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Sildenafil- and tadalafil-associated optic neuropathy: implications for men after prostate cancer treatment

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The phosphodiesterase 5 (PDE5)-selective inhibitors sildenafil (Viagra), tadalafil (Cialis), and vardenafil (Levitra) are frequently prescribed for treatment of erectile dysfunction (ED).¹

These medications have implications for men with prostate cancer who undergo treatment with radical prostatectomy or radiation therapy (brachytherapy or external beam radiation), as these treatments are associated with an increased risk for ED. Instances of nonarteritic ischemic optic neuropathy (NAION) and permanent vision loss following ingestion of PDE5-selective inhibitors have been reported.^{2–4}

Investigators affiliated with the Research on Adverse Drug Events and Reports (RADAR), an established pharmacovigilance program, reviewed the literature as well as US Food and Drug Administration (FDA) reports to determine the frequency and clinical characteristics of PDE5-selective inhibitor-associated NAION and permanent vision loss in men with ED.

Reports and associated toxicities

We reviewed case descriptions of PDE5-selective inhibitor-associated optic neuropathy events reported to the FDA between 1998 and 2004 or in the peer-reviewed literature between 1998 and 2005. Thirty-nine cases of optic neuropathy in sildenafil- or tadalafil-treated patients were identified as case reports (n = 18) or in FDA databases (n = 21). Affected men were similar in age (median, 62 years), and 90% of the cases were reported among men who had ingested PDE5-selective inhibitors and suffered permanent vision loss. Importantly, the quality of the case reports in the FDA database is suboptimal given that they often lack important information on duration of PDE5-selective inhibitor use, time since ingestion of the most recent dose, identification of affected eye, fundoscopic examination findings, and response to de-challenge. A plausible explanation as to cause-and-effect relative to PDE5-selective inhibitor therapy and NAION does not exist.

Recommendations

PDE5-selective inhibitor therapy is noted in 19% of the FDA reports of drug-associated ocular toxicities, which makes it the most commonly reported drug class associated with this toxicity.⁵ Patients with vasculopathy who also take antihypertensive medications, including or PDE5-selective inhibitors may be at increased risk for NAION due to nocturnal hypotension. Various factors can reduce blood flow to the optic nerve head below critical levels, and the final insult could be medications or hypotensive events.

PDE5-selective inhibitors have been administered to 30 million men, many of whom are older, vasculopathic, and at risk for NAION. A few published case reports include descriptions of men without vasculopathic risk factors in whom NAION occurred within a reasonable time after PDE5-selective inhibitor ingestion, although these men did have an identifiable risk factor (ie, a small optic cup-to-optic disc ratio).

Absent more completely described adverse events in FDA safety databases, and lacking an animal model or scientific study revealing a biological basis for NAION due to treatment with PDE5-selective inhibitors, most instances of NAION related to these inhibitors should be viewed as an expected coincidence. Future occurrences of visual disturbances after PDE5-selective inhibitor ingestion should be comprehensively reported to the FDA, including information on drug duration and dose, time from PDE5-selective inhibitor ingestion to onset of findings, and ophthalmologic examination findings. Men should avoid PDE5-selective inhibitors if they have previously suffered NAION in one eye, as they may be more prone to developing NAION in the contralateral eye.

Fast Facts

Phosphodiesterase 5 (PDE5)-selective inhibitors block the degradative action of PDE5 on cyclic guanosine monophosphate (cGMP) in smooth muscle cells that line the blood vessels supplying blood to the penis. These medications were the first effective oral treatment for erectile dysfunction. Physiologically, the process of erection involves the release of nitric oxide in the vasculature of the corpus cavernosum as a result of sexual stimulation. Nitric oxide activates the enzyme guanylate cyclase resulting in increased levels of cGMP and subsequent smooth muscle relaxation in the blood vessels supplying the corpus cavernosum. This leads to an increased inflow of blood to the penile vessels, which causes an erection. PDE5-selective inhibitors increase blood flow to the penis during sexual stimulation. PDE5-selective inhibitors are primarily metabolized by the cytochrome P450 enzyme CYP3A4; therefore, the potential exists for adverse drug interactions with other drugs that inhibit or induce CYP3A4.

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Biography

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