ERECTILE DYSFUNCTION

Can erectile dysfunction drug use lead to ischaemic optic neuropathy?

H D Pomeranz

Eye care providers could easily screen patients who are concerned about this optic nerve anatomical risk factor

In this issue of the *BJO*, McGwin and colleagues (p 154) examine an issue that has been the subject of controversy and debate over the past year. Several case reports published between 2000 and 2005 suggest a temporal association between erectile dysfunction drug (EDD) use (sildenafil, tadalafil, and vardenafil) and non-arteritic anterior ischaemic optic neuropathy (NAION).¹⁻⁷ Media reports in May and July 2005, about individuals who have decided to sue Pfizer because of vision loss caused by NAION that occurred in association with EDD use, have brought further attention to this controversy.

NAION is a frequent cause of untreatable, sudden, irreversible vision loss in individuals older than 40 years. The condition is characterised by optic disc oedema, frequently associated with nerve fibre layer haemorrhages, an afferent papillary defect and visual field loss, typically altitudinal. A decrease in arterial circulation to the prelaminar part of the optic disc is believed to cause the ischaemic optic nerve injury. The underlying aetiology is not well understood. Risk factors associated with NAION include the presence of a small cup to disc ratio, atherosclerosis, hypertension, hyperlipidaemia, nocturnal hypotension, ischaemic heart disease, diabetes, and prothrombotic tendencies, among others.

Most of the case reports of NAION associated with EDD use document that the vision loss occurred less than 24 hours after EDD use, frequently upon awakening the morning after EDD ingestion. In most of the cases, sexual intercourse did not occur after EDD use, so physical exertion related to sexual intercourse cannot be blamed for the vision loss. The case report by Bollinger and Lee¹ documents repeated episodes of transient vision loss after tadalafil use, eventually leading to irreversible vision loss after the fifth use of the drug; this report lends the greatest evidence of a possible cause and effect relation between NAION and EDD use.

All of the men in these case reports also had the so called "disc at risk," or small cup to disc ratio typically noted in

most individuals diagnosed with NAION. Most of the men who developed NAION also had vascular risk factors such as hypertension, diabetes, or hyperlipidaemia. These vascular risk factors are frequently the same risk factors that lead to erectile dysfunction. There were definitely men in the case reports with none of these risk factors. Several of these patients had a history of prostate surgery or psychological factors that can lead to erectile dysfunction as well. Because of the overlap in underlying risk factors associated with NAION and erectile dysfunction, it has been difficult to determine whether EDD use is truly an independent risk factor for NAION. Pfizer states that there are no reports of NAION in its pre-marketing drug study population for sildenafil (Viagra). Pfizer also claims that a greater number of cases of EDD related NAION would have been reported by now if the association were not truly coincidental. The pharmaceutical company believes that because the half life of sildenafil is relatively short, cases of NAION that occur at 6 hours or more after ingestion of sildenafil are not related.

Further investigation into these issues will provide more information about potential risk that may be helpful for future patient counselling and management

Some of the reasons that there may not be more reported cases are that (1) physicians and other eye care providers do not ask men about EDD use at the time a diagnosis of NAION is made (or subsequently), (2) men who have been diagnosed with NAION over the past 7 years do not recall when they last used EDD before the onset of vision loss as a result of NAION, (3) men who themselves have raised the possibility of a temporal association between EDD use and NAION have been told by their physicians that this was not the case. Many of these reasons have been true of NAION cases associated with sildenafil

use that I have personally reviewed over the past several years. No one has carried out a study of EDD use in patients with NAION until now.

McGwin *et al*¹ designed a retrospective study of men with NAION and age matched controls and administered a telephone survey inquiring about EDD use. The investigators studied whether there was a relation between EDD use in men with NAION and vascular risk factors. They found that men with NAION were not more likely to report a history of EDD use than age matched controls. However, they did find a significant association between NAION and EDD use in men with a history of myocardial infarction and possibly hypertension, although they lacked sufficient numbers of subjects to demonstrate statistical significance for the latter. Although the study was not optimal because of its small number of subjects, retrospective nature and reliance on patient recall, it is the first study to examine the issue of possible temporal relation between EDD and NAION compared to a control group, rather than relying on a cohort of case reports.

An optimal group of patients in whom to carry out a large scale study of this issue would be the veteran population, a group in whom vascular and erectile dysfunction problems occur at a significantly high incidence to make a retrospective or prospective study possible. In the United States, the electronic medical record is consistently used across Veterans Administration Medical Centers and documents medication dosage, initial prescription dates and renewals, and also documents diagnostic codes. With data available from the electronic medical record, a study need not rely on patient recall of medication usage and date of diagnosis of NAION, although it would still rely on patient recall of the amount of time that elapsed between last EDD use and onset of vision loss. Preliminary discussions have already taken place to plan such a study (Mary Lawrence, MD, personal communication).

