PERSPECTIVE

Erectile dysfunction drugs and risk of anterior ischaemic optic neuropathy: casual or causal association?

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Phosphodiesterase type 5 (PDE5) inhibitor drugs for erectile dysfunction have revolutionised the treatment of male sexual dysfunction and are among the best selling drugs worldwide. Several cases of non-arteritic anterior ischaemic optic neuropathy (NAION) have been reported since 2005 in users of these agents. NAION is a sudden irreversible cause of visual loss with a poorly understood aetiology that affects up to 10 adults per 100 000 each year. Following a series of such case reports, WHO and FDA have labelled the association between use of PDE5 inhibitors and risk of NAION as ''possibly'' causal. There have been several recent studies of this association, including a rechallenge case report and a large managed care database study. However, the inability to confirm or refute claims of an association between NAION and EDD is generating clinical and regulatory uncertainty. Questions surrounding use of PDE5 inhibitors and risk of NAION highlight weaknesses in current systems used to identify and evaluate uncommon adverse effects of medication use. This paper reviews all the recent evidence on PDE5 inhibitors and the risk of NAION.

The phosphodiesterase type 5 (PDE5) inhibitor class of erectile dysfunction drugs has revolutionised the treatment of male sexual dysfunction. Three PDE5 inhibitors—sildenafil (Viagra; Pfizer, New York), vardenafil (Levitra; Bayer), and the longer acting tadalafil (Cialis; Eli Lilly)—are among the best selling drugs worldwide,[1] used by over 40 million men.[2] Sildenafil was approved by the Food and Drug Administration (FDA) in March 1998, and vardenafil and tadalafil in November 2003. Several cases of non-arteritic anterior ischaemic optic neuropathy (NAION) have been reported since 2005 in users of PDE5 inhibitors. NAION is a sudden irreversible cause of visual loss with a poorly understood aetiology. It affects between two and 10 adults per 100 000 each year.[3] Following a series of such case reports, the World Health Organisation (WHO) and FDA have labelled the association between the use of PDE5 inhibitors and the risk of NAION as ''possibly'' causal. These agencies have required such warnings to be posted on drug information sheets and on the drug manufacturers' websites.

In the past two years there have been several studies of this association, including a rechallenge case report, a large managed care database study, and discussions on strategies for dealing with the possible association.[4] In this article we review all of the recent evidence available on PDE5 inhibitors and the risk of NAION. In so doing we also highlight the strengths and limitations of current approaches to the identification of uncommon adverse effects of therapeutic drugs (table 1). Our intent is to provide clinicians with a framework with which to evaluate the evidence of such associations.

PREMARKETING RANDOMISED TRIALS

Like virtually all drug approval processes, the safety monitoring for the PDE5 inhibitor drugs involved preclinical testing in animals followed by three phases of clinical studies enrolling into randomised trials. The numbers required for premarketing trials depend on the plausible effect of the new drug and the frequency of the outcome of disease. Approximately 3700 patients treated with sildenafil and 1500 treated with placebo were recruited as part of phase II/III placebo controlled trials.[5] Although trials of such size can often identify adverse drug reactions that occur among 1 in 100 patients (assuming that the adverse events develop reasonably rapidly during the study's scheduled follow up), less common (or delayed) adverse effects may not be readily discernible.[6] So, although it has been reported[7] that about 13 000 individuals have been studied to date in randomised trials of PDE5 inhibitors for a mean duration of 35 000 patient-years, this does not necessarily exclude a moderate or even strong association between use of these drugs and the risk of NAION. This is because even if, say, a twofold relative risk exists for NAION among users of PDE5 inhibitors compared with non-users, the incidence of the condition would increase from only about 1 per 10 000 to about 2 per 10 000 among users. The reliable detection of a twofold (or less extreme) excess risk for a condition as uncommon as NAION would require sample sizes and durations of trial monitoring well beyond those currently customary for late phase randomised studies. Furthermore, given that participants in such trials may not necessarily be representative of the population of eventual drug users (for example, trial participants may be healthier because of restrictive entry requirements), a more rigorous assessment of drug safety often requires postmarketing surveillance. In the case of sildenafil, patients taking nitrates were excluded from the phase II/III studies, and the

