ORIGINAL RESEARCH—ED PHARMACOTHERAPY

10-Year Analysis of Adverse Event Reports to the Food and Drug Administration for Phosphodiesterase Type-5 Inhibitors

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ABSTRACT

Introduction. To ensure public safety all Food and Drug Administration (FDA)-approved medications undergo postapproval safety analysis. Phosphodiesterase type-5 inhibitors (PDE5-i) are generally regarded as safe and effective.
Aim. We performed a nonindustry-sponsored analysis of FDA reports for sildenafil, tadalafil, and vardenafil to evaluate the reported cardiovascular and mortality events over the past 10 years.
Methods. Summarized reports of adverse events (AEs) for each PDE5-i were requested from the Center for Drug Evaluation and Research within the FDA. These data are available under the Freedom of Information Act and document industry and nonindustry reports of AEs entered into the computerized system maintained by the Office of Surveillance and Epidemiology.
Main Outcome Measure. The data were analyzed for the number of AE reports, number of objective cardiovascular events, and reported deaths.
Results. Overall, 14,818 AEs were reported for sildenafil. There were 1,824 (12.3%) reported deaths, and reports of cardiovascular AEs numbered 2,406 (16.2%). Tadalafil was associated with 5,548 AEs and 236 deaths were reported. Vardenafil was associated with 6,085 AEs and 121 reports of deaths. The percentage of reported severe cardiovascular disorders has stabilized at 10% to 15% of all AE reports for sildenafil and tadalafil and 5% to 10% for vardenafil. Only 10% of AE reports sent to the FDA for PDE5-i were from pharmaceutical manufacturers.
Conclusion. Reports of deaths associated with PDE5-i remain around 5% of total reported events. Despite inherent limitations from evaluating FDA reports of AEs, it is important that these reports be reviewed outside pharmaceutical industry support in order to provide due diligence and transparency. **Lowe G and Costabile RA. 10-year analysis of adverse event reports to the Food and Drug Administration for phosphodiesterase type-5 inhibitors. J Sex Med 2012;9:265–270.**

Key Words. Phosphodiesterase Inhibitor; Adverse Events; Death; Cardiovascular Disease; Food and Drug Administration

Introduction

Phosphodiesterase type-5 inhibitors (PDE5-i) are first line therapy for treatment of erectile dysfunction (ED). Postmarketing studies sponsored largely by the pharmaceutical industry have consistently concluded there is not an increased risk of cardiovascular side effects from PDE5-i in patients appropriate for sexual activity [1–4]. Evaluation of the postmarketing safety database for sildenafil citrate, from 1998 to 2007, revealed 853 cardiac adverse events (AEs) reported including myocardial infarction, palpitations, or tachycardia [2]. This represented 4.76% of the total 17,909 AEs reported. It is very difficult to clearly determine the numbers of men using PDE5-i. The estimates range from 15 million [5] to 83.6 million [6,7]. Therefore postmarketing reports of AEs represent a small number of patients adversely affected by PDE5-i.

The United States Food and Drug Administration's (U.S. FDA) largest division is the Center for Drug Evaluation and Research (CDER), critical for monitoring drug safety and effectiveness. The review process continues after approval of a new medication and is based on reported AEs. The agency determines if a change in product labeling, preventative measures or even review of approval decision is necessary. This information is critical since many clinical trials do not evaluate effects over prolonged periods and are selective in the patients that enter clinical trials. Initial PDE5-i trials excluded patients with active angina, diabetes, hypertension, and New York Heart Association functional classification of II or greater [8,9]. Phase IV postmarketing evaluation extends the reviewed patient population to include patients who may have been excluded in clinical trials. The MedWatch program allows patients and healthcare professionals to report concerns for a particular pharmaceutical or medical product by submitted reports to the FDA. Additionally pharmaceutical companies must submit any and all postmarketing adverse reports to the FDA. When sufficient concern exists, MedWatch alerts are based on these reports to ensure rapid communication to the healthcare community.

The last MedWatch alert for an approved PDE5-i appeared in 2007 documenting a concern for sudden decreases or loss of hearing following usage [10]. Sildenafil was associated with 15 reports of sudden hearing loss, and 5 reports each occurred for vardenafil and tadalafil.

In this study we aim to document the rate of reported significant adverse cardiovascular events or mortality associated with each PDE5-i over the decade following release of these compounds by a review of industry and nonindustry submitted reports to the FDA. One would expect the cumulative number of AEs to rise over time (with increased use of PDE5-i) with the percentage of adverse reports associated with cardiovascular events or mortality remaining constant. An independent assessment separate from industry-reported studies of this data is also part of the due diligence process in evidence based medicine.

Methods

The CDER has an active postmarketing surveillance program to document AEs. The Adverse Event Reporting System (AERS) is a computerized information database maintained in the Office of Surveillance and Epidemiology for storing and monitoring drug safety. Reporting events from providers and patients is voluntary in the United States, but adverse reports to manufacturers must be sent by the manufacturer to the AERS. Consumers and health care providers are also able to report AEs. The information contained within the AERS for each medication is available to the public based on the Freedom of Information Act.

A written request from our institution was sent to the CDER in October 2010 to request the raw data contained within the AERS for sildenafil, vardenafil, and tadalafil. The information obtained represented all the reports of AEs recorded in AERS. Contained within this information is the date of report, patient age and gender, outcome including death, report source, drug name, concomitant drugs, suspected role of each drug, dose, and route of administration. All details are not present for each AE listed. This database does not allow determination of preexisting conditions, medical supervision details, or time association between medication administration and AE. Only those events recording a PDE5-i as the primary suspect drug were reviewed. No evaluation was performed on the reports documenting a PDE5-i as a concomitant secondary drug.

The AE reports for sildenafil, vardenafil, and tadalafil were evaluated for the total number of AE reports , reported deaths, and reported cardiovascular events. Only events with objective data suggesting cardiovascular events were evaluated. Information in the report was evaluated as a cardiovascular event if there was evidence of myocardial infarction, circulatory collapse, ventricular extrasystoles, tachycardia, bradycardia, atrial fibrillation, cardiac failure, hypertension, hypotension, and coronary artery thrombosis. An AE reporting angina was not documented as a cardiovascular event unless associated with tachycardia, bradycardia, or other objective measures of cardiac dysfunction since chest pain is a subjective complaint. The events associated with mortality or cardiovascular disorders were recorded in 6-month intervals beginning in January 2000, the first date provided by the FDA. Some reports included cardiovascular disease with subsequent death and were counted in each category. PDE5-i as treatment for pulmonary hypertension was excluded given the differences in medication dosing and expected mortality rate from the disease state.

Results

The total number of AEs reported was 26,451. There were 2,181 (8.2%) deaths reported.