Acute Nonarteritic Anterior Ischemic Optic Neuropathy and Exposure to Phosphodiesterase Type 5 Inhibitors

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ABSTRACT

Introduction. Nonarteritic anterior ischemic optic neuropathy (NAION), a rare visual disorder, has been reported in men using phosphodiesterase type 5 inhibitors (PDE5i) for erectile dysfunction.

Aim. We examined whether intermittent use of PDE5i is associated with acute NAION onset within approximately five half-lives following drug ingestion.

Methods. One hundred two ophthalmology centers in the United States and Europe identified potential cases of NAION. An expert adjudication committee conducted a blind review of the records of those with recent PDE5i use to classify cases as Definite, Possible, or not NAION. Subjects provided information on PDEi use via telephone interview. Each NAION case's PDE5i exposure immediately prior to onset was compared against his recent patterns of use in an observational case–crossover design. A sample size of 40 cases with intermittent PDE5i exposure in the 30 days prior to NAION onset was needed to detect an odds ratio (OR) of 3.0 with 80% power.

Main Outcome Measures. The daily relative risk for acute NAION on days within five half-lives of PDE5i use vs. other days was estimated via an OR obtained from conditional logistic regression.

Results. Among 43 Definite NAION cases with PDE5i exposure in the prior 30 days, the OR was 2.15 (95% confidence interval [CI]: 1.06, 4.34). When 21 Possible NAION cases were included (n = 64), the OR was 2.36 (95% CI: 1.33, 4.19).

Conclusions. We found an approximately twofold increased risk of acute NAION within five half-lives of PDE5i use compared with use in a more prior time period. Bias from inaccurate recall of exposure was unlikely to have substantially affected the results. Based on our results, we estimate that weekly use of PDE5i adds three NAION cases per 100,000 men 50 years and older annually. **Campbell UB, Walker AM, Gaffney M, Petronis KR, Creanga D, Quinn S, Klein BEK, Laties AM, Lewis M, Sharlip ID, Kolitsopoulos F, Klee BJ, Mo J, and Reynolds RF. Acute nonarteritic anterior ischemic optic neuropathy and exposure to phosphodiesterase type 5 inhibitors. J Sex Med 2015;12:139–151.**

Key Words. Nonarteritic Anterior Ischemic Optic Neuropathy (NAION); Phosphodiesterase Type 5 Inhibitors (PDE5i); Sildenafil; Case–Crossover Study; Erectile Dysfunction (ED)

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Introduction

Phosphodiesterase type 5 inhibitors (PDE5i) are first-line pharmacotherapy for male erectile dysfunction (ED) worldwide [1]. Sildenafil citrate (Viagra®, Pfizer, New York, NY, USA) was first approved for ED treatment in 1998 by the U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA), followed by tadalafil (Cialis®, Eli Lilly, Indianapolis, IN, USA) in 2002 (FDA)/2003 (EMA), and vardenafil (Levitra®, Bayer Healthcare Pharmaceuticals, Wayne, NJ, USA) in 2003. More recently, additional PDE5i have come on the market, including udenafil (Zydena®, Dong-A PharmTech, Seoul, South Korea) and avanafil (Stendra®, Vivus, Mountain View, CA, USA). PDE5i are effective and highly tolerable, and serious adverse events are rare. The most worrisome adverse consequences are thought to be associated with relaxation of vascular smooth muscle. In particular, use of PDE5i is contraindicated in patients receiving nitrates, due to the potentially life-threatening hypotensive effect of combining these medications [2].

Cases of nonarteritic anterior ischemic optic neuropathy (NAION) in men using PDE5i have been documented in case series and individual reports [3–6]. NAION is a rare visual disorder believed to be a consequence of hypoperfusion in the optic nerve, with disc swelling and optic nerve head infarction [7]. The exact pathogenesis of NAION is not known [8]. According to Miller and Arnold (2014), almost all patients with NAION have a "disc at risk", as reflected by a low cup-to-disc ratio. Disc swelling may be most dangerous in patients with this crowded optic disc. Miller and Arnold recommend that patients with discs at risk be counseled about the risk of developing NAION if they use PDE5i [8].

NAION usually presents as sudden, painless, partial vision loss in one eye, typically noticed upon awakening. The visual loss varies in magnitude, may be static or may worsen before stabilization within 2–3 months; most cases exhibit no deterioration past the point of stabilization, and some cases experience spontaneous improvement in visual acuity. Studies of treatment with diphenylhydantoin, systemic corticosteroids, intravitreal injections with bevacizumab and erythropoietin, hyperbaric oxygen, and surgery have not shown them to be effective [8]. ED shares several risk factors with NAION, including older age, hypertension, hyperlipidemia, diabetes, and smoking [3,9]. Most NAION case reports mention several risk factors, thereby complicating their interpretation.

Systematic reviews of clinical trials and postmarketing surveillance studies of PDE5i have not indicated an association with NAION, although none of these was designed to specifically evaluate this risk. No cases were reported in an internal review of data from more than 13,000 men enrolled in Pfizer-sponsored clinical trials of sildenafil [10] or in a European prospective cohort study of 3,813 men who were prescribed sildenafil [9,11]. Postmarketing surveillance studies conducted in the United Kingdom identified one case among 16,129 men prescribed tadalafil [12] and one case among 22,471 men prescribed sildenafil [13]. At the time of initiation of the present study (2008), U.S. class labeling described the reports of NAION, noted the difficulty in separating any drug-induced effect from the effects of patient risk factors, and advised termination of PDE5i use in the event of sudden vision loss. Class labeling in the European Union contraindicated PDE5i use in patients who had already experienced NAION.

To address the limitations of existing data, the U.S. FDA requested and Pfizer committed to perform an observational study to evaluate whether as-needed use of PDE5i, taken together as a class, is associated with the development of acute NAION within approximately five half-lives of drug ingestion. Pfizer submitted the protocol for the study reported here to the FDA and the EMA before initiation.

Methods

Study Design

A case–crossover design is a variant of the standard case–control study, in which each case subject serves as his own control. Developed to assess effects of intermittent exposures on diseases with abrupt onset [14,15], the case–crossover design is well suited to address the question of whether as-needed use of PDE5i is associated with the onset of acute NAION, where the timing of onset can be identified by the patient. A key advantage is that it entails control of time-invariant personal characteristics through self-matching and avoids the potential biases associated with control selection. The case–crossover design is being used more frequently in pharmacoepidemiologic safety studies [16].

In a case–crossover study, a designated control period prior to disease onset is divided into dis-