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Abbreviations: NAION, non-arteritic anterior ischaemic optic neuropathy

Table 1 Strengths and limitations of different study designs to infer associations between drug use and adverse outcomes

Type of study	Strengths	Limitations
Premarketing trials	Should avoid biases	Limited power Limited follow up
Post marketing surveillance	Large amount of person-years of follow up	Patchy and inconsistent data collection Information biases
Case reports	Rapid Hypothesis-generating	No comparison group Highly prone to various biases Selective reporting
Observational studies	Fairly rapid Involve a comparison group	Recall biases Indication biases
Registry based studies	Rapid Powerful Avoid recall biases	Uncommon outcomes often not recorded Indication biases

premarketing studies did not identify an increase in the incidence of cardiovascular events.[8] Anecdotal reports of 12 cardiovascular deaths associated with an interaction of sildenafil and nitrates occurred in the postmarketing phase. Consequently, the American College of Cardiology and the American Heart Association published guidelines that suggested phosphodiesterase 5 inhibitor use is contraindicated in patients using nitrates.[9]

POSTMARKETING DRUG SAFETY ASSESSMENT

Postmarketing safety assessment relies on the gathering of data from a variety of sources to identify and estimate the impact of any adverse drug reactions.[10] Adverse drug reactions are reported to agencies such as the FDA, MedWatch (www.fda.gov/medwatch/index.html), the WHO spontaneous reporting database (www.who-umc.org), and the National Registry of Drug Induced Ocular Side Effects at the Casey Eye Institute, Portland, Oregon (www.eyedrugregistry.com). Although each country typically has its own reporting agency, most share their findings with the WHO. Pharmaceutical companies also receive spontaneous reports of possible adverse drug reactions. Other sources include case reports and series published in the medical literature, review of claims or medical record databases, and independent clinical studies.

CASE REPORTS

The possibility of an association between NAION and PDE5 inhibitors was initially raised by case reports (table 2). Since the first report in 2005, 20 individual cases have been published in scientific journals in the form of case reports and case series (table 1). We identified an additional 62 potential cases of NAION that had been reported to the FDA between 1 January 2004 and 31 October 2006. As with all voluntary reports in the FDA MedWatch programme, complete details are not usually available. The information provided includes the age of the patient, the drug, dose, the reported diagnosis, and in some cases the length of the drug use before the adverse event occurring. A significant limitation is that the diagnosis is not confirmed by an independent expert, nor are there standard criteria for the diagnosis to be made. Fifteen of the cases were clearly reported as ''ischaemic neuropathy'', while others are vague descriptions such as ''sudden unilateral blindness'', ''optic neuropathy'', or ''visual field defect.'' The mean age of these individuals was 59.8 (range 42 to 69). Visual symptoms developed within 6 to 36 hours after use of the drugs, often upon waking the morning after EDD ingestion.[11] Some patients had used PDE5 inhibitors for months or years; others had taken them only once or just a few times. Information on sexual activity after the use of erectile dysfunction drugs was often unavailable; in several men, it was specifically reported not to have occurred. The majority of patients reported had an underlying anatomical ''disc at risk'' (that is, a small cup to disc ratio with a small optic disc), and the presence of at least one vascular risk factor (for example, hypertension, diabetes, hyperlipidaemia, or smoking).[12] One patient, who experienced four separate episodes of transient vision loss after four occasions of tadalafil use, ultimately developed NAION after use on a fifth occasion, providing the only report so far of a diagnosis following drug rechallenge.[13] This case represents clinical evidence of a temporal association of NAION with EDD use.

There are major limitations to the evidence provided by individual case reports or case series. These include very small sample sizes, distortion because of recall (and other information) biases, the lack of any appropriate comparison group, inability to adjust for possible confounding factors (such as the overlap of risk factors that may predispose both to NAION risk and conditions such as hypertension and diabetes that increase the likelihood of use of PDE5 inhibitors), and a high likelihood of selective reporting and publication bias. Nonetheless, case reports often provide early clues to potential adverse outcomes and have been particularly informative when the potential side effect is extremely rare in the absence of drug use (for example, phocomelia secondary to thalidomide; Reye's syndrome secondary to aspirin use).

