Non-arteritic anterior ischemic optic neuropathy (NAION) and phosphodiesterase type-5 inhibitors

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Objective: *To determine whether a causative relationship exists between non-arteritic anterior ischemic optic neuropathy (NAION) and the use of phosphodiesterase-5 (PDE-5) inhibitors for the treatment of erectile dysfunction.*
Methods: *A comprehensive review of the literature was performed to identify the contemporary understanding of NAION pathophysiology, epidemiology, and occurrence in men using the oral PDE-5 inhibitors sildenafil (Viagra, Pfizer), vardenafil (Levitra, Bayer AG), and tadalafil (Cialis, Lilly-ICOS LLC) for the treatment of erectile dysfunction.*
Results: *NAION is the second most common acquired optic neuropathy in men aged 50 years and older. Risk factors for NAION, cardiovascular disease, and erectile dysfunction are shared and include age, dyslipidemia, diabetes, hypertension, and cigarette smoking. To date, less than 50 cases of NAION associated with PDE-5 use have been reported to the United State's Food and Drug Administration (FDA) and five Canadian cases alerted to Health Canada. Given the large number of men safely using these agents and a limited number of events, it is not possible to determine whether NAION is directly linked to the use of PDE-5 inhibitors, underlying cardiovascular risk factors, ocular anatomical defects, a combination of these variables, or as yet unidentified factors.*
Conclusions: *PDE-5 inhibitors have gained widespread use for the treatment of erectile dysfunction due to their safety, efficacy, and ease of use. Their role in the pathogenesis of NAION remains controversial. Reasonable and informed consent regarding the possible but low risk of NAION with the use of sildenafil, vardenafil and tadalafil is recommended. Loss or decreased vision, whether painful or painless, demands urgent patient assessment and immediate cessation of PDE-5 inhibitor use.*

Key Words: impotence, phosphodiesterase type-5 inhibitors, non-arteritic anterior ischemic optic neuropathy, NAION, erectile dysfunction

Introduction

The oral phosphodiesterase type-5 inhibitors (PDE-5i) sildenafil (Viagra, Pfizer), vardenafil (Levitra, Bayer AG), and tadalafil (Cialis, Lilly-ICOS LLC) have revolutionized the treatment of erectile dysfunction (ED), emerging as the preferred first-line treatments for ED due to their combination of safety, ease-of-use, and efficacy across patient populations and etiologies. Factors such as growing awareness of ED and available therapies, increased life expectancy, and the rising incidence of conditions such as cardiovascular disease and diabetes will likely result in an increased number of men seeking care for sexual health concerns over the next two decades as the prevalence of ED reaches 300 million men worldwide.[1] With an ever-expanding choice of treatments, clinicians treating ED patients must maintain an up-to-date understanding of the indications, efficacies, and side-effects of

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therapies in order to effectively manage these patients.

Although visual side effects are well-known to be associated with PDE-5i use, these effects are transitory, benign and generally well tolerated.[2,3] Most reports of altered vision related to PDE-5i use have been attributed to cross-reactivity with PDE6; selectivity is usually expressed in terms of potency (IC50) to inhibit PDE-5 as opposed to inhibiting non-target PDEs (or other proteins). Sildenafil and vardenafil cross-react slightly with PDE-6, as the IC50s for PDE-5 are only 4- to 10-fold lower than those for PDE-6. This may explain why some patients using sildenafil, and rarely with vardenafil, complain of transient visual disturbances (not observed with tadalafil). These effects typically are described around the time of maximal serum concentration of the PDE-5i when some degree of PDE-6 inhibition spill-over occurs. However, recent reports of vision loss in men treated with PDE-5i for ED have ignited a flurry of lay press coverage. Specifically, the controversy revolves around the pathogenesis of non-arteritic anterior ischemic optic neuropathy (NAION), subsequent transient or permanent vision loss, and a possible relationship to the use of sildenafil, vardenafil, or tadalafil. In this report, a comprehensive review of the literature summarizes the current understanding of NAION pathophysiology, epidemiology, risk factors, and the plausibility of a causative relationship between disease occurrence and use of PDE-5i therapy for ED.

Pathophysiology of NAION

NAION is an infarction of the optic nerve head as it passes through the sclera at a point just behind the optic disc.[4] Blood supply from the short posterior ciliary arteries is compromised at the level of the lamina cribosa, leading to sudden, painless unilateral vision loss.[5] The initial ischemic insult in NAION triggers an apoptotic cascade and up to 10%-25% of patients will demonstrate progressive loss of vision in the primary affected eye within the first month after onset, up to 30% will gradually improve one to two lines on visual chart testing, and 60% will have stable lesions.[4,6] The resultant visual deterioration is influenced by the recurrence of attacks, involvement of the central portion of the visual field, and by the existence of co-morbid systemic diseases such as pernicious anemia or collagen-vascular disease.[7] Estimates of subsequent contralateral eye involvement range from 10% to 70%.[8] Currently, there are no proven treatments for NAION,[9,10] although most authorities suggest initiating aspirin therapy (325 mg/day) in patients without contraindications as an attempt to mitigate further or contralateral eye involvement.[6]

