SEXUAL MEDICINE REVIEWS REVIEW

Cardiovascular Safety of Phosphodiesterase Type 5 Inhibitors After Nearly 2 Decades on the Market

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ABSTRACT

Background: The phosphodiesterase-5 (PDE5) inhibitors that have been available for nearly 20 years are highly effective in treating erectile dysfunction and have been consistently shown to be safe when used according to package insert instructions.

Aim: To review the cardiovascular (CV) safety of PDE5 inhibitors used to treat erectile dysfunction.

Methods: PubMed, the Derwent Drug File, and Embase were searched to identify papers published from 1990–2016 presenting CV safety data for PDE5 inhibitors.

Outcomes: This narrative review focuses mainly on papers published in the last 10 years with CV safety data for sildenafil, tadalafil, or vardenafil.

Results: Similar to earlier studies, newer studies demonstrate that PDE5 inhibitors do not show an increased incidence of serious CV adverse events such as cardiac death or myocardial infarction. There are drug–drug interactions with PDE5 inhibitors that for the most part are now commonly known, and PDE5 inhibitors are generally safe to use with other commonly used drugs including antihypertensive agents.

Conclusion: PDE5 inhibitors are a class of drugs that when used appropriately demonstrate a favorable CV safety profile and present some encouraging signals for new CV indications, which will require additional study. **Kloner RA, Goldstein I, Kirby MG, et al. Cardiovascular Safety of Phosphodiesterase Type 5 Inhibitors After Nearly 2 Decades on the Market. Sex Med Rev 2018;XX:XXX–XXX.**

Key Words: Cardiovascular System; Phosphodiesterase Inhibitors; Erectile Dysfunction; Safety

INTRODUCTION

Mechanism of Action of Phosphodiesterase-5 Inhibitors

For a penile erection to occur, vasodilation of the blood vessels with accompanying increased blood flow and storage in the penis is necessary.[1] Cases of erectile dysfunction (ED) are commonly due to inadequate vasodilation and reduced blood flow within the penile blood vessels. A major mechanism for increasing blood flow and storage in the corpora cavernosa of the penis involves nitric oxide.[2] Sexual stimulation normally releases nitric oxide from neurons in the penis as well as from the endothelial cells that line the penile arteries. Within smooth muscle cells, nitric oxide results in the production of cyclic guanosine monophosphate (cGMP), a second messenger that ultimately causes relaxation of the smooth muscles in the penile vasculature and vasodilation of penile blood vessels (including the sinusoids of the corpus cavernosa) that fill with blood and cause an erection. cGMP is inactivated by the enzyme phosphodiesterase-5 (PDE5), which is normally released during the relaxation phase following ejaculation. PDE5 inhibitors, such as sildenafil, vardenafil, and tadalafil, improve erectile function by reducing the breakdown of cGMP, thereby allowing better and longer vasodilation and increased engorgement.[3] PDE5 is found in high concentrations in the blood vessels of the corpora cavernosa of

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the penis as well as the pulmonary vasculature, but it is also present at lower concentrations in the systemic vasculature, where it performs a comparable function.[4,5]

POTENTIAL CARDIOVASCULAR CONCERNS DURING TREATMENT WITH PDE5 INHIBITORS

PDE5 inhibitors have revolutionized the treatment of ED and are also commonly used to treat pulmonary hypertension.[6] While PDE5 inhibitors are generally efficacious and well tolerated, there were some cardiovascular (CV) safety concerns in the early days of their use regarding the possibility that PDE5 inhibitors could precipitate adverse CV events (Table 1). However, the results of large-scale data analyses have demonstrated that there is no increase in adverse CV events (including death) in men taking PDE5 inhibitors compared with control groups. Nitrates remain a contra-indication for the use of PDE5 inhibitors (within 24 hours of taking sildenafil and vardenafil and within 48 hours of taking tadalafil), because when nitrates are administered with these agents, potentially significant hypotension develops in a small number of individuals.[7] A more recently licensed drug used to treat pulmonary hypertension, riociguat, which increases the synthesis of cGMP, is also contra-indicated for use with PDE5 inhibitors due to concerns over additive vasodilation.[8] A warning also exists regarding the use of PDE5 inhibitors with alpha-blockers because of the possibility of orthostatic hypotension.[7] When PDE5 inhibitors are added to most anti-hypertensive drugs, small and clinically insignificant additional decreases in blood pressure occur.[7] Because PDE5 inhibitors are vasodilators, they should be avoided in patients with obstruction in the left ventricular outflow track or aortic valve and pre-existing hypotension, because they have the potential to precipitate hypotension. Because no data are available on the use of PDE5 inhibitors in patients with very recent myocardial infarction (MI) or stroke, these drugs should be avoided in these patient populations.