OBSERVATIONAL STUDIES

Observational studies compare drug exposure in patients with NAION with an appropriate group of unaffected controls. As it is not feasible to monitor initially healthy participants and then wait until sufficient numbers of disease cases accrue in uncommon conditions such as NAION, the retrospective case–control approach of identifying patients with existing diagnoses of NAION has been used instead. One such study of 38 patients with NAION at the University of Alabama and 38 age and sex matched control patients[14] reported that men with NAION had an odds ratio of 1.75 (95% confidence interval (CI), 0.48 to 6.30)—that is, statistically not significant) for having used PDE5 inhibitors. A significant odds ratio of 10.7 (95% CI, 1.3 to 95.8) was seen in those with a history of myocardial infarction. The limitations of this study illustrate the potential problems of convenience case–control studies. The possibility of biases in the selection of controls was suggested by the imbalance between cases and controls in proportion with African-American ethnicity. There was considerable scope for information biases because interviewers were not blinded to the case–control status of respondents; controls may have underreported the use of erectile dysfunction drugs to telephone interviewers because of embarrassment; and the timing of ascertainment of use of PDE5 inhibitors differed considerably between cases and

Table 2 Demographic and clinical data on patients reported in case reports with non-arteritic anterior ischaemic optic neuropathy (NAION) with phosphodiesterase use

Patient	Age	Eye	VA	Drug	Dose (mg)	Onset after use	Associated symptom	VF defect	Disc at risk	HT	HC	S
1[28]	59	OS	20/30	Tadalafil	20	–	Blue area, flashing lights, blurred VA	Gen	–	N	N	N
2[29]	59	OD	LP	Sildenafil	25	Next AM	Bright colours, sore eye	Inf	–	Y	Y	–
3[30]	59	OS	HM	Sildenafil	25	Few hours	Colour changes	Gen	–	Y	Y	–
4[30]	58	OD	HM	Sildenafil	50	1 h	Red face, loss of vision	–	Y	Y	Y	–
5[30]	67	OD	20/200	Sildenafil	50	Next AM	Loss of vision	Sup	–	Y	N	U
6[30]	50	OS	20/160	Sildenafil	100	Next AM	Flash of light	Inf	Y	Y	–	N
7[30]	69	OS	20/125	Sildenafil	50	Next AM	Loss of vision	–	–	Y	N	N
8[30]	66	OD	20/25	Sildenafil	–	36 hours		–	Y	Y	Y	N
9[30]	60	OD	20/20	Sildenafil	–	Next AM	Shade over eye	–	Y	Y	Y	N
10[30 31]	52	OS	20/20	Sildenafil	50	30 min	Headache, sweating, blue flashes, blurred VA OU	Inf	Y	N	N	N
11[31]	69	OD	20/80	Sildenafil	NA	45 min	Loss of vision	Inf	–	N	Y	N
12[32]	42	OD	20/200	Sildenafil	50	Next AM	Blurred VA	Gen	Y	N	N	N
13[31]	62	OS	20/50	Sildenafil	50	–	Blurred VA	Inf	Y	N	N	N
14[31]	59	OD	20/25	Sildenafil	50	Hours	Darkening of VA	Inf	Y	Y	Y	Y
15[33]	48	OS	20/20	Sildenafil	–	90 min			–	N	N	N
16[34]	61	OD	CF	Sildenafil	–	Next AM			–	Y	Y	Y
17[35]	69	OD		Sildenafil	50	Next AM	Blurred VA	Inf	Y	N	N	N
18[36]	61	OD	CF	Sildenafil	100	Next AM	Loss of VA	Inf	Y	N	N	Y
19[37]	59	OS	20/20	Tadalafil	20	15 h	''Greying of vision''	Inf	Y	N	N	N
20[13]	67	OD	20/30	Tadalafil	20	2 h	Recurrent transient VF loss with drug use	Inf	Y	Y	–	–

Gen, generalised defect; HC, hypercholesterolaemia; HT, hypertension; Inf, inferior altitudinal defect; N, no; next AM, next morning; OD, right eye; OS, left eye; S, smoking; Sup, superior altitudinal defect; VA, visual acuity; VA OU, binocular visual acuity; VF, visual field; Y, yes.

controls, increasing the scope for recall biases. Controls were randomly selected; however, the details of the randomisation were not given. Although most such limitations can be minimised by optimum design, conduct, and analysis of observational studies, the potential problem of ''indication biases'' persists: it is difficult to disentangle reliably the putative consequence of drug use (in this case, the risk of NAION) from the reason the drug was taken in the first place (for example, because of vascular risk factors that would predispose both to erectile dysfunction and an increased risk of NAION).