Epidemiology and risk factors for NAION

Spontaneous NAION is the most common acute optic neuropathy and ranks second only to glaucoma as a cause of acquired optic neuropathy for men aged 50 and older.[11] Estimated annual incidence is 2.3 to 10.3 per 100 000 and is more common in Caucasians than African Americans, Asians, or Hispanics.[4,12,13] Most patients do not become legally blind but the degree of visual acuity and visual field loss is usually significant.[4]

Risk factors common to NAION and ED include hypertension, diabetes mellitus, hypercholesteremia, age over 50 years, coronary artery disease, and smoking.[11] NAION also tends to occur in eyes that have no or a small optic disc cup (the so-called "disc at risk" or congested disc), although this morphology is not exclusive and can also predispose patients with giant cell arteritis to arteritic anterior ischemic optic neuropathy (AAION).[14] The axons themselves are packed more tightly together in the narrowed scleral canal and the optic disc is slightly elevated, leading to a compartment-like syndrome as microvascular ischemia results in axoplasmic stasis, edema, and compression of the small capillaries at the optic nerve head.[15-17] Other conditions associated with NAION include nocturnal hypotension, sleep apnea, anemia, pulmonary arterial hypertension, Factor V Leiden mutation, and elevated homocysteine levels.[5,10,18]

Studies of ocular perfusion and PDE5-inhibitors

Several studies have been performed to examine what, if any, effect PDE-5 inhibition has on blood flow within various compartments and vascular beds of the eye, Table 1. Although no modality currently used measures perfusion directly, it may be inferred by Doppler flowmetry. In five separate studies evaluating ocular perfusion in healthy subjects, using laser or ultrasound Doppler flowmetry, sildenafil administration either increased[19-21] or did not change[22,23] circulation. Another study examined ocular blood flow via Doppler ultrasonography in patients with erectile dysfunction (etiology not defined) and found that flow increased (ophthalmic and short posterior ciliary arteries) or did not change (central retinal artery) after sildenafil administration.[24] Similarly, there was no change in retinal arterial or venous diameter in healthy patients after receiving sildenafil.[25]

TABLE 1. **Studies of human ocular perfusion after sildenafil administration**

Study	Number of subjects	Population	Study method	Result (after sildenafil)
Koksal et al 2005	30	Human, erectile dysfunction	Doppler ultrasonography	Increased flow ophthalmic art, short posterior ciliary art, no change central retinal art
Kurtulan et al 2004	38	Human, erectile dysfunction	Doppler ultrasonography	No significant change in retinal circulation. Ocular side effects not correlated with changes in retinal artery flow*
Metelitsina et al 2006	14	Human, age-related macular degeneration	Retinal vein diameters	Significant vasodilation of retinal veins
Metelitsina et al 2005	15	Human, age-related macular degeneration	Laser Doppler flowmetry	No significant change in foveolar choroidal circulation
Polak et al 2003	12	Human, healthy	Laser Doppler flowmetry, retinal vessel diameters	Significant increase in retinal vein diameters and retinal blood flow
Grunwald et al 2002	15	Human, healthy	Retinal vessel diameters	No significant effect on vessel diameters
Paris et al 2001	12	Human, healthy	Laser Doppler flowmetry	Significant increase in retinal flow

*"Unformed flashes of light" (2 patients), "blurred vision", "increased light sensitivity", "sensation of flying objects" (1 patient each)

Is there an association between NAION and PDE-5 inhibitors?

Patients taking PDE-5 inhibitors often harbor multiple common risk factors for ED and NAION, Table 2. Given that an estimated 27 million men worldwide that have used sildenafil (up to 1 billion doses), in addition to tadalafil or vardenafil users, the expected incidence of NAION in this group should be many-fold higher than the 43 cases reported to the Food and Drug Administration (June 2005) and five cases to Health Canada (October, 2005).[4,5,11] If we take the most conservative incidence of NAION in the general population (2.3 cases per 100 000) and the fact that there are at least 27 million users of PDE-5 inhibitors, we would expect at least 621 cases in this population, begging the question of whether PDE-5i exert a protective influence on the evolution of NAION.

To date, the FDA maintains that a causal relationship between NAION and PDE-5i has not been established. Review of safety data from over 100 clinical studies of sildenafil (> 13 000 men) did not identify any cases of NAION, with similar findings for vardenafil and tadalafil.[11,26,27] However, post-marketing surveillance has identified NAION-type visual loss in 43 FDA-reported cases (38 sildenafil, 4 tadalafil, 1 vardenafil), with 18 of these cases reported in current literature (sildenafil 16, tadalafil 2).[11,26,28-35] The median age of men in PDE-5i associated NAION was 60 years, most demonstrated anatomic or vascular risk factors for NAION, and usually occurred within hours of ingestion (ranging from minutes to a day). Seven patients noted visual loss the following morning.[11] All patients in this series had pre-existing hypertension, diabetes, elevated cholesterol, or

