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Correspondence: Azhar A. Khan, Urology Research Registrar, Bristol Urological Institute, Southmead Hospital, Bristol, UK.
e-mail: docazhar@gmail.com

THE PHOSPHODIESTERASE INHIBITORS AND NON-ARTERITIC ANTERIOR ISCHAEMIC OPTIC NEUROPATHY: INCREASED VIGILANCE IS NECESSARY

Amrith R. Rao, Ali Thwaini, Hashim U. Ahmed, Iqbal S. Shergill and Suks Minhas – The Institute of Urology, London, UK

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INTRODUCTION

The main action of the cGMP phosphodiesterase inhibitors (PDEIs) sildenafil, tadalafil and vardenafil is on the PDE5 enzyme. However, they act on the other PDE enzymes, including PDE6i, which is present in the rods and cones of the retina. Therefore, disturbances in colour vision and excessive brightness have been reported as adverse events of PDEIs; both side-effects seem to be dose-dependent although completely reversible. Due to these potentially debilitating effects, such medication is contraindicated in patients with hereditary degenerative retinal disorders such as retinitis pigmentosa.

Recently there has been an alarming increase in the reporting of sudden loss of vision due to non-arteritic anterior ischaemic optic neuropathy (NAION) occurring in men taking PDEIs. This has raised significant concern in the medical community and in the media, culminating in CBS, the USA television network, raising the issue on their evening news [1].

NAION is the most common cause of acute optic nerve disease in men age >50 years and therefore shares several common risk factors with erectile dysfunction (ED), e.g. hypertension, diabetes mellitus, atherosclerosis, smoking, myocardial infarction and hypercholesterolaemia. The common criteria for the diagnosis of NAION includes: (a) a history of sudden painless monocular/binocular loss of vision; (b) optic disc oedema noted on fundoscopic examination, that eventually resolves, leaving optic disc pallor; (c) a visual field defect corresponding to the pathology at the level of the optic nerve head; (d) lack of findings on examination suggesting another disorder that could be causing the symptoms; (e) exclusion of the more common arteritic AION by clinical history, examination and erythrocyte sedimentation rate.

Although in 40% of patients the condition does not change, the prognosis is variable amongst the remaining 60%. There is subsequent improvement in 40% of patients and 20% have deterioration [2].

The first reported case of NAION in relation to the use of sildenafil for ED was in 2000 [3]. Up to 2005, 43 men with NAION taking PDEIs were reported to the USA Food and Drug Administration (FDA, 38 sildenafil, four tadalafil, one vardenafil), with 26 having continued or permanent visual loss [4]. The significance of the difference among these three different drugs might either be a real effect or reflect the predominant and longer-term use of sildenafil in the market. In response, the FDA issued a statement advising patients who have sudden or gradually decreasing visual impairment in one or both eyes to stop taking these medicines, and call a doctor or healthcare provider immediately.

Furthermore, those patients taking or considering taking these products were strongly advised to inform their healthcare professionals if they had ever suffered severe loss of vision, reflecting a previous episode of NAION. Such patients were deemed at increased risk of developing NAION if a PDEI were prescribed. The FDA also approved the updated labelling of these drugs by their respective companies, cautioning the possibility of NAION [5].

The Drug Safety Research Unit from the UK analysed a cohort of 8893 patients from a Prescription-Event Monitoring study and found only one reported case of NAION. Although epidemiological data suggest that one case of NAION might be expected in such a large cohort, it is clear that physicians who prescribe PDEIs should specifically ask about previous sudden visual disturbance before prescribing, whilst continuing to show pharmacovigilance and report any new cases [6].

Most of the reported cases in which NAION has occurred in men taking a PDE5I also have underlying anatomical or vascular risk factors associated with the development

of NAION [7]. Sildenafil overdose has also been reported to cause NAION in combination with obstruction of the cilio-retinal artery [8].

With so few cases reported so far, the data for the association is far from clear. Recently McGwin *et al.* [2], in a retrospective case-control study, found no increase in the risk of NAION in all patients taking sildenafil. However, they did caution that there was a higher risk of NAION in men with a previous history of myocardial infarction and hypertension taking sildenafil. This finding has not been further substantiated. By contrast, in a study comparing the incidence of NAION in those taking PDEIs and the rate in those using atorvastatin, it was shown that there were 18 times more NAION reports per million prescriptions than for atorvastatin. However, the assumption that those taking atorvastatin had greater rates of ischaemic heart disease and hypertension is tentative, as only the dispensing of the drugs was assessed, with no regard to obtaining clinical history. Similarly, tadalafil had 25 times more reports than atorvastatin [9]. As most of the cases involved sildenafil, the relevant manufacturer, Pfizer, issued a statement that in a review of 103 clinical trials of sildenafil conducted by them and involving nearly 13 000 patients, there were no reports of NAION [10].

The mechanism by which NAION is induced by PDEIs is still unclear. It was postulated that PDE5i might alter the perfusion of the optic nerve head by modifying nitric oxide levels and interfering with vascular autoregulation [7]. In most cases of NAION, there is a small dense optic disc ('disc at risk'), which if concomitant with conditions of vascular engorgement (from small vessel disease) might lead to a form of 'compartment syndrome' within the confines of the rigid scleral canal, hence leading to optic ischaemic damage and atrophy [11]. As many patients with ED might have microvascular insufficiency (the same group that have a greater risk of spontaneous NAION) it was also postulated that PDEIs might precipitate ischaemic effects. However, this has not been supported by the detection of increased pulsatile blood flow in the ocular circulation caused by sildenafil [12]. The only other neuro-opthalmic complication reported has been third-nerve palsy leading to diplopia, developing 36 h after ingestion of 50 mg of sildenafil citrate [13].

A discussion of the management of NAION is difficult, as studies have so far evaluated treatments for NAION in situations other than those caused by this class of drugs. Nonetheless, interventions such as the use of hyperbaric oxygen or optic nerve-sheath decompression have failed to show any advantages in such groups [14,15].

It is clear that more research is warranted to allay public alarm, precipitated by the media, for a complication that has such a low incidence. Increased vigilance, both at the time of prescribing these popular drugs and continually afterwards, by all physicians and the patient, is needed to avoid such toxicity, and the advice should be to stop the medication if visual problems develop in this small minority of patients.

CONFLICT OF INTEREST

None declared.

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Correspondence: Iqbal S. Shergill, The Institute of Urology, 48 Riding House St, London, W1W 7EY, UK.
e-mail: super_iqi@hotmail.com, super_iqi@yahoo.co.uk

Abbreviations: **PDEI**, phosphodiesterase inhibitors; **(N)AION**, (non-arteritic) anterior ischaemic optic neuropathy; **ED**, erectile dysfunction; **FDA**, USA Food and Drug Administration.