REGISTRY BASED STUDIES

A particular type of observational study involves the use of large scale patient registries. Such registry based studies can offer considerable statistical power because they are based on the observation of large numbers of people for prolonged durations. They may also eliminate certain information biases because drug use is recorded before the diagnosis of the suspected adverse event. Such registries may, however, lack important details for particular scientific questions. For example, the UK General Practice Research Database is one of the world's largest computerised databases of anonymised longitudinal medical records from primary care, involving data on drug use and disease outcomes collected on about 13 million patients during about 40 million person-years at risk (www.gprd.com/home). Unfortunately this database lacks precise information on the diagnosis of NAION (www.gprd.com). Similarly, the diagnostic codes in the 4.1 million men aged at least 50 years in the US National Veterans Health Administration's[15] pharmacy and clinical database do not distinguish anterior ischaemic optic neuropathy from arteritic ischaemic optic neuropathy, because there is no NAION specific ICD-9 code. Consequently, in a study of use of PDE5 inhibitors in this database, Margo and Dustin[15] defined NAION as ischaemic optic neuropathy (ICD-9-CM 377.41), with a subsidiary diagnosis of ''possible'' NAION that included papillitis and optic neuritis. About 11% of the men in the database had been dispensed a PDE5 inhibitor and 3777 had recorded a diagnosis of NAION (with a further 1530 recording a diagnosis of possible NAION) using the study's definitions. The relative risk for NAION was 1.02 (95% CI, 0.92 to 1.12) in men prescribed PDE5 inhibitors, 1.34 (1.17 to 1.55) for possible NAION, and 1.10 (1.02 to 1.20) for a combination of NAION and possible NAION. As acknowledged by the report's authors, there are potential limitations in these data, such as an inability to determine whether the disease diagnosis was correct, an inability to determine the temporal relation of drug use to NAION onset, and a lack of adjustment for potential confounding factors, such as vascular risk factors (although the latter might be expected to weaken any associations). Even so, the weak to modest (and, in the case of NAION, non-significant) associations reported in such a large analysis provide some assurance against a major hazard of use of PDE5 inhibitors for NAION. In addition, it is well recognized that patients may obtain this class of drug outside their insurance plan or without a prescription, but would still present to their physician if NAION occurred, resulting in an underestimation of association. They also suggest that any further investigation of this hypothesis in observational studies may require at least several hundred cases of NAION and a similar number of controls in order to assess any such moderate effects with sufficient power.

STUDIES OF POSSIBLE MECHANISMS

Unless an epidemiological association is very strong, the inference of causation generally requires a plausible mechanism of action that would mediate the adverse effect of drug exposure. Convincing evidence for any such mechanism is currently missing in relation to NAION, partly because the pathogenesis of NAION itself is poorly understood and partly because technologies that enable study of the microvasculature of the optic nerve (which is needed to advance understanding of its haemodynamic regulatory mechanisms) are still under development. Nonetheless, it has been suggested that systemic arterial hypotension, particularly nocturnal hypotension, may precipitate NAION,[16 17] given the mild hypotensive effects of