TABLE 2. **Shared major risk factors for NAION and erectile dysfunction**

Age > 50 years
Hypercholesteremia
Hypertension
Coronary artery disease
Diabetes mellitus
Cigarette smoking

hyperlipidemia, known microvascular risk factors for spontaneous NAION. A single report also describes a patient who took tadalafil five times in 1 month, developing transient and then permanent inferior visual field loss consistent with NAION.[35]

The hypothesized pathophysiologic link to PDE-5i induced NAION involves ocular ischemia and systemic nocturnal hypotension. However, ocular hemodynamics in men with ED, as measured by color Duplex ultrasonography, are not affected by 100 mg sildenafil dosing and the minimal decrease in systemic blood pressure by sildenafil, tadalafil, and vardenafil at recommended doses seems an unlikely cause as much stronger systemic anti-hypertensive agents are rarely associated with this condition.[23,36,37] However, PDE-5i mediated vasodilatation of ocular endothelium underlying dysfunction may be a final insult in vessels that are already at high risk for ischemic events.[38] It is possible that PDE-5i act more specifically upon blood flow around the optic nerve; Hayreh et al have suggested that nocturnal arterial hypotension may play a role in ischemic optic neuropathy as concurrent use of antihypertensives and PDE-5i in vasculopathic patients at risk for NAION may reduce nocturnal optic nerve head blood below a critical level, resulting in ischemic injury to ganglion cells, followed by axonal and visual field loss and decreased visual acuity.[39] Simply stated, well-researched explanations for how PDE-5i could cause NAION do not exist. The recent development of two animal models may help elucidate the molecular and cellular mechanisms of optic neuropathy, and specifically serve as a paradigm for research on possible PDE-5i related NAION.[40,41]

The World Heath Organization criteria for an association between a treatment and adverse effect requires that a clinical event occurs within a reasonable time from drug administration; the onset of NAION in the 7 men hours reported after ingestion of sildenafil reported by Pomeranz et al may support an association between this agent and NAION.[33] However, the same authors caution that until a scientific study or animal model reveals a pathophysiologic link between NAION and treatment by PDE-5i, most case reports of these events may be an expected coincidence as men using these agents are frequently older, vasculopathic, and at increased baseline risk for NAION.[42]

Concerns of a possible, but unproven, link between NAION and PDE-5i use resulted in FDA-approved product labeling changes for sildenafil, tadalafil, and vardenafil in mid-2005 advising men using PDE-5 inhibitors that in rare instances, a sudden decrease or loss of vision in one or both eyes has been observed. Current understanding is limited by incomplete knowledge of the potential pathophysiologic links between NAION and PDE-5i, PDE-5i associated-NAION incidence rates dependent on patient/clinician self-reporting, and the lack of data from animal models. Given current evidence, it is not possible to determine whether these events are directly related to use of PDE-5 inhibitors or to other factors, however men are instructed to stop taking these medications immediately and contact their physician should visual changes or loss occur.[11]

Clinical suggestions

The clinician treating men with ED is responsible for providing a reasonable and informed consent regarding the possible but low risk of NAION with the use of sildenafil, vardenafil and tadalafil, Table 3. Irrespective of erectile function, patients with significant visual problems should be evaluated by an eye professional. If diagnosed with NAION, this should prompt an evaluation for systemic comorbidities that are risk factors for NAION, and these patients should not take PDE-5 inhibitors until other risk factors are optimized. Although one report identifies a connection between NAION and cataract removal[42] there is a paucity of literature linking NAION to other ocular disorders such as macular degeneration, previous eye trauma, glaucoma, etc. Additionally, PDE-5 inhibitors have not been linked to significant vision disorders, although concomitant PDE-6 inhibition may lead to a variety of vision side effects such as color-tinged vision and increased sensitivity to light. Loss or decreased vision, whether painful or painless, demands urgent patient

TABLE 3. **Clinical suggestions based on current evidence**

Reasonable and informed consent (less than 50 cases of NAION reported)
Loss or decreased vision requires urgent medical attention and cessation of PDE-5 inhibitor use
Report adverse events
Consider prophylaxis against contralateral NAION with aspirin in appropriate patients

assessment and, until more robust data is available, immediate cessation of PDE-5 inhibitor use. Adverse events should be reported as they occur, improving post-marketing surveillance and helping determine whether the association of NAION and PDE-5 inhibitors is coincidental or causal. Prophylactic aspirin 325 mg/day may be initiated to protect the contralateral eye from subsequent NAION in appropriate patients.[43]

Conclusions

PDE-5 inhibitors are the recommend first-line treatment of erectile dysfunction for most men due to their safety, efficacy, and ease of use. Their role in the pathogenesis of NAION dysfunction remains controversial. Reasonable and informed consent regarding the possible but low risk of NAION with sildenafil, vardenafil and tadalafil use is recommended. Loss or decreased vision, whether painful or painless, demands urgent patient assessment and, until further data elucidates the role of PDE-5 inhibitors in the evolution of NAION, immediate cessation of their use. □

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