The media attention mentioned above raised concerns about whether patients who are considering EDD use could be screened in advance to assess for possible risk factors for NAION. While only a small percentage of patients over 40 years of age who have small cup to disc ratios will ultimately develop NAION (regardless of EDD use), eye care providers could easily screen patients who are concerned about this optic nerve anatomical risk factor. The report by McGwin *et al* suggests that vascular risk factors, such as history of myocardial infarction or ischaemic heart disease, are also important issues to consider in assessing possible risk for NAION in association

with EDD use. At this time, the only consensually agreed upon contraindication against use of EDD is for patients who have already experienced NAION in one eye, since the risk for fellow eye involvement (without EDD use) is estimated to be in the range of 15–20% over 5–10 years. Other patients who are worried about their risk of developing NAION should discuss their concerns with their physicians, although their overall risk of developing NAION is low. Further investigation into these issues will provide more information about potential risk that may be helpful for future patient counselling and management.

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Correspondence to: Howard D Pomeranz, North Shore Long Island Jewish Health System, 600 Northern Blvd Suite 214, Great Neck, NY 11021, USA; hpomeran@nshs.edu

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Age related macular degeneration

Which treatment is best for which AMD patient?

P Kroll, C H Meyer

A comparison of different treatment approaches for vascular age related macular degeneration

The treatment of choroidal neovascularisation (CNV) in age related macular degeneration (AMD) has changed enormously during the last decade.¹ While 10 years ago there was only argon laser coagulation, today we have several treatment options for classic, occult, and mixed subtypes available: classic CNV responds well to photodynamic therapy (PDT) with “off label” triamcinolone, while occult CNV can be treated by PDT, transpupillary thermotherapy (TTT), subretinal surgery, macular translocation, and anti-angiostatic therapy. The choice often depends on a variety of personal and environmental circumstances. Firstly, increased age and reduced health status of the patient may exclude them from surgery. Secondly, while first eyes may benefit from subretinal surgery, second eyes may be eligible for macular translocation. Thirdly, the initial visual acuity (VA) and the type of lesion often limit the success in PDT and also the financial coverage by medical insurance.

The beneficial results were initially presented by the Macular Photocoagulation Study (MPS), with laser reducing severe visual loss in extrafoveal and juxtafoveal CNV. As the mechanism of conventional photocoagulation relies on thermal damage to the neuroretina, through an estimated temperature rise to 42°C, severe central scotomas and recurrent CNV are often experienced in

patients with subfoveal lesions.² This treatment is currently used only in selected cases with small extrafoveal lesions. This limitation of photocoagulation led to an increase in new treatments.

Transpupillary thermotherapy (TTT) is a subthreshold photocoagulation delivering moderate heat to the choroid and retinal pigment epithelium (RPE) using a diode laser (810 nm). The goal is to achieve relative sparing of the overlying neuroretina by a limited temperature elevation of approximately 10°C.³ However, it might be difficult to deliver an appropriate irradiation in every case, as a standardised measure of the chorioretinal temperature is not available.⁴ Stolba *et al* present, in this issue of the *BJO* (p 158), their own long term experience with TTT in occult CNV. Overall, 70% of patients showed an improved (14%) with unchanged (56%) visual acuity (VA) at the 24 month visit. While previous studies reported less successful data, this study gives further evidence that TTT may be the treatment of choice in occult CNV. A modification using indocyanine green mediated photothrombosis through a 810 nm laser achieved a visual stabilisation in 55%, improved VA in 33% at 12 months according to Farah *et al*.⁵

Photodynamic therapy (PDT) using a sensitising agent such as verteporfin, in conjunction with low power diode laser, achieves a selective photothrombosis of the CNV. The Treatment of AMD with

PDT (TAP) Study demonstrated a decreased risk of vision loss in predominantly classic CNV.⁶ In addition, the presumed selective approach in PDT has been questioned, as the binding LDL receptors for benzoporphyrin are also present in other retinal structures,⁷ and possibly cause minor functional alterations after PDT.⁸ An initial upregulation of vascular endothelial growth factor (VEGF),^{9,10} and damage to the blood-retina barrier after PDT^{11,12} seem to indicate that a combined therapy with intravitreal triamcinolone or VEGF inhibitors may reduce the recurrence and consecutive high re-treatment rate.¹³ The TAP round table presented a treatment algorithm for all subtypes of vascular AMD.¹⁴ Without any doubt PDT remains the treatment of choice in predominant classic CNV.

With increasing life expectancy we will face more patients with vascular AMD searching for cost effective approaches

The goal of “subretinal surgery” was to remove the CNV after a pars plana vitrectomy (PPV) through a small retinotomy to reduce the progression of the disease, yielding a long term stabilisation of the visual function.¹⁵ However, the surgical benefits are limited by the removal of adjacent RPE adherent to the removed CNV, frequently extending the preoperative size of the CNV itself.¹⁶ Although the results of the Submacular Surgery Trial (SST) indicated no benefit from this treatment,¹⁷ we think that patients with massive subretinal haemorrhages¹⁸ or of a short duration in the first eye and a preferably extrafoveal location of the CNV may benefit from subretinal surgery. We performed subretinal surgery in 50 eyes and determined decreased VA in 44%, a stabilised VA in 24%, and improved VA in 32% after a long term follow up of 4 years.¹⁹

RPE cell suspension,²⁰ or the free autologous transplantation of a full thickness graft “patch” from the mid-peripheral