ORIGINAL RESEARCH—ED PHARMACOTHERAPY

Are Phosphodiesterase Type 5 Inhibitors Associated with Vision-Threatening Adverse Events? A Critical Analysis and Review of the Literature

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ABSTRACT

Introduction. Phosphodiesterase type 5 (PDE5) inhibitors are the first line drugs for treatment of erectile dysfunction. Sildenafil (Viagra[R]), tadalafil (Cialis[R]), and vardenafil (Levitra[R]) are from the same class of drugs that inhibit PDE5. Transient visual symptoms such as change in color perception and increased light sensitivity are well-known adverse effects of these drugs and occur in 3–11% of sildenafil users. Vision-threatening (serious) ocular complications, such as nonarteritic ischemic optic neuropathy and cilio-retinal artery occlusion have rarely been reported in PDE5 inhibitor users.

Aims. To highlight and analyze the most recently published case literature on serious ocular complications of PDE5 inhibitors.

Methods. Search of the peer-reviewed English literature was conducted using Medline. The following databases also were searched: Cumulative Index to Nursing and Allied Health Literature, Cochrane Library, Global Health, and MD Consult. The causality assessment of the reported adverse drug reactions was analyzed by applying both the World Health Organization (WHO) Probability Scale and the criteria utilized by the National Registry of Drug-Induced Ocular Side Effects.

Main Outcome Measures. To scientifically and objectively find out if PDE5 inhibitors are associated with vision-threatening ocular complications.

Results. Eight case reports of serious PDE5 inhibitor-associated ocular complications were identified since January 2006 until February 2011. Case reports included cases of anterior and posterior nonarteritic ischemic optic neuropathy, central retinal vein occlusion, cilio-retinal artery occlusion, acute angle closure glaucoma and optic atrophy after sildenafil use.

Conclusion. There is lack of conclusive evidence to indicate a direct cause–effect relationship between PDE5 inhibitor use and vision-threatening ocular events. Men who use PDE5 inhibitors appear to suffer vision-threatening complications at the same frequency as the general population. However, minor visual adverse effects occur in 3–11% of users and they are transient and reversible. **Azzouni F and Abu samra K. Are phosphodiesterase type 5 inhibitors associated with vision-threatening adverse events? A critical analysis and review of the literature. J Sex Med 2011;8:2894–2903.**

Key Words. Sildenafil; Tadalafil; Vardenafil; Ocular Complications; Phosphodiesterase Inhibitors; Erectile Dysfunction; Viagra and Eye

Introduction

Phosphodiesterase (PDE) is the enzyme responsible for the degradation of cyclic guanosine monophosphate (cGMP) and cyclic adenine monophosphate (cAMP) to GMP and AMP, respectively [1]. There are at least 11 isoenzymes of PDE in the body and this may have therapeutic implications for a wide variety of conditions [1,2].

Sildenafil (Viagra[R]) is an inhibitor of PDE type 5 (PDE5) and to a lesser degree PDE type 6 (PDE6). It was first approved by the Food and Drug Administration (FDA) for use in men with erectile dysfunction on March 27, 1998 [3]. As of August 2008, sildenafil has been prescribed to more than 37 million men, and more than a billion tablets (averaging six per second) have been dispensed worldwide [4].

Other PDE5 inhibitors include vardenafil (Levitra[R]) and tadalafil (Cialis[R]). Sildenafil has been the most extensively studied PDE5 inhibitor [2,5].

Inhibition of PDE5 by sildenafil increases the levels of cGMP, which causes smooth muscle relaxation of the corpora cavernosa and penile arteriolar smooth muscles. This relaxation leads to a drop in arterial resistance and increases blood flow into these tissues [1,6].

In addition to the vasculature of the penis, PDE5 was found in the lungs [7]. The relaxing effect of sildenafil on arterial smooth muscles has extended its use to involve the treatment of pulmonary arterial hypertension (PAH). Recent studies have shown promising results of this drug in the management of PAH secondary to underlying lung diseases such as chronic obstructive pulmonary disease (COPD) [7–9]. Sildenafil is being investigated for the treatment of acute myocardial infarction in humans and acute stroke in animal models [6,10,11].

PDE6 is a unique isoenzyme in its restricted localization to the retina, where it is located in the rod and cone outer segments, and plays a role in the conversion of light stimulation to electrical signal [12]. PDE5 inhibitors have been linked to a variety of visual symptoms [13,14]. These visual effects may be attributable to the known effect of PDE5 inhibitors on retinal PDE6. The relative selectivity of these drugs for PDE5 over PDE6 as indicated in manufacturer's prescribing information is 10-fold for sildenafil [15], 15-fold for vardenafil [16], and 700-fold for tadalafil [17].

The most common visual symptoms that have been linked to PDE5 inhibitors include changes in color perception characterized by a blue tinge to the environment and changes in brightness perception, usually in the form of increased sensitivity to light [3,13,18,19]. These symptoms occur in 3–11% of men taking sildenafil 25–100 mg [13], 0.3–2% of vardenafil [20,21], and 0.1% of tadalafil users [22]. These symptoms are mild, dose-dependent, and completely reversible.

Serious ocular complications in association with PDE5 inhibitors have been reported previously. These complications include nonarteritic anterior ischemic optic neuropathy (NAAION) with attendant vision loss, cilio-retinal artery occlusion, central retinal vein occlusion (CRVO), and pupil sparing third nerve palsy [8,23–33].

Since these medications are widely used for the treatment of erectile dysfunction, benign prostate hyperplasia [34], and their recent FDA approval for the treatment of PAH [7,35], it is expected that these serious ocular complications will be reported more often. The aim of this article is to highlight and analyze the most recent published literature on serious ocular complications of PDE5 inhibitors since January 2006.

Methods

We conducted a critical search for peer-reviewed English literature for case reports of serious ocular complications in relation to the use of PDE5 inhibitors using Medline. The following databases were also searched: Cumulative Index to Nursing and Allied Health Literature (CINAHL), Cochrane Library, Global Health and MD Consult. Sensitive search strategies of subject headings and text words were used and included the following: sildenafil, vardenafil, tadalafil, ocular complications, phosphodiesterase inhibitors, erectile dysfunction drugs, Viagra, and eye.

Studies were included only if they presented a case report of serious ocular complications in association with the use of PDE5 inhibitors.

One hundred sixty-seven articles were identified in total. Thirty-four FDA-recorded cases of PDE5 inhibitor-related serious ocular complications that were reported in the literature before January 2006 were extensively reviewed and analyzed in previous articles [19,23,24,36]. We focused our search on cases reported between January 2006 and 2011. Sixty-two articles were found in the literature during this time frame. After reviewing these articles, eight articles that reported serious ocular complications in relation to the use of PDE5 inhibitors were identified (Table 1) [37–44].