Over the past 10 years, there have been few updated reports regarding the CV safety of PDE5 inhibitors. The purpose of this article is to review papers that have been published primarily during the 10 years from 2006–2016 that provide an update on the CV safety of PDE5 inhibitors. This article will focus on the 3 major PDE5 inhibitors used in the United States: sildenafil, tadalafil, and vardenafil. The efficacy and general safety of these PDE5 inhibitors in patients with ED are essentially equal, although some differences exist, particularly with regard to duration of action.[9]

Table 1. Potential cardiovascular safety concerns during treatment with phosphodiesterase-5 inhibitors

Physiologic change during PDE5 inhibitor therapy/concomitant medication	Potential concern
Release of NO, production of cGMP	Smooth muscle relaxation, increased blood flow
Vasodilation	Hypotension
Concomitant medication	
Nitrates	Hypotension
Riociguat	Additive vasodilation
Alpha-blockers	Orthostatic hypotension

cGMP = cyclic guanosine monophosphate; NO = nitric oxide; PDE5 = phosphodiesterase-5.

LITERATURE SEARCH

In this narrative review, a search of the published literature (ie, PubMed, the Derwent Drug File, and Embase) on the CV safety of the PDE5 inhibitors sildenafil, tadalafil, and vardenafil was conducted on April 4, 2016, using the following search terms: (phosphodiesterase type 5 inhibitor OR sildenafil OR Viagra OR Revatio OR tadalafil OR Cialis OR Adcirca OR vardenafil OR Levitra OR Staxyn OR Vivanza) AND (cardiovascular OR myocardial OR infarct OR cardiac OR heart OR ventricular OR fibrillation OR cardiomyopathy) AND (nitrate OR nitroglycerin). The search was limited to English language, published from January 1, 1990, to April 1, 2016, humans (valid for PubMed and Embase only), and containing an abstract (valid for PubMed and Embase only). An evaluation of the identified articles was conducted by 2 independent reviewers. Of the articles retrieved, articles with CV safety data for sildenafil, tadalafil, or vardenafil that were predominantly published from 2006–2016 were retained and summarized qualitatively.

LARGE CV SAFETY STUDIES

Findings from publications of large CV safety studies are summarized in Table 2.[10–16]

Review of Double-Blind, Placebo-Controlled Trials and Post-Marketing Safety Database of Sildenafil

Giuliano et al[10] published an important article on the CV safety of sildenafil in 2010. Data from 67 double-blind, placebo-controlled, sildenafil trials were evaluated, together with the post-marketing safety database, in men who received 50- or 100-mg doses of sildenafil for the treatment of ED. This analysis included >14,000 men from clinical studies and >39,000 patients from the manufacturer's post-marketing safety database. The men in the clinical trials were a mean age of 55 years; most had a history of ED for 4.5 years, and most cases of ED were organic in nature. Concomitant CV risk factors and/or CV disease were common in these men (ie, diabetes mellitus, hypertension, coronary artery disease, angina, MI, stroke); those with severe cardiac failure, unstable angina, or a recent stroke or MI event were excluded. Headache and facial flushing were the most common adverse events, which is consistent with the known pharmacology of PDE5 inhibitors as vasodilators and consistent with the product labeling (Supplementary Table 1[10]). Of note these events diminished substantially after continued use of sildenafil for 8–16 weeks