.

Because of the lack of a model in which to test for a relationship between sildenafil and NAION, a definite causal relationship cannot be established at this time. An animal model for NAION has been developed (14) and may provide an experimental paradigm. In view of the fact that other medications for treatment of erectile dysfunction, such as tadalafil and vardenafil, have undergone clinical trials for FDA approval and are now available by prescription, it is critical that irreversible ocular side effects such as NAION be ruled out in this class of drugs.

Pfizer's postmarketing experience with sildenafil led to the addition of the following statements to the *Physicians Desk Reference* in 2002:

"Serious cardiovascular, cerebrovascular, and vascular events, including myocardial infarction, sudden cardiac death, ventricular arrhythmia, cerebrovascular hemorrhage, transient ischemic attack, hypertension, subarachnoid and intracerebral hemorrhages, and pulmonary hemorrhage

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have been reported post marketing in temporal association with the use of Viagra. Most, but not all, of these patients had preexisting cardiovascular risk factors. Many of these events were reported to occur during or shortly after sexual activity, and a few were reported to occur shortly after the use of Viagra without sexual activity. Others were reported to have occurred hours to days after the use of Viagra and sexual activity. It is not possible to determine whether these events are directly related to Viagra, sexual activity, to the patient's underlying cardiovascular disease, to a combination of these factors, or to other factors (2)."

Based on the fact that 14 cases of NAION have now been reported soon after use of sildenafil, we believe that ophthalmologists should ask all men with NAION about the use of sildenafil, given that this information may not be volunteered without specific inquiry. We recommend that patients with a history of monocular NAION be cautioned that sildenafil may increase the risk of NAION in the fellow eye. We also suggest that physicians report cases of ocular ischemia in patients using sildenafil to the National Registry of Drug-Induced Ocular Side Effects and that Pfizer consider investigating this association.

ACKNOWLEDGMENTS

The contribution of cases by Gary Cowan, MD, David H. Zackon, MD, and Michael Zgrabik, MD is gratefully acknowledged.

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