PDE5 inhibitors on arterial blood pressure. It is possible that PDE5 inhibitors may accentuate the physiological nocturnal hypotension enough to decrease the perfusion pressure in the posterior ciliary arteries, resulting in ischaemia to an optic nerve head and setting off the cascade of a compartment syndrome which is thought to occur in a small, crowded optic nerve. Alternatively, activation of the nitric oxide–cyclic GMP pathway may reduce optic nerve head perfusion or disrupt autoregulation by potentiation of nitric oxide.[18] In a randomised crossover study of young, healthy volunteers (mean age, 39 years), alterations in ocular blood flow measurements after oral ingestion of sildenafil citrate were noted, and the investigators concluded that PDE5 inhibitors could affect autoregulation at the optic nerve head.[19] In older vasculopathic patients with a disc at risk, these changes may be even more significant. It has been suggested that patients with abnormal endothelial cell function may respond differently to PDE5 inhibitors and therefore alterations in optic nerve haemodynamics may have may have more severe or different sequelae than in healthy volunteers. Hence, such transient fluxes in circulation may be sufficient to elicit the final insult of critical ischaemia to a patient with underlying vasculopathic risk factors who has an anatomically susceptible optic nerve.

PHARMACOVIGILANCE AND PHARMACOSURVEILLANCE

The main limitations of current postmarketing safety systems arise from their voluntary and generally uncoordinated nature. Because the reporting of adverse drug reactions is not compulsory, the level of detail in available data is often sketchy, frequently lacking information on, for example, drug dosage, the exact temporal associations between drug use and putative adverse event, the duration of therapy, and any previous dechallenge and rechallenge episodes (that is, responses to cessation or readministration of the drug following initial putative adverse outcomes). Because different jurisdictions and organisations tend to collect data with varying degrees of completeness, there is considerable scope for information biases (such as underreporting, underascertainment, or overascertainment)[20] and non-comparability of available data. As it is estimated that only about 1% of all adverse drug reactions and about 10% of those considered serious are ever reported,[21 22] leading authorities have recently proposed alternative approaches to the monitoring drug safety in the USA.[23 24] Such general limitations of postmarketing safety systems may be compounded in the specific case of PDE5 inhibitors, for which direct-to-consumer advertising leads to use of drugs by patients who have not had appropriate medical evaluation for its use.[25] Hence, patients may not offer information on the use of a specific drug unless directly questioned; conversely, physicians unaware of putative adverse events may not ask patients with visual loss about the use of any PDE5 inhibitors. The patchiness of current systems is suggested by the fact that, to date, only several dozen cases of NAION associated with PDE5 inhibitor use have been reported, despite an estimated five million yearly users in the USA. If the incidence of NAION is 2–10/100 000, then one would expect 100–500 cases a year of NAION where there was recent or distant use of a PDE5 inhibitor, even if there was no excess associated with use of these drugs.

CURRENT SITUATION

Given the uncertainties in the epidemiological and mechanistic evidence, both the FDA and WHO have concluded that there is at present a lack of conclusive evidence of a causal relation between use of PDE5 inhibitors and risk of NAION. Nevertheless, as a precaution, the FDA has advised patients[26] ''to stop taking these medicines, and call a doctor or healthcare provider right away if they experience sudden or decreased vision loss in one or both eyes'', and that people ''taking or considering taking these products [should] inform their health care professionals if they have ever had severe loss of vision, which might reflect a prior episode of NAION.'' Similarly, the European Medicine Evaluation Association (EMEA) has advised patients taking or considering taking PDE5 inhibitors to inform their health care professionals if they have ever had severe loss of vision, and to seek referral to an ophthalmologist. Such visual loss could indicate a previous episode of NAION, and such patients are assumed to be at an increased risk of developing NAION in the second eye.

More generally, questions surrounding the use of PDE5 inhibitors and the risk of NAION highlight weaknesses in current systems and databases used to identify and evaluate uncommon adverse effects of therapeutic drug use.[27] The current inability to confirm or refute claims of uncommon adverse effects of new drugs tends to generate persisting uncertainty. This puts regulatory authorities in a difficult position, where caution is an understandable response, and can hamper risk–benefit calculations by physicians and patients for drugs that might improve quality of life substantially. The Senate has made an initial attempt to address these inadequacies by passing S.1082 (The Food and Drug Administration Revitalization Act), a bill to provide the FDA with increased power to monitor drugs in the postmarketing phase. This bill provides a fundamental change in the philosophy of drug agencies, allowing the government to establish a surveillance system to track adverse reactions of prescription drugs.[28] It remains to be seen whether this bill will become law. Failure to improve on current systems will ultimately harm patients, and hinder physicians in providing optimal drug treatments.

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